Université de Montréal

Short-term memory of temporal aspects of noxious and innocuous thermal sensation: psychophysical and fMRI studies

par Mina Khoshnejad

Département de Neurosciences
Faculté de Médecine

Thèse présentée à la Faculté des études supérieures
en vue de l'obtention du grade de Philosophiae Doctor (Ph.D.)
en sciences neurologiques

Sept, 2017

Université de Montréal
Faculté des études supérieures et postdoctorales

Cette thèse intitulée :

Short-term memory of temporal aspects of noxious and innocuous thermal sensation: psychophysical and fMRI studies

Présentée par :
Mina Khoshnejad

a été évaluée par un jury composé des personnes suivantes :

Dr. Elaine Chapman, président-rapporteur
Dr. Pierre Rainville, directeur de recherche
Dr. Pierre Jolicoeur, membre du jury
Dr. Ron Kupers, examinateur externe
Dr. Isabelle Peretz, représentant du doyen de la FES

Résumé

La douleur peut être considérée comme un système de protection qui signale une menace et qui nous avertit des dégâts imminents aux tissus. En tant que mécanisme de défense, il nécessite l'apprentissage et la mémoire des expériences du passé pour la survie et les comportements liés à la douleur. Par conséquent, notre expérience de la douleur actuelle est fortement influencée par les expériences antérieures et l'apprentissage. Cependant, malgré son importance, notre compréhension actuelle de l'interaction entre le système de la douleur et le système de mémoire est très limitée. La mémoire de la douleur est un sujet de recherche très vaste. Il nécessite une compréhension des mécanismes impliqués à chaque étape du système de mémoire (mémoire immédiate, à court terme et à long terme) et l'interaction entre eux. Parmi les étapes multiples de la mémoire, la mémoire à court terme de la douleur est une zone qui est moins recherchée, alors qu'il existe une énorme quantité de recherche neuroscientifique dans la mémoire à court terme sur d'autres modalités, en particulier la vision. L'étude de la mémoire à court terme de la douleur est particulièrement importante car cette trace de la mémoire à court terme de la douleur est ensuite convertie en mémoire à long terme et affecte ensuite les expériences futures de la douleur. Cette thèse est largement axée sur la mémoire à court terme de la douleur.

La complexité et la multi dimensionnalité de la douleur ajoutent encore un autre élément à la recherche sur la mémoire de la douleur. Par exemple, la trace de la mémoire de la douleur peut contenir des traces de mémoire de diverses composantes de la douleur telles que la réponse sensorielle affective, cognitive et motrice et l'interaction entre elles. Par conséquent, une première étape dans l'exploration neuroscientifique de la mémoire de la douleur nécessite la réduction de l'expérience de la douleur tout en englobant tous ces différents composants à un seul composant. Dans la recherche présentée ici, nous avons généralement examiné cela par des instructions d'attention ‘ top-down’ pour assister à la dimension sensorielle de la douleur. La recherche précédente sur la mémoire à court terme de la douleur a également porté principalement sur la dimension sensorielle de la douleur. Cependant, parmi les dimensions

sensorielles de la douleur, la mémoire à court terme de l'intensité et de la dimension spatiale de la douleur a fait l'objet de recherches antérieures. Malgré son importance, la dimension temporelle de la douleur est restée complètement inexplorée dans la recherche sur la mémoire de la douleur.

La recherche menée dans cette thèse est consacrée à l'exploration de la mémoire à court terme de la durée de la douleur. La durée de la douleur peut être suivie de manière indépendante, mais peut également être suivie conjointement avec la dimension d'intensité telle que le suivi dynamique de l'intensité de la douleur dans le temps. Les études menées dans cette thèse traitent spécifiquement du traitement isolé de la durée de la douleur ainsi que du traitement conjoint de la dimension durée / intensité de la douleur.

La première étude psychophysique a exploré la nature de la représentation mentale du modèle de mémoire de la douleur thermique dynamique et a également été conçue pour aborder les différences de la dimension sensorielle et affective de la douleur thermique dans la mémoire à court terme. La deuxième étude psychophysique portait sur les propriétés de la mémoire à court terme de la sensation thermique non douloureux en comparant le suivi dynamique de la sensation et le suivi isolé de la durée d'un événement thermique non douloureux. La troisième étude poursuit l'exploration du traitement dynamique de la durée conjointement avec l'intensité par rapport au traitement isolé de la durée dans la mémoire à court terme en utilisant des stimuli thermiques douloureuse une résonance magnétique fonctionnelle (IRMF).

Dans l'ensemble, les résultats des études psychophysiques ont montré une transformation significative de la durée et de la dynamique de la sensation thermique douloureux et non-douloureux dans la mémoire à court terme; comme la perte d'informations somatosensorielles temporelles en mémoire. Nous avons en outre montré une amélioration du rappel de la durée dans le suivi dynamique de la durée, en comparaison avec le suivi de la durée isolée. Nous avons également montré des différences dans les corrélats neuronaux de la mémoire à court terme de la durée de douleur par rapport à la dynamique de douleur. L'étude de l'IRMF a montré des similitudes frappantes dans les corrélats neuronaux sous-jacents à la

mémoire à court terme de douleur et d'autres modalités telles que la contribution des coticés fronto-pariétales ainsi que les corticaux sensoriels impliqués dans le traitement perceptuel.

Mots-clés: Douleur, Mémoire à court terme, Durée, Psychophysique, Imagerie

Abstract

Pain can be viewed as a protective system that signals threat and alerts us to impending tissue damage. As a defense mechanism, it necessitates the learning and memory of past painful experiences for survival and pain-related behavior. Therefore our current pain experience is heavily influenced by previous experiences and learning. However, despite its importance, our current understanding of the interaction between the pain system and the memory system is very limited. Pain memory is a very broad topic of research on its own. It requires an understanding of the mechanisms involved at each stage of the memory system (immediate, short-term, and long-term memory), and the interaction among them. Among the multiple stages of memory, the short-term memory of pain is an area that is less researched, while there are enormous amount of neuroscientific research in short-term memory of other modalities, particularly vision. Investigation of the short-term memory of pain is especially important as the short-term memory trace of pain is converted to long-term memory and subsequently affects future pain experiences. This thesis is broadly focused on the short-term memory of pain.

The complexity and multi-dimensionality of pain adds yet another element to the research on pain memory. For example, the memory trace of pain may contain memory traces of various components of pain such as sensory, affective, cognitive, and motoric responses, and the interactions among them. Therefore, an initial step in the neuroscientific exploration of pain memory requires narrowing down the pain experience, which encompasses all of these various components, to one single component. In the research presented here, we achieved this using top-down attentional instructions to attend to the sensory component of pain. The previous research on short-term memory of pain also focused mainly on the sensory component of pain. However, within the sensory component of pain the short-term memory of intensity and spatial dimension of pain has been the focus of previous research. Despite its importance, the temporal dimension of pain remained completely unexplored in pain memory research.

Thus, the research conducted in this thesis is devoted to the exploration of short-term memory of the duration of pain. Pain duration can be tracked independently, but it can also be tracked conjointly with intensity, such as in dynamic tracking of pain intensity over time. The studies addressed in this thesis examined the isolated processing of pain duration as well as conjoint processing of the duration and intensity of pain.

The first psychophysical study explored the nature of the mental representation of the memory template of dynamic thermal pain sensation and, additionally, addressed the differences between the sensory versus affective dimensions of thermal pain sensation in short-term memory. The second psychophysical study focused on properties of the short-term memory of innocuous thermal sensation by comparing dynamic tracking of sensation versus isolated tracking of duration of an innocuous thermal event. The third study explored the dynamic processing of duration conjointly with intensity, versus the isolated processing of duration in short-term memory, using noxious thermal stimuli and functional magnetic resonance imaging (fMRI).

Overall, the results of the psychophysical studies showed significant transformation of duration and dynamics information of noxious and innocuous thermal sensation in short-term memory, such as loss of temporal somatosensory information. Additionally, we showed improvement in duration recall during dynamic tracking versus isolated tracking of duration. The fMRI study revealed differences in neural correlates of short-term memory of pain duration versus pain dynamics. Importantly, it also showed striking similarities between neural correlates underlying the short-term memory of pain and those underlying other modalities, such as a contribution of fronto-parietal cortices as well as sensory cortices involved in perceptual processing.

Keywords: Pain, Short-term memory, Duration, Psychophysical, Imaging

Table of Contents

List of Tables

Chapter 4:

Chapter 6 – Article 1:

Chapter 6 – Article 2:

Chapter 6 – Article 3:

List of Figures

Chapter 4 – Review of short-term memory studies of pain

Chapter 6 – Article 1:

Chapter 6 – Article 2:

Chapter 6 – Article 3:

List of Abbreviations

ACC	anterior cingulate cortex
aIC	anterior insular cortex
ANOVA	analysis of variance
BG	basal ganglia
BOLD	blood-oxygen-level-dependent
CNV	contingent negative variation
DLPFC	dorsolateral prefrontal cortex
DMS	delayed match-to-sample
DPA	delayed paired association
ERP	event-related potential
e-VAS	electronic visual analogue scale
FDR	false discovery rate
fMRI	functional magnetic resonance imaging
FWER	family-wise error rate
GLM	general linear model
IC	insular cortex
IFG	inferior frontal gyrus
IPS	intra-parietal sulcus
IT	inferotemporal cortex
LTM	long-term memory
MCC	mid cingulate cortex
MEG	magnetoencephalography
MFG	medial frontal gyrus
mPFC	medial PFC
MT	middle temporal cortex
MTG	middle temporal gyrus
MVPA	multivariate pattern analysis
NS	nociceptive specific
OFC	orbitofrontal cortex
OFC	orbitofrontal cortex
PAG	periaqueductal grey
PCA	principal component analysis
PD	Parkinson’s disease
PFC	prefrontal cortex

PM	pain matrix
PMC	premotor cortex
PPC	posterior parietal cortex
rTMS	repetitive transcranial magnetic stimulation
SFG	superior frontal gyrus
SI	primary somatosensory cortex
SII	secondary somatosensory cortex
SMA	supplementary motor area
SMG	supramarginal gyrus
SPG	superior parietal gyrus
SPL	superior parietal lobule
STM	short-term memory
STT	spinothalamic tract
TMS	transcranial magnetic stimulation
V1	primary visual cortex
VAS	visual analogue scale
VLPFC	ventrolateral prefrontal cortex
VMPFC	ventromedial prefrontal cortex
VMpo	ventromedial posterior nucleus
VPI	ventral posterior inferior
VPL	ventral posterior lateral
VPM	ventral posterior medial
VWM	visual working memory
WDR	wide dynamic range
WM	working memory

Acknowledgements

First, I would like to thank my supervisor, Dr. Pierre Rainville, whose excellent guidance, support and encouragement, allowed me to pursue my interests, and develop passion for the research I have been doing. I totally indebted to him, for his great mentorship, and for his continual support in allowing me to explore and peruse my curiosity and interests.

I also thank Kristina Martinu, for her generous help in acquiring the psychophysical and fMRI data. She has been a great friend to me, and supported me in so many ways.

I especially thank my husband Nima, who was so supportive through the thick and the thin, during my Phd Journey. I dedicate this to him and our 3 year old son who is the joy of our life.

I finally thank my mom and dad, for their continual support and love.

Chapter 1: General Introduction

The perception of pain is a complex phenomenon involving sensory, affective, cognitive, and motor components that result from a distributed neural processing network of cortical and subcortical regions. Recent advances in pain research expanded our understanding of interactions among multiple components of pain and the mechanisms underlying the perception of pain. One of the important factors that contributes to our perception of pain is the memory of past pain experiences. However, little research has been done concerning the mechanisms and neural processes involved in the memory of pain. Pain memory is a very broad topic encompassing a classical interactive multi-stage information processing system that comprises immediate, short-term, and long-term memory. There are some studies on immediate memory and some clinical studies on long-term recall of pain. However, only a few studies have examined short-term memory of pain. Understanding the mechanisms and properties of short-term memory of pain is important as it is an intermediate stage that relates immediate memory and long-term memory. In particular, the transformation of pain-related information that occurs in short-term memory is relayed to long-term memory and is known to impact the perception of future pain. This thesis is broadly focused on the topic of explicit short-term memory of pain.

With regard to multiple components of pain, the sensory aspect of pain is a most prominent aspect and consists of multiple attributes such as intensity, spatial, and duration. However, neuroscientific examination of sensory characteristics of pain has largely focused on the intensity and spatial attributes. In particular, no previous research has explored the short-term memory of pain duration. The experimental studies described in this thesis are designed to provide some understanding of properties and neural correlates of the temporal processing of pain as well as the conjoint processing of duration and intensity of pain in short-term memory.

The organization of this thesis is described here. Chapter 2 provides an overview of the pain system and the functional roles of cortical and sub-cortical regions generally involved in processing pain-related information. Chapter 3 provides a summary of the memory system followed by a comprehensive overview of the functional roles of the

main cortical areas involved in short-term memory of visual and tactile modality. Chapter 4 is devoted to a review of the few studies that have examined short-term memory of pain. This chapter is in preparation for submission as a review paper. Chapter 5 is a general overview of the theoretical perspective, properties, and neural mechanisms involved in time perception. Chapter 6 comprises three published articles as follows: Article 1 is a psychophysical study concerning the nature of mental representations for the retention of pain dynamics and the ensuing transformation of pain-related information in short-term memory; Article 2 is a second psychophysical study investigating the properties of short-term memory of the duration of innocuous thermal stimuli; and Article 3 is an imaging study on short-term memory of pain dynamics and duration. General conclusions are proposed in Chapter 7.

Chapter 2: Pain System

2.1. Introduction

Pain is an unpleasant sensory experience associated with tissue damage. The perception of pain is evoked by high threshold mechanical, thermal, and noxious chemical stimuli, and is detected by specialized peripheral sensory neurons called nociceptors. Nociceptors in turn transfer information about noxious stimuli through multiple ascending pathways to the neocortex, where the perception of pain is elicited. Pain is highly individual and subjective, and is elicited by interactions among multiple processing components.

Noxious stimuli provoke multiple autonomic and physiological responses such as withdrawal reflexes, increases in heart rate, and changes in skin conductance, as well as behavioral responses such as the generation of unpleasant emotional states accompanied by a motivational force to escape or avoid the potential harm. First established in a formal integrative neuropsychological model by Melzack and Casey, pain is generally recognized as a multidimensional experience comprising of sensory, affective, motivational and cognitive components (Melzack and Casey 1968). The sensory-discriminative component comprises of multiple aspects such as recognition of the noxious nature of the stimuli, the quality of pain (burning, pricking, stabbing, etc.), as well as its location, intensity, and duration. The affective component of pain is itself separated into two sub-components: immediate unpleasantness of the experience as well as a more elaborate reflection of the long-term meaning and consequences of pain, which is termed secondary pain affect. The cognitive component involves attention, anticipation, and memory of past experiences, and through interactions with other components modulates our perception of pain. It has been discussed that there is a causal relationship between multiple components of pain such that the sensory-discriminative dimension leads to an immediate emotional reaction that integrates with past memories of having pain and in turn leads to secondary pain affect (Wade et al. 1996).

Traditionally, it has been taught that these components, especially the sensory vs. affective components, are dissociated and processed in parallel via lateral and medial pain

pathways, with the former mainly processed in post-central gyrus and the latter processed in limbic areas such as the anterior cingulate cortex. However, recently there has been a shift to the acknowledgment that the sensation of pain is a complex phenomenon and that its various components interact with each other. In this chapter, a brief review of the transmission of nociceptive information from the spinal cord to the cortex is provided (section 2.2), followed by a description of the role of cortical and sub-cortical structures involved in processing pain-related information (section 2.3). Finally, recent ideas involving the specificity of the identified cortical pain network are discussed in section 2.4.

2.2. Somatic sensation

Somatic sensation is divided into four distinct sub-modalities: touch, proprioception, pain, and temperature sense. Like other sensory modalities, somatic sensation is a result of signal processing at various stages (peripheral, spinal, brain stem, and cerebral cortex) evoked by somatic sensory event. The touch and proprioception modalities are transmitted by dorsal column medial lemniscal pathways to the thalamus and cerebral cortex, while information about pain and temperature sensation is transmitted by the anterolateral system. As the work in this thesis used noxious and innocuous thermal stimuli, a description of major ascending pathways of the anterolateral system is provided. Pain and temperature pathways generally consist of a three-neuron chain that transmits pain and temperature information from the periphery to the cerebral cortex. The main components of the pain and temperature pathways are described below.

2.2.1. First-order neuron

Transmission of pain begins with activation of nociceptors in response to noxious stimuli in the surrounding tissues (for a review of cellular and molecular mechanisms see

Basbaum et al. 2009). Nociceptors are the peripheral ending terminals of the first-order sensory neurons and are found in skin, muscle, joints, and viscera, and are activated by noxious cold, heat, intense mechanical stimuli, and a variety of chemical mediators. The first-order sensory neurons innervating limbs and the trunk have their cell bodies located in dorsal root ganglia of the spinal cord and their axons terminate predominantly in the dorsal horn of the spinal cord. The first-order sensory neurons innervating the head and face have their cell bodies in the trigeminal ganglion and their axons terminate in the trigeminal nucleus in the medulla.

There are several classes of nociceptor: I) unimodal, II) polymodal, and III) silent (Kandel et al. 2000). The unimodal nociceptors consist of thermoreceptors that selectively respond to noxious thermal stimuli (both cold <5 °C and hot > 45 °C temperatures) or mechanoreceptors that selectively respond to intense pressure. These nociceptors transmit information via small diameter thinly myelinated Aδ fibers with a fast conduction velocity of 5-30 m/s. Polymodal nociceptors respond to noxious stimuli of mechanical, thermal, and chemical nature. They transmit the nociceptive information via unmyelinated C fibers with a slow conduction velocity of about 1 m/s. Unimodal and polymodal nociceptors innervate skin and deep tissues. Silent nociceptors innervate viscera and are difficult to activate within normal range of noxious stimulus intensity. They become active after tissue damage in response to endogenous chemical stimuli (inflammatory mediators) associated with tissue injury, and respond to noxious thermal or mechanical stimuli after becoming activated. They also transmit information through C fibers. The basic function of nociceptors is to transmit information to second-order neurons about actual or potential tissue damage.

Transmission of temperature information begins with the activation of ***thermal receptors***, which are the peripheral ending of first-order neurons whose cell bodies are located in dorsal root ganglions and whose axons terminate in the dorsal horn. Thermal receptors fire as a function of temperature difference between skin and objects contacting the body, or the air. Thermal receptors have a steady-state firing rate at normal skin temperature. Warming the skin evokes an increase in the firing rate of the warmth

receptors and decreases of the firing rate of cold receptors. Cooling the skin produces opposite effects: an increase in the firing rate of cool receptors and a decrease in the firing rate of warmth receptors. The relative activity by warmth and cool receptors evokes the perception of temperature. Thermal receptors transfer information by Aδ and C fibers to the dorsal horn of the spinal cord (Kandel et al. 2000).

2.2.2. Second-order neuron

By activation of nociceptors, noxious mechanical, thermal, or chemical energy is transformed to electric action potentials by the membrane receptors through transduction phenomenon and transmit nociceptive information to the second-order neurons predominantly in the dorsal horn of the spinal cord. These neurons in the dorsal horn are classified as nociceptive specific (NS), which respond exclusively to noxious stimuli, or wide-dynamic-range (WDR), which respond to both noxious and innocuous stimuli. Projection neurons are mainly from lamina I (consisting of both NS and WDR), lamina V (WDR neurons), and to a lesser degree from lamina VI, VII, and VIII. Nociceptors innervating the head and face are transmitted similarly to the second-order neurons located in the trigeminal nucleus in the medulla (Kandel et al. 2000).

2.2.3. Third-order neuron

The axons of second-order neuron decussate and ascend via the anterolateral system to innervate the third-order neurons in supra-spinal targets such as the thalamus, the periaqueductal gray (PAG), and brain stem nuclei. The anterolateral system consists of multiple pathways, including a direct pathway to the thalamus via the **spinothalamic tract**, as well as indirect pathways to the thalamus by way of synapses in the reticular formation of the medulla via the **spinoreticular tract**, brainstem nuclei via the **spinomesencephalic tract,** or the hypothalamus via **spinohypothalamic tract.**

The ***spinothalamic tract (STT)***, which is the main ascending pain pathway, originates mainly from second-order neurons in lamina I and V of spinal dorsal horn and transfers noxious and thermal information from the limbs and trunk directly to the contralateral thalamus. Pain and temperature sensation from the head, face, and neck is transferred by an analogous pathway called the ***trigeminothalamic tract*** to the thalamus. The main somatosensory relay nuclei of the STT is the ventral posterior nuclear group, which includes the ventral posterior lateral (VPL), ventral posterior medial (VPM), and ventral posterior inferior (VPI) nuclei. While the VPL receives information from the STT, the VPM receives information from the trigeminothalamic tract. There is controversy with regard to the projection sites to VPL nuclei from the dorsal horn: while some suggest that they receive projections from lamina V (Craig 2006), others assert that superficial layers (lamina I) mainly project to the VPL (Willis, Zhang et al. 2001).

It has been shown that VPL and VPM nuclei consist of thermo-sensitive and nociceptive neurons (Apkarian and Shi 1994; Bushnell et al. 1993). In addition, electrophysiological studies in awake monkeys showed that VPM neurons show graded responses to increasing intensity of somatosensory stimulation, which suggests that they play a role in the sensory-discriminative aspect of nociception and thermal sensation (Bushnell et al. 1993). It has been shown that VPL/VPM neurons project to primary somatosensory cortex (SI) (Gingold et al. 1991). VPI nuclei receive projections from both lamina I and V (Craig 2006), and project to secondary somatosensory cortex (SII) (Friedman and Murray 1986; Stevens et al. 1993). The three nuclei of the ventral posterior nuclear group are thought to contribute primarily to sensory-discriminative aspects of pain.

The STT also has dense projections to multiple nuclei in the posterior complex (PO) such as the suprageniculate nucleus (Sg) and limitans nucleus (L) (Boivie 1979; Davidson et al. 2008; Ralston and Ralston 1992). Another group of important posterior thalamic nuclei that was more recently identified is the posterior part of the ventromedial nuclei (VMpo), which is specifically activated by noxious and thermal stimulation and receives projection from lamina I (Craig et al. 1994; Craig 2006; Dostrovsky and Craig

1996). It has been shown that VMpo projects to the posterior insula (Craig 2014), an area that has is well-known to be involved in pain processing (Garcia-Larreaa and Magnina).

Other termination sites of the STT include the medial division of the thalamus such as the dorsal medial nuclei (MD) (Apkarian and Hodge 1989; Craig 2004). MD nuclei project to the lateral and medial prefrontal cortex (PFC), orbitofrontal cortex (OFC) (Ray and Price 1993), and anterior insula (Mufson and Mesulam 1984). In addition, the intralaminar nuclear group also receives projections from the STT (Boivie 1979) and projects to anterior cingulate cortex (ACC) (Vogt et al. 1979), which also has a well-known role in pain affect.

The **spinoreticular tract** originates from laminae V and VIII of the dorsal horn. Most of the axons of the spinoreticular tract ascend ipsilaterally and transmit nociceptive and thermal information to the brainstem reticular formation, prior to making synapses in the thalamus. The major thalamic recipient of this tract is the intralaminar nuclear group, which projects to limbic areas such as the ACC and likely contributes to affective components of pain (e.g. alerting).

The **spinomesencephalic tract** originates from laminae I and V of the dorsal horn and projects to midbrain structures such as the periaqueductal gray (PAG). The PAG gives rise to fibers that modulate nociceptive transmission through descending pain inhibition systems via projections back to the spinal dorsal horn. In addition, some spinomesencephalic fibers project to parabrachial nuclei at the junction of the midbrain and pons, which in turn project to the amygdala (Bernard et al. 1992) and contribute to the affective component of pain and possibly to pain-related associative learning (e.g. fear-conditioning) (Rogan et al. 1997).

The **spinohypothalamic pathway** arises from neurons in laminae I, V, and VIII; projects directly to the hypothalamus; and is well-positioned to regulate autonomic and metabolic responses to pain (Kandel et al. 2000).

2.3. Cortical and subcortical regions involved in pain processing

Growing neuroscientific evidence indicates the involvement of a distributed network of pain processing areas often referred to as the 'pain matrix' (PM) including primary and secondary somatosensory cortices, anterior cingulate cortex (ACC), insular cortex (IC), the basal ganglia (BG), and frontal and prefrontal cortices (PFC) (Apkarian et al. 2005; Duerden and Albanese 2013; Treede et al. 1999). An important anatomical study using injection of herpes virus in monkeys to track cortical areas receiving spinothalamic input demonstrated the targeting of SI, SII, IC and ACC (Dum, Levinthal et al. 2009), and therefore provide strong evidence for the nociceptive activity of the PM. The joint activation of these regions is necessary for the conscious experience of pain. In the following sections, our current understanding of the functional role of these areas is described.

2.3.1. Primary and secondary somatosensory cortex

Electrophysiological investigations revealed the existence of nociceptive neurons in primary somatosensory cortex. Single-cell studies on anesthetized monkeys show that the discharge rate of SI neurons is modulated by changes in the intensity of a pain stimulus, and that the temporal course of their discharge rate corresponds to stimulus duration (Chudler, Anton et al. 1990, Kenshalo and Isensee 1983). In awake monkeys, it has also been shown that the discharge rate of nociceptive neurons in SI is augmented by increases in stimulus intensity, and is correlated with the monkey's speed of detection of graded increases in stimulus intensity (Kenshalo Jr, Chudler et al. 1988). Intensity encoding properties have also been observed in imaging studies. For example, it has been shown that graded changes in the intensity of pain sensation correlate with BOLD (blood-oxygen-level dependent) activation in distributed cortical areas including contralateral SI and bilateral SII (Coghill et al. 1999). However, in early imaging studies there were

inconsistencies regarding the role of SI in pain perception. In particular, it has been argued that attention to pain modulates the activity in SI (Bushnell, Duncan et al. 1999). Further evidence for the involvement of SI in intensity encoding of pain come from a study showing that hypnotic suggestion used to modulate pain intensity selectively caused changes in SI activity (Hofbauer et al. 2001). Imaging studies also suggest that SI is involved in dynamic encoding of pain intensity. Porro and colleagues showed that the temporal profile of changes in pain intensity over several minutes was positively correlated to the changes in BOLD signal in SI (Porro, Cettolo et al. 1998). This suggests that SI is involved in encoding both temporal and intensity aspects of pain. Electrophysiological studies have additionally shown that neurons in SI are somatotopically organized and have small receptive fields (Nelson, Sur et al. 1980, Pons, Garraghty et al. 1985), making them suitable for spatial localization. Somatotopic organization in SI has also been observed by imaging studies in humans using noxious stimuli (Bingel, Lorenz et al. 2004; Ogino, Nemoto et al. 2005). In fact, it has been shown that transcranial magnetic stimulation (TMS) over SI disrupts the spatial localization of painful stimuli (Porro, Martinig et al. 2007). Overall, electrophysiological and imaging studies suggest that SI is involved in the encoding of spatial location, intensity, and duration of noxious stimuli.

In contrast to SI, electrophysiological studies in nonhuman primates have shown that relatively small populations of SII neurons are responsive to noxious stimuli, have large receptive fields, and poorly encode noxious stimulus intensity (Dong et al. 1989; Dong et al. 1994; Robinson and Burton 1980). However, the majority of imaging studies report activation of SII during pain processing (Duerden and Albanese 2013). Electrophysiological studies in monkeys have shown that SII neurons encode stimulus duration by their firing rate (Dong et al. 1989). The involvement of SII in the sensory-discriminative aspect of pain is also suggested by imaging studies in humans showing that the magnitude of SII activation is correlated with the ratings of the sensory-discriminative dimension of pain (Maihofner et al. 2006; Maihofner and Kaltenhauser 2009). Moreover, TMS over the SII has been shown to disrupt the perception of the

intensity of a noxious stimulus (Lockwood, Iannetti et al. 2013). This is in line with a study showing a correlation of BOLD activation in SII with graded increases in stimulus intensity (Coghill et al. 1999). Electrophysiological studies have also shown that neurons in area 7b have multi-sensory characteristics (e.g. respond to fearful visual stimuli and noxious stimuli) (Dong et al. 1994). An imaging study also showed that SII is activated when participant watched pain-evoking images (images of pain applied to hand/foot area) (Vachon-Presseau et al. 2012). It has been suggested that neurons in area 7b might have a role in attention to and detection of potentially harmful stimuli (Dong et al. 1994; Robinson and Burton 1980). This finding is replicated in imaging studies in humans where it has been shown that graded increases in the intensity of noxious stimuli causes a sharp increase in SII activation at stimuli intensities above pain threshold (in comparison to SI, which shows graded increases in activation corresponding to graded increases in stimulus intensity) (Timmermann et al. 2001). Additionally, lesion studies have shown that lesions to SII and adjacent parietal operculum cause alterations in pain threshold (Greenspan and Winfield 1992; Greenspan et al. 1999). Overall, the results of electrophysiological, imaging, and lesion studies suggest a role of SII in the recognition of the noxious nature of stimuli, as well as in the sensory-discriminative aspect of pain perception.

2.3.2. Insula

Several lines of evidence point to the involvement of the insula in pain perception. Single-cell recordings in monkeys revealed the existence of nociceptive neurons in the insula (Robinson and Burton 1980; Zhang et al. 1999). Imaging studies also consistently report robust activation in bilateral insula in response to noxious stimulation (Duerden and Albanese 2013). Lesions studies have shown elevated heat pain thresholds in patients with lesions in the posterior insula (Greenspan and Winfield 1992; Greenspan et al. 1999). In an early study it was shown that when patients with insular lesions were tested with supra-threshold noxious stimuli, they exhibited pain asymbolia, a condition in which

individuals can recognize noxious stimuli as painful but exhibit inappropriate affective responses (Berthier et al. 1988). The converging lines of evidence from electrophysiological, imaging, and lesion studies highlight the key role of the insula in pain perception; however, its exact role in processing pain information is not yet clear.

In recent years, our understanding of the functional roles of anterior vs. posterior parts of the insula has improved. The posterior part of the insula is somatotopically organized and may be involved in sensory aspects of pain processing (Brooks, Zambreanu et al. 2005; Henderson et al. 2007). Some researchers argue that the posterior insula is specific to pain processing (Segerdahl et al. 2015) while other areas in the PM might be more involved in secondary cognitive processes such as attention, expectation, and memory. On the other hand, the anterior insular cortex is more implicated in affective and cognitive aspects of pain (Garcia-Larrea and Peyron 2013; Schweinhardt and Bushnell 2010), although Coghill and colleagues have suggested the insula is part of a large network whose activity is associated with intensity encoding of noxious stimuli (Coghill et al. 1999). For example, the insula has been involved in subjective feelings of pain in the absence of stimuli (Kong et al. 2006) or when the noxious stimuli are specifically attended to (Brooks et al. 2002). Moreover, in recent years pain has been conceived as a homeostatic emotion and associated with interoceptive feelings (i.e. feelings from the body) (Craig 2003). It has been argued that right anterior insular cortex is the neural basis for the integration of all interceptive signals from the body and interoceptive awareness (i.e. feeling of bodily changes) (Craig 2009). This is supported by studies showing that interoceptive feelings are associated with aIC activation (Critchley et al. 2004). Overall, insights from these various studies supports the distinct roles of posterior vs. anterior insula, and a posterior-to-anterior information flux in the insula has been suggested (Frot et al. 2014).

The reciprocal connections of the insula with the prefrontal cortex, ACC, amygdala, parahippocampal gyrus, and SII suggest a multi-faceted role of this area in pain processing (Mufson et al. 1981; Mesulam and Mufson 1982). For example, it has been suggested that such extensive connectivity subserves tactile and pain-related

learning and memory (Lenz et al. 1997). The insula has also been shown to play a key role in pain modulation in placebo studies (for an example see Craggs et al., 2007).

Together the results of electrophysiological, imaging, and lesion studies point to the involvement of the insula in a wide variety of functions related to pain processing including learning, memory, evaluative processes, expectation, and affective processing.

2.3.3. Anterior Cingulate Cortex (ACC)

The anterior cingulate cortex is an integral part of the pain network and several lines of evidence pinpoint its involvement in pain processing. For example, electrophysiological investigation in patients undergoing cingulotomy confirms that the ACC contains neurons that respond to noxious stimulation (Hutchison et al. 1999). In addition, robust activation of the ACC is consistently reported in neuroimaging studies of acute experimental pain (Duerden and Albanese 2013).

The ACC is part of the limbic system and historically it was considered to be related to the affective dimension of pain (for a review on the interaction between emotion and pain in the ACC see Vogt 2005). Animal studies also strongly favor the involvement of the ACC in affective processing of pain (for a review see Fuchs et al. 2014). Surgical removal of the ACC is also sometimes performed to alleviate the suffering of chronic pain patients (Agarwal et al. 2016). Patients with lesions in the ACC still experience pain and can localize it, but they seem to associate less emotional unpleasantness with it (Foltz and White 1962). One study providing direct evidence for the involvement of the ACC in pain affect is a PET study in which subjects were instructed to manipulate the unpleasantness of their pain through hypnosis (Rainville et al. 1997). This study showed that subjective ratings of pain unpleasantness were correlated with activation in the ACC. Overall there is strong evidence for the involvement of the ACC in pain affect.

However, there is also strong evidence for projections from the cingulate cortex to motor cortices (Dum et al. 2009; Morecraft and Van Hoesen 1992) and spinal cord (Dum and Strick 1991; Dum and Strick 1996) in monkeys, which suggests a role of the cingulate cortex in motor control. It has been shown that cingulate motor areas are somatotopically organized (He et al. 1995), and a meta-analysis showed that cingulate motor areas overlap with pain processing areas (Dum et al. 2009). Thus, activation in the cingulate cortex might be related to the generation of motor responses to painful stimuli.

On the other hand, there is also evidence for a somatotopic organization in ACC, which may pinpoint its possible involvement in sensory-discriminative aspect of pain (Arienzo et al. 2006). There is also fMRI evidence that shows some regions in ACC can differentiate between different levels of noxious stimulation and can therefore code for stimulus intensity (Buchel et al. 2002). Also, some lesion studies showed a reduction in subjective intensity of pain following cingulotomy (Davis et al. 1994; Talbot et al. 1995). Altogether, neuroscientific evidence strongly suggests a role for the ACC in processing the sensory-discriminative aspect of pain.

The ACC is typically discussed in relation to a variety of cognitive processes and therefore it has also been discussed as having a role in secondary processes important for pain perception. For example, the ACC is shown to be involved in attention toward pain (Peyron et al. 1999). However, another fMRI study showed a functional distinction in ACC for cognitive vs. pain-related processes (Davis et al. 1997). Therefore, there seems to be evidence for the involvement of the ACC in processing cognitive aspects of pain.

There is also evidence for the involvement of the ACC in pain modulation. Real-time fMRI experiments have shown that the degree to which an individual modulates their pain is reflected ACC activity (Chapin et al. 2012; deCharms et al. 2005). Placebo analgesia was also associated with increased activation in the ACC (Petrovic et al. 2002). This suggests a possible role of the ACC in pain modulation.

Overall, although the ACC has been mainly implicated in processing the affective aspect of pain, the response properties of the ACC are also generally consistent with a

role in processing sensory-discriminative and cognitive aspects of pain, as well as pain modulation.

2.3.4. Basal Ganglia (BG)

Several lines of evidence support the involvement of the basal ganglia in pain processing. Neurophysiological studies in monkeys (Romo and Schultz 1989) and rats (Bernard et al. 1992; Chudler et al. 1993; Chudler and Dong 1995; Chudler 1998) have revealed the existence of nociceptive neurons in the BG. Lesion studies also show that patients with lesions involving the putamen have reduced pain sensitivity and reductions in pain-related cortical activation (Starr et al. 2011). Moreover, Parkinson's disease patients that have undergone pallidotomy have significant reductions in Parkinson's-related pain (Honey et al. 1999). The BG has also been consistently reported to be activated in fMRI studies of acute experimental pain (Borsook et al. 2010; Duerden and Albanese 2013). Altogether, neuroscientific evidence confirms the involvement of the BG in pain processing, although their exact role is still under debate.

Neurophysiological studies have shown that some of the nociceptive neurons in BG encode stimulus intensity in their firing rates (Chudler 1998). FMRI studies have also shown that spatial information about noxious stimuli such as laterality is reflected in putamen activation (Bingel et al. 2002). Another fMRI study showed that the putamen is somatotopically organized in response to hand- and foot-related noxious stimulation (Bingel et al. 2004). Together, these studies suggest a role of the BG in processing the sensory-discriminative aspect of pain.

Some studies suggest the BG are also involved in processing the emotional component of pain. For example, an fMRI study showed that activation in the BG was associated with affective qualities of pain (Scott et al. 2006). The BG has also been shown to be involved in cognitive aspects of pain such as reward processing for pain termination. For example, one fMRI study showed positive vs. negative BOLD signal

changes in response to pain onset vs. offset in the nucleus accumbens, a structure that has been long implicated in reward-aversion processing (Becerra et al. 2001). Together, these results provide evidence for the involvement of the BG in processing emotional and cognitive aspects of pain.

Moreover, the role of the BG has been discussed in relation to sensorimotor integration (see review: Chudler and Dong 1995) and orientation of the organism that enables the generation of motoric responses to noxious stimuli, such as withdrawal reflexes. This is consistent with the known role of the BG in motor processing and their connectivity with areas such as the PFC and motor cortices.

The BG have also been implicated in pain modulation. For example, suppression of pain sensation while enduring pain was associated with reduction of BOLD responses in the caudate (Freund et al. 2007; Freund et al. 2009). Moreover, activation in the caudate has been associated with placebo responses to pain (Scott et al. 2008).

Altogether, the BG is likely to be involved in most aspects of pain processing including the sensory-discriminative, affective, and cognitive dimensions of pain as well as motor responses and pain modulation.

2.3.5. Prefrontal cortex (PFC)

Regions of the prefrontal cortex such as the medial PFC (mPFC), dorsolateral PFC (DLPFC), ventrolateral PFC (VLPFC), and orbitofrontal cortex (OFC) have been implicated in both pain processing and pain modulation. Prefrontal activity during pain is generally related to cognitive processing of pain sensation.

Imaging studies have shown that PFC activation reflects attention toward the stimuli (Peyron et al. 1999). There is evidence that prefrontal activity is associated with anticipation of pain (Ploghaus et al. 1999). An anticipatory role of the PFC is generally discussed in relation to cognitive modulation of pain. For example, placebo studies have shown that placebo analgesia was associated with increased PFC activation during

anticipation of pain (Wager, Rilling et al. 2004), which may trigger descending modulation.

Moreover, it has been shown that perceived controllability over experimentally induced pain is associated with greater activation in the VLPFC during the anticipation of pain, and lower pain ratings (Salomons, Johnstone et al. 2007). It has been discussed that this may be due to PFC involvement in regulating the emotional aspect of uncontrollable pain. In another study extensive bilateral DLPFC and OFC activation was observed in the differences between normal heat pain and equally intense heat allodynia which discussed to be related in mediating emotional responses to pain caused by inflammation (Lorenz et al. 2002). In a later study the same group showed that PFC cortex activation in heat allodynia provide a top-down regulation of pain by modulating the cortico-cortical, and cortico-subcortical network involved in pain processing (Lorenz et al. 2003). It has also been shown that performance of a cognitively demanding task results in lower pain ratings and enhanced activation of the OFC (Petrovic et al. 2000). This may suggest a role of OFC in pain modulation.

Overall, converging lines of evidence pinpoint to the involvement of PFC in cognitive aspect of pain processing as well as pain modulation.

2.3.6. Motor cortex

Pain inevitably causes an orienting response towards the site of injury and movement away from the painful stimulus. Therefore motor-related structures are generally expected to be involved in the response to painful stimulation. Motor areas including primary motor, pre-motor, and supplementary motor cortices are consistently reported to be activated in fMRI studies of acute experimental pain (Burns et al. 2016; Duerden and Albanese 2013). Additionally, it has also been shown that motor cortex stimulation can alleviate pain in chronic pain conditions (Garcia-Larrea et al. 1999; Nuti

et al. 2005). There is thus strong evidence for the involvement of the motor cortex in pain perception and modulation.

The relationship between pain and the motor cortex is very complex. Some insight for the nature of this relationship comes from studies on chronic pain. There is evidence that some chronic pain conditions such as complex regional pain syndrome and phantom limb pain are related to motor cortex reorganization (Mercier and Leonard 2011). There is also some evidence that motor training can provide pain relief. For example, in phantom limb patients it has been shown that virtual movement of the phantom limb by viewing a reflection of the intact limb in a mirror can alleviate pain (Ramachandran and Rogers-Ramachandran 1996). The effect of motor training on the reduction of pain in phantom limb patients is also reflected by changes in motor cortex activation that may be suggestive of the reversal of motor cortex reorganization in these patients. For example a fMRI study looking at the effects of mental imagery training of phantom arm/hand movement showed reduction in pain scores that were associated with changes in the activation of contralateral motor cortex in the hand/arm area (MacIver et al. 2008). These observations are in line with a view that these chronic pain conditions might be due to incongruity between motor intention, visual feedbacks, and proprioception (Harris 1999). Interestingly, another study showed that a series of limb movements with various degrees of sensory-motor conflict can induce the sensation of pain in healthy participants (McCabe et al. 2005). Altogether these results highlight the importance of sensory-motor integration for processing pain information in healthy volunteers and chronic pain patients.

Overall, converging lines of evidence from experimental studies of both acute and chronic pain highlight an important role of the motor cortex in the pain processing network. The role of the motor cortex is generally attributable to the orienting and withdrawal responses, as well as sensory-motor integration during the processing of pain-related information.

2.4. Controversies regarding the pain matrix

Pain is the conscious processing of nociceptive afferent input and is influenced by mnemonic, emotional, and cognitive factors. Accordingly, painful stimulation induces brain activation supporting functions such as attention, expectation, cognitive evaluation, and long-term/short-term memory processes. Thus, there are controversies regarding the functional interpretation of pain-evoked brain responses as a direct measure of the actual pain experience, as many of the so-called pain-related activations may reflect such secondary processes.

For example, Legrain and colleagues argue that a number of elements within the pain matrix (PM) can be triggered by any behaviorally-relevant stimulus, and thus are not specific to pain (Legrain et al. 2011). They describe the PM as a salience detection network responsible for detecting events that are potentially harmful to the body's integrity, regardless of stimulus modality (Legrain et al. 2011; Mouraux et al. 2011).

In addition, a recent fMRI study argues against the specificity of the PM as a measure of nociceptive processing (Liang et al. 2013). In this study, stimuli of four sensory modalities – tactile, painful, auditory and visual – were delivered in four separate fMRI scans, and three anatomical masks corresponding to the primary sensory cortices (PSC) for auditory, visual, and tactile/pain stimuli were defined for each participant. Multivariate pattern analysis (MVPA) demonstrated that each of the sensory stimuli types elicited patterns of neural activity that were not only distinct in their corresponding PSC, but also in non-corresponding PSC (for example, tactile and auditory stimuli could be differentiated using the fMRI responses sampled in auditory cortex). These results show that PSCs (including SI/SII) encode the modality of non-corresponding stimuli and are therefore not specific to pain. Moreover, Garcia-Larrea argues that the posterior insula is the only region in humans exhibiting features that are necessary and sufficient to generate the experience of pain (Garcia-Larrea 2012).

On the other hand, a recent study using a machine-learning-based regression technique showed that pain reports can be predicted from the pattern of fMRI activity

across brain regions associated with heat pain (Wager et al. 2013). These regions included the ventrolateral thalamus, posterior and anterior insula, SII, ACC, and PAG. Wager et al. showed that this neurologic signature for pain had more than 90% sensitivity and specificity for pain at the individual level. Moreover, this pain signature not only predicted pain report, but could also discriminate between pain versus warm, and pain versus anticipation.

Overall, there are conflicting views on the specificity of the PM for pain. However, with regard to the sensory aspect of pain, it seems to be a reasonable criterion that regions potentially involved in processing basic sensory aspects such as duration, intensity, and location of noxious stimulus should receive direct nociceptive input (Dum, Levinthal et al. 2009). Therefore the PM includes the candidate regions in processing basic sensory aspects of pain, most of which – as reviewed thoroughly in the previous section – are implicated in the sensory-discriminative aspect of pain.

Chapter 3: Short-term memory system

3.1. An overview

Working memory (WM) has been one of the most studied topics in cognitive neuroscience. It is fundamental to the performance of many cognitive tasks such as problem solving or mental arithmetic, and a diverse set of daily activities such as remembering a phone number or playing chess. Cognitive neuroscience research on WM has largely used sensory or lexical stimuli to examine the properties and neural correlates of WM. As this thesis is focused on the sensory aspects of pain, a review of sensory WM is provided. Much of the information about sensory working memory comes from studies of the visual system; however, there is a growing body of literature addressing other sensory modalities. In particular, tactile WM is the closest to pain, and is reviewed along with the visual system in this chapter. In recent years advances in cognitive neuroscience of memory have enhanced our understanding of how our brain retains information. Here, a review of theoretical accounts, mechanisms, and neural systems involved in WM is provided.

3.2. Theoretical frameworks and properties of different types of memory

Various theoretical views have been proposed to explain the processing of information in memory. In the early models, information processing of memory systems was thought to be serial across multiple stages (Sternberg 1966). The initial stage consists of what is generally called ‘sensory memory’ or ‘afterimage’ (Cowan 1988; Cowan 2015). which lasts only few hundred milliseconds, depending on the dynamic properties of sensory systems, but which contains large-capacity storage, and acts as a gateway for attended information to be incorporated into the memory structure.

At the second stage, the information enters a temporary storage referred to as ‘short-term memory’ responsible for short-term retention of information, which last

several seconds. An important characteristic of this stage that has been the focus of much research is its capacity limit (i.e. the maximum number of items that can be held in short-term memory). Miller (1956) suggested that the capacity of short-term memory is limited to about seven items, where each item is defined in terms of chunks of information. Later, Cowan (2001) demonstrated that this limit was closer to four items. Information held in short-term memory is susceptible to decay, but diverse rehearsal strategies can be employed to improve its short-term retention. The rehearsal strategies relate to internal representations of information that are formed such as sensory or analogue representations (i.e. the way things felt), or amodal representations (i.e. use of quantity or magnitude-estimate format), which are more resistant to decay.

Finally, the information transfers into the more stable 'long-term memory' with a large-capacity storage incorporating all previous knowledge learned. In a broad context, long-term memory is subdivided into conscious recollection about facts and events, which is termed explicit memory (or declarative memory), and unconscious, effortless recollection of knowledge, which is termed implicit memory (or non-declarative memory). Explicit memory in turn is further divided into semantic memory (i.e. knowledge about the world in general) and episodic memory (i.e. autobiographical memory of personal experiences). Implicit memory is subdivided into knowledge gained through previous exposure to related information (priming), associative responses (conditioning), or performance (i.e. procedural learning).

Since the work of Sternberg (1966), this multi-staged construct of memory has been improved. For example, Atkinson and Shiffrin incorporated interactions between multiple stages into the model (Atkinson and Shiffrin 1968), a property that has been further emphasized in later accounts (Baddeley and Hitch 1974; for reviews see Baddeley 2012 and Cowan 2008). In these later models, the structure of the short-term memory unit has been challenged. For example, Baddeley proposed that "different stores" are responsible for the maintenance of different kinds of information such as visuospatial and phonological information, and are under the control of a central executive unit that regulates the content of memory (Baddeley 1996). They later added another buffer (i.e.

episodic buffer) to the model, responsible for the integration of information across senses and time (Baddeley 2000; for a review, see Baddeley 2012). The model by Baddeley has been very influential but other prominent accounts have been proposed. Cowen challenged the idea of specialized storage buffers for maintenance of distinct types of information (Cowan 1999; Cowan 2015). This alternative view attributes an amodal functional role to attention for the short-term retention of information which interacts with information activated from long-term memory storage. Within this framework it is conceivable that the same network responsible for representing the perceptual information is re-activated for the maintenance of relevant information by bringing this information within the 'focus of attention'.

Moreover, in recent accounts the operational role of short-term memory extended to the online manipulation of information and executive processes besides the general maintenance function. The term 'working memory' (WM) is used to reflect this additional involvement of dynamic operations on representations in short-term memory. Recent accounts of WM functioning describe the interplay between these two sub-processes. For example, the time-based resource-sharing model suggests that the processing and storage functions compete for attention (Barrouillet and Camos 2007). For recent reviews of theoretical models of WM and the implementation of their neural mechanism see D'Esposito (2007) and Martini et al (2015).

Working memory may involve the retention of basic stimulus-related features such as intensity, size, color, or location, for which we use the term 'sensory working memory' (i.e. coming from sensation) to separate it from non-sensory material such as lexical or semantic information. There has been much research performed on visual working memory and some on auditory and tactile working memory. In particular, the pioneering research and large body of literature on visual WM has advanced our understanding of different components and mechanism of WM. As the tactile modality is closest to pain, this chapter will provide a brief review of our current understanding of the neural mechanisms underlying tactile and visual WM.

3.3. Definition of working memory and general overview

Sensory WM is responsible for the retention of relevant sensory information when the information is no longer available through the senses (see section 3.4 in which the nature of mental representation in WM is discussed). As the term 'working memory' implies, WM is composed of two components; active maintenance and active manipulation. Active maintenance is the storage component where the information is accessible in an active state, while active manipulation involves top-down control processes that operate on the content of stored information as well as rehearsal strategies that support the active maintenance.

Sustained neural activity during a delay epoch separating a sensory stimulus and a contingent later motor response is compelling evidence that this activity is mnemonic in nature. Early neurophysiological studies in monkeys showed such sustained neuronal firing in the PFC (Goldman-Rakic 1995), and this finding was originally proposed to denote stored memory representation. Subsequent research on WM both in monkeys and humans also highlights the involvement of PFC in WM across various experimental designs and modalities (Marois 2015). However, studies on visual WM showed that sustained activation during a memory delay is not only observed in PFC but was also shown in posterior parietal as well as sensory cortices responsible for perceptual processes of sensory information (Marois 2015). The involvement of sensory cortices is consistent with the view that WM involves the activation of representations stored in the same areas involved in perceptual processing of sensory information (Pasternak and Greenlee 2005).

Advances in WM research also suggest functional roles other than storage for frontal and posterior parietal cortices in WM. Recent views claim that sustained activation might alternatively represent the processes that subserve WM (for example see Postle 2006 and Curtis and Lee 2010). Indeed, various cognitive processes can contribute

to WM, such as attention (see section 3.5), and the processes involved in top-down control of information such as manipulation and updating of information as well as confounding processes such as response selection, which are inherent to any behavioral task involving performance.

In recent years there has been an effort to segregate the processes involved in WM functioning, and their neural basis, with most of the research conducted in the visual modality. In sections 3.6, 3.7, and 3.8, a summary of recent advances in the understanding of the functional role of the PFC sensory and posterior parietal cortices in WM are discussed.

3.4. The nature and neural correlates of mental representations in working memory

For the operation of WM, internal mental representations should be created and actively maintained. However, the nature of these mental representations is debated. There are multiple aspects that can be considered. One aspect that is relevant to delayed-response paradigms frequently employed in WM studies is whether the representation maintained during the memory interval is sensory or motor in nature. In other words, what is remembered – the recently presented sensory stimuli, or the future motor response? This was examined in an fMRI study that tried to dissociate motor coding from sensory coding by using oculomotor delayed-response task (Curtis et al. 2004). They showed that when subjects hold a motor code, sustained activation is elicited in oculomotor centers such as the FEF, while when subjects hold spatial locations in mind, sustained activation is observed in posterior parietal regions (for a thorough review and more detailed discussion of these results see Curtis 2006). These results show that the type of information coded into memory is reflected by the brain network supporting the perceptual sensory vs. motoric plan.

With regard to sensory representation, other studies also point to the fact that the active maintenance of visual information is mediated by cortical regions that support the perceptual processing of sensory information (for a review see Pasternak and Greenlee 2005). A meta-analysis on delay-period activity shows that the dorsal-ventral stream segregation for spatial/object processing of visual stimuli is also applied to the retention epoch (Wager and Smith 2003). A clear example is the fMRI study by Ranganath et al. in which participants learned a series of houses, faces, and face-house associations prior to scanning (Ranganath et al. 2004). During the fMRI session they performed a delayed match-to-sample (DMS) task in which they had to maintain either faces or houses in response to corresponding cue stimuli, or a delayed paired association (DPA) task in which they had to recall faces/houses that matched the face/house cue stimuli complementing the conjoint picture of face/house association. Their results revealed enhanced activation in the fusiform gyrus, an area involved in face perception, when participants maintained faces in the DMS trials as well as when they had to recall faces in response to house cues in the DPA trials. The reciprocal results were obtained for the memory of houses in the parahippocampal gyrus, a region more sensitive to the perceptual processing of houses.

3.5. Role of attention in working memory

Several proposals suggest that attention and working memory are closely linked (Awh et al. 2006; Cowan 2015; Marois and Ivanoff 2005). For example, both spatial attention and spatial WM activate a similar network of fronto-parietal regions (Corbetta, Kincade et al. 2002). The interaction between attention and working memory is multi-faceted and can be considered at various stages of information processing. For example, it has been shown that selective attention is important for the encoding of information into WM (Irwin and Gordon 1998; Schmidt et al. 2002; Vogel et al. 1998). Others have suggested that attention is also involved in retrieving information from WM (e.g. Theeuwes et al. 2011).

In addition, attention is also needed to maintain the integrity of information in WM by rehearsing the contents currently held in memory. In this view, attention needs to be selectively oriented to the target mental representations to maintain these representations as active. It has been shown that the same prefrontal and posterior parietal regions involved in maintaining attention on external stimuli are recruited to maintain an inward focus on internal representations (Lepsien and Nobre 2006; Nobre et al. 2004; for a review see Chun and Johnson 2011). Studies on WM point to the involvement of the fronto-parietal network in the attentional aspects of information maintenance. For example, neurophysiological studies in monkeys show that selective attention to memoranda requires the involvement of the fronto-parietal network (Jacob and Nieder 2014; Suzuki and Gottlieb 2013). Evidence from fMRI also showed that fronto-parietal regions are involved in orienting and maintaining attention to visuospatial information (Corbetta et al. 2002) as well as in cognitive control of attention (Tamber-Rosenau et al. 2011). The attention-based rehearsal is also shown to involve sensory cortices. For example, it has been shown that spatial attention supports rehearsal in spatial working memory, and is modulated by the activity in early sensory areas (Awh et al. 1998). Moreover, with regard to object information, a fMRI study revealed that orienting attention to faces vs. scenes in WM modulated the activity in fusiform and parahippocampal gyri, which respectively involved in processing this information (Lepsien and Nobre 2006). Altogether, current evidence supports the notion that attention plays an integral role for rehearsal of task-relevant representation in WM by recruiting fronto-parietal and sensory cortices.

3.6. Contribution of prefrontal cortex

The PFC has been consistently reported to be involved in sensory working memory studies. Here a review for multiple roles suggested for PFC based on electrophysiological and imaging evidence is provided.

3.6.1. Storage

In a series of electrophysiological experiments, Goldman-Rakic and colleagues showed persistent firing of PFC neurons in awake monkeys in the delay period of WM tasks. This original finding was interpreted as the involvement of these neurons in the short-term storage of information. For example, Funahashi et al., using an oculomotor delayed response task in which monkeys had to make a saccade to a remembered spatial location, showed that neurons in the PFC were tuned for a specific position in space in the contralateral visual field during the delay epoch (Funahashi et al. 1989; Funahashi et al. 1990). In a subsequent study, they further examined whether the PFC neurons were selective to spatial position vs. saccade direction by using an anti-saccade task as a control in an attempt to dissociate neuronal selectivity to sensory vs. motor components of the task (Funahashi et al. 1993). They showed that the majority of neurons code the location of visual stimuli in WM. In another study, Wilson et al. showed that the regions in the PFC ventrolateral to the principal sulcus are involved in the delay epoch in the WM of object identity (Wilson et al. 1993). These results suggest functional segregation in the PFC for maintaining 'what' and 'where' information, analogous to ventral and dorsal visual streams for processing 'what' vs. 'where' information. This pioneering finding was later challenged by neurophysiological studies by Miller and colleagues, utilizing tasks that engage both 'what' and 'where' information (Rainer et al. 1998; Rao et al. 1997). Within the same trial monkeys were trained to use the 'what' information in the first part of the trial to remember the 'where' information in the second part. They showed that the same neurons in the PFC can be either object-tuned or location-tuned. This suggests that the role of these neurons may not be in the coding of specific features but rather in the active maintenance of task-relevant features.

In the tactile modality the neuronal basis of WM has been studied using vibrotactile stimuli in monkeys performing delayed discrimination tasks (Romo and Salinas 2003). This study shows that neurons in the PFC increased their firing rate during

the maintenance epoch. Moreover these neurons coded the to-be-remembered stimulus frequencies in their graded firing rates. This parametric representation of vibrotactile stimulus in PFC has also been shown in humans using EEG with graded synchronization of beta-band oscillations during the delay epoch (Spitzer et al. 2010).

The segregation in the PFC by type of information in WM, which is in line with the theoretical framework of the independent storage buffer suggested by Baddeley and Hitch, may indicate an involvement of PFC in the storage process of WM. Imaging studies in humans also reliably report activation in PFC consistent with neurophysiological studies in monkeys, which were originally interpreted to implya role of the PFC in the maintenance of memoranda (for an example see Courtney et al. 1997). However, imaging studies also provide contradictory findings with regard to PFC dichotomy based on type of information that has to be retained. For example, an early meta-analysis showed segregation in the PFC of object vs. spatial attributes of visual information in WM (an object task activated the DLPFC while a spatial task activated pre-motor cortex) (Smith and Jonides 1999). Later studies have had inconsistent results. While some have failed to find a significant difference (Postle 2006; Wager and Smith 2003), a more recent meta-analysis shows a subdivision in PMC for object vs. spatial information (dorsal vs. ventral PMC for spatial vs. object information, respectively) (Rottschy et al. 2012).

In order to investigate the role of PFC in the storage of information further, some studies systematically manipulate factors that affect maintenance, such as the memory load or the length of the delay interval. Studies that manipulated the delay interval length up to 24 seconds reported that the DLPFC activation spanned the entire delay (Jha and McCarthy 2000; Leung et al. 2002). Studies that manipulated the load effect generally showed that the higher the number of items to be maintained in short-term memory, the stronger the PFC activity (Druzgal and D'Esposito 2003; Jha and McCarthy 2000). Altogether, these findings suggest that PFC has a role in the maintenance of information.

However, there are alternative interpretations of PFC delay activity other than the storage function. For example, it is plausible that top-down control processes of maintaining higher loads increases PFC activation, while the information may be stored elsewhere. Several aspects of top-down control processes are reviewed in the following subsection.

3.6.2. Top-down control

The top-down component of WM is a broad term that encompasses general executive processes such as distractor resistance, interference resolution, refreshing, updating, manipulation, and retrieval of information. A recent meta-analysis of studies that used diverse content and executive processes of WM did not show PFC dichotomy by type of executive function (Nee et al. 2013).

One class of control processes is the ability to ignore distractors and focus attention on relevant information. This top-down modulatory effect in WM is shown to be reflected by suppressing (distractor) or enhancing (target) neural activity in sensory cortical regions (Gazzaley et al. 2005), with PFC argued to be responsible for this modulatory process (Postle 2005; Zanto et al. 2011). For example, the dynamic interplay between PFC and visual cortex may mediate this effect for visual distractors (Gazzaley et al. 2007). PFC is also involved in the resolution of proactive interference – that is interference caused by prior relevant material (Jonides and Nee 2006; Nee et al. 2007). Other operations performed on the content of WM that involve PFC include refreshing of one item in WM. In refresh tasks, subjects are instructed to focus on the more recently presented item (Johnson et al. 2005; Raye et al. 2002). Yet another essential operation which involves PFC is to selectively replace some of the contents of working memory (i.e. updating) with newly acquired information and discard those no longer relevant (Roth et al. 2006).

The PFC is also shown to be involved in active retrieval of information from memory. Petrides (1996) suggests that the VLPFC is involved in retrieval while the DLPFC is involved in manipulation of information in memory (for the specific involvement of VLPFC in retrieval from memory in visual, auditory, and tactile domains see Kostopoulos and Petrides (2003), Kostopoulos and Petrides (2016), and Kostopoulos et al. (2007), respectively). With regard to manipulation of information, the PFC is also discussed to be involved in chunking strategies (Bor et al. 2003), in which the memorandum is segmented into organized sets of information. It has also been suggested that PFC is involved in regulating the capacity of WM (Edin et al. 2009).

Altogether, the neuroscientific evidence suggests a role for the PFC in a diverse set of executive processes involved in WM such as distractor resistance, interference resolution, refreshing, updating, manipulation, and retrieval of information.

3.6.3. Alternative accounts

There are alternative accounts of WM functioning which argue against sub-components of storage vs. manipulation. For example, Postle (2006) suggests that the same systems involved in sensory or goal-directed processing are recruited for WM functioning in interaction with attentional systems.

Neuroimaging studies that tried to dissociate mnemonic delay period activity from activity evoked by the process of selecting a memory-guided response showed involvement of PFC in response selection (Rowe et al. 2000; Rowe et al. 2005). Therefore the PFC activation might be related to abstract rules involved in response selection. Moreover, as all delayed response tasks require a motor response, PFC activation might be at least partly independent of mnemonic function and related to motor aspects of the task (Pochon et al. 2001). Others argue that PFC might play a general role in temporal integration of events separated in time and the establishment of a relationship between them (Fuster 2001; Miller and Cohen 2001).

To summarize, the PFC activation during the delay epoch of a delayed-response task might involve some active representations of memoranda, top-down control processes, future motor plans, or some abstract rules. However there is not yet a consensus as to what exactly this persistent activity represents and the nature of the code used.

3.7. Contribution of sensory cortices

Recent theoretical accounts of WM emphasizes the recruitment of modality-specific sensory cortices for the retention of sensory information in short-term memory (Pasternak and Greenlee 2005; Postle 2006). The evidence in support of this hypothesis in tactile and visual modality is briefly reviewed.

3.7.1. Visual modality

Psychophysical studies of visual WM demonstrate that recall performance generally decreases with longer memory delays for some but not all visual features. This delay length effect is generally interpreted as reflecting decay of the memory trace. For example, some dimensions such as luminance contrast, direction of motion, and color show a slight decay while spatial frequency and motion speed are quite resistant to decay (for a review see Magnussen 2000). Moreover, psychophysical studies that used ‘memory masking’ (i.e. introducing an interference stimuli during the delay) showed that interfering stimuli have no effect on the recall accuracy when the visual feature of the interfering item is distinct from the memorized feature of the target item (for reviews Magnussen 2000; Pasternak and Greenlee 2005). These effects suggest that separate storage processes are involved for the retention of different attributes. Moreover the memory masking studies showed that if the interfering stimuli of the same feature have the same property as the memoranda (e.g. the same direction of motion) there is no effect

in performance accuracy, while there is a degradation in performance when the property differs from the memoranda. When the interfering item shares the target property of the item to be recalled, the interfering stimulus may act as a bottom-up refresher of the memoranda, thereby preventing decay. Altogether the psychophysical studies seem to be in accord with the sensory recruitment hypothesis.

The involvement of the visual cortex in the retention of visual information has been confirmed in neurophysiological studies in monkeys. For example, Super et al. (2001) recorded from primary visual cortex (V1) and, using a WM task of spatial location, showed sustained activity in V1 during the delay epoch. In the ventral visual stream, memory-related activity for color and motion has been observed in area V4, an early stage of the ventral stream, and for color and shape in the inferotemporal cortex (IT), a late stage of the ventral visual stream (Ferrera et al. 1994). Memory-related activity of complex object information was also observed in IT (Miyashita and Chang 1988). In the dorsal visual stream there is evidence for the involvement of the middle temporal gyrus (MT) (early dorsal stream) in memory delay when monkeys have to remember the direction of motion (Bisley et al. 2004), as well as in area 7a in the posterior parietal cortex (late stage dorsal stream) for memory of spatial location (Constantinidis and Steinmetz 1996). Altogether these neurophysiological studies confirm the involvement of visual cortex in the retention of different features of visual stimuli.

Evidence supporting the view that the visual cortex is involved in the retention of visual information is also provided by lesion and stimulation studies. Fuster and colleagues (1981) showed that cooling area IT during a delayed-match-to-sample task impaired performance. Bisley and Pasternak (2000) showed that lesions in middle temporal cortex (MT) of monkeys affected the encoding and retention of motion direction in a delayed discrimination task. In another study using the same task, applied stimulation to area MT during the retention epoch resulted in a degradation of performance (Bisley et al. 2001). These results show that memory for visual information is likely held in visual areas.

Many imaging studies also support the involvement of visual areas in memory of visual information. However, although some imaging studies of visual WM show sustained activity in visual cortex, other failed to replicate this effect (for a thorough review see Postle 2006). Nevertheless, recent studies using pattern classification techniques consistently show that the content of visual WM can be decoded from BOLD activity in visual cortex (Christophel et al. 2012; Christophel and Haynes 2014; Lee et al. 2013; Riggall and Postle 2012; for a review see Sligte et al. 2013), even in the absence of elevated BOLD signal (Harrison and Tong 2009; Riggall and Postle 2012). Interestingly, all of these studies failed to decode WM content from PFC activity. For example, Christophel et al. (2012) showed that the identity of complex visual color patterns can be decoded from the BOLD activity in early visual cortex and PPC, but not in PFC. In a subsequent study they confirmed this finding using a complex motion trajectory of random dots (Christophel and Haynes 2014). Moreover, it has been shown that the classification performance is sensitive to memory load (Emrich et al. 2013). In another study using a delayed-match-to-sample task, subjects performed verbal or visual WM tasks on the same visual objects, identifying either the subcategory of object (verbal) or an object's fragment (visual) presented at probe, matched with that presented at sample (Lee et al. 2013). The results of that work showed that the content of object information (visual) could be decoded from extrastriate cortex, while the content of verbal information could be decoded from PFC. These results might show differential involvement of sensory vs. PFC based on the type of information (lexical vs. visual) that has to be held in memory. Altogether the imaging and pattern classification studies strongly suggest an involvement of visual areas in visual WM.

In summary, psychophysical, neurophysiological, lesion, stimulation, and imaging studies support the involvement of visual cortex in the maintenance of visual information in working memory.

3.7.2. Tactile modality

Some psychophysical studies using paired-discrimination tasks and manipulation of the delay length have shown rapid decay of tactile memory traces (Gallace et al. 2008; Miles and Borthwick 1996; Sinclair and Burton 1996). Rapid decay of tactile information implies that subjects were not relying on a categorical form of encoding, which would be expected to be more resistant to decay. Interestingly, Sinclair and Burton (1996) showed rapid decay from 0.5-5 seconds but no further degradation after 5 seconds, which indicates that a two-stage memory process might be involved. Studies using interference tasks also support sensory representations in memory. For example Gilson and Baddeley (1969) showed that articulatory suppression only affected performance after 10 seconds in a delayed tactile-location task, and Miles and Borthwick (1996) replicated this finding for a delay of 10-30 seconds. Moreover, in an interesting behavioral experiment using delayed-discrimination tasks, Harris et al (2001) found that accuracy in a vibrotactile WM task decreased when the distance between vibration spots increased. In addition they showed that the impaired performance resulting from an interference vibration induced in the delay-memory epoch is larger when the interference vibration is applied to same finger as the comparison finger. As it is known that the information about stimulus location is conveyed to the topographically organized somatosensory cortex and the same topography was also reflected on the performance of tactile WM tasks, the authors argue that this is consistent with the involvement of somatosensory cortex in tactile WM. Overall these psychophysical studies support the sensory analog format and an involvement of somatosensory cortex in tactile WM (for a thorough review of tactile WM see Gallace et al. 2008 and Burton and Sinclair 2000).

However, with regard to the involvement of primary somatosensory cortex (SI) in tactile WM, there seems to be no clear evidence from neurophysiological studies. For example, neurophysiological studies in monkeys using passive touch do not seem to support the involvement of SI in tactile WM (but see Zhou and Fuster, 1996, who showed sustained SI activity in delayed discrimination involving haptic active touch). For

example, one study using a vibrotactile delayed discrimination task showed that SI neurons display a sharp offset following stimulus termination (Romo and Salinas 2003). In another delayed discrimination task study using tactile and auditory stimuli in monkeys, Lemus et al (2010) recorded from neurons in primary somatosensory and auditory cortices and showed that the identity of stimuli could be decoded from primary sensory cortices only during the stimulus epoch, not during the delay epoch. These results may suggest that maintenance of the sensory information occurs outside of primary sensory cortices. In this line, Vergara et al (2016), using the exact same task, found that neurons in pre-supplementary motor area (pre-SMA) monotonically encoded stimulus frequency of both tactile and auditory stimuli during the delay period of the task. Such modality-independent activity suggests neural coding for an amodal format of tactile short-term memory representations (for a more theoretical elaboration of these results, see Constantinidis 2016). Altogether, neurophysiological studies in monkeys provide no evidence for the involvement of SI in tactile WM.

Contrary to the studies in monkeys, experiments using vibrotactile WM tasks in humans have shown that SI plays an important role in the maintenance of tactile memory trace. For example, TMS of contralateral SI impairs vibrotactile discrimination when applied during the early delay but not when applied during the late delay or to the ipsilateral site (Harris et al. 2002). The involvement of SI in tactile WM is also evident from event-related potential (ERP) studies. Katus and colleagues used ERP and a delayed match-to-sample task paradigm to study tactile WM; participants were presented two tactile sample stimuli on one finger of each hand and were asked to remember their spatial location (Katus, Muller et al. 2015). A cue presented 500-600 milliseconds after the sample set indicated which of these two stimuli had to be maintained in memory for the comparison with the probe stimuli. The cue elicited a sustained activity in the somatosensory cortex contralateral to the cued hand. In another study, they further manipulated the memory load by increasing the number of stimuli sites in the sample set and showed that the ERP over SI contralateral to the cued hand is sensitive to memory load and to individual differences in tactile WM (Katus, Grubert et al. 2015),. Altogether,

TMS and ERP studies in humans provide clear evidence for the involvement of SI in the retention of tactile information.

A few fMRI studies also point to the involvement of SI in tactile WM. For example, Ricciardi and colleagues used a spatial discrimination task in both visual and tactile modalities (Ricciardi et al. 2006). Comparison of the BOLD activation in the maintenance epoch of tactile vs. visual trials allowed controlling for non-specific task effects while revealing modality specific coding of sensory information in WM. Results showed the involvement of bilateral somatosensory cortex in tactile trials. Both tasks also recruited similar fronto-parietal regions including posterior parietal cortex and DLPFC, as well as ACC, consistent with an interplay between modality-specific sensory cortices and amodal executive control systems. In a study using a vibrotactile paired-discrimination task, Preuschhof and colleagues showed that maintenance of vibrotactile frequency was associated with activation in the medial and ventral PMC, VLPFC, and inferior parietal lobule, while SI showed engagement only in the encoding and decision making epochs of the task (Preuschhof et al. 2006). However, the absence of SI activation during the retention epoch in that study might be related to the dimension of tested tactile stimuli. While Ricciardi et al. tested spatial tactile memory, Preuschhof et al. tested memory for frequency of vibrotactile stimulation. Altogether, the few fMRI studies available provide some support for the involvement of S1 in tactile WM.

Evidence for the involvement of SII in tactile memory is provided by neurophysiological studies in monkeys. SII has been implicated in the sensory form of memory (sensory after effect) in studies by Burton and Sinclair showing that SII neurons continue firing in response to vibrotactile stimulation for about 500 milliseconds to 1 second after stimulus offset (for a review see Burton and Sinclair 2000). SII was also reported to be involved in tactile WM in neurophysiological studies in monkeys. For example Romo and Salinas, using a vibrotactile frequency discrimination task, observed memory-related activity for SII neurons, in addition to PFC, during the early delay (around 1-2 seconds after stimulus offset) (Romo and Salinas 2003). Compared to SI neurons that had a sharp offset following stimulus termination, the SII neurons prolonged

their response by few hundred milliseconds after the stimulus offset, and about one-third of these neurons modulated their activity by stimulus frequency. Altogether, neurophysiological studies in monkeys provide some support for the involvement of SII in the retention of tactile-related information.

Imaging studies in human have also confirmed the involvement of SII in tactile WM. In a magnetoencephalography (MEG) study, Haegens et al (2010) found that gamma-band activity increased in SII during the retention epoch. In an another study using fMRI, Klingberg et al (1996) showed the specific involvement of SII in short-term memory of vibrotactile sensation, while similar fronto-parietal regions were recruited in tactile, visual, and auditory versions of the task. Using fMRI and a tactile delayed discrimination paradigm, another study also found that SII is particularly involved in encoding and maintenance of texture-related information when contrasted with location-related information of tactile stimuli (Kaas et al. 2013). Altogether, the available fMRI and MEG studies show the involvement of SII in tactile WM.

Taken together, the results from ERP and imaging studies highlight the contribution of somatosensory cortex (SI and SII) to the retention of various types of tactile-related information. The tested dimensions included spatial location, frequency of vibrotactile stimulation, and tactile surface textures. Future studies on the distinctions among these various dimensions are critical for gaining a better understanding of the differences between feature-specific sensory recruitment of tactile information in WM.

3.8. Contribution of the posterior parietal cortex

Early neurophysiological studies in monkeys suggest an involvement of posterior parietal cortex in WM (Chafee and Goldman-Rakic 1998; Constantinidis and Steinmetz 1996; Friedman and Goldman-Rakic 1994; for a review of neurophysiological studies of WM see Constantinidis and Procyk 2004). Numerous neuroimaging studies report bilateral posterior parietal cortex (PPC) activity in combination with prefrontal cortex

during diverse WM tasks (for a meta-analysis see Wager and Smith, 2003; for reviews see Curtis and D'Esposito, 2003; Postle, 2006). Lesion studies have shown that posterior parietal damage leads to impaired performance on visual WM tasks (for an example see Berryhill and Olson, 2008; for a review see Berryhill, 2012). Moreover, TMS studies have shown that TMS of neural populations within posterior parietal cortex during the delay epoch alters memory performance using visual (Hamidi et al. 2008), and vibrotactile (Ku et al. 2015) stimuli. Altogether, evidence from neurophysiological, imaging, lesion, and TMS studies support a role for the posterior parietal cortex in WM.

However, there are conflicting accounts for the contribution of posterior parietal cortex in the storage vs. top-down control processes in WM (for a review see Berryhill 2012). Here a brief review of the literature on the role of posterior parietal cortex in WM is provided.

3.8.1. Storage

Sensitivity to memory load (i.e. the number of items that must be remembered) is taken as an evidence for maintaining WM representation. Such sensitivity has been observed in posterior parietal cortex (PPC). Using fMRI, it has been shown that the BOLD signal in intra parietal sulcus (IPS) increases with increasing memory load (Todd and Marois 2004; Xu and Chun 2006). Moreover, PPC activation predicts individuals' visual storage capacity (Todd and Marois 2005). There is also electrophysiological evidence that the amplitude of the signal in PPC is modulated by memory load and reaches a plateau when the memory capacity is reached (Vogel and Machizawa 2004). Altogether, electrophysiological and imaging studies provide evidence that PPC is sensitive to memory load, which suggests its role in the storage mechanism.

Multi-voxel pattern analysis (MVPA) of imaging studies that tried to decode the information about the memoranda from the delay period activity of PPC provides contradictory findings. For example, it has been shown that the identity of complex visual

color patterns (Christophel et al. 2012), and complex motion trajectories (Christophel and Haynes 2014) can be decoded from the BOLD activity in PPC. In contrast, Riggall and Postle (2012) failed to decode the content of VWM from PPC, though they could decode the specific task instruction from the delay period activity in PPC (as well as frontal areas). A more recent study examined decoding of orientation of the visual stimulus from delay period activity in the presence of distractor images from visual and posterior parietal cortex (Bettencourt and Xu 2016). The results showed that decoding was unaffected by distraction interference in the PPC, but not in visual cortex (for more elaboration on these results see Ester et al 2016). This suggests that posterior parietal cortex plays a central role in the storage of information. Altogether, the MVPA studies support a role for posterior parietal cortex in the storage mechanism.

3.8.2. Top-down control

A meta-analysis of fMRI experiments that examined diverse executive processing involved in WM showed a contribution of posterior parietal cortex in conjunction with prefrontal cortex in the manipulation of information in WM (Nee et al. 2013). Patients with lesions to the superior parietal lobule (SPL) showed impaired performance on tests involving the manipulation of information in working memory, but not on working memory tests requiring only rehearsal and retrieval processes (Koenigs et al. 2009). These studies suggest that posterior parietal cortex is involved in top-down control processes in WM.

Posterior parietal cortex is part of the dorsal attentional network involved in top-down control of attention (For a review see Corbetta et al., 2002). Recently, different parts of PPC has been shown to be involved in top-down vs. bottom-up attentional orienting (Shomstein 2012), which has also been confirmed by neurophysiological studies in monkeys (Buschman and Miller 2007). There is a close link between attention and WM (Cowan 1999; Marois and Ivanoff 2005), which suggests that PPC might contribute to attentional control of WM. Attention is multi-faceted, and diverse types of attention might be required for WM functioning. Neurophysiological studies in monkeys

showed that parietal regions in combination with frontal regions are involved in selective attention to memoranda in the face of distractors in visual working memory tasks (for example see Suzuki and Gottlieb, 2013; Jacob and Nieder, 2014). Using fMRI and a visual orienting task, Corbetta et al showed that PPC is involved in orienting and maintaining attention to visuospatial information during the delay epoch (Corbetta and Shulman 2002). A lesion study showed that patients with lesions to PPC show deficits in sustained attention as well as in maintaining attention to spatial locations (Malhotra et al. 2009). A few fMRI studies also showed that parietal cortex is involved in cognitive control of attention for WM functioning (Bledowski et al. 2009; Tamber-Rosenau et al. 2011). Bledowski et al. (2009) showed that dissociable fronto-parietal networks are involved for selection and retrieval of the most relevant items in WM (i.e. prioritizing one item among multiple items in WM) and updating the focus of attention. Tamber-Rosenau et al. (2011) showed that external and internal shifts of attention between items held in WM are mediated by the fronto-parietal network. Altogether, these studies suggest that posterior parietal cortex might be involved in attentional control, for holding the WM representations (i.e. bringing the items into focus of attention).

Chapter 4: Review of short-term memory studies of pain

4.1. General overview

Acute pain sensations generally diminish soon after the offset of a noxious event; however the memory trace of pain might persists in the CNS through various mechanisms. Theoretical accounts of memory suggest that memory system involves an interactive multi-stage information processing mechanism consists of immediate, short-term and long-term memory (Baddeley 2017). Based on these theoretical grounds, pain also follows transformation in memory from immediate offset of a noxious event (immediate memory) to a few seconds later (short-term memory) and then to months or years later (long-term memory). In addition, implicit or explicit processes may differentially influence the transformation of information in memory. There are some illustrations for each stage of pain memory in its implicit and explicit form.

The implicit form of immediate memory involves non-associative forms of learning and memory. Phenomena such as sensitization (Kandel et al. 2000), temporal summation (Kandel et al. 2000), and offset analgesia (Yelle et al. 2008) are cases of implicit immediate memory, which illustrate how the recent sensory history shapes pain perception. Implicit forms of short-term memory may involve associative learning that allows non-nociceptive cues to acquire pain predictive value and, in turn, change pain perception (Taylor et al. 2017). Implicit long-term memory of pain can be acquired through associative or non-associative form of learning, which is shown to be present even in infancy. For example a study showed that frequent blood sampling of infant born from diabetic mother increase pain responses (Taddio et al. 2002), which represent an associative form of LTM. The same group also published another study (Taddio et al. 1995) showed that neonatal circumcision is associated with greater pain responses to routine vaccination at 4-6 months of age, which represent non-associative form of LTM. Overall, there are some illustrations for implicit form of pain memory, which does not require an overt attempt to remember pain.

On the other hand, explicit memory processes are typically called upon when we are asked to report voluntarily our previous pain experiences. Such report may rely on the

maintenance of very recent sensory experiences in STM or the retrieval/reconstruction of the pain felt from LTM. The present review describes the few experimental pain studies that examined the explicit STM of pain within a few sec after the offset of a noxious event. On the other hand, explicit LTM of pain is the area of pain memory that is more explored and the examples are abundant (Babul et al. 1993; Beese and Morley 1993; Everts et al. 1999).

From a theoretical perspective, investigation of STM of pain is important as it feeds into LTM storage, and therefore shapes the LTM of pain. Moreover, in clinical studies of LTM of pain, retrospective evaluations of pain are often obtained after variable temporal gaps covering short- and long-term memory spans, while our understanding of the transformation occurring in short-term memory and the mechanisms involved is very limited.

Notably, STM is quite well-researched in other modalities and our understanding of properties and neural substrate of STM has increased in recent years. However, a comparison of STM of pain versus other modalities has not yet been done. In this section, we review the few STM studies of acute experimental pain, which examined memory for pain location and intensity, and provide a comparison of neural correlates of STM for pain versus those for visual modalities. Examination of the differences and similarities of STM of pain versus other modalities may enhance our understanding of the processing of pain in memory.

4.2. Sensory short-term memory of pain

The paradigms employed for studying sensory working memory generally involve three stages: *i)* an encoding phase where a stimulus is presented and one or more sensory features are encoded, *ii)* a maintenance phase where sensory-related information is maintained in memory after stimulus offset, and *iii)* a retrieval phase where the information is retrieved from memory to guide a sensory decision and/or produce a

behavioral response based on the target feature(s) of the sensation. The paradigms used for studying working memory of pain can be categorized into delayed discrimination paradigms and delayed ratings paradigms. Spatial and/or intensity attributes of pain sensation have been investigated in these studies.

The delayed discrimination paradigms consist of two stimulus presentations separated by a temporal interval. Cognitive processes during the encoding phase consist of perceptual processing as well as encoding of the task-relevant feature of the first stimulus. The encoded information has to be maintained in memory during the delay epoch. The retrieval epoch consists of perceptual processing of the second stimuli, retrieval of stimulus-related features of the first stimuli, and the discrimination/judgment of task-related features between the two stimuli. In the studies using delayed discrimination paradigms, the difference in the location of two noxious stimuli (Oshiro et al. 2007), their intensity (Oshiro et al. 2009; Rainville et al. 2004), or both (Albanese et al. 2007; Lobanov et al. 2013), was manipulated to investigate the brain regions involved in WM of these sensory attributes.

The delayed rating paradigm consist of a stimulus presentation during which sensory-related information is encoded into memory, a delay epoch during which information should be maintained in memory, and a recall epoch during which the information should be retrieved from memory to produce a behavioral response reflecting the remembered intensity (Fairhurst et al. 2012; Kong et al. 2006).

For both of these paradigms, the design of the proper control task is also important to isolate encoding from perceptual processes and the maintenance-related activity from a rest-related activity devoid of the retention of sensory-related information. Notably, the retrieval epoch of both types of paradigms also involves the motor preparation/response for reporting the discrimination outcome (in discrimination paradigms) or the recall of the pain presented during the stimulus epoch (delayed ratings paradigm). This pinpoints the importance of the design of the proper motor control task

that is as equivalent as possible in terms of motor preparation and response, in order to isolate the retrieval processes.

To our knowledge pain short-term memory was studied in only six imaging studies (Albanese et al. 2007; Fairhurst et al. 2012; Kong et al. 2006; Lobanov et al. 2013; Oshiro et al. 2007; Oshiro et al. 2009) and one psychophysical study (Rainville et al. 2004), which are reviewed in the next two sections.

4.2.1. Review of behavioral measures of recall performance

One psychophysical study using a delayed discrimination paradigm (Rainville et al. 2004) aimed to investigate the properties of the short-term memory of painful thermal sensation intensity.

For the delayed discrimination paradigm, Rainville and colleagues manipulated various parameters such as inter-stimulus interval and temperature difference of the stimulus pair. Their results confirmed that larger differences in temperature between the stimulus pairs improve performance consistent with the perceptual ability to discriminate the intensity of pain sensations. Notably, performance declined rapidly and linearly with increases in the duration of the inter-stimulus interval, consistent with a gradual deterioration of pain sensory information in short-term memory. This was interpreted as a decay of an analog representation of the sensation. In a separate experiment they studied the interaction between temperature difference and inter-stimulus interval by manipulating both. Interestingly, the gradual decline in performance was not found for the largest temperature difference, which might suggest an abstract-categorical encoding only for the largest temperature difference. Effects were comparable with painful and non-painful stimuli, suggesting that these results are not specific to pain and that similar mechanisms are involved across temperature ranges.

Behavioral results from imaging studies that used delayed-discrimination paradigms (Oshiro et al. 2007; Oshiro et al. 2009) generally show that increasing the

distance or intensity difference between the two stimuli led to an increase in response speed and correct response rates. However, this behavioral effect was not confirmed in one study on delayed-discrimination of pain intensity (Albanese et al. 2007). In this study, the pairs of stimuli were adjusted individually to maintain a higher level of discrimination difficulty and prevent the use of stimuli categorization to perform the task (e.g. mild/moderate/strong pain). Consequently, the overall task performance was low (59%; chance = 50%). However, in this study the task also involved a spatial component and a conjoint spatial/intensity aspect of pain had to be retained (the comparison involved the specification of the location of stronger/weaker stimuli) which might have contributed to the differential effects. Lobanov and colleagues compared spatial and intensity discrimination directly and showed that spatial discrimination generally was associated with faster response speeds and higher correct response rates compared to intensity discrimination (Lobanov et al. 2013). This implies that differences between the results of the two tasks could reflect task difficulty as well as the differences in the target dimension.

In both of the imaging studies using delayed rating paradigms, three ranges of temperatures corresponding to high pain, low pain, and warm sensation were employed (Fairhurst et al. 2012; Kong et al. 2006). Both studies showed that the delayed ratings of the intensity of pain corresponded to the actual temperature range that was delivered during stimulus presentation. However, perceptual ratings of pain intensity were not acquired in either of these studies, and therefore a direct comparison of perceptual and retrospective ratings of pain was not possible and no claim can be made about pain recall accuracy.

Taken together, the studies using paired discrimination paradigms imply a deterioration of recall performance either by increasing the duration of the retention period, or by differences in the target dimension of paired stimuli. The delayed ratings paradigms that directly compared the perceptual with retrospective recall of pain intensity also point to a loss of intensity-related information in memory. Moreover, manipulating

the stimulus temperature from noxious high to low and innocuous warm resulted in a proportionate decrease in recalled pain intensity.

4.2.2. Review of imaging results

Table 1 and 2 summarize the imaging results of pain sensory memory studies using delayed discrimination and delayed rating paradigms, respectively. Due to the limited number of studies available and given the fundamental differences in their design, a quantitative meta-analytical approach was not possible. However, a qualitative comparison is proposed with a visual representation of the activation sites reported in the different studies (Figure 1-5). The figures were generated using the GingerAle software based on the coordinates reported in each study (Albanese et al. 2007; Fairhurst et al. 2012; Kong et al. 2006; Lobanov et al. 2013; Oshiro et al. 2007; Oshiro et al. 2009). The results of the two types of paradigms (Table 1 and Table 2) are shown and discussed separately to avoid task-related confounds.

In Table 1, pain-evoked activation during the first stimulus epoch is reported along with activation during the memory epoch and the retrieval epoch. Pain-evoked activation was reported as a reference for the examination of the presence of sensory traces persisting or reactivated in the memory and retrieval epochs. However, the lack of conjunction analysis in these studies does not allow a direct investigation of this possibility. In addition, only Albanese et al. (2007) used a perceptual control task to allow for a more clear separation of maintenance- and retrieval-specific processes from perceptual and attentional processes. All other studies assessed brain responses associated with memory processes relative to baseline.

Contrary to delayed discrimination paradigms, the studies employing a delayed rating paradigm performed a conjunction analysis but did not report the pain-evoked activation separately. Kong et al. (2006) reported stimulus-evoked activation of high pain vs. low pain, but did not report stimulus-evoked activation relative to baseline. Therefore,

in Table 2 pain-evoked activation is not reported. Moreover, none of the delayed rating studies modelled the delay between the stimulus offset and the report, and thus the activation associated with the maintenance or retention of pain information during the memory epoch is not assessed. In Table 2, a conjunction analysis of activity during the pain stimulus and the retrieval phase is reported. However, the coordinates of the conjunction analysis are not provided in Kong et al (2006), therefore it is only included in Table 2. We also included a separate column for the retrieval epoch consisting of contrasts of retrieval vs. motor control in Kong et al (2006) and retrieval vs. baseline in Fairhurst et al. (2012) (Table 2).

In the following sections, a summary of activation sites in the stimulus, retention, and retrieval phases of the tasks is described with respect to the spatial vs. intensity dimensions. As only one study used a task requiring both spatial and intensity discrimination (Albanese et al. 2007), the result of this study was discussed and shown separately in Figures 1-5 as a conjoint spatial/intensity dimension. In order to compare the memory-related activation of pain modality vs. other modalities, the activation sites of the meta-analysis of WM studies using visual stimuli and delayed discrimination tasks (Daniel et al. 2016) is overlayed on all the figures that depict the delayed discrimination studies of Table 1.

Study & Subject	Dimension & Stimulus	Control conditions & Contrasts used	Duration of each epoch(s)	Search criteria & Correction	Pain induced activation and Brain activation in Memory and Discrimination (Retrieval)		
					Pain	Mem	Retr
Oshiro et al. 2007 12 subject (6M/6F)	Spatial (ΔS: 0, 4, 8, 12 cm) Noxious heat (left leg)	**Baseline** Pain: (stim1+stim2) vs. baseline Retr: Stim2 vs Stim1 Mem: Delay vs Baseline	 Pain: 20 Retr: 15 Mem: 30	Whole brain cluster threshold	Bilateral thalamus, caudate, globus pallidus/putamen, SII, aIC, Frontal operculum, ACC, Cerebellum and right SMA	**right** ---------- **Left** IFG, Frontal operculum, DLPFC, DFC, IPL, S1/M1/Pre-motor	**right** thalamus, caudate, ACC, SPL, IPL, DLPFC, DFC, SMA **Left** S1/M1 , ACC, IPL, SMA
Oshiro et al. 2009 12 subject M/6F)	Intensity (ΔT: 0, 0.5, 1, 2 °C) Noxious heat (left leg)	**Baseline** Pain: (stim1+stim2) vs. baseline Retr: Stim2 vs Stim1 Mem: Delay vs Baseline	 Pain: 20 Retr: 15 Mem: 30	Whole brain Cluster threshold	Bilateral thalamus, putamen/globus pallidus, SII, aIC, ACC, SMA, DFC, DLPFC, PPC, Cerebellum	**Right** S1, caudate, VMPFC, DFC **left** caudate, S1/M1, ACC, VMPFC, DFC, DLPFC, PPC/IPL, frontal polar cortex	**right** thalamus, caudate, ACC, aIC, DLPFC **left** thalamus, caudate, SI/M1, ACC, aIC, DLPFC, PPC/IPL, frontal polar cortex, DFC
Lobanov et al. 2013 18 subject (9 M/9F)	Spatial (ΔS: 0,4,16 cm) & Intensity (ΔT: 0, 1, 2 °C) Noxious heat (left leg)	**Spatial vs. Intensity examined** Pain: (stim1+stim2) vs. baseline Retr: Stim2 vs Stim1 Mem: Delay vs Baseline	 Pain: 20 Retr: 15 Mem: 30	Whole brain Cluster threshold	Bilateral thalamus, putamen, caudate, SII, IC, and right S1	**Right** ACC, IC, DLPFC, , Amygdala, temporal pole *(Spat>Int)* ---------- *(Int>Spat)* IC, frontal operculum, OFC, Crblm - *(Spat&Int)* **Left** IC, temporal pole *(Spat>Int)* ---------- *(Int>Spat)* IC, frontal operculum, IPS, OFC, Crblm . *(Spat&Int)*	**Right** S2, ACC, IPS, SPL, FEF *(Spat>Int)* Crblm *(Int>Spat)* Thalamus, caudate, putamen, IC, ACC, OFC, DLPFC , Frontal Operculum, IPS (Spat&Int) **Left** S2, IC, IPS, FEF (Spat>Int) Frontal pole, IFG, Crblm . . *(Int>Spat)* Thalamus, caudate, putamen, IC, ACC, OFC, DLPFC, Operculum, IPS, M1 *(Spat&Int)*
Albanese et al. 2008 8 subject (4M/4F)	Conjoint Spatial (right ,left) &Intensity (ΔT: 0.1, 1.5 °C) Noxious heat (right hand)	**Perceptual control** Pain: stim1 vs. baseline Retr: Stim2 vs Stim2(Control) Mem: Delay vs Delay(control)	Pain: 6 Retr: 6 Mem: 6, 8, 10	Whole brain/ Pain Mask Bonferroni-corrected	Bilateral SII, aIC, and right (S1/PPC), *(pain mask)* Not reported *(whole brain)*	**Right:** aIC , aIC/IFG *(pain mask)* aIC/IFG, VLPFC pre-SMA *(whole brain)* **Left:** aIC, S1/PPC *(pain mask)* Thalamus, VLPFC *(whole brain)*	**Right:** ----- *(pain mask)* VLPFC, pre-SMA *(Whole brain)* **Left:** aIC *(pain mask)* ACC ,VLPFC *(whole brain)*

Table 1. Brain activations in studies using delayed discrimination paradigms.

Study & Subject	Dimension & Stimulus	Control conditions & Contrasts used	Duration of each epoch (s)	Search criteria & Correction	Conjunction of pain induced activation & retrieval epoch and Brain activation in the Retrieval epoch. (Memory epoch not modeled)	
					Conjunction of Pain & Retr	Retr
Kong et al. 2006 16 subject (8M/8F)	Intensity Noxious heat (high &low) (left hand)	**Motor control** Pain: stim vs. baseline Retr: retr vs motor control Mem: Not modeled	 Pain: 10 Retr: 10 Mem: 4	Whole brain cluster threshold	Bilateral aIC and ACC/MPFC	**right** Medial PFC/ACC, aIC/Frontal operculum, Middle/Inferior /Orbital PFC, SPL/IPL, angular gyrus **Left** Medial PFC/ACC, aIC/Frontal operculum, Inferior PFC/ Putamen, Occipital gyrus
Fairhurst et al.2012 15 subject (6M/9F)	overall experience Noxious heat (high & low)right forearm)	**baseline** Pain: stim vs. baseline Retr: retr vs baseline Mem: Not modeled	 Pain:6 Retr: 6 Mem: 11	Whole brain Cluster threshold	Bilateral thalamus, aIC, parietal cortex, Crblm, Pre-motor, visual cortex, and Left S1, DLPFC	**right** IC, BG, IPL, Crblm, Mid cingulate, thalamus, S1, S2, SMA **Left** IC, BG, IPL, Crblm, DLPFC, M1/pre motor, Precuneus

Table 2. Brain activation in studies using delayed recall paradigms.

4.2.2.1. Brain activation in the stimulus epoch

Pain-evoked activations reported during the stimulus encoding phase are generally consistent with those often reported in pain imaging literature (Apkarian et al. 2005; Duerden and Albanese 2013). The anterior insula in particular is reported in all studies. The thalamus, putamen, and SII are also reported in all studies using discrimination paradigms. However, note that Albanese et al. (2007) used a ROI analysis that did not include the thalamus and BG, so these areas were not reported. Other parts of the typical pain-activated network such as the SI, ACC, posterior parietal cortex (PPC), and motor areas were also reported in some studies. However, only Albanese et al. included a perceptual control condition and tested the direct contrast between memory encoding and perceptual processing. Their results revealed a significantly stronger response associated with memory encoding only in the left anterior insula and additional positive but sub-significant responses in right SI/PPC and left SII.

4.2.2.2. Brain activation in the retention epoch

Examination of the retention epoch reveals that fronto-parietal regions generally activated in WM studies of other modalities are also activated in WM of pain sensation (Figure 1). These activation sites include left PPC as well as left DLPFC which are consistently activated across all dimensions, with the specific site of activation partially overlapping across dimensions. Interestingly, the specific site of left DLPFC completely overlaps with the WM studies of visual modality, while the activation site of left PPC only overlaps with the activation of the pain memory of spatial dimension.

However, there was also dimension-specific activation of the fronto-parietal network. Bilateral ventromedial prefrontal cortex (VMPFC) and medial orbitofrontal cortex (OFC) were specifically activated in the retention of intensity-related information. On the other hand, the left-ipsi ventrolateral prefrontal cortex (VLPFC) extending into left-ipsi lateral OFC and left-ipsi frontal pole as well as the right-contra DLPFC were

specifically activated in the retention of spatial-related information. Interestingly the right DLPFC completely overlaps with the activation of WM studies of visual modality. For the conjoint intensity/spatial dimension, memory-related activation observed in bilateral VLPFC, which was distinct from the left VLPFC activation of the spatial dimension.

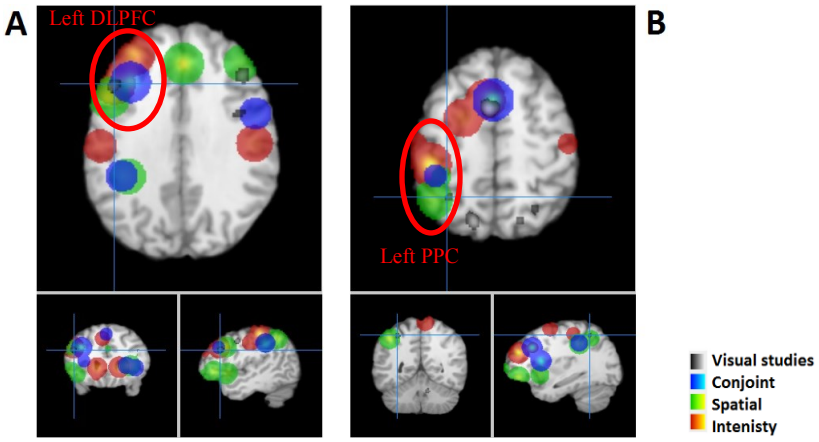

Figure 1. Fronto-parietal activation in the retention epoch.
Fronto-parietal activation in the retention phase partially overlaps across intensity (in red), spatial (green), and conjoint spatial/intensity (blue) dimensions in the left DLPFC (panel A) and left PPC (panel B). Activation in the previously published meta-analysis of WM studies using visual stimuli and delayed discrimination task is shown in black (Daniel et al. 2016)

The involvement of the right lateral prefrontal cortex (LPFC) in the memory of spatial information of pain sensation is consistent with the commonly reported right side activation of PFC for spatial information in the visual domain (Reuter-Lorenz et al. 2000; Rottschy et al. 2012; van Asselen et al. 2006). Unexpectedly, no spatial-information-related peak was reported in the right lateral posterior parietal cortex activity but intensity-related activity was detected at the limit between the right paracentral lobule and the precuneus.

Aside from the fronto-parietal network, parts of the network generally involved in pain processing (Apkarian et al. 2005; Duerden and Albanese 2013) were also activated in the retention epoch. The cingulate cortex was activated in one study on intensity

memory (anterior mid-cingulate cortex, aMCC), while the memory for conjoint intensity and spatial information activated an area immediately superior to the aMCC in the medial superior frontal gyrus (consistent with the location of the pre-supplementary motor area). The direct contrasts between intensity and spatial memory reported by Lobanov showed a stronger response to the spatial than the intensity task in the cingulate area.

The activation of other frequently reported pain-related sites varied across dimensions. Bilateral caudate, S1, and left M1/premotor cortex were specifically activated in the retention of intensity-related information. On the other hand, the bilateral frontal operculum/insula was specifically activated in the retention of spatial information. For the conjoint spatial/intensity dimension, bilateral anterior insula/inferior frontal gyrus (IFG) activation was observed with a partial overlap with frontal operculum/insula sites that were specifically activated in the retention of spatial-related information.

4.2.2.3. Brain activation in the discrimination/retrieval epoch

In the delayed discrimination studies (Table 1), the activation in the discrimination epoch is examined and compared with the activation in the memory epoch. As dimension-specific activation was observed, the activation map in the retrieval epoch is described for each dimension separately. Moreover, since delayed recall paradigms (Table 2) only used the intensity dimension, activation in the retrieval epoch for the intensity dimension is compared in delayed recall vs. delayed discrimination paradigms.

Intensity dimension: The brain activation in the retention and discrimination epoch of delayed discrimination of pain intensity (Oshiro, Quevedo et al. 2009) is depicted in Figure 2. Discrimination of pain intensity corresponds with activation in bilateral DLPFC, and left-ipsi medial OFC. Comparison of memory and discrimination epochs for the intensity dimension reveals partial overlap of activation in the left-ipsi DLPFC, and left-ipsi medial OFC. The PPC was also activated in the discrimination epoch, but the extent of activation in the PPC is more widespread and posterior compared

to that observed in the memory epoch. Similar to the memory epoch of the intensity dimension, specific activation in the BG was observed, but the activation was more widespread compared to the memory epoch and extended to bilateral insula. Activations in the aMCC extending to the SMA almost totally overlapped with the memory epoch. Overall, the pattern of activation in the memory and discrimination epochs seems to be similar and partially overlapping.

Comparison of the retention and discrimination of pain-intensity information with a meta-analysis of visual working memory studies that employed delayed-match-to-sample tasks reveals striking similarities in activation sites in bilateral DLPFC, the left PPC, right aIC, left putamen, and bilateral SMA. Particularly, the activation site in the left DLPFC, which overlaps in both the retention and retrieval phases of delayed discrimination studies of pain intensity, completely overlaps with the working memory studies of visual modality.

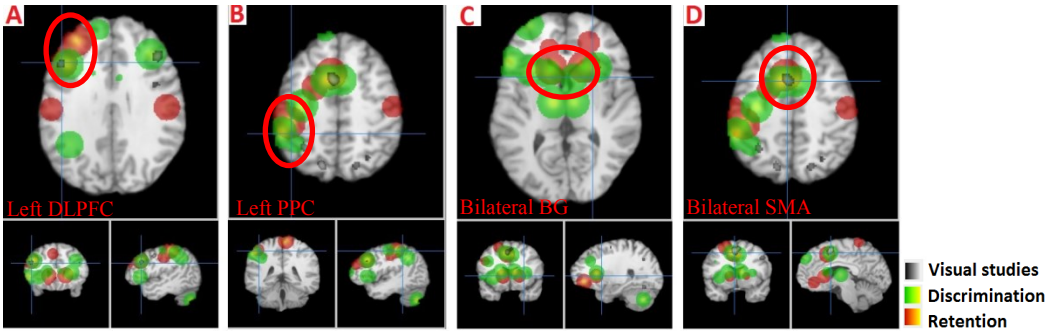

Figure 2. Activation in the retention (red) and discrimination (green) phases of the intensity dimension.
Activation partially overlapped in left DLPFC, left PPC, bilateral BG, and SMA, as depicted in panel A, B, C and D. Activation in the meta-analysis of WM studies using visual stimuli and delayed discrimination task is shown in black (Daniel et al. 2016).

Comparison of delayed recall vs. delayed discrimination: Brain activation in the discrimination epoch of delayed discrimination paradigms (Table1) and the retrieval

epoch of delayed recall paradigms (Table 2) is depicted in Figure 3. In the recall paradigm, the left DLPFC was activated in the retrieval epoch, and only partially overlapped with the activation seen in the discrimination epoch of the delayed discrimination paradigm. Bilateral activation was observed in the PPC in the delayed recall studies, and a partial overlap was observed only in the posterior part of the left PPC. Moreover, activation in the BG and bilateral insula partially overlapped. Interestingly, activation in mid cingulate cortex (MCC) in the delayed recall and delayed discrimination paradigms almost completely overlapped and extended to the SMA and motor areas in the delayed recall paradigms.

Overall, the fronto-parietal activation seems to be partially distinct in delayed-recall and delayed discrimination studies.

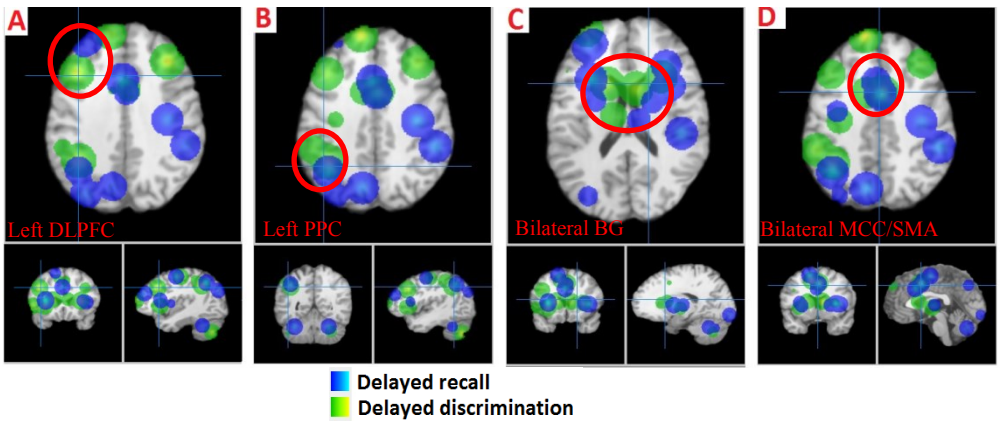

Figure 3. Activation in the discrimination (green) and delayed recall (blue) phases of delayed discrimination and delayed recall paradigms, respectively.
Activation seems to be partially distinct across the two types of paradigms, especially in left DLPFC, left PPC, bilateral BG, and MCC/SMA, as depicted in panel A, B, C, and D.

Spatial dimension: The brain activation in the retention and discrimination epoch of delayed discrimination of pain location (Oshiro et al. 2007) is depicted in Figure 4. In the discrimination of spatial dimension of pain, right-contra DLPFC activation was

observed that overlapped with the activation site in the retention epoch but the left-ipsi DLPFC was only present in the retention and not the discrimination epoch. Extensive bilateral PPC activations were observed for the discrimination of spatial information with the left-ipsi activation in more posterior parts of PPC overlapping with the memory epoch. Right-contra activation of the caudate was observed in the discrimination epoch that was absent in the memory epoch. Additionally, left-ipsi activation of the insula was observed that partially overlapped with left-ipsi insular activation in the memory epoch. Activation in the aMCC overlapped with the activation in the memory epoch but extended to the MCC and SMA. Overall, the pattern of activation in the memory and discrimination epochs seemed to be similar and partially overlapping.

Comparison of retention and discrimination of pain-spatial information with a meta-analysis of visual working memory studies that employed delayed-match-to-sample tasks reveals striking similarities in activation sites in the right DLPFC, bilateral PPC, left aIC, and bilateral SMA. Particularly, the activation site in the right DLPFC, which is specific in processing spatial-related information in working memory, overlaps in the retention and discrimination phases of delayed discrimination studies of pain intensity, and completely overlaps with the working memory studies of visual modality.

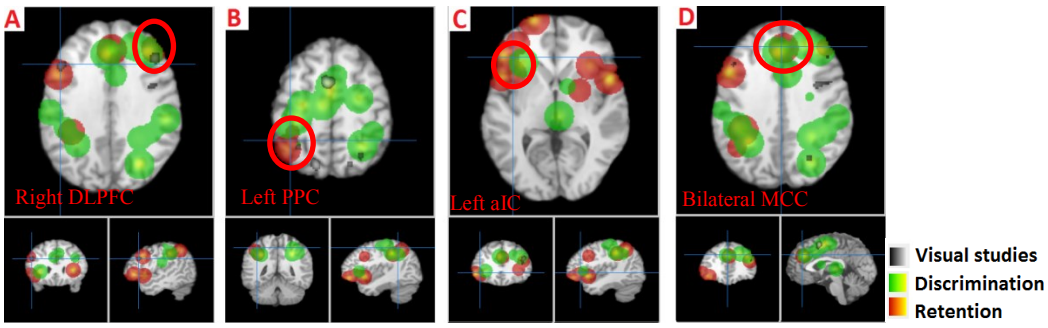

Figure 4. Activation in the retention (red) and discrimination (green) phases of the spatial dimension.
Activation partially overlapped in right DLPFC, left PPC, left aIC, and bilateral MCC, as depicted in panel A, B, C and D respectively. Activation in the meta-analysis of WM studies using visual stimuli and delayed discrimination task is shown in black (Daniel et al. 2016).

Conjoint spatial/intensity dimension: The brain activation in the retention and discrimination epochs of delayed discrimination of conjoint spatial/intensity dimensions of pain (Albanese et al. 2007) is depicted in Figure 5. In the discrimination of conjoint intensity/spatial information, bilateral activation in VLPFC was observed which did not overlap on either side with the activation in VLPFC of the memory epoch. Moreover in the discrimination epoch no activation in the PPC was observed, contrary to the left-contra PPC activation in the memory epoch. Activation in the left-contra insula in the discrimination epoch partially overlapped with the activation in the memory epoch. Additionally, the aMCC was significantly activated only in the discrimination epoch. Parts of the activation in the aMCC overlapped with the activation of the SMA found in the memory epoch. Overall, the activation patterns in the fronto-parietal network during the memory and discrimination epochs seemed to be distinct, while activation in the pain-related area partially overlapped.

Comparison of retention and retrieval of conjoint spatial/intensity pain-related information with a meta-analysis of visual working memory studies that employed delayed-match-to-sample tasks reveals some similarities in activation sites in bilateral LPFC, right aIC, and bilateral SMA.

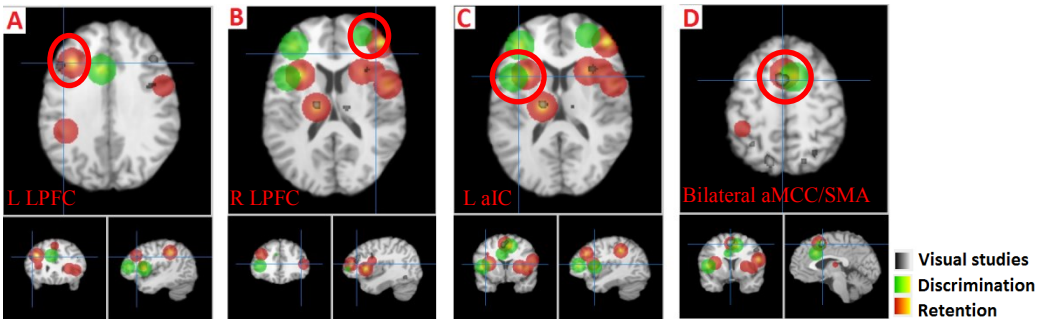

Figure 5. Activation in the retention (red) and discrimination (green) phase of the conjoint intensity/spatial dimension.
Distinct pattern of activation has been observed in right and left LPFC, as depicted in panels A and B. Activation partially overlapped in left aIC and bilateral aMMC/SMA, as depicted in panels C and D. Activation in the meta-analysis of WM studies using visual stimuli and delayed discrimination task is shown in black (Daniel et al. 2016)

4.3. Discussion

We reviewed the few published imaging studies of pain sensory memory. These studies generally used two types of paradigms: delayed discrimination and delayed recall. However, only the studies that used delayed discrimination reported brain activation in the delay (memory) epoch. We compared the brain activation pattern involved in the retention of pain intensity and location as well as conjoint intensity/spatial dimensions. We aimed to compare the similarities and differences involved in the retention of these various sensory dimensions of pain. We also compared the delay epoch activation in pain memory studies with a recent meta-analysis that used delayed discrimination paradigms in visual studies (Daniel et al. 2016). The comparison of visual and pain memory studies revealed striking similarities in fronto-parietal regions as well as the involvement of pain regions such as the SI, BG, and insula. The possible role of these regions in pain memory is discussed in the following sections.

On the other hand, the activation in the discrimination epoch not only required the retrieval of pain related information from the first stimulus, and therefore may share some brain activation that is involved in pain memory, but also involved activation related to

the perception of the second stimulus, the comparison of the first and second stimuli, as well as response preparation. Similarly, the activation in the retrieval of delayed recall paradigms not only involved the retrieval of pain-related information but also required the processes involved in the conversion of pain sensory magnitude to a semantic and/or numeric value. For this reason, we limit the discussion to the activation pattern in the memory epoch and those regions that overlapped in the memory and discrimination/retrieval epochs.

Role of PFC in working memory of spatial and intensity dimension of pain

The PFC was consistently activated in the memory and retrieval epochs across all studies. Interestingly, activation in the left LPFC overlaps with findings of a meta-analysis of WM studies on vision (Daniel et al. 2016). There is ample evidence for the involvement of the LPFC in WM, and it is believed to be involved in a variety of processes such as the active representations of memories or top-down control processes (Lara and Wallis 2015). We speculate that the common activation of the LPFC is consistent with a general role of the PFC in WM. However, the right side activation was only observed in spatial WM of pain which also overlaps with the activation of WM studies of visual modality. This is in line with studies showing right lateralized activity in PFC and PPC for visuospatial processing (Reuter-Lorenz et al. 2000; Smith et al. 1996; van Asselen et al. 2006).

In addition to the left LPFC, there was dimension-specific activation in the PFC. Bilateral VMPFC and medial OFC were specifically activated during the retention of intensity-related information. On the other hand, the right-contra DLPFC, and the left-ipsi VLPFC extending into the left-ipsi lateral OFC and the left-ipsi frontal pole were specifically activated in the retention of spatial-related information. For the conjoint intensity/spatial dimension, memory-related activation was observed in bilateral VLPFC. The dimension-specific activation in the PFC might relate to processing domains of sensory features of pain in WM.

The segregation in PFC by type of information in WM is in line with the theoretical framework of the independent storage buffer suggested by Baddeley (2012). Early electrophysiological studies in monkeys suggest functional segregation in PFC for maintaining 'what' and 'where' information (Wilson et al. 1993), but this was later challenged by Miller and colleagues (Rainer et al. 1998; Rao et al. 1997). An early meta-analysis of imaging studies showed segregation in the PFC of object vs. spatial attributes of visual information in WM (Smith and Jonides 1999). However, later studies provided inconsistent results (Rottschy et al. 2012; Wager and Smith 2003). There is some evidence for a PFC dichotomy based on the type of information to be retained; this is consistent with the findings of studies that show a differential pattern of PFC activation for memory of spatial versus intensity attributes of pain.

On the other hand, regions of the PFC, such as the MPFC, DLPFC, VLPFC, and OFC have been implicated in pain processing (Duerden and Albanese 2013). Prefrontal activity during pain is generally discussed to be related to the cognitive aspect of pain sensation. For example, imaging studies showed that PFC activation reflect attention toward the stimuli (Peyron et al. 1999), or anticipation of pain (Ploghaus et al. 1999). Moreover it has been shown that activation of VLPFC relates to perceived controllability over pain (Salomons et al. 2007). It has also been shown that performance of a cognitively demanding task while receiving a painful stimuli enhanced activation of the OFC, which may pinpoint to the involvement of OFC in cognitive aspect of pain (Petrovic et al. 2000). Overall, converging lines of evidence pinpoint to the involvement of the PFC in the cognitive aspect of pain. However, the exact role of different parts of the PFC such as VMPFC vs. VLPFC in processing different features of pain in WM is not clear. Future WM studies on spatial and intensity dimensions of pain might provide further evidence for functional segregation in the PFC based on different dimensions of pain.

Role of posterior parietal cortex in working memory of spatial and intensity dimension of pain

In the pain memory studies, left PPC was activated across spatial, intensity, and conjoint spatial/intensity dimensions in the memory epoch. However comparison of the WM of visual and pain studies showed overlap in the left PPC with only spatial WM.

In studies in vision, the activation of PPC has generally been attributed to the processing of spatial information (Mishkin et al. 1983). However recently it has been shown that PPC is involved in non-spatial cognition (Yamazaki et al. 2009). Particularly there has been a large emphasis on the role of PPC in attention. Posterior parietal cortex is discussed to be part of the fronto-parietal network involved in dorsal and ventral attentional system (For a review see Corbetta et al. 2002). Imaging studies in vision consistently show the contribution of posterior parietal cortex to spatial attention (Corbetta et al. 1993) as well as non-spatial visual attention (Wojciulik and Kanwisher 1999). It has also been shown that PPC play a key role in sustained attention (Yamazaki 2009). There is also a close link between WM and attention (Cowan 1999). Neurophysiological studies in monkeys showed that posterior parietal regions in combination with frontal regions are involved in selective attention to memoranda in face of distractors in visual working memory tasks (for example see Suzuki and Gottlieb 2013). Using fMRI and a visual orienting task, Corbetta and Shulman (2002) showed that the posterior parietal cortex is involved in orienting and maintaining attention to visuospatial information during the delay epoch. A few fMRI studies also showed that posterior parietal cortex is involved in cognitive control of attention for WM functioning (Bledowski et al. 2009; Tamber-Rosenau et al. 2011). Altogether these studies suggest that posterior parietal cortex might be involved in attentional control, for holding the WM representations online. Therefore activation in the parietal cortex in the pain memory studies might relate to aspects of attention in the context of working memory. This view is in line with imaging studies in pain, where it is shown that posterior parietal cortex has a role in attention towards pain (Duncan and Albanese 2003; Peyron et al. 1999).

In the retrieval epoch, left PPC was activated for both spatial and intensity memory, while the ride side PPC was exclusively activated in the spatial WM. In studies in vision, the right side activation of PPC has been related to spatial processing (Corbetta et al. 1993; Coull and Frith 1998; Nobre et al. 1997). Therefore it is possible that the right side activation of the PPC in spatial memory task is related to the spatial processing of pain-related information.

Role of SI and BG in memory of pain intensity

Memory of pain intensity involved activation in SI and caudate (Oshiro et al. 2009). In the discrimination phase, the activation in caudate was larger and extended to putamen. Both SI and BG have long been implicated in pain processing and have been frequently reported as part of a pain-evoked activation in brain imaging studies (Duerden and Albanese 2013).

SI has long been considered to be involved in sensory processing of pain. Particularly it has been shown that SI is implicated in encoding intensity of pain. Single-cell studies on anesthetized and awake monkeys, show that the discharge rate of SI neurons is modulated by changes in intensity of pain stimulus (Chudler et al. 1990; Kenshalo and Isensee 1983; Kenshalo Jr. et al. 1988). FMRI studies in humans showed that graded changes in the intensity of pain sensation correlated with BOLD activation in distributed cortical areas including contra-SI (Coghill et al. 1999). Another study showed that dynamic temporal profile of pain intensity was positively related to the changes in BOLD signal in SI (Porro et al. 1998). Moreover, hypnotic suggestion to modulate pain intensity, selectively cause changes in SI activity (Hofbauer et al. 2001). Altogether neuroscientific evidence suggests an involvement of SI in encoding of pain intensity.

Various parts of the BG such as the caudate and putamen have been implicated in pain processing (Apkarian et al. 2005; Borsook et al. 2010), yet the exact role of these regions is not clear. Neurophysiological studies show that some of the nociceptive neurons in caudate and putamen encode for stimulus intensity by their firing rates

(Chudler 1998). One imaging study showed that that rating pain intensity when contrasted to rating visual stimulus magnitude, activate caudate, and putamen (Baliki et al. 2009). The putamen has been shown to be involved in sensory processing of pain in other studies, as well (Coghill et al. 1999; Starr et al. 2011). For example, Coghill and colleagues showed that activation in the putamen correlated with graded intensity of pain sensation. Therefore, there is some evidence that the caudate and putamen might be involved in the intensity encoding of pain.

Together, SI and the BG have been shown to be involved in processing intensity of pain and their involvement in the maintenance of pain intensity possibly relates to their re-activation in processing pain intensity in memory consistent with the sensory recruitment hypothesis for WM (Pasternak and Greenlee 2005).

Role of insula in memory of spatial and conjoint spatial/intensity dimensions of pain

Memory of the spatial location of pain activated the bilateral aIC extending to mid-insula. Memory of the conjoint spatial/intensity of pain activated bilateral anterior insula, with the site of activation partially overlapping with that for memory of spatial location. The left aIC was also present in the discrimination phase of spatial and the conjoint intensity/spatial conditions. Altogether, aIC seems to play the key role in the WM of spatial and conjoint intensity/spatial information.

The insula is one of the integral parts of the pain matrix and has consistently been reported in imaging studies of experimental pain (Duerden and Albanese 2013). However, the anterior insula has mainly been implicated in affective and cognitive aspects of pain (Brooks et al. 2002; Garcia-Larrea and Peyron 2013; Schweinhardt and Bushnell 2010), though there is also some evidence for the involvement of the insula in the sensory aspect of pain. Activation of the insular cortex has been correlated with the intensity of noxious stimulation, (Coghill et al. 1999; Derbyshire et al. 1997; Peyron et al. 2002). However, despite evidence for the involvement of the IC in intensity encoding of pain, this region was absent in the memory of pain intensity. One possible reason for the

absence of IC activation in the intensity condition might be the lack of a proper control task in the study by Oshiro and colleagues (2007), in which the memory-delay activation was contrasted with baseline, while another study used a perceptual control task for examining memory-related activation (Albanese et al. 2007). However, as Albanese and colleagues used a conjoint spatial/intensity condition it is hard to relate the insular activity to either the spatial or intensity dimension. Given that one study shows somatotopic organization in ipsilateral aIC (Henderson et al. 2007), it is also possible that the aIC may be involved in the memory of the spatial aspect of pain.

The reciprocal connections of the insula with the prefrontal cortex, ACC, amygdala, parahippocampal gyrus and SII (Mesulam and Mufson 1982; Mufson, Mesulam et al. 1981) suggest a multi-faceted role of this area in pain processing. For example it has been suggested that such extensive connectivity subserves pain-related learning and memory (Lenz et al. 1997). Interestingly the right side activation also partially overlaps with the meta-analysis of working memory studies in vision (Daniel et al. 2016). The aIC is generally implicated in cognitive control such as attentional and working memory processes (Menon and Uddin 2010; Wager and Barrett 2017). Therefore it is plausible that at least the part of the aIC that overlaps in WM studies of pain and vision, using a delayed discrimination paradigm, is involved in working memory in general. However it should be noted that the activation in memory of spatial and conjoint spatial/intensity is much more widespread than that observed in Daniel et al (2016), which may suggest functional segregation in the aIC in working memory vs. pain-related processes.

It has been shown that the aIC is predominantly connected to the VLPFC (Wiech, Jbabdi et al. 2014). Interestingly in both spatial and conjoint intensity/spatial condition, activation in VLPFC was observed which partially overlapped across conditions. In contrast VMPFC was activated in in the intensity condition. Future research employing WM tasks may investigate the functional connectivity of the aIC and VLPFC, in the context of memory.

Role of cingulate cortex in pain memory

The ACC or MCC was activated consistently across all studies reported in Table 1 and 2 in the retrieval epoch. However there was inconsistency with regard to its activation in the retention epoch. The cingulate cortex was activated in one study on intensity memory (anterior mid-cingulate cortex, aMCC) and was absent in the study on spatial memory. There is fMRI evidence that shows different regions in ACC can differentiate between different levels of noxious stimulation, and can therefore code for stimulus intensity (Buchel et al. 2002). Also some lesion studies showed a reduction in subjective intensity of pain following cingulotomy (Davis et al. 1994; Talbot et al. 1995). It is important to note that both studies compared memory-related activation vs. baseline. However, the direct contrasts between intensity and spatial memory reported by Lobanov showed a stronger response to the spatial than the intensity task in the anterior cingulate area. This may pinpoint to the involvement of the ACC in processing spatial-related information. This is in line with the somatotopic organization in ACC (Arienzo et al. 2006). Altogether, activation in the ACC in the retention epoch may be related to processing sensory-discriminative aspect of pain in memory.

However, the memory for conjoint intensity and spatial information in Albanese et al. (2007), which was the only study that used a perceptual control condition for evaluating memory-related activation, did not correlate with activation in ACC, but instead correlated with activation in pre-SMA superior to the aMCC. It is important to note that although the ACC often reported in fMRI studies of working memory, it was absent in the meta-analysis by Daniel et al. (2016), which only focused on studies that used delayed-match-to-sample tasks (similar to the studies shown in Table 1). However as there is only one fMRI study on pain memory that employed perceptual control and a delayed-match-to-sample task, it is hard to draw any firm conclusion with regard to its role in working memory of pain. Future studies on WM of pain using proper control

conditions and a delayed discrimination task would provide further support for contribution vs. lack of involvement of the ACC in the WM of pain.

In the retrieval epoch, the ACC was consistently activated across all studies. The ACC is an integral part of the pain network, and robust activation of ACC is consistently reported in neuroimaging literature of acute experimental pain (Duerden and Albanese 2013). The ACC is generally discussed to be related to affective processing of pain (Foltz and White 1962; Rainville et al. 1997). The ACC is also shown to be involved in cognitive aspects such as attention towards pain (Peyron et al. 1999). Therefore the activation of the ACC in the retrieval epoch and the memory epoch might relate to its role in processing the cognitive aspect of pain, in addition to its possible role in sensory-discriminative aspect of pain processing.

On the other hand, single-cell recording, functional neuroimaging, and electrophysiological studies have provided support for involvement of the ACC in a variety of executive processes such as conflict resolution, response monitoring, and error detection (Awh and Gehring 1999; Brown and Braver 2005; Carter et al. 1999; Devinsky et al. 1995; Kerns et al. 2004; Mulert et al. 2003). The ACC has also been shown to play a role in aspects of attention (Davis et al. 2000; Kondo et al. 2004; Wu et al. 2017). Therefore the activation of the ACC in pain memory might also relate to aspects of cognitive control such as attention, response selection, and performance monitoring.

Chapter 5: Review of time-perception literature

5.1. An overview

Timing is a crucial cognitive ability that is fundamental for everyday life. It includes a variety of functions such as estimating how long an interval lasts or predicting the onset of an event. The study of time perception is particularly interesting since there are no specific 'time' receptors as there are for vision, audition, or somatosensation. Yet we have the ability to perceive and estimate duration in the sub-second to minute range. In the last two decades there has been growing research for elucidating the neural mechanisms underlying time perception. Like in other domains of cognition, various theoretical models have been developed to explain timing mechanisms and have guided research on time perception. This chapter provides an overview of basic categories of research and mainstream theoretical accounts and properties of temporal processing, specifically in the supra-second range. A section is also devoted for the evidence provided from neurophysiological, neuropsychological, electrophysiological, and imaging research on the involvement of key brain regions frequently reported in temporal-processing studies.

5.2. Basic definitions and multiple categories of research

Temporal processing falls within diverse categories of research including 'explicit timing', 'implicit timing' and 'temporal order judgment'. Explicit timing involves an explicit judgment of how long an interval lasts, while implicit timing involves temporal predictions such as when to catch a ball or when a traffic light changes to green (for a general review on implicit vs. explicit timing refer to Coull et al. 2011). On the other hand, temporal order judgments require ordinal representation of events across time (for a review see Marshuetz and Smith 2006).

Another categorization in timing literature is prospective vs. retrospective time judgment. In prospective timing, subjects know in advance that they have to estimate the duration while in retrospective judgment they have no prior knowledge that they have to

estimate duration. It is evident that in the former condition subjects have intensified attention to the passage of time and intentionally encode temporal information while in the latter subjects are likely to be less attentive to the passage of time and rely on reconstructive processes to assess time and therefore estimate time in an incidental manner. One issue that limits the retrospective evaluation studies is the fact that it can only be tested once, since afterward subjects would know that the task is about time estimation and will begin attending to time, which makes the subsequent trials prospective (for a review see Grondin 2010, and for a meta-analysis see Block and Zakay 1997).

Here we restrict this chapter to prospective explicit timing, as the paradigms investigated in this thesis fall within this category. Explicit timing is generally assessed using 'perceptual timing' vs. 'motor timing' paradigms. One of the most common paradigms employed in *perceptual timing* is temporal discrimination tasks, in which participants have to compare the duration of a probe stimulus to that of a target stimulus previously stored in working memory. Control tasks, requiring comparison of non-temporal stimulus features (e.g. color, length, or brightness), account for processes of non-interest such as attention, working memory, or sensorimotor task demands. In *motor timing* tasks, subjects have to use a motor response to represent their estimation of elapsed duration. One of the most common examples of motor timing is paced finger tapping in which participants have to synchronize their motor response to a pacing stimulus. Temporal reproduction is another example of motor timing in which subjects have to reproduce the duration of a stimulus that has elapsed by some operation such as button press. For a review of various paradigms employed to study explicit timing see Coull et al. (2011) and Grondin (2010).

5.3. Range of duration

We use temporal information across a wide range of durations from milliseconds to seconds, minutes, hours, and days. One important factor in the time perception research is the range of durations tested. Pharmacological studies show a distinction for durations below and above the one second range (Rammsayer 1999). Psychophysical evidence also shows that the properties of time estimation differ under these two duration ranges (for a review see Buhusi and Meck, 2005; Grondin, 2010). Moreover, neuroimaging evidence indicates that the brain activation differs for temporal processing in sub- vs. supra-second ranges (Lewis and Miall 2003; Wiener et al. 2010). Temporal estimation of durations less than one second is generally assessed in an automatic manner while the processing of longer intervals requires support of voluntary executive and cognitive functions. The processing of durations less than one second is involved in speech (Schirmer 2004), motor coordination (Loras et al. 2013) and music perception (Cariani 2001), but this is beyond the focus of this chapter. On the other hand, duration in the range of hours and beyond is seldom studied in humans and is not addressed here (for a review in this range, see Hinton and Meck 1997).

For durations in the order of several seconds, there seems to be a temporal window within which there is a unitary perception of the events occurring as a whole, which precludes distinguishing the events into past or future. This so-called ‘psychological present’, originally introduced by William James (1890) and later elaborated by Fraisse and Pöppel, is suggested to be approximately 3 seconds (Fraisse 1984; Pöppel 1997; Pöppel 2004). This is also discussed in recent work by Block and Gruber (2014). Events exceeding this temporal window may require memory processes that link the moments to the previous temporal gestalt. In the supra-second range, multiple cognitive factors play a key role such as attentional and working memory processes (see Buhusi and Meck 2009). This issue is further discussed and elaborated in section 5.4.

5.4. Theoretical models

Theoretical accounts for the processing of temporal information generally fall under two broad categories: intrinsic and dedicated (Ivry and Schlerf 2008).

The intrinsic models assume that there is no central mechanism specialized for duration processing. One view for this class of models is that time is represented in a modality-specific manner (Ivry and Schlerf 2008). There is evidence for this modality-specific representation in psychophysical (Grondin 1993; Yuasa and Yotsumoto 2015) and imaging studies on time perception (Bueti et al. 2008; Jantzen et al. 2005). One of the prominent models within this class, referred to as the 'state dependent network model,' suggests that time is an intrinsic property of the dynamics of neural networks and that durations can be distinguished by specific spatial patterns of elicited neural activity (Buonomano and Merzenich 1995; Buonomano 2000; Karmarkar and Buonomano 2007). Another model suggests that time is represented by the magnitude of the neural response to a stimulus (Eagleman and Pariyadath 2009).

On the other hand, dedicated models postulate specialized timing mechanisms and brain systems underlying duration representation in the brain. The clock model, the dominant model in the dedicated class of models, consists of an oscillator (pacemaker) that emits pulses that are counted by an accumulator (Church 1984; Gibbon et al. 1984; Treisman 1963). The pulse tally provides a linear metric of time and the current pulse count is compared to a reference for known durations stored in memory, for duration estimation. Later an attentional-gate component was added to the model that accounts for the fact that the less/more attention allocated to duration results in fewer/more pulses and shortening/lengthening of perceived duration (Zakay and Block 1996). There are also pacemaker-accumulator-free models in this category. For example, the memory-decay model suggests that working memory decay is a time-dependent process where different times correspond to distinct amounts of decay (Staddon and Higa 1999; Staddon 2005). Other examples in this class of model are the oscillator models, in which instead of pacemaker-accumulator elements, a series of oscillators act as a clock by detection of

coincidental activation of multiple neural oscillators active spontaneously at different frequencies (Matell and Meck 2000; Matell and Meck 2004).

5.5. Modulation in perceived duration by stimulus characteristics

There is no specific receptor for the perception of duration, thus in order to process the temporal aspects of a stimulus, non-temporal stimulus characteristics are often employed. These other stimulus dimensions are used to mark the onset/offset (empty interval) or to fill the interval to be timed. Interestingly, filled intervals are shown to last subjectively longer than empty intervals in the range of milliseconds to 1.2 seconds (Craig 1973; Hasuo et al. 2011; Hasuo et al. 2014; Wearden et al. 2007), but it has also been reported for durations up to 3 seconds (Ihle and Wilsoncroft 1983). Moreover the structure of sub-intervals filling the interval affect perceived duration, such that intervals containing regular sub-intervals last longer than irregular ones (Horr and Di Luca 2015).

In the case of filed intervals, the perceived duration is generally modulated by manipulation of various sensory factors such as changes in physical characteristics of stimuli. Cases of such change-based modulations are abundant. For example, subjective time increases as a function of the number of stimuli that occur over an interval and the complexity of those stimuli (Schiffman and Bobko 1974), size (Xuan et al. 2007), motion (i.e. moving stimuli last longer than stationary stimuli) (Brown 1995), speed (Kaneko and Murakami 2009), or changes in frequency (Kanai et al. 2006).

Altogether, various changes in stimulus characteristics lead to subjective time compression/dilation, and many theories have been developed based on the modulation caused by those factors. For example, one perspective on the mechanism underlying duration perception initially proposed by William James (1890) is the concept of awareness of change in an interval to be timed. Fraisse (1984) also suggested that

perception of duration is a function of the number of changes that occurred during the interval.

5.6. Psychophysical studies on the contribution of cognitive factors to duration judgment

In the supra-second range, cognitive factors such as attention and working memory play a key role in the perception of duration. Increased attention to time generally increases the perceived duration and distraction from time results in a decreased perceived duration (for a review see Buhusi and Meck 2009). An early attentional model of time perception argued that limited attentional resources are shared between a 'temporal information processor' and a 'non-temporal information processor', and thus may account for the observed attentional effect (Thomas and Weaver 1975). The studies investigating the effects of sharing attention between temporal and magnitude properties of stimuli on duration judgments are in accord with this perspective by showing that increased attention toward the intensity attribute of the stimulus results in *shorter* estimates of duration (Casini and Macar 1997; Casini et al. 1992; Macar et al. 1994). Another example in this line of research is when subjects are expecting an interruption in the signal to be timed. In this case, the longer they are anticipating the occurrence of the break, the more attention is allocated to the arrival of the break, which results in less attention to time and therefore shorter interval reproduction (Fortin et al. 2005). Another example is manipulating the length of the foreperiod (the anticipatory period when subjects are expecting to receive the stimuli whose duration they have to judge). Increasing the foreperiod increases the likelihood that an interval will be presented and this expectation prepares attention to time resulting in longer perceived intervals (Grondin and Rammsayer 2003).

The influence of attention on duration judgment is evident from dual task experiments in which a concurrent non-temporal task must be performed in addition to a

temporal task. In almost all dual task experiments, an interference effect is observed where the performance of a non-temporal task results in impairment in temporal judgments (i.e. shorter and more variable perceived time) (Brown 1997). There are two perspectives with regard to the observed effect. One perspective argues for the allocation of attentional resources. The resource theory of attention (Navon and Gopher 1979) postulates that a limited pool of energy is responsible for all cognitive processes, including time estimation, and so as attention is divided between concurrent temporal and distractor tasks, timing performance is impaired. Interestingly, it has been shown that practice reduces the interference effect (Brown 2008). This would be in line with the resource theory of attention as automaticity is referred to a reduction in the resources required to perform a task. This perspective is best explained by the attentional gate model (Zakay and Block 1997). The idea is that when attention is directed towards the temporal dimension, a gate is opened allowing the stream of pulses to be transferred to a counter. When attention is directed to the non-temporal task, the gate is closed and thus reduces the number of pulses that are counted.

However, the interference effect is not bidirectional for all distractor tasks (i.e. temporal task affects the performance of non-temporal task and vice versa). Brown (1997) showed that among a number of non-temporal tasks (mental arithmetic, visual search, pursuit motor tracking), only mental arithmetic showed a bidirectional interference. The specialized resource theory explains that the lack of bidirectional interference is due to the fact that the distractor task and the timing task did not share the same resource pool. However, Brown suggests a working memory perspective and postulates the cost of coordination between temporal and non-temporal task, operated by the central executive component of working memory (Baddeley 1996), underlies the observed effects. Other studies have provided evidence for this perspective. For example Dutke (2005), using a dual task experiment, selectively manipulated the coordination between the temporal and non-temporal task and showed that dual task coordination affects the duration judgment. Fortin and Breton (1995) used a memory search task and concurrent temporal tasks where the interval whose duration had to be reproduced

contained a set of items that had to be remembered. They showed that manipulation of the number of items that must be held in working memory did not affect temporal reproduction. In another version of the task, subjects also had to compare the probe stimuli with a memory set while reproducing the duration. Interestingly, this condition caused impaired performance of temporal reproduction. This result therefore suggests that demand on the processing component of working memory affects duration judgments. Moreover it has been shown that individuals with higher WM capacity are generally more accurate in their duration judgment (Broadway and Engle 2011). Altogether, these results suggest that working memory contributes to duration estimation.

Various other studies also highlight the general role of executive processes in temporal processing, which includes control of attention and coordination of information. An example is the bidirectional interference effect observed for classic executive tasks such as random number generation (Brown 2006), or sequencing (Brown and Merchant 2007). To assess the contribution of executive function, Brown and colleagues (2013) conducted a series of dual task experiments using non-temporal tasks relying on three main executive functions of shifting, updating, and inhibition (Miyake, Friedman et al. 2000). Brown et al (2013) showed bidirectional influence for all of the three executive tasks tested. However, another study examined the interference between timing and non-temporal tasks involving shifting, inhibition, updating, and access, and only showed bidirectional interference for updating (Ogden et al. 2011). These results generally highlight that explicit timing in duration judgment or reproduction tasks and general executive processing rely on the same resource pool.

5.7. Neural substrate of timing

Advances in the neuroscientific enquiry of timing identified distributed brain regions that sub serve temporal processing. Neurophysiological, neuropsychological, imaging and electrophysiological studies seem to be in accord with the involvement of

some key regions in temporal processing. In the following sections, the evidence for the contribution of the main regions is reviewed.

Cerebellum: The cerebellum is a structure that is frequently discussed to be involved in timing (for reviews see Ivry, 1996; Ivry and Spencer, 2004). It has been initially suggested that the cerebellum is mainly involved in the sub-second range (Ivry 1996). TMS of the cerebellum specifically impairs timing of sub-, not supra-second, durations (Del Olmo et al. 2007; Fierro et al. 2007; Koch et al. 2007). However, there is abundant neuropsychological evidence for timing deficits in patients with cerebellar lesions in both the sub-second (Harrington et al. 2004; Ivry and Keele 1989; Spencer et al. 2003) and supra-second ranges (Gooch et al. 2010; Malapani et al. 1998) in both motor timing and perceptual timing paradigms. Imaging studies also frequently report activation in the cerebellum for both perceptual and motor timing, but there seem to be confounding results for its involvement in both duration ranges (Bueti et al. 2008; Jahanshahi et al. 2006) or, more specifically, in the sub-second range (Lewis and Miall 2003; Wiener et al. 2010).

Prefrontal cortex: There is also neurophysiological evidence for duration-tuned neurons in the PFC of monkeys (Genovesio et al. 2006; Niki and Watanabe 1979; Yumoto et al. 2011). Neuropsychological studies in patients with lesions in right prefrontal cortex showed impairment in timing tasks only in the supra-second range (Kagerer et al. 2002; Koch et al. 2002; Nichelli et al. 1995; Wiener and Coslett 2008). Moreover, timing deficits of patients with prefrontal lesions worsen by increasing attentional (Casini and Ivry 1999) or working memory load (Mangels et al. 1998). This is consistent with the hypothesis that the contribution of prefrontal cortex might be to the increased attention and working memory demands of timing long duration (Lewis and Miall 2006; Macar et al. 2002), as PFC is strongly associated with working memory and attention (for a general review see D'esposito and Postle, 2015). Consistently, TMS of right prefrontal cortex impairs timing of supra-, not sub-second, durations (Jones et al. 2004; Koch et al. 2003; Koch et al. 2009).

Neuroimaging studies often report activation in the PFC (for a review see Lewis and Miall, 2003). Studies that compared sub- vs. supra-second duration ranges generally reported PFC activation for the supra-second range (Murai and Yotsumoto 2016; Pouthas et al. 2005; Rubia et al. 1998; for a meta-analysis see Wiener et al., 2010), though some others have reported PFC activation in both duration ranges (Lewis and Miall 2006; Macar et al. 2002). However, there appears to be a general agreement on the involvement of PFC in working memory aspects of temporal processing (Lewis and Miall 2003; Lewis and Miall 2006; Macar et al. 2002). Interestingly, when equating the control task (non-temporal task) with the temporal task in terms of the cognitive demands and task difficulty, activity in PFC vanishes (Livesey et al. 2007).

Electrophysiological studies also show a direct relationship between a slow negative wave developing over frontal areas (contingent negative variation; CNV) and cognitive timing (Macar and Vidal 2003; Pfeuty et al. 2005; Pouthas et al. 2000; Tarantino et al. 2010). For example an ERP study comparing intensity vs duration discrimination of visual stimuli showed distinct ERP patterns for the two tested dimensions with the specific involvement of right frontal cortex for duration dimension (Pouthas et al. 2000). Another electrophysiological study found an inverse relationship of current density measures over PFC and temporal performance (Casini et al. 1999).

Altogether evidence from neurophysiological, electrophysiological, and imaging studies highlight the role of PFC in duration estimation, a role that has been also discussed as related to working memory demands of temporal processing.

Basal ganglia (BG): The BG is considered central for time-keeping functions (Ivry 1996; Ivry and Spencer 2004). Indeed some views on interval timing such as the beat-frequency model argue that cortico-striatal circuits modulated by dopaminergic input from the BG coordinates representation of duration by detecting the coincident patterns of cortical activations (Matell and Meck 2004; Meck et al. 2008).

There is abundant evidence for timing deficits in patients with BG dysfunction such as Parkinson's disease (PD) (Artieda et al. 1992), or Huntington's disease (Agostino

et al. 2017; Rao et al. 2014; for a review see Avanzino et al., 2016). Interestingly, although these diseases are characterized by motor dysfunction, the timing deficits are observed for both perceptual and motor timing. For example, one of the earliest studies showed impaired temporal discrimination in PD patients across modalities when compared with controls (Artieda et al. 1992). There is evidence for impaired temporal processing in PD patients in both the sub-second (Harrington et al. 1998) and supra-second (Smith et al. 2007) range. However, others have failed to replicate this finding (for example see Wearden et al. 2008). One study showed that there is interval timing heterogeneity among PD patients, which likely explains the mixed findings (Merchant et al. 2008).

Imaging studies often report activation in the BG in both the sub- and supra-second range (Jahanshahi et al. 2006), and in both perceptual and motor timing (Bueti et al. 2008; for a review see Coull et al., 2011). In a delayed discrimination task, the striatum was shown to be involved in both the encoding (Coull et al. 2008; Harrington et al. 2009) and decision phases of the task (Harrington et al. 2009). Coull and colleagues also showed that increased BG activation during the encoding phase was associated with enhanced temporal performance (Coull et al. 2008). It is important to note that striatal regions are often activated along with frontal areas (Ferrandez et al. 2003; Hinton and Meck 2004), in accord with the involvement of fronto-striatal circuits in interval timing.

Motor cortex: There is neurophysiological evidence for the involvement of premotor (Crowe et al. 2014; Merchant et al. 2013; Mita et al. 2009; Ohmae et al. 2008) and primary motor cortex (Renoult et al. 2006; Roux et al. 2003) of monkeys in interval timing. However, electrophysiological human studies also suggest the involvement of SMA in interval timing. For example in an ERP study, Macar et al. (1999) showed that the amplitude of slow brain potentials (CNV amplitude) measured in the SMA is parametrically modulated by temporal performance in both temporal production and temporal discrimination tasks (also see Macar and Vidal 2002).

Imaging studies often report activation in motor areas such as pre-motor and/or SMA in both perceptual and motor timing tasks (for a review see Macar et al. 2002; for a meta-analysis see Wiener et al. 2010). In particular, the SMA is commonly reported in imaging studies (Coull et al. 2008; Coull et al. 2015; Macar et al. 2002; Macar et al. 2004; for a review see Macar et al. 2006; Coull et al. 2011). Parametric modulation of attention to temporal vs. non-temporal attributes of stimuli showed that increasing attention to time corresponds with increasing activation in SMA as well as pre-motor, right frontal operculum, and putamen (Coull et al. 2004). Altogether, these findings highlight the importance of motor areas in interval timing.

Parietal cortex: There is neurophysiological evidence that neurons in the posterior parietal cortex of monkeys encode the duration of stimulus by their firing rates (Leon and Shadlen 2003). It has also been shown that repetitive TMS (rTMS) to the supramarginal gyrus in the inferior parietal lobule causes dilation of perceived duration, highlighting its role in duration perception (Wiener et al. 2010). Moreover, a morphological study revealed individual differences, in that increased performance in temporal estimation was associated with smaller gray matter volume in the inferior parietal lobule (Hayashi et al. 2014).

Parietal cortex is often activated along with frontal areas in neuroimaging studies of perceptual and motor timing (for a review see Rubia and Smith 2004; for a meta-analysis see Wiener et al. 2010), however some studies failed to find significant parietal activation when contrasted with a control task (Coull et al. 2008; Smith et al. 2003). Parietal cortex is discussed as being involved in aspects of sustained attention (Pardo et al. 1991; Petersen and Posner 2012) and its involvement in temporal processing is postulated to be associated with sustained attention to temporal processing (Lewis and Miall 2006). This might explain the lack of its activation in studies that employed control tasks that equated in terms of sustained attention (for example Smith et al., 2003; Coull et al., 2008). However, it has been shown that the left parietal cortex is selectively involved in orienting attention to time (Coull and Nobre 1998) compared to orienting attention to space. Another perspective on the role of parietal cortex in timing is its involvement in

magnitude processing in general. The right parietal cortex has been discussed as being involved in magnitude processing including duration, size, or number (Bonato et al. 2012; Bueti and Walsh 2009; Walsh 2003).

Altogether, the evidence provided from studies discussed here suggests that the parietal cortex plays a role in timing, which might be more specifically related to the attentional aspect of temporal processing, or to magnitude estimation

Chapter 6: Articles

6.1. General objectives and hypotheses of the thesis

The experimental part of this thesis is presented in the following pages. Three studies have been conducted addressing complementary goals related to the processes underlying the STM of thermal sensations and/or pain.

Article 1- Khoshnejad et al 2014: Only one previous study examined the properties of STM of pain. This study (Rainville et al., 2004), which is reviewed in Chapter 4, only focused on intensity attributes of pain and showed decay of intensity information. In study 1, we aimed to examine the replicability of these finding with regards to intensity measures of pain in dynamic reports of pain. We also looked at the properties of temporal attributes of dynamic pain reports in STM. Additionally sensory vs. affective dimensions of pain are often segregated in pain literature; here we aimed to show whether such distinction also applied with delayed reports of pain.

The main objective of the first study was to examine the properties of STM of thermal pain dynamics, and test whether there is some deterioration of information in short-term memory with regards to both temporal and intensity parameters of pain. We additionally examined whether the separation of pain dimensions (sensory/affective) is also preserved in STM. Similar to previous psychophysical studies on pain which showed decay of pain intensity information in STM, we expected decay of information with regards to the recall of temporal and non-temporal parameters in STM. We also hypothesized that the separation between pain dimensions would be preserved in memory.

Article 2- Khoshnejad et al. 2016: In the time literature, reviewed in chapter 5, it is shown that stimulus characteristics affect duration recall. In particular, introducing changes during an interval that has to be reproduced results in time dilation. However these effects have not been studied in the somatosensory modality. Here, we aimed to show that these effects are also observed with innocuous thermal stimuli. Moreover,

various lines of research in the time literature show that attention modulates duration recall. Here we additionally aimed to investigate the effects of attention on duration recall of thermal sensation.

The main objective of study 2 was to examine the effects of segmentation of the thermal stimulus, produced by fluctuations in temperature, on STM of duration of innocuous thermal sensation. We additionally examined the effect of top-down attention on duration judgment. Similar to previous studies in the time literature, we hypothesized that changes during an interval that has to be timed (i.e. segmentation) facilitates duration recall. Similar to previous studies in the time literature, we additionally hypothesized that attention facilitates duration recall.

Article 3- Khoshnejad et al. Pain 2017: Only a few studies, reviewed in chapter 4, examined neural correlates of the STM of pain. These studies mainly focused on spatial and intensity attributes of pain. Here we aimed to examine the neural correlates of the STM of duration attribute of pain. The objective was to examine the neural correlates of the STM of pain dynamics and pain duration. We expected that the STM of pain duration and pain dynamics involves distributed brain activation in regions involved in pain perception, time perception and WM.

Article 1: Remembering the dynamic changes in pain intensity and pain unpleasantness: A psychophysical study

Title: Remembering the dynamic changes in pain intensity and pain unpleasantness: A psychophysical study

Authors:
Mina Khoshnejad [a, b, c]
Marie C. Fortin [d]
Farzan Rohani [e]
Gary H. Duncan [b, f]
Pierre Rainville [b, c, f]

Affiliations:
[a]Department of Neurosciences, Université de Montréal, Montréal, Québec, Canada
[b]Groupe de recherche sur le système nerveux central (GRSNC), Université de Montréal, Montréal, Québec, Canada
[c]Centre de recherche de l'Institut universitaire de gériatrie de Montréal, Université de Montréal, Montréal, Québec, Canada
[d]SafeBridge Consultants Inc., Mountain View, CA, USA
[e]Google Inc., Mountain View, CA, USA
[f]Department of Stomatology, Faculté de médecine dentaire, Université de Montréal, Montréal, Québec, Canada

Corresponding author:
Pierre Rainville, PhD
Pierre.Rainville@Umontreal.ca

Publication status:
Manuscript published in PAIN, Vol 155, March 2014.

Authors' contributions: MCF, GHD and PR contributed to the conception and design of the study; MF acquired and analyzed the data using classical psychophysical methods; MK applied dynamic PCA and FR and PR contributed to the interpretation of PCA outputs; MK drafted the manuscript with PR and all authors revised and approved the published version.

ABSTRACT

This study investigated the short-term memory of dynamic changes in acute pain using psychophysical methods. Pain intensity or unpleasantness induced by painful contact-heat stimuli of 8, 9, or 10 s was rated continuously during the stimulus or after a 14-s delay using an electronic visual analog scale in 10 healthy volunteers. Because the continuous visual analog scale time courses contained large amounts of redundant information, a principal component analysis was applied to characterize the main features inherent to both the concurrent rating and retrospective evaluations. Three components explained about 90% of the total variance across all trials and subjects, with the first component reflecting the global perceptual profile, and the second and third components explaining finer perceptual aspects (eg, changes in slope at onset and offset and shifts in peak latency). We postulate that these 3 principal components may provide some information about the structure of the mental representations of what one perceives, stores, and remembers during the course of few seconds. Analysis performed on the components confirmed significant memory distortions and revealed that the discriminative information about pain dimensions in concurrent ratings was partly or completely lost in retrospective ratings. Importantly, our results highlight individual differences affecting these memory processes. These results provide further evidence of the important transformations underlying the processing of pain in explicit memory and raise fundamental questions about the conversion of dynamic nociceptive signals into a mental representation of pain in perception and memory.

Keywords: memory psychophysics, pain dimensions, PCA, segmentation, chunking

1. Introduction

In clinical or experimental situations, the amount of pain felt is assessed by subjective reports: the patient or volunteer is asked to provide a rating that represents their current or past experience using a validated visual, numerical, or verbal scale. However, the accuracy of pain recall has been debated. Although some studies show that the recollection of pain is moderately accurate [2,8,18,28,30,32], others argue for important and systematic distortions of the remembered pain [6,17,19,31,37,38,47,48,55]. The nature of the information available in memory about past painful experiences remains unclear. One immediate problem with the methods used in previous research is that subjects may encode, store, and/or remember an indirect measure of pain by translating the sensory information into a more stable memory representation (eg, a number or a word) rather than memorizing the actual pain experienced. A few investigators have used online continuous ratings to monitor the ongoing perceptual changes in the magnitude of experimentally induced pain [15,16] or spontaneous fluctuations in clinical pain [21]. These methods are less likely to lead to a simple conversion into a more stable format, but to our knowledge, they have not yet been used to determine how much of the dynamic pain information is actually preserved in memory.

In addition to the dynamic aspect of pain, it is generally accepted that pain can be described along sensory-discriminative (intensity) and affective-motivational (unpleasantness) dimensions [42,51,52,54,56]. Previous research has suggested that long term pain recall largely reflects the aversive emotional context at encoding [22,23]. Few data exist, however, on the relevance of this distinction in short-term memory processes. One of the goals of this study was to take advantage of online continuous rating procedures to evaluate in greater depth the memory distortions affecting the recall of pain intensity and unpleasantness over a very brief time interval.

Comparing dynamic temporal profiles of continuous visual analog scale (VAS) reports, obtained in concurrent/perceptual and retrospective/ memory conditions, may

provide insight into possible transformations induced by the encoding, storage, and/or retrieval processes. The comparison between the 2 pain dimensions may also reveal whether specific aspects of the real-time pain experience are weighted differently throughout memory processing. Another important but neglected issue is whether individuals vary in how they memorize dynamic information about pain sensation and affect. This study was designed to address these questions by using a multivariate analysis (principal component analysis, PCA) applied to dynamic data. PCA was utilized to decompose the temporal profiles into a few components explaining most of the overall variance, thereby greatly reducing the dimensionality of the data. This allowed us to test differences related to memory, pain dimension, and individual variability in terms of independent patterns of information (components) extracted from VAS curves that might provide some insight about the inherent structure of the mental representation of ongoing changes in pain magnitude over time.

2. Materials and Methods

2.1. Subjects

Ten subjects (7 men and 3 women with an average age of 26 years, 5 ± 9 years) took part in this experiment. They were recruited on the campus of the Université de Montréal. All participants provided informed consent before the beginning of the experiments. The protocol was approved by the Human Research Ethic Committee of Université de Montréal and was in accordance with the 1975 Helsinki Declaration of Human Rights. Subjects were free to withdraw from the study at any point during the experiments, but no one did.

2.2. Stimulation and procedure

Subjects were comfortably seated in a soundproof room, and thermal (heat) stimulation was applied on the volar surface of the forearm with a MEDOC TSA-2001 contact thermode of 30 × 30 mm. The temporal profile of the stimuli consisted of 3 phases: onset, plateau, and offset. The temperature of the stimuli started rising from 37^0 C, reached 47^0 C in 2 s (onset), and then remained at that fixed intensity during 4, 5 or 6 s (plateau), and returned back to baseline at 37^0 C in 2 s (offset) (Fig. 1). The total duration of the stimuli was thus 8, 9, or 10 s. The thermal probe was moved to 1 of 4 spots on the forearm between trials to minimize the risk of sensitization.

Continuous ratings were performed using an electronic VAS (e-VAS) consisting of a 9-cm sliding potentiometer. Cursor movement along the axis of the scale was converted to a numerical scale from 0 to 100 units of pain intensity or pain unpleasantness. The 2 pain dimensions were described according to previous studies [52,54,56]. The 2 extremities of the e-VAS were labeled ‘‘No pain’’ and ‘‘Most intense pain imaginable,’’ or ‘‘No unpleasantness’’ and ‘‘Most unpleasant pain imaginable.’’ The e-VAS signal was sampled at 200 Hz, using a Biopac MP150 system, and recorded using the AcqKnowledge program 3.7.1.

The experiment was designed to investigate the effect of memory on the subjective report of the temporal profile of painful thermal stimuli after a delay of 14 s (Fig. 1). This delay was chosen on the basis of the results of our earlier study showing important memory distortions within this time frame [55]. Importantly, concurrent and retrospective ratings were obtained in separate blocks of trials to reduce the risk that subjects might memorize their motor response rather than their pain experience in retrospective rating trials. Each block of trials started with the instruction to rate pain intensity or pain unpleasantness (pain dimension effect), either concurrently or retrospectively (memory effect). In concurrent rating trials, subjects were asked to move the cursor to report the pain felt as precisely as possible throughout the sensation. In retrospective trials, the rating scale was covered with a towel during the stimulus and the

delay and subjects were asked to attend to and memorize the pain experienced, and to try to reproduce the experience they felt as precisely as possible. Practice trials were performed as necessary to familiarize the subjects with the task conditions.

The experimental protocol thus consisted of 4 main conditions [memory (2) × pain dimensions (2)], tested in separate blocks: simultaneous intensity (SI), simultaneous unpleasantness (SU), retrospective intensity (RI), and retrospective unpleasantness (RU).

Each of these 4 conditions was tested in 2 separate blocks of 6 trials including 2 trials for each of the 3 stimulus duration (duration effect; pseudo-randomized within block) for a total of 8 blocks and 48 trials. Therefore, each stimulus was presented 4 times in each condition. We also investigated whether such perceptual and memory processes of the different dimensions of pain varied across individuals (subject effect).

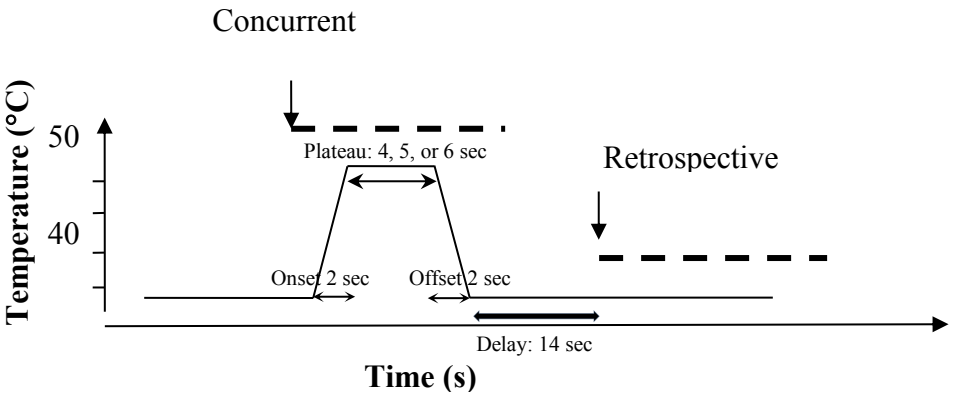

Figure 1. Temporal profile of the actual stimulus delivered consists of three phases: onset, plateau, and offset.
In separate trials, subjects rated the intensity or the unpleasantness of pain concurrently with the stimulus or after a 14sec delay after the offset of the stimulus. Dashed line indicates when concurrent and retrospective ratings are produced.

2.3. Data analysis

The analysis was designed to summarize the VAS time courses in order to investigate the following: (1) differences between retrospective and concurrent pain evaluations (memory effect), (2) differences in pain evaluations with regards to pain intensity or unpleasantness (pain dimension effect), (3) differences in pain evaluations with regards to duration of the stimulus (duration effect), and (4) inter-individual differences in pain evaluations (subject effect), as well as the various interactions among these effects.

All the VAS curves were realigned temporally to the onset of VAS responses (time 0), resampled at 64 ms, and smoothed using a moving average of 5 data points (320 ms). A classical psychophysical approach that is often used for the analysis of such a dataset is based on measuring various parameters from the continuous VAS curve (eg, area under the curve, maximum, time to maximum, maximum slope). We explored the data using such an approach as described in the Supplementary materials. A correlation analysis on these extracted measures is also reported in the Supplementary materials. This exploratory analysis motivated us to use PCA as our main analytic approach, to reduce the dimensionality of the data set, as explained below. All analyses were performed in Matlab 7.1.

2.3.1. Principal component analysis

Because there is a large number of correlated parameters that can be extracted from the VAS curves (Supplementary materials), it is difficult to decide how many parameters are needed to adequately describe the VAS profiles and which parameter should be prioritized.

PCA [1,50] permits analysis of complex multivariate data sets by reducing the dimensionality of the data to a few new independent variables that together explain most of the variability. Here, PCA was performed by entering each VAS curve as a single

multivariate observation, with each data point of the VAS profile entered as 1 measure. In order to have the same number of measures for each VAS profile, all trials were standardized to the lengthiest trial across subjects by entering the value 0 for all the data points that occurred after termination of the rating. The PCA was done across all trials from all subjects, irrespective of the 2 main experimental manipulations (memory × pain dimension). Because each time point is considered as a single variable in a temporal PCA analysis, and because the number of time points (variables) of the VAS curves is not the same for 8-, 9-, and 10-s data, we performed PCA separately for 8-, 9-, and 10-s data sets.

The PCA function in Matlab (princomp) returns 3 values: Coefficients, Scores, and Latent. Coefficients are the weights associated with the linear combinations of the original variables that generate the principal components, which is used to interpret the meaning of each component. Scores contain the coordinates of the original data in the new coordinate system defined by the principal components. Finally, Latent is used to assess the variance explained by each component.

In the PCA analysis, the mean VAS curve (across all trials, subjects, and conditions) is initially subtracted for the calculation of the score of each trial and for each component in PCA. The new data set, which corresponds to the transformation of each VAS curve into a single point in the space of components, is calculated as follows:

$$\text{VAS curve}_{\text{trial i}} = \text{score}_{ij} \times \text{comp}_i \qquad (j=1, 2, 3, \ldots, P) \quad (1)$$

Score and comp were used to create prototypical graphs in order to visualize the contribution of each component to the VAS time courses of each experimental condition. Analysis of variance (ANOVA) performed on score was used to contrast the experimental conditions with respect to the components extracted. Finally, score was used for clustering the VAS curves into different groups.

2.3.2. Prototypical graphs

In order to better understand what the components represent and how conditions vary according to those components, we reconstructed the VAS curves for each condition on the basis of the PCA output. We reconstructed the prototypical graphs according to Eq. (1), modified according to the following formulas:

Prototypical VAS $curve_k$=Grand mean + mean of $score_{k1}$×$comp_1$+ mean of $score_{k2}$ × $comp_2$ + mean of $score_{k3}$×$comp_3$

(k = conditions : SI, SU, RI, and RU) (2)

More generally,

Prototypical VAS $curve_k$ =Grand mean + mean of $score_{kj}$ × $comp_j$ (3)

Where k = conditions (SI, SU, RI, and RU) and j indicates component (1, 2, and 3). $Score_{kj}$ is the mean of all scores across trials and subjects for condition k (k = SI, SU, RI, and RU) and component j (j = 1, 2, and 3). The grand mean is included in the equation because the mean VAS curve (across all trials, subjects, and conditions) is initially subtracted for the calculation of the score of each trial and for each component in PCA.

2.3.3. Analysis of variance

After the PCA analysis, each trial was recoded on the basis of the corresponding score on each of the 3 components (ie, 1 value for each component and each trial). The

score associated with each trial was entered as an independent observation in the ANOVA.

Four main factors were studied in order to address 4 main questions. First, we examined how the dynamic evaluations of pain are modified in retrospective compared to simultaneous rating trials (memory effect). The second question examined whether the pain dimensions under study result in any differences in the subjects' evaluations (pain dimension effect) and whether the memory effect varies between pain dimensions (memory × pain dimension interaction). The third question involved probing the coding of temporal information by the (duration effect) and examining whether this temporal coding is adequately preserved in retrospective evaluations (memory × duration interaction). The fourth question tested whether there were differences between subjects regarding the aforementioned effects that might reflect individual differences in processes related to pain memory and pain dimensions (subject × memory × pain dimension).

2.3.4. Classification

In order to explore the differences between conditions, the results were further examined in the space of the principal components using standard classification techniques [33]. A discriminant analysis using a linear classifier that was based on the first 3 principal components was used to visualize and statistically confirm that the data belonging to the different conditions were grouped into different parts of the component's space.

In contrast to the ANOVA, which test the effect of each factor on each component separately (ie, univariate approach), the discriminant analysis allows for the separation of different levels of experimental manipulations by taking into account all the information provided by all 3 components rather than each component in isolation. This approach allows separating the data points belonging to each level of a given factor (eg, pain dimension: intensity, and unpleasantness) by trying to group all the trials of a given subject into different parts of the 3D component space using a linear surface (ie, the

discriminant function is a linear plane separating the transformed data points in the space of components 1, 2, and 3).

Because there are important individual differences confirmed by ANOVA, classification was performed for each subject and duration separately. Classification was done to test the separation of concurrent vs retrospective trials (effects of memory) and of intensity vs unpleasantness trials (effects of pain dimension). Specifically, we performed pairwise classification looking at the separation of intensity and unpleasantness, in concurrent (SI vs SU) and retrospective evaluations (RI vs RU). We also looked at the separation of concurrent and retrospective conditions in intensity (SI vs RI) and unpleasantness ratings (SU vs RU). We used the ‘‘leave one out’’ method for cross-validation, which simply ignores one trial in order to determine the discriminant function and calculate the misclassification rate for the trials left out iteratively for all the trials in each subject. After classification had been done, ANOVA was performed on the correct classification rates (ie, for each of the pairwise classification) to statistically compare (1) the discrimination between pain dimensions in the concurrent (SI vs SU) and the retrospective condition RI vs RU) and (2) the memory effect on intensity (SI vs RI) and unpleasantness condition (SU vs RU) across the 3 tested durations.

3. Results

The mean VAS profile per condition for each of the 10 subjects is depicted in Fig. 2.

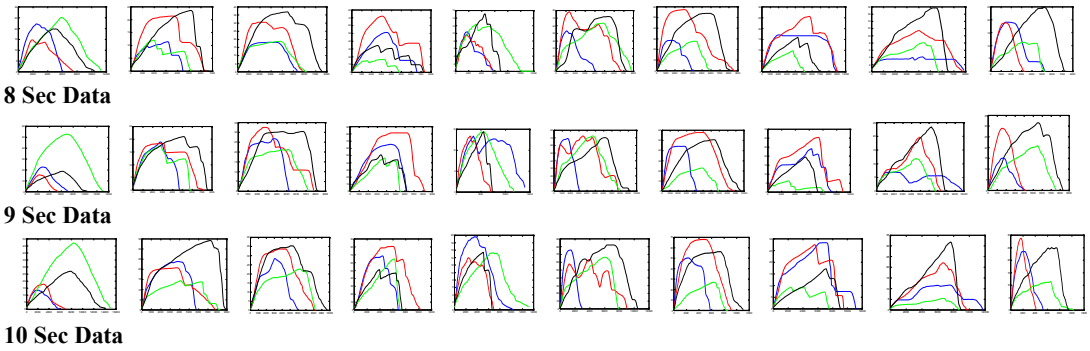

Figure 2. Mean VAS profiles for 8 sec, 9 sec and 10 sec trials in each subject (subject 1 to 10 from left to right) in the conditions simultaneous intensity (SI - black), simultaneous unpleasantness (SU - green), retrospective intensity (RI - red), and retrospective unpleasantness (RU - blue).
Note that the y-axis is scaled individually for better visualization

3.1 Principal component analysis

The PCA applied to the VAS profiles was performed separately for each of the stimulus durations of 8, 9, and 10 s across all trials and subjects. The analysis produced comparable components, suggesting variance structures that are consistent across those 3 durations. Fig. 3 illustrates the temporal profiles of the coefficients associated with the first 3 components that explained about 90% of the variance in the continuous ratings. The first component accounted for 60% to 67% of the total variance, the second 18% to 19%, the third 6% to 9%, and the fourth only 3% to 5%. Because much of the variance is explained by these 3 components, we considered only these components in follow-up analyses. The bar graphs in Fig. 4 illustrate the scores associated with each component across conditions and subjects (mean of the 4 trials per condition per subject). The

coefficient graphs (Fig. 3) can be examined in conjunction with the bar graphs of scores (Fig. 4) and the VAS profiles (Fig. 2) to better interpret the meaning of each component.

Qualitative examination of the temporal profile of the first component (Fig. 3) shows that it represents the general time course of the sensation, with the total time approximately matching the 3 durations tested. Component 2 shows deflections during the onset and offset phases of the stimulus which are separated by a time interval approximately matching the plateau duration. Thus, component 2 appears to capture variance in the pain perceived around the beginning and the end of the plateau. This component may reflect the magnitude of temporal summation during the plateau and/or a shift in the onset/offset slopes. On the basis of the more detailed examination of the curves, positive values for component 2 in Fig. 4, correspond to a low onset slope and late offset, with larger temporal summation (note that the coefficient graph associated with component 2 is negative at onset and positive at offset). In contrast, negative values in Fig. 4 correspond to a larger onset slope and earlier offset, with less temporal summation. For example, component 2 is positive in simultaneous intensity ratings and negative in retrospective intensity ratings in subjects 6, 7, and 10 (Fig. 4), reflecting a general shift of the curves to the left and a clear reduction in temporal summation effects in the retrospective rating profiles (Fig. 2). The fact that these effects (onset, offset, temporal summation) were captured by a single component implies that they were not independent in the present experimental context.

The third component has 2 maxima, marking approximately the beginning and end of plateau, and a minimum almost halfway through the plateau. This component may represent the variability observed in pain in the middle of the plateau as well as subtle fluctuations during the ascending and descending slopes of the profiles. Therefore, it captures more subtle aspects of the temporal profiles (ie, less than 10% of variance).

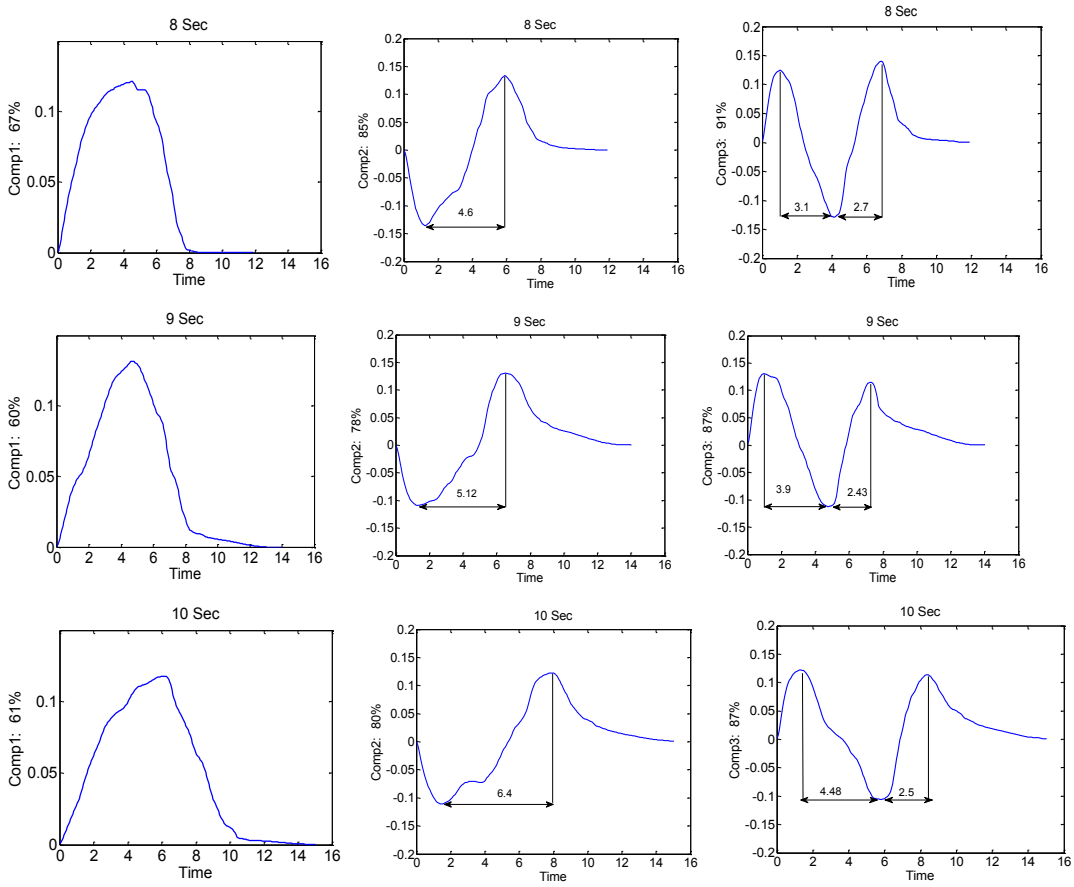

Figure 3. Coefficients associated with the first three components of the PCA (Comp1-3) across three durations (first row 8 sec data, second row 9 sec data, and third row 10 sec data).

Cumulative variance explained by the components is shown on the y axis; for example for the 8 sec data, component 1 explains 67% of total variance, component 1 and 2 together explain 85% of total variance, and finally component 1, 2 and 3 explain 91%. The first component clearly corresponds to the overall profile of the rating. The second component shows a first peak (min) at about 1.5 sec and a second peak (max.) after a delay that approximates the duration of the stimulus plateau (4, 5, and 6sec for the 8, 9 and 10sec stimulus duration, respectively). This component appears to code for differences between the onset and offset of the plateau and may correspond to the magnitude of the temporal summation of pain during the plateau. The third component also shows a first positive peak at about 1,5sec, and another one about 6, 7, and 8sec later, that might account for subtle variations at onset and offset. This third component also includes a unique peak (min) that accounts for variance during the stimulus plateau.

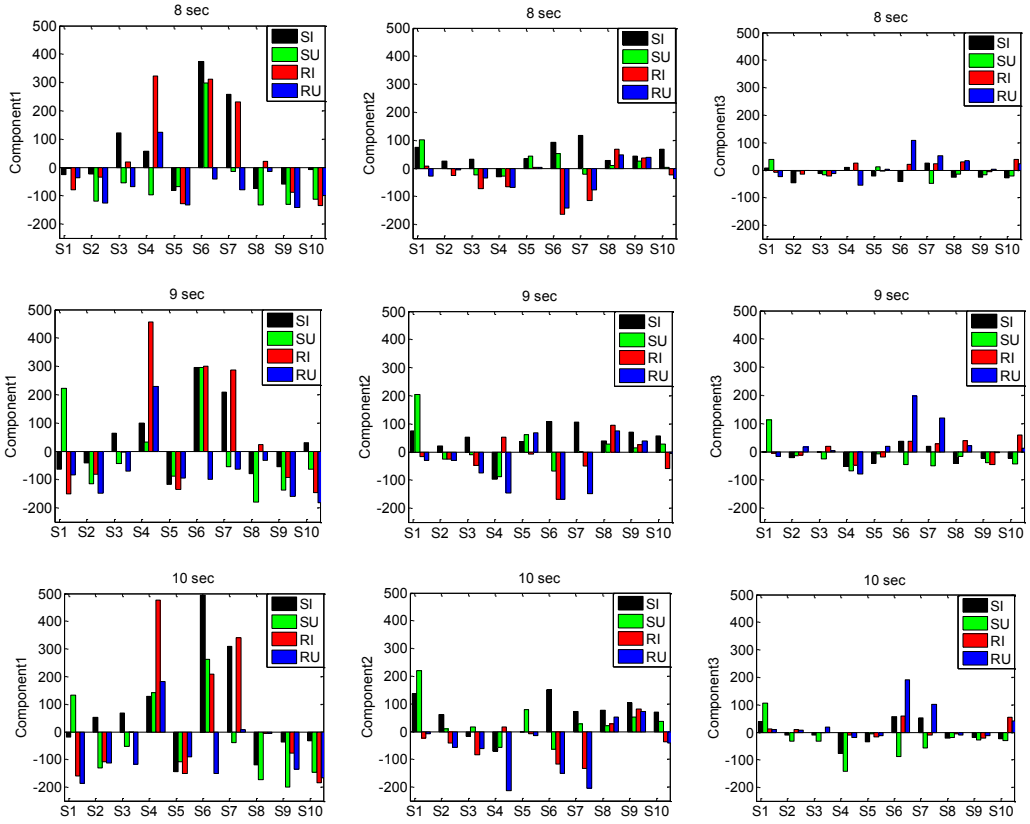

Figure 4. PCA outputs (Scores) for each individual across the four conditions (mean of 4 trials per condition) and across the three tested durations; first row 8 sec data, second row 9 sec data, and third row 10 sec data.
Left panel: Component1, Middle panel: Component2, and Right panel: Component3.

3.2. Prototypical graphs

The data were reconstructed separately for each condition with the use of only component 1, components 1 and 2, and components 1, 2, and 3 to illustrate the unique contribution of each component to each condition profile (Fig. 5). The resulting profiles for component 1 show that the ratings were generally lower for unpleasantness (SU and RU) than intensity (SI and RI) and for retrospective (RI and RU) than simultaneous (SI and SU) conditions. Adding the second component reveals the leftward shift in the temporal profiles (larger onset slope and earlier offset) in the retrospective (RI and RU) relative to the corresponding concurrent conditions (SI and SU, respectively). These

curves also show that this shift is accompanied by a general decrease in the slope during the period corresponding to the stimulus plateau. Adding component 3 to these profiles produced only subtle changes, consistent with the relatively small amount of variance captured by this component. However, it is interesting to note that these changes were more clearly apparent in unpleasantness ratings. This is consistent with the generally higher absolute scores observed for component 3 in unpleasantness ratings (compare amplitude of absolute scores for SU and RU vs SI and RI in Fig. 4). This suggests that unpleasantness ratings may include unique variance reflecting independent affective processes producing additional fluctuations.

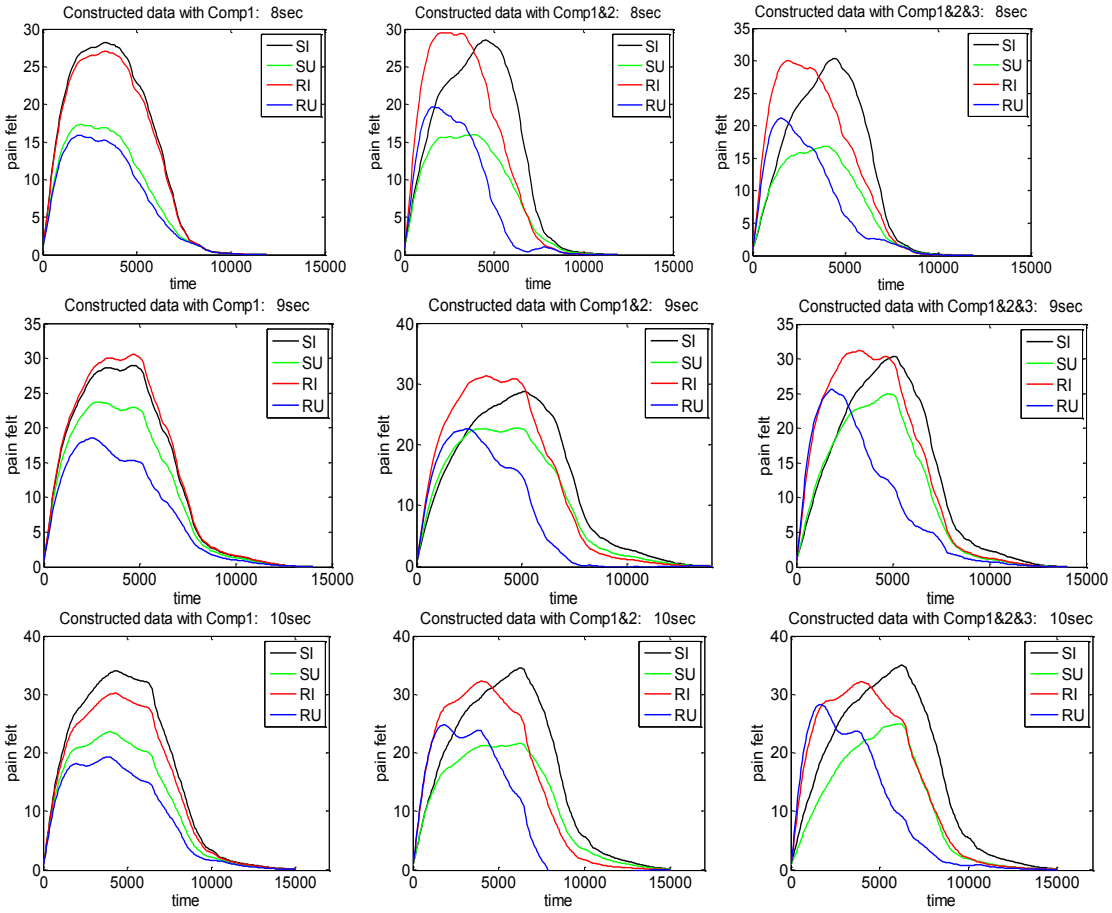

Figure 5. Reconstructed VAS curves for each condition (SI, SU, RI and RU) with the use of only component1, component1 and 2, and finally component 1, 2 and 3 (left to right).
Prototypic graphs illustrate the unique contribution of each component to each profile.

3.3. ANOVA on the components

The results of the ANOVAs on the components are summarized in Table 1. Detailed results of the ANOVAs are provided in Supplementary Table S1. ANOVA confirmed several main effects on the components; however, memory and pain dimensions interacted with the subject factor across all 3 components, while duration and subject interacted only for components 2 and 3. There was also a 3-way interaction of memory by pain dimension by subject across all 3 components. Contrast analyses on the main effect of memory reveal that mean PCA scores for component 1 are lower in the

retrospective condition, reflecting the overall lower pain reported in retrospective vs concurrent conditions. Component 2 shows a similar effect (lower in retrospective) reflecting larger onset slope, and earlier offset in the retrospective condition (Fig. 5). A reversed effect is found on component 3, suggesting that in the retrospective trials, subjects report more fluctuations in the middle of the plateau than they do in the concurrent trials or more high frequency variability between trials. Also for component 1, which shows a main effect of pain dimension, mean PCA scores for intensity have a higher value than unpleasantness. To further examine the 3-way interaction of subject by memory by pain dimension, a classification analysis in the space of components 1, 2, and 3 was performed.

Table 1. Significant main effects and interactions defined by ANOVA on the components 1-3.

	Results of ANOVA		
Independent Variable	***Main effects***	***2-Way Interactions***	***3-Way Interactions***
Comp1	Subj, Mem, Dim	Subj x Mem, Sub x Dim	Subj x Mem x Dim
Comp2	Subj, Mem	Subj x Mem, Sub x Dim, Subj x Dur, Mem x Dur, Dim x Dur	Subj x Mem x Dim, Subj x Mem x Dur
Comp3	Subj, Mem	Subj x Mem, Sub x Dim, Subj x Dur, Mem x Dim	Subj x Mem x Dim, Mem x Dim x Dur

ANOVA, analysis of variance; PCA, principal component analysis; Subj. subject; Dim, pain dimension (intensity and unpleasantness); Dur, stimulus duration (8, 9, or 10 sec); Mem, memory effect (retrospective vs. concurrent rating). Only significant effects are reported ($P<0.01$). Supplementary Table S2 provides detailed statistical results

3.4. Classification with discriminant analysis

Given the importance of individual differences in the ANOVA results, discriminant functions were computed separately for each subject to account for individual variability. An example for 1 subject is given in Fig. 6. (For better visualization, classification is shown in the 2D space of components 1 and 2 only.) The correct classification rate (mean ± SD) for the separation of pain dimension was significantly higher in concurrent ratings (0.78 ± 0.21) compared to retrospective ratings (0.62 ± 0.29) ($F(1) = 6.55$, $P = .013$). This demonstrates that the discrimination between

intensity and unpleasantness is largely lost in memory (chance = 50%). The correct classification rate for the separation between retrospective and concurrent ratings was comparable for intensity (0.79 ± 0.19) and unpleasantness (0.79 ± 0.24) ($F(1) = 0$, $P = .96$), consistent with a similar memory effect found across pain dimensions. There was no effect of or interaction with duration in these analyses (all P values >.05). This implies that discrimination (intensity vs unpleasantness or retrospective vs concurrent ratings) did not differ significantly across the 3 durations tested.

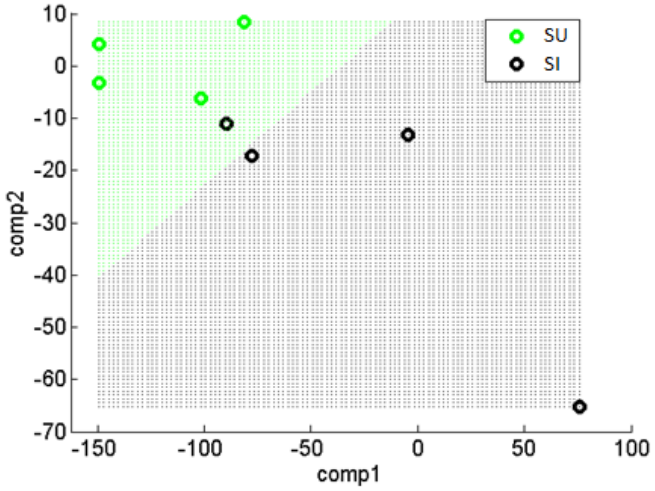

Figure 6. Classification of the two conditions (SI: simultaneous intensity and SU: simultaneous unpleasantness) in the space of component 1 and component 2 with a linear classifier (represented by the line separating the two shaded areas).
Here the function adequately classifies 7/8 points in the two-dimensional space.

4. Discussion

Consistent with some previous studies [6,17,19,31,37,38,47,48,55], our results provide further support for the vulnerability of retrospective pain reports to important memory distortions. These effects were found using both standard psychophysical measures (Supplementary materials) and dynamic PCA. Moreover, to our knowledge, this is the first study showing differentiation between pain dimensions in continuous

ratings. However, the discriminant analysis further confirmed that the 2 pain dimensions were better discriminated in the concurrent than the retrospective rating condition, emphasizing the loss of pain dimension-specific information in memory.

Importantly, results show important distortions in the coding, storage, and/or retrieval of dynamic sensory-affective information that vary significantly across individuals. Factors leading to such individual differences may be variously related to differences in immediate and working memory efficacy and capacity [20,29], differences in attention processes [7,61], differences in perceptual awareness or introspective ability [10,14,53], differences in temporal processing [9], and even differences in psychological factors like anxiety [4] or intellectual abilities [49,63], as well as individual differences in the subjective experience of pain [12,35,46]. Some of these factors (eg, anxiety) may also contribute to the main effect of memory, assuming they might differentially affect key processes distinguishing the concurrent and retrospective conditions (eg, anxiety during pain might differentially affect the accuracy of perceptual vs memory encoding).

Because the VAS time courses contained large amount of redundant information, we used PCA as our main analytic approach to reduce the dimensionality of the data set. Although our interpretations of the principal components extracted remain speculative, we propose that they might reflect some properties of the mental representation of ongoing changes in pain magnitude over time during both perceptual and retrospective trials. Our speculations are based on some theoretical accounts of short-term/working memory in other modalities that address 2 fundamental questions regarding the processing and recalling of dynamic information.

4.1. Time-magnitude processing

The first question is whether the temporal and magnitude properties of the pain experience (for intensity, unpleasantness, or both) are bound together or processed separately. It has been shown in the visual modality [11] that if color and shape are presented together (as opposed to separate features), they will be remembered with higher

accuracy. Likewise, we speculate that perceiving and recalling dynamic changes in pain requires the processing of the 2 properties (time and magnitude) as bound units of information rather than separate features. There is, however, some debate regarding the nature of object representations held in working memory; although some [39,62] postulate that information is held in memory in the form of bound objects rather than separate features, others [64] argue for parallel stores for independent features along with a separate mechanism for binding the information across these features. The same question applies to remembering the temporal dynamics of pain experiences. Does our memory system also maintain the percept of the pain magnitude at a given time in bound units? Although a definite answer to these questions is beyond the scope of the present study, on the basis of our PCA results, we hypothesize that this might be the case.

The second question is whether subjects try to remember a group of discrete information such as maximum pain felt and maximum changes in pain, or whether they try to form some more abstract representations that enable them to encode and maintain the temporal dynamics of the experience. This is a fundamental question relevant to recalling the temporal dynamics of any sensation. Do we memorize each and every change in sensation throughout time, or do we integrate, through a process of binding, the major changes that represent certain characteristics of dynamic profiles into 1 unit in memory? Although PCA cannot directly determine the processes involved in the perception and memory of pain over time, we speculate that the 3 PCA components might reflect the unified 2-dimensional representations (ie, time magnitude) that are formed by binding the various elements of temporal profiles into a few perceptual features. These 3 main components may be interpreted within the general theoretical framework of chunking of information [25,57], which generally means grouping of related items into a chunk, with elements of 1 chunk having weak associations with elements of another chunk [25]. In fact, the principle applied in PCA is resonant to the notion of chunking because PCA uses the redundancy of information to reconstruct a few components that explain most of the variance of the data. Although subjects may take advantage, perceptually, of the relation among the parameters of the dynamic experience

and try to remember as much information as possible, it seems more plausible that they formed global representations combining discrete parameters and try to process these as chunks of information in order to aid in the construction of relevant memories.

4.2. Memory capacity limits and temporal segmentation of dynamic information

In this context, one would also expect some limits on the manageable amounts of relevant information. Indeed, studies on immediate and working memory argue that there are some limits on how much can be kept in mind at once [3,13,24,40,41]. This limit can be quantified in terms of chunks of information. In a famous inspiring article, Miller [41] proposed the capacity limit of short-term memory to be 7 ± 2 items. More recent studies have proposed a smaller estimate of about 4 items [3,24,40]. Likewise, the capacity limit of working memory has been estimated by Cowan [13] to be 4 ± 1. Moreover, studies investigating the limits of human information processing by manipulating the number of variables that should be processed together came up with a maximum number of 4 [26]. The results of the PCA suggests that 3 components explained most of the variance in the rating profiles across the concurrent and retrospective conditions, consistent with such chunking processes and with the limitations found for other types of information processed in short-term and working memory.

But how and through what mechanism do these chunks of information emerge? A theory that might be most relevant to this question is called event segmentation theory [68], which proposes that continuous flux of information is spontaneously segmented into meaningful chunks of information. According to this theory, event segmentation is a mechanism inherent to the organization of our perceptual systems, which occurs as a side effect of trying to anticipate the upcoming information and facilitates the perception and memory of complex dynamic input [60]. The theory explains that we have mental representations of what is happening called the event model, which is fed by both sensory input (bottom up) as well as knowledge structure (top down) based on previously encountered events. The bottom-up system involves the detection of salient information,

while the top-down system drives the prediction about what will happen next. At the time of increase in the prediction error (ie, divergence from expectations), our event models would be updated. Those key moments are perceived as event boundaries [34,68,70,72]. Moreover, the theory proposes that segmentation occurs simultaneously on multiple time scales in a hierarchical fashion, which means that while we segment ongoing information into small temporal units (fine grained), we also segment it into large units (coarse grained) [68], and we automatically group the fine-grained segments into coarse-grained segments [45,68]. There is abundant evidence [27,44] for such hierarchical segmentation from studies on higher-order executive processing, action planning [36], and procedural learning [71], and some studies suggest that this ability is functional in infants [58,65] and elaborates throughout life [5,43]. Moreover, a few studies [59,66,67,69] looking at segmentation of movies or animation of simple geometric objects have shown that low-level perceptual features play an important role in segmentation, especially at fine grain.

On the basis of these theoretical models, we speculate that the same principles may be applied to perceiving changes in pain overtime. We hypothesize that the 3 principal components identified by PCA may represent the outcome of the temporal segmentation. The first component would correspond to the coarse-grained segmentation, which, on the basis of the knowledge learned during familiarization trials and consolidated throughout the experiment, depicts the global structure of the experience consisting of a painful sensation rising up, reaching its maximum, and then fading out. The second component is a fine-grained segmentation marked by the 2 major event boundaries, the beginning and end of plateau, while the third component reflects the perception of additional changes in pain (eg, in the middle of the fine-grained segment).

To conclude, the question “How do we remember ongoing changes in pain magnitude over several seconds?,” which inspired the study, might be answered from the perspective of event segmentation. We hypothesize that in the retrospective trials, subjects remember the global picture of the experience and simultaneously try to remember, to various degrees, fine-grained segments embedded in the coarse-grained representation. Following this perspective, the results demonstrate important memory

distortions affecting both coarse and fine-grained information as well as a loss of discrimination between pain dimensions (intensity vs unpleasantness). A better understanding of these processes has major implications for pain assessment, which typically relies on the report of the pain felt in the previous seconds, minutes, hours, or days.

Conflict of interest statement

The authors report no conflict of interest.

Acknowledgments

We thank Leo Tenbokum for his technical help during data acquisition. This study was funded by the Natural Science and Engineering Research Council of Canada (NSERC; #341472-07).

References:

[1] Abdi H, Williams LJ. Principal component analysis. Wiley Interdiscip Rev Comput Stat 2010;2: 433-459.

[2] Babul N, Darke AC, Johnson DH, Charron-Vincent K. Using memory for pain in analgesic research. Ann Pharmacother 1993;27: 9-12.

[3] Baddeley A. The magical number seven: still magic after all these years? Psychol Rev. 1994;101: 353-356.

[4] Basten U, Stelzel C, Fiebach CJ. Trait anxiety and the neural efficiency of manipulation in working memory. Cogn Affect Behav Neurosci. 2012;12: 571-588.

[5] Bauer PJ, Mandler JM. One thing follows another: Effects of temporal structure on 1- to 2-year-olds' recall of events. Dev. Psychol. 1989;25: 197-206.

[6] Beese A, Morley S. Memory for acute pain experience is specifically inaccurate but generally reliable. Pain 1993;53: 183-189.

[7] Bredemeier K, Simons DJ. Working memory and inattentional blindness. Psychon Bull Rev. 2012;19: 239-244.

[8] Breme K, Altmeppen J, Taeger K. How reliable is our memory for acute postoperative pain. Der Anaesthesist 2000;49: 18-24.

[9] Broadway JM, Engle RW. Individual differences in working memory capacity and temporal discrimination. PloS one 2011;6:e25422.

[10] Buda M, Fornito A, Bergström ZM, Simons JS. A Specific Brain Structural Basis for Individual Differences in Reality Monitoring. J Neurosci. 2011;31: 14308-14313.

[11] Ceraso J. Unit Formation in Perception and Memory. In: HB Gordon, editor. Psychology of Learning and Motivation, Vol 19. Academic Press, 1985. pp. 179-210.

[12] Coghill RC. Individual differences in the subjective experience of pain: new insights into mechanisms and models. Headache 2010;50: 1531-1535.

[13] Cowan N. The Magical Mystery Four: How is Working Memory Capacity Limited, and Why? Curr Dir Psychol Sci. 2010;19: 51-57.

[14] Cullen J, Buda M, Darby G, Simons JS. Time-travelling and mind-travelling: examining individual differences in self-projection. Psychiatr Danub. 2011;23: 182-186.

[15] Davis KD, Pope GE. Noxious cold evokes multiple sensations with distinct time courses. Pain 2002;98: 179-185.

[16] Davis KD, Pope GE, Crawley AP, Mikulis DJ. Neural correlates of prickle sensation: a percept-related fMRI study. Nat Neurosci. 2002;5: 1121-1122.

[17] Eich E, Reeves JL, Jaeger B, Graff-Radford SB. Memory for pain: relation between past and present pain intensity. Pain 1985;23: 375-380.

[18] Erskine A, Morley S, Pearce S. Memory for pain: a review. Pain 1990;41: 255-265.

[19] Everts B, Karlson B, Wahrborg P, Abdon N, Herlitz J, Hedner T. Pain recollection after chest pain of cardiac origin. Cardiology 1999;92: 115-120.

[20] Fandakova Y, Shing YL, Lindenberger U. Heterogeneity in memory training improvement among older adults: a latent class analysis. Memory. 2012;20: 554-567.

[21] Foss JM, Apkarian AV, Chialvo DR. Dynamics of pain: fractal dimension of temporal variability of spontaneous pain differentiates between pain States. J Neurophysiol. 2006;95:730-736.

[22] Gedney JJ, Logan H. Memory for stress-associated acute pain. J Pain. 2004;5: 83-91.

[23] Gedney JJ, Logan H, Baron RS. Predictors of short-term and long-term memory of sensory and affective dimensions of pain. J Pain. 2003;4: 47-55.

[24] Gobet F, Clarkson G. Chunks in expert memory: evidence for the magical number four ... or is it two? Memory. 2004;12: 732-747.

[25] Gobet F, Lane PC, Croker S, Cheng PC, Jones G, Oliver I, Pine JM. Chunking mechanisms in human learning. Trends Cogn Sci. 2001;5: 236-243.

[26] Halford GS, Baker R, McCredden JE, Bain JD. How many variables can humans process? Psychol Sci. 2005;16: 70-76.

[27] Hard BM, Lozano SC, Tversky B. Hierarchical encoding of behavior: translating perception into action. J Exp Psychol Gen. 2006;135: 588-608.

[28] Hunter M, Philips C, Rachman S. Memory for pain. Pain 1979;6: 35-46.

[29] Jarrold C, Towse JN. Individual differences in working memory. Neuroscience 2006;139: 39-50.

[30] Jensen MP, Wang W, Potts SL, Gould EM. Reliability and validity of individual and composite recall pain measures in patients with cancer. Pain Med. 2012;13: 1284-1291.

[31] Kent G. Memory of dental pain. Pain 1985;21: 187-194.

[32] Koyama Y, Koyama T, Kroncke AP, Coghill RC. Effects of stimulus duration on heat induced pain: the relationship between real-time and post-stimulus pain ratings. Pain 2004;107: 256-266.

[33] Krzanowski WJ. Principles of multivariate analysis: a user's perspective: Oxford University Press, Inc., 1988.

[34] Kurby CA, Zacks JM. Segmentation in the perception and memory of events. Trends Cogn Sci. 2008;12: 72-79.

[35] Larkin M. Individual differences in pain perception confirmed. Lancet Neurol. 2003;2: 454.

[36] Lichtenstein EH, Brewer WF. Memory for goal-directed events. Cogn Psychol. 1980;12: 412-445.

[37] Linton SJ. Memory for chronic pain intensity: correlates of accuracy. Percept Mot Skills. 1991;72: 1091-1095.

[38] Linton SJ, Melin L. The accuracy of remembering chronic pain. Pain 1982;13: 281-285.

[39] Luck SJ, Vogel EK. The capacity of visual working memory for features and conjunctions. Nature 1997;390: 279-281.

[40] Mathy F, Feldman J. What's magic about magic numbers? Chunking and data compression in short-term memory. Cognition 2012;122: 346-362.

[41] Miller GA. The magical number seven plus or minus two: some limits on our capacity for processing information. Psychol Rev. 1956;63: 81-97.

[42] Miron D, Duncan GH, Bushnell MC. Effects of attention on the intensity and unpleasantness of thermal pain. Pain 1989;39: 345-352.

[43] Nelson K. Event knowledge : structure and function in development. Hillsdale, N.J. : L. Erlbaum Associates, 1986.

[44] Newell A, Simon HA. Human problem solving: Prentice-Hall, 1972.

[45] Newtson D, Engquist G. The perceptual organization of ongoing behavior. J Exp Soc Psychol. 1976;12: 436-450.

[46] Nielsen CS, Stubhaug A, Price DD, Vassend O, Czajkowski N, Harris JR. Individual differences in pain sensitivity: genetic and environmental contributions. Pain 2008;136: 21-29.

[47] Niven CA, Brodie EE. Memory for labor pain: context and quality. Pain 1996;64: 387-392.

[48] Norvell KT, Gaston-Johansson F, Fridh G. Remembrance of labor pain: how valid are retrospective pain measurements? Pain 1987;31: 77-86.

[49] Numminen H, Service E, Ahonen T, Korhonen T, Tolvanen A, Patja K, Ruoppila I. Working memory structure and intellectual disability. J Intellect Disabil Res. 2000;44: 579-590.

[50] Pearson K. On lines and planes of closest fit to systems of points in space. Philosophical Magazine 1901;2: 559-572.

[51] Price DD. Psychological and neural mechanisms of the affective dimension of pain. Science 2000;288: 1769-1772.

[52] Price DD, Harkins SW, Baker C. Sensory-affective relationships among different types of clinical and experimental pain. Pain 1987;28: 297-307.

[53] Pun C, Emrich SM, Wilson KE, Stergiopoulos E, Ferber S. In and out of consciousness: sustained electrophysiological activity reflects individual differences in perceptual awareness. Psychon Bull Rev 2012;19: 429-435.

[54] Rainville P, Carrier B, Hofbauer RK, Bushnell MC, Duncan GH. Dissociation of sensory and affective dimensions of pain using hypnotic modulation. Pain 1999;82: 159-171.

[55] Rainville P, Doucet JC, Fortin MC, Duncan GH. Rapid deterioration of pain sensory-discriminative information in short-term memory. Pain 2004;110: 605-615.

[56] Rainville P, Feine JS, Bushnell MC, Duncan GH. A psychophysical comparison of sensory and affective responses to four modalities of experimental pain. Somatosens Mot Res. 1992;9: 265-277.

[57] Simon HA. How Big Is a Chunk?: By combining data from several experiments, a basic human memory unit can be identified and measured. Science 1974;183: 482-488.

[58] Sommerville JA, Woodward AL. Pulling out the intentional structure of action: the relation between action processing and action production in infancy. Cognition 2005;95: 1-30.

[59] Speer N, Swallow K, Zacks J. Activation of human motion processing areas during event perception. Cogn Affect Behav Neurosci. 2003;3: 335-345.

[60] Swallow KM, Zacks JM, Abrams RA. Event boundaries in perception affect memory encoding and updating. J Exp Psychol Gen. 2009;138: 236-257.

[61] Unsworth N, McMillan BD, Brewer GA, Spillers GJ. Everyday attention failures: An individual differences investigation. J Exp Psychol Learn Mem Cogn. 2012;38: 1765-1772.

[62] Vogel EK, Woodman GF, Luck SJ. Storage of features, conjunctions and objects in visual working memory. J Exp Psychol Hum Percept Perform. 2001;27: 92-114.

[63] Was CA, Dunlosky J, Bailey H, Rawson KA. The unique contributions of the facilitation of procedural memory and working memory to individual differences in intelligence. Acta Psychol. 2012;139: 425-433.

[64] Wheeler ME, Treisman AM. Binding in short-term visual memory. J Exp Psychol Gen. 2002;131: 48-64.

[65] Wynn K. Infants' Individuation and Enumeration of Actions. Psychol Sci. 1996;7: 164-169.

[66] Zacks JM. Using movement and intentions to understand simple events. Cogn Sci. 2004;28: 979-1008.

[67] Zacks JM, Braver TS, Sheridan MA, Donaldson DI, Snyder AZ, Ollinger JM, Buckner RL, Raichle ME. Human brain activity time-locked to perceptual event boundaries. Nat Neurosci. 2001;4: 651-655.

[68] Zacks JM, Speer NK, Swallow KM, Braver TS, Reynolds JR. Event perception: a mind-brain perspective. Psychol Bull. 2007;133: 273-293.

[69] Zacks JM, Swallow KM, Vettel JM, McAvoy MP. Visual motion and the neural correlates of event perception. Brain Res. 2006;1076: 150-162.

[70] Zacks JM, Tversky B. Event structure in perception and conception. Psychol Bull. 2001;127: 3-21.

[71] Zacks JM, Tversky B. Structuring information interfaces for procedural learning. J Exp Psychol Appl. 2003;9: 88-100.

[72] Zacks JM, Tversky B, Iyer G. Perceiving, remembering, and communicating structure in events. J Exp Psychol Gen. 2001;130: 29-58.

Supplementary material

S.1. Methods

S.1.1. Classical psychophysical analysis

In addition to the principal component analysis applied to the continuous VAS-profiles, a classical psychophysical approach was implemented by extracting several parameters from the VAS curves, and examining the effect of the independent variables. A typical VAS curve along with its derivative is shown in Fig. S1.

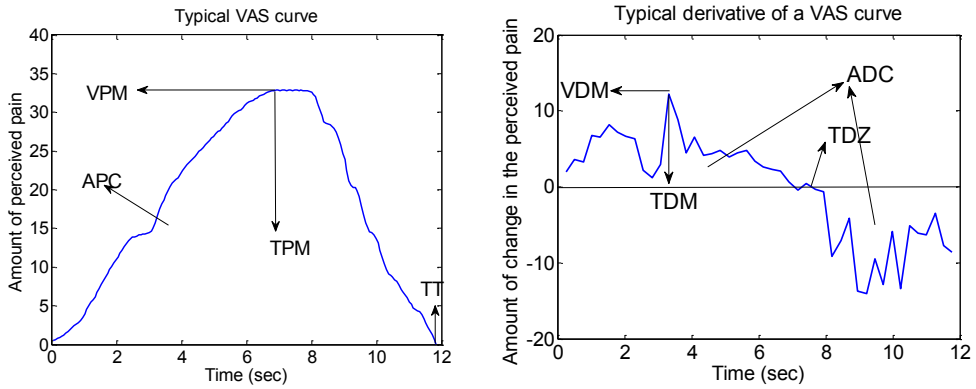

Figure S1. Typical raw time course of continuous e-VAS ratings (left panel) and its derivative (right panel) showing some of the parameters extracted.

Ten measures were extracted on a trial-by-trial basis from the VAS curves and respective derivatives as follow:

1) ***APC:*** *Area* under the VAS *Profile Curves* (Total pain felt).
2) ***VPM:*** *Value* of VAS *Profile* at *Maximum* (Maximum pain felt).
3) ***TPM:*** *Time* that *Profiles* reach their *Maximum*.
4) ***TT:*** *Total Time*.

5) ***ADC:*** *Area* under the rectified (absolute vale) *Derivative Curve* (Total change in slope).
6) ***VDM:*** *Value* of *Derivative* of VAS at *Maximum* (Value of maximum change in slope).
7) ***TDM:*** *Time* that *Derivative* of VAS profiles reach their *Maximum* (Time of Maximum change in slope).
8) ***TDZ:*** Last *Time* that *Derivative* of profiles cross *Zero* which corresponds to the beginning of the decreasing phase (sensation offset).
9) ***TPM-TDM:*** Time interval from the maximum slope to the peak pain (late part or decelerating part of the ascending phase)
10) ***TPM-TDM/TT:*** Time interval from the late part of the ascending phase relative to perceived total time.

The analysis consisted of 1) ANOVA on each of these extracted parameters to assess the effect of experimental conditions, and 2) Correlation analysis looking at the correlation among the extracted parameters.

S.2. Results

S.2.1. ANOVA results

The results of the ANOVA on Memory (2) X Pain Dimension (2) X Duration (3) X Subject (10), performed on each extracted parameter, are summarized in Table S1. Main effects of all 4 factors were found on most dependent variables. Stimuli of longer durations were perceived consistently longer as confirmed by the significant main effect of duration on most of the dependent variables extracted. More specifically, the maximum of the VAS profile was significantly higher for stimuli of longer duration, consistent with the notion of temporal summation.

Importantly, the main effect of Memory implies a significant distortion of memory with respect to several perceptual parameters, consistent with previous studies questioning the accuracy of pain recall [6,17,19,31,37,38,47,48,55]. The main effect of Pain Dimension indicates that the differentiation between the two pain dimensions found in previous studies [52,54,56] using static ratings is replicated in dynamic ratings. The main effect of Duration confirmed that subjects adequately discriminated the 1-sec difference between the three stimuli while the main effect of Subject indicates reliable individual differences in the temporal profiles. However, these main effects were also modulated in several two- or three-way interactions.

Memory and Pain Dimension interacted as a result of a memory-related reduction or loss of the distinction between pain intensity and unpleasantness on several dependent variables in the retrospective ratings. Moreover two-way interaction terms of 'Subject × Memory' and 'Subject × Pain Dimension', indicate important individual differences underlying the memory processes as well as the processes involved in distinguishing sensory and affective dimensions of pain. Memory also interacted with Pain Dimension as part of a three-way interaction including the Subject factor, thereby suggesting that the differential coding of sensory and affective information in memory varied significantly across subjects. Altogether these interaction effects imply important memory distortions at the group level, although they are not necessarily found systematically in all subjects; thus, no simple corrections can be applied to prevent misinterpreting individual retrospective reports of pain.

		Results of ANOVA																					
	Dependent variables	**APC**			**VPM**			**TPM**			**TT**			**ADC**			**VDM**			**TDM**			**TDZ**			**TPM-TDM**			**(TPM-TDM)./TT**		
		df	F	P	df	F	P	df	F	P	df	F	P	df	F	P	df	F	P	df	F	P	df	F	P	df	F	P	df	F	P
Main effects	**Subj**	9	80.08	0.00*	9	181.18	0.00*	9	14.11	0.00*	9	20.29	0.00*	9	140.14	0.00*	9	113.43	0.00*	9	9.33	0.00*	9	18.63	0.00*	9	5.94	0.00*	9	7.34	0.00*
	Mem	1	4.03	0.05	1	12.61	0.00*	1	289.12	0.00*	1	184.62	0.00*	1	5.71	0.02	1	99.59	0.00*	1	27.80	0.00*	1	246.49	0.00*	1	101.21	0.00*	1	39.40	0.00*
	Dim	1	92.14	0.00*	1	69.08	0.00*	1	41.95	0.00*	1	41.00	0.00*	1	114.5	0.00*	1	3.82	0.05	1	9.97	0.00*	1	52.89	0.00*	1	9.20	0.00*	1	0.03	0.85
	Dur	2	39.00	0.00*	2	18.64	0.00*	2	53.12	0.00*	2	77.71	0.00*	2	17.81	0.00*	2	2.03	0.13	2	13.26	0.00*	2	74.03	0.00*	2	11.63	0.00*	2	0.26	0.77
2-Way Interactions	**Subj×Mem**	9	25.86	0.00*	9	8.47	0.00*	9	23.02	0.00*	9	44.58	0.00*	9	6.83	0.00*	9	13.87	0.00*	9	2.03	0.04	9	34.60	0.00*	9	13.93	0.00*	9	3.04	0.00*
	Subj×Dim	9	20.92	0.00*	9	8.90	0.00*	9	4.89	0.00*	9	18.62	0.00*	9	13.91	0.00*	9	1.05	0.40	9	5.07	0.00*	9	8.02	0.00*	9	4.57	0.00*	9	1.75	0.08
	Subj×Dur	18	1.70	0.04	18	0.88	0.60	18	1.34	0.16	18	1.27	0.20	18	1.12	0.33	18	0.43	0.98	18	4.54	0.00*	18	1.24	0.23	18	1.63	0.05	18	1.86	0.02
	Mem×Dim	1	2.19	0.14	1	0.07	0.80	1	0.03	0.86	1	0.80	0.37	1	1.55	0.21	1	0.31	0.58	1	0.35	0.56	1	0.41	0.52	1	0.07	0.79	1	0.31	0.58
	Mem×Dur	2	1.01	0.36	2	0.16	0.86	2	7.83	0.00*	2	8.38	0.00*	2	0.42	0.66	2	1.65	0.19	2	0.73	0.48	2	10.35	0.00*	2	5.62	0.00*	2	1.02	0.36
	Dim×Dur	2	1.77	0.17	2	2.85	0.06	2	0.10	0.90	2	0.61	0.55	2	1.31	0.27	2	1.89	0.15	2	1.98	0.14	2	0.00	1.00	2	0.79	0.46	2	0.51	0.60
3-Way Interactions	**Subj×Mem×Dim**	9	4.81	0.00*	9	2.68	0.00*	9	2.13	0.03	9	4.37	0.00*	9	4.47	0.00*	9	0.90	0.52	9	3.85	0.00*	9	3.87	0.00*	9	2.10	0.03	9	2.74	0.00*
	Subj×Mem×Dur	18	1.60	0.06	18	1.26	0.21	18	1.11	0.34	18	1.36	0.15	18	1.12	0.33	18	0.71	0.81	18	1.14	0.31	18	1.57	0.06	18	0.38	0.99	18	0.44	0.98
	Subj×Dim×Dur	18	0.84	0.66	18	0.89	0.59	18	0.49	0.96	18	1.41	0.12	18	1.05	0.40	18	0.55	0.93	18	1.74	0.03	18	0.60	0.90	18	0.78	0.73	18	1.06	0.39
	Mem×Dim×Dur	2	1.19	0.30	2	0.96	0.38	2	2.16	0.12	2	0.77	0.46	2	1.50	0.22	2	4.01	0.02	2	1.46	0.23	2	1.39	0.25	2	0.38	0.68	2	0.21	0.81
4-Way Interactions	**Subj×Mem×Dim×Dur**	18	1.08	0.37	18	0.72	0.79	18	0.57	0.92	18	0.84	0.66	18	0.81	0.69	18	1.00	0.46	18	1.71	0.04	18	1	0.46	18	0.45	0.97	18	1.02	0.43

Table S1. 4-Way ANOVA results on the extracted parameters from VAS curves (significant results with p=<0.01 are highlighted).
Dependant variable in the firt row of the Table are defined in section 2.4.1. For each dependent variable, degrees of freedom (df), F value (F), and Pvalue (P) for each of the main effects and interaction terms are reported. Subj: Subject, Dim: Pain Dimension (intensity and unpleasantness), Dur: stimulus Duration (8, 9, or 10s), Mem: Memory effect (retrospective vs concurent rating).

		Results of ANOVA								
	Inependent variables	**Comp1**			**Comp2**			**Comp3**		
		df	F	P	df	F	P	df	F	P
Main effects	**Subj**	9	87.17	0.00*	9	5.29	0.00*	9	15.32	0.00*
	Mem	1	9.46	0.00*	1	22.12	0.00*	1	63.03	0.00*
	Dim	1	130.88	0.00*	1	4.43	0.04	1	1.34	0.25
	Dur	2	0.01	0.99	2	0.00	1.00	2	0.01	0.99
2-Way Interactions	**Subj×Mem**	9	26.29	0.00*	9	2.64	0.01*	9	12.68	0.00*
	Subj×Dim	9	19.56	0.00*	9	3.15	0.00*	9	2.86	0.00*
	Subj×Dur	18	1.68	0.04	18	8.23	0.00*	18	2.08	0.01*
	Mem×Dim	1	2.97	0.09	1	0.76	0.38	1	10.66	0.00*
	Mem×Dur	2	0.92	0.40	2	58.21	0.00*	2	1.38	0.25
	Dim×Dur	2	0.80	0.45	2	4.67	0.01*	2	0.71	0.49
3-Way Interactions	**Subj×Mem×Dim**	9	5.18	0.00*	9	2.76	0.00*	9	11.20	0.00*
	Subj×Mem×Dur	18	1.26	0.21	18	6.52	0.00*	18	1.40	0.13
	Subj×Dim×Dur	18	0.54	0.94	18	1.25	0.22	18	0.65	0.86
	Mem×Dim×Dur	2	1.42	0.24	2	1.14	0.32	2	4.41	0.01*
4-Way Interactions	**Subj×Mem×Dim×Dur**	18	0.78	0.72	18	1.64	0.05	18	1.13	0.32

Table S2. 4-Way ANOVA results on the components (Comp1-3) obtained from the PCA (significant results with p=<0.01 are highlighted).
For each component, degrees of freedom (df), F value (F), and Pvalue (P) for each of the main effects and interaction terms are reported. Subj: Subject, Dim: Pain Dimension (intensity and unpleasantness), Dur: stimulus Duration (8, 9, or 10s), Mem: Memory effect (retrospective vs concurent rating).

A significant interaction of Memory by Duration was also found on several temporal parameters and can be visualized in the bar graphs in Fig. S2. In the concurrent condition the responses increased with stimulus duration from 8 to 9 and 10 sec, consistent with an accurate perceptual discrimination. This Duration effect was generally weaker or absent in the retrospective conditions. Furthermore, as the bar graphs indicate,

most subjects' underestimated temporal parameters (TT and TPM) in the retrospective compared to the simultaneous condition (Memory effect), while two subjects showed the opposite pattern (subjects 4 and 8). This highlights a general underestimation of duration and a loss of discriminative temporal information with potentially important individual differences in these memory-related time distortions.

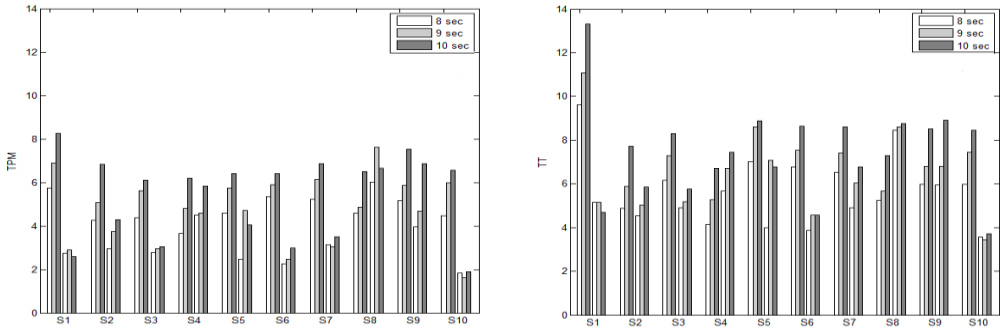

Figure S2. Effects of memory and stimulus duration (8-9-10s) on the time to maximal pain (TPM, left panel) and total time (TT, right panel).
For each subject (S1-S10), the first three bars represent the concurrent condition followed by another three bars representing the retrospective conditions for each of the three stimulus durations coded with different shades of grey (8, 9 and 10 sec). The time to maximal pain and total time generally increased with the duration (8-9-10s) of the stimulus (Main effect of Duration) while retrospective ratings underestimated perceptual duration in most subjects (Main effect of Memory). The temporal coding was partly or completely lost in most subjects in the retrospective condition (Memory X Duration). However, this effect interacted with Subject, suggesting significant variations in these effects between participants.

S.2.2. Correlation analysis

Correlation analysis over the parameters extracted is described in Table S3. This corollary analysis revealed that many of the extracted parameters are highly redundant with each other. This implies that several variables are potentially reflecting partly the same process that is governing the subject's perceptual reports and that some unique features may have been overlooked if the appropriate measure has not been included in this set of dependent variables. Correlation analysis motivated us to use PCA as our main

analytic approach, in order to get rid of the problem of redundancy among extracted parameters as well as reducing the dimensionality of the dataset.

	TDM	TPM	TDZ	TT	VDM	VPM	APC	TPM-TDM	ADC	(TPM-TDM)./TT
TDM	1.00	0.36	0.34	0.28	-0.16	0.04	0.07	-0.31	0.05	-0.57
TPM	0.36	1.00	0.92	0.83	-0.27	0.08	0.36	0.77	0.09	0.41
TDZ	0.34	0.92	1.00	0.89	-0.20	0.10	0.42	0.71	0.15	0.28
TT	0.28	0.83	0.89	1.00	-0.19	0.11	0.48	0.65	0.16	0.13
VDM	-0.16	-0.27	-0.20	-0.19	1.00	0.79	0.55	-0.17	0.77	-0.10
VPM	0.04	0.08	0.10	0.11	0.79	1.00	0.86	0.05	0.96	-0.02
APC	0.07	0.36	0.42	0.48	0.55	0.86	1.00	0.32	0.85	0.06
TPM-TDM	-0.31	0.77	0.71	0.65	-0.17	0.05	0.32	1.00	0.06	0.80
ADC	0.05	0.09	0.15	0.16	0.77	0.96	0.85	0.06	1.00	-0.04
(TPM-TDM)./TT	-0.57	0.41	0.28	0.13	-0.10	-0.02	0.06	0.80	-0.04	1.00

Table S3. Linear correlation analysis results (Pearson-r) on the extracted parameters (significant results with r=>0.5 are highlighted).

Article 2: The delayed reproduction of long time intervals defined by innocuous thermal sensation

Title: The delayed reproduction of long time intervals defined by innocuous thermal sensation

Authors:
Mina Khoshnejad[1, 3, 4]
Kristina Martinu Aurousseau[4]
Simon Grondin[5]
Pierre Rainville[2,3,4]

Affiliations:
Department of (1) neuroscience and (2) stomatology, (3) Groupe de recherche sur le système nerveux central (GRSNC), Centre de recherche en neuropsychologie et cognition (CERNEC), (4) Centre de recherche de l'Institut universitaire de gériatrie de Montréal, Université de Montréal, Montréal, Québec, Canada, and (5) École de psychologie, Université Laval, Québec, Canada.

Corresponding author:

Mina Khoshnejad

E-mail: mina.khoshnejad@umontreal.ca

Publication status:
Manuscript published in *Experimental Brain Research*, vol. 234, issue 4, 2016.

Authors' contributions: MK and PR contributed to the conception and design of the study; MK and KMA acquired the data; MK and PR contributed to the analysis design and interpreted results with SG; MK drafted the manuscript with PR and SG and all authors revised and approved the published version.

Abstract

The presence of discrete events during an interval to be estimated generally causes a dilation of perceived duration (event-filling effect). Here, we investigated this phenomenon in the thermal modality using multi-seconds (19 s) innocuous cool stimuli that were either constant (continuous interval) or fluctuating to create three discrete sensory events (segmented interval). Moreover, we introduced a delay following stimulus offset, before the reproduction phase, to allow for a direct comparison with our recent study showing an underestimation of duration in a delayed-reproduction task of heat pain sensations (Khoshnejad et al. 2014). The event-filling effect was tested by comparing the delayed-reproduction of the segmented and the continuous stimuli in experimental conditions asking participants to i) reproduce the dynamics of the sensation (i.e. changes in sensory intensity over time) or ii) reproduce only the interval duration (i.e. sensation onset-to-offset). A perceptual (control) condition required participants to report changes in sensation concurrently with the stimulus. Results of the dynamic task confirmed the underestimation of duration in the delayed-reproduction task but this effect was only found with the continuous and not with the segmented stimulus. This implies that the dilation of duration produced by segmentation might compensate for the underestimation of duration in this delayed-reproduction task. However, this temporal dilation effect was only observed when participants were required to attend and reproduce the dynamics of sensation. These results suggest that the event-filling effect can be observed in the thermal sensory modality and that attention directed towards changes in sensory intensity might contribute to this effect.

Keywords: psychophysics, time perception, memory, thermal sensation, segmentation

Introduction

There are several indications in the time perception literature that the perceived duration of an interval is modulated by various sensory and cognitive factors. In prospective timing conditions, participants are informed that a judgment about duration will be required and robust effects are typically produced by the filling of the interval with the stimulus. For example, results generally show that relatively brief intervals (100-1200 msec range) marked by a continuous auditory signal are perceived as longer than empty intervals of the same duration defined by two brief stimuli at the onset and offset (Craig 1973; Hasuo et al. 2011; Ten Hoopen et al. 2008; Wearden et al. 2007). Craig (1973) also observed this effect using visual and vibrotactile stimuli. Another form of filled-duration illusion can be produced by manipulating the number of sensory events occurring during the interval. This event-filling effect is characterized by the perception of longer duration when intermittent brief stimuli are presented during the interval (Adams 1977; Buffardi 1971; Mitsudo et al. 2011; Thomas and Brown 1974). For example, Buffardi et al (1971) reported very robust event-filling effects in the visual, tactile and auditory modalities using a prospective paradigm involving the temporal discrimination of pairs of short intervals (1.056 sec) filled with 0 to 5 intervening elements.

Time perception has been investigated using somatosensory stimulation in only a few studies. Ogden et al (2015a) reported longer duration estimates of short intervals (242-1500 msec) defined by the presentation of visual shapes when the end of the interval was associated with the presentation or the anticipation of a brief (300 msec) thermal painful stimulus (heat pain). This is consistent with earlier work showing that the anticipation of pain leads to longer time estimations (e.g. Hare (1963) using electrical stimulation shocks). On the other hand, concurrent application of pleasant tactile stimulation with the visual shape presentation has been shown to result in shorter estimate of duration of visual shapes (348-1365 msec) (Ogden et al. 2015b). This result has been

suggested to reflect the positive vs. negative affect of the somatosensory stimulation employed consistent with similar effect of emotional stimuli observed across other modalities. However, to our knowledge, no study has yet examined the event-filling effect using intervals defined by affectively neutral thermal stimuli. In the present study, we examine prospective timing of intervals defined by innocuous (cool) thermal stimuli using an interval reproduction method.

Investigating time perception using thermal modality is challenging because the stimuli onsets and offsets are generally slow using standard thermal induction methods relying on radiant heat or contact heating/cooling Peltier devices (but see Ogden et al. 2015a), using a thermo-resistor heating element combined with a Peltier device). However, this does not preclude from the investigation of multi-seconds intervals. In a recent study on the memory of thermal pain, we observed that the delayed reproduction of the temporal dynamics of the sensation was characterized by an underestimation of the latency of the maximum pain and of the overall duration of the pain experienced (Khoshnejad et al. 2014). This finding is consistent with the earlier observation of Hellström and Carlsson (1997) that time is underestimated during a cold pressor test compared to a non-painful control condition. In addition to the empirical evidence of a distortion of temporal aspects of thermal sensation in delayed reports, there might be important theoretical insights to gain from the thermal modality as the temperature sense is thought to be different in several aspects from tactile, visual or auditory sensations. Indeed, the perception of temperature depends on neurological systems that are largely distinct from the tactile system and closely tied to interoceptive function (Craig 2002; Craig 2003; Craig 2009). The central role of interoception in some theories of time perception (Craig 2009; Wittmann 2009) calls for investigations of the thermal modality using psychophysical methods.

We propose to examine time perception using innocuous cool thermal stimuli. In this context, changes in temperature are conceived as event boundaries, consistent with the event segmentation theory (Zacks et al. 2007). This theory was originally proposed to explain perceptual mechanisms required for the processing of information in a dynamic

context. At its core, the theory claims that when exposed to continuous flow of information, individuals segment the interval of time into smaller units separated by salient changes in sensory inputs or expectations. This model of event segmentation has been shown to be applicable to the processing of low-level perceptual features of sensory events where, for example, changes in motion is shown to play a key role in the perception of event boundaries during dynamic animation of visual objects (Zacks et al. 2006). It is argued that such processes have a direct implication for memory processing (Swallow et al. 2009), and would facilitate the maintenance and recall of information (note that this theory has been mainly related to the memory of movies (Zacks et al. 2001; Speer et al. 2003) or texts (Speer and Zacks 2005)). Here, in addition to defining the intervals based on the onset-offset of thermal stimuli, we manipulated the number of segments during the interval using controlled fluctuations in temperature, to create (bottom-up) sensory events and to test the event-filling effect. In addition to the enhanced recall performance due to this bottom-up automatic segmentation process, we examined if attentional mechanisms directed towards the dynamic flow of information might enhance the segmentation process and improve recall. We aimed to examine the effect of top-down processes by manipulating the attention allocated to the dynamic changes in the thermal sensation during the interval to be reproduced.

The goals of this study are (1) to test the replicability of our previous results (Khoshnejad et al. 2014), showing an underestimation of the duration of painful thermal stimuli in delayed reports, using innocuous cool stimuli, (2) to assess how variations in thermal sensation within a long time interval affect the delayed reproduction of interval duration, and (3) to examine how the (top-down) monitoring and delayed reproduction of sensory intensity over time (dynamic condition), as opposed to onset-to-offset duration only, might affect the reproduction of the interval duration. Two stimulation conditions are compared where (a) a *continuous* thermal stimulation fills the interval, and (b) additional variations in thermal intensity (bottom-up sensory events) are intercalated in the interval thereby creating *segmented stimuli*.

The target experimental task involves the delayed reproduction of the intensity of the cool sensation over time, 15 sec after the end of the thermal sensation, using an electronic visual-analog scale (e-VAS). Onset-to-offset duration of this dynamic reproduction condition is compared to a control perceptual condition where the participant is instructed to track the intensity of the cool sensation over time as precisely as possible *during* the presentation of the thermal stimulus using the e-VAS. Secondarily, the reproduction of the duration of each supplementary temperature changes included in the segmented stimuli is compared to the corresponding durations in the control perceptual condition. Finally, in a distinct reproduction task, the participant is instructed to reproduce only the onset-to-offset duration of the interval, ignoring any additional change in coolness intensity. The delayed dynamic reproduction condition is compared to this "duration-only" condition to assess the effect of additional sensory intensity tracking (i.e. top-down attention) on duration reproduction. With the exception of the memory delay introduced in our paradigm, based on our previous study, the duration-only condition replicates more closely the interval reproduction method typically used in time perception studies that does not involve the dynamic tracking of sensory intensity. Based on segmentation theory and the event-filling effect, segmented stimuli are expected to produce longer duration reproductions. This effect is expected to be enhanced when participants are instructed to engage top-down attentional processes to monitor and reproduce all changes in stimulus intensity in the dynamic condition as opposed to monitoring and reproducing only the overall duration of the interval.

Methods

Participants

Fourteen healthy volunteers participated in the study (age 24-38 y.o.; 6 males and 8 females). 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 "Institut universitaire de gériatrie de Montréal." Informed consent was obtained from all individual participants included in the study.

Material and stimuli

The stimulation consisted of an innocuous cool temperature applied to the volar surface of the left forearm using a 9cm^2 contact probe (TSA-II NeuroSensory Analyzer, Medoc Advanced Medical Systems, Ramat Yishai, Israel). Two stimulus types have been applied (continuous vs. segmented) as shown in Figure 1. The COVAS program (Medoc) was used to design the stimulus temporal profile.[1] For both stimulus types, temperature was designed to decrease from a baseline of 32°C (approximating skin temperature) and to reach the plateau of 21°C with a fall rate of 5°C/s. The stimuli were designed to be either fixed at 21°C (continuous) for a duration of 13.7 sec or fluctuated (segmented), going from 21°C to 30°C three times (rise and fall speed of 10°C/s). In the segmented stimuli, the plateau duration of segments 1, 2 and 3, was set to 2.5 sec, 1.5 sec and 3.5 sec, respectively, and the temperature returned to 30°C for 0.3 sec in the intervals between segments 1-2 and segments 2-3. Both stimulus types ended with the temperature going back to baseline with the rise rate of 5°C/s. The overall duration of each stimulus was 19 sec as depicted in Figure 1 (upper panels). The thermal probe was moved to 1 of 4 spots on the forearm between trials to minimize the risk of habituation or sensitization.

Participants rated the cool sensation using an electronic Visual Analogue Scale (e-VAS). The e-VAS consisted of a sliding potentiometer of 9 cm in length. The two extremities of the e-VAS were labeled "No cool sensation" and "Most intense cool sensation imaginable before becoming painful". The e-VAS cursor was always at the left extremity at the beginning of a trial (value = 0) and the signal was sampled at 10 Hz using a BIOPAC MP150 system, and recorded using the Acknowledge program 3.7.1.

[1] Note that due to thermode inaccuracies, duration parameters prescribed in the COVAS program were adjusted to insure that the overall duration of the two stimuli was identical as reflected in the recorded output temperature. Temperature profiles were reliable, as shown by the small SD across the whole duration of both stimuli (see Figure 1).

Cursor movements were converted linearly to a scale from 0 to 10 units of coolness intensity.

In pilot experiments, participants often required slightly more than 19 sec (actual stimulus duration) to finish rating the stimulus, therefore in all the experimental conditions, the thermode remained on the forearm for an extra 2 sec after stimulus offset. This gave participants enough time to finish rating their sensation while avoiding biasing perceptual reports by the removal of the thermode. This offset perceptual delay was confirmed in the perceptual control task (see Figure 1).

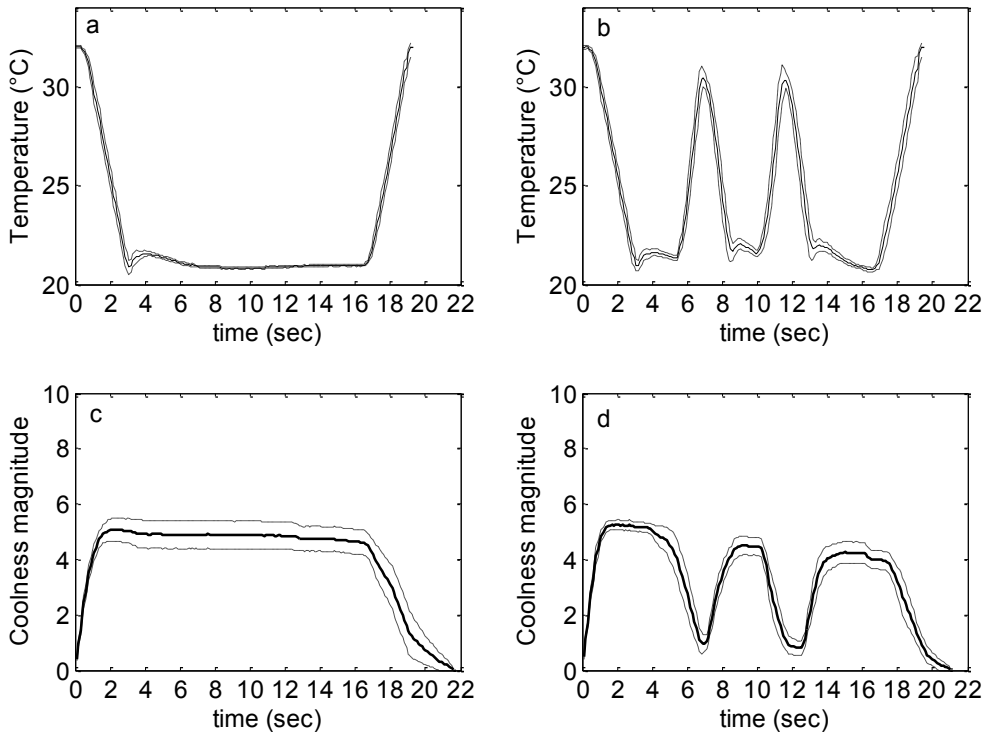

Fig 1. Stimulus temporal profiles in the continuous (a) and segmented (b) conditions.
Continuous lines represent the average temperature output of the thermal stimulator across 24 repetitions of each stimulus type. Dashed lines represent the average temperatures ± standard deviation of the 24 trials (24 trials per stimulus type in total administrated in the course of experiment). Perceptual reports of coolness magnitude over time in the synchronized dynamics condition for one participant in continuous (c) and segmented trials (d). Continuous lines represent the average of the ratings across the 6 trials of each stimulus types in the synchronized dynamics conditions. Dashed lines represent the ±SEM across the 6 trials. Note that time 0 corresponds to the response onset (i.e. all responses are aligned on response onset) to insure that the duration measure is based on response- rather than stimulus-dependent events in all conditions.

Procedure

Three tasks were administered that involved the assessment of duration. In the control task, referred to as "synchronized dynamics", participant were asked to move the cursor of the e-VAS to report the intensity of the cool sensation felt as precisely as

possible throughout time during the presentation of the stimulus. In the target experimental task, called “delayed dynamics”, participants were asked to attend to the dynamics of the sensation (i.e., intensity and time). After a 15-s delay following the removal of the thermode from the skin, they were asked by the experimenter to reproduce the coolness felt as precisely as possible by moving the cursor of the e-VAS, respecting the unfoldment in time. In another experimental task, called “delayed duration”, participants were asked to attend only to the duration of the sensation and, after a 15-s delay following the removal of the thermode from the skin, to reproduce the stimulus duration by bringing the cursor quickly to the right end of the e-VAS to mark the onset, and bring it back to the left end to mark the offset. The duration measurement in all conditions is the time when participants started moving the cursor to the time they brought it back to 0.

Finally, another control task was included, which does not involve any time judgment. In this task, referred to as “delayed intensity”, participants were asked to attend to the intensity of the cool sensation and, after a 15-s delay following the removal of the thermode from the skin, to provide an evaluation of the intensity of the sensation felt with a single rating reported by bringing the cursor of the e-VAS to a position that best represented the overall coolness felt. This condition was designed to verify that the effects of stimulus type (continuous vs segmented) on the recalled duration in the experimental conditions are not confounded with potential differences in the overall coolness produced by the two stimuli.

The four tasks involved different instructions and responses so they were administered in separate blocks of trials. Within each block, participants received three repetitions of each type of stimulus (continuous vs. segmented) in a pseudo-randomized manner. Each of the 4 tasks was tested in 2 separate blocks (i.e. total number of 8 blocks). The order of blocks across conditions was also pseudo-randomized between subjects. Therefore, a total of 6 trials (3 per block) were administrated for each combination of stimulus types by task. In all conditions except “synchronized dynamics”, the rating scale on the e-VAS was covered with a towel during the stimulus presentation and the 15-sec

delay. The towel was removed by the experimenter at the end of this delay when participants were asked to produce their response. Participants were asked explicitly to refrain from using a counting strategy for estimating duration. Two to four practice trials were performed at the beginning of the experiment, as necessary, to familiarize participants with the task conditions.

Data analyses

All analyses were performed by conducting repeated-measures ANOVAs in MATLAB 7.1. We averaged the responses in each stimulus condition (continuous and segmented) and task within each block and included 'block' as a fixed factor to account for possible effects of repetition. Subject was included as a random factor in all the analyses performed.

The effects of reproduction delay and stimulus types (continuous vs. segmented) were assessed by comparing mean duration in the two tasks in which participants reported the changes in sensation over time (synchronized dynamics vs. delayed dynamics; 2 × 2 ANOVA). This analysis tested the underestimation effect which predicts that the reported duration in the delayed reproduction task will be shorter than in the synchronized task, and the event-filling effect which predicts that delayed duration estimates will be longer and closer to perceptual duration for segmented stimuli than continuous stimuli. Complementary analyses were performed comparing the reported duration of segments 1, 2 and 3 of the segmented trials in 'synchronized dynamics' and 'delayed dynamics' conditions (3 × 2 ANOVA). For this analysis, the duration from the onset to the offset of each segment was measured using the valleys (minimum) between segments in the continuous rating curves. Trials in which participants did not produce 3 segments in their report were excluded from this analysis (4% of trials).

Duration estimates of continuous and segmented stimuli were also compared across the conditions involving the delayed reproduction of the dynamics of the sensation versus the delayed reproduction of the time interval only (2 × 2 ANOVA). We predicted

that reproducing coolness intensity over time would enhance the event-filling effect and would thereby lead to the report of longer duration estimates for segmented trials.

Finally, the overall coolness reported in response to segmented and continuous stimuli was compared using ratings obtained in the delayed intensity task. This allowed verifying that the stimulus conditions did not introduce a potential confound associated with the overall intensity of coolness felt.

Results

Figure 1 (lower panels) provides an example of the mean rating produced by one participant in the synchronized dynamics condition (perceptual control) for the continuous (a) and the segmented trials (b).

Overall duration in synchronized vs. delayed dynamics tasks

ANOVA comparing stimuli in the synchronized dynamics and delayed dynamics tasks showed a significant main effect of stimulus types and a significant interaction of stimulus type by task (Table 1). The main effect of task also approached significance (Table 1). The effect of block and interactions with this factor were not significant. Decomposition of the significant interaction term revealed no difference between segmented vs. continuous trials in the perceptual control condition (synchronized dynamics; mean difference: 0.33 sec; 95% CI: -1.55 to 2.20, Figure 2). However, the delayed reproduction was longer for segmented trials than continuous trials (mean difference: 2.44 sec; 95% CI: 0.56 to 4.31). Consistent with this, contrast analyses further showed comparable duration reports of segmented stimuli in synchronized and delayed dynamics tasks, while the duration reports of continuous stimuli were shorter in the delayed reproduction task (mean difference: 2.01 sec; 95% CI: 0.13 to 3.89, Figure 2).

Table 1. Summary of ANOVAs

	df	*F*	*p*	η^2
ANOVA 1: Overall duration in synchronized (sync.) vs. delayed (del.) dynamics tasks				
Stimulus (Stim: continuous vs segmented)	1,91	7.41	0.008	0.21
Task (sync. vs del.)	1,91	3.54	0.06	0.14
Block (1 vs 2)	1,91	1.61	0.21	0.09
Stim X Task	1,91	4.32	0.04	0.16
Stim X Block	1,91	0.02	0.88	0.01
Task X Block	1,91	1.2	0.28	0.08
Stim X Task X Block	1,91	0.09	0.76	0.02
ANOVA 2: Segments duration in the synchronized (sync.) vs. delayed (del.) dynamics tasks				
Segment (Seg.: 1, 2, 3)	1,143	21.5	0.0001	0.39
Task (sync. vs del.)	1.143	1.16	0.28	0.06
Block (1 vs 2)	1,143	3.26	0.07	0.1
Seg X Task	1,143	14.7	0.0001	0.32
Seg X Block	1,143	0.32	0.73	0.04
Task X Block	1,143	0.22	0.63	0.02
Seg X Task X Block	1,143	0.02	0.97	0.01
ANOVA 3: Overall duration in delayed dynamics (dyn.) vs. delayed duration (dur.) tasks				
Stimulus (Stim: continuous vs segmented)	1,91	13.9	0.0003	0.17
Task (dyn. vs dur.)	1,91	18.2	0.0001	0.20
Block (1 vs 2)	1,91	8.61	0.004	0.14
Stim X Task	1,91	3.91	0.051	0.09
Stim X Block	1,91	0.47	0.50	0.03
Task X Block	1,91	0.01	0.90	0.006
Stim X Task X Block	1,91	0.25	0.62	0.02
ANOVA 4: Global coolness intensity ratings				
Stimulus (Stim: continuous vs segmented)	1,39	0.05	0.82	0.01
Block (1 vs 2)	1,39	0.51	0.47	0.05
Stim X Block	1,39	0.006	0.93	0.006

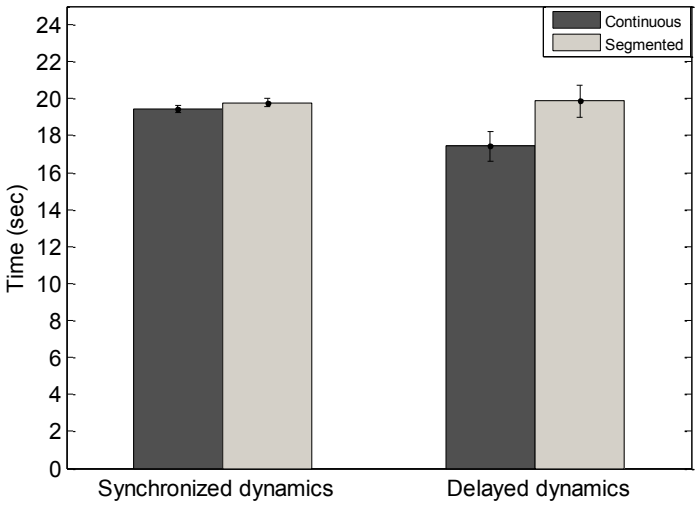

Fig 2. Mean and standard error of duration in synchronized dynamics and delayed dynamics conditions across continuous and segmented trials.
Significant effects are shown by * ($p < .05$).

Segments duration in the synchronized vs. delayed dynamics tasks

ANOVA examining each segment duration showed a main effect of segments, and an interaction of task by segments (Table 1). The main effect of task was not significant and there was no main effect of block or interaction with this factor (Table 1). Contrast analysis on the significant interaction term revealed that segment duration estimates differed significantly between the three segments in the synchronized dynamics condition as shown in Figure 3 (mean difference between segment 1 and segment 2: 1.99 sec; 95% CI: 1.09 to 2.89; mean difference between segment 2 and segment 3: 2.48; 95% CI: 1.58 to 3.38). This segment duration effect was not found in the delayed dynamics condition where participants produced the 3 segments with almost equal durations.

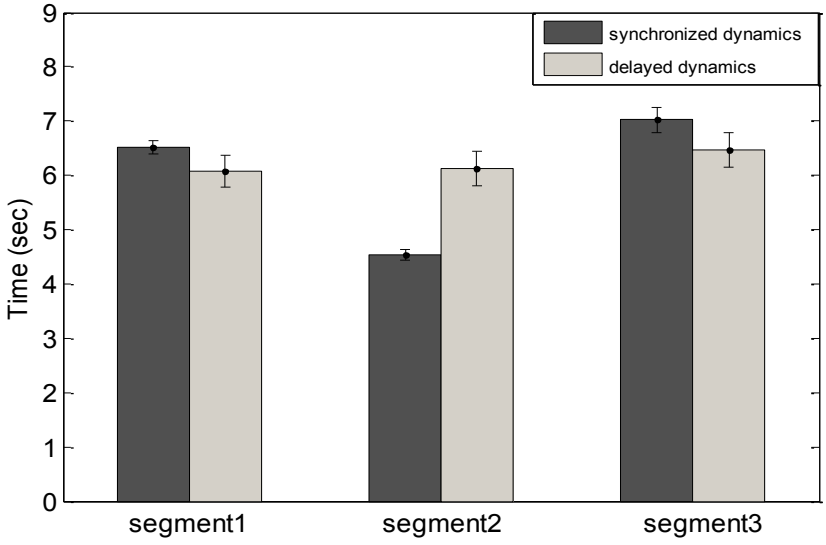

Fig 3. Mean and standard error of segments' duration in synchronized dynamics and delayed dynamics conditions for the segmented trials.
Significant effects are shown by * ($p < .05$).

Delayed dynamics vs. delayed duration tasks

The ANOVA comparing delayed dynamics vs. delayed duration tasks across stimuli showed main effects of task and stimulus type, as well as a marginally significant interaction between these two factors (Table 1). The main effect of block was also significant but it did not interact with any other factor (Table 1).

The main effect of stimulus type showed that the reproduction of segmented trials was longer than continuous trials, consistent with the event-filling effect (mean difference: 1.59 sec; 95% CI: 0.75 to 2.44). The main effect of task also showed that reproduction durations were generally longer in the dynamics task than the delayed duration task (mean difference: 1.82 sec; 95% CI: 0.97 to 2.67). Based on our *a priori* hypothesis, we performed contrast analyses on the marginally significant interaction term (see Figure 4). The reproduction of segmented trials lasted longer than continuous trials only in the delayed dynamics task (mean difference 2.44 sec; 95% CI: 0.86 to 4.01) but not in the delayed duration task (mean difference: 0.75; 95% CI: -0.83 to 2.33).

Decomposing the interaction in the complementary way showed that the reproduction of segmented stimuli lasted longer in 'delayed dynamics' than 'delayed duration' (mean difference: 2.66 sec; 95% CI: 1.09 to 4.24) but this task effect was not found with the continuous stimuli (mean difference: 0.98 sec; 95% CI: -0.6 to 2.56).

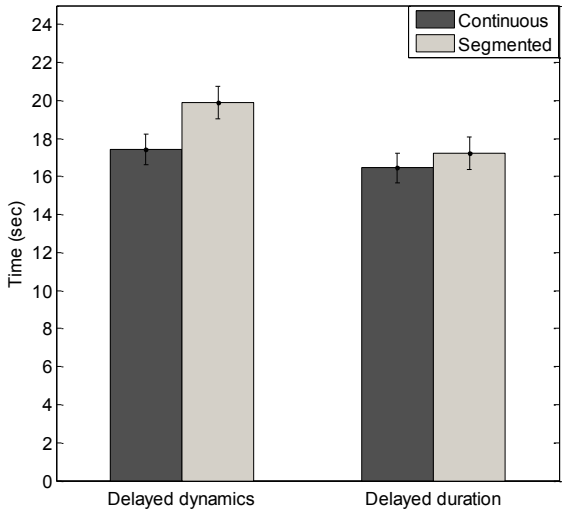

Fig 4. Mean and standard error of duration in delayed dynamics and delayed duration conditions across continuous and segmented trials.
Significant effects are shown by * ($p < .05$).

Global coolness intensity ratings

We acquired post-intensity rating in a separate experimental condition ('delayed intensity') to make sure that the effects of stimulus type on memory are not confounded with potential differences in the overall coolness felt across continuous vs. segmented trials. The ANOVA confirmed that the main effect of stimulus type was not significant (Table 1). There was no main effect of block or interaction with this factor (Table 1).

Discussion

The present results confirm that the duration of continuous multi-seconds innocuous thermal sensation is underestimated in a delayed-reproduction task. However, this reproduction bias was not found for the segmented stimuli in the delayed dynamic task (Figure 2).Nevertheless, the durations of the three unequal segments that were perceived as unequal in the synchronized dynamic condition, was reproduced as three equal segments in the delayed dynamics condition (Figure 3). Furthermore, the advantage of segmented over continuous stimuli was only found when participants reproduced the changes in sensory intensity over time (delayed dynamic condition) as opposed to reproducing only the duration of the stimulus (Figure 4).

The underestimation of duration in delayed reproduction that we previously reported with continuous heat pain stimuli (Khoshnejad et al. 2014) is hereby shown to generalize to innocuous cool sensation. Interestingly, this underestimation effect was not found with the segmented stimuli for which the duration of the delayed reproduction of the dynamic sensation matched the duration of the concurrent rating of the sensation (Figure 2). In the time perception literature, the inclusion of salient sensory events during an interval is consistently reported to result in the dilation of perceived duration (Adams 1977; Buffardi 1971; Thomas and Brown 1974). This robust effect is shown to be independent of the sensory modality tested, and to increase with the number of events (Buffardi 1971). These results are usually obtained in a 1 sec range but have been reported with longer intervals (e.g. 5-sec range; Thomas and Brown 1974). However, most previous studies used empty interval containing discrete event fillers. The present results show that the event-filling effect is observed with a longer interval and that it is also produced by continuous ‘dynamic’ event fillers. This is also in line with the advantage of using a segmentation strategy in duration judgments such as counting or foot tapping as reported by Grondin et al. (1999) (see Killeen and Weiss 1987 for a theoretical account).

The present study also allowed examining each sub-interval of the segmented stimuli in the dynamic reproduction condition. Thomas and Brown (1974) have proposed a theoretical model for the event-filling effect suggesting that "discrete events are encoded into 'chunks' which are then decoded serially such that the produced interval is the sum of decoding of the sub-intervals" (p. 453). This theory could explain the event-filing effect if the duration of each shorter sub-interval is remembered more accurately than the overall duration of the complete interval. However, the present results indicate that the three unequal segments were reproduced as three equal segments of average duration, an effect that may reflect an assimilation process. This suggests that it is the segmentation in three sensory events rather that the accurate recall and summation of the duration of each segment that improved time estimation. This appears to be more consistent with a strategy based on counting the number of events as suggested originally by Buffardi (1971) based on their observation that a larger number of events leads to longer estimated duration.

Notably, in the present study, the duration of each segment was chosen in the range of 1.5-3.5 sec, with a lower bound longer than the sub-second range for which distinct neural processing is required (compare to the supra-second range; see Lewis and Miall 2003), and the upper bound roughly around the range of the "psychological present" or "specious present". This notion, introduced by James (1890) and later elaborated by Fraise (1984) and Pöppel (1978, 1997), reflects a temporal window for which the sense of a unitary perception of events occur as a whole with a range around 2-3 sec. However, there is debate about the exact duration of this temporal window; with a lower limit discussed to be around 1.2 sec (Grondin 2012; Grondin et al. 2015) and an upper limit around 7 sec (Block and Gruber 2014). Events exceeding this temporal window may therefore require memory processes that relate the present moment with the previous moments (Wittmann 1999). However, this does not mean that the duration of each sub-interval has no impact on duration estimates. A recent study showed that the relative length and ordering of sub-intervals affects duration judgments (Matthews 2013). In this study, a theoretical model for the judgment of segmented intervals is proposed,

where the total duration estimation is the sum of the weighted perceived sub-interval's duration, with the weight associated with each sub-interval decaying exponentially such that the most recent segment has the maximum weight. Here, the order of the three unequal segments was constant but the last one had the longest duration, which may have contributed to the longer duration estimation of the segmented stimuli.

Importantly, the longer duration estimate of the segmented stimuli was not found when participants were not required to monitor and reproduce changes in coolness intensity (Figure 4). This implies that the segmentation based solely on stimulus-driven bottom-up processes is insufficient to produce the longer duration effect. This may suggest a contribution of executive processes to duration estimation (e.g. Brown 1997, Brown 2006, Brown et al. 2013, Brown et al. 2015; Mioni et al., 2014, Ogden et al. 2011, Ogden et al. 2014). One possible explanation is that the increased attention to the changes in sensory intensity required in the dynamic conditions reinforced the segmentation process (e.g. through top-down enhancement of sensory contrasts), leading to longer duration judgements.

An earlier study manipulated the *level of segmentation* in a long interval (140-155s) to be timed using lexical or tactile stimuli (Zakay et al. 1994). Tactile stimuli consisted of 11 objects with different shapes among Hebrew letters, with three extra distinct objects as the salient objects. The lexical stimuli consisted of a list of 30 words, with three famous politician's names as the salient words. This study showed that grouping the three salient events as the first 3 events vs. distributing them uniformly through the interval, did not affect prospective time judgments for both modalities. If segmentation of the interval helped duration judgment of long intervals, one would expect that the latter condition should have a larger influence than the former. However, the study did not include a condition with no salient event at all which would have allowed a more direct comparison with the present findings. Yet another recent study, which used *objecthood* to induce segmentation in a dynamic visual display, showed that segmentation leads to *shorter* time estimates (Liverence and Scholl 2012). This contradictory finding may suggest that the effects of segmentation on duration judgments

by salient low-level perceptual processes may be different than those induced by higher-order object-related processes. This calls for further research to examine the effects of the specific features used to induce segmentation.

An alternative perspective on the phenomenon might consider that the dynamic condition can be conceived as a dual-task where time and intensity need to be processed concurrently with limited attentional resources. The studies investigating the effects of attentional sharing between temporal and magnitude properties of stimuli on the judged duration showed that more attention towards the changes in the intensity of the stimulus presented during an interval to be timed, results in *shorter* estimates of duration (Casini et al. 1992; Casini and Macar 1997; Grondin and Macar 1992; Macar et al. 1994). This supports an early attentional model of time perception (Thomas and Weaver 1975) suggesting that limited attentional resources are shared between a 'timer' and a 'stimulus processor' (or a distracting task). The present observation that the dynamic monitoring of segmented stimuli resulted in *longer* duration estimates than the duration only condition, does not match these prior results and do not support the proposed attentional interpretation. However, it is important to note that the previous studies investigating this question differ from the current paradigm, both in terms of modality tested as well as the specific attentional instructions. Here, participants were asked to monitor changes in intensity as they unfold in time in the dynamic conditions, while attentional sharing studies require participants to systematically devote portions of their attention to intensity and/or duration of stimulus.

One of the limitations of the present study is that the continuous magnitude-estimation task used to direct top-down attention towards changes in sensation may have introduced some confounding factors associated with the visuo-motor processes required to perform the task. Although the rating scale was covered during the stimulus and the delay in the delayed reproduction conditions, we cannot strictly exclude the possibility that the longer estimates produced in the delayed dynamic condition compared to delayed duration, might reflect the engagement of multimodal processes associated with implicit visuo-motor preparation. Another factor adding some complexity to the interpretation of

the present results in relation to the time perception literature is the delay between the stimulus offset and the interval reproduction. The inclusion of this delay was motivated by our previous observation that both the intensity and duration of heat pain sensations appear to be distorted in short-term memory (Rainville et al., 2004; Khoshnejad et al., 2014). Some of the effects reported here may be associated with memory processes that might have less impact in the immediate reproduction or discrimination tasks typically used in prospective time perception studies. Varying the duration of this delay experimentally (as in Rainville et al. 2004) might help assess this possibility. Finally, the total duration of the stimulus used was kept constant across tasks and conditions and the order of the three parts of the segmented stimuli was fixed. The generalizability of the present findings may therefore be restricted to a limited range of duration. Furthermore, the absence of trial-by-trial variability in stimulus duration might have affected the strategy adopted by participants, possibly relying on a memory template consolidated across repeated trials. Future studies should test the replicability of the present findings and investigate potential effects of trial-by-trial variations in the duration of the stimuli and the order of the different segments of the segmented stimuli.

Taken together, the present results confirm the event-filling effect in the thermal modality using continuous dynamic event-fillers and in a longer duration range that those usually tested in prospective time studies. The beneficial effect of the presence of the multiple events during an interval to be timed was absent when participants were asked to attend only to the time dimension compared to attending to dynamic sensations. This suggests that the event-filling effect driven by changes in sensory intensity is dependent on attention being directed at those changes. Further research is warranted to assess more directly (i.e. within-study) the possible differences between the thermal modality and other sensory modalities in the perception and memory of time.

Acknowledgments We thank Jen-I Chen for her help with the equipment and Ian Bercovitz for his help with statistical analysis. This study was funded by the National Science and Engineering Research Council (NSERC) of Canada (Grant Number 341472-2013).

Conflict of Interest: The authors declare that they have no conflict of interest.

References

Adams RD (1977) Intervening stimulus effects on category judgments of duration. Perception & Psychophysics 21:527-534 doi: 10.3758/BF03198733

Block RA, Gruber RP (2014) Time perception, attention, and memory: a selective review. Acta Psychol (Amst) 149:129-133 doi: 10.1016/j.actpsy.2013.11.003

Brown SW (2006) Timing and executive function: Bidirectional interference between concurrent temporal production and randomization tasks. Memory & Cognition 34:1464-1471 doi: 10.3758/BF03195911

Brown SW (1997) Attentional resources in timing: interference effects in concurrent temporal and nontemporal working memory tasks. Percept Psychophys 59:1118-1140

Brown SW, Collier SA, Night JC (2013) Timing and executive resources: dual-task interference patterns between temporal production and shifting, updating, and inhibition tasks. J Exp Psychol Hum Percept Perform 39:947-963 doi: 10.1037/a0030484

Brown SW, Johnson TM, Sohl ME, Dumas MK (2015) Executive Attentional Resources in Timing: Effects of Inhibitory Control and Cognitive Aging. J Exp Psychol Hum Percept Perform doi: 10.1037/xhp0000078

Buffardi L (1971) Factors affecting the filled-duration illusion in the auditory, tactual, and visual modalities. Perception & Psychophysics 10:292-294 doi: 10.3758/BF03212828

Casini L, Macar F (1997) Effects of attention manipulation on judgments of duration and of intensity in the visual modality. Mem Cognit 25:812-818

Casini L, Macar F, Grondin S (1992) Time Estimation and Attentional Sharing (short communication). In: Macar F, Pouthas V, Friedman W (eds) Time, Action and Cognition. Springer Netherlands, pp 177-180

Craig AD (2002) How do you feel? Interoception: the sense of the physiological condition of the body. Nat Rev Neurosci 3:655-666 doi: 10.1038/nrn894

Craig AD (2003) Interoception: the sense of the physiological condition of the body. Curr Opin Neurobiol 13:500-505

Craig AD (2009) Emotional moments across time: a possible neural basis for time perception in the anterior insula. Philos Trans R Soc Lond B Biol Sci 364:1933-1942 doi: 10.1098/rstb.2009.0008

Craig J (1973) A constant error in the perception of brief temporal intervals. Perception & Psychophysics 13:99-104 doi: 10.3758/BF03207241

Fraisse P (1984) Perception and Estimation of Time. Annual Review of Psychology 35:1-37 doi: doi:10.1146/annurev.ps.35.020184.000245

Grondin S (2012) Violation of the scalar property for time perception between 1 and 2 seconds: evidence from interval discrimination, reproduction, and categorization. J Exp Psychol Hum Percept Perform 38:880-890 doi: 10.1037/a0027188

Grondin S, Laflamme V, Mioni G (2015) Do not count too slowly: evidence for a temporal limitation in short-term memory. Psychon Bull Rev 22:863-868 doi: 10.3758/s13423-014-0740-0

Grondin S, Macar F (1992) Dividing Attention between Temporal and Nontemporal Tasks: A Performance Operating Characteristic -POC- Analysis. In: Macar F, Pouthas V, Friedman W (eds) Time, Action and Cognition. Springer Netherlands, pp 119-128

Grondin S, Meilleur-Wells G, Lachance R (1999) When to start explicit counting in a time-intervals discrimination task: A critical point in the timing process of humans. Journal of Experimental Psychology: Human Perception and Performance 25:993-1004 doi: 10.1037/0096-1523.25.4.993

Hare RD (1963) The estimation of short temporal intervals terminated by shock. J Clin Psychol 19:378-380

Hasuo E, Nakajima Y, Tomimatsu E, Grondin S, Ueda K (2014) The occurrence of the filled duration illusion: a comparison of the method of adjustment with the method of magnitude estimation. Acta Psychol (Amst) 147:111-121 doi: 10.1016/j.actpsy.2013.10.003

Hasuo E, Nakajima Y, Ueda K (2011) Does filled duration illusion occur for very short time intervals? Acoustical Science and Technology 32:82-85 doi: 10.1250/ast.32.82

Hellstrom C, Carlsson SG (1997) Busy with pain: disorganization in subjective time in experimental pain. Eur J Pain 1:133-139

James W (1890) The Principles of Psychology. H. Holt

Khoshnejad M, Fortin MC, Rohani F, Duncan GH, Rainville P (2014) Remembering the dynamic changes in pain intensity and unpleasantness: a psychophysical study. Pain 155:581-590 doi: 10.1016/j.pain.2013.12.015

Killeen PR, Weiss NA (1987) Optimal timing and the Weber function. Psychol Rev 94:455-468

Lewis PA, Miall RC (2003) Brain activation patterns during measurement of sub- and supra-second intervals. Neuropsychologia 41:1583-1592

Liverence BM, Scholl BJ (2012) Discrete events as units of perceived time. J Exp Psychol Hum Percept Perform 38:549-554 doi: 10.1037/a0027228

Macar F, Grondin S, Casini L (1994) Controlled attention sharing influences time estimation. Mem Cognit 22:673-686

Matthews WJ (2013) How does sequence structure affect the judgment of time? Exploring a weighted sum of segments model. Cogn Psychol 66:259-282 doi: 10.1016/j.cogpsych.2013.01.001

Mioni G, Grondin S, Stablum F (2014) Temporal dysfunction in traumatic brain injury patients: primary or secondary impairment? Frontiers in Human Neuroscience 8:269 doi: 10.3389/fnhum.2014.00269

Mitsudo T, Gagnon C, Takeichi H, Grondin S (2011) An Electroencephalographic Investigation of the Filled-Duration Illusion. Frontiers in Integrative Neuroscience 5:84 doi: 10.3389/fnint.2011.00084

Ogden RS, Moore D, Redfern L, McGlone F (2015a) The effect of pain and the anticipation of pain on temporal perception: A role for attention and arousal. Cogn Emot 29:910-922 doi: 10.1080/02699931.2014.954529

Ogden RS, Moore D, Redfern L, McGlone F (2015b) Stroke me for longer this touch feels too short: The effect of pleasant touch on temporal perception. Conscious Cogn 36:306-313 doi: 10.1016/j.concog.2015.07.006

Ogden RS, Salominaite E, Jones LA, Fisk JE, Montgomery C (2011) The role of executive functions in human prospective interval timing. Acta Psychol (Amst) 137:352-358 doi: 10.1016/j.actpsy.2011.04.004

Ogden RS, Wearden JH, Montgomery C (2014) The differential contribution of executive functions to temporal generalisation, reproduction and verbal estimation. Acta Psychol (Amst) 152:84-94 doi: 10.1016/j.actpsy.2014.07.014

Poppel E (1997) A hierarchical model of temporal perception. Trends Cogn Sci 1:56-61 doi: 10.1016/s1364-6613(97)01008-5

Pöppel E (1978) Time Perception. In: Held R, Leibowitz H, Teuber H-L (eds) Perception. Springer Berlin Heidelberg, pp 713-729

Rainville P, Doucet JC, Fortin MC, Duncan GH (2004) Rapid deterioration of pain sensory-discriminative information in short-term memory. Pain 110:605-615 doi: 10.1016/j.pain.2004.04.024

Speer NK, Swallow KM, Zacks JM (2003) Activation of human motion processing areas during event perception. Cogn Affect Behav Neurosci 3:335-345

Speer NK, Zacks J (2005) Temporal changes as event boundaries: processing and memory consequences of narrative time shifts. Journal of memory and language 53:125-140

Swallow KM, Zacks JM, Abrams RA (2009) Event Boundaries in Perception Affect Memory Encoding and Updating. Journal of experimental psychology. General 138:236 doi: 10.1037/a0015631

Ten Hoopen G, Miyauchi R, Nakajima Y (2008) Time-based illusions in the auditory mode. In: Grondin S (eds) Psychology of time. Bingley, UK: Emerald, PP 139–187

Thomas E, Brown I (1974) Time perception and the filled-duration illusion. Perception & Psychophysics 16:449-458 doi: 10.3758/BF03198571

Thomas EC, Weaver W (1975) Cognitive processing and time perception. Perception & Psychophysics 17:363-367 doi: 10.3758/BF03199347

Wearden JH, Norton R, Martin S, Montford-Bebb O (2007) Internal clock processes and the filled-duration illusion. J Exp Psychol Hum Percept Perform 33:716-729 doi: 10.1037/0096-1523.33.3.716

Wittmann M (1999) Time Perception and Temporal Processing Levels of the Brain. Chronobiology International 16:17-32 doi: 10.3109/07420529908998709

Wittmann M (2009) The inner experience of time. Philos Trans R Soc Lond B Biol Sci 364:1955-1967 doi: 10.1098/rstb.2009.0003

Zacks JM, Braver TS, Sheridan MA, et al. (2001) Human brain activity time-locked to perceptual event boundaries. Nat Neurosci 4:651-655 doi: 10.1038/88486

Zacks JM, Speer NK, Swallow KM, Braver TS, Reynolds JR (2007) Event perception: a mind-brain perspective. Psychol Bull 133:273-293 doi: 10.1037/0033-2909.133.2.273

Zacks JM, Swallow KM, Vettel JM, McAvoy MP (2006) Visual motion and the neural correlates of event perception. Brain Res 1076:150-162 doi: 10.1016/j.brainres.2005.12.122

Zakay D, Tsal Y, Moses M, Shahar I (1994) The role of segmentation in prospective and retrospective time estimation processes. Mem Cognit 22:344-351

Article 3: Brain processing of the temporal dimension of acute pain in short-term memory

Title: Brain processing of the temporal dimension of acute pain in short-term memory

Authors:
Mina Khoshnejad[1,2]
Mathieu Roy[2,3]
Kristina Martinu[2]
Jen-I Chen[2,4]
Julien Cohen-Adad[2,5]
Simon Grondin[6]
Pierre Rainville[2,4,7]

Affiliations:
1 Department of Neuroscience, Université de Montréal, Montréal, Canada,
2. Centre de recherche de l'institut universitaire de gériatrie de Montréal, Université de Montréal, Montréal, Canada,
3. Department of Psychology, McGill University, Montreal, Quebec, Canada
4 Department of Stomatology, Université de Montréal, Montréal Canada,
5. École Polytechnique de Montréal, Montréal, Québec, Canada
6 École de psychologie, Université Laval, Québec, Canada
7. Groupe de recherche sur le système nerveux central (GRSNC), and Centre de recherche en neuropsychologie et cognition (CERNEC), Université de Montréal, Montréal Canada,

Corresponding author:

Mina Khoshnejad
E-mail: mina.khoshnejad@umontreal.ca

Publication status:
Manuscript published in PAIN, volume 234, July 2017.

Authors' contributions: MK, MR and PR contributed to the conception and design of the study; JCA and JC optimized the fMRI acquisition sequence; MK, KM and JC acquired the data; MK, MR and PR contributed to the analysis design and interpretation; MK analyzed the data with inputs from MR, JC and PR; MK, MR, SG and PR contributed to interpretations; MK drafted the manuscript with SG and PR, and all authors revised and approved the published version.

ABSTRACT

The dynamics of noxious sensation shapes pain perception, yet the memory of the temporal dimension of pain remains almost completely unexplored. Here, brain activity during the memory of pain duration was contrasted with that associated with the memory of pain intensity using functional magnetic resonance imaging (fMRI) and a delayed-reproduction task. Participants encoded, maintained during a short delay, and reproduced (1) the 'duration' of pain (i.e. onset-to-offset), (2) the 'dynamics' of pain (i.e. evolution of pain over time), or (3) the intensity of pain (i.e. control with no explicit temporal processing required). Results show that the inferior frontal gyrus/insula and adjacent striatal structures as well as the supramarginal and middle temporal gyri are activated in the duration task compared to the control intensity task. Specific examination of the memory delay of the duration task further revealed activation in the supramarginal gyrus extending to the parietal operculum (possibly SII) and primary somatosensory cortex (SI). In contrast, the memory delay of the dynamic task involved the bilateral supplementary motor area and the fronto-parietal attentional network. While SI, SII and insula may contribute to the memory trace of pain sensation, other areas less commonly reported in pain studies are associated with time processing and may therefore contribute to the processing of temporal aspects of pain. Results further suggest a differential role of core timing regions of the brain depending on specific task instructions and attentional allocations to the single dimension of time, as compared to the conjoint processing of both time and intensity.

Introduction

Pain memory refers to a number of processes that can be mapped onto classical neuroscientific models of memory [39, 41]. This includes implicit processes reflecting the immediate sensory memory (i.e. habituation/sensitization), the learning of pain-relevant associations, and the alterations in sensitivity due to prior pain experiences. Pain also engages explicit processes to encode and voluntarily remember past experiences in short-term (STM) and long-term memory (LTM). Explicit LTM involves episodic-autobiographical and semantic-factual memory about pain. Explicit STM shapes the episodic LTM of pain and is often called upon during clinical assessments. The present study examines the basic neural processes underlying the explicit STM of pain using experimental methods in healthy participants.

Only a handful of studies examined the explicit STM of pain. The few imaging studies that looked at the neural correlates of STM of pain intensity and location [1, 12, 30, 36, 42, 43], showed an involvement of fronto-parietal cortices generally involved in working memory (WM) as well as some core pain-related regions (e.g. primary somatosensory cortex, insula [2, 10]). This is consistent with the notion that cortices involved in perceptual coding of the basic stimulus attributes may also be involved in short-term retention of this information [44].

Pain is inherently dynamic, such that the temporal and intensity dimensions are typically integrated; yet, our understanding of neural correlates of the temporal dimension of pain is very limited compare to the intensity dimension. The neural processes of the spatial and intensity dimensions of pain in STM are dissociable (see [36]), consistent with memory research of spatial and non-spatial features in other modalities [57]. The present study aimed to examine whether such distinction also applies for temporal vs. intensity attributes of pain.

A recent meta-analysis of over 40 neuroimaging studies on time perception [58] revealed that, in the supra-second duration ranges and using tasks involving the reproduction methods (similar to the current study), a broad activation network is

involved including the insula, cingulate gyrus, precentral gyrus, claustrum, parietal lobule, supramarginal gyrus (SMG), middle frontal gyrus (MFG) and superior frontal gyrus (SFG). These regions might therefore be involved in the retention of time-related pain information.

In this study we employed a prospective delayed-reproduction task [16, 17] to examine brain regions involved in the short-term retention of temporal information. Participants were asked to attend to the duration, the dynamics, or the intensity (control), of heat pain sensation, and to reproduce the attended feature(s) after a short delay. The inclusion of the dynamic task was based on our earlier study which showed improvement in duration recall of innocuous thermal sensation in a dynamic tracking vs. duration-only task [26]. This suggests that the dynamic tracking of intensity might involve brain processes that reflect more than a simple additive combination of duration and intensity processing. In contrast to a control condition involving the STM of pain intensity, tasks requiring STM of temporal information were expected to activate areas previously associated with both pain and time processing.

2. Methods

2.1. Participants

Twenty four right-handed healthy participants (12 males and 12 females; mean age ± std = 28.8 ± 4.8) took part in the study. Participants were recruited using ads posted at the Université de Montréal and McGill classifieds, personal contacts, and word-of-mouth. Exclusion criteria included self-reported neurological, psychiatric or pain conditions, as well current usage of drugs or medication, including over-the-counter analgesics. All experimental procedures conformed to the standards set by the latest revision of the Declaration of Helsinki and were approved by the “Comité mixte d’éthique de la recherche du Réseau de neuroimagerie du Québec” at the “Centre de

recherche de l'Institut universitaire de gériatrie de Montréal" (CMER-RNQ-13-14-006). All participants gave written informed consent, acknowledging their right to withdraw from the experiment without prejudice, and received a compensation of $50 ($Can) for their travel expenses, time, and commitment to the study.

2.2. Experimental Procedures

Participants took part in two sessions held on separate days. The first session was conducted in the laboratory where participants first rated series of thermal stimuli to produce a stimulus-response function that was then used to select individually-adjusted temperatures for the experimental tasks (see section 2.2.1). All participants then performed one complete run out of the 4 imaging runs outside of the scanner to familiarize with the experimental task. The second session was conducted at the "Unité de Neuroimagerie Fonctionnelle" to acquire BOLD images of the brain while subjects performed the tasks during 4 runs of functional scans, as described below (see section 2.3).

2.2.1. Stimulation

The stimulation consisted of noxious heat temperatures applied using a $9cm^2$ contact probe (TSA-II NeuroSensory Analyzer, Medoc Advanced Medical Systems, Ramat Yishai, Israel). The stimulus temporal profiles were designed by using Medoc's Computerized Visual Analogue Scale (COVAS program). Following classical psychophysical methods applied to thermal pain perception [47, 48], the pain stimulus-response function was assessed using the method of constant stimuli with four repetitions of six temperatures (39, 41, 43, 45, 47, 49 °C) applied in a pseudo-randomized order to four separate spots on the volar surface of the participants' left forearm. After each stimulus, participants were asked to report the amount of pain felt using a slide potentiometer to move a cursor over an electronic Visual Analogue Scale (VAS) with

their right hand. The VAS was displayed horizontally on a computer screen with its two extremities labeled “0-no pain” and “10-Most intense pain imaginable”. Participants were asked to bring the cursor of the VAS to a position that best represented the pain sensation felt. A stimulus response function was then computed to interpolate (±0.5 °C) the temperatures approximating 7/10 and 5/10 on the VAS (High and Low temperature conditions, respectively). These individually-selected temperatures were used in the experimental tasks. The selection of stimulus intensities matching given pain levels has been validated in seminal studies on clinical and experimental pain measurements [21, 46]. This method has been applied in a variety of behavioral and brain imaging studies to assess and/or control for individual differences in heat pain sensitivity [40] and prevent floor/ceiling effects [e.g. 15, 54, 56].

During the experimental tasks, all stimuli were designed to start from a baseline of 35°C (approximating skin temperature) with temperature rise/fall rates adjusted to reach the destination temperatures in 2 sec. The plateau was set to 6 or 7 sec such that the overall stimulus duration was 10 (Short) or 11 (Long) seconds. As shown in Figure 1B, the stimulator required a few seconds to stabilize at the target temperature of the plateau, but the temperature profile was highly reproducible between trials (i.e. SD is negligible) and both stimulus temperature (45.0 to 49.0°C) and duration (10 or 11 sec) were controlled satisfactorily.

2.2.2. Experimental Tasks

The paradigm involved three memory tasks (Figure 1A) controlled by E-Prime software (PST Inc.). These tasks were designed to involve memory for *changes in pain intensity over time* (Task 1 – pain dynamics), memory for *pain onset-to-offset duration* (Task 2 – pain duration) and memory for *overall pain intensity* (control Task 3 – pain intensity). Two additional perceptual tasks not described further here examined the effects of concurrent-continuous pain ratings as a follow-up to our earlier psychophysical study [25]. Each of the three memory tasks involved five epochs: Cue, Stimulus

presentation, Memory Delay, Retrieval and Inter-trial-interval (Baseline). In Task 1, participants were asked to attend to, and encode the dynamics of pain (i.e. changes in pain intensity over time) during the stimulus epoch, then to maintain the dynamic information in memory during the delay, and to reproduce (report) the dynamic sensation felt using the VAS in the retrieval epoch. In Task 2, they were asked to pay attention and encode the overall duration of pain felt (i.e. onset-to-offset) during the stimulus epoch, try to maintain the duration information in memory during the delay, and to reproduce (report) the duration of pain in the retrieval epoch. Participants were explicitly asked to avoid counting as a strategy for estimating the duration. In this task, participants were instructed to reproduce the duration of the pain felt by bringing the cursor of the VAS all the way to the right extremity of the scale to mark the onset of the interval reproduction, and to bring it back to the extreme left once the remembered duration had elapsed. Finally, in Task 3, participants were asked to attend and encode the intensity of the pain felt during the stimulus epoch, to maintain the intensity information in memory during the delay, and to report, in the retrieval epoch, the overall intensity of the pain felt. Pain intensity was reported by bringing the VAS cursor to a location that best represented their remembered sensation. At the end of the retrieval epoch of the intensity task, subjects were instructed to bring back the cursor to 0.

During the imaging session, written instruction cues were projected on a screen that the participant could see through a mirror positioned on the head coil. The first line of the instructions asked subjects to « Encode », « Wait » and « Report », during the stimulus, delay, and retrieval epoch, respectively. The second line of the instructions was constant in a given trial, from cue onset to the end of retrieval epoch, and specified the task condition as follows: Task 1: “changes in pain over time”, Task 2: “duration” and Task 3: “intensity”. In all tasks, visual feedback was provided during the retrieval epoch by showing movements of the cursor over the pain-VAS displayed horizontally below the task instructions.

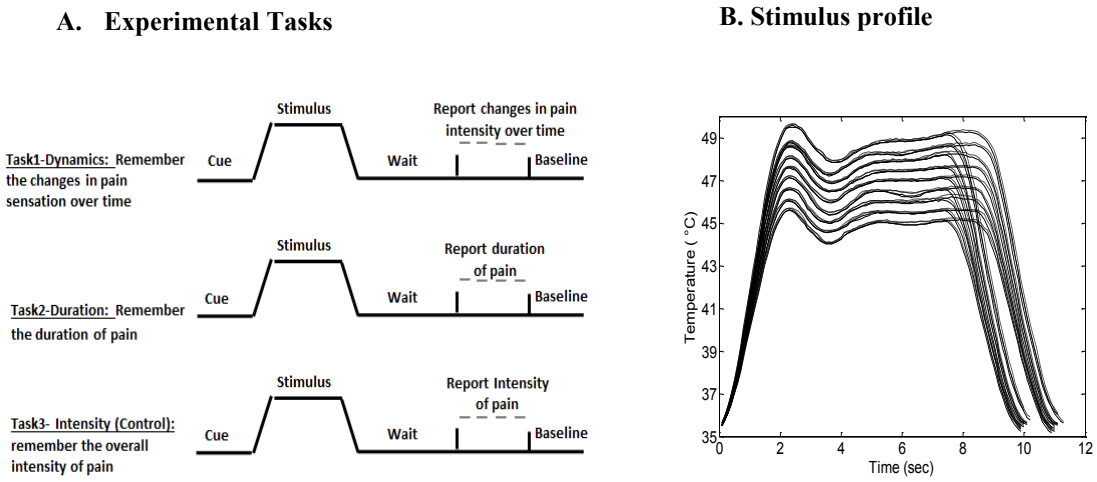

Figure 1. Experimental stimuli and tasks.
A) The experimental paradigm consists of 3 memory tasks. Each task consists of 5 epochs of: Cue, Stimulus presentation, Memory Delay, Retrieval, and ITI. Cue and ITI were 4.5-7.5 sec long, Stimulus epoch was either 11 sec or 12 sec long, Wait epoch was either 6 or 12 sec long, and retrieval epoch was 11.5 sec long. B) Stimulus temporal profiles: the graph shows all temperatures that have been used in the study; plateau of 45.0, 45.5, 46.0, 46.5, 47.0, 47.5, 48.0, 48.5, and 49.0 °C. Two temperatures (High and Low) were selected for each participant to produce strong (VAS = 7/10) and moderate (VAS = 5/10) pain according to the individual stimulus-response function assessed before the imaging session. Continuous lines represent the average temperature output of the thermal stimulator across 20 repetitions. Dashed lines represent the average temperature + 1 standard deviation of 20 trials. Rise /fall rate of temperatures used, were adjusted to produce an overall duration of 10 or 11 sec (plateau of 6 or 7 sec).

2.3. Brain Imaging Session

A short series of individually-adjusted stimuli targeting VAS ratings of 5/10 and 7/10 were administered at the beginning of the scanning session, prior to image acquisition. If necessary, temperatures were re-adjusted to produce the target pain intensities. The thermal probe was moved to a different location on the subject's left forearm and stabilized using athletic tape (MTape®, Mueller Sports Medicine, Inc., Prairie du Sac, WI, USA) before each functional imaging run.

Four functional imaging runs were performed in which each of the three tasks was repeated 4 times, for a total of 12 memory trials per run and 16 trials per memory task per subject. The duration of the cue epoch and the inter-trial interval (ITI) was set to 4.5, 5.5, 6.5, or 7.5 sec, pseudo-randomized across all trials of the 4 functional runs. The temperature of the stimulus applied was either Low or High (VAS = 5/10 or 7/10, respectively), and lasted 10 or 11 sec (Short or Long stimulus, respectively). However, the duration of the stimulus epoch was set to 11 and 12 seconds rather than 10 and 11 seconds to account for the slight perceptual offset-delay observed in concurrent rating conditions (not reported here). The memory delay was either 6 or 12 seconds. Based on pilot tests and our previous study using a similar delayed rating task [25], the retrieval epoch was set to 11.5 sec to ensure that there was sufficient time for the retrospective rating of the stimuli. These parameters provided 8 different combinations of stimulus intensity (2) × stimulus duration (2) × delay duration (2), which were tested in each of the three tasks, giving a total of 24 unique memory trials. These 24 trials were administered twice in a pseudo-randomized order across functional runs.

2.3.1. Behavioral Measures

The number of temperatures, durations or delays tested were not disclosed to the participants who were simply asked to try to report as precisely as possible the dynamics, the duration, or the intensity of each sensation. In order to verify that participants paid attention and performed the tasks adequately, the following measures were recorded and analyzed: total reproduced duration and maximum pain of the dynamic VAS reports (Task 1), reproduced onset-to-offset pain duration (Task 2), and reported pain intensity (Task 3). The expected effects of stimulus duration (Long vs. Short) and stimulus temperature (High vs. Low) were tested using ANOVA on these measures to confirm the psychophysical validity of the tasks. Subject was included as a random factor and a full factorial model was used in all the ANOVAs performed. The first analysis was performed on the reports of duration (Tasks 1 and 2). The longer stimuli were expected to produce

longer duration reproduction in both tasks. More intense stimuli were also expected to produce higher pain reports on the maximum pain measures in Task 1 as well as in intensity reports in Task 3, as tested in the second and third ANOVA, respectively.

2.3.2. Image Acquisition

MRI data was acquired on a 3 Tesla Siemens MAGNETUM Trio Tim scanner using a 32-channel RF head coil. Functional scans were acquired using T2*-weighted echo-planar (EPI) sequence with parameters optimized to reduce signal dropout and distortion in the orbitofrontal and temporal pole regions (parallel imaging with GRAPPA 2, bandwidth = 1732 Hz/Px, TR = 3000 ms, TE = 20 ms, flip angle = 90°, FOV = 220 mm). A total of 290 whole brain volumes were acquired in each functional run. Each volume comprised 50 ascending sequential axial slices of 3mm thickness, with orientation adjusted to -30 degrees tilt relative to the AC-PC plane (matrix = 74 x 74, in-plane resolution = 2.97 x 2.97 mm^2). Due to technical issues, the first run of two participants only included 272 volumes and 109 volumes, respectively.

Structural images were acquired between the second and the third functional scan using high-resolution (1 mm isotropic voxels) T1-weighted multi-echo MPRAGE sequence (ME-MPRAGE) with the following parameters: 176 slices per whole-brain volume, TR = 2530 ms, TE = 1.64, 3.50, 5.36, 7.22, 13, and 15ms combined to form one root mean squared (RMS) volume, flip angle = 7°, FOV = 256 mm, matrix = 256 × 256, parallel imaging with GRAPPA 2, and a bandwidth of 651 Hz/Px.

2.4. Imaging Data Analyses

Brain imaging data was preprocessed and analysed in SPM8 (Welcome Trust Centre for Neuroimaging, London, UK) executed in Matlab 7.12.0.635 (R2011a) (Matworks, Natick, MA) and SPM-based codes from the fMRI data analysis toolbox developed by the Cognitive and Affective Neuroscience Lab (T.D. Wager and

collaborators) available online at https://github.com/canlab. The preprocessing of fMRI data consisted of the following consecutive steps. Functional images were corrected for slice timing acquisition and successive volumes were realigned. Structural T1-weighted images were registered to the mean functional image for each subject, and then normalized to the MNI space. The functional images were warped to SPM's normative atlas using warping parameters estimated from structural images and finally smoothed with a 6-mm FWHM Gaussian kernel.

The four runs were concatenated in each subject and first-level general linear model (GLM) analyses were conducted using boxcar regressors coding for task events (see below) convolved with a canonical hemodynamic response function. A high-pass temporal filter of 128 seconds was applied. The following nuisance covariates were also included: a regressor coding for each run, linear drift across time within each run, the six estimated head movement parameters (x, y, z, roll, pitch, and yaw), their mean-centered squares, their derivatives, and squared derivative for each run, as well as volumes with outlier signal (spikes).

Second-level analyses were conducted using robust regression [55]. All results were thresholded at $p<0.05$, FWER-corrected based on cluster extent defined using a primary (voxel-wise) threshold of $p=0.005$. The results based on two other primary p-thresholds of 0.01, and 0.001, are also shown for display purposes. The xyz coordinates of the geometric center of each cluster are reported. The coordinates of the local maxima within each significant cluster are also reported to provide additional spatial information. A complementary whole brain voxel-wise threshold was applied to these local maxima based on a false discovery rate (FDR) of $q<0.05$ to combine the sensitivity of cluster analysis with the spatial specificity of the voxel-wise FDR-thresholding approach.

2.4.1. Models tested

Two separate models were tested. The first model tested for activation across all the epochs of each task (Global Task model). The second model was designed to reveal

areas showing differential activity more specifically during the memory delay epoch (Task-epochs model).

Model 1 – Global task model: In the first model, one predictor was defined for each task (Task 1, Task 2, and Task 3), using a single boxcar function starting at the onset of the cue with a duration covering all epochs of the trial until the end of the retrieval. Although this model lacks temporal/functional specificity, it was included to detect sustained effects of the task set; i.e. overall task-related activity not tied to a specific sub-process (i.e. encoding, maintenance or retrieval).

Model 2 – Task-epochs model: In the second model, Cue, and Stimulus epochs of each task were modeled as separate predictors which resulted in 3 predictors (one per task) for the cue epoch (cue1, cue2, cue3), and stimulus epoch (stim1, stim2, stim3). The Delay epoch of long delay trials (12 sec) was divided into WaitLongFirst and WaitLongSecond, representing the first 6 sec and the second 6 sec of long delay respectively. The Delay epoch of Short duration (6 sec) was defined as a separate regressor (WaitShort). These three unique regressors for the delay epoch were defined for each task (i.e. WaitLongFirst1-2-3, WaitLongSecond1-2-3, and WaitShort1-2-3), resulted in 9 unique predictors for the wait epoch. For the retrieval epoch, two unique predictors were assigned for retrieval following the long delay vs. short delay (RetrLong and RetrShort) per task, which resulted in 6 predictors for the retrieval epoch. Overall 21 task-related predictors were defined for this GLM analysis.

2.4.2. Contrasts of interest

In order to examine effects related to *pain duration memory* using the above two models, we focused our analyses on the dynamic and duration tasks using the intensity memory task (Task 3) as the control (see Table 1). Furthermore, we examined potential differences between the dynamic and duration task to explore the functional implications of dynamic intensity monitoring on duration memory. In model 2, we specifically focused on the retention epoch. The delay epoch was modeled such that we could

separate the first 6 sec, and the second 6 sec of the long delay (12 sec). Especially, since the first 6 sec of the long wait epoch is assumed to be identical to the 6 sec of the short wait epoch, we combined the two as a unique contrast of interest (WaitShort+WaitLongFirst), to examine differential task-related activity in the retention phase. The second part of the long delay was excluded from the contrasts to reduce the potential expectation-related confound of the onset of the retrieval, which is likely to be more present in the second 6 sec of the long wait.

Table 1. Contrasts of interests tested across the two models (models 1-2).
In the formula, Task 1 corresponds to the dynamic task (Dyn), Task 2 corresponds to the duration task (Dur) and Task 3 corresponds to the intensity control task (Int).

Model	Contrast	Description	Formula
1	a. Dyn-Task	Dynamic Task vs Intensity Task	(task1)-(task3)
1	b. Dur-Task	Duration Task vs Intensity Task	(task2)-(task3)
1	c. DynVsDur-Task	Dynamic Task vs Duration Task	(task1)-(task2)
2	a. Dyn-Delay	Dynamic vs. Intensity delay	(WaitShort1+WaitLongFirst1)-(WaitShort3+WaitLongFirst3)
2	b. Dur-Delay	Duration vs. Intensity delay	(WaitShort2+WaitLongFirst2)-(WaitShort3+WaitLongFirst3)
2	c. DynVsDur-Delay	Dynamic vs. Duration delay	(WaitShort1+WaitLongFirst1)-(WaitShort2+WaitLongFirst2)

Although analyses based on model 2 focused on the memory delay, stimulus-evoked responses were also examined in preliminary analyses by combining the three stimulus epochs of the memory tasks (i.e. stim1, stim2 and stim3) simply to confirm the expected pattern of pain-related activity. Noxious heat produced patterns of activation and deactivation similar to the ones commonly seen in pain imaging studies [2, 10]. Activation was seen in the insula, parietal operculum/secondary somatosensory cortex (SII), anterior cingulate cortex (ACC), MFG, and basal ganglia. Negative BOLD responses were seen in occipital cortex and a set of brain areas consistent with the default-mode network – posterior cingulate cortex (PCC), precuneus as well as medial

prefrontal cortex (MPFC), and middle temporal gyrus (MTG). Task effects were also examined in the encoding phase (i.e. during the pain stimulus); however, these latter contrasts did not result in significant differential brain activation and are therefore not discussed further.

2.4.3. Parametric modulation of brain activation in the retention epoch by reproduced duration

A follow-up analysis examined trial-by-trial variations in behavioural responses to identify regions where activity increased as a function of reproduced duration during the delay epoch of the dynamic and duration tasks. We also tested changes in activity as a function of reproduced duration in the dynamic and the duration tasks compared to changes in activity as a function of recalled intensity in the intensity task, to reveal potential regions involved more specifically in maintaining the temporal vs. intensity information. The analysis was performed by adding a trial-by-trial regressor (parametric modulator) to the retention epoch predictor to reflect the variability in reproduced duration in the dynamic and duration tasks. Similarly, a trial-by-trial parametric modulator reflecting recalled intensity was added to the analysis of the retention epoch of the intensity task.

3. Results

3.1. Behavioural results

Behavioural measures were analyzed to confirm that participants performed the tasks adequately. A first ANOVA (section 3.1.1) performed on the *total duration*, included a comparison of Task 1 and Task 2. A second ANOVA (section 3.1.2) was performed on the *maximum pain* of Task 1, and a third ANOVA (section 3.1.3) was

performed on the *intensity* reports of Task 3. Figure 2 summarizes the behavioral results in each of the experimental conditions.

3.1.1. Duration (Tasks 1 and 2)

The reproduction of pain duration was shorter than real pain duration in all conditions for both Tasks 1 and 2. The random effect 3-way ANOVA (2 stimulus temperature × 2 stimulus duration × 2 task) performed on duration reproductions of Task 1 and Task 2 showed a significant main effect of stimulus duration (F (1,161) = 5.3, p= 0.02) confirming that the reproductions of the long (11-s) stimuli were longer than that of the short (10-s) stimuli. The main effect of stimulus temperature (F (1,161) = 38.7, $p <$ 0.0001) was significant, indicating that the reproductions of durations involving the higher stimulus intensity (strong pain) were also longer than the ones involving lower stimulus intensity (moderate pain). Moreover, the main effect of task (F (1,161) = 270.6, $p < 0.0001$) was also significant, showing longer duration reproductions with the dynamic task (Task 1) than with duration-only task (Task 2). None of the interaction effects reached significance (all p's > .05).

3.1.2. Maximal pain (Task 1)

The random effect 2-way ANOVA (2 stimulus temperature × 2 stimulus duration) on maximal pain showed a main effect of stimulus temperature (F (1, 69) = 185.5, $p <$ 0.0001), confirming that the higher temperature was reproduced as more painful than the lower temperature. There was also a main effect of stimulus duration with the long (11-s) stimulus reproduced as more painful than the short (10-s) stimulus, consistent with temporal summation (F (1, 69) = 8.5, p = 0.005). The interaction was not significant (p > .05).

3.1.3. Intensity (Task 3):

The random effect 2-way ANOVA (2 stimulus temperature × 2 stimulus duration) on pain intensity showed a main effect of stimulus temperature (F (1, 69) = 297.2, p < 0.0001), confirming that higher temperature was reported as more painful compared to the low temperature. Main effect of stimulus duration was also significant (F (1, 69) = 16.8, p = 0.0001); longer stimuli were also reported as more painful than shorter stimuli, consistent with temporal summation. The interaction effect did not reach significance (p > .05).

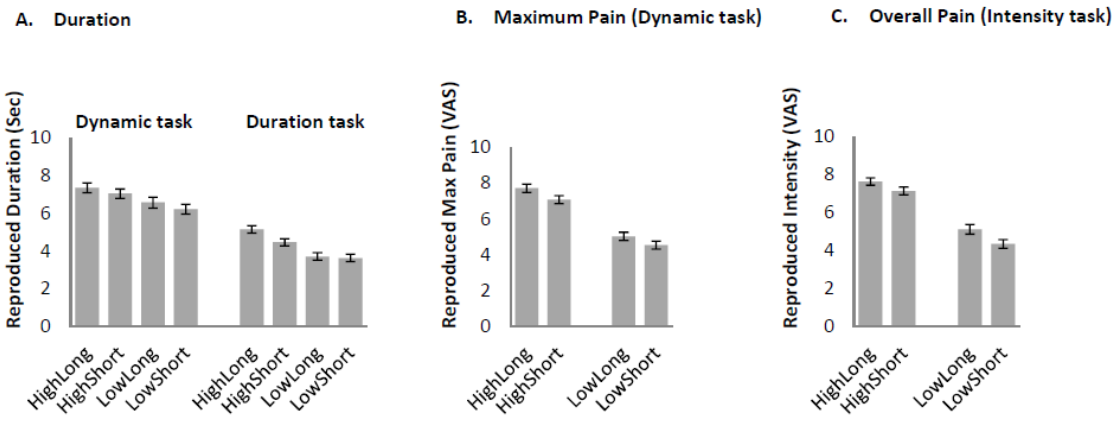

Figure 2. Behavioural results for (A) reproduced duration in dynamic and duration tasks, (B) reproduced maximum pain in the dynamic task, and (C) reproduced overall pain in the intensity task.
The bar graphs show averages (± SEM) across subjects for the two stimulus temperatures (High and Low), and the two stimulus duration (Long and Short). Statistically significant effects of stimulus intensity and duration are found for all three measures, as reported in the text.

3.2. FMRI results

Brain imaging results are organized to first summarize the Task-relevant contrasts in each of the 2 models tested, followed by the second level analysis on reproduction modulators.

3.2.1. Task effects on BOLD responses:

Model 1 – Global Task effect: The global effect of the **dynamics task** compared to the control intensity task (1a) did not show any significant effect. The contrast of the **duration task** with the control intensity task (1b) revealed two clusters: 1) a large cluster in the right (R) insula extending to the R IFG, R putamen, R thalamus, R MTG, and R superior temporal gyrus (STG), and 2) a smaller one in R SMG extending to the parietal operculumn/SII, as shown in Figure 3A, and detailled in Table 2. The contrast of the **dynamic vs. duration tasks** (1c) did not reveal any significant cluster at primary $p < 0.005$. However at a lower primary p threshold of 0.01 (cluster defining threshold), there was one negative cluster in the R insula that extended to the R IFG as well as adjacent striatal structures (Figure 3B).

Additionally, we extracted the mean beta values for the duration task as well as the control intensity task separately, for all the clusters reported in Table 2 (See supplementary Figure S1). Positive beta values were confirmed for the target task and negative values were observed for the control task (not significant in the insula). This indicates that the significant task contrasts reflected at least partly a positive effect of the target task regressor (Table 2).

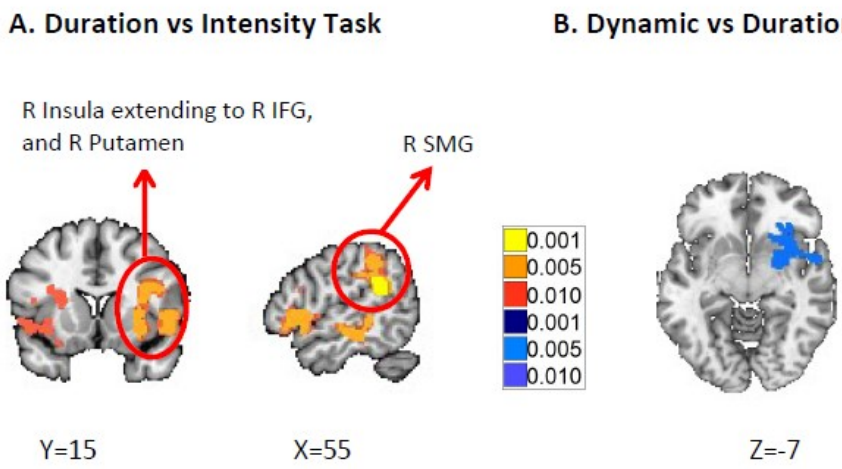

Figure 3. Cortical activation of the global task effects (Model 1) in the duration vs. intensity tasks (A. Dur; contrast 1b in Table 1; see coordinates of local maxima in Table 2) and dynamic vs. duration tasks (B. Dyn vs. Dur; contrast 1c in Table 1). Illustrations are shown for BOLD responses cluster-thresholded with 3 primary p= [0.01, 0.005, 0.001] for display only (see color legend). Duration-related activation was observed in the right insula that extends to the IFG and adjacent striatal structures, as well as the right supramarginal gyrus that extends to the parietal operculum/SII. There was no activation for the contrast between the dynamic and intensity tasks (Contrast 1a, not shown). Arrows and circles are used to point to the regions that are discussed in the discussion.

Table 2. Global Effect of the Duration Task vs. the Intensity (control) Task (Model 1b).

Cluster Identification (cluster extent)	*Local maxima*	*X*	*Y*	*Z*
1. R. Insula (k=1718 voxels)		38	8	2
	R Insula*	34	14	8
	R IFG*	56	20	4
	R Putamen*	26	0	-4
	R Thalamus	10	-6	8
	R MTG*	60	-24	-10
	R STG*	44	-12	-8
2. R. supramarginal gyrus (SMG) (k=571 voxels)		56	-36	34
	R. SMG*	56	- 44	24

Significant clusters are reported at FWE-corrected threshold of $P < 0.05$ (cluster extent $k \geq 451$). X, Y, Z coordinates are indicated for the geometric center of the cluster and the local maxima within the cluster. In cases where there were multiple local maxima in one anatomical location, the coordinates of the highest peak is reported.
* Local maxima significant at voxel-wise FDR correction $q < .05$ (here p-uncorrected < 0.00007).
R: right, IFG: inferior frontal gyrus, MTG: middle temporal gyrus, SMG: supramarginal gyrus.

Model 2 – Delay effect: The contrasts of the delay epoch of the dynamic task (2a) showed 3 activation clusters consisting of 1) the R SFG extending to the left (L) SFG (bilateral SMA), R MFG, and the R precentral gyrus, 2) the L precuneus extending to the R precuneus as well as the bilateral superior parietal gyrus (SPG) and the R cuneus, and 3) the L cerebellum extending to the L lingual gyrus, as shown in Figure 4A and Table 3. The contrast of the delay epoch of the duration task (2b) revealed 1 cluster in the R SMG that extended to the parietal opeculum/SII and R post-central gyrus, as shown in Figure 4B and Table 4. The direct contrast of dynamic vs. duration tasks (2c) did not revealed any significant cluster at primary $p < 0.005$. However, the R SFG (SMA) was activated at a lower primary threshold of p=0.01 (cluster defining threshold) (Figure 4C).

Additionally, we extracted the mean beta values for the dynamic task, the duration task as well as the control intensity task separately, for all the clusters reported in Table 3 (See supplementary Figure S2). Positive beta values were confirmed for the target tasks (not significant in the cerebellum) and negative beta values were observed for the control intensity task (not significant in SFG). With the exception of the non-significant activation in the cerebellum, these analyses confirm that the clusters reported in the

contrasts of target tasks vs. control intensity task reflect at least in part a positive response to the target task (Table 3).

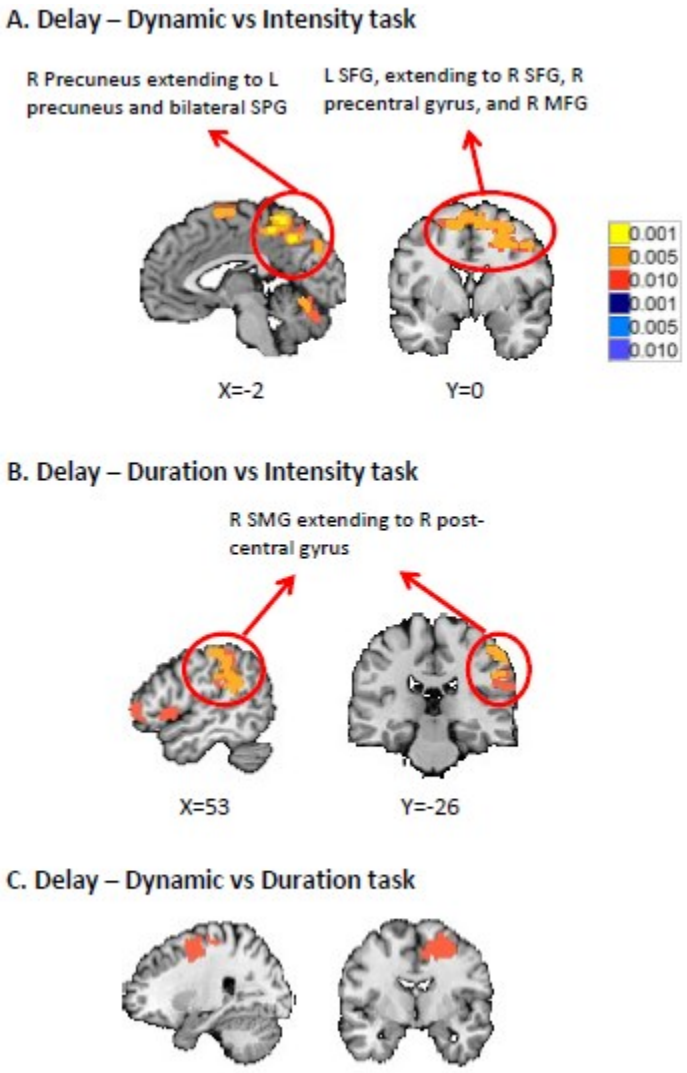

Figure 4. Cortical activation associated with the delay period of the dynamic (A. contrast 2a) and duration task (B. Contrast 2b) compared to the control intensity task and for the contrast between the dynamic and duration tasks (C. contrast 2c), as assessed with Model 2.

The results show that bilateral SMA, and right DLPFC, as well as bilateral precuneus and SPL are involved in the retention of dynamic information, while supramarginal gyrus that extends to parietal operculum/SII and R post-central gyrus are involved in the retention of duration information (see coordinates of local maxima in Tables 3 and 4). Arrows and circles are used to highlight the regions addressed in the discussion.

Table 3. Delay Effect of the Dynamic Task vs. the Intensity Task (control) on brain activity (Model 2a).

Cluster Identification (cluster extent)	*Local maxima*	*X*	*Y*	*Z*
1. R. SFG (k=1000 voxels)		18	0	60
	R SFG	8	2	66
	L SFG	-8	4	66
	R MFG	30	6	48
	R Precentral Gyrus	46	2	46
2. L. Precuneus (k=1783 voxels)		-2	-56	48
	L Precuneus	-10	-54	52
	R Precuneus	6	-58	54
	R SPG	20	-68	52
	L SPG	-24	-44	48
	R Cuneus	10	-76	36
3. L. Cerebellum (k=522)		-10	-72	-12
	L Cerebellum	-8	-76	-12
	L Lingual Gyrus	-10	-82	-4

Significant clusters are reported at FWE corrected threshold of $P < 0.05$ (cluster extent $k \geq 388$). X, Y, Z coordinates are indicated for the geometric center of the cluster and the local maxima within the cluster. In cases where there were multiple local maxima in one anatomical location, the coordinates of the highest peak is reported.

* Local maxima significant at voxel-wise FDR correction $q < .05$ (here p-uncorrected < 0.000007).

R: right, L: left, SFG: superior frontal gyrus, MFG: middle frontal gyrus, SPG: superior parietal gyrus

Table 4. Delay Effect of the Duration Task vs. the Intensity Task (control) on brain activity (Model 2b).

Cluster Identification (cluster extent)	*Local maxima*	*X*	*Y*	*Z*
1. R. SMG (k=478 voxels)		52	-34	38
	R SMG*	54	-42	24
	R Post-Central Gyrus*	54	26	50

Significant clusters are reported at FWE corrected threshold of $P < 0.05$ (cluster extent $k \geq 425$). X, Y, Z coordinates are indicated for the geometric center of the cluster and the local maxima within the cluster. In cases where there were multiple local maxima in one anatomical location, the coordinates of the highest peak is reported.

* Local maxima significant at voxel-wise FDR correction $q < .05$ (here p-uncorrected < 0.00002).

R: right, SMG: supramarginal gyrus

3.2.2. Parametric modulation of reproduced duration

Positive activation was found in the R DLPFC in the parametric modulation analysis of the retention epoch of the **dynamic task** with reproduced duration (Figure 5).

Parametric modulation of reproduced duration and recalled intensity in the retention epoch of the duration and intensity task, respectively, did not reveal any brain activation. No differential brain response was found in the direct contrast between the parametric modulation of the dynamic and duration task with reproduced duration and that of the control intensity task with recalled pain intensity.

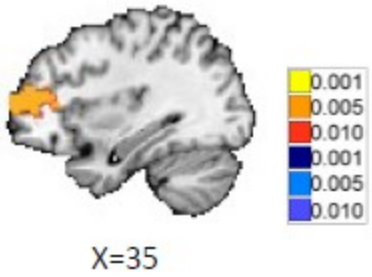

Figure 5. Results of the parametric modulation of the retention epoch of the dynamic task with reproduced duration.
Longer duration reproduction corresponds to increase accuracy (i.e. reduced underestimation) and is associatd with stronger activation in right DLPFC. (note that parametric modulation of reproduced duration in the duration task and recalled intensity in the intensity task did not yield any significant brain activation; not shown).

4. Discussion

Memory of pain plays a vital role in the anticipation of, and behavioural response to future pain. Clinical studies highlight the importance of pain duration in the prediction of pain outcomes [3, 11, 31]. However, understanding the memory of the temporal dimension of pain has received very little attention despite its importance. This study is the first attempt to explore brain correlates of the STM of the temporal dimension of pain. The global task analysis showed that the insula extending to IFG and adjacent striatal structures, MTG, as well as SMG extending to parietal operculum/SII, are activated in the duration task (Figure 3A), suggesting their involvement in the processing of the duration dimension of pain sensation. No similar effect was observed in the dynamic task. This

raises the possibility of partly separable systems/subsystems involved when processing temporal information in isolation or in conjunction with intensity.

Interestingly, the analysis of the memory delay of the duration task revealed activation of the SMG extending to the contralateral parietal operculum/SII as well as the contralateral post-central gyrus (SI) (Figure 4B). These areas have been reported consistently in pain perception studies [2, 10, 13]. The involvement of SI in somatosensory WM has also been found using tactile stimuli, and spatial delayed match-to-sample tasks in event related potential (ERP) [23, 24] and fMRI studies [51]. Moreover, transcranial magnetic stimulation over contralateral SI during the delay epoch has been shown to impair tactile discrimination [20]. One pain fMRI study also showed that SI/PPC is involved in the combined retention of spatial and intensity information [1]. SII has also been involved in innocuous tactile memory in neurophysiological studies in monkeys [52], as well as Magnetoencephalography [18] and fMRI studies in humans [22, 29]. Altogether, these studies are consistent with an involvement of SI and SII in somatosensory WM. Our - results further suggest that these areas may be involved in the memory of the duration of pain sensations.

Memory for dynamic aspects of pain (vs. intensity) showed stronger activity in bilateral SMA and adjacent motor/pre-motor cortices (Figure 4A, 4C) with additional involvement of right DLPFC and bilateral SPG. The fronto-parietal network observed in the dynamic task constitutes the core regions of the dorsal attentional system [6] which has also been related to the attentional and WM aspects of temporal processing [32, 33, 34, 50]. However, these regions are also activated in some pain perception studies [2, 10]. We speculate that the particular involvement of the SMA in the dynamic task may relate to the retention of the integrated time-intensity information of pain sensation consistent with the role previously shown for this area in time processing [7, 58].

The present results further imply that partly distinct brain regions of SMG extending to SI and parietal operculum/SII, vs. bilateral SMA and fronto-parietal network might be involved in memory processing of the isolated temporal information (duration

task) vs. integrated temporal-intensity information (dynamic task), respectively. Moreover, the behavioral results indicate that performance was improved by the additional monitoring of pain intensity-related information across time (Figure 2A). These results may help elucidate the differential role of core timing regions such as the insula, IFG, SMA, as well as SMG, depending on specific task instructions and attentional allocations to the single dimension of time, or conjoint intensity/temporal dimensions.

4.1. Involvement of the insula/IFG in duration processing of pain sensation

Results demonstrate that the R IFG extending into the R anterior and mid-insula is more strongly associated with memory of pain duration than memory of pain intensity in the global task model. Therefore, insula/IFG activation for duration processing of pain may reflect at least in part a task-set. The sustained activity throughout the duration task vs. control (intensity) task may reflect attention to the temporal attribute of pain, as well as general processing of this dimension in memory throughout the trial.

The insula is an integral part of the pain network [2, 10], and is sensitive to the attentional context [4]. Some studies on STM of pain showed that the R IFG or the R insula are involved in the retention of spatial [36, 42] or conjoint spatial/intensity information [1]. Moreover the R insular cortex has been involved in the retrospective evaluation of pain in delayed rating tasks [12, 30]. On the other hand, imaging studies on time perception often report activation in insula or in IFG [58]. Our results therefore provide support for the involvement of Insula/IFG in the processing of pain duration in STM.

4.2. Involvement of the SMA in the short-term retention of pain dynamics

Implication of the SMA in temporal processing has been suggested in the work of Coull and Macar. In their studies, subjects were asked to judge the duration of visual

stimuli while their color [8, 9, 37] or position [7] changed, analog to the present study involving dynamic changes in pain intensity. Consistent with the present findings, these previous reports showed that increased attention to time involves increased activity in SMA [9, 37].

It has been argued that the widespread activation often reported in a variety of time studies reflects cognitive demands of the time task [35]. Methodologically, dynamic stimuli have been utilized in control conditions requiring continual monitoring and integration of non-temporal information, in order to better isolate timing networks; e.g. judging the spatial extent of a moving dot or line [7, 32, 33] or averaging the color of a visual stimulus [8, 9, 35]. These studies mainly show the involvement of the SMA in timing. However, none of these studies directly controlled for attention to dynamic vs. duration information only. Since pain is inherently dynamic and because all stimuli were identical across tasks, the control task (intensity task) may arguably be considered comparable in terms of cognitive demands (i.e. requiring continual integration of information), such that the contrast between tasks reflects the relative focus on the temporal vs. the intensity dimension. The present results are therefore in agreement with a role of the SMA in duration processing, and further emphasize its involvement in the retention of temporal information when changes in non-temporal attributes are monitored and attended to. A potential limitation of this interpretation is that the dynamic task may have required more complex motor-preparatory processes for response production, and this might explain the stronger activity in motor-related areas during the memory delay. However, such a role does not preclude its contribution to temporal memory, as activity generally associated with motor preparation may also contribute to the sensory-memory trace in delayed-decision tasks [45, 53].

4.3. Involvement of the DLPFC

Behavioural results showed that the increase in reproduced duration in the dynamic task was associated with increases activation in the DLPFC during the delay-

period. However, this effect disappeared when directly contrasted to the parametric modulation of delay-period activation by recalled intensity in the intensity control task. These results may therefore reflect a contribution of the PFC that is not specific to the temporal processing in memory.

The PFC is frequently reported in neuroimaging studies on time perception but its role has been associated with either WM or the attentional component of temporal processing [34]. This dual perspective on the role of PFC is also reflected in lesion studies [5,19,38]. Based on these previous findings, our current results may reflect the contribution of executive processes to the improvement of performance in the dynamic task.

4.4. Limitations

This is the first study looking at the neural correlates of STM of temporal aspect of pain, and several limitations should be acknowledged. In fMRI there is no "absolute" baseline and the choice of an appropriate control task is debatable and will inevitably affect the results of task contrasts. Here, clusters showing significant effects in the task contrasts generally displayed positive BOLD responses in the target tasks. However, the control intensity condition also showed some significant or non-significant negative BOLD responses relative to baseline, suggesting that this control may have contributed to the observed net effect of the task contrast. This does not invalidate the results of the task contrasts but it does highlight the importance of pursuing this research examining other dimensions of pain (e.g. spatial [36,42]) to better circumscribe dimension-specific effects. Moreover, the duration and the dynamics of pain are possibly more difficult to remember than intensity. This implies that some of the observed activations in the contrasts of experimental conditions vs. intensity (control) might be related to higher task difficulty rather than duration processing per se. The study also focused on acute experimental pain in young healthy subjects and therefore it might not be generalizable to older subjects or clinical populations. Moreover, this study did not include individual factors such as

affective/anxiety states which are known to predict long-term pain recall in clinical populations [14, 27, 28]. However, experimental pain is generally considered to be less anxiogenic than clinical pain, and thermal heat pain has been reported to evoke relatively low affective responses compared to other types of experimental pain models [49].

4.5. Conclusion

Understanding the psychology and neurobiology of pain memory is an ambitious research program with ramifications into multiple domains of systems neuroscience. The present study provides an admittedly modest first attempt to investigate the neural correlates of the memory of temporal aspects of pain experiences. We specifically examined STM of pain among various types of memory. In a broader context, studying STM of pain is the primary and important step that may enhance our understanding of the memory transformations shaping pain representations. Results provide evidence consistent with the involvement of the insular cortex and SMG extending to parietal operculum/SII in the processing of temporal information in memory of pain duration, as well as higher-order motor cortices, associated with timing-related function, in the retention of pain dynamics. Future studies on temporal processing should further compare pain directly with innocuous somatosensory sensation as well as other sensory modalities to assess putative anatomo-functional segregation associated with the specific sensory vehicle of temporal information. Comparisons between sensory modalities and refined tasks developed in the cognitive and affective neuroscience of time perception and memory may further allow examining the functional roles of saliency, arousal, motor, and executive brain systems in the processing of temporal aspects of pain.

Acknowledgments: We thank Carollyn Hurst and André Cyr for their technical support in MRI data acquisition and Tor D. Wager and C.W. Woo for sharing their analysis scripts (https://github.com/canlab). This project was conducted as part of research programs funded by the National Science and Engineering Research Council (NSERC) of

Canada to study the *Cerebral basis for the mental representation of pain* (PR, Grant Number RGPIN-341472-2013) and for *Uncovering the architecture of the temporal mind* (SG, Grant number RGPIN-2016-05028). PR also received support from the Fonds de la recherche Québec – Santé and from the Canadian Institute for Health Research (CIHR). The authors declare that they have no conflict of interest.

References:

[1] Albanese MC, Duerden EG, Rainville P, Duncan GH. Memory traces of pain in human cortex. The Journal of neuroscience : the official journal of the Society for Neuroscience 2007;27(17):4612-4620.

[2] Apkarian AV, Bushnell MC, Treede RD, Zubieta JK. Human brain mechanisms of pain perception and regulation in health and disease. European journal of pain 2005;9(4):463-484.

[3] Bekkering GE, Hendriks HJ, van Tulder MW, Knol DL, Simmonds MJ, Oostendorp RA, Bouter LM. Prognostic factors for low back pain in patients referred for physiotherapy: comparing outcomes and varying modeling techniques. Spine 2005;30(16):1881-1886.

[4] Brooks JC, Nurmikko TJ, Bimson WE, Singh KD, Roberts N. fMRI of thermal pain: effects of stimulus laterality and attention. NeuroImage 2002;15(2):293-301.

[5] Casini L, Ivry RB. Effects of divided attention on temporal processing in patients with lesions of the cerebellum or frontal lobe. Neuropsychology 1999;13(1):10-21.

[6] Corbetta M, Patel G, Shulman GL. The Reorienting System of the Human Brain: From Environment to Theory of Mind. Neuron 2008;58(3):306-324.

[7] Coull JT, Charras P, Donadieu M, Droit-Volet S, Vidal F. SMA Selectively Codes the Active Accumulation of Temporal, Not Spatial, Magnitude. Journal of cognitive neuroscience 2015;27(11):2281-2298.

[8] Coull JT, Nazarian B, Vidal F. Timing, storage, and comparison of stimulus duration engage discrete anatomical components of a perceptual timing network. Journal of cognitive neuroscience 2008;20(12):2185-2197.

[9] Coull JT, Vidal F, Nazarian B, Macar F. Functional anatomy of the attentional modulation of time estimation. Science (New York, NY) 2004;303(5663):1506-1508.

[10] Duerden EG, Albanese MC. Localization of pain-related brain activation: a meta-analysis of neuroimaging data. Human brain mapping 2013;34(1):109-149.

[11] Dunn KM, Croft PR. The importance of symptom duration in determining prognosis. Pain 2006;121(1-2):126-132.

[12] Fairhurst M, Fairhurst K, Berna C, Tracey I. An fMRI study exploring the overlap and differences between neural representations of physical and recalled pain. PloS one 2012;7(10):e48711.

[13] Garcia-Larrea L. The posterior insular-opercular region and the search of a primary cortex for pain. Neurophysiologie clinique = Clinical neurophysiology 2012;42(5):299-313.

[14] Gedney JJ, Logan H, Baron RS. Predictors of short-term and long-term memory of sensory and affective dimensions of pain. The journal of pain : official journal of the American Pain Society 2003;4(2):47-55.

[15] Grant JA, Courtemanche J, Rainville P. A non-elaborative mental stance and decoupling of executive and pain-related cortices predicts low pain sensitivity in Zen meditators. Pain 2011;152(1):150-156.

[16] Grondin S. Methods for studying psychological time. Psychology of time 2008:51-74.

[17] Grondin S. Timing and time perception: A review of recent behavioral and neuroscience findings and theoretical directions. Attention, Perception, & Psychophysics 2010;72(3):561-582.

[18] Haegens S, Osipova D, Oostenveld R, Jensen O. Somatosensory working memory performance in humans depends on both engagement and disengagement of regions in a distributed network. Human brain mapping 2010;31(1):26-35.

[19] Halbig TD, Yves von Cramon D, Schmid UD, Gall C, Friederici AD. Processing of temporal duration information in working memory after frontodorsal tumour excisions. Brain and cognition 2002;50(2):282-303.

[20] Harris JA, Miniussi C, Harris IM, Diamond ME. Transient storage of a tactile memory trace in primary somatosensory cortex. The Journal of neuroscience : the official journal of the Society for Neuroscience 2002;22(19):8720-8725.

[21] Heft MW, Gracely RH, Dubner R, McGrath PA. A validation model for verbal description scaling of human clinical pain. Pain 1980;9(3):363-373.

[22] Kaas AL, van Mier H, Visser M, Goebel R. The neural substrate for working memory of tactile surface texture. Human brain mapping 2013;34(5):1148-1162.

[23] Katus T, Grubert A, Eimer M. Electrophysiological Evidence for a Sensory Recruitment Model of Somatosensory Working Memory. Cerebral cortex (New York, NY : 1991) 2015;25(12):4697-4703.

[24] Katus T, Muller MM, Eimer M. Sustained maintenance of somatotopic information in brain regions recruited by tactile working memory. The Journal of neuroscience : the official journal of the Society for Neuroscience 2015;35(4):1390-1395.

[25] Khoshnejad M, Fortin MC, Rohani F, Duncan GH, Rainville P. Remembering the dynamic changes in pain intensity and unpleasantness: a psychophysical study. Pain 2014;155(3):581-590.

[26] Khoshnejad M, Martinu K, Grondin S, Rainville P. The delayed reproduction of long time intervals defined by innocuous thermal sensation. Experimental brain research Experimentelle Hirnforschung Experimentation cerebrale 2016;234(4):1095-1104.

[27] Klages U, Kianifard S, Ulusoy O, Wehrbein H. Anxiety sensitivity as predictor of pain in patients undergoing restorative dental procedures. Community dentistry and oral epidemiology 2006;34(2):139-145.

[28] Klages U, Ulusoy O, Kianifard S, Wehrbein H. Dental trait anxiety and pain sensitivity as predictors of expected and experienced pain in stressful dental procedures. European journal of oral sciences 2004;112(6):477-483.

[29] Klingberg T, Kawashima R, Roland PE. Activation of multi-modal cortical areas underlies short-term memory. The European journal of neuroscience 1996;8(9):1965-1971.

[30] Kong J, White NS, Kwong KK, Vangel MG, Rosman IS, Gracely RH, Gollub RL. Using fMRI to dissociate sensory encoding from cognitive evaluation of heat pain intensity. Human brain mapping 2006;27(9):715-721.

[31] Kovacs FM, Abraira V, Zamora J, Fernandez C. The transition from acute to subacute and chronic low back pain: a study based on determinants of quality of life and prediction of chronic disability. Spine 2005;30(15):1786-1792.

[32] Lewis PA, Miall RC. Brain activation patterns during measurement of sub- and supra-second intervals. Neuropsychologia 2003;41(12):1583-1592.

[33] Lewis PA, Miall RC. Distinct systems for automatic and cognitively controlled time measurement: evidence from neuroimaging. Current opinion in neurobiology 2003;13(2):250-255.

[34] Lewis PA, Miall RC. A right hemispheric prefrontal system for cognitive time measurement. Behavioural processes 2006;71(2–3):226-234.

[35] Livesey AC, Wall MB, Smith AT. Time perception: manipulation of task difficulty dissociates clock functions from other cognitive demands. Neuropsychologia 2007;45(2):321-331.

[36] Lobanov OV, Quevedo AS, Hadsel MS, Kraft RA, Coghill RC. Frontoparietal mechanisms supporting attention to location and intensity of painful stimuli. Pain 2013;154(9):1758-1768.

[37] Macar F, Coull J, Vidal F. The supplementary motor area in motor and perceptual time processing: fMRI studies. Cognitive processing 2006;7(2):89-94.

[38] Mangels JA, Ivry RB, Shimizu N. Dissociable contributions of the prefrontal and neocerebellar cortex to time perception. Brain research Cognitive brain research 1998;7(1):15-39.

[39] Milner B, Squire LR, Kandel ER. Cognitive Neuroscience and the Study of Memory. Neuron 1998;20(3):445-468.

[40] Nielsen CS, Price DD, Vassend O, Stubhaug A, Harris JR. Characterizing individual differences in heat-pain sensitivity. Pain 2005;119(1-3):65-74.

[41] Noel M, Palermo TM, Chambers CT, Taddio A, Hermann C. Remembering the pain of childhood: applying a developmental perspective to the study of pain memories. Pain 2015;156(1):31-34.

[42] Oshiro Y, Quevedo AS, McHaffie JG, Kraft RA, Coghill RC. Brain mechanisms supporting spatial discrimination of pain. The Journal of neuroscience : the official journal of the Society for Neuroscience 2007;27(13):3388-3394.

[43] Oshiro Y, Quevedo AS, McHaffie JG, Kraft RA, Coghill RC. Brain mechanisms supporting discrimination of sensory features of pain: a new model. The Journal of neuroscience : the official journal of the Society for Neuroscience 2009;29(47):14924-14931.

[44] Pasternak T, Greenlee MW. Working memory in primate sensory systems. Nature reviews Neuroscience 2005;6(2):97-107.

[45] Petit L, Courtney SM, Ungerleider LG, Haxby JV. Sustained activity in the medial wall during working memory delays. The Journal of neuroscience : the official journal of the Society for Neuroscience 1998;18(22):9429-9437.

[46] Price DD, Bush FM, Long S, Harkins SW. A comparison of pain measurement characteristics of mechanical visual analogue and simple numerical rating scales. Pain 1994;56(2):217-226.

[47] Price DD, McGrath PA, Rafii A, Buckingham B. The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. Pain 1983;17(1):45-56.

[48] Price DD, McHaffie JG, Stein BE. The psychophysical attributes of heat-induced pain and their relationships to neural mechanisms. Journal of cognitive neuroscience 1992;4(1):1-14.

[49] Rainville P, Feine JS, Bushnell MC, Duncan GH. A psychophysical comparison of sensory and affective responses to four modalities of experimental pain. Somatosensory & motor research 1992;9(4):265-277.

[50] Rao SM, Mayer AR, Harrington DL. The evolution of brain activation during temporal processing. Nature neuroscience 2001;4(3):317-323.

[51] Ricciardi E, Bonino D, Gentili C, Sani L, Pietrini P, Vecchi T. Neural correlates of spatial working memory in humans: a functional magnetic resonance imaging study comparing visual and tactile processes. Neuroscience 2006;139(1):339-349.

[52] Romo R, Salinas E. Flutter discrimination: neural codes, perception, memory and decision making. Nature reviews Neuroscience 2003;4(3):203-218.

[53] Simon SR, Meunier M, Piettre L, Berardi AM, Segebarth CM, Boussaoud D. Spatial attention and memory versus motor preparation: premotor cortex involvement as revealed by fMRI. Journal of neurophysiology 2002;88(4):2047-2057.

[54] Villemure C, Bushnell MC. Mood influences supraspinal pain processing separately from attention. The Journal of neuroscience : the official journal of the Society for Neuroscience 2009;29(3):705-715.

[55] Wager TD, Keller MC, Lacey SC, Jonides J. Increased sensitivity in neuroimaging analyses using robust regression. NeuroImage 2005;26(1):99-113.

[56] Wager TD, Rilling JK, Smith EE, Sokolik A, Casey KL, Davidson RJ, Kosslyn SM, Rose RM, Cohen JD. Placebo-induced changes in FMRI in the anticipation and experience of pain. Science (New York, NY) 2004;303(5661):1162-1167.

[57] Wager TD, Smith EE. Neuroimaging studies of working memory: a meta-analysis. Cognitive, affective & behavioral neuroscience 2003;3(4):255-274.

[58] Wiener M, Turkeltaub P, Coslett HB. The image of time: a voxel-wise meta-analysis. NeuroImage 2010;49(2):1728-1740.

Supplementary Materials

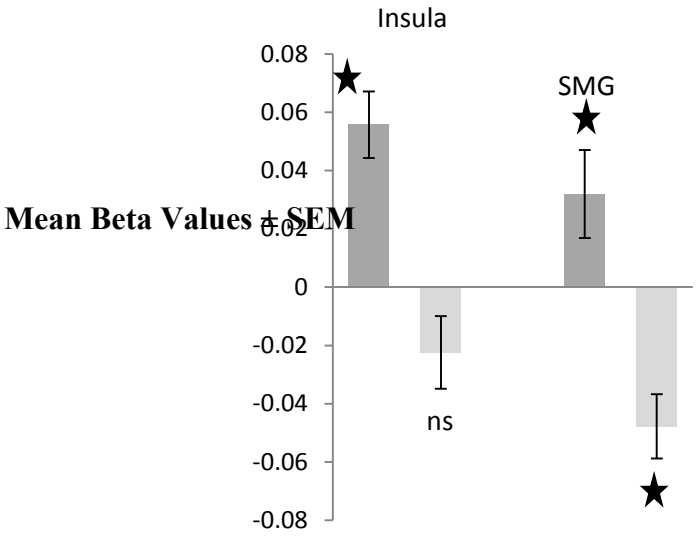

Figure S1. Mean beta values extracted for the target task (dark grey) and the control task (light grey) for the clusters identified for the task contrasts in model 1 (Global task model).
Star symbol (★) indicates a significant deviation from 0 ($p < .05$).

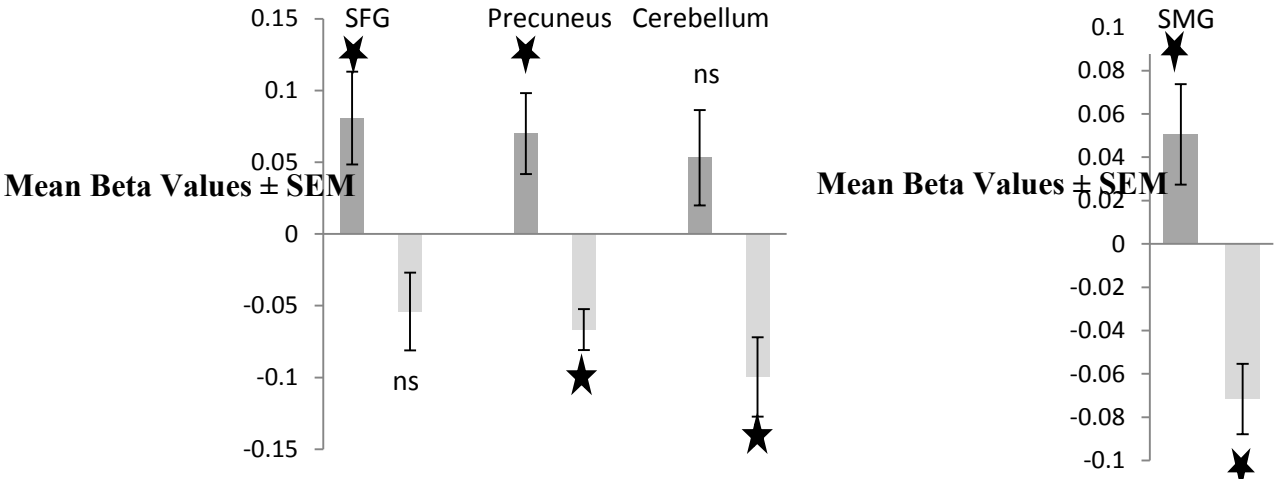

Figure S2. Mean beta values extracted for the target tasks (dark grey) and the control task (light grey) for the clusters identified for the task contrasts in model 2 (Task-epochs model).
Left panel corresponds to the dynamic task and right panel corresponds to the duration task. Star symbol (★) indicates a significant deviation from 0 ($p < .05$).

Chapter 7: General conclusion

7.1. An overview

Memory traces of pain persist in the central nervous system and can significantly affect the behavioral response to future pain. Despite its importance, pain memory has not been researched thoroughly compared to other sensory modalities. Theoretical accounts of memory suggest that the memory system involves an interactive multi-stage information processing mechanism consisting of immediate, short-term, and long-term memory. Based on this theoretical background, pain also follows a transformation in memory from the immediate offset of a noxious event (immediate memory), to a few seconds later (short-term memory), and finally to months or years later (long-term memory). There are some studies on immediate and long-term memory of pain, while short-term memory of pain has received little attention.

Short-term memory is responsible for short-term retention of information that lasts several seconds. This thesis, along with the few other experimental studies of acute pain reviewed in Chapter 4, examined the explicit short-term memory of acute pain. Research on short-term memory of pain has largely focused on intensity or spatial attributes. Thus, the mechanisms and neural correlates of short-term memory for the temporal attributes of pain have not been previously explored. The experimental work described in this thesis was designed to address the properties and neural correlates of the short-term memory of temporal attributes of pain. With regard to temporal processing of pain, one question that we tried to address is the conjoint processing of duration and intensity during dynamic tracking of pain. While in study 1 we investigated the nature of conjoint information processing, in studies 2 and 3 we compared the conjoint processing vs. isolated processing of duration for innocuous and noxious stimuli using psychophysical and imaging methods.

7.2. General summary of the main results of the studies

Study 1: Pain inherently is a dynamic experience with fluctuations in intensity over time. Even exposure to a brief noxious stimulus of constant stimulus energy results in a dynamic perceptual experience that does not precisely map to the stimulus temporal profile. This is evident from the continuous ratings of pain acquired in study 1 following exposure to heat pain stimuli of a constant temperature. From the information processing standpoint, the temporal profile of pain ratings corresponds to a large amount of information that is complex to manipulate and maintain in short-term memory. Therefore, one ultimate question is how we remember changes in pain over time.

Study 1 taps into a fundamental question about the nature of mental representations for the perception and memory of pain dynamics. We acquired continuous pain ratings concurrent with heat pain stimuli as well as retrospective pain ratings after a short delay. We applied principal component analysis on the continuous pain ratings in order to draw independent components that explain most of the variance in the continuous pain ratings. We showed that a large amount of redundant information could be summarized in terms of three independent components, and we hypothesized that these three components reflect the mental representation used for memory of pain dynamics. The first component represents the global image of the pain felt (i.e. pain increasing, then decreasing after a while), the second represents the changes in pain felt at the beginning and end of the stimulus plateau, and the third component represents the changes in pain felt in the middle of the plateau. We infer that participants likely used these three types of independent information to maintain and recall the dynamics of pain.

In study 1, we also compared concurrent vs. retrospective pain ratings to explore whether pain-related information undergoes a transformation in short-term memory. We showed that information about the three components is distorted in short-term memory. We additionally examined the memory effects on several temporal and intensity parameters extracted from continuous curves (i.e. total duration of pain, time to maximum pain, maximum pain felt, etc.). Similarly, the analysis on these parameters

reveals significant memory distortions. In particular, the temporal parameters were shorter in the retrospective vs. the perceptual condition, revealing a deterioration of temporal information in short-term memory. Overall, the results of study 1 show a significant distortion of pain-related information in short-term memory.

Study 2: In study 2, we looked at the short-term memory of the duration of innocuous thermal stimuli in order to investigate whether the memory distortion of the temporal aspect of pain was also present for non-painful thermal stimuli. We showed that, using a similar stimulus profile with a constant plateau and continuous ratings of sensation, the same results were observed (i.e. underestimation of total duration of sensation after a delay).

In this study we also explored additional properties of temporal processing by including another type of stimulus that featured fluctuations in intensity (segmented stimuli). We aimed to investigate whether the classical temporal property of the event-filling effect (i.e. dilation of perceived duration when an interval is filled with multiple events rather than a single event) was present using innocuous thermal stimuli. Investigating the temporal memory of segmented non-painful stimuli could be considered a first step toward future pain memory research using segmented stimuli. The results confirmed the event-filling effect in a somatosensory modality and showed that segmented stimuli facilitate the recall of duration.

Since dynamic tracking of sensation inherently requires conjoint processing of duration and intensity, we also included a separate condition consisting of the isolated processing of duration. We achieved this by manipulating the task instructions, asking the subjects to attend to the conjoint attribute of duration/intensity vs. the single attribute of duration in separate conditions. We showed that for the segmented stimuli, the isolated processing of duration resulted in underestimation of duration in memory compared to the conjoint processing of duration/intensity. Therefore, the improvement of duration recall was dependent on conjoint processing of duration/intensity. In conclusion, study 2 showed that the classical temporal properties of the event-filling effect (segmentation) are

applicable to non-painful thermal stimuli, and that this effect is modulated by the instruction to attend to and monitor dynamic changes in the intensity of sensation.

Study 3: In study 3, we again used attentional manipulation to compare memory processing of the conjoint duration/intensity attribute (dynamic condition) to processing of the isolated duration attribute (duration condition), using noxious thermal stimuli. Results showed that the recall of duration was more accurate and closer to perceptual responses in the dynamic condition vs. the duration condition. Therefore, we showed that monitoring changes in pain facilitates the recall of duration. We also used fMRI in this study to investigate the neural correlates of short-term memory for pain dynamics and pain duration in comparison to pain intensity. The results showed that memory of pain dynamics activates the fronto-parietal network and bilateral SMA extending to adjacent premotor cortices while memory for pain duration activated SI and SMG extending to SII as well as insula. Therefore our results argue for distinct processes involved for the retention of pain dynamics vs. duration. Some of these regions, such as the SI, SII and posterior insula, are known to be central to pain sensory processing while others, such as the SMA, anterior insula, SMG, and frontal cortices, are known to be involved in temporal processing. This was the first study that showed a core temporal processing network known to be involved in the processing of duration for other sensory modalities is also implicated in processing temporal aspects of pain. On the other hand, activation of core pain processing regions such as SI and SII during memory of pain duration argues for the involvement of regions required for sensory processing of pain in the retention of pain duration. This is in accordance with the sensory recruitment hypothesis for short-term memory that is inspired by studies showing that, for modalities other than pain, the main areas involved in perceptual processing of stimuli are also involved in the retention of information about those stimuli (Pasternak and Greenlee 2005). In summary, study 3 examined the neural correlates underlying short-term memory for temporal aspects of pain, either in isolation or in conjunction with intensity.

7.3. Clinical importance of pain memory research

Research on pain memory is multi-faceted and has significant clinical implications. One aspect relates to whether the memory of pain can elicit the sensation of pain in the absence of nociceptive input. This has been a subject of scientific investigation for a few decades. It has been shown in rats that the memory of painful irritation of the paw is not eliminated by denervation (Dennis and Melzack 1979). This finding resonates well with the known phenomenon of phantom limb pain. It has been suggested that the root cause of phantom limb pain is the memory of pain caused by damage to the limb prior to amputation (Katz and Melzack 1990). Thus, it is plausible that in such circumstances the memory of pain has the potential to provoke the sensation of pain. Recent research on chronic pain suggests that chronic pain is a conditioned response to non-noxious stimuli and that it is associative learning of non-nociceptive and nociceptive input that leads to pain (Price and Inyang 2015). Therefore, it is argued that ultimately the memory of pain is the root cause of chronic pain and that the reversal of pain memory might be the key to treating chronic pain disorders. In general, these studies highlight that pain memory is encoded in the brain and affects the perception of future pain.

One of the primary functions of pain is to warn us about potential threat associated with immediate or future tissue damage. For example, the memory of burning pain one felt when touching a hot pot would make someone vigilant against touching a hot pot in the future. Such instances are abundant in everyday life. However this function might serve a dual role. It has been shown that patients' memories of unpleasant medical procedures can negatively influence their decisions about future treatment choices (Erskine et al. 1990). For example, individuals who felt discomfort in a previous dental treatment are more reluctant to make future dental visits (Smyth 1994). This is also true for screening procedures such as colonoscopy (Redelmeier et al. 2003) or mammography (Baines et al. 1990). This has motivated some researchers to pursue non-pharmacological approaches to altering painful memories. For example, it has been shown that the amount

of pain felt just before the end of a colonoscopy session significantly shapes the memory of the overall session (Redelmeier et al. 2003). It has also been shown that introducing a short non-painful interval to the end of the procedure during which the tip of the colonoscope remained in the rectum decreased the overall pain ratings and increased the return rates for subsequent colonoscopy procedures (Redelmeier et al. 2003). Experimental pain research can play an important role in exploring the features that have significant impact on pain recall.

Another aspect of pain memory research is whether painful memories are susceptible to change and whether pain recall varies across individuals. Currently, there is debate with regard to accuracy of pain recall. While some studies argue that pain can be recalled accurately (Nunnink and Meana 2007; Singer et al. 2001), others argue against it (Daoust et al. 2017). It has been shown that there are individual differences in the perception of pain (Coghill 2010; Schulz et al. 2011; Schulz et al. 2012), so it is plausible that individual differences could be a factor affecting pain recall. A longitudinal study of the recollection of women's labor pain from two months to five years after birth shows that average pain scores of recollected labour pain intensity declined over time (Waldenstrom and Schytt 2009). However, this study showed that there is significant individual variation in the recollection of labour pain. A sub-population remembered pain as equal or even worse, in the course of five years. This calls for future experimental and clinical studies to investigate what factors impact individual differences in pain recall.

Altogether there is significant clinical relevance for research on pain memory, and experimental studies play a primary role in investigating the mechanisms of pain memory and how it affects the perception of future pain.

7.4. Limitations of experimental studies of pain memory

It is known that a variety of demographic factors such as gender, age, ethnicity, etc., affect the perception of pain (Fillingim 2005). For example, older persons are

especially vulnerable to the negative impacts of pain (Gibson and Farrell 2004). Another study showed that racial/ethnic minorities underreport the intensity of pain in acute and chronic conditions compare to whites and subsequently receive less adequate treatment (Green et al. 2003; Mossey 2011). These demographic factors can also play a significant role in pain recall. Moreover, other individual factors such as affective/anxiety states are known to predict long-term pain recall in clinical populations (Gedney et al. 2003; Klages et al. 2006; Kyle et al. 2016; Lin et al. 2017).

However, in most experimental studies on pain and pain memory various individual factors that could potential affect pain and pain memory have not been assessed or recorded. These studies often recruit healthy young participants from university settings and therefore the results of these studies might not be generalizable to older subjects, ethnic minorities, clinical populations, etc. Importantly, individual differences in anxiety states are not often recorded in pain studies and therefore it is not clear how much the results of a certain study are driven by individual differences in state anxiety and fear.

Another potential limitation in memory research in general is covert mental processes underlying memory. Imaging studies examine brain activity during memory delay in the absence of sensory input or overt motor response. Activation in the memory delay is often contrasted with the baseline activation, during which subjects are asked to do nothing, or contrasted with a control condition. Most of the studies on pain memory reviewed in Chapter 4 used a contrast with baseline. However, there is no absolute baseline as during baseline subjects may engage in a variety of covert mental processes such as mind-wandering, reflecting on previous trials, or anticipation of following trials. Indeed there is growing body of evidence that suggests a particular pattern of brain activation and deactivation occurs during the resting state (Raichle et al. 2001; van den Heuvel and Hulshoff Pol 2010). This spontaneous activity, often referred to as the ‘default mode network,’ is associated with a variety of internally-oriented mental processes (e.g. self-referential cognition or future-oriented thought). This means that

positive, negative, or even null effects in a memory condition relative to such baseline are difficult to interpret.

Alternatively, some studies use control conditions. For example, in study 3 we used the intensity task as the control condition to examine memory of pain duration. This provides a valid control for all irrelevant-aspects of the task such as sustained attention motor preparation and allows inferring with some confidence that the significant effects reported are associated with processing of pain duration rather than pain intensity in memory. We used intensity as the control condition as it is the most prominent feature of pain, although other unidimensional sensory attributes could also be used as control. Therefore the generalizability of the results of a given study is limited given that the observed effect might be related to the control task. This is a potential limitation of various memory studies that use control tasks in general. Therefore the generalizability and robustness of the observed effects of a study is reliant on replication of the results across a variety of control conditions and different experimental paradigms.

7.5. Future research avenues

The studies described in this manuscript generally focused on memory of the temporal attributes of pain. However, our understanding of the processing of temporal attributes of pain during pain perception is also very limited. Future studies using attentional instructions to process duration vs. other sensory attributes of pain may enhance our understanding of the perception of temporal attributes of pain.

In study 1, we showed that subjects' reports of the dynamics of pain can be decomposed into three components that relate to distinctive phases of dynamic pain processing. One direct follow-up question for future imaging studies using similar dynamic stimuli concerns the neural correlates of PCA components. More specifically, certain brain areas show changes in neural activity akin to the shape of the components. Similarly to study 1, in study 3 dynamic reports were acquired and therefore PCA

analysis can also be applied to these behavioral reports. Future analysis of the imaging data of study 3 can therefore provide a map between behavioral outputs related to the mental representation held in memory and brain activation responsible for the retention of those representations.

One of the well-studied effects on short-term memory is the load effect. It has been shown that increasing memory load generally leads to lower performance, and some studies show that PFC activation reflects this effect (Druzgal and D'Esposito 2003; Jha and McCarthy 2000). It would be interesting to manipulate the memory load in future studies on pain memory. For example, using dynamic stimuli consisting of multiple segments such as those implemented in study 2 would allow manipulation of the number of intensity fluctuations, the intensity of each segment, and the duration of each segment.

It would also be interesting to examine whether the properties of short-term memory, as well as its neural correlates, would be similar when comparing various types of experimentally induced pain such as laser or electrical pain. Future studies using the same paradigms as those reported here but using other modalities of pain would enhance our understanding of whether the observed effects are similar across different types of pain.

In time perception literature, there is generally a distinction between sub-sec vs. multi-sec duration range. This effect is well-documented for modalities other than pain. It would be interesting to compare temporal processing for both perception and memory of pain across these two duration ranges.

7.6. Conclusion

The studies conducted in this thesis investigated fundamental neuroscientific questions about explicit short-term memory of pain. We explored the duration of pain, both in conjunction with intensity in dynamic tracking of pain intensity across time (dynamic condition), as well as in isolation (duration condition). In general, our

behavioral results show deterioration of duration information in short-term memory. Our imaging results show distinct patterns of neural activation for memory processing during the dynamic and duration conditions when compared to the control condition (intensity). Results suggest that the conjoint processing of duration and intensity (dynamic condition) is not simply an additive effect of duration and intensity processing. In general the brain activation showed the involvement of some core pain regions (such as SI, SII, and insula), some core time processing regions (such as SMA), as well as a fronto-parietal network generally involved in working memory. Our results concerning the involvement of some pain processing regions in the memory-delay are also consistent with short-term memory studies of other modalities, where it has been shown that primary sensory areas responsible for perception are also implicated in the retention of sensory information. These results also provide some insights that regions involved in temporal processing of other modalities are also implicated in temporal processing of pain.

Overall, our understanding of the memory processing for pain-related information is very limited compared to other modalities. Indeed only a handful of studies have examined properties and neural correlates of the memory of various dimensions of pain. Examination of these studies show striking similarities between short-term memory of pain and other modalities including activation of the fronto-parietal network as well as activation of sensory areas involved in perceptual processing. Future studies using experimental designs incorporating other sensory dimensions as well as a comparison of noxious vs. innocuous stimuli can provide a better understanding of the memory of the sensory dimension of pain.

Bibliography

Agarwal, N., P. A. Choi, S. S. Shin, D. R. Hansberry and A. Mammis (2016). "Anterior cingulotomy for intractable pain." Interdisciplinary Neurosurgery 6: 80-83.

Agostino, P., E. Gatto, M. Cesarini, J. Etcheverry, A. Sanguinetti and D. Golombek (2017). "Deficits in temporal processing correlate with clinical progression in Huntington's disease." Acta Neurologica Scandinavica.

Albanese, M.-C., E. G. Duerden, P. Rainville and G. H. Duncan (2007). "Memory Traces of Pain in Human Cortex." The Journal of Neuroscience 27(17): 4612-4620.

Apkarian, A. V., M. C. Bushnell, R. D. Treede and J. K. Zubieta (2005). "Human brain mechanisms of pain perception and regulation in health and disease." European Journal of Pain 9(4): 463-484.

Apkarian, A. V. and C. J. Hodge (1989). "Primate spinothalamic pathways: III. Thalamic terminations of the dorsolateral and ventral spinothalamic pathways." Journal of Comparative Neurology 288(3): 493-511.

Apkarian, A. V. and T. Shi (1994). "Squirrel monkey lateral thalamus. I. Somatic nociresponsive neurons and their relation to spinothalamic terminals." Journal of Neuroscience 14(11): 6779-6795.

Arienzo, D., C. Babiloni, A. Ferretti, M. Caulo, C. Del Gratta, A. Tartaro, P. M. Rossini and G. L. Romani (2006). "Somatotopy of anterior cingulate cortex (ACC) and supplementary motor area (SMA) for electric stimulation of the median and tibial nerves: an fMRI study." NeuroImage 33(2): 700-705.

Artieda, J., M. A. Pastor, F. Lacruz and J. A. Obeso (1992). "Temporal discrimination is abnormal in Parkinson's disease." Brain 115(1): 199-210.

Atkinson, R. C. and R. M. Shiffrin (1968). "Human memory: A proposed system and its control processes." Psychology of learning and motivation 2: 89-195.

Avanzino, L., E. Pelosin, C. M. Vicario, G. Lagravinese, G. Abbruzzese and D. Martino (2016). "Time processing and motor control in movement disorders." Frontiers in human neuroscience 10.

Awh, E. and W. J. Gehring (1999). "The anterior cingulate cortex lends a hand in response selection." Nature Neuroscience 2(10): 853-854.

Awh, E., J. Jonides and P. A. Reuter-Lorenz (1998). "Rehearsal in spatial working memory." Journal of Experimental Psychology: Human Perception and Performance 24(3): 780.

Awh, E., E. Vogel and S.-H. Oh (2006). "Interactions between attention and working memory." Neuroscience 139(1): 201-208.

Babul, N., A. C. Darke, D. H. Johnson and K. Charron-Vincent (1993). "Using memory for pain in analgesic research." Ann Pharmacother 27(1): 9-12.

Baddeley, A. (1996). "Exploring the Central Executive." The Quarterly Journal of Experimental Psychology Section A 49(1): 5-28.

Baddeley, A. (2000). "The episodic buffer: a new component of working memory?" Trends Cogn Sci 4(11): 417-423.

Baddeley, A. (2012). "Working memory: theories, models, and controversies." Annual review of psychology 63: 1-29.

Baddeley, A. D. and G. Hitch (1974). "Working memory." Psychology of learning and motivation 8: 47-89.

Baines, C. J., T. To and C. Wall (1990). "Women's attitudes to screening after participation in the National Breast Screening Study. A questionnaire survey." Cancer 65(7): 1663-1669.

Baliki, M. N., P. Y. Geha and A. V. Apkarian (2009). "Parsing pain perception between nociceptive representation and magnitude estimation." Journal of Neurophysiology 101(2): 875-887.

Barrouillet, P. and V. Camos (2007). "The time-based resource-sharing model of working memory." The cognitive neuroscience of working memory 455: 59-80.

Basbaum, A. I., D. M. Bautista, G. Scherrer and D. Julius (2009). "Cellular and molecular mechanisms of pain." Cell 139(2): 267-284.

Becerra, L., H. C. Breiter, R. Wise, R. G. Gonzalez and D. Borsook (2001). "Reward circuitry activation by noxious thermal stimuli." Neuron 32(5): 927-946.

Beese, A. and S. Morley (1993). "Memory for acute pain experience is specifically inaccurate but generally reliable." Pain 53(2): 183-189.

Bernard, J. F., G. F. Huang and J. M. Besson (1992). "Nucleus centralis of the amygdala and the globus pallidus ventralis: electrophysiological evidence for an involvement in pain processes." Journal of Neurophysiology 68(2): 551-569.

Berryhill, M. E. (2012). "Insights from neuropsychology: pinpointing the role of the posterior parietal cortex in episodic and working memory." Frontiers in Integrative Neuroscience 6: 31.

Berryhill, M. E. and I. R. Olson (2008). "The right parietal lobe is critical for visual working memory." Neuropsychologia 46(7): 1767-1774.

Berthier, M., S. Starkstein and R. Leiguarda (1988). "Asymbolia for pain: a sensory-limbic disconnection syndrome." Ann Neurol 24(1): 41-49.

Bettencourt, K. C. and Y. Xu (2016). "Decoding the content of visual short-term memory under distraction in occipital and parietal areas." Nature neuroscience 19(1): 150-157.

Bingel, U., J. Glascher, C. Weiller and C. Buchel (2004). "Somatotopic representation of nociceptive information in the putamen: an event-related fMRI study." Cerebral Cortex 14(12): 1340-1345.

Bingel, U., J. Lorenz, V. Glauche, R. Knab, J. Glascher, C. Weiller and C. Buchel (2004). "Somatotopic organization of human somatosensory cortices for pain: a single trial fMRI study." NeuroImage 23(1): 224-232.

Bingel, U., M. Quante, R. Knab, B. Bromm, C. Weiller and C. Buchel (2002). "Subcortical structures involved in pain processing: evidence from single-trial fMRI." Pain 99(1-2): 313-321.

Bisley, J. W. and T. Pasternak (2000). "The multiple roles of visual cortical areas MT/MST in remembering the direction of visual motion." Cerebral Cortex 10(11): 1053-1065.

Bisley, J. W., D. Zaksas, J. A. Droll and T. Pasternak (2004). "Activity of neurons in cortical area MT during a memory for motion task." Journal of Neurophysiology 91(1): 286-300.

Bisley, J. W., D. Zaksas and T. Pasternak (2001). "Microstimulation of cortical area MT affects performance on a visual working memory task." Journal of Neurophysiology 85(1): 187-196.

Bledowski, C., B. Rahm and J. B. Rowe (2009). "What "works" in working memory? Separate systems for selection and updating of critical information." Journal of Neuroscience 29(43): 13735-13741.

Block, R. A. and R. P. Gruber (2014). "Time perception, attention, and memory: a selective review." Acta Psychol (Amst) 149: 129-133.

Block, R. A., P. A. Hancock and D. Zakay (2010). "How cognitive load affects duration judgments: A meta-analytic review." Acta Psychol (Amst) 134(3): 330-343.

Block, R. A. and D. Zakay (1997). "Prospective and retrospective duration judgments: A meta-analytic review." Psychon Bull Rev 4(2): 184-197.

Boivie, J. (1979). "An anatomical reinvestigation of the termination of the spinothalamic tract in the monkey." Journal of Comparative Neurology 186(3): 343-369.

Bonato, M., M. Zorzi and C. Umiltà (2012). "When time is space: evidence for a mental time line." Neuroscience & Biobehavioral Reviews 36(10): 2257-2273.

Bor, D., J. Duncan, R. J. Wiseman and A. M. Owen (2003). "Encoding strategies dissociate prefrontal activity from working memory demand." Neuron 37(2): 361-367.

Borsook, D., J. Upadhyay, E. H. Chudler and L. Becerra (2010). "A key role of the basal ganglia in pain and analgesia - insights gained through human functional imaging." Molecular Pain 6: 27-27.

Broadway, J. M. and R. W. Engle (2011). "Lapsed attention to elapsed time? Individual differences in working memory capacity and temporal reproduction." Acta psychologica 137(1): 115-126.

Brooks, J. C., T. J. Nurmikko, W. E. Bimson, K. D. Singh and N. Roberts (2002). "fMRI of thermal pain: effects of stimulus laterality and attention." NeuroImage 15(2): 293-301.

Brooks, J. C., L. Zambreanu, A. Godinez, A. D. Craig and I. Tracey (2005). "Somatotopic organisation of the human insula to painful heat studied with high resolution functional imaging." NeuroImage 27(1): 201-209.

Brown, J. W. and T. S. Braver (2005). "Learned predictions of error likelihood in the anterior cingulate cortex." Science 307(5712): 1118-1121.

Brown, S. W. (1995). "Time, change, and motion: the effects of stimulus movement on temporal perception." Percept Psychophys 57(1): 105-116.

Brown, S. W. (1997). "Attentional resources in timing: Interference effects in concurrent temporal and nontemporal working memory tasks." Attention, Perception, & Psychophysics 59(7): 1118-1140.

Brown, S. W. (2006). "Timing and executive function: Bidirectional interference between concurrent temporal production and randomization tasks." Memory & Cognition 34(7): 1464-1471.

Brown, S. W. (2008). "The attenuation effect in timing: Counteracting dual-task interference with time-judgment skill training." Perception 37(5): 712-724.

Brown, S. W., S. A. Collier and J. C. Night (2013). "Timing and executive resources: dual-task interference patterns between temporal production and shifting, updating, and inhibition tasks." Journal of Experimental Psychology: Human Perception and Performance 39(4): 947.

Brown, S. W. and S. M. Merchant (2007). "Processing resources in timing and sequencing tasks." Attention, Perception, & Psychophysics 69(3): 439-449.

Buchel, C., K. Bornhovd, M. Quante, V. Glauche, B. Bromm and C. Weiller (2002). "Dissociable neural responses related to pain intensity, stimulus intensity, and stimulus awareness within the anterior cingulate cortex: a parametric single-trial laser functional magnetic resonance imaging study." Journal of Neuroscience 22(3): 970-976.

Bueti, D., B. Bahrami and V. Walsh (2008). "Sensory and association cortex in time perception." Journal of Cognitive Neuroscience 20(6): 1054-1062.

Bueti, D. and V. Walsh (2009). "The parietal cortex and the representation of time, space, number and other magnitudes." Philosophical Transactions of the Royal Society of London B: Biological Sciences 364(1525): 1831-1840.

Bueti, D., V. Walsh, C. Frith and G. Rees (2008). "Different brain circuits underlie motor and perceptual representations of temporal intervals." Journal of Cognitive Neuroscience 20(2): 204-214.

Buhusi, C. V. and W. H. Meck (2005). "What makes us tick? Functional and neural mechanisms of interval timing." Nature Reviews Neuroscience 6(10): 755-765.

Buhusi, C. V. and W. H. Meck (2009). "Relative time sharing: new findings and an extension of the resource allocation model of temporal processing." Philosophical Transactions of the Royal Society of London B: Biological Sciences 364(1525): 1875-1885.

Buonomano, D. V. (2000). "Decoding temporal information: A model based on short-term synaptic plasticity." Journal of Neuroscience 20(3): 1129-1141.

Buonomano, D. V. and M. M. Merzenich (1995). "Temporal information transformed into a spatial code by a neural network with realistic properties." Science 267(5200): 1028-1030.

Burns, E., L. S. Chipchase and S. M. Schabrun (2016). "Primary sensory and motor cortex function in response to acute muscle pain: A systematic review and meta-analysis." European Journal of Pain 20(8): 1203-1213.

Burton, H. and R. J. Sinclair (2000). "Attending to and remembering tactile stimuli: a review of brain imaging data and single-neuron responses." Journal of Clinical Neurophysiology 17(6): 575-591.

Buschman, T. J. and E. K. Miller (2007). "Top-down versus bottom-up control of attention in the prefrontal and posterior parietal cortices." Science 315(5820): 1860-1862.

Bushnell, M., G. Duncan and N. Tremblay (1993). "Thalamic VPM nucleus in the behaving monkey. I. Multimodal and discriminative properties of thermosensitive neurons." Journal of Neurophysiology 69(3): 739-752.

Bushnell, M. C., G. H. Duncan, R. K. Hofbauer, B. Ha, J. I. Chen and B. Carrier (1999). "Pain perception: is there a role for primary somatosensory cortex?" Proceedings of the National Academy of Sciences U S A 96(14): 7705-7709.

Cariani, P. (2001). "Temporal Codes, Timing Nets, and Music Perception." Journal of New Music Research 30(2): 107-135.

Carter, C. S., M. M. Botvinick and J. D. Cohen (1999). "The contribution of the anterior cingulate cortex to executive processes in cognition." Reviews in the Neurosciences 10(1): 49-58.

Casini, L. and R. B. Ivry (1999). "Effects of divided attention on temporal processing in patients with lesions of the cerebellum or frontal lobe." Neuropsychology 13(1): 10.

Casini, L. and F. Macar (1997). "Effects of attention manipulation on judgments of duration and of intensity in the visual modality." Memory & Cognition 25(6): 812-818.

Casini, L., F. Macar and M.-H. Giard (1999). "Relation between level of prefrontal activity and subject's performance." Journal of Psychophysiology 13(2): 117.

Casini, L., F. Macar and S. Grondin (1992). Time estimation and attentional sharing. Time, Action and Cognition, Springer: 177-180.

Chafee, M. V. and P. S. Goldman-Rakic (1998). "Matching patterns of activity in primate prefrontal area 8a and parietal area 7ip neurons during a spatial working memory task." Journal of Neurophysiology 79(6): 2919-2940.

Chapin, H., E. Bagarinao and S. Mackey (2012). "Real-time fMRI applied to pain management." Neuroscience Letters 520(2): 174-181.

Christophel, T. B. and J. D. Haynes (2014). "Decoding complex flow-field patterns in visual working memory." NeuroImage 91: 43-51.

Christophel, T. B., M. N. Hebart and J. D. Haynes (2012). "Decoding the contents of visual short-term memory from human visual and parietal cortex." Journal of Neuroscience 32(38): 12983-12989.

Chudler, E. H. (1998). "Response properties of neurons in the caudate-putamen and globus pallidus to noxious and non-noxious thermal stimulation in anesthetized rats." Brain Research 812(1-2): 283-288.

Chudler, E. H., F. Anton, R. Dubner and D. R. Kenshalo, Jr. (1990). "Responses of nociceptive SI neurons in monkeys and pain sensation in humans elicited by noxious thermal stimulation: effect of interstimulus interval." Journal of Neurophysiology 63(3): 559-569.

Chudler, E. H. and W. K. Dong (1995). "The role of the basal ganglia in nociception and pain." Pain 60(1): 3-38.

Chudler, E. H., K. Sugiyama and W. K. Dong (1993). "Nociceptive responses in the neostriatum and globus pallidus of the anesthetized rat." Journal of Neurophysiology 69(6): 1890-1903.

Chun, M. M. and M. K. Johnson (2011). "Memory: enduring traces of perceptual and reflective attention." Neuron 72(4): 520-535.

Church, R. M. (1984). "Properties of the internal clock." Ann N Y Acad Sci 423: 566-582.

Coghill, R. C. (2010). "Individual Differences in the Subjective Experience of Pain: New Insights into Mechanisms and Models." Headache 50(9): 1531-1535.

Coghill, R. C., C. N. Sang, J. M. Maisog and M. J. Iadarola (1999). "Pain intensity processing within the human brain: a bilateral, distributed mechanism." Journal of Neurophysiology 82(4): 1934-1943.

Constantinidis, C. (2016). "A Code for Cross-Modal Working Memory." Neuron 89(1): 3-5.

Constantinidis, C. and E. Procyk (2004). "The primate working memory networks." Cognitive, Affective & Behavioral Neuroscience 4(4): 444-465.

Constantinidis, C. and M. A. Steinmetz (1996). "Neuronal activity in posterior parietal area 7a during the delay periods of a spatial memory task." Journal of Neurophysiology 76(2): 1352-1355.

Corbetta, M., J. M. Kincade and G. L. Shulman (2002). "Neural systems for visual orienting and their relationships to spatial working memory." Journal of Cognitive Neuroscience 14(3): 508-523.

Corbetta, M., F. M. Miezin, G. L. Shulman and S. E. Petersen (1993). "A PET study of visuospatial attention." Journal of Neuroscience 13(3): 1202-1226.

Corbetta, M., G. Patel and G. L. Shulman (2008). "The reorienting system of the human brain: from environment to theory of mind." Neuron 58(3): 306-324.

Corbetta, M. and G. L. Shulman (2002). "Control of goal-directed and stimulus-driven attention in the brain." Nature Reviews Neuroscience 3(3): 201-215.

Coull, J. T., P. Charras, M. Donadieu, S. Droit-Volet and F. Vidal (2015). "SMA Selectively Codes the Active Accumulation of Temporal, Not Spatial, Magnitude." Journal of Cognitive Neuroscience 27(11): 2281-2298.

Coull, J. T., R.-K. Cheng and W. H. Meck (2011). "Neuroanatomical and Neurochemical Substrates of Timing." Neuropsychopharmacology 36(1): 3-25.

Coull, J. T. and C. D. Frith (1998). "Differential activation of right superior parietal cortex and intraparietal sulcus by spatial and nonspatial attention." NeuroImage 8(2): 176-187.

Coull, J. T., B. Nazarian and F. Vidal (2008). "Timing, storage, and comparison of stimulus duration engage discrete anatomical components of a perceptual timing network." Journal of cognitive neuroscience 20(12): 2185-2197.

Coull, J. T. and A. C. Nobre (1998). "Where and when to pay attention: the neural systems for directing attention to spatial locations and to time intervals as revealed by both PET and fMRI." Journal of Neuroscience 18(18): 7426-7435.

Coull, J. T., F. Vidal, B. Nazarian and F. Macar (2004). "Functional anatomy of the attentional modulation of time estimation." Science 303(5663): 1506-1508.

Courtney, S. M., L. G. Ungerleider, K. Keil and J. V. Haxby (1997). "Transient and sustained activity in a distributed neural system for human working memory." Nature 386(6625): 608-611.

Cowan, N. (1988). "Evolving conceptions of memory storage, selective attention, and their mutual constraints within the human information-processing system." Psychol Bull 104(2): 163-191.

Cowan, N. (1999). "An embedded-processes model of working memory." Models of working memory: Mechanisms of active maintenance and executive control 20: 506.

Cowan, N. (2001). "The magical number 4 in short-term memory: a reconsideration of mental storage capacity." Behav Brain Sci 24(1): 87-114; discussion 114-185.

Cowan, N. (2008). "What are the differences between long-term, short-term, and working memory?" Prog Brain Research 169: 323-338.

Cowan, N. (2015). Chapter 2 - Sensational Memorability: Working Memory for Things We See, Hear, Feel, or Somehow Sense A2 - Jolicoeur, Pierre. Mechanisms of Sensory Working Memory. C. Lefebvre and J. Martinez-Trujillo. San Diego, Academic Press: 5-22.

Craggs, J. G., D. D. Price, G. N. Verne, W. M. Perlstein and M. M. Robinson (2007). "Functional brain interactions that serve cognitive–affective processing during pain and placebo analgesia." NeuroImage 38(4): 720-729.

Craig, A. (2006). "Retrograde analyses of spinothalamic projections in the macaque monkey: input to ventral posterior nuclei." Journal of Comparative Neurology 499(6): 965-978.

Craig, A. D. (2003). "Interoception: the sense of the physiological condition of the body." Curr Opin Neurobiol 13(4): 500-505.

Craig, A. D. (2003). "A new view of pain as a homeostatic emotion." Trends Neurosci 26(6): 303-307.

Craig, A. D. (2004). "Distribution of trigeminothalamic and spinothalamic lamina I terminations in the macaque monkey." Journal of Comparative Neurology 477(2): 119-148.

Craig, A. D. (2006). "Retrograde analyses of spinothalamic projections in the macaque monkey: input to ventral posterior nuclei." Journal of Comparative Neurology 499(6): 965-978.

Craig, A. D. (2009). "How do you feel--now? The anterior insula and human awareness." Nature Reviews Neuroscience 10(1): 59-70.

Craig, A. D. (2014). "Topographically organized projection to posterior insular cortex from the posterior portion of the ventral medial nucleus in the long-tailed macaque monkey." Journal of Comparative Neurology 522(1): 36-63.

Craig, A. D., M. C. Bushnell, E. T. Zhang and A. Blomqvist (1994). "A thalamic nucleus specific for pain and temperature sensation." Nature 372(6508): 770-773.

Craig, J. C. (1973). "A constant error in the perception of brief temporal intervals." Attention, Perception, & Psychophysics 13(1): 99-104.

Crowe, D. A., W. Zarco, R. Bartolo and H. Merchant (2014). "Dynamic representation of the temporal and sequential structure of rhythmic movements in the primate medial premotor cortex." Journal of Neuroscience 34(36): 11972-11983.

Curtis, C. E. (2006). "Prefrontal and parietal contributions to spatial working memory." Neuroscience 139(1): 173-180.

Curtis, C. E. and M. D'Esposito (2003). "Persistent activity in the prefrontal cortex during working memory." Trends Cogn Sci 7(9): 415-423.

Curtis, C. E. and D. Lee (2010). "Beyond working memory: the role of persistent activity in decision making." Trends Cogn Sci 14(5): 216-222.

Curtis, C. E., V. Y. Rao and M. D'Esposito (2004). "Maintenance of spatial and motor codes during oculomotor delayed response tasks." Journal of Neuroscience 24(16): 3944-3952.

D'Esposito, M. (2007). "From cognitive to neural models of working memory." Philosophical Transactions of the Royal Society of London B: Biological Sciences 362(1481): 761-772.

D'esposito, M. and B. R. Postle (2015). "The cognitive neuroscience of working memory." Annual review of psychology 66.

Daniel, T. A., J. S. Katz and J. L. Robinson (2016). "Delayed match-to-sample in working memory: A BrainMap meta-analysis." Biological psychology 120: 10-20.

Daoust, R., M.-J. Sirois, J. S. Lee, J. J. Perry, L. E. Griffith, A. Worster, E. Lang, J. Paquet, J.-M. Chauny and M. Émond (2017). "Painful Memories: Reliability of Pain Intensity Recall at 3 Months in Senior Patients." Pain Research & Management 2017: 5983721.

Davidson, S., X. Zhang, S. G. Khasabov, D. A. Simone and G. J. Giesler (2008). "Termination Zones of Functionally Characterized Spinothalamic Tract Neurons

Within the Primate Posterior Thalamus." Journal of Neurophysiology 100(4): 2026-2037.

Davis, K. D., W. D. Hutchison, A. M. Lozano and J. O. Dostrovsky (1994). "Altered pain and temperature perception following cingulotomy and capsulotomy in a patient with schizoaffective disorder." Pain 59(2): 189-199.

Davis, K. D., W. D. Hutchison, A. M. Lozano, R. R. Tasker and J. O. Dostrovsky (2000). "Human anterior cingulate cortex neurons modulated by attention-demanding tasks." Journal of Neurophysiology 83(6): 3575-3577.

Davis, K. D., S. J. Taylor, A. P. Crawley, M. L. Wood and D. J. Mikulis (1997). "Functional MRI of pain- and attention-related activations in the human cingulate cortex." Journal of Neurophysiology 77(6): 3370-3380.

deCharms, R. C., F. Maeda, G. H. Glover, D. Ludlow, J. M. Pauly, D. Soneji, J. D. E. Gabrieli and S. C. Mackey (2005). "Control over brain activation and pain learned by using real-time functional MRI." Proceedings of the National Academy of Sciences of the United States of America 102(51): 18626-18631.

Del Olmo, M. F., B. Cheeran, G. Koch and J. C. Rothwell (2007). "Role of the cerebellum in externally paced rhythmic finger movements." Journal of Neurophysiology 98(1): 145-152.

Dennis, S. G. and R. Melzack (1979). "Self-mutilation after dorsal rhizotomy in rats: effects of prior pain and pattern of root lesions." Exp Neurol 65(2): 412-421.

Derbyshire, S. W., A. K. Jones, F. Gyulai, S. Clark, D. Townsend and L. L. Firestone (1997). "Pain processing during three levels of noxious stimulation produces differential patterns of central activity." Pain 73(3): 431-445.

Devinsky, O., M. J. Morrell and B. A. Vogt (1995). "Contributions of anterior cingulate cortex to behaviour." Brain 118(1): 279-306.

Dong, W. K., E. H. Chudler, K. Sugiyama, V. J. Roberts and T. Hayashi (1994). "Somatosensory, multisensory, and task-related neurons in cortical area 7b (PF) of unanesthetized monkeys." Journal of Neurophysiology 72(2): 542-564.

Dong, W. K., L. D. Salonen, Y. Kawakami, T. Shiwaku, E. M. Kaukoranta and R. F. Martin (1989). "Nociceptive responses of trigeminal neurons in SII-7b cortex of awake monkeys." Brain Research 484(1–2): 314-324.

Dostrovsky, J. O. and A. D. Craig (1996). "Cooling-specific spinothalamic neurons in the monkey." Journal of Neurophysiology 76(6): 3656-3665.

Druzgal, T. J. and M. D'Esposito (2003). "Dissecting contributions of prefrontal cortex and fusiform face area to face working memory." Journal of Cognitive Neuroscience 15(6): 771-784.

Duerden, E. G. and M. C. Albanese (2013). "Localization of pain-related brain activation: a meta-analysis of neuroimaging data." Human Brain Mapping 34(1): 109-149.

Dum, R. P., D. J. Levinthal and P. L. Strick (2009). "The Spinothalamic System Targets Motor and Sensory Areas in the Cerebral Cortex of Monkeys." The Journal of neuroscience : the official journal of the Society for Neuroscience 29(45): 14223-14235.

Dum, R. P. and P. L. Strick (1991). "The origin of corticospinal projections from the premotor areas in the frontal lobe." Journal of Neuroscience 11(3): 667-689.

Dum, R. P. and P. L. Strick (1996). "Spinal Cord Terminations of the Medial Wall Motor Areas in Macaque Monkeys." The Journal of Neuroscience 16(20): 6513-6525.

Duncan, G. H. and M. C. Albanese (2003). "Is there a role for the parietal lobes in the perception of pain?" Adv Neurol 93: 69-86.

Dutke, S. (2005). "Remembered duration: Working memory and the reproduction of intervals." Attention, Perception, & Psychophysics 67(8): 1404-1413.

Eagleman, D. M. and V. Pariyadath (2009). "Is subjective duration a signature of coding efficiency?" Philosophical Transactions of the Royal Society B: Biological Sciences 364(1525): 1841-1851.

Edin, F., T. Klingberg, P. Johansson, F. McNab, J. Tegnér and A. Compte (2009). "Mechanism for top-down control of working memory capacity." Proceedings of the National Academy of Sciences 106(16): 6802-6807.

Eldon L. Foltz and Lowell E. White (1962). "Pain “Relief” by Frontal Cingulumotomy." Journal of Neurosurgery 19(2): 89-100.

Emrich, S. M., A. C. Riggall, J. J. Larocque and B. R. Postle (2013). "Distributed patterns of activity in sensory cortex reflect the precision of multiple items maintained in visual short-term memory." Journal of Neuroscience 33(15): 6516-6523.

Erskine, A., S. Morley and S. Pearce (1990). "Memory for pain: a review." Pain 41(3): 255-265.

Ester, E. F., R. L. Rademaker and T. C. Sprague (2016). "How Do Visual and Parietal Cortex Contribute to Visual Short-Term Memory?" eNeuro 3(2): ENEURO.0041-0016.2016.

Everts, B., B. Karlson, P. Wahrborg, N. Abdon, J. Herlitz and T. Hedner (1999). "Pain recollection after chest pain of cardiac origin." Cardiology 92(2): 115-120.

Fairhurst, M., K. Fairhurst, C. Berna and I. Tracey (2012). "An fMRI study exploring the overlap and differences between neural representations of physical and recalled pain." PloS one 7(10): e48711.

Ferrandez, A.-M., L. Hugueville, S. Lehéricy, J.-B. Poline, C. Marsault and V. Pouthas (2003). "Basal ganglia and supplementary motor area subtend duration perception: an fMRI study." NeuroImage 19(4): 1532-1544.

Ferrera, V. P., K. K. Rudolph and J. H. Maunsell (1994). "Responses of neurons in the parietal and temporal visual pathways during a motion task." Journal of Neuroscience 14(10): 6171-6186.

Fierro, B., A. Palermo, A. Puma, M. Francolini, M. Panetta, O. Daniele and F. Brighina (2007). "Role of the cerebellum in time perception: a TMS study in normal subjects." Journal of the neurological sciences 263(1): 107-112.

Fillingim, R. B. (2005). "Individual differences in pain responses." Curr Rheumatol Rep 7(5): 342-347.

Fortin, C., M.-C. Bédard and J. Champagne (2005). "Timing during interruptions in timing." Journal of Experimental Psychology: Human Perception and Performance 31(2): 276.

Fortin, C. and R. Breton (1995). "Temporal interval production and processing in working memory." Attention, Perception, & Psychophysics 57(2): 203-215.

Fraisse, P. (1984). "Perception and estimation of time." Annual review of psychology 35(1): 1-37.

Freund, W., R. Klug, F. Weber, G. Stuber, B. Schmitz and A. P. Wunderlich (2009). "Perception and suppression of thermally induced pain: a fMRI study." Somatosens Mot Res 26(1): 1-10.

Freund, W., G. Stuber, A. P. Wunderlich and B. Schmitz (2007). "Cortical correlates of perception and suppression of electrically induced pain." Somatosens Mot Res 24(4): 203-212.

Friedman, D. P. and E. A. Murray (1986). "Thalamic connectivity of the second somatosensory area and neighboring somatosensory fields of the lateral sulcus of the macaque." Journal of Comparative Neurology 252(3): 348-373.

Friedman, H. R. and P. S. Goldman-Rakic (1994). "Coactivation of prefrontal cortex and inferior parietal cortex in working memory tasks revealed by 2DG functional mapping in the rhesus monkey." Journal of Neuroscience 14(5 Pt 1): 2775-2788.

Frot, M., I. Faillenot and F. Mauguiere (2014). "Processing of nociceptive input from posterior to anterior insula in humans." Human Brain Mapping 35(11): 5486-5499.

Fuchs, P. N., Y. B. Peng, J. A. Boyette-Davis and M. L. Uhelski (2014). "The anterior cingulate cortex and pain processing." Frontiers in Integrative Neuroscience 8: 35.

Funahashi, S., C. J. Bruce and P. S. Goldman-Rakic (1989). "Mnemonic coding of visual space in the monkey's dorsolateral prefrontal cortex." Journal of Neurophysiology 61(2): 331-349.

Funahashi, S., C. J. Bruce and P. S. Goldman-Rakic (1990). "Visuospatial coding in primate prefrontal neurons revealed by oculomotor paradigms." Journal of Neurophysiology 63(4): 814-831.

Funahashi, S., M. V. Chafee and P. S. Goldman-Rakic (1993). "Prefrontal neuronal activity in rhesus monkeys performing a delayed anti-saccade task." Nature 365(6448): 753.

Fuster, J. M., R. H. Bauer and J. P. Jervey (1981). "Effects of cooling inferotemporal cortex on performance of visual memory tasks." Exp Neurol 71(2): 398-409.

Fuster, J. n. M. (2001). "The Prefrontal Cortex—An Update: Time Is of the Essence." Neuron 30(2): 319-333.

Gallace, A., H. Z. Tan, P. Haggard and C. Spence (2008). "Short term memory for tactile stimuli." Brain Research 1190: 132-142.

Garcia-Larrea, L. (2012). "The posterior insular-opercular region and the search of a primary cortex for pain." Neurophysiol Clin 42(5): 299-313.

Garcia-Larrea, L. and R. Peyron (2013). "Pain matrices and neuropathic pain matrices: a review." Pain 154 Suppl 1: S29-43.

Garcia-Larrea, L., R. Peyron, P. Mertens, M. C. Gregoire, F. Lavenne, D. Le Bars, P. Convers, F. Mauguiere, M. Sindou and B. Laurent (1999). "Electrical stimulation of motor cortex for pain control: a combined PET-scan and electrophysiological study." Pain 83(2): 259-273.

Garcia-Larreaa, L. and M. Magnina "The Nociceptive Thalamus: A Brief History."

Gazzaley, A., J. W. Cooney, K. McEvoy, R. T. Knight and M. D'Esposito (2005). "Top-down enhancement and suppression of the magnitude and speed of neural activity." Journal of Cognitive Neuroscience 17(3): 507-517.

Gazzaley, A., J. Rissman, J. Cooney, A. Rutman, T. Seibert, W. Clapp and M. D'Esposito (2007). "Functional interactions between prefrontal and visual association cortex contribute to top-down modulation of visual processing." Cerebral Cortex 17 Suppl 1: i125-135.

Gedney, J. J., H. Logan and R. S. Baron (2003). "Predictors of short-term and long-term memory of sensory and affective dimensions of pain." The Journal of Pain 4(2): 47-55.

Genovesio, A., S. Tsujimoto and S. P. Wise (2006). "Neuronal activity related to elapsed time in prefrontal cortex." Journal of Neurophysiology 95(5): 3281-3285.

Gibbon, J., R. M. Church and W. H. Meck (1984). "Scalar timing in memory." Ann N Y Acad Sci 423: 52-77.

Gibson, S. J. and M. Farrell (2004). "A review of age differences in the neurophysiology of nociception and the perceptual experience of pain." Clin J Pain 20(4): 227-239.

Gilson, E. Q. and A. D. Baddeley (1969). "Tactile short-term memory." Q Journal of Experimental Psychology 21(2): 180-184.

Gingold, S. I., J. D. Greenspan and A. V. Apkarian (1991). "Anatomic evidence of nociceptive inputs to primary somatosensory cortex: relationship between spinothalamic terminals and thalamocortical cells in squirrel monkeys." Journal of Comparative Neurology 308(3): 467-490.

Goldman-Rakic, P. S. (1995). "Cellular basis of working memory." Neuron 14(3): 477-485.

Gooch, C. M., M. Wiener, E. B. Wencil and H. B. Coslett (2010). "Interval timing disruptions in subjects with cerebellar lesions." Neuropsychologia 48(4): 1022-1031.

Green, C. R., K. O. Anderson, T. A. Baker, L. C. Campbell, S. Decker, R. B. Fillingim, D. A. Kalauokalani, K. E. Lasch, C. Myers, R. C. Tait, K. H. Todd and A. H. Vallerand (2003). "The unequal burden of pain: confronting racial and ethnic disparities in pain." Pain Med 4(3): 277-294.

Greenspan, J. D., R. R. Lee and F. A. Lenz (1999). "Pain sensitivity alterations as a function of lesion location in the parasylvian cortex." Pain 81(3): 273-282.

Greenspan, J. D. and J. A. Winfield (1992). "Reversible pain and tactile deficits associated with a cerebral tumor compressing the posterior insula and parietal operculum." Pain 50(1): 29-39.

Grondin, S. (1993). "Duration discrimination of empty and filled intervals marked by auditory and visual signals." Percept Psychophys 54(3): 383-394.

Grondin, S. (2010). "Timing and time perception: a review of recent behavioral and neuroscience findings and theoretical directions." Atten Percept Psychophys 72(3): 561-582.

Grondin, S. and T. Rammsayer (2003). "Variable foreperiods and temporal discrimination." The Quarterly Journal of Experimental Psychology: Section A 56(4): 731-765.

Haegens, S., D. Osipova, R. Oostenveld and O. Jensen (2010). "Somatosensory working memory performance in humans depends on both engagement and disengagement of regions in a distributed network." Human Brain Mapping 31(1): 26-35.

Hamidi, M., G. Tononi and B. R. Postle (2008). "Evaluating frontal and parietal contributions to spatial working memory with repetitive transcranial magnetic stimulation." Brain Research 1230: 202-210.

Harrington, D. L., K. Y. Haaland and N. Hermanowitz (1998). "Temporal processing in the basal ganglia." Neuropsychology 12(1): 3.

Harrington, D. L., R. R. Lee, L. A. Boyd, S. Z. Rapcsak and R. T. Knight (2004). "Does the representation of time depend on the cerebellum? Effect of cerebellar stroke." Brain 127(3): 561-574.

Harrington, D. L., J. L. Zimbelman, S. C. Hinton and S. M. Rao (2009). "Neural modulation of temporal encoding, maintenance, and decision processes." Cerebral Cortex 20(6): 1274-1285.

Harris, A. J. (1999). "Cortical origin of pathological pain." Lancet 354(9188): 1464-1466.

Harris, J. A., I. M. Harris and M. E. Diamond (2001). "The Topography of Tactile Working Memory." The Journal of Neuroscience 21(20): 8262-8269.

Harris, J. A., C. Miniussi, I. M. Harris and M. E. Diamond (2002). "Transient storage of a tactile memory trace in primary somatosensory cortex." Journal of Neuroscience 22(19): 8720-8725.

Harrison, S. A. and F. Tong (2009). "Decoding reveals the contents of visual working memory in early visual areas." Nature 458(7238): 632-635.

Hasuo, E., Y. Nakajima, E. Tomimatsu, S. Grondin and K. Ueda (2014). "The occurrence of the filled duration illusion: a comparison of the method of adjustment with the method of magnitude estimation." Acta Psychol (Amst) 147: 111-121.

Hasuo, E., Y. Nakajima and K. Ueda (2011). "Does filled duration illusion occur for very short time intervals?" Acoustical Science and Technology 32(2): 82-85.

Hayashi, M. J., M. Kantele, V. Walsh, S. Carlson and R. Kanai (2014). "Dissociable neuroanatomical correlates of subsecond and suprasecond time perception." Journal of Cognitive Neuroscience 26(8): 1685-1693.

He, S. Q., R. P. Dum and P. L. Strick (1995). "Topographic organization of corticospinal projections from the frontal lobe: motor areas on the medial surface of the hemisphere." Journal of Neuroscience 15(5 Pt 1): 3284-3306.

Henderson, L. A., S. C. Gandevia and V. G. Macefield (2007). "Somatotopic organization of the processing of muscle and cutaneous pain in the left and right insula cortex: a single-trial fMRI study." Pain 128(1-2): 20-30.

Hinton, S. C. and W. H. Meck (1997). "The 'internal clocks' of circadian and interval timing." Endeavour 21(2): 82-87.

Hinton, S. C. and W. H. Meck (2004). "Frontal–striatal circuitry activated by human peak-interval timing in the supra-seconds range." Cognitive Brain Research 21(2): 171-182.

Hofbauer, R. K., P. Rainville, G. H. Duncan and M. C. Bushnell (2001). "Cortical representation of the sensory dimension of pain." Journal of Neurophysiology 86(1): 402-411.

Honey, C. R., A. J. Stoessl, J. K. Tsui, M. Schulzer and D. B. Calne (1999). "Unilateral pallidotomy for reduction of parkinsonian pain." J Neurosurg 91(2): 198-201.

Horr, N. K. and M. Di Luca (2015). "Filling the blanks in temporal intervals: the type of filling influences perceived duration and discrimination performance." Frontiers in Psychology 6(114).

Hutchison, W. D., K. D. Davis, A. M. Lozano, R. R. Tasker and J. O. Dostrovsky (1999). "Pain-related neurons in the human cingulate cortex." Nature Neuroscience 2(5): 403-405.

Ihle, R. C. and W. E. Wilsoncroft (1983). "The filled-duration illusion: limits of duration of interval and auditory fillers." Percept Mot Skills 56(2): 655-660.

Irwin, D. E. and Gordon, R. D. (1998). "Eye movements, attention and trans-saccadic memory." Visual cognition 5(1-2): 127-155.

Ivry, R. B. (1996). "The representation of temporal information in perception and motor control." Current Opinion in Neurobiology 6(6): 851-857.

Ivry, R. B. and S. W. Keele (1989). "Timing functions of the cerebellum." Journal of Cognitive Neuroscience 1(2): 136-152.

Ivry, R. B. and J. E. Schlerf (2008). "Dedicated and intrinsic models of time perception." Trends in Cognitive Science 12(7): 273-280.

Ivry, R. B. and R. M. Spencer (2004). "The neural representation of time." Current Opinion in Neurobiology 14(2): 225-232.

Jacob, S. N. and A. Nieder (2014). "Complementary roles for primate frontal and parietal cortex in guarding working memory from distractor stimuli." Neuron 83(1): 226-237.

Jahanshahi, M., C. R. Jones, G. Dirnberger and C. D. Frith (2006). "The substantia nigra pars compacta and temporal processing." Journal of Neuroscience 26(47): 12266-12273.

James, W. (1890). "The Principles of." Psychology 2.

Jantzen, K. J., F. L. Steinberg and J. A. Kelso (2005). "Functional MRI reveals the existence of modality and coordination-dependent timing networks." NeuroImage 25(4): 1031-1042.

Jha, A. P. and G. McCarthy (2000). "The influence of memory load upon delay-interval activity in a working-memory task: an event-related functional MRI study." Journal of Cognitive Neuroscience 12 Suppl 2: 90-105.

Johnson, M. K., C. L. Raye, K. J. Mitchell, E. J. Greene, W. A. Cunningham and C. A. Sanislow (2005). "Using fMRI to investigate a component process of reflection: prefrontal correlates of refreshing a just-activated representation." Cognitive Affective Behavioral Neurosci 5(3): 339-361.

Jones, C. R., K. Rosenkranz, J. C. Rothwell and M. Jahanshahi (2004). "The right dorsolateral prefrontal cortex is essential in time reproduction: an investigation with repetitive transcranial magnetic stimulation." Experimental Brain Research 158(3): 366-372.

Jonides, J. and D. E. Nee (2006). "Brain mechanisms of proactive interference in working memory." Neuroscience 139(1): 181-193.

Kaas, A. L., H. van Mier, M. Visser and R. Goebel (2013). "The neural substrate for working memory of tactile surface texture." Human Brain Mapping 34(5): 1148-1162.

Kagerer, F. A., M. Wittmann, E. Szelag and N. v. Steinbüchel (2002). "Cortical involvement in temporal reproduction: evidence for differential roles of the hemispheres." Neuropsychologia 40(3): 357-366.

Kanai, R., C. L. Paffen, H. Hogendoorn and F. A. Verstraten (2006). "Time dilation in dynamic visual display." J Vis 6(12): 1421-1430.

Kandel, E. R., J. H. Schwartz, T. M. Jessell, S. A. Siegelbaum and A. J. Hudspeth (2000). Principles of neural science, McGraw-hill New York.

Kaneko, S. and I. Murakami (2009). "Perceived duration of visual motion increases with speed." J Vis 9(7): 14.

Karmarkar, U. R. and D. V. Buonomano (2007). "Timing in the absence of clocks: encoding time in neural network states." Neuron 53(3): 427-438.

Katus, T., A. Grubert and M. Eimer (2015). "Electrophysiological Evidence for a Sensory Recruitment Model of Somatosensory Working Memory." Cerebral Cortex 25(12): 4697-4703.

Katus, T., M. M. Muller and M. Eimer (2015). "Sustained maintenance of somatotopic information in brain regions recruited by tactile working memory." Journal of Neuroscience 35(4): 1390-1395.

Katz, J. and R. Melzack (1990). "Pain 'memories' in phantom limbs: review and clinical observations." Pain 43(3): 319-336.

Kenshalo, D. and O. Isensee (1983). "Responses of primate SI cortical neurons to noxious stimuli." Journal of Neurophysiology 50(6): 1479-1496.

Kenshalo Jr, D., E. Chudler, F. Anton and R. Dubner (1988). "SI nociceptive neurons participate in the encoding process by which monkeys perceive the intensity of noxious thermal stimulation." Brain research 454(1-2): 378.

Kerns, J. G., J. D. Cohen, A. W. MacDonald, R. Y. Cho, V. A. Stenger and C. S. Carter (2004). "Anterior cingulate conflict monitoring and adjustments in control." Science 303(5660): 1023-1026.

Khoshnejad, M., M. C. Fortin, F. Rohani, G. H. Duncan and P. Rainville (2014). "Remembering the dynamic changes in pain intensity and unpleasantness: A psychophysical study." Pain 155(3): 581-590.

Khoshnejad, M., K. Martinu, S. Grondin and P. Rainville (2016). "The delayed reproduction of long time intervals defined by innocuous thermal sensation." Exp Brain Research 234(4): 1095-1104.

Khoshnejad, M., M. Roy, K. Martinu, J. I. Chen, J. Cohen-Adad, S. Grondin and P. Rainville (2017). "Brain processing of the temporal dimension of acute pain in short-term memory." Pain 158(10): 2001-2011.

Klages, U., S. Kianifard, Ö. Ulusoy and H. Wehrbein (2006). "Anxiety sensitivity as predictor of pain in patients undergoing restorative dental procedures." Community Dentistry and Oral Epidemiology 34(2): 139-145.

Klingberg, T., R. Kawashima and P. E. Roland (1996). "Activation of multi-modal cortical areas underlies short-term memory." European Journal of Neuroscience 8(9): 1965-1971.

Koch, G., M. Oliveri and C. Caltagirone (2009). "Neural networks engaged in milliseconds and seconds time processing: evidence from transcranial magnetic stimulation and patients with cortical or subcortical dysfunction." Philosophical Transactions of the Royal Society of London B: Biological Sciences 364(1525): 1907-1918.

Koch, G., M. Oliveri, G. A. Carlesimo and C. Caltagirone (2002). "Selective deficit of time perception in a patient with right prefrontal cortex lesion." Neurology 59(10): 1658-1658.

Koch, G., M. Oliveri, S. Torriero and C. Caltagirone (2003). "Underestimation of time perception after repetitive transcranial magnetic stimulation." Neurology 60(11): 1844-1846.

Koch, G., M. Oliveri, S. Torriero, S. Salerno, E. L. Gerfo and C. Caltagirone (2007). "Repetitive TMS of cerebellum interferes with millisecond time processing." Experimental brain research 179(2): 291-299.

Koenigs, M., A. K. Barbey, B. R. Postle and J. Grafman (2009). "Superior parietal cortex is critical for the manipulation of information in working memory." Journal of Neuroscience 29(47): 14980-14986.

Kondo, H., N. Osaka and M. Osaka (2004). "Cooperation of the anterior cingulate cortex and dorsolateral prefrontal cortex for attention shifting." NeuroImage 23(2): 670-679.

Kong, J., N. S. White, K. K. Kwong, M. G. Vangel, I. S. Rosman, R. H. Gracely and R. L. Gollub (2006). "Using fMRI to dissociate sensory encoding from cognitive evaluation of heat pain intensity." Human brain mapping 27(9): 715-721.

Kong, J., N. S. White, K. K. Kwong, M. G. Vangel, I. S. Rosman, R. H. Gracely and R. L. Gollub (2006). "Using fMRI to dissociate sensory encoding from cognitive evaluation of heat pain intensity." Human Brain Mapping 27(9): 715-721.

Kostopoulos, P., M.-C. Albanese and M. Petrides (2007). "Ventrolateral prefrontal cortex and tactile memory disambiguation in the human brain." Proceedings of the National Academy of Sciences 104(24): 10223-10228.

Kostopoulos, P. and M. Petrides (2003). "The mid-ventrolateral prefrontal cortex: insights into its role in memory retrieval." European Journal of Neuroscience 17(7): 1489-1497.

Kostopoulos, P. and M. Petrides (2016). "Selective memory retrieval of auditory what and auditory where involves the ventrolateral prefrontal cortex." Proceedings of the National Academy of Sciences U S A 113(7): 1919-1924.

Ku, Y., D. Zhao, M. Bodner and Y. D. Zhou (2015). "Cooperative processing in primary somatosensory cortex and posterior parietal cortex during tactile working memory." European Journal of Neuroscience 42(3): 1905-1911.

Kyle, B. N., D. W. McNeil, B. Weaver and T. Wilson (2016). "Recall of Dental Pain and Anxiety in a Cohort of Oral Surgery Patients." J Dent Res 95(6): 629-634.

Lara, A. H. and J. D. Wallis (2015). "The Role of Prefrontal Cortex in Working Memory: A Mini Review." Front Syst Neurosci 9: 173.

Lee, S. H., D. J. Kravitz and C. I. Baker (2013). "Goal-dependent dissociation of visual and prefrontal cortices during working memory." Nature Neuroscience 16(8): 997-999.

Legrain, V., G. D. Iannetti, L. Plaghki and A. Mouraux (2011). "The pain matrix reloaded: a salience detection system for the body." Prog Neurobiol 93(1): 111-124.

Lemus, L., A. Hernandez, R. Luna, A. Zainos and R. Romo (2010). "Do sensory cortices process more than one sensory modality during perceptual judgments?" Neuron 67(2): 335-348.

Lenz, F. A., R. H. Gracely, A. T. Zirh, A. J. Romanoski and P. M. Dougherty (1997). "The sensory-limbic model of pain memory: Connections from thalamus to the limbic system mediate the learned component of the affective dimension of pain." Pain Forum 6(1): 22-31.

Leon, M. I. and M. N. Shadlen (2003). "Representation of time by neurons in the posterior parietal cortex of the macaque." Neuron 38(2): 317-327.

Lepsien, J. and A. C. Nobre (2006). "Attentional modulation of object representations in working memory." Cerebral cortex 17(9): 2072-2083.

Lepsien, J. and A. C. Nobre (2006). "Cognitive control of attention in the human brain: insights from orienting attention to mental representations." Brain Research 1105(1): 20-31.

Leung, H. C., J. C. Gore and P. S. Goldman-Rakic (2002). "Sustained mnemonic response in the human middle frontal gyrus during on-line storage of spatial memoranda." Journal of Cognitive Neuroscience 14(4): 659-671.

Lewis, P. A. and R. Miall (2006). "A right hemispheric prefrontal system for cognitive time measurement." Behavioural Processes 71(2): 226-234.

Lewis, P. A. and R. C. Miall (2003). "Brain activation patterns during measurement of sub- and supra-second intervals." Neuropsychologia 41(12): 1583-1592.

Lewis, P. A. and R. C. Miall (2003). "Distinct systems for automatic and cognitively controlled time measurement: evidence from neuroimaging." Curr Opin Neurobiol 13(2): 250-255.

Liang, M., A. Mouraux, L. Hu and G. D. Iannetti (2013). "Primary sensory cortices contain distinguishable spatial patterns of activity for each sense." Nat Commun 4: 1979.

Lin, C. S., S. Y. Wu and C. A. Yi (2017). "Association between Anxiety and Pain in Dental Treatment: A Systematic Review and Meta-analysis." J Dent Res 96(2): 153-162.

Livesey, A. C., M. B. Wall and A. T. Smith (2007). "Time perception: manipulation of task difficulty dissociates clock functions from other cognitive demands." Neuropsychologia 45(2): 321-331.

Lobanov, O. V., A. S. Quevedo, M. S. Hadsel, R. A. Kraft and R. C. Coghill (2013). "Fronto-parietal Mechanisms Supporting Attention to Location and Intensity of Painful Stimuli." Pain 154(9): 1758-1768.

Lockwood, P. L., G. D. Iannetti and P. Haggard (2013). "Transcranial magnetic stimulation over human secondary somatosensory cortex disrupts perception of pain intensity." Cortex 49(8): 2201-2209.

Loras, H., A. K. Stensdotter, F. Ohberg and H. Sigmundsson (2013). "Individual differences in motor timing and its relation to cognitive and fine motor skills." PLoS One 8(7): e69353.

Lorenz, J., D. J. Cross, S. Minoshima, T. J. Morrow, P. E. Paulson and K. L. Casey (2002). "A unique representation of heat allodynia in the human brain." Neuron 35(2): 383-393.

Lorenz, J., S. Minoshima and K. L. Casey (2003). "Keeping pain out of mind: the role of the dorsolateral prefrontal cortex in pain modulation." Brain 126(Pt 5): 1079-1091.

Macar, F., J. L. Anton, M. Bonnet and F. Vidal (2004). "Timing functions of the supplementary motor area: an event-related fMRI study." Brain Research Cogn Brain Research 21(2): 206-215.

Macar, F., J. Coull and F. Vidal (2006). "The supplementary motor area in motor and perceptual time processing: fMRI studies." Cognitive processing 7(2): 89-94.

Macar, F., S. Grondin and L. Casini (1994). "Controlled attention sharing influences time estimation." Memory & cognition 22(6): 673-686.

Macar, F., H. Lejeune, M. Bonnet, A. Ferrara, V. Pouthas, F. Vidal and P. Maquet (2002). "Activation of the supplementary motor area and of attentional networks during temporal processing." Experimental Brain Research 142(4): 475-485.

Macar, F. and F. Vidal (2002). "Time processing reflected by EEG surface Laplacians." Experimental brain research 145(3): 403-406.

Macar, F. and F. Vidal (2003). "The CNV peak: an index of decision making and temporal memory." Psychophysiology 40(6): 950-954.

Macar, F., F. Vidal and L. Casini (1999). "The supplementary motor area in motor and sensory timing: evidence from slow brain potential changes." Experimental Brain Research 125(3): 271-280.

MacIver, K., D. M. Lloyd, S. Kelly, N. Roberts and T. Nurmikko (2008). "Phantom limb pain, cortical reorganization and the therapeutic effect of mental imagery." Brain 131(Pt 8): 2181-2191.

Magnussen, S. (2000). "Low-level memory processes in vision." Trends Neurosci 23(6): 247-251.

Maihofner, C., B. Herzner and H. Otto Handwerker (2006). "Secondary somatosensory cortex is important for the sensory-discriminative dimension of pain: a functional MRI study." European Journal of Neuroscience 23(5): 1377-1383.

Maihofner, C. and M. Kaltenhauser (2009). "Quality discrimination for noxious stimuli in secondary somatosensory cortex: a MEG-study." European Journal of Pain 13(10): 1048 e1041-1047.

Malapani, C., B. Dubois, G. Rancurel and J. Gibbon (1998). "Cerebellar dysfunctions of temporal processing in the seconds range in humans." NeuroReport 9(17): 3907-3912.

Malhotra, P., E. J. Coulthard and M. Husain (2009). "Role of right posterior parietal cortex in maintaining attention to spatial locations over time." Brain 132(Pt 3): 645-660.

Mangels, J. A., R. B. Ivry and N. Shimizu (1998). "Dissociable contributions of the prefrontal and neocerebellar cortex to time perception." Cognitive Brain Research 7(1): 15-39.

Marois, R. (2015). Chapter 3 - The Brain Mechanisms of Working Memory: An Evolving Story A2 - Jolicoeur, Pierre. Mechanisms of Sensory Working Memory. C. Lefebvre and J. Martinez-Trujillo. San Diego, Academic Press: 23-31.

Marois, R. and J. Ivanoff (2005). "Capacity limits of information processing in the brain." Trends Cogn Sci 9(6): 296-305.

Marshuetz, C. and E. E. Smith (2006). "Working memory for order information: Multiple cognitive and neural mechanisms." Neuroscience 139(1): 195-200.

Martini, M., M. R. Furtner, T. Maran and P. Sachse (2015). "Information maintenance in working memory: an integrated presentation of cognitive and neural concepts." Frontiers in Systems Neuroscience 9: 104.

Matell, M. S. and W. H. Meck (2000). "Neuropsychological mechanisms of interval timing behavior." Bioessays 22(1): 94-103.

Matell, M. S. and W. H. Meck (2004). "Cortico-striatal circuits and interval timing: coincidence detection of oscillatory processes." Cognitive brain research 21(2): 139-170.

Matell, M. S. and W. H. Meck (2004). "Cortico-striatal circuits and interval timing: coincidence detection of oscillatory processes." Cognitive Brain Research 21(2): 139-170.

McCabe, C. S., R. C. Haigh, P. W. Halligan and D. R. Blake (2005). "Simulating sensory-motor incongruence in healthy volunteers: implications for a cortical model of pain." Rheumatology (Oxford) 44(4): 509-516.

Meck, W. H., T. B. Penney and V. Pouthas (2008). "Cortico-striatal representation of time in animals and humans." Current Opinion in Neurobiology 18(2): 145-152.

Melzack, R. and K. L. Casey (1968). "Sensory, motivational and central control determinants of pain: a new conceptual model." The skin senses 1.

Menon, V. and L. Q. Uddin (2010). "Saliency, switching, attention and control: a network model of insula function." Brain Structure and Function 214(5-6): 655-667.

Merchant, H., M. Luciana, C. Hooper, S. Majestic and P. Tuite (2008). "Interval timing and Parkinson's disease: heterogeneity in temporal performance." Experimental Brain Research 184(2): 233-248.

Merchant, H., O. Pérez, W. Zarco and J. Gámez (2013). "Interval tuning in the primate medial premotor cortex as a general timing mechanism." Journal of Neuroscience 33(21): 9082-9096.

Mercier, C. and G. Leonard (2011). "Interactions between Pain and the Motor Cortex: Insights from Research on Phantom Limb Pain and Complex Regional Pain Syndrome." Physiother Can 63(3): 305-314.

Mesulam, M. M. and E. J. Mufson (1982). "Insula of the old world monkey. III: Efferent cortical output and comments on function." Journal of Comparative Neurology 212(1): 38-52.

Miles, C. and M. Borthwick (1996). "Tactile short-term memory revisited." Memory 4(6): 655-668.

Miller, E. K. and J. D. Cohen (2001). "An integrative theory of prefrontal cortex function." Annu Rev Neurosci 24: 167-202.

Miller, G. A. (1956). "The magical number seven plus or minus two: some limits on our capacity for processing information." Psychol Rev 63(2): 81-97.

Mishkin, M., L. G. Ungerleider and K. A. Macko (1983). "Object vision and spatial vision: two cortical pathways." Trends in Neurosciences 6(Supplement C): 414-417.

Mita, A., H. Mushiake, K. Shima, Y. Matsuzaka and J. Tanji (2009). "Interval time coding by neurons in the presupplementary and supplementary motor areas." Nature neuroscience 12(4): 502-507.

Miyake, A., N. P. Friedman, M. J. Emerson, A. H. Witzki, A. Howerter and T. D. Wager (2000). "The unity and diversity of executive functions and their contributions to

complex “frontal lobe” tasks: A latent variable analysis." Cognitive psychology 41(1): 49-100.

Miyashita, Y. and H. S. Chang (1988). "Neuronal correlate of pictorial short-term memory in the primate temporal cortex." Nature 331(6151): 68-70.

Morecraft, R. J. and G. W. Van Hoesen (1992). "Cingulate input to the primary and supplementary motor cortices in the rhesus monkey: evidence for somatotopy in areas 24c and 23c." Journal of Comparative Neurology 322(4): 471-489.

Mossey, J. M. (2011). "Defining racial and ethnic disparities in pain management." Clin Orthop Relat Res 469(7): 1859-1870.

Mouraux, A., A. Diukova, M. C. Lee, R. G. Wise and G. D. Iannetti (2011). "A multisensory investigation of the functional significance of the "pain matrix"." NeuroImage 54(3): 2237-2249.

Mufson, E. J. and M. M. Mesulam (1984). "Thalamic connections of the insula in the rhesus monkey and comments on the paralimbic connectivity of the medial pulvinar nucleus." Journal of Comparative Neurology 227(1): 109-120.

Mufson, E. J., M. M. Mesulam and D. N. Pandya (1981). "Insular interconnections with the amygdala in the rhesus monkey." Neuroscience 6(7): 1231-1248.

Mulert, C., J. Gallinat, H. Dorn, W. M. Herrmann and G. Winterer (2003). "The relationship between reaction time, error rate and anterior cingulate cortex activity." International Journal of Psychophysiology 47(2): 175-183.

Murai, Y. and Y. Yotsumoto (2016). "Context-Dependent Neural Modulations in the Perception of Duration." Front Integr Neurosci 10: 12.

Navon, D. and D. Gopher (1979). "On the economy of the human-processing system." Psychological review 86(3): 214.

Nee, D. E., J. W. Brown, M. K. Askren, M. G. Berman, E. Demiralp, A. Krawitz and J. Jonides (2013). "A meta-analysis of executive components of working memory." Cerebral Cortex 23(2): 264-282.

Nee, D. E., J. Jonides and M. G. Berman (2007). "Neural mechanisms of proactive interference-resolution." NeuroImage 38(4): 740-751.

Nelson, R. J., M. Sur, D. J. Felleman and J. H. Kaas (1980). "Representations of the body surface in postcentral parietal cortex of Macaca fascicularis." Journal of Comparative Neurology 192(4): 611-643.

Nichelli, P., K. Clark, C. Hollnagel and J. Grafman (1995). "Duration processing after frontal lobe lesions." Annals of the New York Academy of Sciences 769(1): 183-190.

Niki, H. and M. Watanabe (1979). "Prefrontal and cingulate unit activity during timing behavior in the monkey." Brain research 171(2): 213-224.

Nobre, A. C., J. T. Coull, P. Maquet, C. D. Frith, R. Vandenberghe and M. M. Mesulam (2004). "Orienting attention to locations in perceptual versus mental representations." Journal of Cognitive Neuroscience 16(3): 363-373.

Nobre, A. C., G. N. Sebestyen, D. R. Gitelman, M. M. Mesulam, R. S. Frackowiak and C. D. Frith (1997). "Functional localization of the system for visuospatial attention using positron emission tomography." Brain 120 (Pt 3): 515-533.

Nunnink, S. and M. Meana (2007). "Remembering the pain: Accuracy of pain recall in endometriosis." Journal of Psychosomatic Obstetrics & Gynecology 28(4): 201-208.

Nuti, C., R. Peyron, L. Garcia-Larrea, J. Brunon, B. Laurent, M. Sindou and P. Mertens (2005). "Motor cortex stimulation for refractory neuropathic pain: four year outcome and predictors of efficacy." Pain 118(1-2): 43-52.

Ogden, R. S., E. Salominaite, L. Jones, J. Fisk and C. Montgomery (2011). "The role of executive functions in human prospective interval timing." Acta psychologica 137(3): 352-358.

Ogino, Y., H. Nemoto and F. Goto (2005). "Somatotopy in human primary somatosensory cortex in pain system." Anesthesiology 103(4): 821-827.

Ohmae, S., X. Lu, T. Takahashi, Y. Uchida and S. Kitazawa (2008). "Neuronal activity related to anticipated and elapsed time in macaque supplementary eye field." Experimental Brain Research 184(4): 593-598.

Oshiro, Y., A. S. Quevedo, J. G. McHaffie, R. A. Kraft and R. C. Coghill (2007). "Brain mechanisms supporting spatial discrimination of pain." Journal of Neuroscience 27(13): 3388-3394.

Oshiro, Y., A. S. Quevedo, J. G. McHaffie, R. A. Kraft and R. C. Coghill (2009). "Brain mechanisms supporting discrimination of sensory features of pain: a new model." Journal of Neuroscience 29(47): 14924-14931.

Pardo, J. V., P. T. Fox and M. E. Raichle (1991). "Localization of a human system for sustained attention by positron emission tomography." Nature 349(6304): 61-64.

Pasternak, T. and M. W. Greenlee (2005). "Working memory in primate sensory systems." Nature Reviews Neuroscience 6(2): 97-107.

Petersen, S. E. and M. I. Posner (2012). "The attention system of the human brain: 20 years after." Annual Review of Neuroscience 35: 73-89.

Petrides, M. (1996). "Specialized systems for the processing of mnemonic information within the primate frontal cortex." Philosophical Transactions of the Royal Society of London B: Biological Sciences 351(1346): 1455-1461; discussion 1461-1452.

Petrovic, P., E. Kalso, K. M. Petersson and M. Ingvar (2002). "Placebo and opioid analgesia-- imaging a shared neuronal network." Science 295(5560): 1737-1740.

Petrovic, P., K. M. Petersson, P. H. Ghatan, S. Stone-Elander and M. Ingvar (2000). "Pain-related cerebral activation is altered by a distracting cognitive task." Pain 85(1-2): 19-30.

Peyron, R., M. Frot, F. Schneider, L. Garcia-Larrea, P. Mertens, F. G. Barral, M. Sindou, B. Laurent and F. Mauguiere (2002). "Role of operculoinsular cortices in human pain processing: converging evidence from PET, fMRI, dipole modeling, and intracerebral recordings of evoked potentials." NeuroImage 17(3): 1336-1346.

Peyron, R., L. Garcia-Larrea, M. C. Gregoire, N. Costes, P. Convers, F. Lavenne, F. Mauguiere, D. Michel and B. Laurent (1999). "Haemodynamic brain responses to acute pain in humans: sensory and attentional networks." Brain 122 (Pt 9): 1765-1780.

Pfeuty, M., R. Ragot and V. Pouthas (2005). "Relationship between CNV and timing of an upcoming event." Neuroscience Letters 382(1-2): 106-111.

Ploghaus, A., I. Tracey, J. S. Gati, S. Clare, R. S. Menon, P. M. Matthews and J. N. Rawlins (1999). "Dissociating pain from its anticipation in the human brain." Science 284(5422): 1979-1981.

Pochon, J. B., R. Levy, J. B. Poline, S. Crozier, S. Lehericy, B. Pillon, B. Deweer, D. Le Bihan and B. Dubois (2001). "The role of dorsolateral prefrontal cortex in the preparation of forthcoming actions: an fMRI study." Cerebral Cortex 11(3): 260-266.

Pons, T. P., P. E. Garraghty, C. G. Cusick and J. H. Kaas (1985). "The somatotopic organization of area 2 in macaque monkeys." Journal of Comparative Neurology 241(4): 445-466.

Poppel, E. (2004). "Lost in time: a historical frame, elementary processing units and the 3-second window." Acta Neurobiologiae Experimentalis (Wars) 64(3): 295-301.

Pöppel, E. (1997). "A hierarchical model of temporal perception." Trends in Cognitive Sciences 1(2): 56-61.

Porro, C. A., V. Cettolo, M. P. Francescato and P. Baraldi (1998). "Temporal and intensity coding of pain in human cortex." Journal of Neurophysiology 80(6): 3312-3320.

Porro, C. A., M. Martinig, P. Facchin, M. Maieron, A. K. Jones and L. Fadiga (2007). "Parietal cortex involvement in the localization of tactile and noxious mechanical stimuli: a transcranial magnetic stimulation study." Behavioural Brain Research 178(2): 183-189.

Postle, B. R. (2005). "Delay-period activity in prefrontal cortex: one function is sensory gating." Journal of Cognitive Neuroscience 17(11): 1679-1690.

Postle, B. R. (2006). "Working memory as an emergent property of the mind and brain." Neuroscience 139(1): 23-38.

Pouthas, V., L. Garnero, A. M. Ferrandez and B. Renault (2000). "ERPs and PET analysis of time perception: spatial and temporal brain mapping during visual discrimination tasks." Human Brain Mapping 10(2): 49-60.

Pouthas, V., N. George, J. B. Poline, M. Pfeuty, P. F. Vandemoorteele, L. Hugueville, A. M. Ferrandez, S. Lehericy, D. Lebihan and B. Renault (2005). "Neural network involved in time perception: an fMRI study comparing long and short interval estimation." Human Brain Mapping 25(4): 433-441.

Preuschhof, C., H. R. Heekeren, B. Taskin, T. Schubert and A. Villringer (2006). "Neural correlates of vibrotactile working memory in the human brain." Journal of Neuroscience 26(51): 13231-13239.

Price, T. J. and K. E. Inyang (2015). "Commonalities between pain and memory mechanisms and their meaning for understanding chronic pain." Progress in Molecular Biology and Translational Science 131: 409-434.

Raichle, M. E., A. M. MacLeod, A. Z. Snyder, W. J. Powers, D. A. Gusnard and G. L. Shulman (2001). "A default mode of brain function." Proceedings of the National Academy of Sciences 98(2): 676-682.

Rainer, G., W. F. Asaad and E. K. Miller (1998). "Memory fields of neurons in the primate prefrontal cortex." Proceedings of the National Academy of Sciences USA 95(25): 15008-15013.

Rainville, P., J.-C. Doucet, M.-C. Fortin and G. H. Duncan (2004). "Rapid deterioration of pain sensory-discriminative information in short-term memory." Pain 110(3): 605-615.

Rainville, P., G. H. Duncan, D. D. Price, B. Carrier and M. C. Bushnell (1997). "Pain affect encoded in human anterior cingulate but not somatosensory cortex." Science 277(5328): 968-971.

Ralston, H. J. and D. D. Ralston (1992). "The primate dorsal spinothalamic tract: evidence for a specific termination in the posterior nuclei (Po/SG) of the thalamus." Pain 48(1): 107-118.

Ramachandran, V. S. and D. Rogers-Ramachandran (1996). "Synaesthesia in phantom limbs induced with mirrors." Proc Biol Sci 263(1369): 377-386.

Rammsayer, T. H. (1999). "Neuropharmacological evidence for different timing mechanisms in humans." The Quarterly Journal of Experimental Psychology. B, Comparative and Physiological Psychology 52(3): 273-286.

Ranganath, C., M. X. Cohen, C. Dam and M. D'Esposito (2004). "Inferior Temporal, Prefrontal, and Hippocampal Contributions to Visual Working Memory Maintenance and Associative Memory Retrieval." The Journal of Neuroscience 24(16): 3917-3925.

Rao, A. K., K. S. Marder, J. Uddin and B. C. Rakitin (2014). "Variability in interval production is due to timing- dependent deficits in Huntington's disease." Movement Disorders 29(12): 1516-1522.

Rao, S. C., G. Rainer and E. K. Miller (1997). "Integration of what and where in the primate prefrontal cortex." Science 276(5313): 821-824.

Ray, J. P. and J. L. Price (1993). "The organization of projections from the mediodorsal nucleus of the thalamus to orbital and medial prefrontal cortex in macaque monkeys." Journal of Comparative Neurology 337(1): 1-31.

Raye, C. L., M. K. Johnson, K. J. Mitchell, J. A. Reeder and E. J. Greene (2002). "Neuroimaging a single thought: dorsolateral PFC activity associated with refreshing just-activated information." NeuroImage 15(2): 447-453.

Redelmeier, D. A., J. Katz and D. Kahneman (2003). "Memories of colonoscopy: a randomized trial." Pain 104(1-2): 187-194.

Renoult, L., S. Roux and A. Riehle (2006). "Time is a rubberband: neuronal activity in monkey motor cortex in relation to time estimation." European journal of Neuroscience 23(11): 3098-3108.

Reuter-Lorenz, P. A., J. Jonides, E. E. Smith, A. Hartley, A. Miller, C. Marshuetz and R. A. Koeppe (2000). "Age differences in the frontal lateralization of verbal and spatial working memory revealed by PET." Journal of Cognitive Neuroscience 12(1): 174-187.

Ricciardi, E., D. Bonino, C. Gentili, L. Sani, P. Pietrini and T. Vecchi (2006). "Neural correlates of spatial working memory in humans: a functional magnetic resonance imaging study comparing visual and tactile processes." Neuroscience 139(1): 339-349.

Riggall, A. C. and B. R. Postle (2012). "The relationship between working memory storage and elevated activity as measured with functional magnetic resonance imaging." Journal of Neuroscience 32(38): 12990-12998.

Robinson, C. J. and H. Burton (1980). "Somatic submodality distribution within the second somatosensory (SII), 7b, retroinsular, postauditory, and granular insular cortical areas of M. fascicularis." Journal of Comparative Neurology 192(1): 93-108.

Rogan, M. T., U. V. Staubli and J. E. LeDoux (1997). "Fear conditioning induces associative long-term potentiation in the amygdala." Nature 390(6660): 604-607.

Romo, R. and E. Salinas (2003). "Flutter discrimination: neural codes, perception, memory and decision making." Nature Reviews Neuroscience 4(3): 203-218.

Romo, R. and W. Schultz (1989). "Somatosensory input to dopamine neurones of the monkey midbrain: responses to pain pinch under anaesthesia and to active touch in behavioural context." Progress in Brain Research 80: 473-478; discussion 465-476.

Roth, J. K., J. T. Serences and S. M. Courtney (2006). "Neural system for controlling the contents of object working memory in humans." Cerebral Cortex 16(11): 1595-1603.

Rottschy, C., R. Langner, I. Dogan, K. Reetz, A. R. Laird, J. B. Schulz, P. T. Fox and S. B. Eickhoff (2012). "Modelling neural correlates of working memory: a coordinate-based meta-analysis." NeuroImage 60(1): 830-846.

Roux, S., M. Coulmance and A. Riehle (2003). "Context- related representation of timing processes in monkey motor cortex." European Journal of Neuroscience 18(4): 1011-1016.

Rowe, J. B., K. E. Stephan, K. Friston, R. S. Frackowiak and R. E. Passingham (2005). "The prefrontal cortex shows context-specific changes in effective connectivity to

motor or visual cortex during the selection of action or colour." Cerebral Cortex 15(1): 85-95.

Rowe, J. B., I. Toni, O. Josephs, R. S. Frackowiak and R. E. Passingham (2000). "The prefrontal cortex: response selection or maintenance within working memory?" Science 288(5471): 1656-1660.

Rubia, K., S. Overmeyer, E. Taylor, M. Brammer, S. Williams, A. Simmons, C. Andrew and E. Bullmore (1998). "Prefrontal involvement in temporal bridging and timing movement." Neuropsychologia 36(12): 1283-1293.

Rubia, K. and A. Smith (2004). "The neural correlates of cognitive time management: a review." Acta neurobiologiae experimentalis.

Salomons, T. V., T. Johnstone, M. M. Backonja, A. J. Shackman and R. J. Davidson (2007). "Individual differences in the effects of perceived controllability on pain perception: critical role of the prefrontal cortex." Journal of Cognitive Neuroscience 19(6): 993-1003.

Schiffman, H. R. and D. J. Bobko (1974). "Effects of stimulus complexity on the perception of brief temporal intervals." Journal of Experimental Psychology 103(1): 156-159.

Schirmer, A. (2004). "Timing speech: a review of lesion and neuroimaging findings." Cognitive Brain Research 21(2): 269-287.

Schmidt, B. K., E. K. Vogel, G. F. Woodman and S. J. Luck (2002). "Voluntary and automatic attentional control of visual working memory." Attention, Perception, & Psychophysics 64(5): 754-763.

Schulz, E., L. Tiemann, T. Schuster, J. Gross and M. Ploner (2011). "Neurophysiological coding of traits and states in the perception of pain." Cerebral Cortex 21(10): 2408-2414.

Schulz, E., A. Zherdin, L. Tiemann, C. Plant and M. Ploner (2012). "Decoding an individual's sensitivity to pain from the multivariate analysis of EEG data." Cerebral Cortex 22(5): 1118-1123.

Schweinhardt, P. and M. C. Bushnell (2010). "Pain imaging in health and disease--how far have we come?" Journal of Clinical Investigation 120(11): 3788-3797.

Scott, D. J., M. M. Heitzeg, R. A. Koeppe, C. S. Stohler and J. K. Zubieta (2006). "Variations in the human pain stress experience mediated by ventral and dorsal basal ganglia dopamine activity." Journal of Neuroscience 26(42): 10789-10795.

Scott, D. J., C. S. Stohler, C. M. Egnatuk, H. Wang, R. A. Koeppe and J. K. Zubieta (2008). "Placebo and nocebo effects are defined by opposite opioid and dopaminergic responses." Archives of General Psychiatry 65(2): 220-231.

Segerdahl, A. R., M. Mezue, T. W. Okell, J. T. Farrar and I. Tracey (2015). "The dorsal posterior insula subserves a fundamental role in human pain." Nature Neuroscience 18(4): 499-500.

Shomstein, S. (2012). "Cognitive functions of the posterior parietal cortex: top-down and bottom-up attentional control." Frontiers in Integrative Neuroscience 6: 38.

Sinclair, R. J. and H. Burton (1996). "Discrimination of vibrotactile frequencies in a delayed pair comparison task." Perception & Psychophysics 58(5): 680-692.

Singer, A. J., A. Kowalska and H. C. Thode, Jr. (2001). "Ability of patients to accurately recall the severity of acute painful events." Academic Emergency Medicine 8(3): 292-295.

Sligte, I. G., D. van Moorselaar and A. R. Vandenbroucke (2013). "Decoding the contents of visual working memory: evidence for process-based and content-based working memory areas?" Journal of Neuroscience 33(4): 1293-1294.

Smith, A., E. Taylor, K. Lidzba and K. Rubia (2003). "A right hemispheric frontocerebellar network for time discrimination of several hundreds of milliseconds." NeuroImage 20(1): 344-350.

Smith, E. E. and J. Jonides (1999). "Storage and executive processes in the frontal lobes." Science 283(5408): 1657-1661.

Smith, E. E., J. Jonides and R. A. Koeppe (1996). "Dissociating verbal and spatial working memory using PET." Cerebral Cortex 6(1): 11-20.

Smith, J. G., D. N. Harper, D. Gittings and D. Abernethy (2007). "The effect of Parkinson's disease on time estimation as a function of stimulus duration range and modality." Brain and Cognition 64(2): 130-143.

Smyth, J. S. (1994). "Some problems of dental treatment. Part 2. Treatment avoidance: some differences between regular and irregular patients." Australian Dental Journal 39(1): 50-54.

Spencer, R. M., H. N. Zelaznik, J. Diedrichsen and R. B. Ivry (2003). "Disrupted timing of discontinuous but not continuous movements by cerebellar lesions." Science 300(5624): 1437-1439.

Spitzer, B., E. Wacker and F. Blankenburg (2010). "Oscillatory correlates of vibrotactile frequency processing in human working memory." Journal of Neuroscience 30(12): 4496-4502.

Staddon, J. E. (2005). "Interval timing: memory, not a clock." Trends in CognitiveScience 9(7): 312-314.

Staddon, J. E. and J. J. Higa (1999). "Time and memory: towards a pacemaker-free theory of interval timing." Journal of the Experimental Analysis of Behavior 71(2): 215-251.

Starr, C. J., L. Sawaki, G. F. Wittenberg, J. H. Burdette, Y. Oshiro, A. S. Quevedo, J. G. McHaffie and R. C. Coghill (2011). "The contribution of the putamen to sensory aspects of pain: insights from structural connectivity and brain lesions." Brain 134(Pt 7): 1987-2004.

Sternberg, S. (1966). "High-speed scanning in human memory." Science 153(3736): 652-654.

Stevens, R. T., S. M. London and A. V. Apkarian (1993). "Spinothalamocortical projections to the secondary somatosensory cortex (SII) in squirrel monkey." Brain research 631(2): 241-246.

Super, H., H. Spekreijse and V. A. Lamme (2001). "A neural correlate of working memory in the monkey primary visual cortex." Science 293(5527): 120-124.

Suzuki, M. and J. Gottlieb (2013). "Distinct neural mechanisms of distractor suppression in the frontal and parietal lobe." Nature neuroscience 16(1): 98-104.

Taddio, A., M. Goldbach, M. Ipp, B. Stevens and G. Koren (1995). "Effect of neonatal circumcision on pain responses during vaccination in boys." Lancet 345(8945): 291-292.

Taddio, A., V. Shah, C. Gilbert-MacLeod and J. Katz (2002). "Conditioning and hyperalgesia in newborns exposed to repeated heel lances." JAMA 288(7): 857-861.

Talbot, J. D., J. G. Villemure, M. C. Bushnell and G. H. Duncan (1995). "Evaluation of pain perception after anterior capsulotomy: a case report." Somatosens Mot Res 12(2): 115-126.

Tamber-Rosenau, B. J., M. Esterman, Y. C. Chiu and S. Yantis (2011). "Cortical mechanisms of cognitive control for shifting attention in vision and working memory." Journal of Cognitive Neuroscience 23(10): 2905-2919.

Tarantino, V., A. C. Ehlis, C. Baehne, A. Boreatti-Huemmer, C. Jacob, P. Bisiacchi and A. J. Fallgatter (2010). "The time course of temporal discrimination: An ERP study." Clin Neurophysiol 121(1): 43-52.

Taylor, V. A., L. Chang, P. Rainville and M. Roy (2017). "Learned expectations and uncertainty facilitate pain during classical conditioning." Pain 158(8): 1528-1537.

Theeuwes, J., A. F. Kramer and D. E. Irwin (2011). "Attention on our mind: the role of spatial attention in visual working memory." Acta Psychol (Amst) 137(2): 248-251.

Thomas, E. A. and W. B. Weaver (1975). "Cognitive processing and time perception." Attention, Perception, & Psychophysics 17(4): 363-367.

Timmermann, L., M. Ploner, K. Haucke, F. Schmitz, R. Baltissen and A. Schnitzler (2001). "Differential coding of pain intensity in the human primary and secondary somatosensory cortex." Journal of Neurophysiology 86(3): 1499-1503.

Todd, J. J. and R. Marois (2004). "Capacity limit of visual short-term memory in human posterior parietal cortex." Nature 428(6984): 751-754.

Todd, J. J. and R. Marois (2005). "Posterior parietal cortex activity predicts individual differences in visual short-term memory capacity." Cogn Affect Behav Neurosci 5(2): 144-155.

Treede, R. D., D. R. Kenshalo, R. H. Gracely and A. K. Jones (1999). "The cortical representation of pain." Pain 79(2-3): 105-111.

Treisman, M. (1963). "Temporal discrimination and the indifference interval: Implications for a model of the" internal clock"." Psychological Monographs: General and Applied 77(13): 1.

Vachon-Presseau, E., M. Roy, M. O. Martel, G. Albouy, J. Chen, L. Budell, M. J. Sullivan, P. L. Jackson and P. Rainville (2012). "Neural processing of sensory and emotional-communicative information associated with the perception of vicarious pain." NeuroImage 63(1): 54-62.

van Asselen, M., R. P. Kessels, S. F. Neggers, L. J. Kappelle, C. J. Frijns and A. Postma (2006). "Brain areas involved in spatial working memory." Neuropsychologia 44(7): 1185-1194.

van den Heuvel, M. P. and H. E. Hulshoff Pol (2010). "Exploring the brain network: A review on resting-state fMRI functional connectivity." European Neuropsychopharmacology 20(8): 519-534.

Vergara, J., N. Rivera, R. Rossi-Pool and R. Romo (2016). "A Neural Parametric Code for Storing Information of More than One Sensory Modality in Working Memory." Neuron 89(1): 54-62.

Vogel, E. K., S. J. Luck and K. L. Shapiro (1998). "Electrophysiological evidence for a postperceptual locus of suppression during the attentional blink." The Journal of Experimental Psychology: Human Perception and Performance 24(6): 1656-1674.

Vogel, E. K. and M. G. Machizawa (2004). "Neural activity predicts individual differences in visual working memory capacity." Nature 428(6984): 748-751.

Vogt, B. A. (2005). "Pain and Emotion Interactions in Subregions of the Cingulate Gyrus." Nature reviews. Neuroscience 6(7): 533-544.

Vogt, B. A., D. L. Rosene and D. N. Pandya (1979). "Thalamic and cortical afferents differentiate anterior from posterior cingulate cortex in the monkey." Science 204(4389): 205-207.

Wade, J. B., L. M. Dougherty, C. R. Archer and D. D. Price (1996). "Assessing the stages of pain processing: a multivariate analytical approach." Pain 68(1): 157-167.

Wager, T. D., L. Y. Atlas, M. A. Lindquist, M. Roy, C.-W. Woo and E. Kross (2013). "An fMRI-Based Neurologic Signature of Physical Pain." New England Journal of Medicine 368(15): 1388-1397.

Wager, T. D. and L. F. Barrett (2017). "From affect to control: Functional specialization of the insula in motivation and regulation." bioRxiv: 102368.

Wager, T. D., J. K. Rilling, E. E. Smith, A. Sokolik, K. L. Casey, R. J. Davidson, S. M. Kosslyn, R. M. Rose and J. D. Cohen (2004). "Placebo-induced changes in FMRI in the anticipation and experience of pain." Science 303(5661): 1162-1167.

Wager, T. D. and E. E. Smith (2003). "Neuroimaging studies of working memory." Cognitive, Affective, & Behavioral Neuroscience 3(4): 255-274.

Waldenstrom, U. and E. Schytt (2009). "A longitudinal study of women's memory of labour pain--from 2 months to 5 years after the birth." BJOG 116(4): 577-583.

Walsh, V. (2003). "A theory of magnitude: common cortical metrics of time, space and quantity." Trends in Cognitive Sciences 7(11): 483-488.

Wearden, J. H., R. Norton, S. Martin and O. Montford-Bebb (2007). "Internal clock processes and the filled-duration illusion." The Journal of Experimental Psychology: Human Perception and Performance 33(3): 716-729.

Wearden, J. H., J. Smith-Spark, R. Cousins, N. Edelstyn, F. Cody and D. O'Boyle (2008). "Stimulus timing by people with Parkinson's disease." Brain and Cognition 67(3): 264-279.

Wiech, K., S. Jbabdi, C. S. Lin, J. Andersson and I. Tracey (2014). "Differential structural and resting state connectivity between insular subdivisions and other pain-related brain regions." Pain 155(10): 2047-2055.

Wiener, M. and H. B. Coslett (2008). "Disruption of temporal processing in a subject with probable frontotemporal dementia." Neuropsychologia 46(7): 1927-1939.

Wiener, M., R. Hamilton, P. Turkeltaub, M. S. Matell and H. B. Coslett (2010). "Fast forward: supramarginal gyrus stimulation alters time measurement." Journal of Cognitive Neuroscience 22(1): 23-31.

Wiener, M., P. Turkeltaub and H. B. Coslett (2010). "The image of time: a voxel-wise meta-analysis." NeuroImage 49(2): 1728-1740.

Willis, W., X. Zhang, C. Honda and G. Giesler (2001). "Projections from the marginal zone and deep dorsal horn to the ventrobasal nuclei of the primate thalamus." Pain 92(1): 267-276.

Wilson, F. A., S. P. Scalaidhe and P. S. Goldman-Rakic (1993). "Dissociation of object and spatial processing domains in primate prefrontal cortex." Science 260(5116): 1955-1958.

Wojciulik, E. and N. Kanwisher (1999). "The generality of parietal involvement in visual attention." Neuron 23(4): 747-764.

Wu, D., H. Deng, X. Xiao, Y. Zuo, J. Sun and Z. Wang (2017). "Persistent Neuronal Activity in Anterior Cingulate Cortex Correlates with Sustained Attention in Rats Regardless of Sensory Modality." Scientific Reports 7.

Xu, Y. and M. M. Chun (2006). "Dissociable neural mechanisms supporting visual short-term memory for objects." Nature 440(7080): 91-95.

Xuan, B., D. Zhang, S. He and X. Chen (2007). "Larger stimuli are judged to last longer." J Vis 7(10): 2 1-5.

Yamazaki, Y., T. Hashimoto and A. Iriki (2009). "The posterior parietal cortex and non-spatial cognition." F1000 Biology Reports 1: 74.

Yelle, M. D., J. M. Rogers and C. Robert C (2008). "Offset analgesia: a temporal contrast mechanism for nociceptive information." Pain 134(1-2): 174-186.

Yuasa, K. and Y. Yotsumoto (2015). "Opposite Distortions in Interval Timing Perception for Visual and Auditory Stimuli with Temporal Modulations." PLoS One 10(8): e0135646.

Yumoto, N., X. Lu, T. R. Henry, S. Miyachi, A. Nambu, T. Fukai and M. Takada (2011). "A neural correlate of the processing of multi-second time intervals in primate prefrontal cortex." PLoS One 6(4): e19168.

Zakay, D. and R. A. Block (1996). "The role of attention in time estimation processes." Advances in Psychology 115: 143-164.

Zakay, D. and R. A. Block (1997). "Temporal cognition." Current Directions in Psychological Science 6(1): 12-16.

Zanto, T. P., M. T. Rubens, A. Thangavel and A. Gazzaley (2011). "Causal role of the prefrontal cortex in top-down modulation of visual processing and working memory." Nature Neuroscience 14(5): 656-661.

Zhang, Z. H., P. M. Dougherty and S. M. Oppenheimer (1999). "Monkey insular cortex neurons respond to baroreceptive and somatosensory convergent inputs." Neuroscience 94(2): 351-360.

Zhou, Y. D. and J. M. Fuster (1996). "Mnemonic neuronal activity in somatosensory cortex." Proceedings of the National Academy of Sciences U S A 93(19): 10533-10537.