Investigations of Spatial and Temporal Aspects of Visuo-nociceptive Interactions

Investigations of Spatial and Temporal Aspects of Visuo-nociceptive Interactions

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Thèse présentée en vue de l'obtention du grade de Docteure en sciences psychologiques et de l'éducation

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Collection des thèses de l'Université catholique de Louvain, 2021

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« Le meilleur pour les turbulences de l'esprit, c'est apprendre.
C'est la seule chose qui n'échoue jamais. »

Marguerite Yourcenar

Résumé

Étudier les mécanismes qui participent à la perception d'une stimulation nociceptive permet de comprendre comment les individus détectent de potentielles menaces présentes dans leur environnement extérieur et y réagissent, afin de protéger l'intégrité de leur organisme. La perception d'une stimulation nociceptive dépend notamment de la présence d'informations appartenant à d'autres modalités sensorielles. L'objectif de cette thèse est d'explorer l'impact d'une stimulation visuelle sur l'activité du système nociceptif, et plus particulièrement, sur les seuils de détection des informations transmises par les fibres Aδ et C. Les résultats des expériences réalisées mettent en évidence l'importance des relations spatiales et temporelles entre les stimuli des différentes modalités sensorielles comme facteurs favorisant leurs interactions.

Abstract

Studying the mechanisms underlying the perception of a nociceptive stimulus allows to understand how individuals detect and react to potential threats present in their surroundings to protect the integrity of their organism. Notably, the perception of a nociceptive stimulus is affected by the presence of information from other sensory modalities. The aim of this thesis is to explore the impact of a visual stimulus on the activity of the nociceptive system, and more particularly, on the detection thresholds of thermo-nociceptive information transmitted through Aδ and C fibers. The results of the experiments highlight the important role of spatial and temporal relationships between the stimuli of different sensory modalities in improving their interactions.

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Remerciements

Après moult rebondissements, j'aurai bel et bien pu bénéficier de quatre années de recherche pour me permettre d'atteindre, dans des conditions idéales, mes objectifs académiques et professionnels. Ces quatre années m'ont permis de développer un apprentissage rigoureux sur ma thématique de recherche, de m'ouvrir à la richesse du monde (universitaire) et d'approfondir mes compétences professionnelles. En outre, ces quatre années incarnent tout en même temps mon cheminement personnel, à l'écoute de mes valeurs. Ces divers éléments ont pu s'allier de manière fructueuse grâce à de nombreuses personnes m'ayant accompagnée tout au long de ce projet, jusque dans son aboutissement.

Ainsi, merci à toi Valéry pour ta détermination, pour la transmission de tes connaissances riches et pointues, pour ta confiance ainsi que pour la volonté dont tu as fait preuve afin que nos besoins mutuels puissent être entendus.

Je tiens à exprimer ma reconnaissance aux membres de mon comité d'accompagnement, Anne Berquin, Olivier Collignon et André Mouraux, pour leur investissement dans mon processus de recherche depuis son commencement, ainsi que pour leurs conseils avisés et nos échanges constructifs. Je remercie également Alessandro Farnè et Flavia Mancini, membres de mon jury de thèse, pour leur analyse fine du travail accompli ainsi que pour leurs suggestions d'amélioration ayant élargi mon champ de réflexion.

L'élan qui m'a portée au bout de ce projet a notamment été conforté par vous, Cam et Lieve, qui n'avez eu de cesse de m'accompagner à chaque étape traversée, tout au long de ces années. Cam, merci de m'avoir ouvert la porte de ton monde et d'avoir été mon acolyte en tout temps. Lieve, tel un phare qui permet aux navigateur·ices de s'orienter en pleine mer, tu as été mon repère. À votre contact, j'ai par ailleurs appris à relativiser mes inquiétudes et à considérer mon travail. Également merci aux Valérettes de m'avoir intégrée dans leur équipe de choc et d'avoir fait part de leurs expériences et de leur soutien.

Merci à Nocions pour les belles rencontres, et plus particulièrement à Arthur, André et Léon pour leur aide précieuse, leur intérêt et le partage de leurs expertises. Domi, tu as coloré mes journées plus moroses par ton grain de folie et ta liberté. Merci à toutes les personnes que j'ai eues la chance de croiser de près ou de loin dans les couloirs du laboratoire. Les échanges informels que nous avons entretenus étaient véritablement porteurs de sens dans l'accomplissement de mon travail.

Mes pensées s'envolent à présent vers mes parents. Vous m'avez transmis un panel d'outils extrêmement précieux me permettant de suivre la voie la plus juste pour moi. Chaque jour de mon parcours, j'ai eu la chance de recevoir votre écoute, votre soutien, votre compréhension. Mimi, Matt, je suis pleine de gratitude pour notre complicité, la force et l'évidence des liens qui nous unissent, ainsi que pour votre amour et votre présence à mes côtés, dans les moments heureux comme dans les coups durs. Merci à mes grands-mères également. Votre bienveillance et vos renforcements permanents m'ont apporté douceur et endurance. Marraine, ma grande complice, merci de me guider dans ma voie professionnelle et de m'accompagner sur mon chemin de vie. Enfin, merci à toute la famille pour la joie qu'elle répand dans les cœurs.

Merci à ma seconde famille, Adé, Thib, Théo, pour nos rires et notre amitié, qui ont été essentiels à mon équilibre. Merci d'avoir écouté mes péripéties et d'avoir nourri ma pensée par vos réflexions. J'ai également une attention particulière pour chacun·e de mes ami·e·s.

Omid, mon amour, tant par tes mots que par tes gestes, tu m'as donné la force de persévérer. Merci pour ton énergie et ta folie vertueuses, pour ton regard juste et clair, pour ta tendresse. Merci de parcourir le chemin à mes côtés depuis hier, depuis toujours.

Abbreviations

ACC: anterior cingulate cortex

CNS: central nervous system

EPS: extrapersonal space

ERP: evoke-related potential

IES: intraepidermal electrical stimulation

LEP: laser-evoked potential

LSD: laser stimulation device

NS: nociceptive-specific (neuron)

OTR: optimal temporal register

PM: premotor (cortex)

PMv: ventral premotor (cortex)

PPS: peripersonal space

PSS: perception of subjective simultaneity

PSE: perception of subjective equality

PZ: polysensory zone

RF: receptive field

RHI: rubber-hand illusion

RT: reaction time

RTE: redundant target effect

SDT: sensory discrimination training

SI: primary somatosensory cortex

SII: secondary somatosensory cortex

SOA: stimulus onset asynchrony

TOJ: temporal order judgment

TWIN: time-window-of-integration

VIP: ventral intraparietal area

WDR: wide dynamic range

General Introduction

Studying the mechanisms underlying the perception of a noxious stimulus is a daunting challenge, which has been undertaken by numerous health professionals, for centuries. Yet, there is still a lot of ground to cover.

Pain is an unpleasant sensation generally elicited in reaction to stimulations exceeding the nociceptive threshold. The information conveyed through the nociceptive system projects toward several brain areas that are also activated in response to salient events (Legrain, Iannetti, Plaghki, & Mouraux, 2011). Pain processing is therefore part of a larger system that also processes information from other sensory modalities. Besides, the painfulness perceived by the stimulation is a personal experience, being associated to cognitive and affective components (Le Bars & Plaghki, 2009). Given the plethora of mechanisms involved in the genesis and perception of pain, but also the dramatic consequences that pain exerts on the mental health and professional spheres, pain obviously fits into a bio-psycho-social model (Berquin & Grisart, 2016). Pharmacological and non-pharmacological therapies have therefore been developed to relieve patients from pain.

Cognitive neuroscience, for its part, highlights factors such as multisensory events, able to alter the perception of a stimulation. Indeed, the perception of a sensory event does not exclusively depend on the properties of the elicited stimuli and their afferent information to the cortex, but is also related to the sensory and attentional contexts in which the event appears (Spence & Driver, 2004). This has been well established for multisensory interactions about touch, vision, audition, but in a lesser extent for nociception. Previous research on visuo-nociceptive modalities has mostly focused on the mechanisms involved in the *localization* of nociceptive stimuli (e.g. De Paepe, Crombez, Spence, & Legrain, 2014; Vanderclausen, Bourgois, De Volder, & Legrain, 2020) and the impact of these stimuli on the perception of the visual space around the body (e.g. Filbrich, Andrea Alamia, Soline Burns, & Legrain, 2017). These studies are crucial to understand how nociception acts as a warning system enabling the individuals to adapt their behavior and react efficiently to potential threats (Legrain & Torta, 2015). We also know that visual information about the body itself can affect the sensation elicited by noxious inputs (e.g. Mancini, Longo, Kammers, & Haggard, 2011). Nevertheless, we do not yet fully understand whether and how the *detection* of nociceptive and potentially painful sensations can be modulated by information provided by external inputs present in the environment and belonging to other sensory modalities.

This thesis is therefore founded on the overarching aim to clarify under which conditions the interactions between visual and nociceptive stimuli influence the detection of a nociceptive stimulus and to deepen our understanding of the mechanisms underlying these interactions, in order to finally study the potential modulation of the detection threshold of the inputs transmitted through the nociceptive system by the presence of visual stimuli.

The introduction of the manuscript conceptually reviews the literature about the neurophysiological mechanisms behind pain and nociception, as well as the spatial and temporal factors governing multisensory interactions, with a focus on vision and nociception. I will refer to animal studies at the neuronal level and to behavioral experiments in brain-damaged patients and healthy volunteers.

The experimental part develops fundamental psychophysical experiments conducted in neurologically healthy volunteers to investigate the extent to which the spatial and temporal factors highlighted in the introduction can be used to observe the influence of a visual stimulus on the detection of a nociceptive stimulus. More specifically, the first chapter entitled “Investigations of Spatial Aspects” will examine the sensory mechanisms that regulate the spatial interactions between visual and nociceptive inputs. The second chapter entitled "Investigations of Temporal Aspects" will address the different conduction velocities of the visual and nociceptive systems to transmit sensory information to the cortex, with the ultimate goal of maximizing the perception of simultaneity of visual and nociceptive inputs, which is supposed to be a major asset to favor their interactions. Thanks to a technique that allows us to selectively activate the different fibers of the nociceptive system, that is, the Aδ and C fibers, we will investigate the temporal relationships between visual and nociceptive stimuli according to each fiber type. The third chapter entitled “Investigations of Spatio-temporal Aspects” will combine the findings of the first chapters. Since spatial and temporal factors are closely linked during multisensory interactions, the impact of space on the perception of synchronicity of visuo-nociceptive stimuli will be first explored. In a second time, the spatial and temporal factors that optimize visuo-nociceptive interactions will be used to study the impact of the position of a visual stimulus on the detection threshold of the inputs transmitted through each fiber type of the nociceptive system.

The last part of the thesis will confront the results of the aforementioned studies to the literature, shed light on the new knowledge about the mechanisms underlying visuo-nociceptive interactions and their consequences on the perception of nociceptive stimuli, and close the topic by elaborating several avenues of reflection for future investigations.

1 PAIN & NOCICEPTION

Pain and nociception are two concepts that are complementary, but important to distinguish from one another.

Nociception is a sensory modality (Sherrington, 1898) whose neural processes encode noxious stimuli (IASP, 1994). The nociceptive system is triggered when its specific sensory receptors, the nociceptors, are activated by high intensity thermal, mechanical or chemical stimuli (Legrain, 2017). The information is then conveyed by Aδ- and C-fiber afferents and initiates autonomic, behavioral and reflex responses to protect the organism from potential damages (Le Bars & Plaghki, 2009). The nociceptive system holds therefore an *interoceptive* function, i.e. by providing information to the brain about possible tissue damages occurring in a specific part of the body, a crucial role in regulating homeostasis. In addition, the nociceptive system holds an *exteroceptive* function, i.e. by warning about the external source of the threatening stimuli that could provoke such damages (e.g. through visual information). By interacting with information from other sensory modalities, the nociceptive system represents an alert system determined by the ability to orient attention toward meaningful stimuli, to localize the source of the stimuli in the surrounding of the body, and to prepare defensive motor actions (Haggard, Iannetti, & Longo, 2013; Legrain, 2017).

Under normal circumstances, pain results from an activation of the nociceptive system. Besides its sensory-discriminative dimension enabling to identify the intensity, location, quality and duration of the input, pain is associated with cognitive and emotional aversive affects, crucial for recruiting the necessary attentional resources to protect the integrity of the body (Le Bars & Plaghki, 2009; Moayedi & Davis, 2013; Senkowski, Hofle, & Engel, 2014).

The nociceptive system refers therefore to the mechanisms that code, transmit and process the sensory information delivered by the nociceptors, whereas pain is the response of the organism to that sensory processing (Legrain, 2017). Last but not least, pain could potentially also occur without activation of the nociceptive system (Melzack, 2001; Nikolajsen & Jensen, 2006) and inversely, nociception does not automatically lead to painful sensations (Lee, Mouraux, & Iannetti, 2009; Treede, Kenshalo, Gracely, & Jones, 1999).

1.1 Neurophysiology & Neuroanatomy

1.1.1 The nociceptive system

Three main mechanisms that compose the nociceptive system can be identified: peripheral, spinal and cortical. The nociceptive information is generated by free-nerve ending nociceptors present into the skin, muscles, joints and viscera of the body. In the context of this thesis, we will focus on the mechanisms underlying the transmission of a thermo-nociceptive input applied on the skin.

At the peripheral level, when a nociceptive stimulus is delivered on the skin, the information is coded and conveyed by the thinly-myelinated Aδ-fiber and unmyelinated C-fiber afferents. There are two types of nociceptors (thermal and mechanical) innervated by Aδ fibers. Type 1 refers to slow-adapting Aδ mechano-heat units (1-AMH). 1-AMH are mainly excited by sharp objects pinching the skin such as noxious mechanical stimuli, and by sustained heat stimulations at high intensities. Type 2 refers to fast-adapting Aδ units (2-AMH) that are mechanically insensitive and respond to noxious heat stimuli such as brief thermo-nociceptive inputs delivered by a CO2 laser (Treede, Meyer, & Campbell, 1998; Treede, Meyer, Raja, & Campbell, 1995). Among unmyelinated fibers, several are sensitive to the heating of the skin. Akin to Aδ fibers, the polymodal C-fiber mechano-heat nociceptors (CMHs) are either fast-adapting (high peak discharge with the onset of the stimulus) or slow-adapting (uniform discharge rate throughout the stimulation). There are also C-warm thermoreceptors and mechano-insensitive C units (CHs) (Lenoir, Plaghki, Mouraux, & van den Broeke, 2018; Schepers & Ringkamp, 2010; Schmidt et al., 1995; Weidner et al., 1999). The nociceptive afferents transmit the information from the receptors to the dorsal horn of the spinal gray matter through a lateral division (see Figure 1). In this first relay, the nociceptive messages are subject to segmental and supraspinal controls from the neurons located in the different laminae. The somatic information next crosses the midline of the grey anterior commissure and is projected to the thalamus. The fibers decussation at the segmental level of the spinal cord implies that the transmission of the noxious and thermal information through the spinothalamic tract is contralateral. The entire process is carried by the anterolateral system, for which, the final steps regarding the information transmission are mainly the somatosensory cortices (SI and SII), the insular, the cingulate cortices and the thalamus.

Other ascending pathways also distribute information from small-diameter sensory fibers towards brain stem nuclei: the spinomesencephalic, spinoreticular and spinolimbic tracts. In turn, the brain stem nuclei project to the thalamus, the hypothalamus and the amygdala. These regions particularly play an important role in the emotional and autonomic processes of pain (Kandel et al., 2013; Le Bars & Plaghki, 2009; Purves et al., 2012).

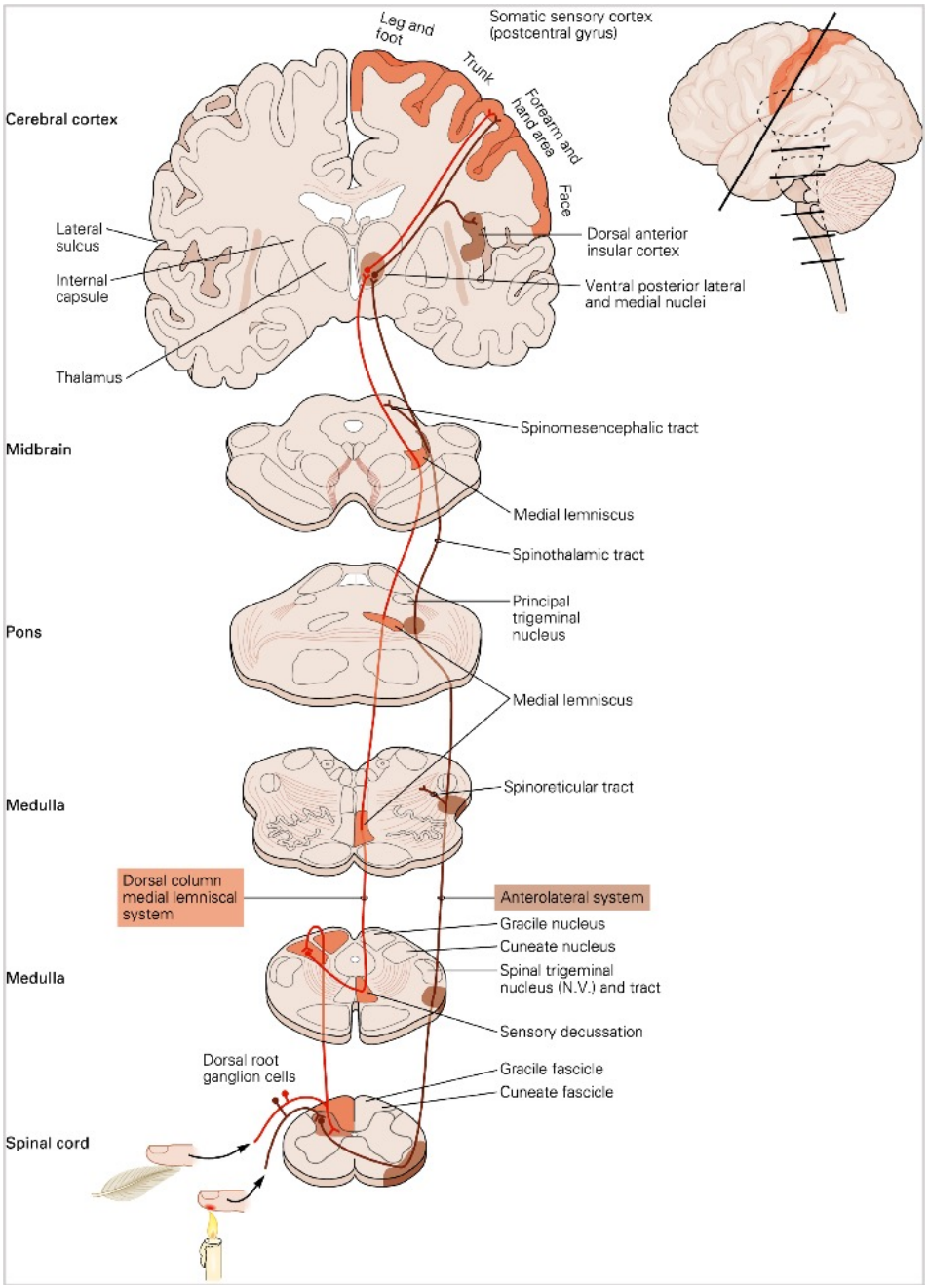

Figure 1. Illustration of the afferent pathways and neuro-anatomical projections of tactile and nociceptive inputs. The transmission of nociceptive information is carried by the anterolateral system whereas the transmission of tactile information is carried by the lemniscal system. *Adapted from Kandel, Schwartz, Jessell, Siegelbaum, and Hudspeth (2013).*

1.1.2 Main differences between Aδ and C-fiber afferents

The majority of the studies conducted in this thesis will investigate visuo-nociceptive interactions separately for Aδ and C fibers. Therefore, we will now describe the main differences between both types of fibers.

Compared to the myelinated Aδ fibers transmitting proprioceptive and tactile inputs, Aδ and C fibers have respectively slow and ultra-slow conduction velocities (Le Bars & Plaghki, 2009). The conduction velocity of the information transmitted through Aδ fibers is about ~10 m/s, nociceptive information therefore reaches the cortex in ~150 ms (Kakigi & Shibasaki, 1991). Reaction times (RTs) to thermo-nociceptive stimuli administered on the hand dorsum, with a temperature above the Aδ-fiber activation threshold, are ~350 ms on average (Plaghki, Decruynaere, Van Dooren, & Le Bars, 2010; Plaghki & Mouraux, 2005). Because C fibers are totally unmyelinated, the conduction velocity of the information is about 1m/s (Opsommer, Masquelier, & Plaghki, 1999), it takes therefore at least 800 ms for the input to be detected, depending on the peripheral distance separating the nociceptors from the cortex (Plaghki & Mouraux, 2005). However, despite their slow conduction velocity, C fibers represent 60 to 90% of the population density of the nociceptive fibers present in the skin (Le Bars & Plaghki, 2009).

Another difference between both fiber types is that Aδ fibers have typically higher activation thresholds than C fibers, that, for their part, elicit sensations at later latencies. The activation threshold of Aδ fibers to heat stimuli is around 46 °C (Churyukanov, Plaghki, Legrain, & Mouraux, 2012; Plaghki & Mouraux, 2005), whereas those of C fibers is usually around 39 °C (Churyukanov et al., 2012). The co-activation of C and Aδ fibers generates a double sensation (see Figure 2), first characterized by a well-localized, brisk and pricking sensation, referred to as the *first pain* and associated to the activation of Aδ fibers, followed by a second diffuse warm sensation, referred to as the *second pain* and associated to the activation of C fibers (Plaghki et al., 2010; Plaghki & Mouraux, 2005).

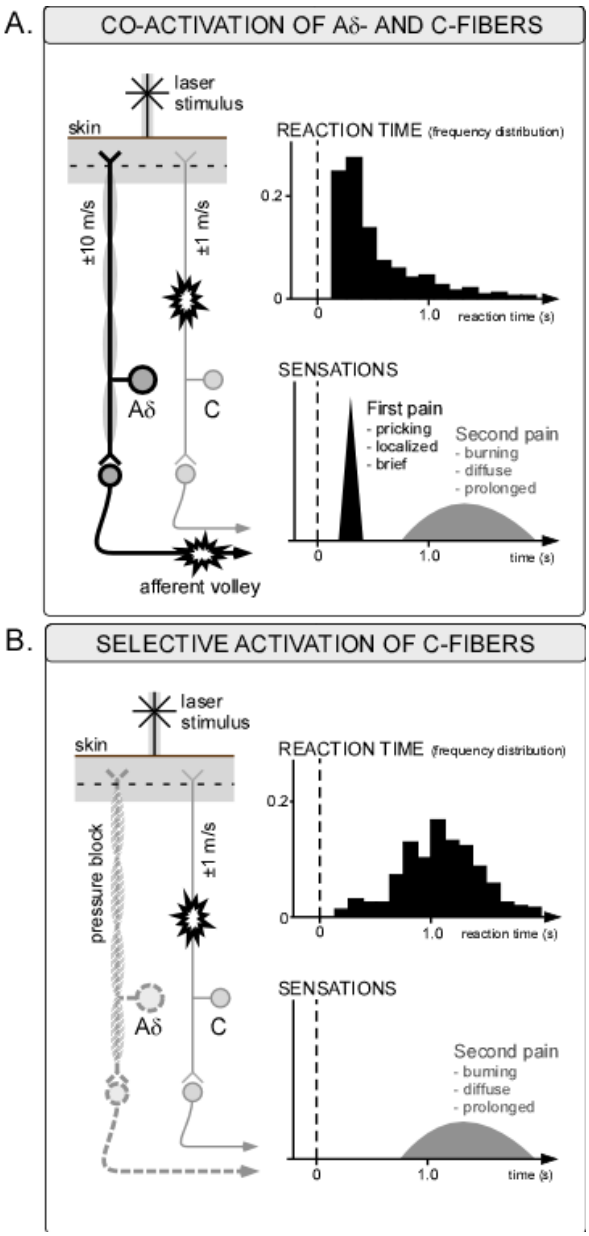

Figure 2. Illustration of the main differences between Aδ and C fibers. The upper part of the figure depicts the "First pain" and "Second pain" sensations elicited by the co-activation of Aδ and C-nociceptors and determined by their respective conduction velocities. Reactions times (RTs) reflect the latency of detection of the Aδ-fiber sensation. The lower part of the figure shows the selective activation of C fibers, and the sensation they elicit, after blocking the superficial radial nerve. RTs correspond to the latency of detection of slow-conducting C fibers. *Adapted from Mouraux (2005, pp. 22).*

Due to the above-mentioned differences, the existence of the two fiber types can be evidenced by experimentally dissociating their behavioral and physiological responses. For instance, using brief radiant heat stimuli (delivered by infrared CO_2 laser), Churyukanov et al. (2012) exploited the fact that C fibers have lower activation thresholds and slower conduction velocities than Aδ fibers, to develop an adaptive procedure that determinates the respective activation thresholds of C and Aδ fibers. During a first phase, to determine the activation threshold of C fibers, the temperature delivered by the CO_2 laser is adapted according to the absolute perception of the participants to the stimuli. Next, during the second phase, higher temperatures of stimulation are delivered. This time, their intensity changes according to the participants' RTs, allowing to isolate the temperatures which only activated the C fibers from temperatures co-activating Aδ fibers. On Figure 3, we can see that the administration of heat stimuli at different intensities during the first and second phases results on a bimodal frequency distribution of the RTs (Churyukanov et al., 2012; Plaghki & Mouraux, 2005). Using a CO_2 laser that delivers stimuli with fast heating ramps (>1000°C) allows to record time-locked responses also reflected in laser-evoked potentials (LEPs). Jankovski, Plaghki, and Mouraux (2013) succeeded to isolate two types of cortical responses, one appearing at a latency compatible with responses of C fibers, the other at an earlier latency compatible with the responses of Aδ fibers. Other methods can be used, such as stimulating tiny surface of skin area (as density of C fibers is higher than Aδ fibers) (Bragard, Chen, & Plaghki, 1996; Lenoir, Plaghki, et al., 2018) or using nerve pressure block (affecting more specifically myelinated fibers) (Nahra & Plaghki, 2003).

To conclude, nociceptive peripheral pathways seem to convey the information in a specific way. However, as the following sections will show, the nociceptive information is progressively integrated with other sensory modalities, at higher stages of the processing.

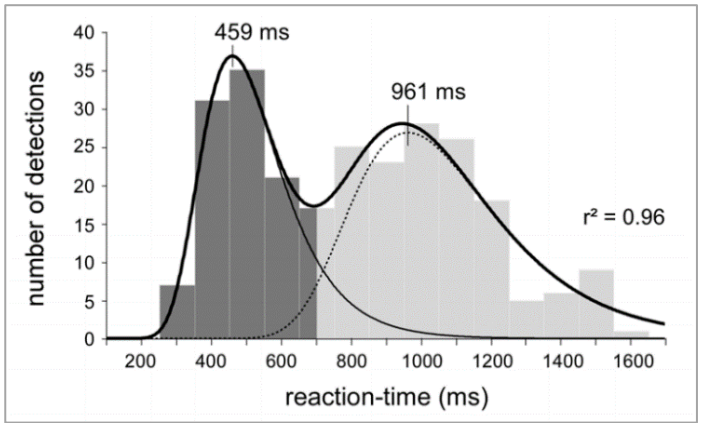

Figure 3. Bimodal distribution of participants' RTs according to the selective stimulation of C and Aδ fibers. Laser stimuli were applied on the hand dorsum using target temperatures ranging from 35 to 51°C. The bimodal distribution of RTs relates to the fact that lower target skin temperatures triggered late-latency detections compatible with the conduction velocity of unmyelinated C fibers and that higher target skin temperatures triggered early-latency detections compatible with the conduction velocity of Aδ fibers. *Adapted from Churyukanov et al. (2012).*

1.1.3 Specificity vs unspecificity, the so-called "pain matrix"

The mechanisms underlying nociception and pain have drawn the attention of myriad of scientists (see Moayedi & Davis, 2013 for review). As addressed in the previous sections, current neuroscience theories teach us that many cortical areas are activated by nociceptive stimuli that are perceived as painful. Over the past decades, a long-lasting debate has fueled the scientific literature about the existence of a specific pain network in the brain, commonly called "the pain matrix". This emerged from the observation that the activity of the primary and secondary somatosensory cortices (SI and SII), insula and anterior cingulate cortex (ACC), recorded by using non-invasive functional neuroimagery and neurophysiology in humans, was correlated to the intensity of noxious stimuli and to the magnitude of the elicited perception of pain (e.g. Garcia-Larrea, Frot, & Valeriani, 2003; Treede et al., 1999).

Actually, the concept of "pain matrix" has been deviated from the original theory of the *Neuromatrix,* which characterizes the brain mechanisms underlying the experience of the body as a unitary percept – the self – , based on the integration of inputs coming from all sensory modalities, and also involving emotional and cognitive functions such as the memory of past experiences or the attention to develop adaptive behavior in the environment (Melzack, 1989, 2001). More specifically, *"the neuromatrix, distributed throughout many areas of the brain, comprises a widespread network of neurons that generates patterns, processes information that flows through it, and ultimately produces the pattern that is felt as a whole body possessing a sense of self"* (Melzack, 2001, pp. 1380).

Since the activity of SI, SII, ACC and the insula correlated with pain intensity, some researchers therefore considered these cortical regions as the neural substrate underlying pain perception. Each area would hold specialized subfunctions to process specific aspects of pain, such as the *lateral pain system* (SI-SII) mostly involved in sensory-discriminative aspects of the nociceptive stimuli and the *median pain system* (ACC-Insula) involved in their affective and cognitive evaluation (e.g. Ingvar, 1999). These assumptions derived on hasty conclusions, that is, that the brain activity recorded during noxious stimulations reflects pain processing. However, other authors questioned the reliability of the link established between the pain matrix activity and the perceived intensity of painful sensations. Indeed, the recorded activity of SI, SII, ACC

and insula is also sensitive to factors unrelated to the intensity of the nociceptive stimuli and the magnitude of the elicited pain perception (Lee et al., 2009; Mouraux, Guérit, & Plaghki, 2004; Mouraux & Plaghki, 2007).

First, it was shown that the magnitude of the brain responses to nociceptive stimuli was more dependent on the context in which the stimuli were administrated, such as their probability of occurrence and their novelty, than on their intensity. Accordingly, those brain responses were interpreted as mostly reflecting the attention allocated to or captured by the nociceptive stimulus (Legrain, Bruyer, Guérit, & Plaghki, 2003; Legrain, Guérit, Bruyer, & Plaghki, 2002; Legrain, Perchet, & Garcia-Larrea, 2009). Similarly, when a nociceptive stimulus is repeated with regular inter-stimulus duration, the magnitude of the LEPs is decreased, even if its perceived intensity remains unchanged (Iannetti, Hughes, Lee, & Mouraux, 2008).

Second, the so-called "pain matrix" activity is also sensitive to the occurrence of non-nociceptive stimuli (Downar, Crawley, Mikulis, & Davis, 2000; Lui et al., 2008) and even to non-somatosensory inputs, such as visual and auditory stimuli (Mouraux, Diukova, Lee, Wise, & Iannetti, 2011; Mouraux & Iannetti, 2009; Tanaka et al., 2008). The regions identified as being nociceptive-specific are actually mostly multimodal. The difference between the brain activities in response to nociceptive stimuli of different intensities was suggested to rather reflect modification of the salience of the stimulus, that is, the physical features that make it standing out and contrasting relative to other surrounding stimuli, and, consequently, more susceptible to capture attention. This cortical network was therefore interpreted as reflecting a salience detection system involved in the detection, the localization and the reaction to any sensory event potentially meaningful for the body's integrity, regardless of the sensory channel through which the sensory inputs are conveyed (Iannetti & Mouraux, 2010; Legrain, 2011; Mouraux & Iannetti, 2009). This updated definition is compatible with that of the *Neuromatrix*, a brain network nourished by multimodal experiences which enable the adaptation of human beings to their environment. Hence, the "pain matrix" is an open window on the study of the multiple factors influencing pain perception, including multisensory phenomena.

2 A MULTISENSORY ENVIRONMENT

In the first part of this introduction, we highlighted that the salience of a nociceptive stimulus, that is, the features that distinguish it from its sensory and cognitive context, largely contributes to its perception. Even if Aδ and C fibers are specifically involved in transmitting nociceptive inputs, the perception of a nociceptive stimulus is supposed to also depend on the co-occurrence of stimuli from other sensory modalities, including visual information. It was for instance shown that, seeing its own limb on which a nociceptive stimulus is applied, modulates the magnitude of the elicited brain responses, decreases the perceived intensity, and changes the pain threshold (Longo, Betti, Aglioti, & Haggard, 2009; Longo, Iannetti, Mancini, Driver, & Haggard, 2012; Mancini, Longo, Canzoneri, Vallar, & Haggard, 2013; Mancini et al., 2011). Even though the robustness of this effect was called into question (see Torta, Legrain, & Mouraux, 2015; Valentini, Koch, & Aglioti, 2015), all agree on an effect of vision on the cortical processing of nociception and pain. Pain being the archetype of an alert response to the presence of physical threats, the system that processes nociceptive stimuli is part of a larger information processing system. The convergence of the different sensory information produces multisensory interactions, which in turn allows to maintain homeostasis and integrity of the body, and to provide a unified percept of the environment. This section offers an overview of the ins and outs responsible for the level of interaction between different stimuli, with an emphasis on visuo-nociceptive modalities.

2.1 MECHANISMS BEHIND MULTISENSORY PROCESSING AND INFLUENCING FACTORS

As already quickly addressed in the discussion about the "pain matrix" concept, the idea that each cortical area is modality-specific has been discarded in recent decades, starting with studies in mammals (e.g. Wallace, 2004). On the one hand, some (sub-) cortical areas preferably receive afferents from one specific modality (e.g. the occipital cortex for visual inputs), but are also sensitive to other sensory inputs (e.g. Macaluso, Frith, & Driver, 2000). On the other hand, information from several senses can converge onto the same neuron (e.g. Stein & Meredith, 1993; Stein & Stanford, 2008). In addition, the so-called cortical convergence zones[1] receive their inputs from different "modality-specific" cortical areas. Several cortical and subcortical structures seem therefore to be inherently multisensory, with higher levels of multisensory processes in some brain

[1] Also known as "Heteromodal zones" or "association cortex" (Calvert & Thesen, 2004).

regions than in others (Bremmer et al., 2001; Driver & Noesselt, 2008; Ghazanfar & Schroeder, 2006; Macaluso & Driver, 2005; Mesulam, 1998). Multisensory processes are thus ubiquitous neurological phenomena across species which fundamentally enable the brain to integrate complex stimuli from the environment and to influence its perception (Meredith & Stein, 1986b). They are essential to efficiently perceive and react to incoming sensory events.

The factors that determine whether several sensory inputs will integrate at the neuron level, i.e. in a bottom-up fashion, or rather after having undergone various cortical processing, i.e. in a top-down manner, remain however controversial in the literature (see Figure 4). Neurocognitive experiments conducted in humans (e.g. Farnè, Brozzoli, Làdavas, & Ro, 2008; Filbrich, Halicka, Alamia, & Legrain, 2018; Morein-Zamir, Soto-Faraco, & Kingstone, 2003) and neurophysiological experiments using single-cell recordings in animals (Graziano, Yap, & Gross, 1994; Meredith & Stein, 1986b; Stein & Meredith, 1993) often shed light on different perspectives. Multisensory integration would refer to automatic processes occurring at early stages of neural processing when different stimuli share spatial and temporal features (Aller, Giani, Conrad, Watanabe, & Noppeney, 2015; Macaluso et al., 2016; Spence, McDonald, & Driver, 2004; Stein & Meredith, 1993; Stein & Stanford, 2008). The extent to which interactions between the stimuli will solicit higher-order level of processes, such as attention, would rather depend on the context. For instance, if the stimuli are not salient enough in the environment, additional attentional processing might be required in order to prioritize the most relevant ones (Talsma, 2015).

When studying multisensory interactions in cognitive neuroscience, the struggle to discriminate between bottom-up and top-down mechanisms is due to the fact that, often, the two are intimately connected. Different simultaneous sensory inputs sharing properties are linked together (bottom-up) in a mental representation that involves higher-order cognitive processes (top-down) (Calvert & Thesen, 2004; Talsma, 2015; Welch, 1999), which cannot be decomposed to the mere addition of each sensory input (Stein et al., 2010). Given that multisensory events are omnipresent in the space around us, attention is automatically oriented through salient events, irrespective of their sensory modality (Driver & Spence, 1998). One could thus consider that bottom-up and top-down mechanisms are two sides of the same coin. On the one hand, when two inputs are integrated in a bottom-up fashion, they likely draw attention toward the sensory event, which in turn, enhances its processing. On the other hand, when attention enables to process two sensory inputs together, it will boost their integration. However, attention is not a *sine qua non* condition for multisensory integration and, does not necessarily result in integration (Macaluso et al., 2016; Talsma, 2015).

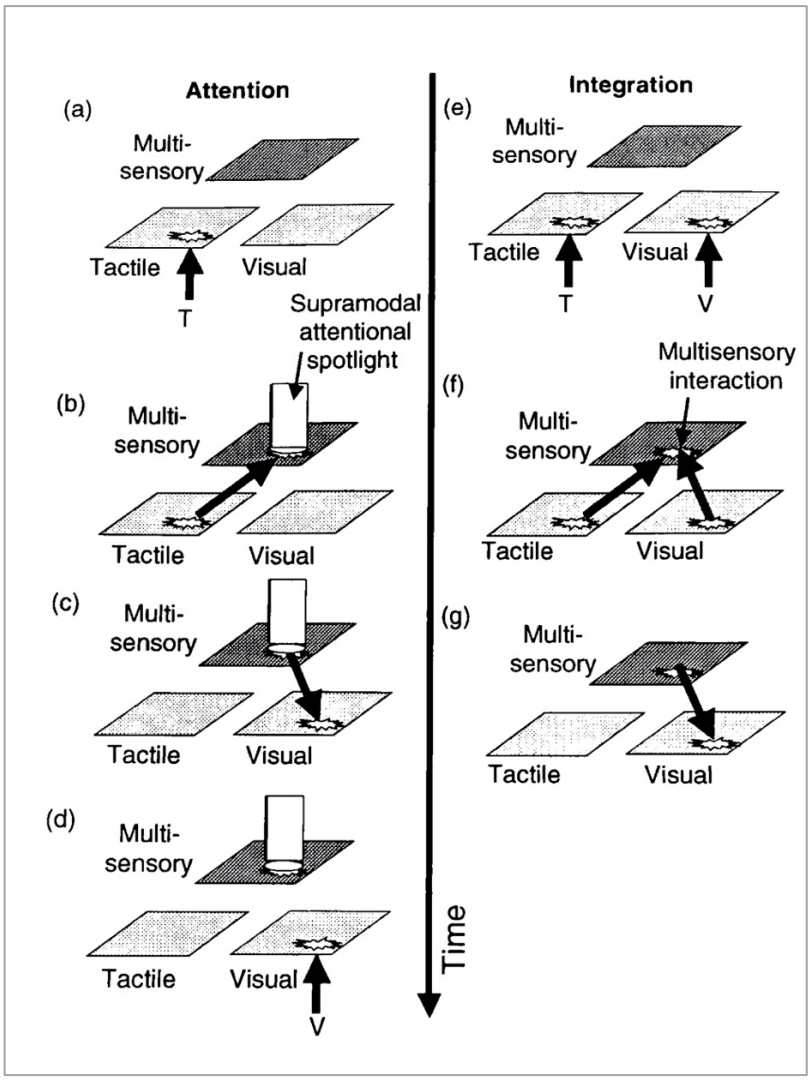

Figure 4. Schematic illustration of the supposed mechanisms underlying spatial attention vs multisensory integration during multisensory interactions. Based on spatial attention processes, (a) a tactile stimulus elicits activation in a corresponding tactile map, (b) that draws attention to its location, (c) within some multimodal brain regions whose activation can then influence the visual stimulus representation in a 'top-down' fashion before the apparition of the visual event (d) whose processing could thus be influenced by the tactile cue within visual areas. By contrast, based on a multisensory integration process, (e) spatial interactions between visual and tactile inputs (f) might only arise when they produce temporally overlapping activations in a feedforward manner at a multimodal level. (g) A top-down feedback can influence unimodal representation only after the feedforward convergence of inputs from different modalities. *Adapted from Spence & Driver, 2004, pp 310.*

Therefore, multisensory interactions can either depend on integrative mechanisms, attentional processes, or both. In the frame of this thesis, what is important to consider is that the magnitude of multisensory interactions varies according to the **saliency** of the stimuli (Legrain et al., 2011; Talsma, Senkowski, Soto-Faraco, & Woldorff, 2010), the **attention** recruited (Macaluso et al., 2016; Spence, 2010; Tiippana, Andersen, & Sams, 2004; Van der Burg, Talsma, Olivers, Hickey, & Theeuwes, 2011), the **spatial** (Fairhall & Macaluso, 2009; Graziano & Cooke, 2006; Macaluso & Driver, 2005; Van der Biest, Legrain, De Paepe, & Crombez, 2016; Vanderclausen, Filbrich, Alamia, & Legrain, 2017; Welch, 1999) and **temporal** relationships of the different stimuli (Botvinick & Cohen, 1998; Meredith, Nemitz, & Stein, 1987; Morein-Zamir et al., 2003; Stein & Stanford, 2008), their respective **intensity** (Senkowski et al., 2014; Stein et al., 2010; Stein & Meredith, 1993; Talsma, 2015) and even features such as the movement, shape, size, orientation or texture that the different stimuli can share (Welch, 1999).

These factors have been largely studied in the general multisensory literature, but to a lesser extent for visuo-nociceptive interactions. Yet, with the nociceptive system acting as a warning signal that enables to detect, localize and react to threatening stimuli (Legrain & Torta, 2015), it is crucial to examine its functions in a multisensory environment. The following sections will review the spatial and temporal factors involved in the perception of nociceptive stimuli, in interaction with visual stimuli, in order to further study their impact on the detection of a nociceptive stimulus.

2.2 Pain and the Representation of Space

In this section, the mechanisms involved in the spatial perception of somatosensory stimuli will first be developed. Each sensory modality codes the spatial location of a stimulus according to its own coordinate system, which represents anatomically the respective sensory surface in its primary sensory areas (Vallar & Maravita, 2009). For example, retinotopy represents the mapping of visual inputs from the retina to neurons in the primary visual cortex, while somatotopy corresponds to the projection of tactile or nociceptive inputs from particular skin areas to specific groups of neurons in somatosensory cortical areas. The ability to localize a tactile or nociceptive stimulus on the body surface depends on its anatomical representation in somatotopic coordinates. Adequate reaction to nociceptive stimuli, implying multisensory processes, therefore relies on the coordination of multiple frames of reference, which are of paramount importance in identifying the body-part that has been damaged, but also the external source of the injury in relation to the body. Second, we will emphasize on the senses that can be recruited by these reference frames, such as visual, tactile, nociceptive and proprioceptive information. Finally, the importance of spatial congruence between the different sensory inputs as well as their spatial localization with regard to the body in the emergence of multisensory interactions will be addressed. Each point will be

illustrated by experiments in non-human primates, supplemented by observations from cognitive pathologies in brain-damaged patients and behavioral experiments in neurologically healthy volunteers.

2.2.1 Somatotopy vs Spatiotopy

Mainly investigated for touch, somatosensory brain areas receive projections from the receptive fields (RFs) of sensory receptors, activated by somatic inputs located on the skin. The projections of the RFs are spatially-organized in subgroups of neurons according to the anatomy of the body. In that somatotopic map (cfr. the *Homunculus* of Penfield, see Figure 5), the cutaneous surface of each body part is represented according to the size and the amount of the sensory RFs (Penfield & Boldrey, 1937; Penfield & Rasmussen, 1950). The somatotopic map thus represents the location of stimuli on skin surface – *"Which limb is stimulated?"* (e.g. Shore, Spry, & Spence, 2002; Vanderclausen, Manfron, De Volder, & Legrain, 2020; Yamamoto & Kitazawa, 2001).

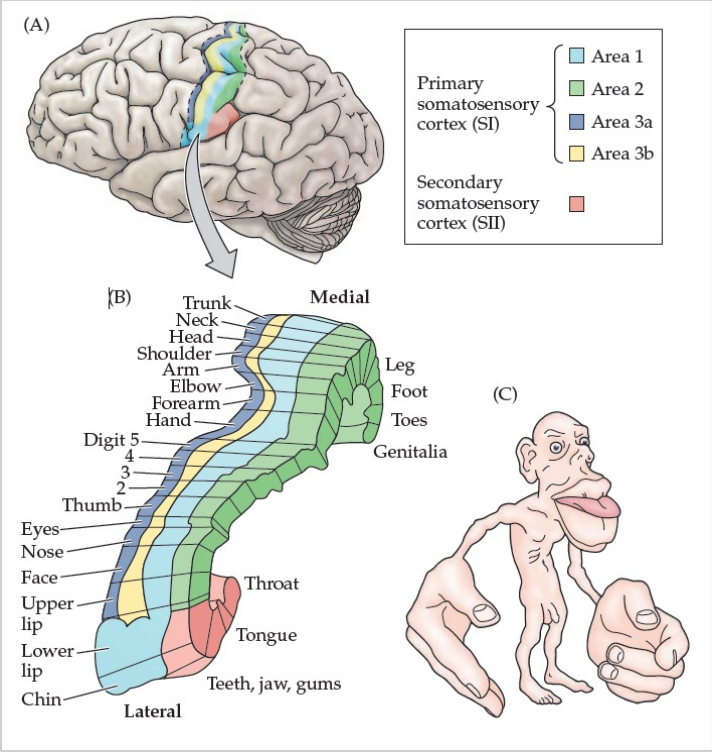

Figure 5. Somatotopic order in the human primary somatosensory cortex for tactile inputs. *Adapted from Purves, pp. 206 (2018).*

Contrary to the popular belief that the acuity to locate nociceptive stimuli would be less precise than that of tactile stimuli, studies have generally shown no difference between both systems (Mancini et al., 2013; Moore & Schady, 1995; Schlereth, Magerl, & Treede, 2001). Indeed, SI, SII (Bingel et al., 2004; Heid et al., 2020; Valentini et al., 2012), the thalamus (e.g. Anderson, Ohara, Lawson, Treede, & Lenz, 2006), putamen, operculum (Baumgärtner et al., 2010), insular (e.g. Brooks, Zambreanu, Godinez, Craig, & Tracey, 2005; Mazzola, Isnard, Peyron, Guenot, & Mauguiere, 2009; Ostrowsky et al., 2002) and cingulate cortices (Andersson et al., 1997), hold maps for the localization of *gross body segments* – face, hand, trunk, foot – of both innocuous *and* noxious stimuli. Additionally, SI and the intraparietal area also contain specific *fine-grained* somatotopic maps for nociceptive stimuli applied on the fingertips (Mancini, Haggard, Iannetti, Longo, & Sereno, 2012; Mancini, Sereno, Lee, Iannetti, & Tracey, 2019). This suggests that, even if the density of the nociceptive fibers is quite low on distal skin regions, the nociceptive system holds a fine spatial organization of nociceptive maps, at least for the digits. As previously mentioned, cingulate and operculoinsular cortices activated by painful and nociceptive stimuli are also associated with a broader brain network involved in the detection of any salient sensory stimulus that might have an impact on body's integrity (e.g. Legrain et al., 2011). The somatotopy of nociceptive inputs therefore constitutes a well-elaborated system, partly different from the somatotopy of tactile inputs (Heid et al., 2020; Mancini et al., 2019), even if both nociceptive- and tactile- afferent systems likely interact in the CNS (Haggard et al., 2013).

The above-mentioned information about the somatotopic organization of somatosensory inputs leads us to the following observations. On the one hand, our knowledge about the fine-grained somatotopy of nociceptive inputs perceived on the *entire* body surface still needs to be deepened (i.e. the interoceptive function of nociception). On the other hand, to correctly locate a stimulus on the body surface and guide action toward it (i.e. to fulfill the role of the exteroceptive function of nociception), the somatotopic frame of reference alone is not sufficient. It is also necessary to process the position of the body limbs in external space to adequately adapt our behavior in response to threatening events (Azañon & Soto-Faraco, 2008; Haggard et al., 2013; Legrain & Torta, 2015). This is endorsed by the *remapping* from the *somatotopic* map to the *spatiotopic* map. The spatiotopic map uses external space as reference frame to enable adequate localization of the stimulated body limbs that constantly move in external space (e.g. Smania & Aglioti, 1995; Vallar & Maravita, 2009). This can be characterized by the following question: *"Where is the stimulated limb?"*. The *remapping* thus integrates the somatosensory stimulus according to the position of the stimulated body-part in external space. In a second step, it allows to identify the position of a threatening event in external space in relation to the position of the body (e.g. Azañon & Soto-Faraco, 2008; Legrain & Torta, 2015; Maravita, Spence, & Driver, 2003; Vanderclausen, Manfron, et al., 2020).

The existence of the spatiotopic frame of reference has been evidenced by manipulating the posture of the hands relative to the body midline (crossed vs uncrossed) during tasks involving localization of tactile (e.g. Aglioti, Smania, & Peru, 1999; Badde, Heed, & Röder, 2014; Crollen, Albouy, Lepore, & Collignon, 2017; Driver & Spence, 1998; Heed & Azañon, 2014; Shore et al., 2002; Yamamoto & Kitazawa, 2001) or nociceptive stimuli (De Paepe, Crombez, & Legrain, 2015; Sambo et al., 2013; Vanderclausen, Bourgois, et al., 2020; Vanderclausen, Manfron, et al., 2020). Indeed, in sighted volunteers, the localization of somatosensory stimuli applied on the hands, while they are crossed over the body midline, induces a conflict between the somatotopic and the spatiotopic representations, as compared to an uncrossed posture (see Figure 6). This results in lower performance to accurately localize the somatosensory stimuli. In the crossed posture, since the right hand is located in the left space (and vice-versa), there would be a mismatch between the automatic coding of the somatosensory stimuli on the body surface and the coding of the position of the stimulated limbs in external space. These findings suggest that somatosensory inputs would be automatically coded according to both somatotopic and spatiotopic frames of reference. However, the weight accorded to each spatial map is sensitive to several factors such as, the availability of visual and proprioceptive information and, the requirements of the task (e.g. Badde, Roder, & Heed, 2015; Crollen et al., 2017; Crollen, Spruyt, Mahau, Bottini, & Collignon, 2019; Gallace, Soto-Faraco, Dalton, Kreukniet, & Spence, 2008; Gallace, Torta, Moseley, & Iannetti, 2011; Heed & Azañon, 2014; Vanderclausen, Bourgois, et al., 2020; Vanderclausen, Manfron, et al., 2020). Manipulating the *distance* between the hands (in an uncrossed posture) has also been used to investigate the remapping of tactile inputs from somatotopic to spatiotopic maps, but the effect on participants' performance to localize the tactile stimuli seems less robust (see Appendix for details). Finally, some studies have suggested similar remapping mechanisms for touch and nociception (Sambo et al., 2013; Vanderclausen, Bourgois, et al., 2020). However, the cortical time-course of the remapping could be different across modalities. Tactile remapping seems to be carried out in a serial fashion with a first somatotopic coding established within SI, followed by the spatiotopic coding when inputs are transmitted from SI to SII and posterior parietal areas (Soto-Faraco & Azañón, 2013). The cortical time-course of nociceptive remapping has not been carefully investigated yet, but given that the spatiotemporal pattern of cortical responses to nociceptive stimuli is not exactly the same as that of tactile stimuli, one might expect some differences in the time-course of the spatial remapping between both modalities (Vanderclausen, 2020).

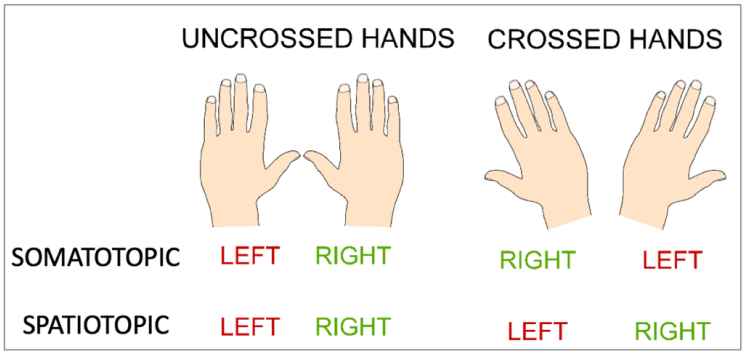

Figure 6. Conflict between the somatotopic and the spatiotopic frames of reference during crossed-hands posture. When the hands are uncrossed, the spatiotopic map is aligned with the somatotopic map. On the contrary, when the hands are crossed over the body midline, there is a mismatch between both representations, the right-hand laying now in the left side of space (and vice-versa). *Adapted from Vanderclausen (2020, pp. 30).*

Interestingly, the posture of the hands also influences the painfulness elicited by nociceptive stimuli. The perceived intensity of nociceptive inputs applied on the hands is decreased in a crossed posture as compared to an uncrossed posture (Valentini et al., 2015), associated with a modulation of the activity of multimodal areas involved in the somatosensory processing (Gallace et al., 2011; Torta et al., 2013). The analgesic effect of crossing the hands would come from the uncommon posture of the arms and thus, from the cognitive costs generated by the potential remapping (Gallace et al., 2011), resulting in limited attentional resources to process nociceptive information (Vanderclausen, Manfron, et al., 2020).

2.2.2 Representations of external space: peripersonal vs extrapersonal space

Adequate coordination between the somatotopic and spatiotopic maps is the first step to implement adaptive behaviors in reaction to potential threats. The information about the localization of the somatosensory stimulus provided by the remapping needs then to be integrated with sensory information present in external space. Several spatial representations around the body, within which humans but also monkeys engage specific interactions, can be identified.

First, by taking the external spatial coordinates into account, the remapping of somatosensory stimuli into spatiotopic maps contributes to the integration of somatic inputs with extra-somatic information into a common representation, the *peripersonal*

space (PPS). The PPS is defined as *"multisensory-motor interfaces, which serve to encode the location of nearby sensory stimuli to generate suitable motor acts"* (Di Pellegrino & Làdavas, 2015 pp. 131). In other words, this multisensory framework represents a safety margin around the body in which the spatial position of sensory events serves as a signal to guide movements toward objects and/or undertake defensive motor reactions against potential threats. The PPS codes both the location of the somatosensory stimuli (tactile and nociceptive) on the body surface and the position of external sensory stimuli in the adjacent space around the body. Given that, in daily-life, objects approaching the body are more likely to threaten the organism than objects that are farther away, and thus need to be efficiently processed to induce adequate reactions, the spatial distance between the external object and the observer determines the degree of multisensory interactions. Importantly, even if our perception of space is global and unitary, studies have revealed multiple peripersonal representations centered around particular body parts (e.g. Brozzoli, Ehrsson, & Farnè, 2014; Farnè, Demattè, & Làdavas, 2005; Maravita et al., 2003; Vallar & Maravita, 2009), implying that visuo-nociceptive interactions are optimized around the stimulated body-limbs (e.g. De Paepe et al., 2014) rather than in a representation of the body as a whole (see Figure 7). In turn, the modular organization of the PPS around the stimulated-limb participate to a global PPS surrounding the whole body and contributing to the representation of the self, distinctly from the environment and from the others (Holmes & Spence, 2004; Serino, 2019).

Second, the PPS gradually gives way to the extrapersonal space (EPS) (Longo & Lourenco, 2006), which is involved in other behaviors than the PPS. The EPS is explored with eye movements, helps in *preparing* reaching movements and is often considered as the "far space", beyond grasping distance (Di Pellegrino & Làdavas, 2015).

The next sections will address studies that evidenced the existence of the PPS, as well as the conditions that optimize visuo-tactile and visuo-nociceptive interactions within that space, based on studies in monkeys and in humans.

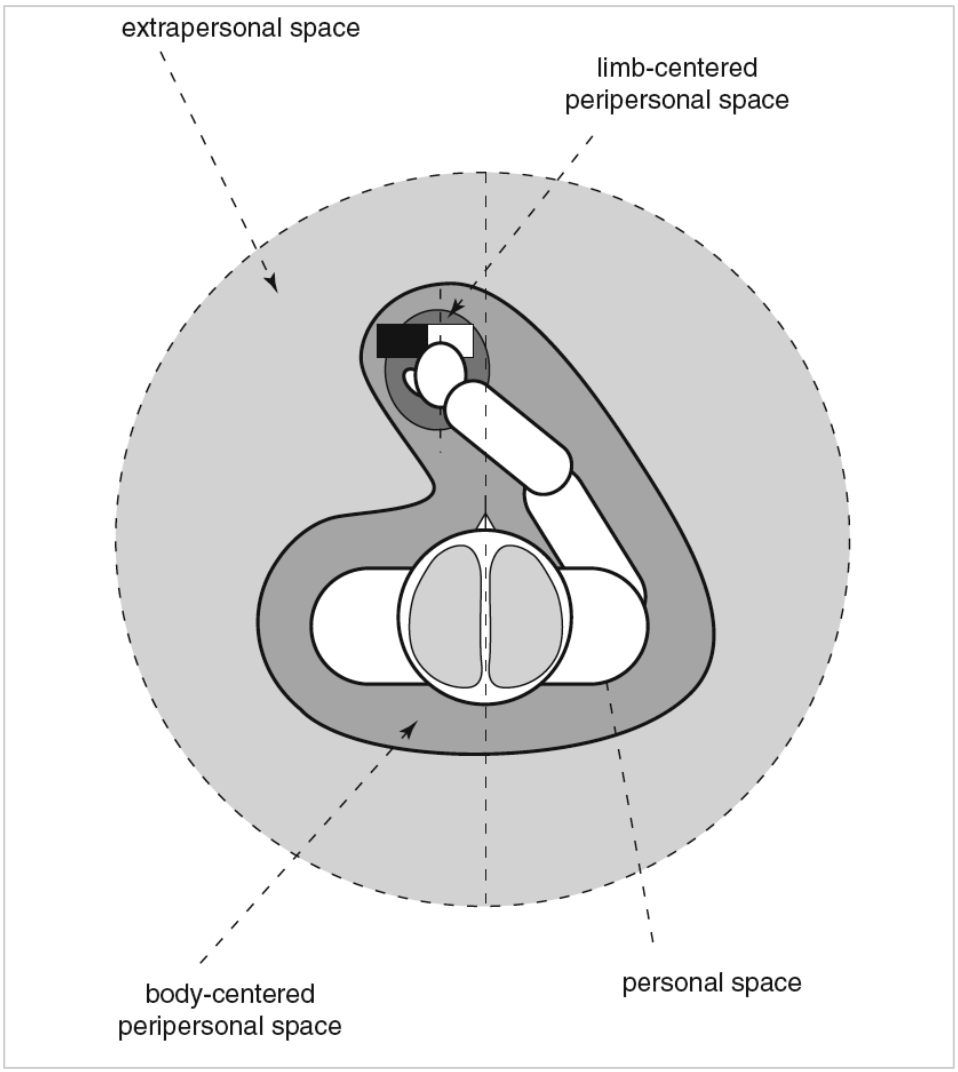

Figure 7. The different representations of space. The figure illustrates each spatial representation with which individuals interact. The personal space is about the body itself. The limb-centered peripersonal space is spatially-locked to the limb stimulated and therefore moves with it. The body-centered peripersonal space corresponds to the spatial representation around the body as a whole. The extrapersonal space represents the space beyond the body. It is often considered to be beyond reaching movements. *Adapted from Legrain and Torta (2015), pp. 10.*

Brain network of the PPS in non-human primates

The pioneering experiment dissociating the PPS from the EPS was conducted by Rizzolatti, Matelli, and Pavesi (1983) in the monkey brain. After the unilateral ablation of the postarcuate premotor cortex, the monkey failed to detect and grasp objects appearing in the PPS while the perception of objects present in the EPS was preserved. On the contrary, the unilateral ablation of Brodmann area 8 provoked deficits in exploratory eye movements for stimuli in the EPS but not in the PPS.

The PPS brain network has then been studied using single-cell electrophysiological recordings in the monkey brain, leading to the discovery of bimodal neurons, integrating visual and tactile information, in a set of interconnected areas. Their striking feature is that their receptive fields (RFs) are spatially aligned, that is, the visual RF matches the location of the tactile RF on the body surface. As we will see, these neurons contribute to the representation of the space surrounding the body according to body-part-centered coordinates (Graziano & Gross, 1998; Graziano, Hu, & Gross, 1997; reviewed in Holmes & Spence, 2004).

Bimodal neurons from the ventral premotor cortex (PMv) preferentially process the spatial information about upper-limbs (Graziano, 1999). Although they are limited in depth, these neurons hold visual RFs that encompass the region of the tactile RFs into the proximal adjacent space (Fogassi et al., 1996; Graziano et al., 1997; Rizzolatti, Scandolara, Matelli, & Gentilucci, 1981). For bimodal neurons with tactile RFs on the arm, the visual RF is thus anchored to the tactile RF and follows the arm movement (Fogassi et al., 1996; Graziano & Gross, 1998; Graziano et al., 1997) rather than the gaze direction. In addition, the visually evoked responses of these bimodal neurons vary according to the distance between the tactile RF and the visual input, with a stronger influence of near as compared to farther stimuli (reviewed in Brozzoli, Makin, Cardinali, Holmes, & Farnè, 2012). These observations indicate that the coding of visual stimuli by bimodal neurons depends on arm-centered coordinates rather than on retinal coordinates (Fogassi et al., 1992; Fogassi et al., 1996; Graziano & Gross, 1998; Graziano et al., 1994; reviewed in Maravita et al., 2003). The face and the head are mostly represented in the ventral intraparietal area (VIP) (Duhamel, Bremmer, BenHamed, & Graf, 1997; Duhamel, Colby, & Goldberg, 1998) and putamen while parietal area 7b favorably processes spatial information related to the arm, face, and also torso (reviewed in Graziano & Cooke, 2006; Graziano & Gross, 1995).

Finally, the size of the RFs of the bimodal neurons is dynamic. By training macaques with rakes to reach food pellets placed in the EPS, Iriki, Tanaka, and Iwamura (1996) reported that the tactile RF of the bimodal visuo-tactile neurons of the intraparietal cortex started to display visual responses. Few minutes of tool-use were thus sufficient to expand the visual RF, with the far stimuli being recoded as near stimuli, and the far space becoming a fruitful ground for multisensory interactions. However, the modulation of visual responses was only observed after *active* use of the tools. The

dynamic aspect of the visual RF hence requires initiating motor actions with the surrounding space. The PPS is shaped by sensorimotor experiences which would enable to hold an updated, multisensory map of body posture (Maravita & Iriki, 2004).

Altogether, the brain regions identified in monkeys by using electrophysiological and behavioral techniques represent a functional network that integrates visual and tactile inputs, whose main function would be to construct a multisensory representation of the body and PPS (Duhamel et al., 1998; Graziano & Cooke, 2006; Vallar & Maravita, 2009). This network would shape spatial maps to guide limbs' movements in space (Graziano & Gross, 1998). To the best of our knowledge, regarding the existence of neurons encoding visual and nociceptive inputs, only one study has been conducted. Neurons from 7b area have been found to fire in presence of both thermal noxious and threatening visual stimuli (Dong, Chudler, Sugiyama, Roberts, & Hayashi, 1994). Therefore, when a potential danger reaches the PPS, the activity of these bimodal neurons would be triggered and would enable to select and coordinate defensive behaviors (Graziano & Cooke, 2006).

Evidence in favor of the PPS in humans: advances from neuropsychological observations

The findings emerging from monkey studies at the single neuron level have been corroborated by neuropsychological observations about visuospatial or visuomotor deficits in brain-damaged people, as well as by behavioral experiments conducted in neurologically healthy volunteers. Based on the fundamentals of neuropsychology, studying the loss of spatial representations in neurological patients opens a window on the mechanisms underlying the multisensory neural coding of space of the "intact" human brain. The main findings of the studies that will now be developed concern the visuo-tactile modalities. The next section will focus on the spatial alignment of visual and nociceptive stimuli in the PPS in healthy volunteers.

Lesions in the dorsal parietal or ventral frontal cortex can produce attentional syndromes such as spatial neglect and/or extinction (Corbetta, Kincade, Lewis, Snyder, & Sapir, 2005; Di Pellegrino, Làdavas, & Farnè, 1997; Jacobs, Brozzoli, Hadj-Bouziane, Meunier, & Farnè, 2011).

Hemispatial neglect characterizes patients unable to explore and report sensory events, on the side of space, or on the body, opposite to the lesion site, due to attentional weakness. Most of the time, it affects the left hemispace since the syndrome appears in 90% of the cases after right hemisphere lesions (e.g. Corbetta et al., 2005; Driver & Vuilleumier, 2001). Interestingly, the neglect can selectively affect the PPS (Halligan & Marshall, 1991) or the EPS (Cowey, Small, & Ellis, 1994). The human brain, such as the monkey brain, seems therefore to also process space in dissociated frames of reference (Brozzoli et al., 2014) and the right hemisphere could play a greater role than the left

hemisphere (Vallar & Maravita, 2009). However, the boundaries between the PPS and the EPS are not strict inasmuch as the PPS can be expanded – under some conditions – to a further space. Akin to findings reported in monkeys, this plasticity has been evidenced by actively using a tool to reach targets in farther space, in which the targets are usually not reachable. Tool use generates a remapping of the PPS from near to far space. First studied in neglect and/or extinction patients for vision (Berti & Frassinetti, 2000) and visuo-tactile interactions (Farnè, Bonifazi, & Làdavas, 2005; Farnè, Iriki, & Làdavas, 2005; Farnè & Làdavas, 2000; Làdavas, 2002; Maravita, Husain, Clarke, & Driver, 2001), researchers achieved to replicate the effect in healthy humans for visuo-tactile (e.g. Holmes, Calvert, & Spence, 2004; Maravita, Spence, Kennett, & Driver, 2002) and visuo-nociceptive (Rossetti, Romano, Bolognini, & Maravita, 2015) interactions. While arousal responses to the sight of far noxious stimuli approaching the hand are usually reduced as compared to when the stimuli are close to or touch the hand, the autonomic responses to far stimuli increase after tool use (Rossetti et al., 2015). In accordance with the enhanced visual activity of the bimodal neurons in monkeys after the use of a rake to reach food pellets (Iriki et al., 1996), the border between PPS and EPS is defined according to functional and repeated interactions with objects in external space, which notably recruit visual and somatosensory modalities at the same time (Brozzoli et al., 2012; Farnè & Làdavas, 2002; Jacobs et al., 2011; Serino, 2019).

Extinction refers to the ability to report a contralesional stimulus when presented alone, but not when presented concomitantly with a stimulus on the side of space ipsilateral to the lesion. Extinction would result from an unbalanced competition of several sensory targets to access to attentional resources, between a damaged and an intact spatial representation (Farnè, Demattè, & Làdavas, 2005; Holmes & Spence, 2004; Jacobs et al., 2011; Serino, 2019). Extinction can be *unimodal*, i.e. between inputs of the same sensory modality (e.g. Bender, 1952; Giuseppe Di Pellegrino, Basso, & Frassinetti, 1997; Liu et al., 2011; Rorden, Jelsone, Simon-Dack, Baylis, & Baylis, 2009) or *crossmodal*, i.e. between inputs from different sensory modalities (e.g. Di Pellegrino et al., 1997; Farnè & Làdavas, 2002; Làdavas & Farnè, 2004; Ladavas, Pavani, & Farnè, 2001; Maravita et al., 2003; Mattingley, Driver, Beschin, & Robertson, 1997). For example, in visuo-tactile extinction, the detection of a tactile stimulus applied on the hand contralateral to the lesion is hampered if, *and only if*, a concurrent visual stimulus occurs next to the ipsilesional hand. What constitutes relevant arguments supporting that the PPS is specifically anchored to the stimulated body-part, such as evidenced by the hand-centered visual RF's discovered in the monkeys' PMv (Graziano & Gross, 1997), is that the perception of tactile stimuli applied on the contralesional limb is extinguished by visual stimuli presented near the opposite homologous limb, whatever the relative position of these limbs. For instance, in an uncrossed posture, the perception of the tactile stimulus applied on patients' left hand is affected by a right-sided visual stimulus concomitantly presented near the right hand, whereas, when the hands are crossed over the body midline, so that the left hand is now in the right side of space, the perception of the left-hand tactile stimulus is still affected by a visual stimulus

presented near the right hand, but that is now left-sided (Di Pellegrino et al., 1997). The effect is however decreased when the visual stimulus is next to a nonhomologous body-part or in far space from the tactile stimulus and, can even be reversed when the visual stimulus is next to the contralesional hand receiving also the tactile stimulus, *facilitating* the perception of the tactile stimulus (Di Pellegrino et al., 1997; Farnè et al., 2005b; Làdavas, 2002; Spence, Nicholls, Gillespie, & Driver, 1998). Furthermore, by developing experimental paradigms that mimic the conditions under which the spatial position of two competitive tactile stimuli could interfere with their perception, researchers achieved to replicate the phenomenon of extinction in neurologically healthy volunteers (Farnè et al., 2008). Extinction would therefore reflect a normal physiological limit of the human brain (Driver & Vuilleumier, 2001; Jacobs et al., 2011).

Evidence for a PPS for visuo-nociceptive interactions: advances from behavioral experiments

The spatial mapping of visual and nociceptive stimuli in the PPS has been first evidenced in healthy volunteers with tasks during which the stimuli from one modality influence the perception of stimuli from the other modality, according to their spatial proximity. One experimental paradigm often used to study these interactions is the exogenous cueing paradigm with temporal order judgment (TOJ) tasks. In the following studies, TOJ tasks consist in presenting pairs of stimuli delivered on each side of space and separated by different stimulus onset asynchronies (SOAs). Participants are asked to report the position of the stimulus they have perceived as occurring first. The pair of stimuli of the task-relevant modality (i.e. target stimuli) is shortly preceded by a stimulus of the other modality (i.e. cue stimulus), located next to one of the two target stimuli. Exogenous cueing paradigm refers to the fact that attention is automatically captured by the cue stimulus while the location of the cue is not predictive of the location of the forthcoming target stimulus (e.g. Filbrich, Alamia, Burns, & Legrain, 2017). In contrast, during endogenous cueing paradigm, attention is voluntarily directed toward the target's location, predicted by the location of the cue (Driver & Spence, 2004).

Therefore, by using an exogenous cueing paradigm, De Paepe et al. (2014) showed for the first time that a visual stimulus and a nociceptive stimulus can also be remapped into a common space, the PPS. Participants performed a TOJ task on pairs of *nociceptive stimuli*, each stimulus applied on each hand dorsum, that were shortly preceded by unilateral or bilateral *visual cues* (the bilateral cues were used as control condition). In one condition, the visual cues could appear next to the stimulated hands, whereas in the other condition, the visual cues appeared in far space, 70 cm in front of participants' hands (see Figure 8). Participants had to judge which nociceptive stimulus occurred first while ignoring the visual cues. The point of subjective simultaneity (PSS) was used as a measure of spatial bias. It defines the amount of time by which one nociceptive

stimulus has to precede or follow the other in order for the two stimuli to be perceived as occurring simultaneously. During the 'unilateral cue' condition, the PSS was shifted in favor of the cued side of space, especially when the unilateral visual cue was located close to the stimulated hand, as compared to 70 cm in front of participants' hands. The close visual cue attracted attention to its location. In other words, nociceptive stimuli presented on the side of space opposite to the visual cue had to be presented several milliseconds before stimuli presented on the cued side of space to have the chance to be judged as occurring simultaneously. The processing of the nociceptive stimulus with the visual cue close to it was therefore prioritized.

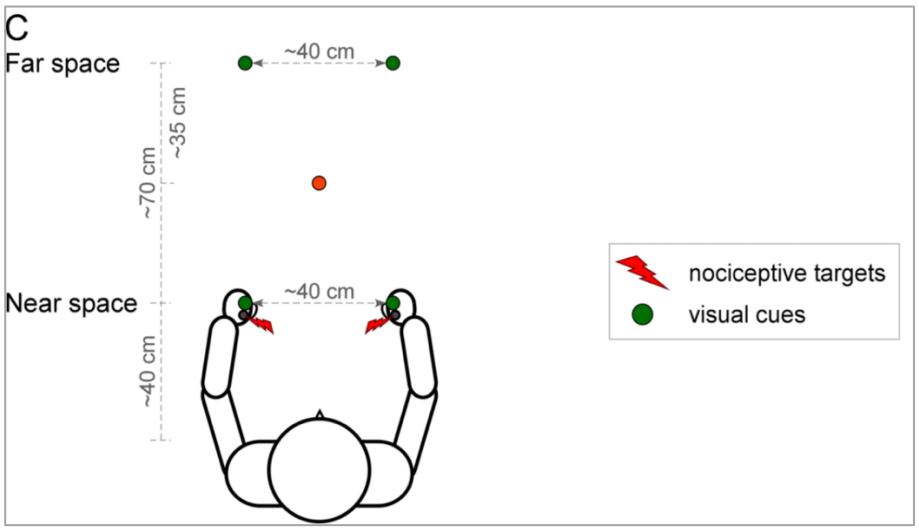

Figure 8. Experimental set-up of a nociceptive TOJ task with visual cues. The red flashes represent nociceptive stimuli. They were applied on both of hands. Visual cue stimuli, represented by green circles, were either presented unilaterally or bilaterally and either on the hands (in near space) or in front of them (in far space). Participants fixated on a red LED that was located equidistant between the near and far visual cues. *Adapted from De Paepe et al. (2014).*

To understand the extent to which spatial mapping of nociceptive stimuli takes into account the position of the body limbs in external space, the authors investigated in a subsequent study the impact of a visual cue on the temporal order judgment of nociceptive stimuli when the hands were in a crossed vs uncrossed posture, relative to the body midline. Once again, in one experimental condition, visual cues were close to the hands while, in another experimental condition, they were in further space, 70 cm in front of the hands. The PSS of the nociceptive stimuli was biased in favor of the cued side of space, regardless of the posture of the hands in external space (crossed vs

uncrossed over the body midline). The effect was more pronounced in the experimental condition where the visual cue was close to the stimulated hands than when it was in far space (De Paepe et al., 2015). This second study confirms that the bias induced by the visual cue on the nociceptive processing results from the remapping of the nociceptive stimuli based on external space coordinates that take into account the position of the limbs. However, these studies do not allow concluding whether the bias induced by the close visual cue on the temporal order judgment of the nociceptive stimuli depended on the spatial proximity of the visuo-nociceptive stimuli relative to the trunk or rather to the stimulated hand. In another TOJ task (De Paepe, Crombez, & Legrain, 2017), the authors therefore investigated whether visuo-nociceptive interactions are optimized in a PPS *spatially-locked* around the stimulated limb or around the body as a whole, by manipulating the relative position of the hands and the position of the visual cues in external space. The visual cues could either appear next to each hand receiving the nociceptive stimuli, with the hands placed close to or far from the trunk (congruent conditions). Alternatively, the visual cues could appear close to the trunk, while the hands were placed further away, and vice-versa, the visual cues far from the trunk while the stimulated hands were close to the trunk (incongruent conditions). De Paepe et al. (2017) found that the influence of the unilateral visual cue on nociceptive judgments was more pronounced when it was close to the stimulated hand, regardless of the position of the stimulated hand relative to the trunk (i.e., irrespective from a whole-body reference). These results suggest that nociceptive and visual stimuli interact best in a spatial representation around the stimulated limb.

Following the studies of de Paepe and colleagues, Filbrich et al. (2017a,b); Filbrich et al. (2018); Vanderclausen, Filbrich, Alamia, and Legrain (2017) investigated how nociceptive stimuli can affect the perception of the visuospatial environment around the body. This time, participants performed TOJ tasks on pairs of *visual stimuli*. Participants were thus asked to report which visual stimulus of the pair they perceived as occurring first while unilateral or bilateral nociceptive cues were applied shortly before on one or on both hand dorsa. Across studies, the position of the visual stimuli as well as the position of the limbs in external space were manipulated. The PSS was always shifted in favor of the cued side of space (i.e. the side of space in which the hand received the unilateral nociceptive cues). More specifically, Filbrich et al. (2017b) mainly reproduced the design of the experiment of De Paepe et al. (2017) where they manipulated both the position of the visual stimuli and the position of the hands relative to the trunk. Participants' judgments were biased in favor of the cued side of space in all experimental conditions, but especially when the hands were placed close to the visual stimuli (see Figure 9). In other words, regardless of the distance of the visual stimuli and the hands from the trunk, visuo-nociceptive interactions were greater when visual stimuli were presented near the hands. Nociceptive stimuli can thus influence the perceptual processing of visual inputs. In addition, these findings are in agreement with those of De Paepe, Crombez, and Legrain (2017) according to which visuo-nociceptive interactions are maximized in a PPS that is spatially-locked to the stimulated limb.

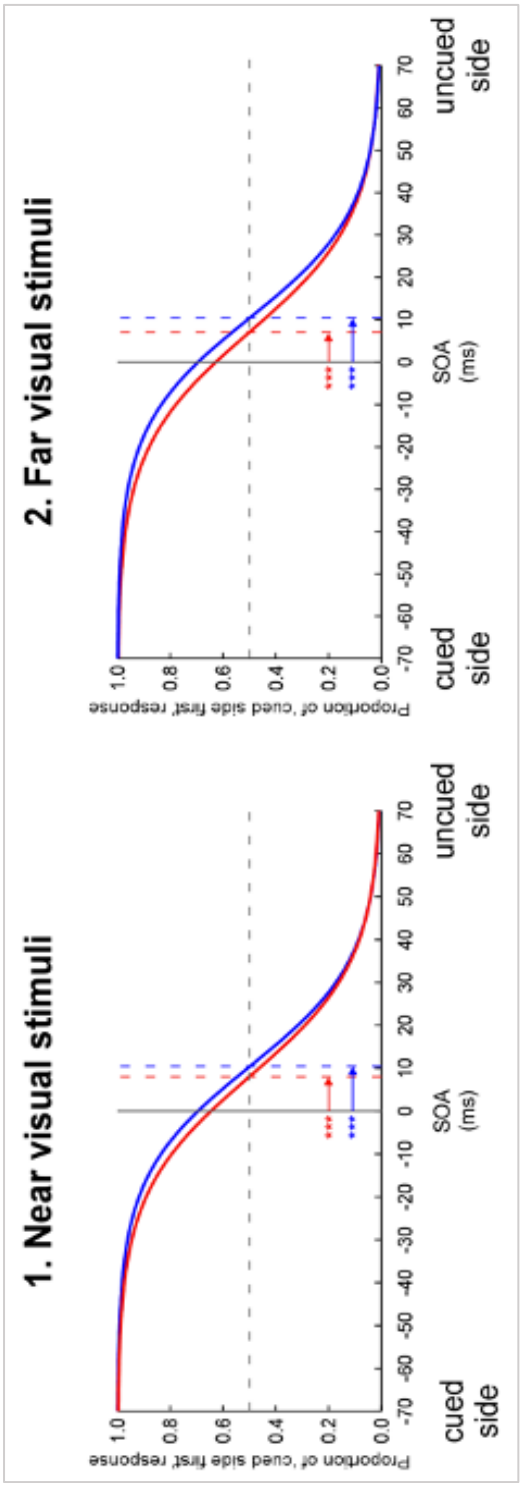

Figure 9. TOJ fitted logistic functions. The figure depicts the fitted logistic functions for (1) the condition in which the visual stimuli were delivered next to the trunk and (2) the condition in which visual stimuli were located far from the trunk. For each graph, the x-axis shows different hypothetical SOAs between the two visual stimuli: negative values indicate that the visual stimulus occurring in the cued side of space was presented first, while positive values indicate that the visual stimulus occurring in the uncued side of space was presented first. The y-axis represents the proportion of trials in which the participants perceived the visual stimulus presented in the cued side of space as occurring first. Blue curves show the conditions in which participants' hands were congruent relative to the position of the visual stimuli (next to the visual stimuli, independently of the position of the hands), whereas the red curves show the conditions in which participants' hands were incongruent relative to the position of the visual stimuli (located either far or close to the trunk). The blue vertical dashed lines represent the PSS values of the congruent condition and the red vertical dashed lines represent the PSS values of the incongruent position. The arrows and asterisks indicate the PSS values significantly different from zero (*$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$). *Adapted from Filbrich et al. (2017b), pp. 13.*

In addition, the influence of the nociceptive cue on the temporal order judgment of visual stimuli would not rely on gaze direction. Akin to De Paepe and colleagues' (2014, 2015, 2017) results, external coordinates seem to govern visuo-nociceptive interactions through a realignment of somatotopic and retinotopic information into a common frame that uses the body-limb as reference (Filbrich et al., 2018). These findings also corroborate the suggestions that have been made in the context of the bimodal neurons in PMv and VIP monkeys, i.e. that visual RFs would be anchored to the body parts hosting tactile RFs and would not be dependent of the retina position (Fogassi et al., 1992; Fogassi et al., 1996; Gentilucci, Scandolara, Pigarev, & Rizzolatti, 1983; Graziano et al., 1997).

The PPS is therefore supposed to constitute a safety margin around the body to protect it from incoming threats (Graziano & Cooke, 2006). Because of the relevance of moving objects in the PPS, for ecological reasons, the impact of dynamic visual stimuli instead of static stimuli on the reaction to nociceptive stimuli has been investigated, using exogenous cueing paradigm during a detection task[2] (De Paepe, Crombez, & Legrain, 2016). The participants had to respond as fast as possible on which hand they perceived the *nociceptive stimuli* while *uninformative visual cues* were approaching or receding from the stimulated hand, in a congruent position, or from the non-stimulated hand, in an incongruent position (see Figure 10). The influence of the visual cue *approaching* the body on the detection of the nociceptive stimulus was greater (RTs decreased as measure as the visual cue was approaching) than the influence of the visual cue *receding* from the body (no modulation of the RTs). Objects that approach the body would trigger early defensive behaviors as compared to receding objects. Participants also reacted faster when the visual cue was spatially congruent to the hand receiving the nociceptive stimulus.

[2] This paradigm was inspired by the study of Canzoneri, Magosso, and Serino (2012) in which the impact of dynamical auditory stimuli on the RTs to tactile stimuli was investigated.

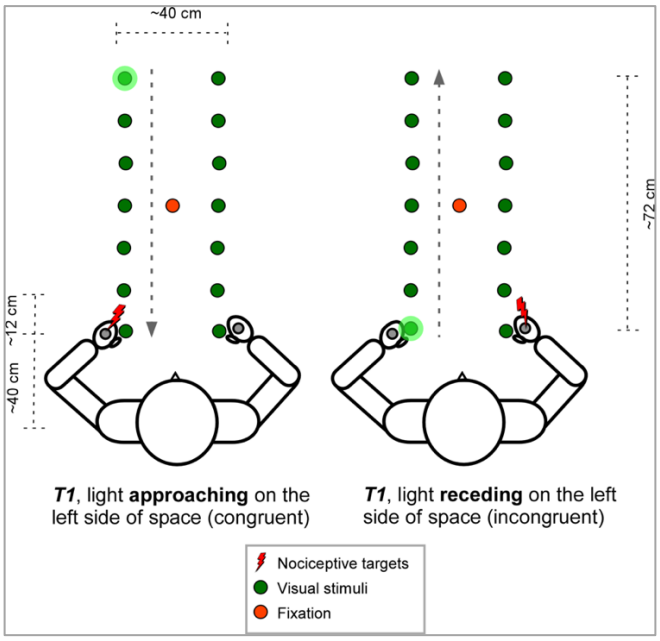

Figure 10. Experimental set-up of a detection task with nociceptive targets and visual cues. The left side of the figure illustrates the congruent condition: the light switches on at 72 cm from the participant and approaches the hand on the left side of space while the participant gets a nociceptive stimulation to the left hand at T1 (170 ms from light onset). The right side of the figure illustrates the incongruent condition with a receding light, that switches on in between the thumb and the index finger at the time of stimulation, and a nociceptive cue was applied this time on the right hand. The dashed arrow indicates the moving direction of the lights. *Adapted from De Paepe et al. (2016), pp.5.*

Finally, considering that the spatial position of different sensory stimuli determines their interactions, authors further investigated whether the spatial position of a visual stimulus could modulate the detection of a nociceptive stimulus. In this order, Filbrich et al. (2019) used a detection task that mimicked the conditions under which the two stimuli could enter in competition, akin to the above-mentioned phenomenon of extinction, but in healthy volunteers. One nociceptive stimulus was applied on one of the two hands, using electrical stimulations activating Aδ fibers with intensity of current corresponding to the absolute detection threshold. The nociceptive stimulus was either delivered alone (single condition) or accompanied by a visual stimulus located close to the stimulated hand (ipsilateral condition) or close to the non-stimulated hand (contralateral condition). As compared to the single condition, the presence of the visual stimulus contralateral to the hand receiving the nociceptive stimulus decreased the probability to report the detection of the nociceptive stimulus. On the contrary, the presence of the visual stimulus in the PPS of the stimulated hand

increased that probability. In other words, participants omitted more often to report the nociceptive stimulus when a visual stimulus was presented near the opposite hand, and less often when this visual stimulus was presented near the stimulated hand (see Figure 11). This study demonstrated for the first time that visuo-nociceptive interactions can affect the detection of nociceptive inputs.

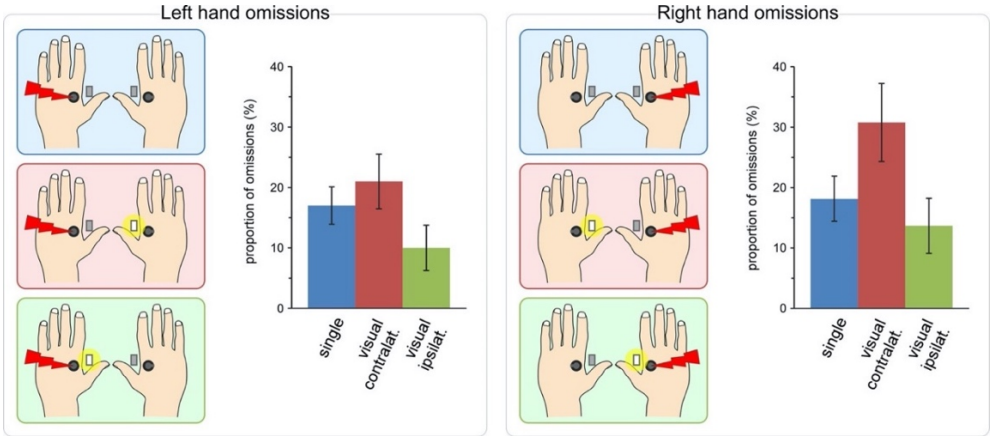

Figure 11. Illustration of visuo-nociceptive crossmodal extinction phenomenon in healthy volunteers. The figure depicts the design and results of 19 participants who performed a detection task composed of two kinds of sensory stimuli: visual inputs delivered by means of white light emitting diodes (LED) and nociceptive stimuli delivered at Aδ-fiber detection threshold by means of intra-epidermal electrical stimulations (IES). The stimuli were randomly administered according to three different experimental conditions. The blue frame and bar represent the single condition during which participants received single nociceptive stimuli either on the left or on the right-hand dorsum; in green, the ipsilateral condition in which participants received pairs of one nociceptive stimulus with one visual stimulus located next to the stimulated hand; in red, the contralateral condition in which visual stimuli appeared close to the opposite non-stimulated hand. Participants were asked to report for each sensory modality what they perceived, on which hand for the nociceptive stimuli, and in which side of space for the visual stimuli. *Adapted from Filbrich et al. (2019), pp.118.*

Neuroanatomical basis of the spatial coding of nociception

Now that we have reviewed the optimal spatial conditions under which visual and nociceptive inputs can interact, it would be interesting to explore the brain mechanisms that are likely to be involved. However, the anatomical substrates that would be responsible for the spatial remapping of nociceptive stimuli into external space remain unknown. Regarding the interactions between vision, proprioception (Makin, Holmes, & Zohary, 2007) and touch (Brozzoli, Gentile, & Ehrsson, 2012; Gentile, Petkova, & Ehrsson, 2011; Jacobs et al., 2011; Lloyd, Shore, Spence, & Calvert, 2003), fMRI techniques combined with behavioral experiments showed that the intraparietal sulcus, the PMv, the putamen and the insula play a role in processing multisensory inputs occurring in the space near the hand. We have already established that the insula was also activated by nociceptive stimuli (e.g. Legrain et al., 2011) and, like the putamen (Baumgärtner et al., 2010), holds body maps of *gross body segments* for innocuous and noxious stimuli (e.g. Brooks et al., 2005; Evrard, 2019; Mazzola et al., 2009; Ostrowsky et al., 2002). The insular cortex is also supposed to be involved in many different other functions such as sensory-discriminative, autonomic, and cognitive-emotional functions, that recruit information from all sensory modalities (Evrard, 2019). Furthermore, the intraparietal area contains specific *fine-grained* somatotopic maps for nociceptive stimuli applied on the fingertips (Mancini et al., 2012; Mancini et al., 2019). It would therefore be hypothesized that the insular cortex and intraparietal area play a role in the spatial mapping of nociceptive inputs with other sensory modalities. Moreover, nociceptive stimuli also activate premotor and posterior parietal areas (Apkarian, Bushnell, Treede, & Zubieta, 2005; Nakata et al., 2008), akin to tactile stimuli. Their activities have however been interpreted as being related to *"pain epiphenomena, such as suppression of movement or actual pain-evoked movement themselves"* (Apkarian et al., 2005 pp. 466) and therefore, until recently, have not received the attention they deserve. Vanderclausen, Bourgois, et al. (2020) have thus hypothesized that premotor and posterior areas could actually be associated to the so-called "pain matrix" network (Legrain et al., 2011) by being involved in the mapping of threatening objects into external space, which would in turn help to prepare spatially guided actions to defend the integrity of the body. However, these assumptions require further investigations.

2.2.3 Conclusion of the multisensory space

Given that the aim of this thesis is to study visuo-nociceptive interactions, and more particularly, the effect of the position of a visual stimulus on the detection threshold of inputs conveyed by thermo-nociceptive fibers, this introduction intends to highlight the factors that need to be considered to meet the conditions under which multisensory interactions, and visuo-nociceptive interactions in particular, can be observed.

We first learned about the mechanisms conveying the nociceptive information from the sensory receptors located in the epidermis to the cortex, through the nociceptive system itself. We discovered that nociceptive and pain sensations project through various cerebral regions that also respond to salient events involving any sensory modality.

Because visuo-nociceptive interactions depend on spatial factors, we then addressed the spatial coding of information of the somatosensory systems. This latter section taught us that two coordinated frames of references, the somatotopic and the spatiotopic maps, enable to code spatial information about somatic events by considering the body position, allowing adequate localization of potential threats. We reviewed the literature about touch and nociception, two systems that, although conveying the sensory information through specific systems, seem to remap according to similar mechanisms. We then considered the nociceptive system in interaction with other sensory modalities, such as vision. Indeed, the remapping of somatosensory inputs from somatotopic toward spatiotopic frames of reference allows building a general representation of the body that slightly extends in its surroundings, the PPS. The PPS therefore optimizes interactions between somatosensory and extra-somatic inputs when they occur close together in space, and especially around the stimulated limb. Based on multisensory information like vision, proprioception, touch or nociception, the multisensory interactions in the PPS enable to guide movements toward objects or to initiate defensive reactions in case of threats for the body's integrity. The multisensory nature of the remapping is thus substantial. Finally, related to the "pain matrix" debate, behavioral experiments confirm that the physiological systems underlying pain are strongly integrated into multisensory representations (e.g. Haggard et al., 2013).

The spatial components underlying interactions between somatic and extra-somatic information have thus been recently highlighted. However, we still do not fully understand which sensory mechanisms predominantly drive interactions between nociceptive and visual stimuli in the PPS. For example, when a nociceptive stimulus applied on our hand interacts with a close visual stimulus, is it because we see the proximity between the stimulated hand and the visual stimulus and/or because we feel the stimulated hand close to the visual stimulus? Is it vision of the limbs, proprioception or both senses that are responsible for these interactions? Some studies in visuo-tactile

modalities have considered this issue but no consensus has yet been reached (see Kennett, Spence, & Driver, 2002; Làdavas, Farnè, Zeloni, & di Pellegrino, 2000; Macaluso, Frith, & Driver, 2002; Mattingley et al., 1997; Pavani, Spence, & Driver, 2000). In any case, the processing of these interactions could potentially differ for nociception as compared to other sensory modalities given the specific role of nociception and pain: the organism needs to *avoid* the source of injury. Additionally, clarifying the role of visual feedback vs proprioceptive feedback in visuo-nociceptive interactions could help for cognitively rehabilitating patients suffering from chronic pain diseases with misrepresentation of the visual space surrounding their body (i.e. complex regional pain syndrome, see Filbrich, Alamia, Verfaille, et al., 2017; Verfaille et al., 2021).

Finally, the spatial congruence of visual and nociceptive inputs in the PPS alone cannot be sufficient to elicit their interactions. We also need to consider their *temporal* congruence. Obviously, in daily life, sensory events solicit our different senses at the same time. Multisensory interactions are thus optimized when the different sensory inputs are perceived at about the same location, and at about the same moment. The next section will therefore address the literature about multisensory timing from animal studies to behavioral experiments in healthy volunteers. The temporal rules specifically regulating visuo-nociceptive interactions are largely unknown, although they are particularly relevant given that nociceptive Aδ and C fibers are poorly or not at all myelinated, and thus extremely slow to transmit the nociceptive information to the cortex, as compared to the transmission of sensory information through the visual system. The differences between the conduction velocities of each sensory system would result in differences in the arrival times of their respective input to the cortex. Are visuo-nociceptive interactions possible under the same temporal conditions than visuo-tactile or visuo-auditory interactions?

2.3 TEMPORAL FEATURES DURING MULTISENSORY INTERACTIONS

Spatial and temporal occurrences help humans – and most animal species – to determine the relationships between sensory inputs and to create an integrative approach to the outside world. When cooking, if the visual information about the boiling oil, splashing out of the pan, is not synchronized with the burning sensation of the oil drop on your forearm, you will probably be less proactive in implementing a strategy to avoid any further burning sensation. The temporal congruence between two inputs is therefore as determining as their spatial congruence in producing multisensory interactions, and thus, in engaging adaptive behaviors to protect the organism.

The perception of time must be considered from three angles (1) *the event time* which is defined by the time at which the physical event occurs, (2*) the brain time* which describes the time course of the brain activity evoked by the physical event – reflected by electrophysiological recordings and (3) *the subjective time* which corresponds to the perception of the individual regarding the appearance of the physical event – studied in behavioral studies (Fujisaki, Kitazawa, & Nishida, 2012). Many factors affect these three interrelated stages. In the framework of this thesis, our main interests are:

- to understand the *brain mechanisms* that define the timing of interactions between different sensory inputs,
- to consider these mechanisms according to the specific properties of the nociceptive vs visual systems,
- to review different theories that intend to explain the *subjective time* of multisensory events in humans.

The final aim will be to identify which external factors affect the perception of time. Since, as we will see, the processing of time is different from one situation to another, reconstructing the actual timing of a sensory event at which the interactions between the different inputs would be optimal, requires to tolerate some variability. A thorough review of the literature will allow us to optimally define the context(s) in which the effect of a visual stimulation on the detection by the brain of inputs transmitted by the nociceptive system could potentially be examined. There will be an initial focus on animal studies at the cellular level, followed by behavioral experiments conducted in humans. Given that studies about temporal rules specifically governing visuo-nociceptive interactions are sparse, the temporal aspects of visuo-tactile and visuo-auditory interactions will also be addressed.

2.3.1 The brain time: insights from studies in subcortical regions of mammals

Similar to studying the monkey's cortex to understand the multisensory representation of space, the superior colliculus (SC) of anesthetized rats, cats (Meredith & Stein, 1983, 1986b; Stein & Meredith, 1993) and monkeys (Wallace, Wilkinson, & Stein, 1996) has been used as a model to investigate the temporal mechanisms involved in multisensory interactions (see also Holmes & Spence, 2005). The SC is a midbrain structure (see Figure 12) involved in the transformation of sensory cues into motor responses (Ghazanfar & Schroeder, 2006; Meredith & Stein, 1986a, 1986b). The deep layers of the SC contain multisensory neurons able to process individually inputs from one modality, but also different sensory inputs at the same time. For example, some neurons respond to mechanical, thermal and somatic noxious stimuli as well as visual and innocuous tactile stimuli. The role of the SC neurons is therefore to integrate, and not segregate, the different senses to trigger attentive and orientation behaviors (Stein & Meredith, 1993) and notably, to protect the body from potential injuries. In fact, there are also several cortical structures, such as the insula-claustrum area (Calvert & Thesen, 2004) that host converging cells for inputs of different sensory modalities. Moreover, these converging cells are present across phylogeny (Meredith & Stein, 1986b; Wallace, Meredith, & Stein, 1992).

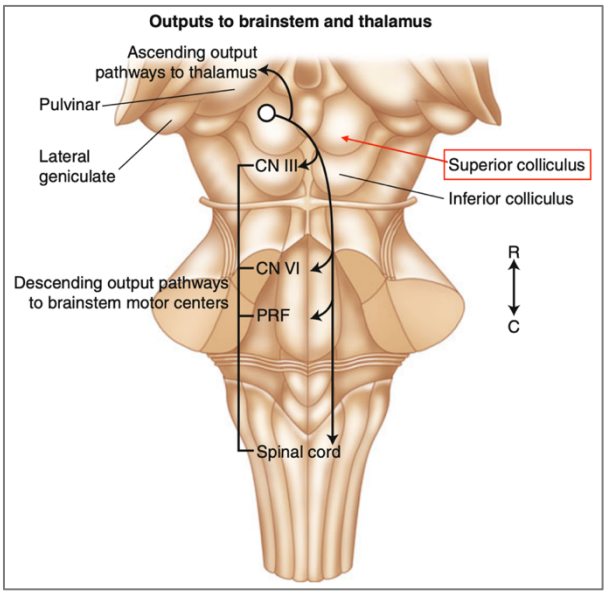

Figure 12. Dorsal aspect of the SC and brainstem of the cat. The deep SC layers send descending projections to motor-related areas of the brainstem and spinal cord as well as ascending projections to the thalamus. *Adapted from Stein, Stanford, Godwin, and McHaffie (2016), pp. 751.*

The responses of the SC neurons are crucially different according to the respective situations:

- Some stimuli delivered alone do not elicit any response whereas when combined with other sensory cues, within particular time-windows, significantly alter the activity of the neurons. Multisensory interactions can thus facilitate the detection of single weak stimuli.
- The convergence of multiple modalities into the same neuron modulates the neurons' activity. An *enhancement* occurs when the different sensory inputs are spatially (within the respective RF of each stimulus) and/or temporally close, whereas the response is *depressed* if the different sensory inputs are spatially and/or temporally disparate (Calvert & Thesen, 2004; Ghazanfar & Schroeder, 2006; Meredith et al., 1987; Meredith & Stein, 1986a, 1986b; Stein & Meredith, 1993).
- Different combinations of sensory modalities, the physical properties of the stimuli and their relationships, their spatial position, as well as the timing of appearance of each stimulus, differently impact the firing of the neurons (Meredith & Stein, 1983).

Given that each of these factors varies the train of activity elicited by each input, establishing a clearly-defined and systematic timing of interactions is not realistic. The concept of "interactive time-window" has therefore been proposed (Meredith et al., 1987). Accordingly, the optimal temporal register (OTR) defines the time at which multisensory interactions are maximal. Oddly, the OTR does not depend on matching the onset of each stimulus according to the latencies of their modality. The OTR would rather rely on *"how the activity patterns resulting from the two inputs overlap"* (Stein & Meredith, 1993, pp. 134). In other words, when the evoked discharge trains of the stimuli exceed the individual latency differences, their interaction is maximized (Meredith et al., 1987; Stein & Meredith, 1990). Adapted from an example provided by Meredith et al. (1987, pp. 3228), we could assume that when one visual and one nociceptive input are delivered at the same time, if the visual stimulus evokes a long discharge train (e.g. 500 ms) and the nociceptive stimulus elicits a short-duration discharge (e.g. 10 ms), the nociceptive stimulus could interact with the visual stimulus at any time within the 500 ms window. Since latencies do not define the wave of excitation/inhibition of the neurons' activity (see Figure 13). Interactions can thus either be produced when the respective stimuli are presented simultaneously or when a small time interval separates them, as long as the discharge trains evoked by each stimulus overlap (see Figure 14). Starting from the OTR, as measure as the interval between the onsets of each sensory stimulus increases, interactions decrease. However, the interactive period is larger than the OTR, meaning that interactions are still possible within the "interactive time-window". This period is flexible and not fixed for any multisensory cell. Hence, the longer the individual stimulus discharge train, the longer the interactive period will be (Meredith et al., 1987). To the best of our knowledge, the interactive time-window of visuo-nociceptive interactions has not been highlighted yet.

The one for visuo-tactile interactions is shorter than 250ms after stimulus onsets (Stein & Meredith, 1993).

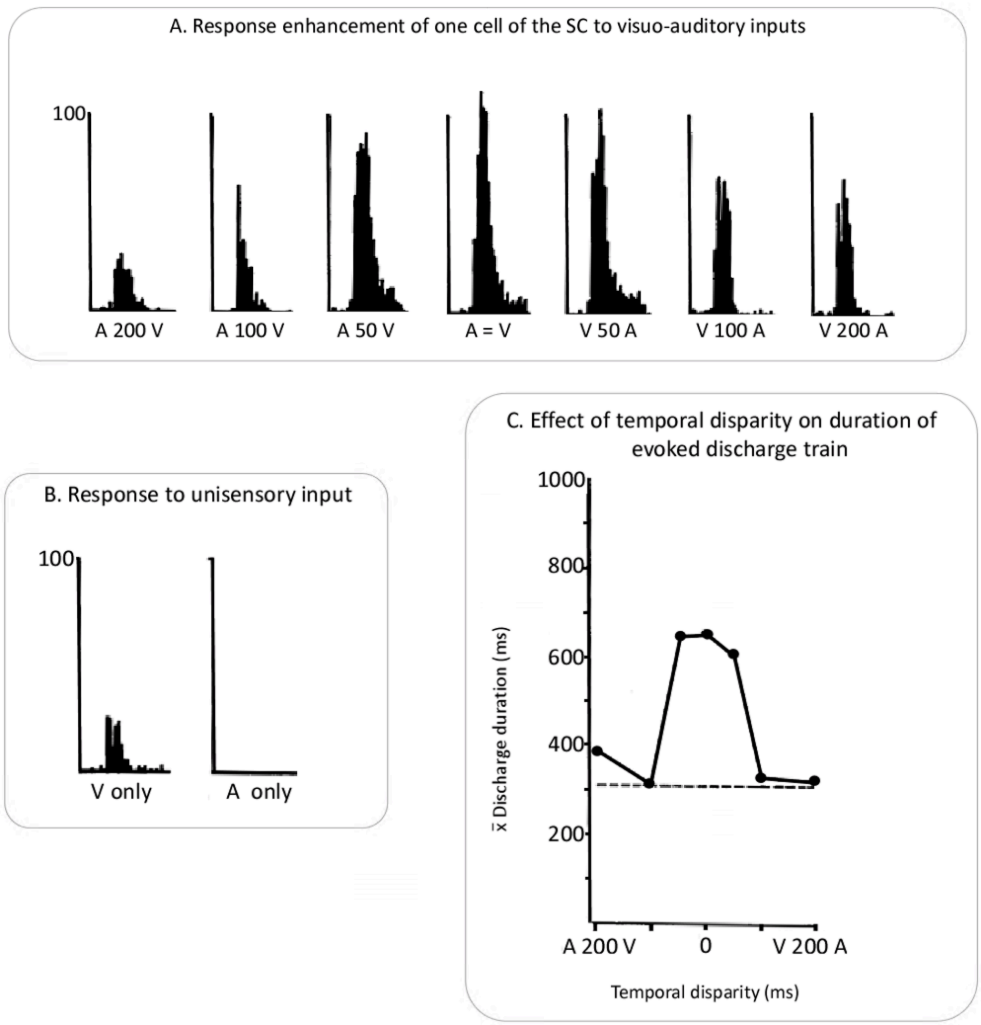

Figure 13. Example of response profiles of one cell of the SC of the cat. The graphs in (A) and in (C) figures show that decreasing temporal disparity between two different sensory inputs can increase the magnitude of response enhancement. Response enhancement is defined by changes in the number of impulses of the neuron, evoked by stimuli from different sensory modalities, as compared to its responses to any of the stimuli individually. In this example, the recordings were made from one single cell of the SC of the cat, that responded to a visual stimulus swept across the visual receptive field (RF). In (A), each graph illustrates the response enhancement of the cell when one visual and one auditory input were delivered at the same spatial location, according to the temporal disparity between each input. Within each histogram, each raster represents one neuronal impulse. The histograms are calibrated for 100 spikes/100 msec time bin (y-axis). The legend of the x-axis corresponds to the

first stimulus that was administered (A = auditory, V = visual) with the time interval in ms that separate it from the onset of the second stimulus. The interactive-time window is represented from -200 ms (auditory stimulus first) to +200 ms (visual stimulus first). The maximal enhancement or optimal temporal register (OTR) occurred when the two inputs were delivered at the same time (A=V). The levels of enhancement (that is, the magnitude of interaction) were progressively decreased at longer interstimulus intervals, until the limits of the interactive period were reached. However, nearly the same enhancement level was evoked when the auditory stimulus was presented 50 msec before the visual stimulus. Interestingly, a significant enhancement was still observed when the visual stimulus preceded the auditory stimulus by 200 ms. The maximal levels of enhancement are thus likely attributable to the long duration of the auditory influence on the cell. In (B), the left graph shows the response of the cell when a visual stimulus was delivered alone. The right graph illustrates that no response was evoked when an auditory stimulus was delivered alone. This represents the mechanisms of neurons of the SC that have a multisensory character only when exposed to a combination of stimuli. In (C), the graph represents the discharge duration of the cell evoked by the presentation of the visual and auditory inputs according to the time interval separating both stimuli. The discharge train of the cell appears to be quite long, about 600 ms from A50V to V50A. *Adapted from Meredith et al. (1987 pp. 3320).*

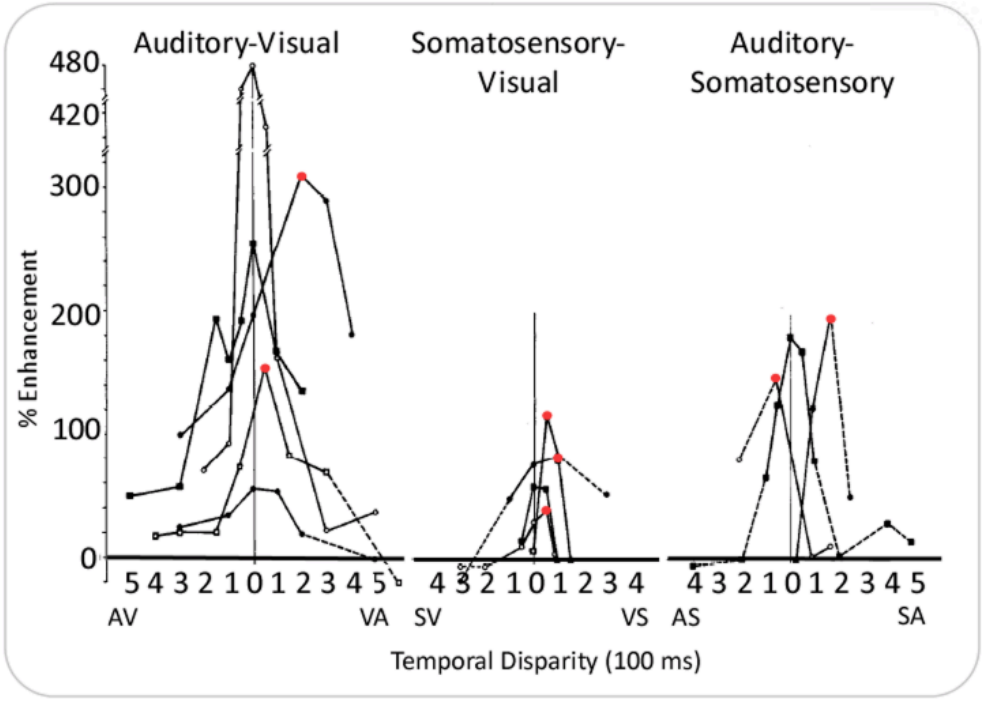

Figure 14. Percentage of enhancement of several cells of the SC according to the combination of different sensory inputs and to different temporal disparities. The figure illustrates the multisensory neuron responses of the cat' SC to the combination of visual and auditory inputs (AV – VA), of somatosensory and visual inputs (SV – VS) and of auditory-somatosensory inputs (AS – SA), spatially congruent, with different time intervals separating the onset of each stimulus. The temporal profiles for multisensory interactions are not different according to the modality combination. Each line on the graphs represents the recordings at different temporal disparities for one cell. The main interest of this figure is to show that, in this example, multisensory interactions were often of greatest magnitude when the onset of stimuli were temporally disparate (2 neurons out of 5 in AV-VA, 3/4 neurons in SV-VS, 2/3 neurons in AS-SA). The y-axis represents the response enhancement of the neurons (in %). The x-axis represents the temporal disparity between the stimuli (by 100ms). The optimal level of response enhancement could also occur when the onset of each stimulus was separated by 100 ms or more (illustrated by the red points). Dashed lines represent the moment at which multisensory interactions started to decrease because the temporal limit of the interactive period was approached. *Adapted from Meredith et al. (1987), pp.3321.*

Following the reasoning of Meredith and colleagues, the question that now arises is: *how can we know the duration of the discharge train of any cell from any stimulus, regardless of the sensory modality, in order to roughly predict the duration of the interactive time-window?* One indicator relates to the physical properties of the stimulus. For instance, for the same cell, when an auditory stimulus is paired with a rapid moving visual stimulus, the discharge train of the cell is shorter than when the same auditory stimulus is paired with a slower moving visual stimulus. The faster visual stimulus reduces the interactive period as compared to the slower visual stimulus (Meredith et al., 1987).

In brief, although each sensory channel processes information according to its own properties at the peripheral level, the cortex associates the different sources of information as belonging to a single event if they are presented close to each other in space in a defined time-window of interactions. Consequently, the same stimuli will be processed as dissociated events in some circumstances, in particular if too long intervals separate them. The duration of the interactive time-window is driven by the duration of the discharge train of the multisensory cell for each sensory stimulus, which is driven by multiple factors, such as the physical properties of the stimuli. In addition, some combinations of stimuli are more salient, producing an improvement in their neuronal responses, while others, less prominent, cause neuronal depression (Stein & Meredith, 1993). The temporal congruence between the different sensory events plays a key role in the salient character of these events. Once again, the importance of salience in the emergence of multisensory phenomena is reflected here. However, the physical properties of the stimuli and their salient character are factors among others. The duration of the interactive time-window is actually not predictable. If the time interval between the inputs is "too long", the likelihood of multisensory interactions would obviously drop, and the neurons' activity would be completely transformed. The sensory information transmitted through descending pathways toward motor effectors, governing overt behaviors, would thus be affected as well. Ultimately, spatial and temporal rules optimize but, in a sense, also limit the possibility of multisensory interactions. These restrictions avoid linking unrelated sensory stimuli together that may lead to inappropriate behaviors (Meredith et al., 1987).

The following sections review the behavioral studies about the temporal mechanisms involved in multisensory interactions in humans in order to understand the extent to which principles derived from electrophysiology in mammalian studies are applicable to multisensory interactions in humans.

2.3.2 The subjective time: temporal aspects during multisensory processes in human beings

Many experiments highlight temporal observations responsible for or produced by multisensory interactions. An example of the fact that temporal congruence is as much important as spatial congruence for observing multisensory integrative phenomena in humans, is the rubber-hand illusion (RHI). The RHI is characterized by the illusion of owning an alien limb, such as a rubber-hand, as if it was an integrated part of the body. This illusion appears when the rubber-hand is stroked with a brush while the real hidden hand receives a tactile stimulus, provided that the rubber-hand is spatially aligned with the real hand, in a realistic way, and that the stimulation of the rubber-hand is simultaneous to the administration of the tactile stimulus on the real hand. Participants therefore feel as if they were receiving the tactile stimulus on the rubber-hand (Botvinick & Cohen, 1998). Importantly, if the different sources of information are not spatially and temporally congruent, no multisensory integration should be observed.

We will therefore attempt to characterize the time-window of multisensory interactions based on human models. In a second time, we will illustrate the disparities that are expected to arise according to the sensory modalities. Finally, we will discuss the theoretical background that explains the paradox between the *brain time* and the *subjective time*, and report the factors that affect the perception of time. The final aim is to define as best as possible the conditions under which the effect of a visual stimulation on the detection of a nociceptive input can be observed.

Time-window of integration to observe multisensory interactions

Following Meredith and colleagues research at the single-neuron level regarding the "interactive time-window" of multisensory neurons, the question whether this interactive time-window is effective at the perceptual level emerged. Several psychophysical models establishing the relations between time and multisensory processes have been proposed since the past century, such as the "race" and "co-activation" models from Raab (1962) and Miller (1982, 1986). Based on these models, the *"Time-Window-of-Integration"* (TWIN) theory by Colonius and Diederich (2004) has been elaborated to understand why saccadic RTs to visual targets are faster when irrelevant stimuli from other modalities are presented in close temporal and spatial proximity. The theoretical grounding of this model will be developed to underline the factors that are crucial to be taken into account when studying the impact of time on multisensory interactions in humans.

The TWIN model affords that multisensory interactions occur only if the early peripheral individual processing of each sensory input terminates within a given time interval, the window of integration. This window of integration would act as a filter, determining if the sensory afferents are sufficiently temporally close to be integrated. The TWIN model is based on three predictions:

1. The perception of synchrony between the different sensory inputs influences the multisensory level of integration. A stimulus that is conveyed faster from the peripheral level to the cortex as compared to another stimulus should be delayed to maximize the probability that both stimuli fall into the time-window of integration.

2. Physical properties of one of the stimuli, such as intensity, affect the interaction with the other stimulus. A very strong stimulus intensity will have a peripheral processing that is speeded up as compared to a lower stimulus, which will decrease the likelihood that both sensory stimuli fall into the time-window of integration.

3. The spatial position of the different stimuli and their laterality (if they are represented in the same hemisphere or not, see Spence, Baddeley, Zampini, James, and Shore (2003) for details) alter the strength of multisensory interactions given that two stimuli are more likely to be temporally bound together if they are from the same spatial location (see also Spence, Shore, & Klein, 2001; Spence & Squire, 2003).

This model relies on principles that are basically similar to the properties of the multisensory neurons in the SC of the cat (Meredith et al., 1987), except for the first prediction. Because of the different conduction velocities of each sensory system conveying the information to the cortex, when two different stimuli are delivered at the same time, they are supposed to be perceived at different times. Colonius and Diederich (2004) and Fujisaki et al. (2012) therefore have suggested desynchronizing the onset of the different sensory stimuli according to their conduction velocity to maximize their probability to interact with each other. The next section will illustrate the major differences between the arrival times of different sensory stimuli when delivered concomitantly, by means of several psychophysical tasks.

Temporal disparities among senses

In order to highlight the differences between the temporal processing of sensory inputs belonging to different sensory systems, we will refer to results from "intermodal" TOJ tasks and simultaneity judgment tasks[3]. The parameter of interest from these studies is still the point of subjective simultaneity (PSS). However, this time, the pairs of stimuli on which participants were asked to make their judgment were composed by one stimulus from one modality and a second stimulus from a different modality. The PSS was therefore used to define the necessary asynchrony between the two different sensory inputs for them to be perceived at the same time.

Most of the studies that have been interested in the PSS of multisensory stimuli by using both TOJ and simultaneity judgment tasks, report that the visual stimulus needs to lead the auditory stimulus by several ms to reach simultaneity. The average amount of time varies according to the studies, extending from 75 ms to 20 ms (Spence et al., 2003; Stone et al., 2001; Zampini, Guest, Shore, & Spence, 2005; Zampini, Shore, & Spence, 2003; Zampini, Shore, & Spence, 2005). In addition, variability between the PSS values of participants is often reported, suggesting that the PSS would be observer-specific, but stable across time (Stone et al., 2001). For visuo-tactile modalities, the visual stimulus also needs to be presented before the tactile stimulus (from 60 ms to 10 ms) to be perceived at the same time (Spence et al., 2003; Spence et al., 2001; Vibell, Klinge, Zampini, Spence, & Nobre, 2007). For both visuo-auditory and visuo-tactile modalities, Spence et al. (2003) attribute this effect to the conduction velocity of each system, with vision being slower as compared to audition and touch.

Regarding visuo-nociceptive stimuli, given that the nociceptive system is particularly slow as compared to the visual system (nociceptive inputs elicit their first cortical response at about 150 ms when conveyed by Aδ fibers and at almost 1 s when transmitted by C fibers (Plaghki & Mouraux, 2005), while visual inputs reach their first cortical relay in less than 100ms (Michel, Seeck, & Murray, 2004)), we can expect that, this time, the nociceptive stimulus would need to be presented before the visual stimulus to be perceived at the same time, and that the amount of time between the two stimuli would be larger with stimuli activating only C fibers as compared to stimuli eliciting Aδ-fiber responses. For instance, Zampini et al. (2007) have shown, during a TOJ task, that a nociceptive stimulus activating Aδ fibers needed to be presented ~40 ms before the visual stimulus to be perceived as simultaneous. However, authors did not assess the PSS between visual stimuli and thermo-nociceptive stimuli selectively activating C-fiber afferents.

[3] The difference between both tasks is that, during simultaneity judgment tasks, participants are asked to respond if the stimuli of the pair are simultaneous or not, whereas during TOJ tasks they are asked to report which stimulus of the pair they perceived as occurring first.

These results raise the following questions: *To what extent does the brain automatically resynchronize the temporal arrival of two inputs? To what extent should the respective onset of each input be artificially desynchronized to favor their interactions under laboratory conditions? How large is the time-window of integration?* The next section will identify several avenues using visuo-auditory examples.

Mechanisms of compensation by the human brain

Under normal circumstances, individuals do not perceive any time lag between the sound of a voice and the movement of the lips when they see someone speak. The brain is thus somehow able to compensate for differences in the neural processing of each sensory system.

First, rather than having a large temporal window for multisensory interactions – as suggested by Meredith et al. (1987) – this window would be moveable according to the distance of the audiovisual event from the body (see Figure 15). The time-window of integration would adapt to the fact that auditory stimuli gradually lag behind visual stimuli as the audiovisual event moves away from the individual (Spence & Squire, 2003; Sugita & Suzuki, 2003). During a 'two-alternative forced-choice' task, participants had to judge whether the light (an array of five green light electrodes that switched on from 1 to 50 m of distance from the subject) was presented before or after the sound (burst white noise). When the visible sound source was 1 m away from the participant, the PSS between the visual and the auditory stimuli was ~5 ms. From 1 to 10 m of distance of the visible sound source from the participant, the PSS increased by ~3 ms each meter. That increment was consistent with the velocity of sound. Because the increase of the PSS was attributed only to the distance of the audiovisual source from the participant, and not to the difference in conduction velocities between the auditory and visual systems, Sugita and Suzuki (2003) suggested that the brain would ensure the perception of simultaneity despite having to deal with asynchronous inputs. This compensation was no longer observed when the distance of the visible sound source exceeded 10 m from the participant.

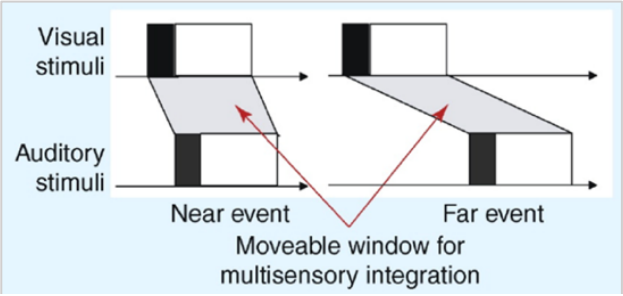

Figure 15. Moveable window of integration. The figure explains the perception of simultaneity of visuo-auditory inputs according to the model of Sugita & Suzuki (2003). The window of integration would be able to create an illusion of synchronicity between the different sensory inputs by taking into account the conduction velocity of each system, when the inputs are not further than 10 m away from the observer. *Adapted from Spence & Squire (2003), pp.519.*

A second explanation is that the perception of simultaneity between visuo-auditory inputs would be sensitive to experience. Before performing a simultaneity judgment task between one visual and one auditory stimulus, participants were exposed during 3 min to the stimuli, that were separated by different time intervals (-235 ms, 0 ms, +235 ms; negative value indicates that the sound was delivered before). The PSS resulting from the simultaneity judgment task (performed afterwards) indicated that participants' judgment was shifted toward the asynchrony they had been previously exposed to (-32 ms, -10 ms and +27 ms respectively), as if the brain reduced the constant lag between the stimuli. The brain would thus continuously recalibrate subjective simultaneity according to real audiovisual events (Fujisaki, Shimojo, Kashino, & Nishida, 2004).

Finally, perception of simultaneity during visuo-auditory events could be explained by the temporal ventriloquism effect (Morein-Zamir et al., 2003). There are two types of ventriloquisms. First, the well-known *spatial* ventriloquism refers to the illusion raised by the ventriloquist that, by coordinating the lip movements of a puppet with oral speech, the puppet is actually talking. The perceived location of the sound is thus *spatially bound toward the location* of the visual stimulus (Lewald & Guski, 2003; Slutsky & Recanzone, 2001). Second, the *temporal* ventriloquism is characterized by the opposite relationship between the two sensory inputs: the perceived time of arrival of the visual stimulus is *temporally bound to the onset* of the auditory stimulus (Morein-Zamir et al., 2003; Spence & Squire, 2003). In a visual TOJ task, the presence of two irrelevant sounds was indeed able to shift the temporal order judgment of two visual stimuli. The visual stimuli of the pair were separated by different SOAs from -180 ms to +180 ms, and located 10 cm above or below a fixation LED (the negative symbol indicates that the lower light appeared first). Two intervening sounds separated by 16 ms, presented at approximately the same location than the lights, between the onset of the first light and the onset of the second light, led to lower performance to judge which light was presented first. The presence of the two sounds would have thus pulled the lights closer in time (see Figure 16), leading to a less clear discrimination between their respective time of arrival. The brain would then be able to ventriloquize the visual stimuli into the temporal alignment of subsequent auditory stimuli (Morein-Zamir et al., 2003).

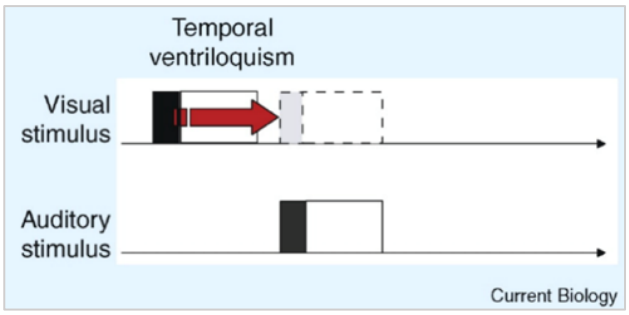

Figure 16. Temporal ventriloquism model correcting for asynchronous inputs to explain multisensory synchrony perception. This figure illustrates the power of auditory stimuli that, under certain conditions, are able to ventriloquize visual stimuli into their temporal alignment. Adapted from *Spence & Squire (2003), pp.519.*

The above-mentioned theories attempt to understand how, and under which conditions, the brain is able to compensate for the different conduction latencies of each sensory input during visuo-auditory events, insofar as individuals do not perceive the lag between the temporal arrivals of each input. One visual and one auditory input can therefore interact with each other even if they do not reach the cortex at the same time. This demonstrates the existence of a window of interaction. Besides, we need to keep in mind that the resynchronization by the human brain of the different conduction velocities could also be explained by neuronal mechanisms similar to the overlapping discharge trains elicited by several sensory inputs in the multisensory neurons of the SC (Meredith et al., 1987). However, to the best of our knowledge, no study has yet investigated these mechanisms in sensory systems with conduction discrepancies as huge as the ones between visual and nociceptive systems. Since our main interest is to establish the optimal experimental conditions for the interaction of a visual and a nociceptive stimulus in order to observe the effect of the spatial position of the visual stimulus on the perception of the nociceptive stimulus, new questions arise.

When we burn ourselves, is the nociceptive information (e.g. the burning sensation) truly synchronized with the visual information (e.g. the object that evoked the burning sensation)?

Is the brain as capable of resynchronizing the difference between the respective arrival times of a visual and a nociceptive input, as it is for a visual and an auditory input?

The perception of simultaneity in order to maximize multisensory interactions could be even more relevant for visual and nociceptive stimuli. These issues have been largely ignored until now and deserve more attention. However, before investigating the temporal aspects of visuo-nociceptive interactions in the experimental part of this thesis, the following section will address the external factors that have been studied in multisensory experiments and that can influence the time-window of integration and the perception of simultaneity.

Space and attention affect the time-window of integration and perception of simultaneity

As already proposed in the context of the "the interactive time-window" of the multisensory neurons (Meredith et al., 1987) and by the predictions of the TWIN model (Colonius & Diederich, 2004), the time-window of integration of multisensory inputs is sensitive to the spatial alignment of the stimuli. Space also influences the perception of simultaneity between different sensory inputs. During TOJ and simultaneity judgment tasks, the temporal asynchrony at which both stimuli are perceived as occurring simultaneously is shorter when they originate from the same location than from opposite sides of space with respect to the body midline (e.g. Spence et al., 2003; Spence et al., 2001; Zampini, Guest, et al., 2005). For instance, in an experiment conducted by Zampini, Guest, et al. (2005), visual stimuli had to be presented ~32 ms before auditory stimuli when their spatial location was different to achieve perception of simultaneity, whereas they had to be presented ~19.4 ms before auditory stimuli when their spatial location was the same. The spatial relationship between the different inputs also affects the performance to judge which stimulus came first, with lower performance reported when the stimuli are spatially congruent. A lower performance is characterized by a higher Just Noticeable Difference (JND), defined as the minimal amount of time that participants need between two different sensory inputs to accurately judge their temporal order in 75% of the trials (Hirsh & Sherrick, 1961). The JND is derived from the slope of the psychometric function. This latter effect would be related to the fact that interactions are greater when the stimuli are spatially close together. These increased interactions would lead to greater difficulty in dissociating the stimuli from each other and thus to less discrimination in judging which came first. The accuracy of participants' responses would therefore be decreased (Chen & Spence, 2017; Spence et al., 2003; Spence et al., 2001; Zampini et al., 2003).

Attention is another important factor that influences the time-window of integration (Colonius & Diederich, 2004; Diederich & Colonius, 2004) and the related multisensory interactions. According to the TWIN model, if the task does not orient attention toward one of the different stimuli, the first detected stimulus 'opens' the time-window of integration. If attention is oriented toward one of the stimuli, the other stimulus needs to be fast enough (or presented before) to terminate into the time-window of integration. Furthermore, orienting attention toward one specific sensory modality facilitates the processing of the sensory inputs related to that modality as compared to unexpected sensory stimuli (Titchener, 1908). Attention therefore also influences the PSS between two inputs from different sensory modalities (Spence & Parise, 2010). First demonstrated during a visuo-tactile TOJ task, when attention was oriented toward touch, the visual stimuli had to be presented ~155 ms before the tactile stimuli to be perceived at the same time, as compared to ~22 ms when attention was oriented toward vision and to ~53 ms under divided-attention condition (Spence et al., 2001). The effect has been replicated in visuo-auditory modalities using a simultaneity

judgment task. The PSS was significantly smaller between the visual and auditory inputs when attention was directed toward vision as compared to when attention was focused on audition. In other words, visual stimuli had to be delivered further in advance before auditory stimuli to reach simultaneity when participants attended to audition relative to vision (Zampini, Shore, et al., 2005). Last but not least, this effect of *'prior entry'* has also been demonstrated on visuo-nociceptive temporal order judgments. Participants had to judge which of the visual (red LED that switched on for 50 ms) or the nociceptive stimulus (delivered using a CO_2 laser during 50 ms), both applied on the forearm of the participant, had been presented first or, if they appeared at the same time. Stimuli were separated by several SOAs (±200, ±160, ±120, ±80, ±40, and 0 ms; negative SOAs indicate that the visual stimulus was presented first). There were three different experimental conditions: divided attention, attending to nociception, attending to vision. Attention was oriented toward one modality by explicitly asking participants to orient their attention toward that modality at the beginning of the block of trials. Knowing that under divided attention condition, the nociceptive stimulus had to be presented ~40 ms before the visual stimulus to be perceived at the same time, the results of the selective attention conditions report that the PSS between the visual and nociceptive stimuli was shorter when attention was directed to pain (~22 ms) than toward vision (~51 ms) (Zampini et al., 2007). Selective attention therefore clearly affects the temporal perception of sensory stimuli, at least for touch, vision, audition and nociception. Specifically in the context of pain, attention would facilitate the processing of its sensory-discriminative dimension, that is, the identification of the intensity, location, quality, and duration of the input (Spence, Bentley, Phillips, McGlone, & Jones, 2002).

In conclusion, to study the impact of the spatial position of a visual stimulus on the detection of a nociceptive stimulus, we need to consider the temporal congruence of the different stimuli, and the fact that the temporal processing of the sensory stimuli is itself affected by attentional orientation and spatial congruence.

2.3.3 Conclusion of the multisensory time

Experiments in mammals and humans agree on the fact that optimal multisensory interactions occur when the asynchrony between the different sensory inputs is reduced as compared to larger time intervals. Such asynchrony between different sensory inputs (as indexed for instance by the PSS during intermodal TOJ tasks) is actually inherent to any multisensory phenomenon, because of the different conduction velocities of each system conveying the sensory information to the cortex. In some cases, even if the perception of simultaneity is not guaranteed, interactions can still occur, as illustrated by the concepts of "interactive time-window" in multisensory neurons of the cat's SC (Meredith et al., 1987) and the possible compensations by the human brain of the mismatch between visual and auditory inputs occurring within the time-window of integration (Fujisaki et al., 2004; Morein-Zamir et al., 2003; Spence & Squire, 2003; Sugita & Suzuki, 2003). Furthermore, perception of simultaneity and the time-window of integration are influenced by attentional and spatial factors. This has been mainly addressed by studies in visuo-tactile or visuo-auditory modalities, while not much is known about the effect of space on the perception of simultaneity of visuo-nociceptive inputs. What is also not known is the extent of the time-window of integration for visuo-nociceptive modalities and thus, if the brain is also able to compensate for the time differences between visual and nociceptive conduction velocities. Given that the nociceptive system is extremely slow as compared to the visual system, it might be relevant to desynchronize the onset of each input to maximize their perception of simultaneity and, their interactions, as suggested by the TWIN model of Colonius and Diederich (2004) and by Fujisaki et al. (2012). This argument is even more relevant under laboratory conditions, since the nature of the stimuli used when studying multisensory interactions are different from the potential threats that individuals can face in everyday life. It is indeed clearly established that multisensory interactions are affected by past experiences and by the level of association between the different inputs (Chen & Spence, 2017; Welch, 1999). Therefore, even if the brain was more or less able to automatically resynchronize visuo-nociceptive inputs, laboratory conditions for studying their interactions might diminish this ability.

These considerations will govern our investigation on the impact of the spatial position of a visual stimulus on the detection of a nociceptive stimulus, eliciting C-fiber responses and Aδ-fiber responses, by taking into account their temporal relationships. Until now, these temporal factors have rarely been considered, although they probably lead to optimized visuo-nociceptive interactions. Moreover, since C fibers are particularly slow and cause diffuse sensations, their interactions with other sensory modalities might not follow the general rules of multisensory interactions established so far.

3 AIMS AND HYPOTHESES

Following the TOJ studies on the interactions between nociception and vision, in particular those testing the impact of nociception on vision (Filbrich et al., 2017a,b; Filbrich et al., 2018), Chapter 1 "Investigations of Spatial Aspects" will address whether perception of the proximity of the hand on which the nociceptive stimulus is applied, relative to the visual stimulus, is based on visual or proprioceptive feedback about the hand position. Previous studies have shown that visuo-nociceptive stimuli interact the most when the visual stimulus is spatially close to the limb on which the nociceptive stimulus is applied, in the PPS of the stimulated limb (De Paepe et al., 2014; De Paepe, Crombez, & Legrain, 2015; De Paepe et al., 2017; Filbrich et al., 2017b; Filbrich et al., 2018; Vanderclausen et al., 2017). However, these interactions could either be due to the *proprioceptive* information of the stimulated hand, that is, the fact to feel the stimulated hand close to the visual stimulus, or to the *visual* information about the stimulated hand, that is, the fact to see the stimulated hand close to the visual stimulus. Therefore, by manipulating the visual information about the location of the hand during a visual TOJ task with nociceptive cues, **Study 1** intends to clarify whether it is vision, proprioception, or a combination of both, that regulate visuo-nociceptive interactions in the PPS. If the spatial biases induced by the nociceptive cues on the judgment of appearance of the visual stimuli strongly depend on the visually perceived proximity between the two stimuli, no visuo-nociceptive interaction should be observed in the condition in which the view of the participants' hands is prevented by a wooden board. On the contrary, if visuo-nociceptive interactions are not mainly driven by visual feedback about the position of the hand, the spatial bias induced by the nociceptive cues on the temporal order judgments of the visual stimuli should not be different between the condition in which the hands are seen and the condition in which the hands are hidden. We also compared these conditions to a third condition in which a translucent glass covered the stimulated hands, with the purpose of controlling for a potential confounding factor in the condition in which the hands were hidden by the wooden board. Indeed, the presence of a barrier separating the stimulated hands from the visual stimuli, rather than the fact of not seeing the stimulated hand, could have explained the potential difference between the condition in which vision of the limb was available from the condition in which vision of the limbs was prevented.

Chapter 2 "Investigations of Temporal Aspects" will focus on a temporal aspect of visuo-nociceptive interactions that has been poorly investigated so far. The perception of simultaneity between the different sensory inputs can be an important factor to optimize their interactions. Considering the important differences in distance and in conduction velocities between the visual and nociceptive systems to convey the sensory information from their respective receptors to their primary cortical targets, the perception of simultaneity between a visual and a nociceptive input is compromised if

they are delivered at the same time. This has been firstly investigated by a study of Zampini et al. (2007) using an intermodal TOJ task in which a nociceptive stimulus needed to be delivered ~40 ms before a visual stimulus presented at the same location, to be perceived as simultaneous. As laser-induced thermal stimuli with strong intensity of stimulation were used, resulting in moderate painful sensations, the induced perceptions were mainly mediated by Aδ fibers. The PSS between a visual stimulus and a thermo-nociceptive stimulus selectively activating C-fiber afferents has thus never been investigated. By using an intermodal TOJ task between thermo-nociceptive and visual stimuli using a procedure to dissociate in the same participants, responses mediated by Aδ fibers and responses specifically mediated by C fibers, **Study 2** investigated which time interval needs to be implemented between both inputs to optimize their perception of simultaneity. For both fiber types, we expected that the thermo-nociceptive stimulus would need to be delivered before the visual stimulus to achieve perception of simultaneity. Considering that the unmyelinated thermo-nociceptive C fibers are ultra-slow in transmitting sensory information, the asynchrony between the C-fiber and the visual stimulations to be perceived at the same time would be greater than the asynchrony observed in the Aδ-fiber condition.

Chapter 3 "Investigations of Spatio-temporal Aspects" is composed of two studies that will combine spatial and temporal determinants of visuo-nociceptive interactions. Since spatial and temporal factors are intimately related during multisensory interactions, it is essential to pursue our research by examining the impact of space on the perception of time. Previous studies involving visuo-auditory and visuo-tactile modalities have investigated the effect of spatial congruence using TOJ/simultaneity judgment tasks (Spence et al., 2001; Zampini, Guest, et al., 2005; Zampini et al., 2003; Zampini, Shore, et al., 2005). When the two sensory inputs were spatially close, the asynchrony to achieve perception of simultaneity was smaller than when the two inputs were spatially incongruent. The performance in judging which stimulus was perceived as occurring first was also affected. However, the impact of spatial congruence on the perception of simultaneity between a visual and a thermo-nociceptive stimulus selectively eliciting Aδ or C fiber responses has never been explored so far. Hence, **Study 3** was based on the same intermodal TOJ task as in Study 2, but we manipulated the spatial position of the visual stimulus relative to the hand on which a laser stimulus was applied. We hypothesized that, for both types of nociceptive fibers, when the visual input appeared on the opposite side of the thermo-nociceptive stimulus, the asynchrony between the two inputs for them to be perceived simultaneously would be greater than when both stimuli originated from the same spatial location.

Whereas previous studies were interested in the impact of visuo-nociceptive interactions on our ability to *localize* nociceptive or visual information (De Paepe et al., 2014; De Paepe et al., 2015; De Paepe et al., 2017; Filbrich et al., 2017b; Filbrich et al., 2018; Vanderclausen et al., 2017), in **Study 4,** we were actually interested in the influence of visuo-nociceptive interactions on our ability to *detect* the nociceptive

stimulations. Filbrich et al. (2019) had previously investigated the influence of a visual stimulus on the detection of nociceptive stimuli using an intensity of stimulation near the activation threshold of Aδ fibers. As compared to a condition during which nociceptive stimuli were applied alone, the number of detections of the nociceptive stimuli was greater when visual stimuli were located next to the stimulated hand, whereas participants more often failed to report nociceptive stimuli when visual stimuli were located near the opposite hand. The visual stimuli were delivered 50 ms after the nociceptive stimuli to take into account the different conduction velocities of each sensory system and to maximize their perception of simultaneity. To estimate this lag, authors subtracted the latency of the first evoked potential of a nociceptive input activating Aδ-fiber afferents, as measured by previous studies (Mouraux & Plaghki, 2007), by the latency of the first evoked potential of a visual input (Michel et al., 2004). In Study 4, we went one step further. We considered the spatial and temporal conditions optimizing visuo-nociceptive interactions to measure the impact of the spatial position of a visual stimulus on the respective activation thresholds of C and Aδ fibers, that is, on the minimal thermal stimulation intensity applied on the hand dorsum that was necessary for the brain to detect the respective nociceptive inputs. Accordingly, we conducted threshold assessment experiments, separately for each fiber type, by using an innovative psychophysical method, the *psi marginal* method (Prins, 2013), that adapted the temperature of each stimulus to the previous responses of the participant, according to two different criteria. The absolute detection was used as a criterion to assess the threshold of C fibers, and the reaction times were used as a criterion to assess the threshold of Aδ fibers. During threshold assessment, visual stimuli were presented according to different conditions:

In the **1st** experiment, the visual stimulus was either administered on the ipsilateral side of the thermo-nociceptive stimulus or on the contralateral side of the thermo-nociceptive stimulus. In the control condition, only thermo-nociceptive stimuli were applied, without any visual stimulus. In the **2nd** experiment, we used the same ipsilateral and contralateral conditions. The control condition consisted this time of administering thermo-nociceptive stimuli accompanied by visual stimuli in front of the participant in farther space. However, as perception of simultaneity between different inputs can be an important factor for multisensory interactions, in a preliminary experiment, we individually measured the necessary asynchrony between a visual and a nociceptive stimulus, conveyed through C or Aδ fibers, for them to be perceived at the same time, using the intermodal TOJ task developed in Chapter 2. The resulting individual PSS values were used to create a lag between the respective presentation of the laser stimulus and the visual stimulus, with the aim of maximizing their perception of simultaneity. As compared to the control conditions, we hypothesized that the spatial congruence between the thermo-nociceptive and visual stimuli (ipsilateral condition) would decrease the respective detection threshold of inputs conveyed by Aδ and C fibers, whereas the position of the visual stimulus close to the opposite, non-stimulated hand (contralateral condition), would increase these detection thresholds.

CHAPTER 1: INVESTIGATIONS OF SPATIAL ASPECTS

Study 1: Seeing or not seeing where your hands are. The influence of visual feedback about hand position on the interaction between nociceptive and visual stimuli[4]

Abstract

Examining the mechanisms underlying crossmodal interaction between nociceptive and visual stimuli is crucial to understand how humans handle potential bodily threats in their environment. It has recently been shown that nociceptive stimuli can affect the perception of visual stimuli, provided that they occur close together in external space. The present study addresses the question whether these crossmodal interactions between nociceptive and visual stimuli are mediated by the *visually* perceived proximity between the visual stimuli and the limb on which nociceptive stimuli are applied, by manipulating the presence vs. absence of visual feedback about the position of the stimulated limb. Participants performed temporal order judgments on pairs of visual stimuli, shortly preceded by nociceptive stimuli, either applied on one hand or both hands simultaneously. The hands were placed near the visual stimuli and could either be seen directly, seen through a glass barrier, or hidden from sight with a wooden board. Unilateral nociceptive stimuli induced spatial biases to the advantage of visual stimuli presented near the stimulated hand, which were greater in the conditions in which the hands were seen than in the condition in which vision was prevented. Spatial biases were not modulated by the presence of the glass barrier, minimizing the possibility that the differential effect between the vision and no-vision conditions is solely due to the presence of the barrier between the hands and the visual stimuli. These findings highlight the importance of visual feedback for determining spatial mapping between nociceptive and visual stimuli for crossmodal interaction.

[4] This study is published as:
Manfron, L., Legrain, V., & Filbrich, L. (2020). Seeing or not seeing where your hands are. The influence of visual feedback about hand position on the interaction between nociceptive and visual stimuli. Multisensory research, 33(4-5), 457-478.

1. Introduction

Perceiving and interacting with the environment around us requires an optimally integrated spatial representation of the body and its surrounding space. In cognitive neuroscience, such a representation of space is conceptualized by the notion of peripersonal frame of reference, a reference frame coordinating the processing and integration of somatic and non-somatic stimuli occurring near the body (see Serino, 2019 for a review). The existence of such peripersonal representations has been studied extensively these recent years, mainly focusing on the mechanisms underlying interactions between visual and tactile stimuli. A peripersonal reference frame for spatial processing of sensory events supposes indeed that perceiving or reacting to a somatic stimulus can potentially be affected by a non-somatic stimulus, and vice-versa. In non-human primates, multiple studies indicate that such visuo-tactile interactions rely on the existence of multimodal neurons, i.e. neurons able to respond to stimuli of different sensory modalities, such as visual and tactile stimuli, mostly in the ventral parts of the premotor cortex (vPM) and the intraparietal sulcus (VIP). More specifically, these neurons associate somatosensory and visual receptive fields with the particularity that the visual receptive field is spatially anchored to the somatosensory receptive field, i.e. spatially limited to the part of space immediately adjacent to the body (Duhamel, Colby, & Goldberg, 1998; Fogassi et al., 1992; Gentilucci et al., 1983; Graziano et al., 1997; Graziano et al., 1994; Rizzolatti, Scandolara, Matelli, & Gentilucci, 1981; Rizzolatti et al., 1981). In humans, the peripersonal frame of reference has been demonstrated by studying brain-damaged patients suffering from crossmodal extinction. These patients have difficulties in perceiving a tactile stimulus applied on the hand contralateral to the damaged cortical hemisphere when it is concomitantly presented with a visual stimulus on the ipsilesional side of space. Importantly, this effect of the visual stimulus on tactile perception is strongest when the visual stimulus is presented in the direct vicinity of the ipsilesional hand and much weaker when it is presented farther away (i.e. in extrapersonal space) or close to a non-homologous ipsilesional body part (e.g. Di Pellegrino et al., 1997; Farnè et al., 2005b; Làdavas, di Pellegrino, Farnè, & Zeloni, 1998). Studies in healthy humans corroborate these findings, showing that perceiving and reacting to a stimulus of one sensory modality, i.e. either tactile or visual, is influenced by the occurrence of a stimulus of the other modality, and that such crossmodal interactions between touch and vision are modulated by the proximity between the two sensory inputs (Holmes & Spence, 2004; Serino, 2019). Furthermore, several neuroimaging and electrophysiological studies have been able to highlight possible neural correlates of such crossmodal interactions in humans, suggesting the importance of premotor and posterior parietal areas for peripersonal space perception, as already shown in non-human primates (e.g. Bremmer

et al., 2001; Gentile et al., 2011; Kennett, Eimer, Spence, & Driver, 2001; Macaluso et al., 2002; Sereno & Huang, 2006).

Whereas the existence and characteristics of the peripersonal reference frame have been extensively studied in the context of the interaction between tactile and proximal visual stimuli, such investigations have only recently been instigated in the context of nociception and pain (Legrain & Torta, 2015). Indeed, it has been hypothesized that the function of such peripersonal representations, besides optimizing the manipulation of innocuous objects, would also be to shape defensive actions against physically threatening and potentially noxious stimuli (Graziano & Cooke, 2006). Next to its interoceptive function of warning the brain about possible body damage by nociceptive stimuli, nociception also has an exteroceptive function of providing information on external stimuli that could have the potential to damage the body (Haggard et al., 2013). A prompt and efficient reaction to nociceptive stimuli therefore requires an optimally integrated multisensory, i.e. peripersonal, representation of the body and its surrounding space, allowing crossmodal interactions with external stimuli, such as visual ones. Studying interactions between the nociception and vision as well as the conditions under which they occur is also clinically relevant, since it has been shown that some specific chronic pain conditions can affect the patients' abilities to represent and perceive the visual space surrounding their body (Bultitude, Walker, & Spence, 2017; Filbrich, Alamia, Verfaille, Berquin, Barbier, Libouton et al., 2017). In addition, targeting these cognitive difficulties has been suggested as a potentially useful method to treat chronic pain (Torta, Legrain, Rossetti, & Mouraux, 2016). Clarifying the role of a peripersonal frame of reference in localizing nociceptive stimuli is thus not only important to apprehend how nociception is integrated with other sensory information to build a full representation of physical threats, but also to deepen the understanding of the pathophysiology of chronic pain disorders.

The involvement of the peripersonal frame of reference in processing sensory inputs that specifically activate skin nociceptors has recently been evidenced in humans. Using temporal order judgment (TOJ) tasks, during which participants discriminate the temporal order of two lateralized stimuli presented in rapid temporal succession, several studies indeed demonstrated that nociceptive stimuli can interact closely with proximal visual stimuli (De Paepe et al., 2015, 2017; De Paepe et al., 2014; Filbrich, Alamia, Burns, et al., 2017; Filbrich et al., 2017b; Filbrich et al., 2018; Vanderclausen et al., 2017). Filbrich et al. (2017b), for example, showed that visual TOJs are systematically biased by the presence of a nociceptive stimulus shortly preceding the visual target stimuli. More precisely, the non-informative nociceptive stimulus applied on a hand attracted attention to its location (i.e. induced a spatial bias) in order to facilitate the processing of the visual stimuli occurring on the same side of space as the limb to which the nociceptive stimulus was applied. Importantly, such an interaction between nociceptive and visual stimuli was mainly dependent on the proximity of the visual stimuli to the hand on which nociceptive stimuli were applied,

irrespective of the relative position of both the stimulated limb and of the visual stimulus with regard to the body considered as a whole, as well as of the direction of gaze (Filbrich, Alamia, Verfaille, et al., 2017; Filbrich et al., 2018; Vanderclausen et al., 2017). While these latter studies demonstrated that nociceptive stimuli can affect the perception and processing of visual stimuli, the reverse has also been observed. De Paepe et al. (2014) showed that nociceptive TOJs can be affected by the presence of a shortly preceding lateralized visual stimulus, provided that the nociceptive and the visual stimuli are presented close together (De Paepe et al., 2015; De Paepe et al., 2017). Additionally, proximal visual stimuli have been shown to facilitate motor responses to nociceptive stimuli (De Paepe et al., 2016), as well as to influence their detection (Filbrich et al., 2019).

The results of these latter studies suggest that nociceptive stimuli can be processed, similarly to touch, according to a peripersonal reference frame, allowing them to interact with visual stimuli when both the nociceptive and the visual stimuli occur close to each other in external space. What is currently not clear, however, is to what extent these crossmodal interactions between nociceptive and visual stimuli are mediated by the visually perceived proximity between the non-somatic stimuli and the limb on which the somatic stimuli are applied. In the context of visuo-tactile interactions, it has for example been shown that the responsiveness of the monkey's vPM multimodal neurons to visual stimuli presented near the stimulated body part can be reduced when the body part is hidden from view (Graziano, 1999). This indicates that seeing the stimulated body part seems to play a crucial role in determining the spatial proximity between touch and vision in peripersonal space. Similar observations have been made in humans, where the accuracy in determining the position of an immobile hand decreases in the absence of visual information about the hand (see discussion in Holmes, 2013), which could in turn lead to difficulties in perceiving the proximity between the somatic and the visual stimulus in the absence of vision. However, empirical studies in humans are not consistent in their conclusions regarding the role of visual feedback in visuo-tactile interactions, possibly related to the differences in the studied populations and experimental paradigms. Whereas some of these studies conclude that visual information plays a predominant role in such interactions, others show that strong crossmodal effects between touch and vision are still possible when vision is prevented (see Kennett et al., 2002; Làdavas et al., 2000; Macaluso et al., 2002; Mattingley et al., 1997; Pavani et al., 2000).

In the present study, we investigated the role of visual feedback about hand position on the above-mentioned crossmodal influence of nociceptive stimuli on the perception of visual space (Filbrich, Alamia, Burns, et al., 2017; Filbrich et al., 2017b; Filbrich et al., 2018; Vanderclausen et al., 2017). This crossmodal influence between nociceptive and visual stimuli could indeed rely on the seen position of the stimulated hand, and thus on its *visually* perceived proximity to the visual stimuli in external space (i.e. visual information about the hand), but also on other feedback, such as proprioceptive

information, for example. More precisely, we tested the effects of lateralized nociceptive cues on visual TOJ while vision of the hands on which nociceptive stimuli were applied was prevented by a wooden board or not. If the crossmodal effects between nociception and vision strongly depend on the *visually* perceived proximity between the two stimuli, the nociceptive cues should not induce any, or at least significantly smaller, spatial biases in the perception of visual target stimuli in the condition in which the view of the participants' hands is prevented, as compared to the condition in which the hands are seen. On the contrary, if visuo-nociceptive interactions are not mainly driven by visual feedback, the nociceptive cues should have similar effects on visual perception whether the hands are seen or not. Furthermore, to exclude the possibility that any potential differential effect between the *vision* vs. *no-vision* conditions could be due to the mere presence of the wooden board between the hands and the visual stimuli in the *no-vision* condition, rather than to the fact that the position of the hands can be seen or not, we also included a condition in which the hands could be seen through a glass placed between the hands and the visual stimuli. Indeed, one could hypothesize that crossmodal visuo-nociceptive interactions could merely be influenced by whether or not the visual stimuli are physically reachable (see Farnè, Demattè, & Làdavas, 2003; Kitagawa & Spence, 2005; Marquardt et al., 2015 for a related discussion in the context of touch). If this was the case, spatial biases in visual perception induced by the nociceptive stimuli should be different in the condition in which a glass is placed between the hands and the visual stimuli as compared to a condition in which the hands are seen directly.

2. Materials and methods

2.1. Participants

Twenty-five volunteers participated in the study. The data of two participants were excluded from the analyses due to inconsistent performance during the task (see Sect. 2.5. Data Analyses). The mean age of the remaining 23 participants (15 women) was 23.68 years (SD= ± 3.19 years, range 21-35 years). Exclusion criteria were non-corrected vision difficulties, any neurological, cardiac, psychiatric or chronic pain disorder, trauma of the upper limbs within the lasts six months preceding the experiment, regular use of psychotropic drugs and intake of analgesic drugs (e.g. NSAIDs and paracetamol) within the 12 hours preceding the experiment. According to the Flinders Handedness survey (Flanders) (Nicholls, Thomas, Loetscher, & Grimshaw, 2013), 22 participants were right-handed and one was left-handed. The local ethics committee (Commission d'Ethique Biomédicale Hospitalo-Facultaire, Saint-Luc

university hospital and Université catholique de Louvain) approved the experimental procedure, in agreement with the Declaration of Helsinki. All volunteers signed a consent form prior to the experiment and received financial compensation for their participation.

2.2. Stimuli and apparatus

Nociceptive stimuli were delivered by means of intraepidermal electrical stimulation (IES) using two stainless steel concentric bipolar electrodes (Nihon Kohden, Tokyo, Japan; Inui, Tsuji, & Kakigi, 2006). Electrical current was generated using DS7a stimulators (Digitimer Ltd, Welwyn Garden, UK). The IES electrodes consisted of a needle cathode (length: 0.1 mm, Ø: 0.2 mm) surrounded by a cylindrical anode (Ø: 1.4mm). Electrodes were gently pressed against the skin of each hand dorsum in order to insert the electrode in the epidermis of the sensory territory of the superficial branch of the radial nerve. IES has been shown to selectively and specifically activate cutaneous nociceptors, without concomitant activation of Aβ-fiber mechanoreceptors (responsible for tactile sensations), provided that very low intensities of stimulation are used (Legrain & Mouraux, 2013; Mouraux et al., 2013; Mouraux, Iannetti, & Plaghki, 2010; Mouraux, Marot, & Legrain, 2014). To guarantee the selective activation of Aδ-fiber nociceptors, IES were set at twice the absolute detection threshold using single 0.5-ms square-wave pulses (Mouraux et al., 2010), determined by means of a staircase procedure (Churyukanov et al., 2012). If necessary, intensity values were adapted to guarantee that stimulus intensities were perceived as equivalent for both hands, by slightly increasing or decreasing the intensity of one of the two stimuli, with 0.5 mA as a maximum value (Favril, Mouraux, Sambo, & Legrain, 2014). During the experiment, stimuli consisted of trains of three consecutive 0.5-ms pulses separated by 5-ms interpulse intervals (Mouraux et al., 2013; Mouraux et al., 2014). Using these parameters, stimuli were perceived as pricking, a sensation typically associated to the activation of Aδ-fiber nociceptors (Mouraux et al., 2010). Stimuli were not necessarily perceived as painful.

Visual stimuli (5 ms duration) were presented by means of two white-light-emitting diodes (LED) with a 17-lm luminous flux, a 6.40-cd luminous intensity, and a 120° diffusion angle (GM5BW97330A, Sharp Corporation, Osaka, Japan). These LEDs were perceived as brief flashes. An additional yellow LED (min. 0.1-cd luminous intensity at 20 mA, 120° diffusion angle, Farnèll element 14, Multicomp, Leeds, UK) was used as fixation point during the task. LEDs were powered by means of an electrical pulse stimulator (Master-8, A.M.P.I., Jerusalem, Israel).

2.3. Procedure

The experiment took place in a dimly illuminated room. The participants were seated on a chair, placed their hands palm-down on a table and rested their head on a chin-rest (placed ~10 cm from the trunk). Each participant performed the visual temporal order judgments (TOJ) under three different *visibility* conditions (Fig. 1). First, in the *full-vision* condition, the two white LEDs were taped on the table, at ~40 cm from the trunk, with a distance of 40 cm between them. The yellow fixation LED was placed at ~75 cm from the trunk, equidistantly from the two white LEDs, in front of the body midline. Each hand was placed next to one white LED (i.e., the right hand next to the right LED and the left hand next to the left LED), with a distance of maximally 1 cm between the LED and the metacarpophalangeal joint of the index finger. Second, in the *no-vision* condition, vision of the hands was prevented by masking them with a wooden board placed on the table (81.5 cm long, 60.5 cm deep, 0.4 cm thick and 9.5 cm high). The white LEDs and the yellow fixation LED were taped on the wooden board at exactly the same distances from the trunk as in the *full-vision* condition. Participants' hands were placed palm-down on the table beneath the board, in the same position as in the *full-vision* condition, so that they were positioned just underneath the white LEDs taped on the board. Finally, the *vision through glass* condition was similar to the *no-vision* condition, with the exception that the wooden board was replaced by a translucent acrylic glass (80 cm long, 60 cm deep, 0.4 cm thick and 9.5 cm high) to allow the hands beneath the LEDs to be seen. Hands and LEDs were positioned exactly as in the *no-vision* condition.

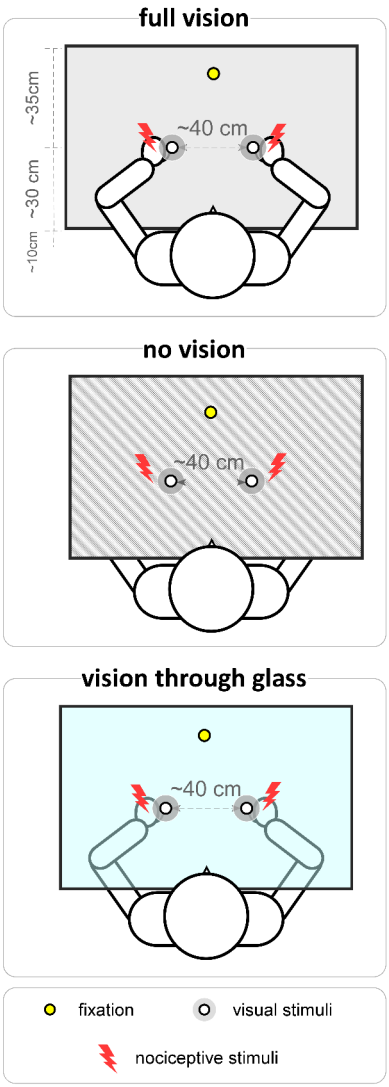

Figure 1. Design of the experiment. Participants performed temporal order judgments (TOJ) on pairs of visual stimuli (target LEDs, illustrated by the white circles with a slight grey halo), preceded by nociceptive stimulations (illustrated by the red flashes) applied either unilaterally, i.e. on one of the hands, or bilaterally, i.e. on both hands simultaneously. The participants' hands were always placed in the same position on the table, but depending on the condition, they were either visible (full vision condition), occluded from sight (no vision condition), or visible through acrylic glass (vision through glass condition). In the full vision condition, the LEDs were fixed on the table, next to the hands, whereas in the no vision and vision through glass conditions the LEDs were fixed on the board that is placed over the hands. A centrally-placed yellow LED (represented by the yellow circle) serves as fixation point. This figure depicts the bilateral cues condition.

A trial started with the illumination of the yellow fixation LED and the participants were instructed to keep their gaze at this fixation point as long as it was switched on, i.e. during the whole trial. After 500ms, a nociceptive stimulus was applied either on the left hand (unilateral stimulation), on the right hand (unilateral stimulation) or on both hands simultaneously (bilateral stimulation). Unilateral nociceptive stimulation was used as cue to attract spatial attention to one of the two hands, with the aim of selectively biasing the perception of the forthcoming visual stimuli. Bilateral nociceptive stimulation was used to orient attention unselectively to both hands, with the aim of controlling for task-unrelated lateralized biases in spatial attention. A bilateral cue condition was chosen instead of a no-cue condition in order to keep a similar level of general alertness between the unilateral and bilateral conditions (see Raz & Buhle, 2006). Two hundred milliseconds after the administration of the nociceptive stimulus/I, a pair of visual stimuli was presented, separated by one out of 20 possible time intervals (SOAs for *stimulus onset asynchronies*): ±200, ±145, ±90, ±75, ±60, ±45, ±30, ±15, ±10 and ±5 ms (negative values indicate that the left LED was illuminated first, positive values indicate that the right one was illuminated first). At each trial, participants were asked to either judge which of the two visual stimuli they perceived as having occurred first, or, depending on the block, perceived as having occurred second, by verbally answering *'left'* or *'right'.* These two different response modalities were used to minimize potential response biases (see Filbrich, Torta, Vanderclausen, Azanon, & Legrain, 2016; Shore, Spence, & Klein, 2001; Spence & Parise, 2010 for a discussion). Responses were unspeeded, and no feedback was given regarding their performance. Once the experimenter encoded the participant's response (by pressing a key of the remote control computer), the yellow fixation LED turned off and the next trial started 2000ms later. After each block, participants qualified the sensations on their hands and rated the perceived intensity of the nociceptive stimuli on a numerical rating scale (NRS) from 0 (= no sensation) to 10 (= very intense sensation) in order to ensure that the stimuli were still perceived as pinprick sensations of equal intensity between the two hands. If necessary, intensities could be adapted or the electrodes displaced and the assessment of the threshold restarted (see Favril et al., 2014 for details).

Before starting the experiment, participants completed a training phase of two blocks to get familiarized with the procedure. The first block was composed of 10 trials in which participants were asked which stimulus they perceived as having occurred first. In a second block of 10 trials, they responded which stimulus they perceived as having occurred second. Trials of the training phase were performed using the same visibility condition as the one used in the first block of the experimental phase. During this training, the participants' performance was not recorded. In the experimental part, participants were presented with six experimental blocks of 60 trials each, with two blocks per visibility condition. The order of the three visibility conditions was counterbalanced between the participants, with one block performed for each response mode (i.e. *'which is first?'* vs *'which is second?*, randomized for each participant). During

each block, visual stimuli were preceded by a unilateral left-sided nociceptive stimulus in 20 trials, by a unilateral right-sided nociceptive stimulus for another 20 trials, and by bilateral nociceptive stimuli in the remaining 20 trials, randomly and equiprobably intermixed. In summary, regardless of the response mode, a total of 120 trials for each visibility condition was presented, with 40 trials of each cueing condition within each visibility condition. For each block, the SOA between the two visual stimuli presented at each trial was determined online based on the adaptive PSI procedure, considering the participant's performance on all previous trials within the specific cue condition (Filbrich, Alamia, Burns, et al., 2017; Kontsevich & Tyler, 1999; Filbrich et al., 2017b). Every two blocks, the wooden or acrylic glass boards were placed or removed, depending on the visibility condition. Each block lasted approximately five minutes and the entire experiment, including instructions and threshold measurements, lasted about one hour.

2.4. Measures

The maximal intensity of the nociceptive stimuli, that is, the maximal intensity of the electrical current used during the experiment was measured separately for each hand in milliampere (mA). For each participant, ratings of the subjective perception of stimulus intensity, as measured with the NRS (from 0 to 10), were averaged across the blocks for each hand separately.

To assess the performance of the participants in the TOJ task, two measures were used: the point of subjective simultaneity (PSS) and the slope. We estimated these measures as the α and β parameters of a logistic function, i.e. $f(x)=1/(1+\exp(-\beta(x-\alpha)))$ respectively. Regarding our hypothesis, the main parameter of interest is the α, defining the threshold of the logistic function, which corresponds to the SOA at which the two visual stimuli are perceived as occurring first equally often (i.e. the 0.5 criterion on the ordinate). Accordingly, this measure corresponds to the PSS, which is defined as the amount of time one stimulus has to precede or follow the other in order for the two stimuli to be perceived as occurring simultaneously (Spence et al., 2001). In the present study, the PSS was used as a measure of spatial bias, indicating whether the judgments on the lateralized visual targets were shifted to the advantage of visual stimuli on one specific side of space. The β parameter defines the slope of the logistic function, which describes the noisiness of the results and can be related to the precision of participants' responses during the experiment (Kingdom & Prins, 2010). Since the adaptive PSI method was used (Kontsevich & Tyler, 1999), the logistic function and its parameters were estimated at each trial. This method is based on an algorithm that adopts a Bayesian framework, with the ultimate goal of estimating the parameters of interest without probing extensively all the SOAs (see Filbrich, Alamia, Burns, et al., 2017 for a more detailed description of the PSI method in TOJ experiments).

To get a single measure of the performance during the unilateral cue condition for each participant and each experimental condition, the average of the PSS values for the left-sided cue condition and the values for the right-sided cue condition (multiplied by –1 for the PSS for the right-sided cue condition) was calculated. For the bilateral cue condition, the proportion of trials in which the left visual stimulus was reported as appearing first was plotted as a function of SOA. For the unilateral cue condition, the proportion of trials in which the visual stimulus presented in the cued side of space was reported as appearing first was plotted as a function of SOA.

2.5. Data analyses

Participants' data were excluded from statistical analyses if the threshold and slope of the psychometric function could not be reliably estimated during the 20 trials of one or several cue conditions (i.e., their respective estimates did not converge on a stable value on the last trials), indicating that their performance was too inconsistent and below chance level.

Analyses were conducted using IBM SPSS Statistics 23 (IBM Corp., Armonk, NY, USA). First, to verify that the two hands were stimulated with similar intensities, the mean scores of the maximal intensity of the nociceptive stimuli were compared between the two hands using a *t*-test for paired samples. Because the self-reported perception of stimulus intensity can be considered as an ordinal variable, the NRS values were compared between the two hands using a non-parametric Wilcoxon signed-rank test.

Before analyzing the TOJ data, data from the two response modalities (*'which is first?'* vs. *'which is second?'*) were averaged for each condition to reduce the potential contribution of responses biases. To highlight potential shifts in TOJs to one side of space, the mean PSS value of each condition was compared to 0 with a one-sample *t*-test. Furthermore, to analyze differences between the conditions, we performed an analysis of variance (ANOVA) for repeated measures on PSS and slope measures, respectively, with *visibility (full vision* vs. *no vision* vs. *vision through glass)* and *cue* (*unilateral* vs. *bilateral*) as within-participant factors. If necessary, Greenhouse-Geisser corrections of degrees of freedom were applied. A priori contrast analyses were used to specifically address our hypotheses. Because we hypothesized that the shifts in visual TOJs induced by the unilateral nociceptive cues could be differently affected according to the visibility condition, three contrasts analyses were planned to compare the three visibility conditions for the unilateral cue condition with each other. Significance level was set at $p \leq 0.05$. Effect sizes were measured using Cohen's d for t-tests and partial η^2 for ANOVAs.

3. Results

3.1. Intensity values

The t-test revealed no significant difference ($t(22)= 0.46$, $p = 0.650$, d = 0.09) regarding the maximal intensity of the nociceptive stimuli between the two hands (M = 0.3 ± 0.1 mA for the left hand and M = 0.29 ± 0.09 mA for the right hand). These values are in the range of intensities that have been shown to selectively activate Aδ nociceptors (Mouraux et al., 2013; Mouraux et al., 2010; Mouraux et al., 2014). Self-reported NRS values were also not significantly different between the left (Mdn = 3.33) and the right hand (Mdn = 3.33) (Z = -0.71, p = 0.474). These results indicate that similar intensities of electrical current were used for the two hands, and that nociceptive stimuli were judged as equally intense between the two hands.

3.2. Temporal Order Judgments

The One-Sample t-test revealed that PSS values of the unilateral cue condition were significantly different from 0 for the three *visibility* conditions (*full-vision:* $t(22) = 7.68$, $p < 0.001$, d = 1.60, M = 20.83, SD = 13; *no-vision:* $t(22) = 7.06$, $p < 0.001$, d = 1.47, M = 16.16, SD = 10.97; *vision through glass:* $t(22) = 8.44$, $p < 0.001$, d = 1.76, M = 21.5, SD = 12.22). Conversely, these differences were not significant in the bilateral condition (*full-vision*: $t(22) = -0.10$, $p = 0.919$, d = -0.02; *no-vision*: $t(22) = 0.68$, $p = 0.505$, d = 0.14; *vision through glass*: $t(22) = -0.54$, $p = 0.593$, d = -0.11). This indicates that in the unilateral cue conditions, visual stimuli presented on the side of space opposite to the nociceptive cue had to be presented several milliseconds before stimuli presented on the cued side of space to have the chance to be judged as occurring simultaneously. In other words, PSS values were significantly biased to the advantage of the visual stimuli presented on the side of space corresponding to the hand to which the nociceptive stimulus was applied. Conversely, no significant bias to the advantage of one of the two sides was observed in the bilateral cue conditions (see Figs.2 and 3).

The ANOVA of the PSS values did not show a significant main effect of the factor *visibility* ($F(2, 22) = 0.13$, $p = 0.877$, $\eta^2_p < 0.01$). On the contrary, there was a significant main effect of the factor *cue* ($F(1, 22) = 39.78$, $p < 0.001$, $\eta^2_p = 0.64$), which also significantly interacted with the factor *visibility* ($F(2, 22) = 4.16$, $p = 0.022$, $\eta^2_p = 0.16$). This suggests that while the visibility of the hands did not affect the PSS in the bilateral cue condition ($F(2, 22) = 1.07$, $p = 0.351$, $\eta^2_p = 0.05$), it had a significant impact on the PSS in the unilateral cue condition ($F(2,22) = 4.76$, $p = 0.013$, $\eta^2_p = 0.18$) (Fig.2). In agreement with our hypotheses, a priori contrast analyses revealed that, as compared to the *no-vision* condition, the PSS was larger in the *full-vision* ($t(22) = 2.24$, $p = 0.035$, d

= 0.47) and in the *vision through glass* conditions ($t(22) = -2.76$, $p = 0.011$, d = 0.58). There was no significant difference between the *full vision* and *vision through glass* conditions ($t(22) = -0.41$, $p = 0.683$, d = 0.09). This suggests that the bias induced by the unilateral cues was greater when the hands were seen, as compared to when their vision was prevented (see Fig. 2).

Regarding the slope, the ANOVA revealed no significant main effect, neither for the factor *visibility* ($F(2, 22) = 2.27$, $p = 0.115$, $\eta^2_p = 0.09$) nor for the factor *cue* ($F(1, 22) = 0.04$, $p = 0.837$, $\eta^2_p < 0.01$). There was, however, a significant interaction between these two factors ($F(2, 22) = 4.38$, $p = 0.013$, $\eta^2_p = 0.18$), suggesting that the *visibility* factor did not significantly impact the slope of the *bilateral cue* condition ($F(2, 22) = 1.53$, $p = 0.228$, $\eta^2_p = 0.06$), but did affect the slope of the *unilateral cue* condition ($F(2, 22) = 3.40$, $p = 0.042$, $\eta^2_p = 0.13$). Indeed, the slope value was greater in the *full-vision* condition ($M = 0.11$, $SD = 0.06$) as compared to the *no-vision* condition ($M = 0.08$, $SD = 0.04$; $t(22)=2.256$, $p = 0.034$, d = 0.47). The other paired comparisons did not reveal any significant differences (slope value of the *vision through glass* condition: $M = 0.09$, $SD = 0.05$; *full-vision* vs. *vision through glass* comparison: $t(22)=1.88$, $p = 0.074$, d = 0.39; *vision through glass* vs. *no-vision* comparison: $t(22)= -0.67$, $p = 0.507$, d = -0.14). This suggests that, when a nociceptive stimulus was applied on one single hand before the presentation of the visual stimuli, preventing vision of the hands made the participants' judgments more noisy, i.e. variable, as compared to the condition in which the hands could be seen directly.

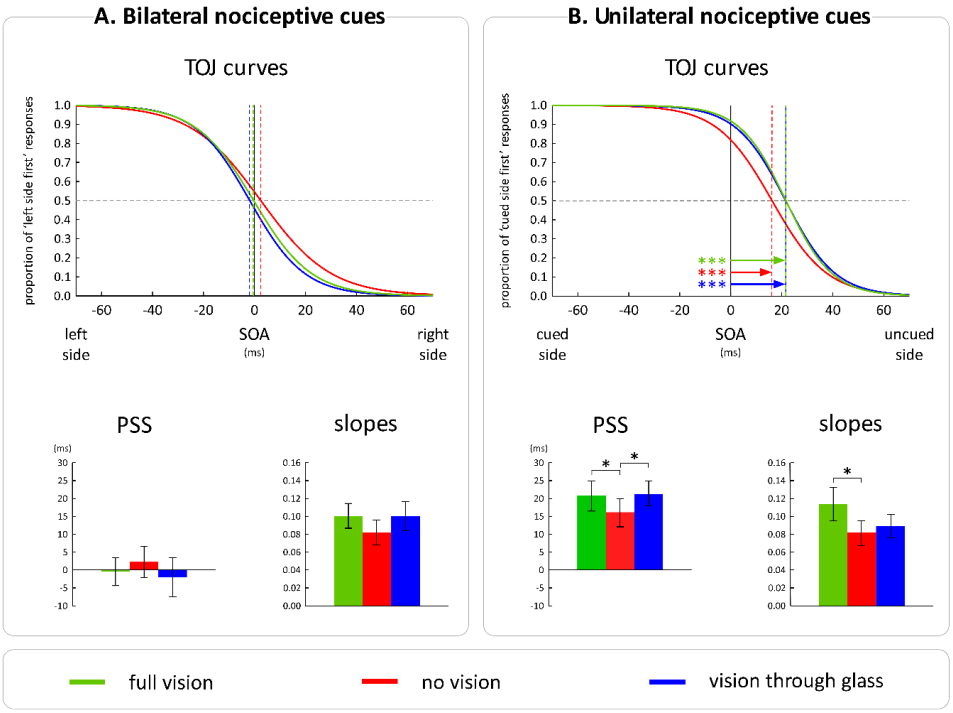

Figure 2. Results of the experiment. The figure illustrates the averaged results of the 23 participants. Data from left-sided nociceptive cue conditions and right-sided nociceptive cue conditions were averaged into a unilateral cue condition. The upper part depicts the fitted logistic functions for the (A) bilateral cue condition and the (B) unilateral cue condition. For the bilateral cue condition (A), the x-axis represents different hypothetical stimulus onset asynchronies (SOAs) between the two visual stimuli: negative SOA values indicate that the visual stimulus occurring in the left side of space was presented first, while positive values indicate that the visual stimulus occurring in the right side of space was presented first. The y-axis represents the proportion of trials in which the participants perceived the stimulus presented in the left side of space as occurring first. For the unilateral cue condition (B), the x-axis represents different hypothetical stimulus onset asynchronies (SOAs) between the two visual stimuli: negative values indicate that the visual stimulus occurring in the cued side of space was presented first, while positive values indicate that the visual stimulus occurring in the uncued side of space was presented first. The y-axis represents the proportion of trials in which the participants perceived the visual stimulus presented in the cued side of space as occurring first. In both (A) and (B), red curves represent the conditions in which participants perform the visual TOJ task in the no vision condition, with the corresponding PSS values indicated by the red vertical dashed lines. Blue curves represent the conditions in which participants perform the visual TOJ task in the visible through glass condition, with the corresponding PSS values indicated by the blue vertical dashed lines. Green curves represent the conditions in which participants perform the visual TOJ task in the full vision condition, with the corresponding PSS values indicated by the green vertical dashed lines. The arrows in (B) indicate the PSS values significantly different from zero. The curves in the unilateral cue condition (B)

are significantly shifted to the uncued side of space, indicating that visual stimuli presented in the uncued side of space had to be presented several ms before the stimuli presented in the cued side of space to have the chance to be perceived as occurring first equally often. The lower part illustrates the mean PSS and slope values, for both bilateral (A) and unilateral (B) cue conditions. Significant differences are indicated with asterisks (* $p \leq .05$, ** $p \leq .01$, *** $p \leq .001$). Error bars represent the 95% confidence intervals adapted according to the method of Cousineau (2005).

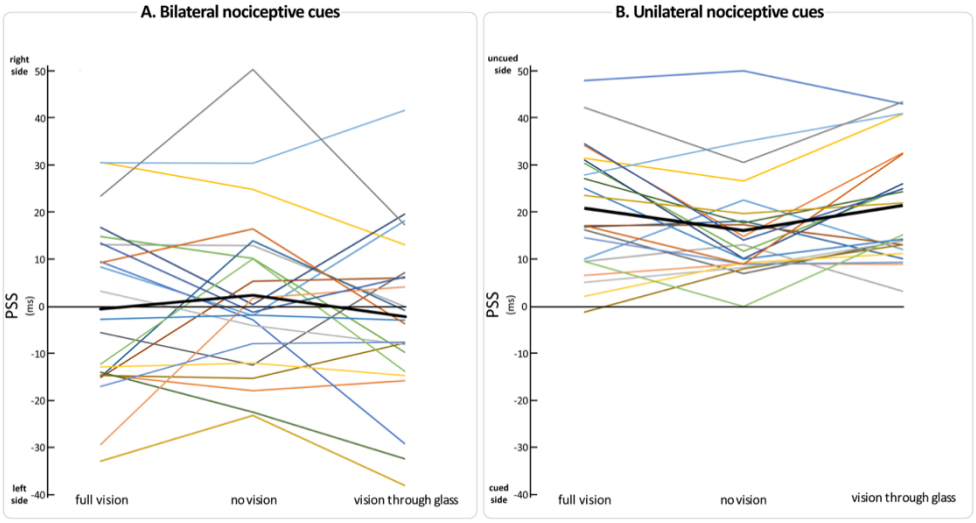

Figure 3. Individual PSS values. The left graphic illustrates the individual PSS values for the bilateral nociceptive cue condition (A), and the right graphic the individual PSS values for the unilateral nociceptive cue condition (B). Within each graphic, values are represented for each visibility condition (full-vision vs. no-vision vs. vision through glass). Each color line represents one of the 23 participants who participated in the task, while the black line represents the group average.

4. Discussion

The aim of the experiment was to test whether the crossmodal influence of nociception on visual perception, which relies on the proximity of both types of stimuli in external space (Filbrich et al., 2017a,b; Filbrich et al., 2018; Vanderclausen et al., 2017), is mediated by visual feedback about the position of the stimulated limb with regard to the visual stimuli. More precisely, we tested if spatial biases in visual TOJs, induced by nociceptive cues applied on the hands positioned next to visual targets, are affected when the visually perceived proximity between the hands and the visual stimuli is disrupted. Participants judged the temporal order of pairs of visual stimuli which were preceded by task-unrelated nociceptive stimuli applied either unilaterally, i.e. on one of the hands, or bilaterally, i.e. on both hands simultaneously. The hands were always placed close to the visual stimuli. While bilateral nociceptive stimuli were used as control condition, unilateral nociceptive stimuli were used as cues to attract spatial attention to one side of space and thus to induce crossmodal spatial biases. According to the theory of prior entry (Titchener, 1908), stimuli on which we focus our attention are perceived earlier than unattended ones. In the present study, the time interval between the two visual stimuli that is necessary for the two to be perceived as occurring at the same time (i.e. the PSS) can thus be used to index the presence of spatial biases.

The results replicated previous findings, showing that the presence of a unilateral nociceptive cue can induce spatial biases in visual perception, with TOJs prioritizing the visual stimulus presented on the same side of space as the hand on which the single nociceptive stimulus was applied (Filbrich et al., 2017a,b; Filbrich et al., 2018; Vanderclausen et al., 2017). Importantly, such significant spatial biases were observed in all three visibility conditions, whether the proximity between the nociceptive cues and visual targets was visually perceived or not. Nevertheless, comparisons between these three visibility conditions revealed that spatial biases were significantly greater in the two conditions in which the hands could be seen, as compared to the condition in which seeing the hands was prevented by the wooden board. This finding could potentially suggest that the visual feedback about the hands' position plays a predominant role in determining spatial congruency between nociceptive and visual stimuli. That crossmodal interactions between somatic and non-somatic stimuli could mainly be due to the visually perceived proximity between the two types of stimuli has indeed previously been suggested by studies in brain-damaged patients. These studies directly compared the influence of seeing vs. not seeing the hands on the strength of the crossmodal extinction of tactile contralesional stimuli by visual stimuli presented near the ipsilesional hand (Làdavas et al., 2000). Strikingly, they observed strong crossmodal effects when the hands were visible, but only mild effects when seeing the hands was prevented. Although the effect was still present when the hands were covered, its magnitude was similar to the one of the crossmodal effect induced by a visual stimulus presented farther away from the hand (i.e. in extrapersonal space). This latter result

potentially suggests that without visual feedback, and solely based on proprioceptive information, the relative location of the stimulated limb with regard to external stimuli could be difficult to determine, thus leading to difficulties in determining whether a visual stimulus is presented near or far from the limb. The importance of seeing the stimulated hand next to the visual stimuli for visuo-tactile interactions has also been corroborated in healthy humans by Maravita et al. (2002). They showed that visual stimuli that are seen close to the reflection of the participants' hands in a distant mirror have a greater impact on the perception of tactile stimuli applied on the hands than visual stimuli that are presented at an equivalent distance but without sight of the hands.

Nevertheless, although we showed a significant difference between the conditions preserving vision of the hands and the condition preventing it, our results and those of the above-mentioned studies do not actually allow us to conclude that the proximity effect in interactions between nociceptive and visual stimuli mainly relies on visual feedback, or that proprioceptive feedback seems less important. First of all, we still observed strong spatial biases in visual TOJs induced by the nociceptive cues in the condition in which seeing the hands was prevented, suggesting that proprioceptive input about the position of the stimulated hands is used to determine the spatial proximity between the nociceptive and visual stimuli. Although we did not directly compare the effects of visual stimuli presented at different distances from the stimulated hand, the present biases in the *no-vision* condition appear much stronger than the effects found with far visual stimuli in previous studies (see Filbrich et al., 2017b) and seem thus different from the above-mentioned results of Làdavas et al. (2000). In addition, previous investigations in the context of visuo-tactile interactions have been able to demonstrate strong crossmodal effects even though vision of the hands was prevented. For instance, Kennett et al. (2002) showed in healthy participants that tactile distractor stimuli can influence visual performance (and vice versa) in a crossmodal congruency task when the stimulated hand is not seen. Similarly, Mattingley et al. (1997) observed in brain-damaged patients suffering from crossmodal extinction that a tactile stimulus applied on the unseen ipsilesional hand can extinguish the perception of a simultaneous contralesional visual stimulus (and vice versa). Furthermore, Macaluso et al. (2002) showed that tactile stimuli can boost the cortical responses to visual stimuli in the visual cortex when both stimuli are spatially aligned in external space, regardless of whether the stimulated hand is seen or not. Notably, there is even one study that obtained larger crossmodal effects between touch and vision in the crossmodal congruency task when the hands were hidden from sight than when they were visible (Kitagawa & Spence, 2005).

Another point that prevents us from concluding on a predominant role of visual feedback in the observed crossmodal interactions relies on the fact that we did not test a condition in which only visual information about the proximity between nociceptive and visual stimuli was provided, i.e. without proprioceptive feedback. Indeed, it could

be that the combination of both visual and proprioceptive feedback about limb position optimizes interaction effects between somatic and extra-somatic stimuli, as compared to a situation in which only one of these feedbacks is available. While it seems certainly difficult to completely suppress any proprioceptive feedback, and thus to properly disentangle the respective roles of vision and proprioception in determining spatial proximity between the body and external objects, proprioceptive feedback can actually be manipulated by experimentally induced illusions. For instance, Pavani et al. (2000) showed significantly larger effects of proximal visual distractors on tactile perception when a fake hand was placed in a realistic position above the hidden stimulated real hand (and thus close to the visual stimuli), as compared to conditions in which the real hand was just hidden. Similarly, Gallace and Spence (2005) showed that simply raising the visual illusion of a changed hand posture, by varying the distance between a hand and its mirror-reflected image, affected participants' performance during tactile TOJ, while the actual hand position (i.e. proprioception) remained unchanged. This suggests that under specific circumstances, e.g. when vision and proprioception are mismatching, visual feedback about limb position can overrule proprioceptive feedback.

In addition to determining the role of the visual feedback about hand position in the interaction between nociceptive and visual stimuli, the present study also addressed the question whether such interactions between somatic and non-somatic stimuli could be mediated by the expectancy of imminent contact with the external object. This question is of particular relevance when stimuli activating the nociceptive system are involved, specifically if an external object (i.e. visual stimulus) is presented close to a hand that is already stimulated with a nociceptive stimulus, as in the present study. Since one of the main functions of the peripersonal representation would be to defend the body against potentially noxious stimuli, one could indeed argue that if the body is protected from any contact with external objects that could potentially threaten its physical integrity, crossmodal interactions between the somatic and non-somatic systems would be disrupted. In the present study it could indeed be possible that the crossmodal effect between nociceptive and visual stimuli in the *no-vision* condition was smaller than in the vision conditions because the potential contact between the visual stimuli and the hand was prevented, rather than because hand position was not seen. To take into account this possibility, the condition with a translucent glass barrier was included, which provided the participants with visual feedback about the spatial proximity between the stimulated hand and the visual stimulus, while rendering any potential physical contact between the nociceptive and visual stimuli impossible. Our results show that the spatial bias induced by the nociceptive stimuli in the condition in which the hands could be seen through the glass was not significantly different from the one observed in the condition in which the hands could be seen directly. In other words, similar crossmodal effects were observed whether a potential contact between nociceptive cues and visual targets was possible or not. Similar results have been previously shown in the context of visuo-tactile interactions. Farnè et al. (2003)

demonstrated in brain-damaged patients that the perceptual extinction of tactile stimuli by near visual stimuli does not change with the presence of a transparent barrier between the two stimuli. Likewise, in healthy participants, Kitagawa and Spence (2005) did not report any differential effect of seeing the hands through a transparent occluder on visual-tactile interactions in the crossmodal congruency task. It seems thus that the multisensory processing in the space surrounding the stimulated body part is not mediated by the expectancy of contact with external objects, even in the context of noxious objects, and that interaction between nociceptive and nearby non-somatic stimuli occurs automatically, whether they are physically separated or not. This has been interpreted as indicating that such crossmodal interactions can occur in a bottom-up fashion without being influenced by higher-order top-down processes, potentially related to their importance for triggering fast and appropriate motor reactions in peripersonal space (Farnè et al., 2003).

However, one has to note that in the present study, contrary to Farnè et al. (2003), contact between the visual stimuli and the hands could not really have been expected by the participants, since the visual stimuli consisted in static flashing LEDs. To disentangle the role of visual feedback about hand position from the expectancy of being touched more thoroughly, it would be interesting to use visual stimuli that can induce the expectancy of an impending physical contact with the body (see also Kitagawa and Spence, 2005). This could boost the relevance of a transparent barrier between the nociceptive stimuli and the near visual stimuli, and make any interaction between the two stimuli more likely to be mediated by its presence.

In conclusion, the present results suggest that visual feedback about the position of the limb on which nociceptive stimuli are applied plays an important role in establishing spatial alignment between nociceptive and visual stimuli in external space, whether both types of stimuli are physically separated or not. What still needs to be determined is whether such visual feedback can be disentangled from proprioceptive feedback, and if spatial mapping between somatic and non-somatic stimuli predominantly relies on one of these feedbacks.

CHAPTER 2: INVESTIGATIONS OF TEMPORAL ASPECTS

STUDY 2: INVESTIGATING PERCEPTUAL SIMULTANEITY BETWEEN NOCICEPTIVE AND VISUAL STIMULI BY MEANS OF TEMPORAL ORDER JUDGMENTS[5]

Abstract

Multisensory interactions between pain and vision allow us to adapt our behavior to optimize detection and reaction against bodily threats. Interactions between different sensory inputs are enhanced when they are perceived closely in space and time. However, thermo-nociceptive and visual stimuli are conveyed to the cortex through specific pathways with their own conduction velocity. The present experiment aims to measure the necessary asynchrony between a nociceptive stimulus and a visual stimulus for both to be perceived as occurring simultaneously. Healthy volunteers performed a temporal order judgment task during which they discriminated the temporal order between a laser-induced nociceptive stimulus applied on one hand dorsum and a visual stimulus presented next to the stimulated hand. Laser stimulus temperature selectively activated Aδ- and/or C- fiber afferents. In order to be perceived as occurring simultaneously with a visual stimulus, a thermo-nociceptive stimulus selectively conveyed by C-fiber afferents must precede the visual stimulus by 577 ms on average, while the stimulus specifically conveyed by Aδ-fiber afferents must precede it by 76 ms on average. This experiment focuses on the necessary asynchrony between thermo-nociceptive and visual inputs for them to be perceived simultaneously, to optimize the conditions under which they interact closely. Since C-fibers are unmyelinated, the asynchrony is much greater than the asynchrony between the nociceptive stimulus additionally activating Aδ-fibers and the visual stimulus. It is crucial to consider these discrepancies in further studies interested in multisensory interactions.

[5] This study is published as:
Manfron, L., Filbrich, L., Nijs, E., Mouraux, A., & Legrain, V. (2020). Investigating perceptual simultaneity between nociceptive and visual stimuli by means of temporal order judgments. *Neuroscience Letters, 735*, 135156.

1. Introduction

Events occurring in our environment are generally perceived as unitary coherent percepts even if they are conveyed by multiple senses. Regarding the perception of pain and the detection of bodily threats, nociception and vision are thought to interact closely to inform about the source and location of harmful stimuli in the surrounding space. For instance, nociceptive and visual stimuli influence each other's perception especially when the visual stimulus occurs in the close vicinity of the limb on which the nociceptive stimulus is applied (De Paepe et al., 2014; Filbrich et al., 2017b). However, the cortical mechanisms underlying the interaction between nociceptive and visual inputs are still largely unknown. In addition to spatial congruence, multisensory research conducted in other sensory modalities, such as vision and audition, also indicates that interactions are maximized when the different stimuli are perceived close together in time (Morein-Zamir et al., 2003; Stein, Meredith, Huneycutt, & McDade, 1993; Sugita & Suzuki, 2003; Filbrich et al., 2017a). However, if information about a given stimulus is conveyed by more than one sensory modality, the afferent input conveyed within each activated sensory modality will, in many instances, reach the cortex at markedly different times. For example, if the physical distance between an audiovisual stimulus and its observer is important, the time required for the sound waves to reach the ear will be far greater than the time required for light to reach the eye. Additional differences in timing may arise from differences in receptor transduction times as well as the time required for that sensory input to reach the cortex. Considering nociception and vision, the slow conduction velocities of thinly-myelinated Aδ fibers (~10 m/s (Kakigi & Shibasaki, 1991)) and unmyelinated C fibers (~1 m/s (Opsommer et al., 1999)) can be expected to introduce very large timing differences, especially when nociceptive stimuli are delivered to the distal end of a limb, i.e. when peripheral conduction distance is large. Visual information is transmitted to the cortex in less than 100 ms (Michel et al., 2004). In contrast, the first cortical responses to nociceptive stimuli delivered to the hand are observed approximately 150 ms after stimulation onset for inputs conveyed by Aδ fibers and up to one second after stimulation onset for inputs conveyed by C fibers (Plaghki & Mouraux, 2005). This implies that, when applied concomitantly, the visual stimulus can be completely processed while the input conveyed by thermo-nociceptive pathways has not even reached the brain yet (Filbrich et al., 2017a).

Such asynchrony between nociceptive and visual stimuli has been assessed in a study conducted by Zampini et al. (2007). In a temporal order judgment (TOJ) task, laser stimuli applied on the dorsal forearm, with an energy above the activation threshold of Aδ-fiber afferents, and visual stimuli projected onto the same skin area, were presented with varying stimulus onset asynchronies (SOAs). Participants were

requested to judge which of the two stimuli they perceived as first or whether they were simultaneous. Participant responses were then used to determine the SOA at which both stimuli were perceived as simultaneous, referred to as the point of subjective simultaneity (PSS). When participants were instructed to equally attend to the two stimuli, the laser stimulus had to precede the visual stimulus by approximately 40 ms for the two stimuli to be perceived as coinciding.

The present study aimed to assess the PSS for visual stimuli and nociceptive stimuli selectively activating unmyelinated C-fiber afferents which – when stimulating the distal end of a limb – require several hundreds of milliseconds to reach the cortex. Importantly, in addition to this delay, the so-called sensation of 'second pain' conveyed by C fibers is often considered as being poorly defined in terms of location and timing compared to the sensation of 'first pain' conveyed by Aδ fibers (Plaghki & Mouraux, 2005). Therefore, in addition to assessing and comparing the PSS for visual and C-fiber inputs to the PSS for visual and Aδ-fiber inputs, we also assessed the slope of the psychometric curves to determine whether temporal discrimination abilities (see Vanderclausen, Bourgois, et al., 2020; Vanderclausen, Manfron, et al., 2020) differed between the two types of visuo-nociceptive pairs. The methods we developed here allow to optimize the conditions under which multisensory interactions between visual and nociceptive stimuli can be observed and investigated.

2. Methods

2.1. Participants

Twenty healthy volunteers participated in the study. Three participants were excluded from the analyses because of technical issues or excessive habituation to the nociceptive stimuli. The mean age of the remaining 17 participants (9 women) was 23.1 years (SD = 1.5, range 21-27 y.). Exclusion criteria were non-corrected vision difficulties, any neurological, cardiac, psychiatric or chronic pain disorder, trauma of the upper limbs within the lasts 6 months preceding the experiment, tissue damage or dermatological disease of the hands, regular use of psychotropic drugs and intake of analgesic drugs within the 12 hours before the experiment. According to the Flinders Handedness survey (Nicholls et al., 2013), 13 participants were right-handed, 3 left-handed and 1 was ambidextrous. The local ethic committee approved the experimental procedure in agreement with the Declaration of Helsinki. All volunteers signed an informed consent prior to the experiment and received financial compensation for their participation.

2.2. Stimuli and apparatus

During the experiment, participants were seated on a chair in front of a table. A cross to fixate participants' gaze was placed on the table surface, in front of their midsagittal plane, 40 cm from their trunk. Participants were asked to place their hands palms down on the table, with the metacarpophalangeal joint between each index finger and the thumb located 1 cm from two landmarks placed 15 cm on either side of the line extending their midsagittal plane (see Figure 1).

Thermo-nociceptive stimuli consisted of radiant heat stimuli delivered to the dorsum of the two hands using a temperature-controlled CO_2 laser stimulator (10.6 μm wavelength, Laser Stimulation Device, SIFEC, Ferrières, Belgium) (Churyukanov et al., 2012). The stimulus profile was made of a 10-ms heating ramp to reach the target temperature, followed by a 90-ms plateau (Lenoir, Algoet, & Mouraux, 2018; Vanderclausen, Bourgois, et al., 2020; Vanderclausen, Manfron, et al., 2020). Beam diameter was 6 mm, with a constant energy distribution across the entire beam. The target of the laser beam was displaced after each stimulus application.

Visual stimuli consisted of flashes lasting 5 ms and delivered by a white light-emitting diode (LED) with a 17-lm luminous flux, a 6.40-cd luminous intensity, and a 120° diffusion angle (GM5BW97330A, Sharp Corporation, Osaka, Japan). The LED was placed on the table, on the marker next to the hand dorsum receiving the laser stimuli, without any contact with the skin.

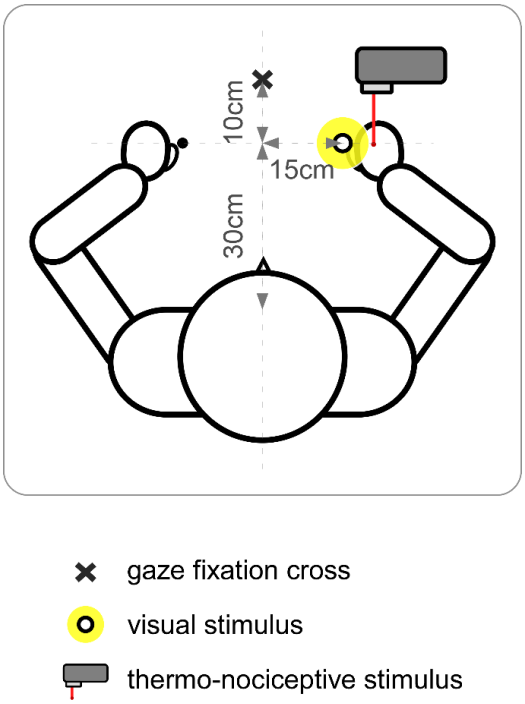

Figure 1. Experimental setup. Participants were asked to judge the temporal order of pairs of thermo-nociceptive and visual stimuli. The temperature-controlled CO2 laser administered thermo-nociceptive stimuli on the hand dorsum (the figure illustrates the stimulation of the right hand). Visual stimuli were delivered by means of a white LED placed near the hand to which the laser stimuli were applied. The hand and the LED were positioned using landmarks, placed 15 cm on either side of the line extending the participant's midsagittal plane. The line joining the two landmarks intersected the midsagittal line perpendicularly, 30 cm from the participant's trunk. Ten cm further, i.e. 40 cm from the participant's trunk, a fixation cross was placed to stabilize the participant's gaze.

2.2.1. Estimation of C-fiber and Aδ-fiber detection thresholds

C-fiber and Aδ-fiber thermal detection thresholds were respectively measured in each participant using an adaptive staircase procedure (see Churyukanov et al., 2012 for details). Absolute detection of the laser stimuli was used as criterion to determine the C-fiber thermal detection threshold, as the thermal detection threshold of C fibers is known to be lower than that of Aδ fibers. To determine the detection threshold of Aδ fibers, reaction times shorter than 650 ms were used as criterion for the detection of Aδ-fiber input. When stimulating the hand dorsum, this cutoff has been shown to effectively discriminate between Aδ- and C-fiber sensations (Churyukanov et al., 2012). Thresholds were estimated on either the left hand or the right hand (counterbalanced across the participants). The C-fiber detection threshold was always estimated before the Aδ-fiber detection threshold (the reverse procedure could have made it difficult to detect low intensity stimuli after having overheated the skin with high intensity stimuli).

Individual detection thresholds were used to determine, for each participant, two target stimulation temperatures. The first target temperature (C-stimulus) corresponded to the average of C-fiber and Aδ-fiber detection thresholds. At this intensity, most stimuli can be expected to activate C-fiber afferents without concomitantly activating Aδ-fiber afferents. The second target temperature (Aδ-stimulus) was set 5°C above the Aδ-fiber detection threshold. At this intensity, most stimuli can be expected to activate Aδ-fiber afferents without producing any burn lesions (see Lenoir, Algoet, et al., 2018 for details). Participants reported the sensation elicited by the C-stimulus as warm and the Aδ-stimulus as pricking.

2.2.2. TOJ task

The TOJ task consisted in four separate blocks of 40 trials each. In two of these blocks, participants performed the TOJ task on pairs of visual and laser C-stimuli. In the other two blocks, they performed the TOJ task on pairs of visual and laser Aδ-stimuli. To avoid overstimulation of the skin, only one type of laser stimulus was tested and applied on each hand. Half of the participants received laser C-stimuli on the left hand and Aδ-stimuli on the right hand, and vice versa for the other half of the participants. The choice of the hands according to the stimulated fibers was counterbalanced between participants. To prevent response biases, for each of these two blocks, participants were asked to report which of the two stimuli was perceived first in one block, and which of the two stimuli was perceived second in the other block (Filbrich et al., 2017a). Unspeeded responses were provided verbally using the words *'visual'* or *'laser'.* The order of the four blocks was counterbalanced for each participant.

Each trial of each block consisted of a pair of visual and laser stimuli. Before each experimental block, participants were presented with two pairs of stimuli of the corresponding condition, in order to be familiarized with the elicited sensation and with the task. During the task, a verbal warning was delivered approximately 500 ms before the onset of the first stimulus of each pair. For pairs of visual and C-stimuli, the C-stimulus was always delivered before the visual stimulus, due to the ultra-slow latency of responses to C-stimuli. The pairs were separated by 16 possible SOAs: +100, +220, +270, +320, +370, +420, +460, +490, +510, +540, +580, +630, +680, +730, +780, +900ms. For pairs of visual and Aδ-stimuli, the Aδ-stimulus could either precede the visual stimulus (positive SOAs) or follow the visual stimulus (negative SOAs), with 14 possible SOAs: ±200, ±150, ±100, ±80, ±60, ±40, ±20ms. SOAs were chosen based on the prior value of the PSS (see below), respectively estimated for each fiber condition. Fourteen SOAs were defined with increasing steps as a function of the distance of the SOA from the prior estimate (Filbrich et al., 2017a,b; Vanderclausen, Bourgois, et al., 2020; Vanderclausen, Manfron, et al., 2020). The number of SOAs was increased for the C-stimuli conditions because of the larger variability of the responses as compared to trials with Aδ-stimuli. These parameters were tested during a pre-testing pilot experiment.

Using these predefined SOAs, the adaptive *psi* method was used to determine the SOA of each trial considering the participants' responses to all previous trials of the block. The *psi* method is a Bayesian adaptive algorithm that can be used to estimate not only the threshold but also the slope of the psychometric function (see Filbrich et al., 2017a; Kontsevich & Tyler, 1999 for details). The adaptive *psi* method estimates the parameters of the psychometric logistic function $f(x)=1/(1+\exp(-\beta(x-\alpha)))$ at each trial (Kingdom & Prins, 2010). The α parameter corresponds to the threshold and characterizes the PSS, that is, the SOA at which visual and thermo-nociceptive stimuli are equally likely to be perceived as first or second. Its prior estimates were set to 500±200 ms for visual/C-stimuli pairs and 70±20 ms for visual/Aδ-stimuli pairs. The β parameter corresponds to the slope of the psychometric curve, and its prior estimates were set to 0.06±0.6 for both types of stimulation pairs. These prior estimates were selected based on a pilot experiment.

After each trial, participants qualified the sensation elicited by the laser stimulus using a list of descriptor words (Nahra & Plaghki, 2003). If the laser stimulus was not perceived, if a C-stimulus was qualified as *pricking* or if an Aδ-stimulus was qualified as *warm*, the trial was discarded and repeated. After each trial, the laser beam was displaced. Participants' responses were encoded by the experimenter using computer keys. The next trial started immediately once the response encoded. There was no fixed inter-trial time interval, but it was not smaller than 3000 ms. Each block lasted approximately five minutes. The entire experiment, including instructions and threshold measurements, lasted about 1 hour and a quarter.

2.3. Measures

The thresholds and intensities of laser stimuli were measured in Celsius degrees.

For each type of stimuli pair, participant's responses for the different SOAs were fitted using a logistic function (see Filbrich et al., 2017a; Kingdom & Prins, 2010), producing two measures for each participant and stimuli pair: α parameter corresponding to the PSS and β parameter corresponding to the slope of the psychometric function. Lower and higher abilities to discriminate the temporal order of the two stimuli will be represented by lower and greater values of β, respectively.

Additional measures were participant height and length of the arm (from the styloid process of the ulna to the acromion). These measures were used to examine the possible relationship between the PSS and peripheral conduction distance.

2.4. Data analyses

For each participant and type of stimulation pair, the estimated PSS (α parameter) and slopes of the psychometric function (β parameter) were averaged across the two response modalities (which is first *vs.* which is second). A one-Sample t test was then performed to test whether the PSS was significantly different from zero, but only for the visual/Aδ-stimulus condition as only positive SOAs were presented during the visual/C-stimulus condition. Next, paired sample t-tests were conducted to compare the PSS and slopes between the two types of stimulation pairs (visual/Aδ-stimulus, visual/C-stimulus). Effect sizes were evaluated by performing Cohen's d.

Finally, linear Pearson's correlations were performed to estimate the relationship between the PSS and the height of the participants, and the length of their arms. Correlations between the PSS of the visual/C-stimulus condition and the PSS of the visual/Aδ-stimulus condition, as well as the slope of the visual/C-stimulus condition and the slope of the visual/Aδ-stimulus condition, were computed to estimate intra-individual consistency across stimuli pair conditions. Significance was set at p-value < 0.05.

3. Results

The mean temperature of the C-fiber detection threshold was 40.9°C (SD = 1.3°C). The mean temperature of the Aδ-fiber detection threshold was 47.4°C (SD = 1.1°C). The mean temperature of the C-stimulus used in the TOJ task was 44.0°C (SD = 1.0°C). The mean temperature of the Aδ-stimulus was 52.4°C (SD = 1.0°C).

Figure 2 illustrates the psychometric functions fitted to the TOJ data. For pairs of visual and C-stimuli, the mean PSS was 577 ms (SD = 99 ms) ranging from 419 to 740 ms. For pairs of visual and Aδ-stimuli, the mean PSS was 76 ms (SD = 16 ms) ranging from 49 to 108 ms. This indicates that, to be perceived as occurring simultaneously, the C-fiber thermo-nociceptive stimulus delivered to the hand dorsum must precede the visual stimulus by 577 ms on average, while the Aδ-fiber thermo-nociceptive stimulus must precede the visual stimulus by 76 ms on average. The one-Sample t-test showed that the latter PSS value was significantly different from 0 ($t(16)=19.73$, $p<0.001$). The difference between the two PSS values was significant ($t(16) = 22.64$, $p<0.001$, d = 5.49) showing that a greater SOA is required for the thermo-nociceptive stimulus to be perceived as simultaneous to the visual stimulus when conveyed through C-fiber afferents as compared to Aδ-fiber afferents.

Mean slope values were 0.009 (SD = 0.005) for the visual/C-stimulus condition, and 0.019 (SD = 0.01) for the visual/Aδ-stimulus condition. The difference between the two slopes was significant ($t(16) = -3.78$, $p = 0.002$, d = -0.92) indicating lower temporal discrimination for inputs conveyed by C fibers as compared to inputs conveyed by Aδ fibers.

The height of the 17 volunteers (M = 174 cm, SD = 8 cm) was not significantly correlated to either of the PSS values (visual/C-stimulus: $r^2 = 0.05$, $p = 0.841$; visual/Aδ-stimulus: $r^2 = 0.35$, $p = 0.169$). There was also no significant correlation between arm length (M = 57 cm, SD = 4 cm) and the PSS values (visual/C-stimulus: $r^2 = -0.11$, $p = 0.674$; visual/Aδ-stimulus: $r^2 = 0.23$, $p = 0.383$). This suggests that inter-individual differences in PSS values were not markedly related to differences in peripheral conduction distance. In contrast, the PSS values for visual/C-stimuli and visual/Aδ-stimuli were significantly correlated ($r^2 = 0.55$, $p = 0.021$). This suggests that participants performed the TOJ task consistently across the experimental conditions. There was no significant correlation between the slope of the psychometric function for visual/C-stimuli and the slope of the function for visual/Aδ-stimuli ($r^2 = 0.17$, $p = 0.503$).

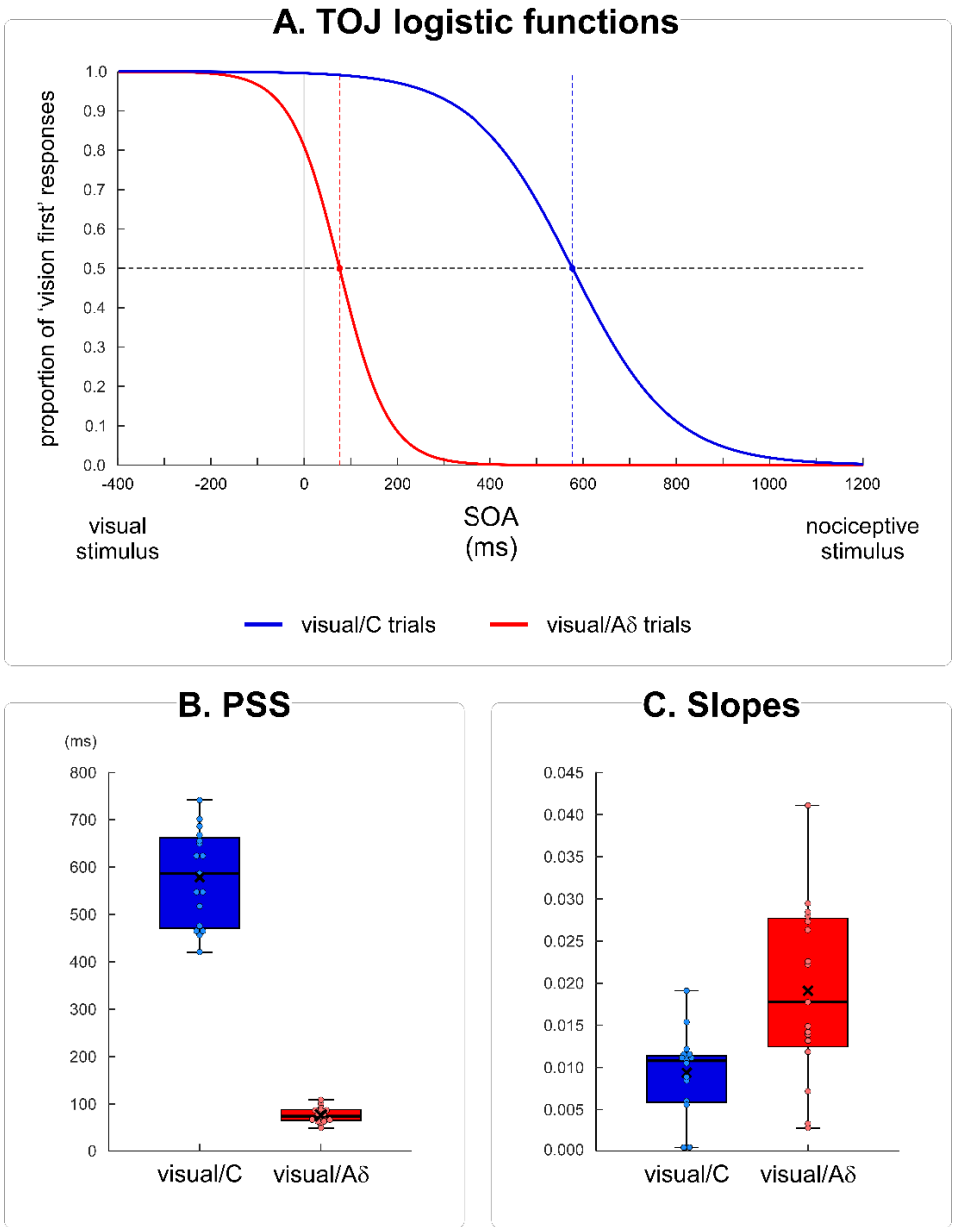

Figure 2. Results of the experiment. A logistic function was fitted to the data of each participant and condition (visual/C-stimulus, visual/Aδ-stimulus). The upper part of the figure illustrates the logistic functions plotted using the PSS and the slope values averaged across the 17 participants. The average psychometric functions for visual/C-stimuli and visual/Aδ-stimuli are shown in blue and red, respectively. X-axis: stimulus onset asynchronies between the visual and nociceptive stimuli (negative SOA values indicate that the visual stimulus preceded the nociceptive stimulus). Y-axis: proportion

of trials in which the participants perceived the visual stimulus as occurring first. The average PSS was 577 ms for visual/C-stimuli and 76 ms for visual/Aδ-stimuli. The lower part of the figure illustrates the detailed results for the PSS (left graph) and the slopes (right graph) of each condition (visual/C-stimulus, visual/Aδ-stimulus). The blue boxplots depict the results for the visual/C-stimulus conditions. The red boxplots depict the results for the visual/Aδ-stimulus conditions. For each boxplot, the bottom of the lower whisker represents the smallest value. The top of the upper whisker represents the largest value. The horizontal line in the rectangle is the median of each condition. The rectangle below the line represents the first quartile of the data. The rectangle above the line represents the third quartile of the data. The entire rectangle represents the interquartile range. The cross represents the mean of the data. Points represent the individual PSS values for the left graph and the individual slope values for the right graph.

4. Discussion

The current study explored, using the PSS of a TOJ task, the necessary asynchrony between the onset of a visual stimulus and the onset of a thermo-nociceptive stimulus activating Aδ- and/or C-fiber afferents for the two stimuli to be perceived at the same time by the participant. Indeed, sensory inputs transmitted to the cortex by the nociceptive system have far greater conduction times than sensory inputs transmitted by the visual system, especially for stimuli delivered to the distal end of a limb (i.e. when peripheral conduction distance is large), and for nociceptive inputs conveyed by unmyelinated C fibers (i.e. when peripheral conduction velocity is very slow)(Kakigi & Shibasaki, 1991; Michel et al., 2004; Opsommer et al., 1999).

Our results indicate that, for the detection of inputs conveyed by Aδ fibers (detection of nociceptive stimuli co-activating C-fiber and Aδ-fiber afferents), nociceptive stimuli delivered onto the hand dorsum should be administrated approximately 76 ms before the visual stimulus for the two to be perceived as simultaneous. For the detection of inputs conveyed by C fibers (detection of nociceptive stimuli selectively activating C fibers), the nociceptive stimulus should be delivered approximately 577 ms before the visual stimulus.

To date, this experiment is the first to have estimated the PSS between C-fiber thermo-nociceptive inputs and visual inputs. The PSS between Aδ-fiber inputs and visual inputs was already investigated by Zampini et al. (2007), in the context of different attentional settings (attention focused on the nociceptive input, attention focused on the visual input, attention divided across the two inputs). Under neutral conditions (attention divided across the two inputs), they found that the nociceptive stimulus should precede the visual stimulus by approximately 40 ms for the two to be perceived as simultaneous. This shorter PSS can partly be explained by the fact that they applied the stimuli on the forearm while we applied the stimuli on the hand dorsum, i.e. peripheral conduction distance was shorter in their study as compared to the present study. The two studies also differ according to several other stimulation

parameters likely to affect the exact PSS values obtained. The technique used to stimulate skin nociceptors and its stimulation parameters can indeed influence the time that is necessary to reach nociceptor activation and therefore, the latency of the brain response to the generated sensory inputs. In addition, Zampini et al. (2007) delivered shorter laser stimuli compared to the stimulation profile of our CO2 laser. They also matched the durations of the visual and laser stimuli. However, such parameters seem to have little impact on participants' judgments in TOJ tasks, being determined by the onsets of the stimuli (Tiippana & Salmela, 2018). Importantly, Zampini et al. (2007) reported greater inter-individual variability for the estimated PSS (ranging from -91 ms to +136 ms across 9 participants) than the PSS values estimated in the present study (ranging from 49 to 108 ms across 17 participants). The lower inter-individual variability observed in the present study could be explained by the fact that the adaptive *psi* method allows a more reliable estimation of the psychometric function even when a limited number of stimuli are used (Kingdom & Prins, 2010).

Neither the PSS for visual/C-stimuli nor the PSS for visual/Aδ-stimuli were correlated with the height of the participants, or with their arm length, both of which should be related to peripheral conduction distance. Furthermore, the significant correlation between the PSS for visual/C-stimuli and the PSS for visual/Aδ-stimuli suggests that the PSS is related to some intrinsic property specific to each participant. Low within-subject variations of PSS across different experimental conditions as compared to inter-individual variations have also been reported in visuo-auditory experiments (e.g. Stone et al., 2001), suggesting that this intrinsic property is not specific to nociception.

Interestingly, the slope of the psychometric function for visual/C-stimuli was markedly shallower than the slope of the psychometric function for visual/Aδ-stimuli. This could be related to the fact that the sensations conveyed by C-fiber inputs are typically not as sharp and brisk as the sensations conveyed by Aδ-fiber inputs (Plaghki & Mouraux, 2005).

5. Conclusions

The PSS reflects the necessary asynchrony between thermo-nociceptive and visual stimuli to optimize the conditions under which both inputs interact. Future studies in multisensory interactions must take into consideration that nociceptive inputs need markedly greater time to reach the cortex than other sensory inputs (depending to which body part the stimuli are applied), especially for inputs conveyed by C-fiber afferents. The experimental paradigm designed in this study could be used as a tool to individually estimate asynchronies between afferents from different sensory modalities.

CHAPTER 3: INVESTIGATIONS OF SPATIO-TEMPORAL ASPECTS

STUDY 3: PERCEPTUAL SIMULTANEITY BETWEEN NOCICEPTIVE AND VISUAL STIMULI DEPENDS ON THEIR SPATIAL CONGRUENCE[6]

Abstract

Visuo-nociceptive interactions depend on spatial and temporal congruency. Although they are both central for an adequate coordination between different sensory information, these factors are however usually considered separately. The current study intends to highlight the effect of spatial congruence on the perception of simultaneity of different sensory inputs. Indeed, each sensory system has its own conduction velocities so that two different concomitantly-sent stimuli should normally be perceived at different times. Participants made temporal order judgments on pairs of visuo-nociceptive stimuli. The visual stimulus was either located next to the hand on which a nociceptive stimulus was applied, in its peripersonal space, or on the other side, next to the non-stimulated hand. The required asynchrony between both stimuli for them to be perceived simultaneously was significantly smaller when they were located next to each other than when they were spatially incongruent. This effect was present both for the selective activation of thermo-nociceptive C fibers and Aδ fibers, eliciting warm or pricking sensations, respectively. We discuss the potential underlying mechanisms according to attentional and integration theories. Spatial and temporal relationships between different inputs should be examined jointly when studying visuo-nociceptive interactions, especially to understand how adaptive behaviors are optimized to respond to potential threats.

[6] Based on:
Manfron, L., Filbrich, L., Molitor, V., Farnè, A., Mouraux, A., & Legrain, V. (in preparation). Perceptual simultaneity between nociceptive and visual stimuli depends on their spatial congruence.

1. Introduction

In everyday life, our senses are constantly challenged by multiple sensory events happening in our environment. In addition, an object is often perceived through different sensory modalities. Hence, proper coordination between the different sensory modalities is crucial to optimize the combination of the different sensory inputs, generate a coherent percept, and trigger appropriate behavioral responses. This is achieved in particular by the co-occurrence of the stimuli in time (Meredith et al., 1987; Spence & Squire, 2003; Stein & Meredith, 1993) and by their proximity in space (e.g. Fairhall & Macaluso, 2009; Graziano & Cooke, 2006; Graziano et al., 1997; Spence, 2001). Although the temporal and spatial components of the different sensory inputs are closely related during multisensory interactions, they have mostly been studied separately. Considering them jointly, especially during visuo-nociceptive interactions, is relevant to understand how humans can efficiently detect and react to potentially harmful sensory events (De Paepe et al., 2014; Legrain et al., 2011).

However, given the differences between the sensory modalities, in terms of distances and latencies to transduce and transmit the sensory inputs from peripheral receptors to the cortex, binding different sensory inputs together requires compensating for the desynchronization of the times at which the different sensory afferents reach the brain. The nociceptive system, i.e. the physiological system specifically involved in the coding and processing of noxious stimuli possibly perceived as painful, consists of thinly-myelinated Aδ fibers with a conduction velocity of ~10m/s (Kakigi & Shibasaki, 1991) and unmyelinated C fibers with a conduction velocity of ~1m/s (Opsommer et al., 1999). For instance, when applying brief heat stimuli on the hand dorsum, the generated nociceptive inputs are expected to elicit their first cortical response at about 150 ms when conveyed by Aδ fibers and at almost 1 s when transmitted by C fibers (Plaghki & Mouraux, 2005). Consequently, given that visual inputs reach their first cortical relay in less than 100ms (Michel et al., 2004), when visual and nociceptive stimuli are applied concomitantly, the sensory input conveyed by nociceptive pathways may not have reached the brain yet while the visual input is already fully processed. Such difference in timing between the sensory pathways has led to experimental situations in which delays between the application of the different sensory inputs are used (e.g. Filbrich et al., 2019; Lewald & Guski, 2003) to maximize the chances that the stimuli reach the cortex in the same time-window (Colonius & Diederich, 2004; Fujisaki et al., 2012) and therefore influence the perception of each other. For instance, during an experiment aimed at investigating the influence of visual stimuli on the perception of nociceptive stimuli applied to the hand dorsum, specifically activating Aδ fibers at the detection threshold, Filbrich et al. (2019) delivered the visual

stimuli 50 ms after the nociceptive stimuli, so that they would be perceived at approximately the same time.

Recently, studies proposed to precisely and individually measure the necessary asynchrony between nociceptive and visual inputs for them to be perceived as occurring simultaneously using temporal order judgment (TOJ) tasks (Manfron, Filbrich, Nijs, Mouraux, & Legrain, 2020; Zampini et al., 2007). During these tasks, laser-induced radiant-heat and visual stimuli were administered to participants in pairs, separated by different time intervals. Participants were asked to judge which of those stimuli was perceived as presented first. Based on their responses, the point of subjective simultaneity (PSS), i.e. the asynchrony between the two stimuli at which they were judged as occurring simultaneously, was measured. In the study of Zampini et al. (2007), the thermo-nociceptive stimuli were applied on the forearm with an energy activating Aδ fibers and the visual stimuli were projected onto the same skin area. The mean PSS value was estimated at ~40 ms (under a condition during which participants' attention was equally shared between the nociceptive and visual stimuli). More precisely, the nociceptive stimulus transmitted through Aδ fibers needed to precede the visual stimulus by 40 ms on average in order for both stimuli to be perceived at the same time. By using a similar paradigm with nociceptive stimuli applied on the hand dorsum, Manfron et al. (2020a) estimated such a delay at ~76 ms. In addition, in that latter study, heat stimuli were also applied using lower energies to selectively activate ultra-slow C fibers without concomitant activation of Aδ fibers. Thermal stimuli mediated by C fibers had to precede visual stimuli by ~577 ms on average to achieve perception of simultaneity.

In these two studies, nociceptive and visual stimuli were always applied in close spatial proximity to each other, that is, the visual stimulus was projected onto or presented near the skin area on which the nociceptive stimulus was applied. Spatial congruence between sensory stimuli was indeed found to be a key feature in determining multisensory interactions (e.g. Brozzoli et al., 2014; Di Pellegrino & Làdavas, 2015; Farnè et al., 2005b; Fujisaki et al., 2012; Macaluso & Maravita, 2010; Serino, 2019; Stein & Meredith, 1993). Interactions between somatic (e.g. tactile, nociceptive) and extra-somatic (e.g. visual, auditory) stimuli are particularly enhanced when the extra-somatic stimuli occur within the peripersonal space of the body, defined as a representation of the body slightly extending in the space adjacent to the stimulated limb (e.g. Di Pellegrino & Làdavas, 2015; Serino, 2019). The peripersonal space plays a critical role in the processing of threatening stimuli as it represents the area of external space where objects can have an immediate impact on the body's integrity (e.g. Graziano & Cooke, 2006; Legrain & Torta, 2015). Accordingly, it has been repeatedly shown that nociceptive and visual stimuli mostly interact when visual stimuli are presented in the proximity of the bodily area on which the nociceptive stimuli are applied (De Paepe et al., 2017; De Paepe et al., 2014; De Paepe et al., 2015, 2016; Filbrich et al., 2017a,b; Filbrich et al., 2019; Filbrich et al., 2018; Vanderclausen

et al., 2017). Therefore, it might reasonably be assumed that the necessary time delay between nociceptive and visual stimuli for them to be perceived simultaneously depends on whether they are spatially congruent or not. For instance, studies having used TOJ or simultaneity judgment tasks between visual and tactile (Spence et al., 2003; Spence et al., 2001) or between visual and auditory stimuli (Spence et al., 2003; Zampini, Guest, et al., 2005; Zampini et al., 2003) showed that the PSS was smaller when two different sensory stimuli were delivered within the same spatial area, as compared to when they were presented at different locations. This suggests that less asynchrony is needed for stimuli of different sensory modalities to be perceived simultaneously when they are spatially congruent. Nevertheless, participants were less accurate to correctly judge the time order between the two stimuli when they were spatially congruent. This latter result was evidenced by a flattening of the slope of the psychometric functions used to fit participants' data. The slope was used to derive the just-noticeable difference (JND), i.e. the minimum amount of time necessary between the two stimuli to perceive their order accurately. The lower the discriminability, the flatter the slope of the psychometric function, and the higher the JND. The increased JND values during spatial congruent conditions would suggest that spatial proximity facilitated the interactions between the stimuli of the different sensory modalities as if they arose from a single sensory event, and, consequently, made them difficult to be perceived as distinct stimuli (Spence et al., 2003; Spence et al., 2001; Zampini et al., 2003).

The present experiment investigated, using TOJ tasks, whether the amount of time by which the nociceptive stimulus has to precede the visual stimulus for them to be perceived simultaneously depends on the spatial proximity between the two stimuli. On the one hand, we hypothesized that spatial congruency between nociceptive and visual stimuli presented in pairs would decrease the PSS between the two stimuli. On the other hand, we expected participants' judgments to be less accurate when the stimuli were spatially congruent, suggesting that proximity in space increases the difficulty to perceive them as separate stimuli. To these aims, we applied laser-induced thermal stimuli on participants' hand dorsum with an energy eliciting either responses mediated by slow-conducting Aδ fibers or responses mediated by ultra-slow-conducting C fibers. The visual stimuli were delivered by means of a white light-emitting diode placed either next to the hand on which the laser stimuli were applied or next to the opposite non-stimulated hand.

2. Methods

2.1. Participants

Thirty-seven volunteers participated in the study, randomly assigned to one of two groups. The number of participants in each group was based on previous studies having used similar experimental paradigms (e.g. Filbrich et al., 2017a,b; Manfron et al, 2020a). Exclusion criteria were non-corrected vision difficulties, any severe neurological or psychiatric diseases, cardiac problems, chronic pain disorders, trauma of the upper limbs within the lasts 6 months preceding the experiment, tissue damage or dermatological disease of the hands, regular use of psychotropic drugs, and intake of analgesic drugs (e.g. NSAIDs and paracetamol) within the 12 hours before the experiment. Having participated in the experiments of our previous study (Manfron et al., 2020a) was also considered as an exclusion criterion. The data of five participants were excluded from the analyses because of technical failures (see data analyses section). The mean age of the remaining 32 participants (19 women, 13 men) was 22.81 years (SD= ± 3.22, range 18-30). According to the Flinders Handedness Survey (Nicholls et al., 2013), 28 participants were right-handed and 4 left-handed. The local ethic committee approved the experimental procedure in agreement with the Declaration of Helsinki. All volunteers signed an informed consent prior to the experiment and received financial compensation for their participation.

2.2. Stimuli and apparatus

Visual stimuli consisted of 5-ms flashes delivered by means of a white light-emitting diode (LED) with a 17-lm luminous flux, a 6.40-cd luminous intensity, and a 120° diffusion angle (GM5BW97330A, Sharp Corporation, Japan).

Thermo-nociceptive stimuli consisted of radiant heat stimuli applied on one of the hand dorsa using a temperature-controlled CO_2 laser stimulator (10,6 μm wavelength, Laser Stimulation Device, SIFEC, Ferrières, Belgium). The laser beam was conveyed through a 10-m optical fiber ending with a head containing the optics used to collimate the laser beam to 6 mm diameter at the target site. The laser head was hold upon the participant's hand by means of an articulated arm attached to a camera tripod system (Manfrotto, Cassola, Italy). The laser head was fixed into a clamp attached to a 3-way head, allowing displacements of the laser target perpendicularly to the hand's dorsum by means of several sliders in all directions. A laser stimulus lasted 100 ms with a 10-ms heating ramp to reach the target temperature, followed by a 90-ms plateau; heating was then stopped. Laser energy was controlled in temperature measured at the skin target site by means of a radiometer in the laser head. The laser output power was thus

adapted to the online measurement of the skin temperature at the site of stimulation, to reach the specified temperature. The target temperature was individually determined according to the activation threshold of unmyelinated C fibers and thinly myelinated Aδ fibers, respectively. Thresholds were estimated using an adaptive staircase procedure (for details, see Churyukanov et al., 2012). The absolute detection threshold was used to determine detections triggered by C-fiber inputs, and reaction times (RTs) to determine detections triggered by Aδ-fiber inputs. This was done separately for each hand. To measure C-fiber activation threshold, series of laser stimuli were delivered with a starting temperature of 39°C and participants were asked to respond whether they felt or not the sensation elicited by each stimulus. When the stimulus was not reported, the temperature of the stimulus of the next trial was incremented by 0.5°C. When it was reported, the temperature was decreased by 0.5°C. The procedure lasted until four reversals were encountered. The average of the four temperatures that led to a reversal was considered as the activation threshold of C fibers. To measure Aδ-fiber activation threshold, a similar procedure was used except that RTs were used as adaptive criterion. As the conduction velocity of Aδ fibers is faster than that of C fibers (Plaghki & Mouraux, 2005), it has been shown that a cut-off of 650 ms effectively discriminates the responses elicited by the activity of Aδ fibers and C fibers respectively, during stimulation of the hand dorsum (Churyukanov et al., 2012). The participants were thus required to press on a button as fast as possible when they felt the stimulus. They held the button in the hand opposite to the one on which laser stimuli were applied. The first stimulus was delivered with a temperature of 46°C. When RTs were greater than or equal to 650 ms, the temperature of the stimulus of the next trial was increased by 0.5°C. When RTs were smaller than 650 ms, the temperature was decreased by 0.5°C. After four reversals, the procedure was stopped and the average of the four temperatures that led to a reversal was considered as the activation threshold of Aδ fibers.

Individual detection thresholds were used to determine, for each participant, the target temperature of the stimuli used during the TOJ task. To avoid overheating of participants' hands and habituation, only one type of fibers was tested for each participant. Half of the participants were presented to stimuli activating only C fibers, while participants of the other group were presented to stimuli eliciting sensations compatible with the activation of Aδ fibers. For each participant of the C-fiber group, the two threshold measurement procedures described above were applied, and the estimated threshold values for C and Aδ fibers were averaged to obtain the target temperature value. At such intensity, stimuli were expected to activate C-fiber afferents without concomitantly activating Aδ-fiber afferents. For each participant of the Aδ-fiber group, only the procedure to determine the Aδ-fiber activation threshold was used, and the experimental target temperature was set 5°C above the Aδ-fiber activation threshold to ensure the stimulation of Aδ fibers without producing any burn lesions (for details, see Lenoir, Algoet, et al., 2018). Participants were asked to qualify the elicited sensation using a list of descriptor words (see Nahra & Plaghki, 2003) to ensure that it

was compatible with the activation of the target fiber. Accordingly, participants of the C-fiber group qualified the sensation elicited by stimuli of the target temperature as warm, while participants of the Aδ-fiber group qualified the sensation as pricking.

2.3. Procedure

During the experiment, participants sat on a chair in front of a table in a lighted room. A fixation cross was located on the table surface, in alignment with their midsagittal plane, pasted at 40 cm from their trunk. They were asked to place their hands palms down on the table, with the metacarpophalangeal joint between each index finger and the thumb located 1 cm from two landmarks. The landmarks were separated by 30 cm from each other along a line perpendicular to participants' midsagittal plane, at 30 cm from their trunk. At equal distance from each landmark (~18 cm), 10 cm above the perpendicular line, participants gazed at the central fixation cross. The white LED was pasted on one of the two landmarks according to the tested condition and the experimental blocks (see Fig. 1).

The TOJ task consisted of 4 blocks of 40 trials each. A trial consisted of a pair of one visual stimulus and one laser stimulus delivered at the target temperature determined according to the group to which they had been assigned (i.e. eliciting sensation compatible with either C-fiber or Aδ-fiber activation). Before the task, two pairs of stimuli were administered to all participants to get familiarized with the task and the sensation elicited by the activation of the specific fibers. Their performance was not recorded. During the task, the laser stimuli were applied on the left hand during two blocks, and on the right hand during the two other blocks (see below). For each hand, the trials of one block were delivered with the visual stimulus presented next to the hand receiving the laser stimulus (ipsilateral condition). During the other block, the visual stimulus was presented next to the opposite hand, i.e. the non-stimulated hand (contralateral condition; Fig. 1).

A trial started with a warning signal from the experimenter. Approximatively 500 ms later, the first stimulus of the visuo-nociceptive pair was delivered, followed by the second stimulus according to different stimulus onset asynchronies (SOAs). For the C-fiber group, stimuli were separated by 16 possible SOAs: +100, +220, +270, +320, +370, +420, +460, +490, +510, +540, +580, +630, +680, +730, +780, +900 ms. For the Aδ-fiber group, there were 14 possible SOAs: ±200, ±150, ±100, ±80, ±60, ±40, ±20 ms. Positive values indicate that the laser stimulus was applied before the visual stimulus, negative values indicate that the visual stimulus was presented before the laser stimulus. The laser stimulus always preceded the visual stimulus in the C-fiber group, because of the ultra-slow latency of responses to C-fiber stimuli. Also, the number of possible SOAs was larger in that group because of the much larger variability of the responses during trials with C-fiber stimuli, as compared to trials with Aδ-fiber stimuli (see Manfron et

al., 2020a). The to-be-presented SOA was determined at each trial using the adaptive *psi* method considering the participant's responses to all previous trials of the block (Kingdom & Prins, 2010). Based on a Bayesian framework, this adaptive procedure estimates the posterior distribution of the parameters of interest by minimizing their expected entropy (i.e. uncertainty) trial by trial, so that the SOA selected at each trial gives the most information to estimate the parameters of interest without probing extensively all the possible SOAs (for further details about the use of the psi method in the context of TOJ tasks, see Filbrich, Alamia, Burns, et al., 2017).

For each trial, participants were asked to judge which of the visual or the thermo-nociceptive stimulus they perceived as occurring first during two blocks, one for each laterality condition (i.e. visual stimulus ipsilateral vs. contralateral to the hand receiving the laser stimulus). During the two other blocks, they were asked to report which stimulus of the pair was perceived as second. Alternating "*which is first"* vs. *"which is second"* responses was intended to avoid response biases (Filbrich, Torta, Vanderclausen, Azañón, & Legrain, 2016). Within each of the two groups, half of the participants of each group responded to "*which is first"* with the laser stimuli applied to the left hand and to "*which is second"* with the laser stimuli applied to the right hand. The reverse was done for the other half of participants. Judgments were reported verbally, with no speed requirement, by using the words '*visual*' or '*laser*'. The order of the four blocks was counterbalanced for each participant. Once the experimenter encoded the participants' response (by pressing a key of the remote-control computer), the next trial started 2000 ms later.

In order to verify that the used temperatures elicited appropriate sensations related to C fibers or Aδ fibers respectively, participants qualified after each trial their perception using a list of descriptor words (Nahra & Plaghki, 2003). A trial was discarded and repeated if the laser stimulus was not perceived, if the C-fiber laser stimulus was qualified as pricking, or if the Aδ-fiber laser stimulus was qualified as warm. Each block lasted approximately 5 minutes. After each block, there was a short break period during which the LED was displaced to the landmark next to the other hand. The entire experiment, including instructions and threshold measurements, lasted about 1 hour and a quarter.

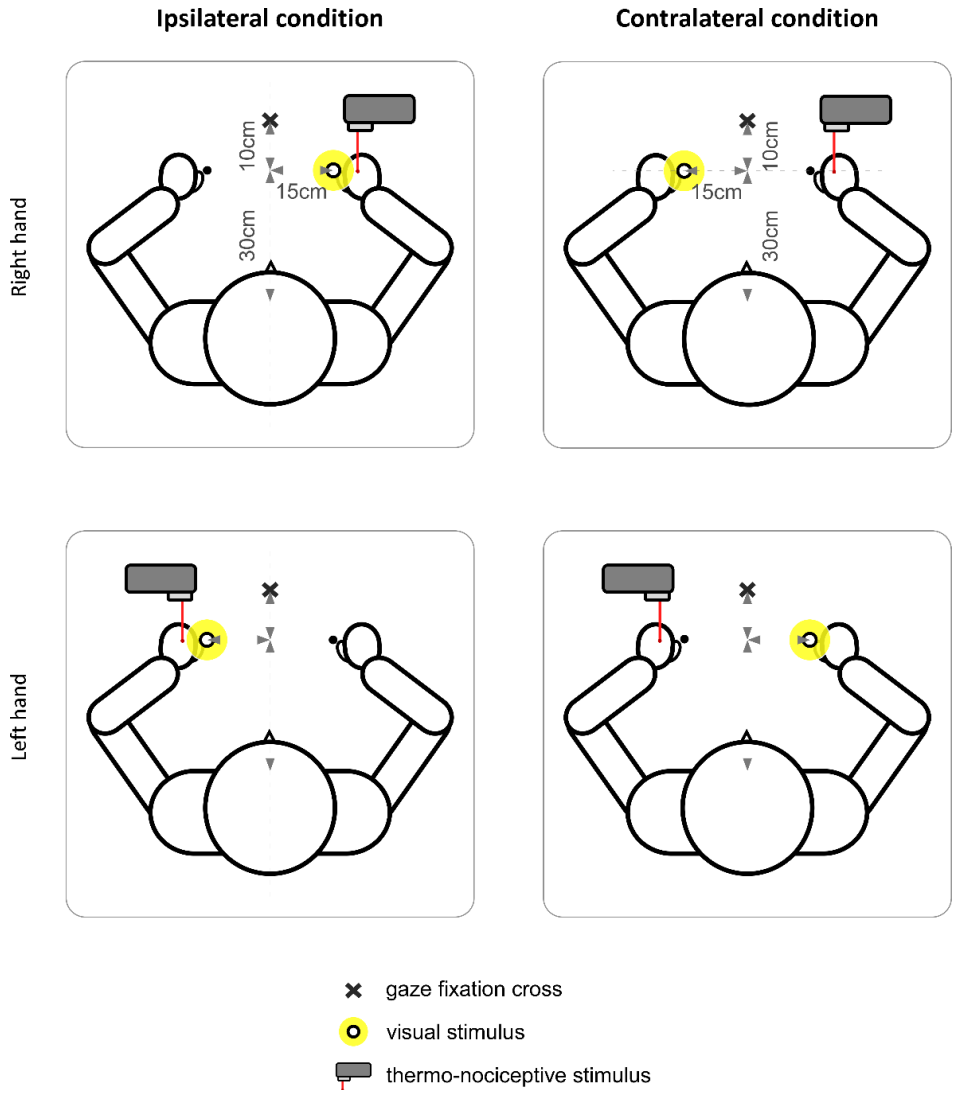

Figure 1. Design of the experiment. Participants performed temporal order judgments (TOJ) on pairs of thermo-nociceptive (CO2 laser illustrated by the red laser beam) and visual (target LED, illustrated by the yellow circle with whiter halo) stimuli. One group only received thermo-nociceptive stimuli eliciting responses of C fibers whereas the other group received nociceptive stimuli eliciting Aδ-fiber responses. In the ipsilateral condition, the visual stimulus was located next to the stimulated hand. In the contralateral condition, the visual stimulus was located next to the non-stimulated hand, contralateral to the stimulated hand. One hand was stimulated at a time. Participants were seated on a chair, palms' down on a table at ~30cm from the trunk, 15 cm on either side of a fixation cross, and fixed their gaze at the cross during the stimulations. The figure depicts the different laterality conditions for the right hand and for the left hand.

2.4. Measures

Activation threshold and target temperature values of laser stimuli were measured in degrees Celsius.

To estimate TOJ performance, the proportion of thermo-nociceptive stimuli perceived as being presented first was computed as a function of the SOAs for each experimental condition. TOJ parameters were estimated by a logistic function $f(x)=1/(1+exp(-\beta(x-\alpha)))$ at each trial (Kingdom & Prins, 2010). Analyses were made on the last estimates of the block, corresponding to the last update of the adaptive procedure. The main parameter of interest was the α value, corresponding to the threshold of the function which characterizes the point of subjective simultaneity (PSS), that is, the SOA at which the thermo-nociceptive stimulus and the visual stimulus are perceived as occurring first equally often (i.e. the 0.5 criterion on the ordinate; Fig.2). Accordingly, the PSS was used as a measure of the amount of time that was needed between the thermo-nociceptive stimulus and the visual stimulus in order for them to be perceived as occurring simultaneously (Spence et al., 2001). Based on Manfron et al. (2020a), its prior estimates were set to 500±200 ms for the C-fiber group and 70±20 ms for the Aδ-fiber group. The β value was analyzed as second parameter of interest. It corresponds to the slope of the psychometric curve and describes the noisiness of the results, i.e. the variability of participants' responses during the experiment (Kingdom & Prins, 2010). Lower and higher abilities to discriminate the temporal order of the two stimuli is represented by lower and greater values of β, respectively. Its prior estimates were set to 0.06±0.6 for both fiber groups.

2.5. Data analyses

Five participants were discarded from the analyses due to technical failures and/or excessive habituation that affected participants' ability to perceive the laser stimuli during the experiment, resulting in high variability in their responses during the TOJ task, as evidenced by flat slopes. Statistical analyses were conducted with IBM SPSS 23. First, we tested whether activation threshold and target temperature values were similar between the two hands by using paired sample t tests for each fiber group. Next, before analyzing TOJ data, data from the two response modalities ("*which is first*" vs. "*which is second*") were averaged for each laterality condition (ipsilateral vs contralateral) and each group (Aδ fibers vs C fibers). Since the response modality depended on the stimulated hand (see above), difference in terms of which hand – left or right – was stimulated was skipped from analyses. Resulting PSS and slope values were then compared using analyses of variance (ANOVAs) for repeated measures with the laterality as within-subject factor (ipsilateral vs. contralateral) and the group as between-subjects factor (C-fiber vs. Aδ-fiber). Effect sizes were measured by means of

partial Eta squared for ANOVAs and Cohen's d for t tests. If necessary, contrast analyses were performed. Significance level was set at p-value < 0.05. Data are expressed in means plus or minus standard deviation (M±SD).

3. Results

3.1. Activation threshold and target temperature values

Comparisons of the threshold values between the two hands did not reveal significant differences neither in the C-fiber group (left hand: 39.94±1.31°C; right hand: 39.78±1.67°C; $t(15) = 0.47$, $p = 0.642$, d = 0.12), nor in the Aδ-fiber group (left hand: 47.47±2.00°C; right hand: 47.92±2.36 °C; $t(15) = -0.99$, $p = 0.337$, d = -0.25). These values are in the range of the temperatures usually associated with C-fiber and Aδ-fiber afferent activation, respectively (Churyukanov et al., 2012; Plaghki et al., 2010). Consequently, the target temperature values used during the experiment were not different between the left and the right hands for both the C-fiber group (left hand: 44.25±1.24°C; right hand: 44.50±1.63°C; $t(15) = -0.89$, $p = 0.388$, d = -0.22) and the Aδ-fiber group (left hand: 52.31±2.02 °C; right hand: 52.69±1.89 °C; $t(15) = -1.695$, $p = 0.111$, d = -0.42).

3.2. TOJ values

The ANOVA performed on the PSS values showed a significant main effect of the group factor ($F(1,30) = 240.17$, $p < 0.001$, $\eta^2_p = 0.89$), confirming that PSS between visual and thermo-nociceptive stimuli was dependent on the type of stimulated thermo-nociceptive fiber. The ANOVA also revealed a significant main effect of *laterality* ($F(1,30) = 10.65$, $p = 0.003$, $\eta^2_p = 0.262$) with no significant interaction with the *group* factor ($F(1,30) = 2.337$, $p = 0.137$, $\eta^2_p = 0.072$). This suggests that the location of the visual stimulus relative to the hand receiving the thermo-nociceptive stimuli affected the PSS in a similar fashion for the two subtypes of thermo-nociceptive stimuli applied (see Fig. 2 and 3). When C fibers were stimulated, PSS values were almost 40 ms greater when the visual stimulus was presented contralaterally to the stimulated hand, as compared to when it was presented ipsilaterally (ipsilateral: 501.22±121.39 ms; contralateral: 539.02±108.74 ms). Such difference was ~12 ms when the Aδ fibers were stimulated (ipsilateral: 79.16±13.38 ms; contralateral: 92.84±18.98 ms).

Regarding the slope values, the ANOVA did not reveal a significant main effect of *laterality* ($F(1,30) = 1.54$, $p = 0.224$, $\eta^2_p = 0.05$). On the contrary, there was a significant main effect of the *group* (F=8.51, p = 0.007, $\eta^2_p = 0.22$) as well as a significant interaction

between the two factors ($F(1,30) = 4.48$, $p = 0.043$, $\eta^2_p = 0.13$). Contrasts analyses revealed that, when the visual stimulus was presented contralaterally to the stimulated hand, the slope value was smaller in the group of participants in whom the thermo-nociceptive stimuli only activated C fibers than in the group of participants in whom it also activated Aδ fibers (see Fig. 2 and 3; C fibers: 0.012±0.008; Aδ fibers: 0.074±0.077; $t(15.337) = 3.20$, $p = 0.006$, d = 1.13). Such a difference was not significant when the visual stimulus was ipsilateral to the stimulated hand (C fibers: 0.037±0.045; Aδ fibers: 0.022, SD = 0.039; $t(30) = 1.00$, $p = 0.321$, d = 0.36). The difference of the slope values between the ipsilateral and the contralateral conditions was not significant, neither in the C-fiber group ($t(15) = 0.99$, $p = 0.339$, d = 0.25), nor in the Aδ-fiber group ($t(15) = -1.87$, $p = 0.081$, d = -0.47).

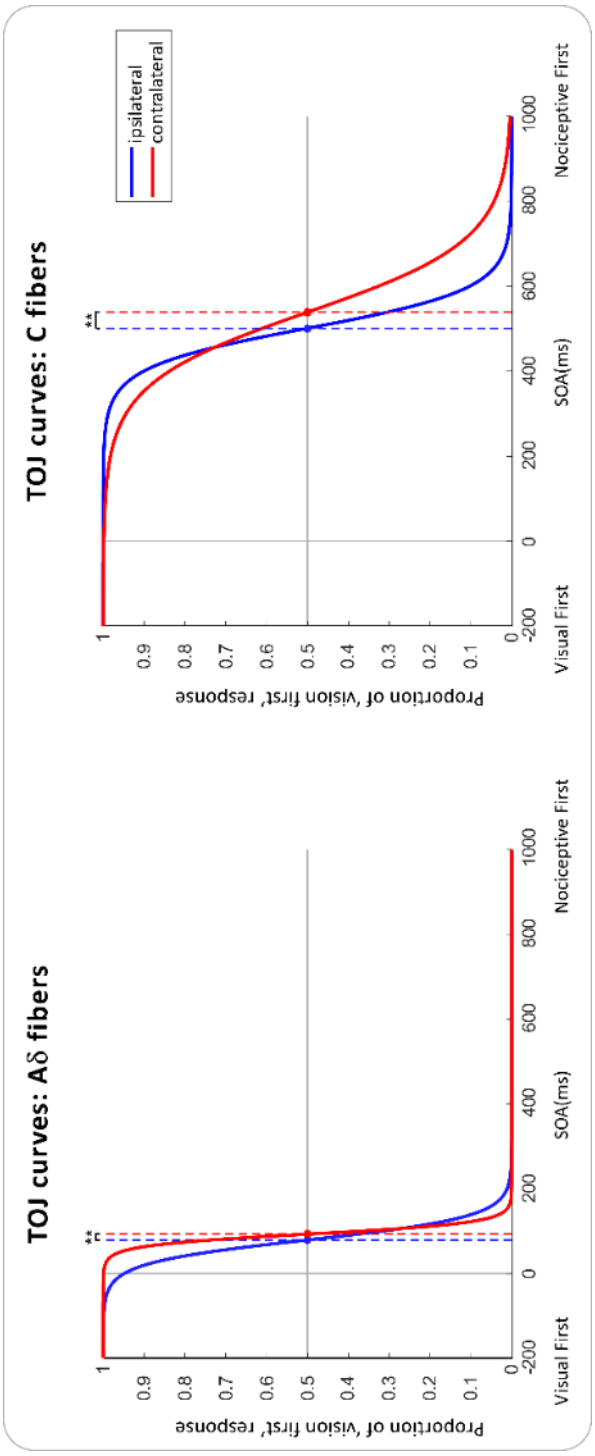

Figure 2. Results. Each graph illustrates the averaged results for the 16 participants of each group. The left figure depicts the fitted logistic functions for the Aδ -fiber group. The right figure depicts the fitted logistic functions for the C-fiber group. The x-axis represents different hypothetical stimulus onset asynchronies (SOAs) between the visual and the nociceptive stimuli: negative values indicate that the visual stimulus was presented first, while positive values indicate that the nociceptive stimulus was presented first. The y-axis represents the proportion of trials in which the participants perceived the visual stimulus first. For both graphs, the blue curve illustrates the condition in which the visual stimulus was presented on the ipsilateral side of the nociceptive stimulus. The red curve illustrates the condition in which the visual stimulus was presented on the contralateral side of the nociceptive stimulus. In both graphs, the asterisks represent the significant differences ($p \leq 0.01$) between the ipsilateral and the contralateral conditions. The visual stimulus always needed to be administered before the nociceptive stimulus. In addition, the PSS of the contralateral condition was larger than the PSS of the ipsilateral condition, for both fiber groups.

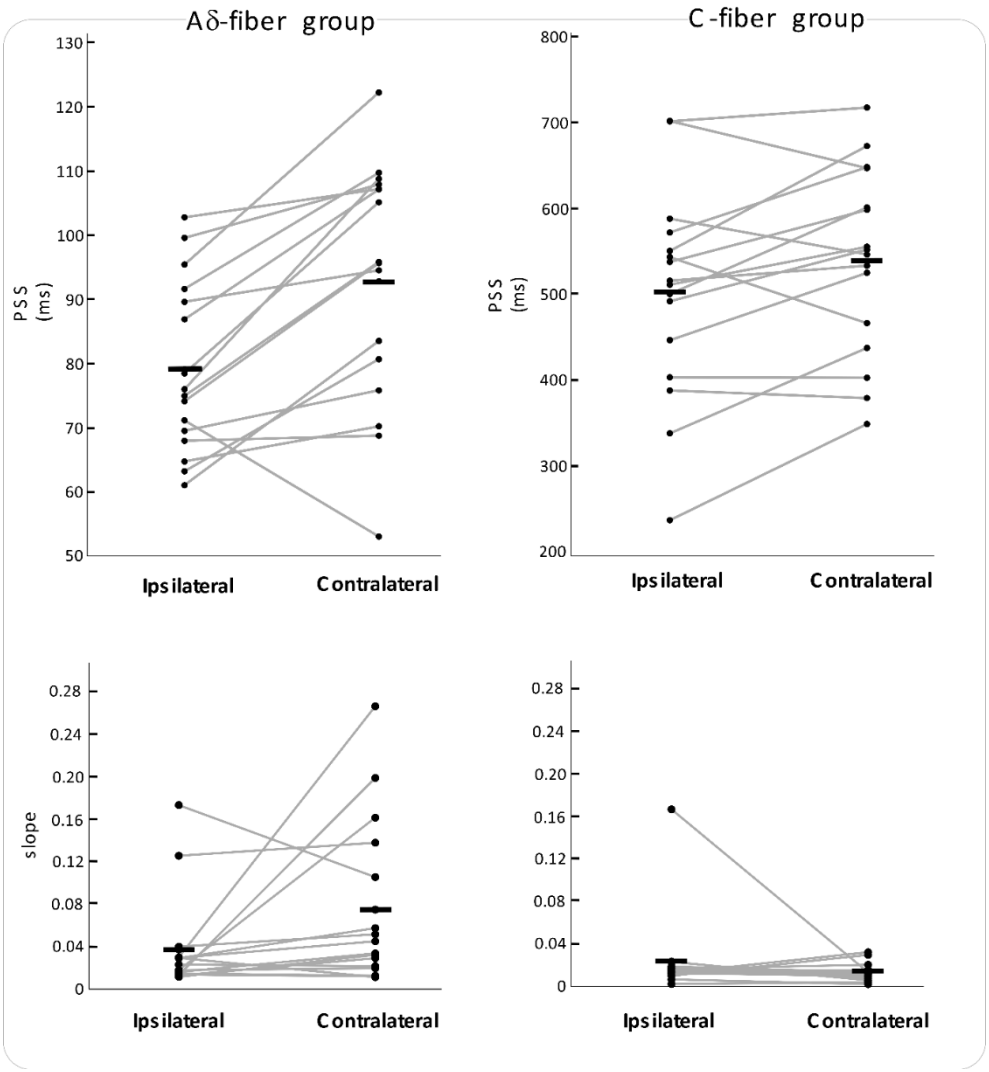

Figure 3. Individual PSS and slope values per group. The figure shows scatter plots displaying individual PSS values (on the top) and individual slope values (on the bottom), represented by the black dots, for each group (Aδ vs C-fiber) according to the visual condition (ipsilateral vs contralateral). The black strips show the means of each parameter. Data of the same participant are linked by a line.

4. Discussion

Efficient multisensory interactions depend on the temporal co-occurrence between stimuli of the different sensory modalities (e.g. Macaluso et al., 2016; Meredith et al., 1987; Morein-Zamir et al., 2003; Spence & Squire, 2003; Stein & Meredith, 1993; Sugita & Suzuki, 2003). It is however a challenge for the brain to resynchronize the different sensory inputs that arrive at the cortical level with different time delays (e.g. Colonius & Diederich, 2004; Fujisaki et al., 2012; Meredith et al., 1987; Spence & Squire, 2003), since they are conveyed through distinct sensory pathways with different distances from their respective receptors and different conduction velocities. Using temporal order judgment (TOJ) tasks, previous studies showed that, in order to be perceived as occurring simultaneously, a thermo-nociceptive stimulus conveyed by slow-conducting Aδ fibers needs to precede a visual stimulus by ~40 ms when applied on the forearm (Zampini et al., 2007). Manfron et al. (2020a) evidenced a delay of ~76 ms with heat stimuli eliciting Aδ-fiber activity applied on the hand dorsum and showed that it increases up to ~577 ms when the heat stimuli were selectively conveyed by ultra-slow C fibers. Since the spatial proximity, that is, whether the different stimuli are delivered at the same location or not, has been shown to alter their perception of simultaneity (Spence et al., 2003; Spence et al., 2001; Zampini, Guest, et al., 2005; Zampini et al., 2003) and their multisensory interactions (e.g. De Paepe et al., 2014; Di Pellegrino & Làdavas, 2015; Filbrich et al., 2017b), the present study investigated whether the time intervals observed in previous studies (Manfron et al., 2020a; Zampini et al., 2007) could be influenced by the spatial position of the visual stimuli relative to the limb on which the thermo-nociceptive stimuli are applied.

Participants performed a TOJ task between visual and thermo-nociceptive stimuli applied on the hand dorsum and eliciting responses conveyed by either Aδ or C fibers. The visual stimulus was presented at a location either near the hand on which the thermo-nociceptive stimulus was applied (ipsilateral condition) or near the opposite non-stimulated hand (contralateral condition). Regardless of which sub-type of thermo-nociceptive fibers was activated, the results showed that the point of subjective simultaneity (PSS) between the visual and the thermo-nociceptive stimuli was significantly smaller in the ipsilateral conditions. These results are in agreement with those of other studies having recurrently shown that the nociceptive and visual stimuli mostly interact when the visual stimuli are presented within the peripersonal space of the participants and, more specifically, in the close vicinity of the limb on which the nociceptive stimuli are applied, whatever the position of the stimulated limb in external space and the visual field in which the visual stimuli appear (De Paepe et al., 2015, 2017; De Paepe et al., 2014; Filbrich et al., 2017a,b; Filbrich et al., 2018; Vanderclausen et al., 2017). The present results are also in line with the studies having shown that the perception of simultaneity between visual and tactile (Spence et al., 2003; Spence et al., 2001) and between visual and auditory stimuli (Spence et al., 2003; Zampini, Guest, et

al., 2005; Zampini et al., 2003) can be influenced by the spatial distance between the stimuli.

Two hypotheses can be proposed to explain the effect of spatial congruence on the perception of simultaneity between stimuli of different sensory modalities. First, according to the attention-switching hypothesis, when the stimuli of the task are not located next to each other, participant's attention must be shifted from the location of the first stimulus of the pair to the location of the second stimulus to correctly judge their temporal order (Spence, 2001; Zampini et al., 2003). In other words, the greater PSS values observed in the contralateral condition would reflect the cost of shifting attention from one location to another. On the contrary, in the ipsilateral condition, participants must only focus on one single location to meet the requirements of the task, improving the interactions between the stimuli as compared to the contralateral condition, and leading to smaller PSS values. Furthermore, in accordance to the prior-entry effect (e.g. Spence, 2001; Spence & Parise, 2010; Titchener, 1908; Filbrich et al., 2017a), it could also be that the first stimulus of the pair has actually attracted attention to its own location, having facilitated the processing of the second stimulus when it occurred at the same location, as compared to when it appeared on the opposite side of space.

Second, according to multisensory integration hypothesis, presenting two sensory stimuli simultaneously – or at least within a similar time-window – at the same location increases the likelihood to bind them together and perceive them as one unique and coherent sensory event, as compared to when they are presented at different location (e.g. Spence, 2001; Spence & Squire, 2003; Stein & Meredith, 1993; Welch, 1999). In the frame of TOJ tasks, the tendency of merging the stimuli into a single integrated percept would speed up their processing. This integration would seem relatively automatic given that, by judging the temporal order of the two stimuli, participants are explicitly asked in those tasks to perceive them as two distinct sensory events. In turn, the disadvantage of integrating the two stimuli would also make it difficult to dissociate them as two distinct events, decreasing the accuracy for judging their temporal order. On the contrary, presenting the stimuli at distinct locations would increase their discriminability and lead to better performances. This was indeed shown in previous TOJ studies by higher JND values (i.e. slopes were flatter) when the two stimuli were delivered at the same location, as compared to when they were presented at distinct locations, supporting the integration hypothesis (Spence et al., 2003; Spence et al., 2001; Zampini et al., 2003). However, in the present study, no significant differences were observed for the slope values between the conditions during which visual and nociceptive stimuli were presented at the same location and those during which they were presented at opposite locations. This suggests that accuracy was not affected by the spatial congruence between the two stimuli. One difference as compared to previous studies is the method that was used. In the previous studies, the different time intervals between the two stimuli (i.e. SOAs) were presented using a constant

stimulation procedure, and slopes were estimated from the straight lines that fitted best the participant's responses. In the present study, SOAs were presented according to an adaptive procedure, and the last estimate of the slope values of the logistic function were used to evaluate participant's responses. Yet, the use of different methods is unlikely to explain the differences between the results of present vs. previous studies. Indeed, the different estimates of the slope values of the TOJ functions seem usually similarly sensitive to the same factors, whatever the methods used to present the stimuli to fit the participants' responses and to derive the slope values of the TOJ functions (Heed & Azañon, 2014; Vanderclausen, Filbrich, De Volder, & Legrain, accepted). In our case, it could rather be that visuo-nociceptive stimuli do not automatically integrate as much as visuo-auditory or visuo-tactile modalities, due to the rarer occurrence of noxious stimuli in daily life and the motivation of individuals to avoid them as much as possible. Alternatively, it could be due to the putative attentional mechanisms explaining the smaller PSS values during the spatial congruent conditions compared to the incongruent conditions.

Only one significant difference between slope values was observed when comparing the performance of the participants having received thermo-nociceptive stimuli selectively inducing C-fiber responses to those having received nociceptive stimuli above the threshold of Aδ fibers, but only when the visual stimuli were presented contralaterally to the stimulated hand. This could possibly be accounted for by the fact that the sensation evoked by C-fiber stimulations is often considered as being poorly defined in terms of location and timing compared to the sensation elicited by Aδ-fiber stimulations (Plaghki & Mouraux, 2005) making temporal order judgments more difficult (Manfron et al., 2020a). However, this does not explain why the difference was present only during the contralateral condition.

In everyday life, the different sensory inputs arising from the same object generally stimulate their respective receptors at the same time and, although the generated inputs are transmitted to the brain with different latencies, we are still able to perceive them as simultaneous. The lag between each input is not perceived as long as they fall within the same time-window of interactions, that tolerate a margin of error (e.g. Colonius & Diederich, 2004; Fujisaki et al., 2004; Morein-Zamir et al., 2003; Spence & Squire, 2003; Sugita & Suzuki, 2003). However, it is not possible to determine the extent of this time-window of interactions for a given situation since it varies according to many different factors, such as the sensory modality of the inputs, their implied link of causality, their spatial congruence, the attention allocated to them, the memory of past experiences as well as the respective intensity and duration of the stimuli (Colonius & Diederich, 2004; Fujisaki et al., 2012; Meredith et al., 1987; Stein & Meredith, 1993). There are two hypotheses that have been put forward to explain how such temporal binding of stimuli of different sensory modalities within that time-window is achieved. Whereas some authors suggested a resynchronization of the input of each sensory modality on the basis of the speed of their respective afferents (e.g. Colonius &

Diederich, 2004), others rather proposed an overlapping of the discharge trains of multisensory neurons elicited by each sensory input, as suggested by electrophysiological recordings of single cells in the superior colliculus of the cat (Meredith et al., 1987).

Finally, since under normal circumstances, multisensory interactions are shaped by past experiences and often concern different inputs that arise from the same sensory event (e.g. Macaluso et al., 2016; Welch, 1999), under experimental conditions using sensory stimuli that are rarely associated together, a temporal lag might be introduced between the different stimuli for the participants to perceive them simultaneously. It is also worth noting that multisensory research often used brief stimuli with sharp onset, while in more ecological environmental situations, multisensory interactions are also supported by long-standing stimulations. The techniques used in present and previous studies about visuo-nociceptive interactions mostly generated responses of the quickly-responding cutaneous thermo-nociceptors. Other thinly-myelinated and unmyelinated fibers are more slowly-adapting and respond preferentially to sustained stimulation profiles (Bromm & Treede, 1984; Meyer & Campbell, 1981; Schepers & Ringkamp, 2010; Treede et al., 1998; Treede et al., 1995). It might be relevant to use other stimulation procedures to investigate interactions between sustained nociceptive and visual stimuli.

In conclusion, the present study demonstrated that presenting visual and thermo-nociceptive stimuli at the same location decreases the necessary time lag between the two stimuli to perceive them as simultaneous. However, contrary to previous studies, spatial congruency did not affect participants' ability to perceive them as distinct sensory events. These results might support the hypothesis of an involvement of attentional rather than integrative mechanisms to judge the temporal order of visuo-nociceptive stimuli according to their spatial congruence. Alternatively, because of the specific nature of pain for the deployment of adaptive behaviors, such interactions could be underpinned by different mechanisms than those underlying interactions between other sensory modalities. Future investigations could exploit the influence of the spatial position of a visual stimulus on its interaction with a nociceptive stimulus to develop, in a larger extent, non-drug interactions that could modulate painfulness. It has for example been shown that the number of detections of nociceptive stimuli activating Aδ fibers at their threshold can be increased or decreased according to the spatial position of visual stimuli (Filbrich et al., 2019). Whether the spatial position of visual stimuli can modulate the detection threshold itself could be investigated separately for inputs conveyed by Aδ and C fibers to the cortex. In this vein, the current experiment could be used to implement the individual PSS between the visual and thermo-nociceptive stimuli, according to their spatial position and for both Aδ- and C-fiber types, to optimize their respective visuo-nociceptive interactions.

STUDY 4: THE IMPACT OF THE SPATIAL POSITION OF A VISUAL STIMULUS ON THE THERMO-NOCICEPTIVE THRESHOLDS OF C AND Aδ FIBERS

Abstract

Visuo-nociceptive interactions enable to develop defensive actions against potential threats, especially when inputs elicited by the threat originate from the same location, close to the body, and at the same time. The current study experimentally combines such conditions to assess if extra-somatic information is able to modulate the detection threshold of inputs transmitted through thermo-nociceptive C vs Aδ fibers. In Experiment 1, participants received laser stimuli, eliciting selectively C-fiber responses and Aδ-fiber responses, alone or accompanied by visual stimuli located either ipsilateral or contralateral to the stimulated hand. In Experiment 2, participants received laser stimuli, eliciting selectively C-fiber responses and Aδ-fiber responses, accompanied by visual stimuli located either ipsilateral, contralateral or far from the stimulated hand. The perception of simultaneity between visual and laser stimuli was optimized by estimating the individual asynchrony in each participant for each fiber type. Thermo-nociceptive thresholds of each fiber type were estimated separately according to the spatial position of visual stimuli, using the *psi-marginal* adaptive method. In Experiment 1, although significant differences emerged during the stimulation of Aδ fibers, methodological issues prevented correct interpretation of the data. In Experiment 2, results suggest that the thermo-nociceptive threshold of Aδ fibers was decreased by visual stimuli located next to the hand receiving the laser stimuli, as compared to when visual stimuli were presented in the other side of space. Spatial and temporal congruence facilitated the perception of the laser stimuli, increasing the sensitivity of the participants. This indicates that the detection threshold of the nociceptive system can be modulated by extra-somatic sensory information. No effect of the visual stimulus on C-fiber thresholds was observed in any of the experiments. The results are discussed according to spatial attention and multisensory integration theories.

1. Introduction

Pain is usually generated by the activity of the nociceptive system, a physiological system specialized in coding, transmitting, and processing information about noxious sensory events (Le Bars & Plaghki, 2009). Nociceptive inputs transmitted to the brain trigger the activity of an extensive network of cortical regions whose function would be to prioritize the processing of any sensory stimulus meaningful for the integrity of the body in order to provide an appropriate response, as for example defensive reactions against physical threats (Legrain et al., 2011). Reacting effectively to a danger requires therefore to be able to locate which part of the body is potentially harmed as well as the source of the harmful object in the external space surrounding the body (Vanderclausen, Bourgois, et al., 2020; Vanderclausen, Manfron, et al., 2020). To do so, the somatic information occurring on the skin, i.e. touch & nociception, is remapped with the extra-somatic information occurring in the surroundings, i.e. vision & hearing, in a common representation, the peripersonal space. The peripersonal space refers therefore to a multisensory representation of external objects in contact with the body, that slightly extends to the external adjacent space (Legrain & Torta, 2015).

Accordingly, it has been shown that nociceptive and visual stimuli interact, that is, they influence the perception of each other, particularly when the visual stimuli are presented near the body-limb on which the nociceptive stimuli are applied (De Paepe et al., 2015; De Paepe et al., 2014; Filbrich et al., 2017a). Neither the position of the stimulated limb in external space (De Paepe et al., 2017; Filbrich et al., 2017b) nor the part of the visual field in which the stimulated limb or the nearby visual stimuli are seen modulates the level of interactions between the visual and nociceptive stimuli (Filbrich et al., 2018). This confirms the ability of the brain to represent and perceive a restricted portion of the visual space that is anchored to the body part in pain. However, most of the aforementioned studies have investigated visuo-nociceptive interactions to identify the underlying mechanisms of the *localization* of nociceptive stimuli on the body, while other potential effects of these interactions, as on the *detection* of nociceptive stimuli, have been largely overlooked.

Hence, we were interested in the impact of the spatial position of a visual stimulus on the processing of nociceptive stimuli while optimizing their perception of simultaneity. In a previous study, the occurrence of visual stimuli increased the probability to detect nociceptive stimuli presented at their absolute detection threshold, when located close to the stimulated hand. In contrast, when the visual stimuli were presented on the other side of space, near the non-stimulated hand, that probability decreased (Filbrich et al., 2019). Here we investigated the impact of visual stimuli on the detection threshold itself of inputs transmitted through the thermo-nociceptive fibers. In other words, we examined whether the location of visual stimuli

can impact the minimal intensity at which the generated inputs were detected by the brain. Whereas most of previous studies investigated multisensory interactions with responses mostly elicited by the activation of Aδ fibers, we used a procedure allowing to dissociate and investigate separately responses to Aδ vs. C fibers. It was hypothesized that the concomitant perception of visual stimuli near the stimulated hand would decrease the detection threshold of each type of nociceptive fiber, as compared to when they were presented far from it. On the contrary, the concomitant perception of visual stimuli near the non-stimulated hand would increase the detection threshold of each fiber type.

In addition to spatial proximity, as stimuli from different modalities are more prone to arise from the same object when they are perceived at the same time, it has been shown that multisensory interactions are enhanced when stimuli are perceived simultaneously, or at least within a restricted time-window (Colonius & Diederich, 2004; Meredith et al., 1987). However, given that transmission distances from respective receptors to the brain, as well as conduction velocities, are variable across the different sensory modalities, the simultaneous application of brief stimuli might generate lags between their respective times of arrival. This is especially the case for the nociceptive system, due to the slow and ultra-slow conduction velocities of the Aδ and C fibers respectively, as compared to the visual system. Some authors therefore desynchronized the application of each stimulus to compensate for these potential lags (Filbrich et al., 2019). More recently, using temporal order judgment (TOJ) tasks, we have shown that a visual stimulus has to follow a laser-induced heat stimulus by ~76 ms for nociceptive inputs transmitted through Aδ fibers and by ~577 ms for inputs transmitted through C fibers, in order to be perceived at the same time (Manfron et al., 2020a). In the present study, during preliminary phases to the threshold assessment of the activation threshold of nociceptive fibers, we used that method to estimate individually the asynchrony that was necessary between the onsets of the nociceptive and visual stimuli for both to be perceived simultaneously. This procedure was applied separately for responses elicited by the activation of Aδ-fiber afferents and responses elicited by the selective activation of C-fiber afferents. Based on these individual estimates, the presentation of the visual stimulus relatively to that of the nociceptive stimulus was delayed during the threshold measurement experiments, with the aim of matching arrival times of the nociceptive and visual inputs, and optimize their interactions.

2. Experiment 1

2.1. Materials and methods

2.1.1. Participants

Twenty-three volunteers participated in the study. Exclusion criteria were non-corrected vision difficulties, any neurological, cardiac, psychiatric and chronic pain disorder, trauma of the upper limbs within the lasts 6 months preceding the experiment, tissue damage or dermatological disease of the hands, regular use of psychotropic drugs and intake of analgesic drugs (e.g. NSAIDs and paracetamol) within the 12 hours before the experiment. Participation in experiments of Chapter 2 and 3 was also an exclusion criterion. Six participants were discarded from analyses due to unstable performances during the experiment (see analyses section for details). The mean age of the remaining 17 participants (nine women – eight men) was 24.12 years (SD=± 3.95, range 19-32 y.). According to the Flinders Handedness Survey (Flanders) (Nicholls et al., 2013), 15 participants were right-handed, one left-handed and one ambidextrous. The local ethic committee approved the experimental procedure in agreement with the Declaration of Helsinki. Participants signed an informed consent prior the experiment and received financial compensation for their participation.

2.1.2. Stimuli and apparatus

Thermo-nociceptive stimuli consisted of radiant heat stimuli applied to one of the two hand dorsa using a temperature-controlled CO_2 laser stimulator (10,6 μm wavelength, Laser Stimulation Device, SIFEC, Ferrières, Belgium). The laser beam was conveyed through a 10-m optical fiber ending with a head containing the optics used to collimate the laser beam to 6 mm diameter at the target site. The laser head was hold upon the participant's hand by means of an articulated arm attached to a camera tripod system (Manfrotto, Cassola, Italy). It was fixed into a clamp attached to a 3-way head, allowing displacements of the laser target perpendicularly to the hand's dorsum, by means of several sliders in all directions. The laser beam target was displaced after each experimental trial to avoid overheating the skin. A laser stimulus lasted 100 ms with a 10-ms heating ramp to reach the target temperature, followed by a 90-ms plateau; heating was then stopped. Laser energy was controlled in temperature measured at the skin target site by means of a radiometer in the laser head. The laser output power was thus adapted to the online measurement of the skin temperature at the site of stimulation to reach the specified temperature. The target temperature was

individually determined according to the respective activation threshold of unmyelinated C fibers and thinly-myelinated Aδ fibers (see Procedure).

Visual stimuli were 5-ms flashes of light delivered using white light-emitting diode (LED) (17-lm luminous flux, a 6.40-cd luminous intensity, and a 120° diffusion angle; GM5BW97330A, Sharp Corporation, Japan). During the first phase of the experiment, one LED was placed on a landmark pasted on the table in front of the participant. During the second phase of the experiment, two LEDs were used and respectively placed on a landmark next to the hand receiving the laser stimuli and on a landmark next to the opposite hand (see Figure 1).

2.1.3. Procedure

The experiment was performed in two sessions separated by one week and scheduled at the same moment of the day for each participant. One session was dedicated to the assessment of the C-fiber activation threshold, the other session to that of the Aδ-fiber activation threshold. The order of sessions was counterbalanced across the participants. During both sessions, stimuli were either applied on the right-hand dorsum or on the left-hand dorsum, the choice of the stimulated hand being also counterbalanced across participants. Each session was divided in two phases. The first phase consisted in individually measuring the delay between the thermo-nociceptive and the visual stimuli to achieve perception of simultaneity, using a TOJ task. The second phase aimed to investigate the impact of the visual stimulus and its location on the respective detection threshold of C- and Aδ fibers, using the average perceptual simultaneity between the two sensory inputs measured in the previous phase. During the experiment, participants sat on a chair in front of a table in a lighted room, with their hand palms down on the table, at the same distance (i.e. at ~15 cm) from their midsagittal plane, using landmarks that were pasted on the table. Each landmark was located next to the metacarpophalangeal joint of each index finger. The line between the two landmarks crossed participants' midsagittal plane at ~30 cm from their trunk; their intersection was marked with a cross, used as fixation point (see Figure 1).

Phase 1: assessment of the perceptual simultaneity between thermo-nociceptive and visual stimuli

Target temperatures used during the TOJ task were determined according to the activation thresholds of C and Aδ fibers estimated separately using an adaptive staircase procedure (Churyukanov et al., 2012). The absolute detection threshold was used to determine C-fiber activation threshold: laser stimuli were applied with a

starting temperature of 39°C; when the stimulus was not perceived, temperature of the next stimulus was incremented by 0.5°C; when it was perceived, temperature of the next stimulus was decreased by 0.5°C. Reaction times (RTs) were used to determine Aδ-fiber activation threshold: laser stimuli were applied with a starting temperature of 46°C; when the stimulus was perceived with RTs slower than 650 ms, the temperature of the next stimulus was incremented by 0.5°C; when it was perceived with RTs faster than 650 ms, the temperature of the next stimulus was decreased by 0.5°C. Stimulation series lasted until four reversals of the temperature were encountered; the average of the four reversal temperatures was taken as the activation threshold of the estimated fibers. During sessions aimed to investigate C fibers, both thresholds were measured, and the target temperature of the TOJ task was determined by the average of the two threshold values (see Lenoir, Algoet, et al., 2018; Manfron, Filbrich, Farnè, Mouraux, & Legrain, in preparation; Manfron et al., 2020a). During sessions aimed to investigate Aδ fibers, only the Aδ-fiber threshold was estimated, and the target temperature was determined by adding 5°C to the threshold value.

The TOJ procedure was largely based on the one used in our previous studies (Manfron et al., in preparation; Manfron et al., 2020a). The LED used to deliver visual stimuli was aligned with participants' midsagittal plane, pasted on the landmark 15 cm above the fixation cross (see Figure 1). The TOJ task consisted of 2 blocks of 30 trials each. A trial consisted in a pair of one visual stimulus and one laser stimulus delivered at the target temperature determined according to the session (i.e. eliciting sensation compatible with either C-fiber or Aδ-fiber activation). A trial started with a warning signal from the experimenter. Approximatively 500 ms later, the first stimulus of the visuo-nociceptive pair was delivered, followed by the second stimulus, according to different stimulus onset asynchronies (SOAs). Stimuli were separated by 16 possible SOAs during C-fiber session (+100, +220, +270, +320, +370, +420, +460, +490, +510, +540, +580, +630, +680, +730, +780, +900 ms), and 14 SOAs during A-δ-fiber session (±200, ±150, ±100, ±80, ±60, ±40, ±20 ms; positive values indicate that the laser stimulus was applied before the visual stimulus, negative values indicate that the visual stimulus was presented before the laser stimulus). The to-be-presented SOA was determined at each trial using the adaptive *psi* method considering the participant's responses to all previous trials of the block (for further details about the use of the psi method in the context of TOJ tasks, see Filbrich, Alamia, Burns, et al., 2017; Kingdom & Prins, 2010). Before the task, two pairs of stimuli were administered to all participants to get familiarized with the task and with the sensation elicited by the activation of the specific fibers. Their performance was not recorded. At each trial, participants judged the temporal order of the two stimuli of the pair by reporting verbally ("*laser*" or "*visual*") which of the two they perceived as first delivered during one block, and as second delivered in the other block. Instructions were counterbalanced: 8 participants started with the "which is first" block, and 9 with the "which is second" block. Once the experimenter encoded the participants' response (by pressing a key of the remote-control computer), the next trial started 2000 ms later. Each block lasted approximately

4 minutes and the entire TOJ task lasted around ten minutes. At the end of the TOJ task, the Point of Subjective Simultaneity (PSS) was computed (see Measures), and its value was used during the next phase as the asynchrony to be implemented between the onset of the nociceptive stimulus and the onset of visual stimulus to maximize chances that participants perceive both stimuli at the same time.

Phase 2: assessment of the activation threshold of nociceptive fibers

Materials used during this phase were the same as during the previous phase except that two LEDs were used for presenting visual stimuli. The LEDs were placed on the landmarks used to position the hands (see Figure 1). For each session, threshold assessment consisted of one block of 240 trials randomly presented according to six interleaved experimental conditions composed of an equivalent number of trials (i.e. 40). In three conditions, trials consisted of a laser-induced thermo-nociceptive stimulus applied on the hand dorsum using an intensity among different possible temperatures ranging from 30 to 50 °C with steps of 0.5 °C during the session assessing the C-fiber threshold, and from 40 to 60 °C with steps of 0.5 °C during the Aδ-fiber threshold assessment session. In the first condition, the laser stimulus was applied alone (*single laser* condition). In the second condition, the laser stimulus was applied on the hand with a flashing visual stimulus next to that hand (*ipsilateral laser* condition). In the third condition, the laser stimulus was applied with a flashing visual stimulus next to the opposite non-stimulated hand (*laser contralateral* condition). In the two latter conditions, the laser stimulus preceded the visual stimulus by the amount of time corresponding to the individual PSS value estimated during the TOJ task in phase 1. The remaining three conditions consisted of catch trials to control for participants guessing the perception of the thermo-nociceptive stimulus. In one of these conditions, no stimulus at all were presented; in the next one, a visual stimulus was flashed alone next to the usually stimulated hand; in the last one, the visual stimulus was flashed alone next to the opposite hand. Before each trial, the experimenter warned participants of the incoming stimuli by saying '*Attention'*. They were asked to respond as fast as possible if they perceived the laser stimulus by pressing the button of a response box held in their non-stimulated hand. They next reported which stimuli they perceived by saying either "*laser*", "*visual*", "*both*" or "*nothing*". The applied temperature was determined at each trial using the *psi-marginal* adaptive method (Prins, 2013) by considering the participant's responses on all previous trials (see Measures for differences from the classic *psi* method). During the C-fiber threshold assessment session, the temperature was adapted based on the probability of detecting the stimulus, and slower than 650 ms. During the Aδ-fiber threshold assessment session, the temperature was adapted based on the probability of detecting the stimulus with RTs compatible with Aδ-fiber conduction velocities (i.e. RTs < 650 ms; see Churyukanov et al., 2012). Participants' response about the stimuli they perceived was encoded by

the experimenter by pressing a key of the remote-control computer generating the start of the next trial. A ten seconds break were made every 10 trials, and a break of ~5 minutes was taken after 120 trials (about 15 minutes). The entire experiment, including instructions, the first and second phases, lasted about 1 hour and 15 minutes.

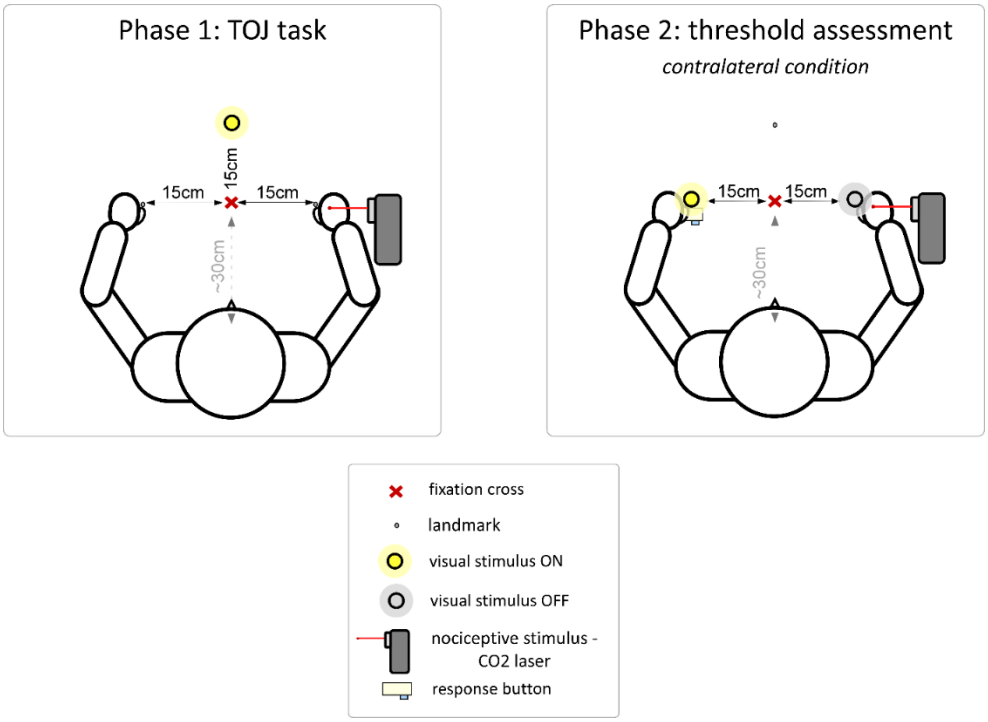

Figure 1. Experimental setup of each phase within one session. Each setup represents right-hand stimulations. For both phases of the experiment, the red beam above the hand represents the CO2 laser administering laser stimuli. The red cross represents the fixation point on which participants fixed their gaze throughout the TOJ task and during the assessment of the thresholds. For the TOJ task (phase 1), a white LED delivering the visual stimuli was pasted on a landmark (illustrated by the grey point) 15 cm above the fixation cross. The non-stimulated hand was placed symmetrically to the stimulated hand. Participants were asked to judge the temporal order of laser and visual stimuli delivered in pairs. For the assessment of the thresholds (phase 2), the white LED used in the TOJ task was displaced on the landmark next to the metacarpophalangeal joint between the thumb and the forefinger of the hand receiving the laser stimuli. In the figure, the laser-contralateral condition is illustrated, the LED is therefore switched-off. Another LED, this time switched-on, was pasted on a landmark next to the metacarpophalangeal joint between the thumb and the forefinger of the non-stimulated hand. Participants held the response button in the non-stimulated hand. Visual stimuli were delivered next to it while laser stimuli were administered on the right-hand dorsum.

2.1.4. Measures

Intensities of the laser stimuli were measured in Celsius degrees (°C). The RTs recorded during the assessment of the thermo-nociceptive thresholds were measured in milliseconds (ms).

To estimate TOJ performance in phase 1, the proportion of thermo-nociceptive stimuli perceived as being presented first was computed as a function of SOAs for each block. Parameters of interest were estimated by the logistic function $f(x)=1/(1+exp(-\beta(x-\alpha)))$ at each trial (Kingdom & Prins, 2010). Analyses were made on the last estimate of the block corresponding to the last update of the adaptive procedure. The main parameter of interest was the α parameter corresponding to the threshold of the function and characterizing the point of subjective simultaneity (PSS), that is, the SOA at which the thermo-nociceptive stimulus and the visual stimulus were perceived as occurring first equally often (in ms). Based on previous experiments (see Study 2 and 3), prior estimates of α were set respectively to 500 ± 200ms for the C-fiber session and to 70 ± 20ms for the Aδ-fiber session. PSS values of the two blocks (i.e. '*which is first*' and '*which is second'*) were averaged and the resulting value was used to individually set the time interval separating the thermo-nociceptive and visual stimuli during the threshold assessment (phase 2). Regarding that objective, the slope value of the psychometric function (i.e. β) was therefore not considered in the analyses of the present experiment. Its prior estimate was nevertheless set at 0.06 ± 0.6 for both fiber types.

The assessment of the thresholds of thermo-nociceptive fibers in phase 2 was based on the *psi marginal* adaptive method, to measure the probability of perceiving the thermo-nociceptive stimuli according to the respective criterion of each fiber type. The main parameters of interest were the α and β, estimated by the same logistic function than the *psi* adaptive method. The α parameter was used to characterize to the activation threshold of the thermo-nociceptive fibers (in °C). For Aδ fibers, its prior estimates were 46 ± 2 °C. For C fibers, its prior estimates were 40 ± 2 °C. Slope values (β parameter) were considered for statistical analyses to estimate the noisiness of the results, i.e., the variability of the participants' responses, and their prior estimates were set at 0.001 ± 6 for both fiber types. Threshold and slope values were estimated separately for each experimental condition (i.e. *no-visual-stimulus*, *ipsilateral*, and *contralateral* conditions). The benefit of the *psi-marginal* adaptive method is to let the lapse and guess rates vary during the adaptive procedure, whereas in the classic *psi* method their values are set in advance. These parameters are usually considered as nuisance parameters because they influence the threshold and slope values without giving any information on the sensory mechanisms assessed. The lapse rate defines the probability of giving an incorrect response whilst the response should have been obvious (e.g. error due to distraction during one trial). The guess rate indicates the

probability of giving a correct answer whereas the stimulus has not been detected by the sensory mechanism underlying the task (e.g. by chance). If their prior estimates are correctly set, their influence is minimized (Prins, 2012; Prins, 2012b; Prins, 2013). However, given that no previous study has investigated thresholds of thermo-nociceptive fibers according to the spatial position of a visual stimulus using an adaptive procedure, we could not make prior assumptions about their fixed values. The *psi-marginal* adaptive method therefore allowed us to set a uniform prior for each parameter.

2.1.5. Data analyses

Statistical analyses were conducted with IBM SPSS 25. The data of 6 participants were discarded from analyses due to unstable adaptation of the *psi marginal* method during at least one experimental condition (as evidenced by a greater SD of the α parameter at the last trial of the adaptive procedure compared to the SD of the first trial administered) either during the threshold assessment of C fibers, or during the threshold assessment of Aδ fibers. The sensation elicited by the activation of C and/or Aδ fibers using CO_2 laser could have been less clearly perceived in some participants, leading to unstable responses during the threshold assessment and preventing from making reliable interpretations. For the remaining participants, descriptive statistics on the PSS values of the TOJ task were reported without any further analyses. Next, the respective impact of the occurrence and location of the visual stimuli on the threshold values of the thermo-nociceptive fibers were analyzed using analyses of variance (ANOVA) for repeated measures. As large differences were expected between C fibers vs Aδ fibers thresholds, these analyses were performed separately for the assessment of each fiber type, with the position of visual stimuli as a within-participant factor (no visual stimuli, ipsilateral or contralateral to the stimulated hand). Regarding the slope values, a two-factor ANOVA was performed by adding the type of thermo-nociceptive fibers as a within-participant factor. Effect sizes were measured by means of partial Eta squared for ANOVA and Cohen's d for t tests. When necessary, contrast analyses were performed. Significance level was set at p-value < 0.05. Data are expressed in means plus or minus standard deviations (M ± SD).

2.2. *Results*

The PSS mean values were respectively 585.35 ± 117.57ms (ranging from 355 ms to 830 ms) for C-fiber mediated stimuli, and 88.70 ± 20.53 ms (ranging from 60 ms to 120 ms) for Aδ-fiber mediated stimuli. This means that, in order to perceive a thermo-nociceptive and a visual stimulus as occurring simultaneously, the onset asynchrony between the two of them was, on average, 585 ms for stimuli specifically activating C fibers, and 88 ms for thermo-nociceptive inputs conveyed through Aδ fibers.

Illustrations of the psychometric functions used to fit threshold assessment values are depicted on Figure 2. The individual threshold values are depicted on Figure 3. Analyses revealed significant differences between the visual-stimuli conditions for Aδ-fiber threshold assessment ($F(2,32) = 3.64$, $p = 0.038$, $\eta^2_p = 0.185$; *ipsilateral* condition: 50.59 ± 2.45 °C, *contralateral* condition: 50.66 ± 2.52 °C, *no-visual-stimulus* condition: 51.49 ± 2.79 °C), but not for C-fiber threshold assessment ($F(2,32) = 1.76$, $p = 0.188$, $\eta^2_p = 0.099$; *ipsilateral* condition: 40.93 ± 1.56 °C, *contralateral* condition: 41.10 ± 1.28 °C, *no-visual-stimulus* condition: 41.43 ± 1.37 °C). Contrasts analyses on Aδ-fiber threshold assessment showed a significantly lower threshold in the *contralateral* condition as compared to the *no-visual-stimulus* condition ($t(16) = -2.14$, $p = 0.048$, d = -0.519). Despite a similar trend for the *ipsilateral* condition relatively to the *no-visual-stimulus* condition, such difference failed to reach significance level ($t(16) = -2.09$, $p = 0.053$, d = -0.507). Finally, the difference between the *ipsilateral* and *contralateral* conditions was not significant ($t(16) = -0{,}24$, $p = 0{,}813$, d = -0.058). Such results suggest that the thermal detection threshold of Aδ fibers was lowered by the co-occurrence of a visual stimulus, whatever its location relative to the hand on which the thermo-nociceptive stimulus was applied, as compared to when no visual stimulus was concomitantly delivered.

The ANOVA performed on the slope values did not reveal any significant difference neither between the assessed fibers ($F(1,16) = 1.20$, $p = 0.289$, $\eta^2_p = 0.070$), between the *visual-stimuli* conditions ($F(2,32) = 0.02$, $p = 0.983$, $\eta^2_p = 0.001$), nor for the interaction between the two factors ($F(2,32) = 0.05$, $p = 0.950$, $\eta^2_p = 0.003$). The individual slope values are depicted on Figure 3.

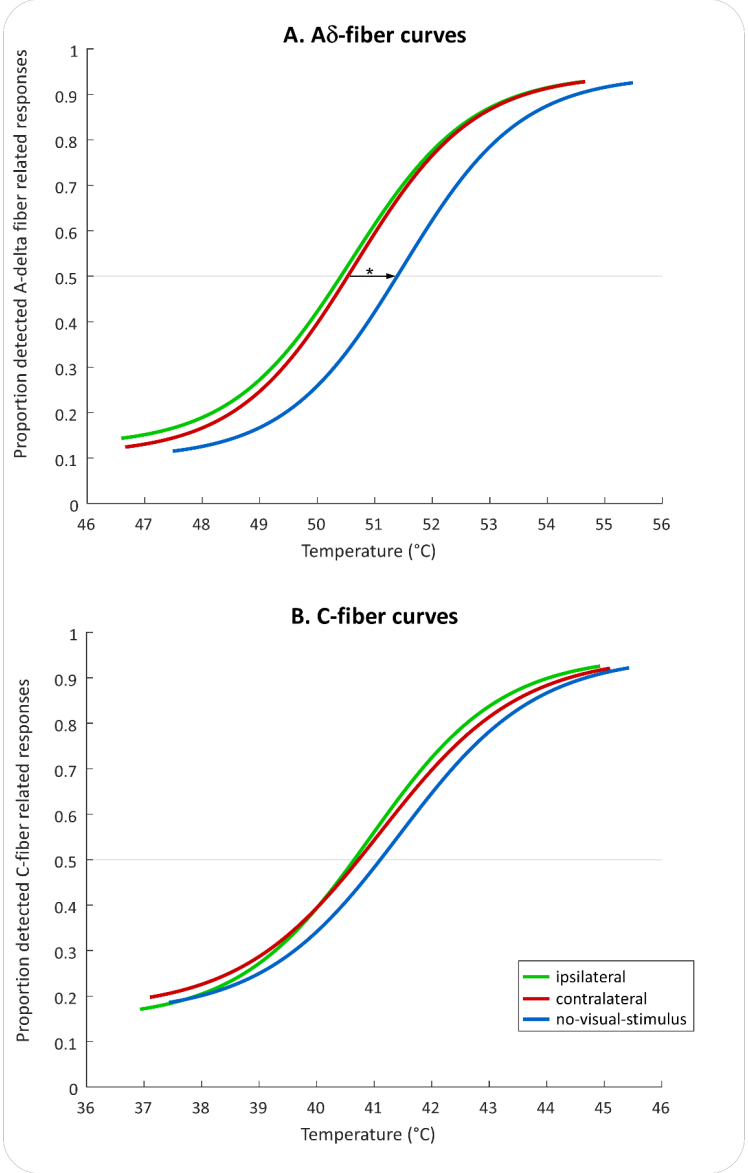

Figure 2. Results of Experiment 1. The figure depicts the averaged results of the 17 participants. The graph at the top represents the fitted logistic functions for thermo-nociceptive thresholds of the Aδ-fiber afferents. The bottom graph illustrates the fitted logistic functions for thermo-nociceptive thresholds of the C-fiber afferents. For each graph, the x-axis represents temperatures whereas the y-axis represents the proportion of detected trials. The blue curves correspond to the single-laser condition, the green curves to the laser-ipsilateral condition and the red curves to the contralateral condition. The arrow indicates that the contralateral condition (red) is significantly different from the no-visual-stimulus condition (green). The significant difference is indicated with an asterisk (* $p \leq 0.05$).

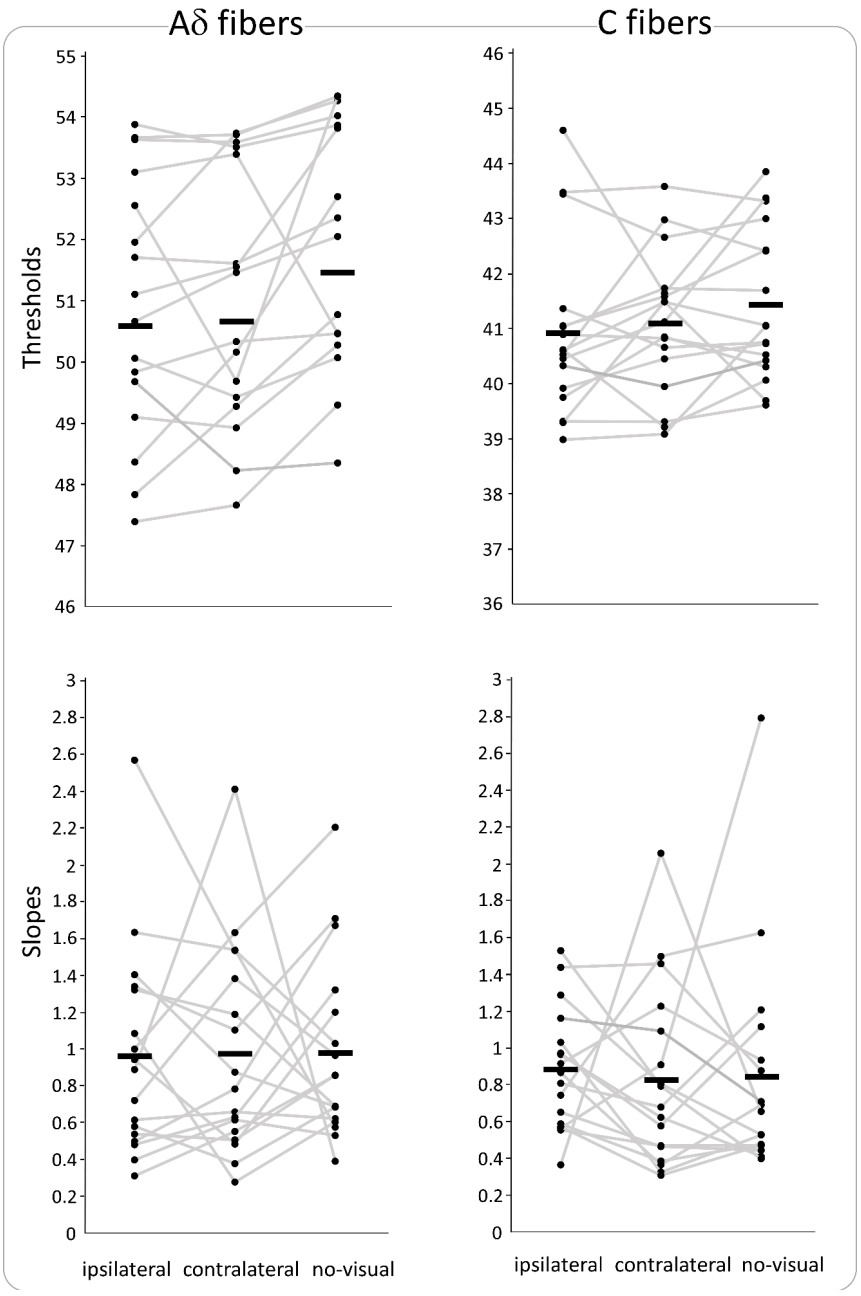

Figure 3. Individual threshold and slope values. The figure shows the individual threshold and slope values of each participant according to the visual conditions (*ipsilateral* vs *contralateral* vs *no-visual-stimulus*) and to the stimulated fiber (Aδ vs C). In each graph, grey lines link the values from one participant. The black lines represent the average value of each experimental condition.

Distribution of the reaction times

Further analyses were conducted to examine the distribution of participants' reaction times to all detected laser stimuli (for both Aδ- and C-fiber threshold assessments). Figure 4 illustrates their density distribution according to each visual stimulus condition. The classic bimodal distribution is observed, at least for ipsilateral and contralateral conditions (no clear cut-off appears for the *no-visual-stimulus* condition), confirming that the range of the delivered temperatures activated two subtypes of afferent fibers with different conduction velocities. However, it should be noted that the standard cut-off of 650 ms used to dissociate Aδ-fiber vs. C-fiber activation (cfr. Churyukanov et al., 2012) seems shifted to ~700 ms for the *ipsilateral* condition and to ~800 ms for the *contralateral* condition.

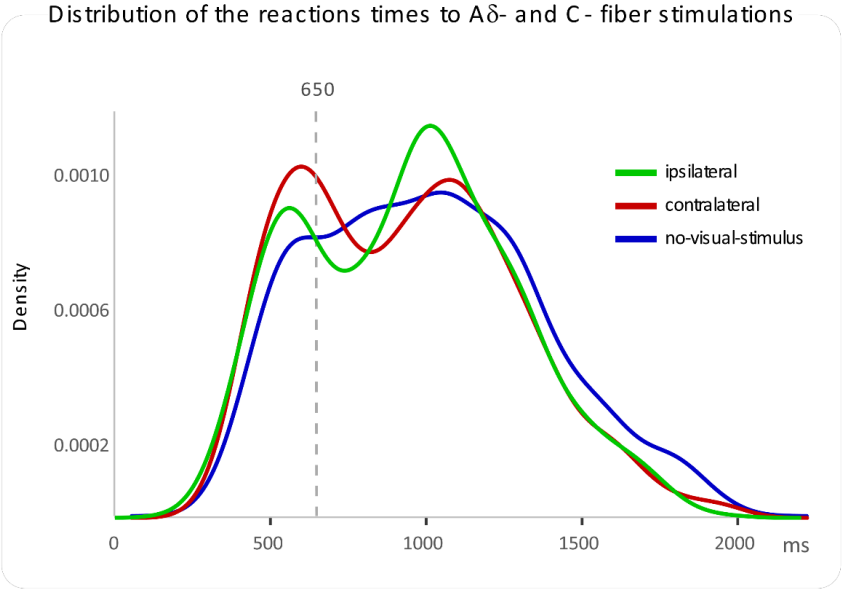

Figure 4. Density of participants' RTs to Aδ and C-fiber stimulations. The curves represent the density of the probability of participants' reaction times (RTs) from all detected trials (during Aδ and C-fiber stimulations) according to each visual condition. Data were adjusted from the top of the bars of histograms. The x-axis corresponds to the RTs. The y-axis corresponds to the density of the data. The green density curve illustrates the *ipsilateral* condition. The shape of the curve is bimodal and indicates that the cut-off between Aδ-fiber responses and C-fiber responses is around 700 ms. The red density curve depicts the *contralateral* condition. The shape of the curve is bimodal and indicates that the cut-off between Aδ-fiber responses and C-fiber responses is around 800 ms. The blue density blue curve shows the *no-visual-stimulus* condition. No clear cut-off appears between Aδ-fiber responses and C-fiber responses. The dashed gray line shows the latency cut-off (650 ms) usually used to discriminate the stimulation of Aδ fibers from C fibers (e.g. Churyukanov et al., 2012; Jankovski et al., 2013).

2.3. Discussion Experiment 1

This experiment was aimed to study the effect of the spatial position of a visual stimulus on the detection thresholds of inputs conveyed by Aδ and C fibers. Since stimuli of different sensory modalities interact mostly when they occur within the same time-window (Colonius & Diederich, 2004; Meredith et al., 1987), the onset of the visual stimulus was delayed relative to that of the laser stimulus, by a time interval corresponding to the PSS between the two stimuli, individually estimated during a preliminary TOJ task. Results showed that, while visual stimuli did not affect the detection threshold of inputs conveyed by C fibers, they decreased the detection threshold of Aδ-fiber inputs relative to the condition in which no visual stimulus was delivered. The effect was significant for the contralateral condition, where visual stimuli appeared next to the non-stimulated hand, and almost reached significance for the ipsilateral condition, where visual stimuli were next to the stimulated hand. These results contrast with our hypothesis that the presence of a visual stimulus next to the stimulated hand would decrease the thermo-nociceptive thresholds of the fibers as compared to the presence of a visual stimulus in far space. However, several methodological issues may explain our findings.

First, because participants always responded to laser stimuli with the non-stimulated hand, i.e. where visual stimuli of the contralateral condition were delivered, the occurrence of the contralateral visual stimulus might have drawn attention to its location, facilitating the motor preparation to respond to laser stimuli (Lu & Proctor, 1995; Simon, 1969) and thus biasing RTs during the assessment of thermo-nociceptive thresholds in the contralateral condition.

Second, RTs to multisensory stimuli are known to be shorter than RTs to unisensory stimuli (Miller, 1982, 1986; Raab, 1962; Shaw et al., 2020). Although the thermo-nociceptive thresholds were measured in °C, participants' RTs to laser stimuli were categorized according to their responses below or above a criterion of time (i.e. 650 ms) used to differentiate the activation of C-fiber afferents from the activation of Aδ-fiber afferents. Since no visual stimulus was delivered during the control condition, this implies that the RTs, and therefore the assessment of the thresholds, could have been affected by a confounding factor. Participants' responses would have been facilitated during the ipsilateral and contralateral conditions as compared to the control condition, in which no visual stimulus was presented.

Finally, the criterion used to dissociate the activation of C fibers from that of Aδ fibers was chosen based on previous experiments during which participants were only required to respond to laser stimuli (as fast as possible for Aδ-fiber mediated responses) that were delivered at *each trial* (Churyukanov et al., 2012; Jankovski et al., 2013; Plaghki et al., 2010). Two stages of processing can be identified: stimulus detection and motor execution. In the current experiment, laser stimuli were not

delivered at each trial. Participants were asked to respond as fast as possible to the laser stimuli if, and only if, they felt a laser stimulus. An additional stage of processing was therefore involved: stimulus detection, stimulus discrimination (responding to laser stimuli and inhibiting the motor response when no laser stimulus was delivered), and motor execution (e.g. Barutchu & Spence, 2021; Donders, 1969; Miller & Low, 2001). That additional step could have slowed participants' RTs compared to a classic detection task. Accordingly, further analyses (see Figure 4) suggested that the cut-off defined at 650 ms might possibly be delayed.

These methodological biases prevent us from properly interpreting the effect of the spatial position of a visual stimulus on detection thresholds of Aδ vs C fibers. They will therefore be taken into account to improve the procedure of the second experiment.

3. Experiment 2

The aim of this experiment was similar to that of Experiment 1 but the procedure was adapted in order to control for potential confounding factors. First, the control condition was composed of trials with a laser stimulus *and* a visual stimulus, located in front of participants at farther distance from their body and equidistant from their two hands. Second, participants reported the perception of thermo-nociceptive stimuli by lifting as fast as possible the index fingers of both hands. Third, the cut-off criterion used to dissociate RTs compatible with the activation of Aδ fibers from those specifically related to that of C fibers was delayed to 750 ms. Finally, to increase the relevance and, consequently, the potential impact of the spatial position of visual stimuli on thermo-nociceptive thresholds, participants were also required to report their localization (Filbrich et al., 2019; Van der Biest et al., 2016).

3.1. Materials and Methods

Methods and procedure are almost identical to those of Experiment 1. Only deviations from the previous protocol are therefore reported.

3.1.1. Participants

Twenty-seven participants were recruited to perform this experiment. Inclusion criteria were the same as in Experiment 1. Seven participants were discarded from analyses due either to technical issues or to unreliable assessment during one of the experimental conditions (see analyses section of Experiment 1). The mean age of the remaining 20 participants (17 women – 3 men) was 23.35 years (SD= ± 3.48, range 19-32 y.). According to the Flinders Handedness Survey (Flanders) (Nicholls et al., 2013), 19 participants were right-handed and one was left-handed.

3.1.2. Stimuli and Apparatus

Stimuli and apparatus for the TOJ task in phase 1 were identical to those used in Experiment 1, except for the LED characteristics (21.5-lm luminous flux, a 7.20-cd luminous intensity, and a 120° diffusion angle, BROADCOM ASMW-FWG0-NHKH6). For the second phase, assessing thermo-nociceptive thresholds, three white LEDs with the same characteristics as the single LED in phase 1 were used to deliver the visual stimuli. Two of them were placed using the same landmarks as for the threshold assessment of Experiment 1. The third LED was placed on the landmark above the fixation point, previously used to paste the LED of the TOJ task (see Figure 5). The

duration of visual stimuli was extended to 100 ms to match the duration of laser stimuli and increase chances that their perception would overlap in time.

To record participants' responses, two metal plates (2 x 4 cm), each attached to a small plastic base, were stuck to the testing table by using double-sided tape. One metal plate was placed under the left index finger, the other under the right index finger. The contact of the index finger with the metal plate was detected using an Arduino (Arduino Nano, Italy). The detection was obtained using a high resistance switch triggered by the change in impedance occurring between the metal plate and an electrode (NEO NAT Ambu ECG) attached to the skin of the participants' arm. When the fingers left the metal plate, a TTL signal was generated by the Arduino and transmitted the RT information to a data acquisition card (NI USB 6343, National Instruments, USA). At each trial, only the RT value of the fastest finger was recorded.

A pilot experiment was performed before the second experiment to compare the RTs to laser stimuli using this new device to the RTs with the response button used in Experiment 1. No significant difference was highlighted (see Appendix n° 1).

3.1.3. Procedure

The TOJ task of phase 1 was identical to that of Experiment 1. For the threshold assessment, the same 6 experimental conditions were presented to participants with the exception that the two conditions without any visual stimulus were replaced by conditions in which visual stimuli were delivered using the central LED. Participants were asked to maintain each index finger in contact with the corresponding metal plate of the response device. During each trial, if and only if they perceived a laser stimulus, they were required to lift as quickly as possible both fingers at the same time. They were then asked to confirm whether they perceived or not the thermal stimulation and to report the location of the visual stimulus (left, right or far). Temperatures of laser stimuli were still adapted to the participants' responses using the *psi-marginal* adaptive method with the exception that the cut-off criterion was set at 750 ms for the assessment of the Aδ fiber threshold.

A five-minutes break was taken every 80 trials. The entire experiment, including instructions, TOJ task and assessment of the thresholds, lasted about one hour and 30 minutes.

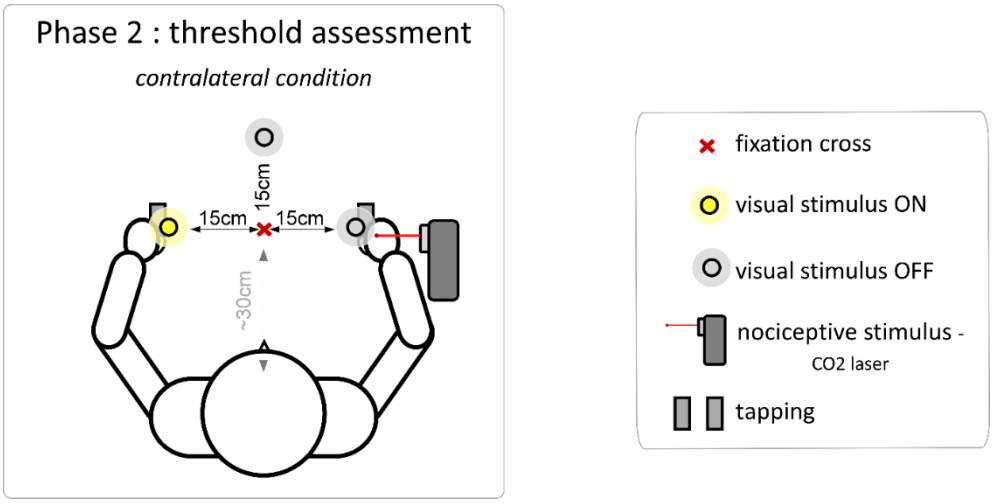

Figure 5. **Experimental setup of phase 2 for Experiment 2**. Participants were required to respond as fast as possible by lifting both index fingers from metal plates (represented by the two grey rectangles) when they received laser stimuli on one of the hands. The figure represents the *contralateral* condition of the detection task. The LED located next to the participant's left hand (illustrated by a yellow circle surrounded by a yellow halo) switched-on for 100 ms while the right-hand dorsum received a laser stimulus activating either Aδ or C fibers (depending on the session) of 100 ms as well. The grey circle in front of the body midline ~45 cm from the trunk and the grey circle located next to the right hand illustrate visual stimuli when LEDs were switched-off. The LED in front of the participant switched-on during the *far* condition whereas the right LED switched-on during the *ipsilateral* condition.

3.1.4. Measures & Analyses

Measures were exactly the same as for Experiment 1 with the exception that the control condition consisted of trials with a laser stimulus and a visual stimulus located centrally in front of the participant (far condition). Classic frequentist analyses were complemented by Bayesian statistics (using Bayesian repeated measures ANOVA with JASP 0.9.2.0, University of Amsterdam, The Netherlands) performed on the threshold and on the slope values. To this aim, we computed a Bayes factor to quantify the alternative hypothesis (HA) relative to the null hypothesis (H0) (BF_{10}, Cauchy prior = 0.707). Interpretations are based on the classification scheme established by Lee and Wagenmakers (2013); Wagenmakers et al., (2017).

3.2. Results

The PSS mean values of the TOJ task were 87.45 ± 14.91 ms (ranging from 65 to 120 ms) for Aδ-fiber mediated stimuli, and 603.40 ± 106.70 ms (ranging from 380 ms to 840 ms) for C-fiber mediated stimuli. These values are consistent with those observed in the previous experiment.

Illustrations of the psychometric functions used to fit the threshold values are depicted in Figure 6. Analyses of the threshold values revealed a significant effect of the visual-stimuli conditions on the detection threshold of Aδ-fiber inputs ($F(2,38) = 3.28$, $p = 0.048$, $\eta^2p = 0.147$; *ipsilateral* condition: 48.80 ± 1.90 °C, *contralateral* condition: 49.31 ± 1.88 °C, *far* condition: 49.20 ± 2.28 °C). Contrast analyses showed that the threshold value of Aδ fibers was lower in the *ipsilateral* condition as compared to the *contralateral* condition ($t(19) = -3.006$, $p = 0.007$, d = -0,67). There was no difference between the *contralateral* and *far* conditions ($t(19) = 0.55$, $p = 0.589$, d = 0.12) or between the *far* and *ipsilateral* conditions ($t(19) = 1.62$, $p = 0.121$, d = 0.36). These results suggest that presenting a visual stimulus near the hand on which the laser stimulus is applied decreases the detection threshold of Aδ-fiber inputs, as compared to when the visual stimulus is presented near the opposite hand. There was no significant impact of the location of the visual stimulus on the detection threshold of C-fiber inputs ($F(2,38)=0.062$, $p = 0.940$ $\eta^2_p = 0.003$; *ipsilateral* condition: 41 ± 1.92 °C, *contralateral* condition: 40.93 ± 2.47 °C, *far* condition: 41.03 ± 1.66 °C). Regarding Bayesian analyses performed on C-fiber thresholds, moderate evidence was shown in favor of H0 ($BF_{10} = 0.142$, error = 1.089), suggesting no effect of the location of the visual stimulus on the detection threshold of C-fiber inputs.

The analyses performed on the slope values did not reveal significant differences between the different types of thermo-nociceptive fibers ($F(1,19) = 0.095$, $p = 0.762$, $\eta^2_p = 0.005$), nor a significant influence of the position of the visual stimulus ($F(2,38)= 0.122$, $p = 0.886$, $\eta^2_p = 0.006$). However, the interaction between both factors was

significant ($F(2,38)=4.305$, p = 0.021, η^2_p = 0.185). Contrast analyses showed a significant difference between the *ipsilateral* and *contralateral* conditions during the stimulation of Aδ fibers ($t(19)$ = -2.343, p = 0.030, d = 0.52; ipsilateral: 0.62 ± 0.26, contralateral: 0.90 ± 0.58). No other significant effect was shown (all $t(19) \leq 1.81$, $p \geq 0.086$). Participants' responses seem thus more variable to detect laser stimuli when visual stimuli appear close to it than when they appear close to the non-stimulated hand during the threshold estimation of Aδ fibers only. Regarding Bayesian analyses, moderate evidence was shown in favor of H0 for the *fiber* factor (BF_{10} = 0.203, error = 0.935) strong evidence was shown in favor of H0 for the *visual-stimulus* factor (BF_{10}= 0.086, error = 1.131) while anecdotal evidence in favor of HA was shown for the interaction between both factors (BF_{10}= 1.888, error = 2.080).

The results from Bayesian statistics corroborate results from the previous classic frequentist analyses. Individual threshold and slope values are illustrated on Figure 7. Further statistical analyses were performed on the catch trial conditions (*ipsilateral* vs *contralateral* vs *far* relatively to the tested hand) in order to examine whether the number of false alarms varied according to the position of the visual stimulus, which could have potentially affected the interpretation of our results. However, no significant effect was evidenced by those analyses (see Appendix 2).

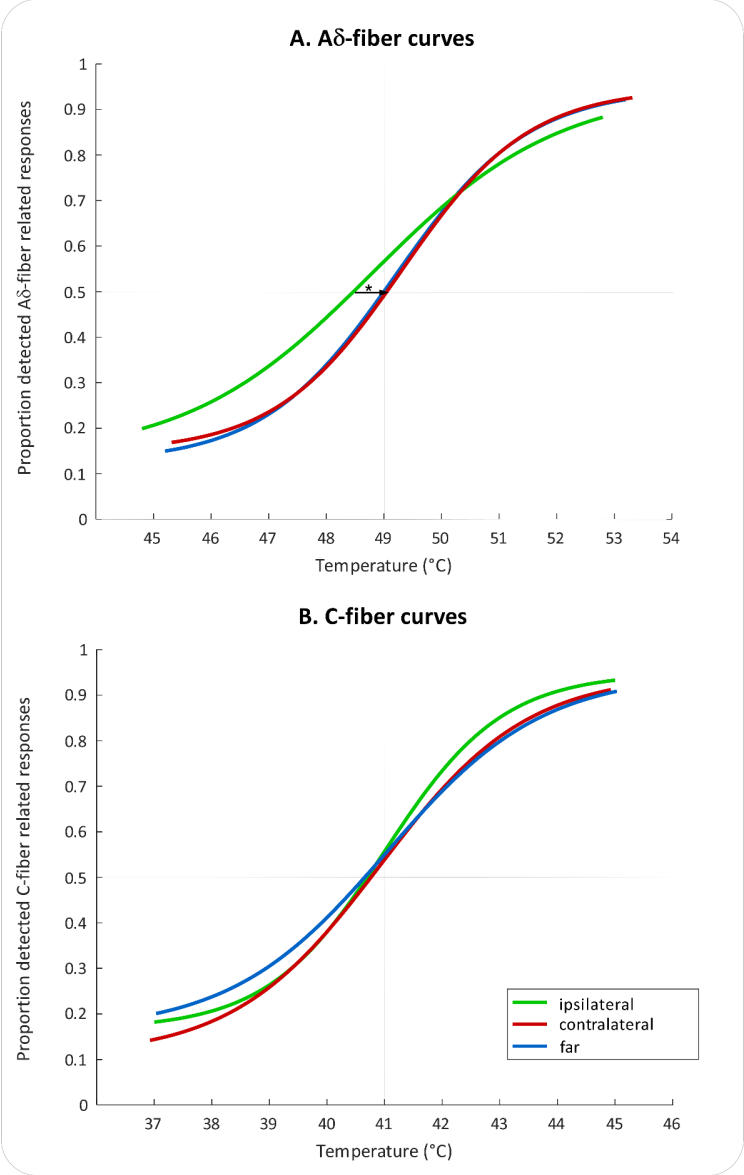

Figure 6. Results of Experiment 2. The figure depicts the averaged results of the 20 participants. The top graph represents the fitted logistic functions for the thermo-nociceptive thresholds of the Aδ-fiber afferents. The bottom graph illustrates the fitted logistic functions for the thermo-nociceptive thresholds of the C-fiber afferents. For each graph, the *x*-axis represents the temperatures whereas the *y*-axis represents the proportion of detected trials. The blue curves correspond to the *far* condition, the green curves to the *ipsilateral* condition and the red curves to the *contralateral* condition. The arrows indicate that the ipsilateral (green) and contralateral (red) conditions are significantly different from each other. Significant differences are indicated with asterisks (* $p \leq 0.05$).

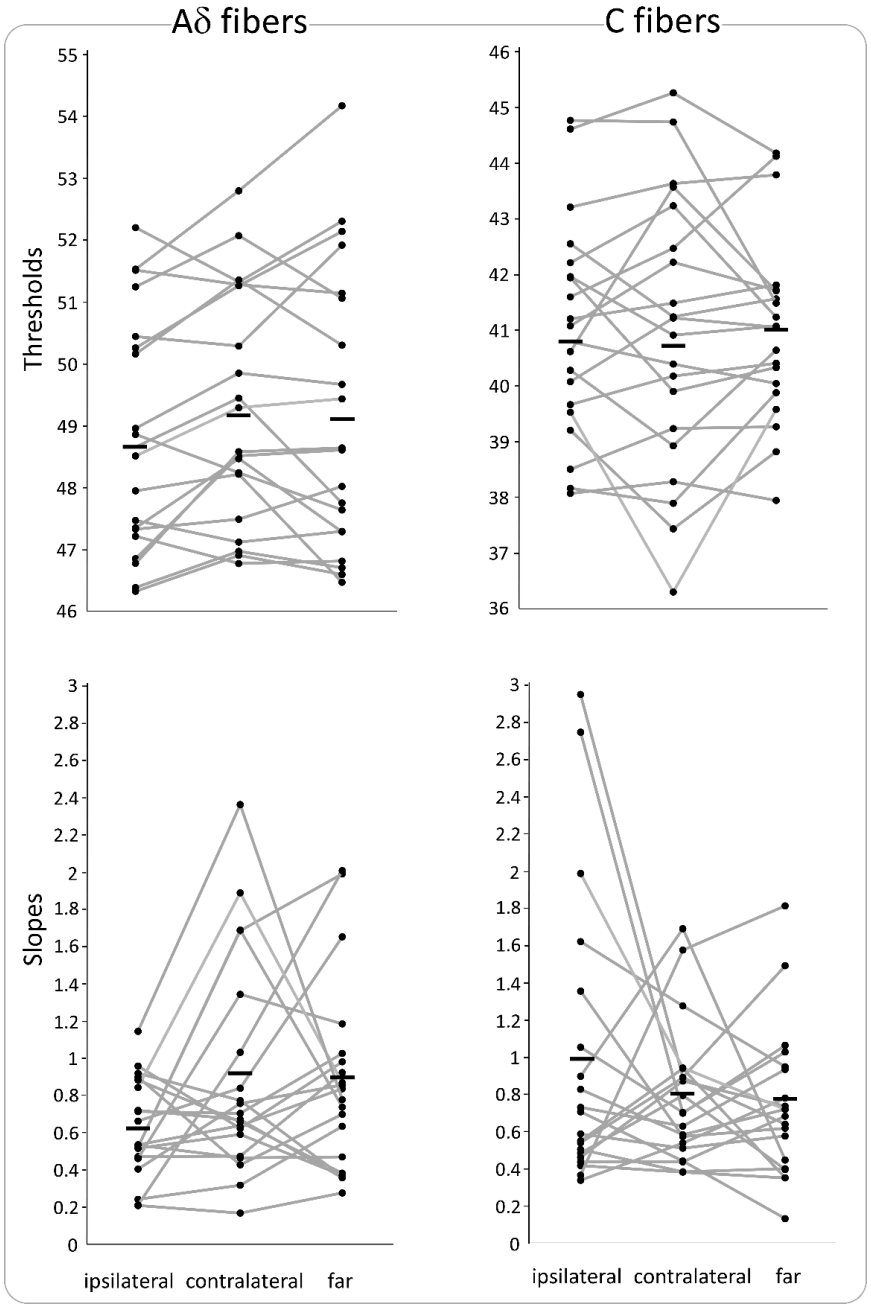

Figure 7. Individual threshold and slope values. The figure shows the individual threshold and slope values of each participant according to the visual conditions (*ipsilateral* vs *contralateral* vs *far*) and to the stimulated fibers (Aδ vs C). In each graph, grey lines link the values from one participant. The black lines represent the average value of each experimental condition.

Distribution of the reaction times

The distributions of participants' reaction times to all detected laser stimuli (for both Aδ- and C-fiber stimulations) were analyzed as for Experiment 1. Figure 8 illustrates their density distribution according to each visual stimulus condition. The classic bimodal distributions are clearly observed, confirming that the range of delivered temperatures activated two subtypes of afferent fibers with different conduction velocities. The cut-off ranges from ~750 ms for the *ipsilateral* condition to ~850 ms for the c*ontralateral* and *far* conditions. Further analyses were performed to investigate if participants' RTs to laser stimuli presented during the assessment of Aδ-fiber thresholds were different according to the visual conditions. No significant differences were found (see Appendix 3).

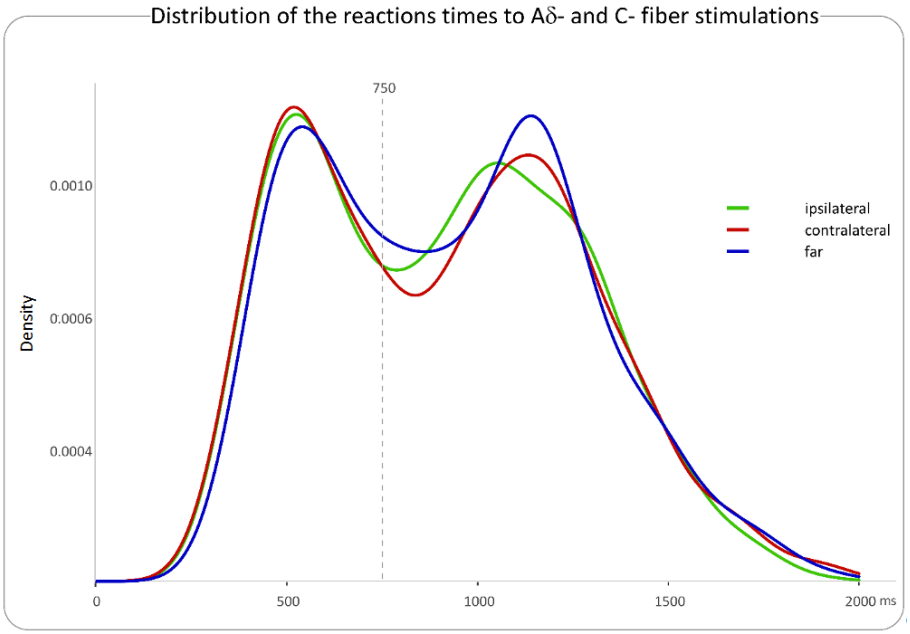

Figure 8. Density distribution of participants' RTs to Aδ and C-fiber stimulations. The curves represent the density of the probability of participants' reaction times (RTs) from all detected trials (during Aδ and C-fiber stimulations) according to each visual condition. Data were adjusted from the top of the bars of histograms. The x-axis corresponds to the RTs. The y-axis corresponds to the density of the data. The green density curve illustrates the *ipsilateral* condition. The shape of the curve is bimodal and indicates that the cut-off between Aδ-fiber responses and C-fiber responses is around 750 ms. The red density curve depicts the *contralateral* condition. The shape of the curve is bimodal and indicates that the cut-off between Aδ-fiber responses and C-fiber responses is around 850 ms. The blue density curve shows the *no-visual-stimulus* condition. The shape of the curve is bimodal, a clear cut-off between Aδ-fiber responses and C-fiber responses can be identified around 850 ms. The dashed gray line shows the latency cut-off (750 ms) exploited to discriminate the stimulation of Aδ fibers from C fibers according to the stages of information processing involved during the threshold assessment.

4. General discussion

The aim of this study was to assess the impact of visual stimuli, and more particularly their spatial location relative to the body, on the detection thresholds of inputs conveyed by Aδ and C fibers, using advanced psychophysical methods. In Experiment 1, we found that the presence of visual stimuli decreased the thermo-nociceptive thresholds of Aδ fibers as compared to a condition in which no visual stimulus was delivered, especially when the visual stimulus was located adjacent to the non-stimulated hand. However, we identified several issues in the procedure of the experiment that could have potentially biased these results. The procedure of Experiment 2 was therefore improved in order to properly interpret our data. When assessing the thresholds of Aδ fibers, we observed that visual stimuli presented near the hand on which laser stimuli were applied, slightly but significantly decreased the detection threshold of the fibers, as compared to when visual stimuli were presented next to the non-stimulated hand. Finally, in none of the experiments an effect of visual stimuli on the detection threshold of inputs transmitted through C fibers could be observed.

Since nociceptive inputs are processed in cortical regions that are also activated by salient stimuli from other sensory modalities (Legrain et al., 2011) and that a given sensory event recruits several sensory channels at the same time, studying the perception of nociceptive stimuli in interaction with other sensory inputs enables to understand how individuals detect, localize, and react to harmful stimuli. Previous studies about visuo-nociceptive interactions mostly investigated the spatial representation underlying the *localization* of a nociceptive input within the peripersonal space (De Paepe et al., 2015, 2017; De Paepe et al., 2014; De Paepe et al., 2016; Filbrich et al., 2017a,b; Filbrich et al., 2018; Vanderclausen et al., 2017).

Another recent study examined the effect of visual stimuli on the *detection* of nociceptive stimuli delivered at an intensity near the activation threshold of Aδ fibers. Filbrich et al. (2019) indeed showed that visual stimuli occurring close to a hand on which nociceptive stimuli were applied, increased the number of nociceptive stimuli reported as perceived, as compared to a condition in which nociceptive stimuli were presented alone. Given that multisensory interactions mainly occur when different stimuli fall within the same time-window (Colonius & Diederich, 2004; Meredith et al., 1987), the administration of the visual stimulus was delayed by 50 ms from the administration of the nociceptive stimulus, based on the latencies of the first evoked potentials of each system (Michel et al., 2004; Mouraux & Plaghki, 2007). The present study extends these findings by showing for the first time that the multisensory environment, surrounding the body-limb on which nociceptive stimuli are applied, can decrease the detection threshold of stimuli conveyed by Aδ fibers. In other words, we demonstrated that visual stimuli presented in the peripersonal space of the hand

receiving laser stimuli decreased the amount of energy transmitted through Aδ fibers that was necessary for the brain to detect the elicited sensory inputs, as compared to when visual stimuli were presented near the opposite limb. In addition, since the time interval between the visual and thermo-nociceptive stimuli for them to be perceived at the same time, and fall within the same time-window, is observer-specific (Manfron et al., 2020a; Stone et al., 2001; Tiippana and Salmela, 2018), we *individually* estimated it in a preliminary phase, using a TOJ task. The aim was to optimize the chances that the different inputs would interact during the threshold assessment phase, by desynchronizing the onset of each stimulus according to their specific conduction velocities.

Furthermore, Filbrich et al. (2019) suggested that visual stimuli located next to the non-stimulated hand were able to decrease the number of perceived nociceptive stimuli. Regarding our study, such an effect would suggest that higher thermo-nociceptive thresholds of Aδ fibers in the contralateral condition should have been observed as compared to the control condition, in which visual stimuli were presented in far space. However, no significant difference between the contralateral and the control conditions was observed. Since there was also no significant difference between the ipsilateral and the control conditions, but well between the ipsilateral and contralateral conditions, the visuo-nociceptive interactions observed during the threshold assessment of Aδ fibers might be mediated by similar multisensory mechanisms than the interactions reported in the study of Filbrich et al. (2019) but in different proportions. Indeed, interactions between different sensory inputs are hypothesized to stem from attentional and/or integrative mechanisms (e.g. Spence et al., 2004). The involvement of each mechanism is partly determined by the task used to study the interactions (Macaluso et al., 2016). Since the experimental context in which thermo-nociceptive thresholds were assessed was different from the detection task conducted in the study of Filbrich et al. (2019), it might be that these mechanisms were differently involved in each experiment. The "extinction" of the perception of a given stimulus by the co-occurrence of another stimulus is often defined in terms of competition between the several sensory targets in accessing attentional resources (e.g. Jacobs et al., 2011). In addition, according to Macaluso et al. (2016); and Talsma et al. (2010), salient stimuli would be typically bound to each other, with the intervention of pre-attentive integrative mechanisms, while competitive stimuli demand top-down attentional modulation to be processed. Interestingly, the salience of sensory events is boosted by the spatial proximity of the different sensory inputs (e.g. Stein & Stanford, 2008; Talsma et al., 2010). Therefore, the impact of the contralateral visual stimuli on the decreased number of perceived nociceptive stimuli reported in the study of Filbrich et al. (2019) could potentially result from attentional processes, whereas the facilitation effect induced by the ipsilateral visual stimulus, could potentially result from pre-attentive integrative processes. Regarding our findings, the pre-attentive integrative mechanisms could have also potentially mediated the impact of the ipsilateral visual stimulus on the detection threshold of inputs transmitted through Aδ fibers. This

hypothesis is supported by the larger variability in participants' responses (i.e. flatter slope) during the ipsilateral condition as compared to the contralateral condition. Based on the "unity assumption" theory (e.g. Chen & Spence, 2017; Welch, 1999), the consequences of two spatially and temporally congruent sensory inputs that integrate in a pre-attentive way is that their maximized interactions lead to less dissociation of each input (e.g. Spence et al., 2003). This could have increased participants' uncertainty about the actual perception of the laser stimuli, compared to the contralateral condition where the stimuli were easier to distinguish due to their distinct spatial position. In addition, for reason of survival, humans must be sensitive to impending threats to their body. When the visual stimulus was contralateral to the laser stimulus, their spatial incongruence may have decreased the power of the 'threat' embodied by the laser stimulus, leading to less interactions between the different stimuli as compared to the ipsilateral condition. However, no clear answer can be provided to the long-standing debate about the nature of the mechanisms (attentional vs integrative) that primarily regulate multisensory interactions (e.g. Macaluso et al., 2016; Talsma et al., 2010).

Finally, using a procedure enabling to selectively stimulate C-fiber afferents, we could investigate for the first time the ability of the information transmitted through C fibers to interact with extra-somatic stimuli such as visual stimuli. No effect of the location of the visual stimuli on the thermo-nociceptive thresholds of C fibers was however observed. There are several reasons why C-fiber afferents might be less likely to interact with extra-somatic stimuli than Aδ-fiber afferents, at least under the same experimental conditions. First, the transmission of unmyelinated fibers is ultra-slow as compared to the transmission of visual information. The chances that the different sensory inputs fall within the same-time window of interactions are poor and the brain would not be able to compensate for their different times of arrival. Second, C fibers are usually activated by low intensity thermal stimuli eliciting warm sensations whereas Aδ fibers are activated by stimuli of higher intensities that evoke pricking and burning sensations. From a functional point of view, we could hypothesize that Aδ fibers inform the cortex about a danger that is potentially more severe than the information conveyed by C fibers. The need to interact with other sensory modality to efficiently detect, localize and react to harmful stimuli could therefore be more important for Aδ fibers than for C fibers. However, it is important to point out that heat-sensitive C fibers are made of several subtypes, such as the warm-sensitive and the mechano-heat nociceptors C fibers (CMHs). Each subtype of unit has its own properties. CMHs are either slow adapting or fast adapting (e.g. Lenoir, Plaghki, Mouraux, & Van den Broeke, 2018; Schepers & Ringkamp, 2010; Weidner et al., 1999). Although the parameters of stimulation we used in both experiments, using the CO_2 laser and the *psi-marginal* adaptive method, could dissociate the selective activation of C-fiber afferents from the co-activation of Aδ-fiber afferents, we did not selectively activate the different subtypes of C-fiber afferents. Considering the parameters of stimulation used in our experiments, such as the surface of the skin stimulated (laser beam of 6 mm) and the lasting of the stimulations (100 ms), we probably mostly generated responses of the quickly-

responding cutaneous thermo-nociceptors. However, in more ecological environmental situations, multisensory interactions are also supported by long-standing stimulations. It might be relevant to use other stimulation procedures to investigate interactions between sustained nociceptive and visual stimuli.

In conclusion, the present study showed that the detection of a stimulus activating the nociceptive system is not only the outcome of the transmission of a sensory input from the nociceptor to the cortex, but also results from interactions with other sensory modalities. Importantly, it has been shown for the first time that close visual stimuli can decrease the detection threshold of inputs conveyed by Aδ-fiber afferents. Although the mechanisms underlying this modulation are not clearly identified yet, our results indicate that it might be possible to influence the neurophysiological activity of the nociceptive system using extra-somatic stimuli. Finally, the lack of influence of visual stimuli on C-fiber activation thresholds suggests that multisensory mechanisms affect the processing of thermo-nociceptive inputs differently depending on the type of nociceptive fiber that conveys the information.

Appendix: supplementary analyses

Reaction times to laser stimuli according to the device

To record participants' RTs, in Experiment 1, participants had to react to laser stimuli by pressing on the button of a response box with the thumb of the non-stimulated hand. In experiment 2, participants had to react to laser stimuli using the new 'tapping' device by lifting both index fingers from their respective metal plates. Since different motor responses were involved to use each device, we hypothesized that the RTs to laser stimuli might be different as well. Therefore, a pilot experiment was conducted with 10 participants before the second experiment to determine if the RTs recorded with the new device for responding to laser stimuli were different from the RTs recorded with the response box. In one block of stimulations, 40 stimuli were delivered on the left-hand dorsum. Participants had to respond as fast as possible by pressing the button of the response box with the thumb of the right hand. The target temperature of 20 stimuli was 48 °C (10 ms heating-ramp; 90ms plateau). The other 20 stimuli reached a temperature of 55 °C with the same stimulation profile. The different target temperatures were randomized. During a second block of stimulations, participants received laser stimuli on their left hand as well. They placed each index finger on the respective metal plates of the tapping device recording the RTs. Participants had to simultaneously lift both fingers from the metal plates as soon as they perceived a laser stimulus. The number of stimuli and their temperature profile were identical to the first block. When both index fingers were lifted, only RTs from the first lifted finger were recorded. The order of the two blocks was counterbalanced between participants.

Measures & Analyses

ANOVA for repeated measures was performed on participants' RTs with *response* (button *vs.* tapping) and *temperature* (48 °C vs. 55 °C) as within participant factors. Effect sizes were estimated with $\eta^2_{p.}$

Results

The main factor of interest, *response* was not significant ($F(1,9)=0.52$; $p=0.487$, $\eta^2_p=0.055$) while the *temperature* was significant ($F(1,9)=98.93$; $p<0.001$, $\eta^2_p=0.917$). Participants were indeed faster to respond to laser stimuli of higher temperatures (570.22 ± 161 ms *vs.* 1000.29 ± 115,32 ms for button condition and 566.71 ± 132.90 ms *vs.* 968.06 ± 102.68 ms for tapping condition). No interaction between both factors was highlighted ($F(1,9)=0.81$, $p=0.390$, $\eta^2_p=0.083$). These results suggest that the RTs to laser stimuli were not different between the devices used to record participants' responses

Number of false alarms according to the position of the visual stimulus

In Experiment 2, participants could have reacted more often to the potential presence of laser stimuli when a visual stimulus was next to the stimulated hand, while they actually did not detect any laser stimulus, as compared to a condition in which the visual stimulus was next to the non-stimulated hand. In order to verify that the number of false alarms could not explain any result reported both during the conditions dedicated to the assessment of the thresholds of C fibers and Aδ fibers, an ANOVA with repeated measures was performed on the catch trials, that is, on the percentages of detecting laser stimuli while no laser stimulus was applied with one factor *fiber* (*Aδ* vs *C fibers*) and one factor *catch trials* (*ipsilateral* vs *contralateral* vs *far* relatively to the tested hand). Results revealed a very low percentage of false alarms during catch trials (ipsilateral Aδ fibers: 1.87±4.43%; contralateral Aδ fibers: 1.5±3.48%; far Aδ fibers: 2±3.20%, ipsilateral C fibers: 2.75±2.68%, contralateral C fibers: 1.5±1.88%; far C fibers: 1.75±2.16%), and no significant difference neither for the main effect of *fiber* ($F(1,19) = 0.086$, $p = 0.773$, $\eta^2_p = 0.004$) nor for the main effect of *catch trials* ($F(2,38) = 1.574$, $p = 0.220$, $\eta^2_p = 0.077$), nor for the interaction between both factors ($F(2,38) = 0.970$, $p = 0.388$, $\eta^2_p = 0.049$). These results suggest that the number of false alarms was not different neither according to the fiber type stimulated nor to the position of the visual stimulus. In other words, the significant differences observed on the threshold and on the slope of the psychometric function during the stimulation of Aδ fibers would illustrate multisensory interactions between the visual and the thermo-nociceptive stimuli.

Reaction times according to the visual-stimulus conditions

Reaction times (RTs) to multisensory stimuli that share the same spatial position, are shorter than RTs to multisensory stimuli that are spatially incongruent (e.g. Spence & Driver, 2004). In the current study, the criterion that determined the activation of Aδ-fiber afferents was based on participants RTs. Therefore, for Experiment 2, we hypothesized that the effect reported of the visual stimulus in the *ipsilateral* condition on the decreased activation threshold of Aδ fibers as compared to the contralateral condition, in which the visual and laser stimuli were not spatially congruent, might result from faster RTs of the participants to react to the laser stimuli rather than to a decreased activation threshold. To test this hypothesis, we performed analyses of variance for repeated measures on the participants' RTs to all detected laser stimuli during the assessment of Aδ-fiber threshold, according to each visual condition (*ipsilateral* vs *contralateral* vs *far*). No significant difference emerged from analyses ($F(2, 870) = 0.53$, $p = 0.588$, $\eta^2_p = 0.001$; *ipsilateral* condition: 756.30 ± 321.48 ms, *contralateral* condition: 755.67 ± 329.01 ms, *far* condition: 776.24 ± 323.59 ms). These findings support that the decreased thermo-nociceptive threshold of Aδ fibers that was observed when the visual stimuli were located close to the hand receiving the laser stimuli, results from a decreased amount of energy transmitted through Aδ fibers required for the brain to detect the elicited sensory inputs.

General Discussion

The way human beings adapt their behavior to the environment surrounding them depends on the interactions between different sensory inputs. One sensory event solicits several sensory channels at the same time and adequate interaction between the different sources of information enables us to deploy adaptive behaviors, such as protective movements to avoid potential threats for the body's integrity. Nociception, by coding, transmitting and processing the sensory information delivered by the nociceptors (Legrain, 2017), holds the double function to warn the brain about damages on the body (interoception) and about the cause(s) of such damages (exteroception) (Filbrich et al., 2019; Haggard et al., 2013). The processing of a nociceptive stimulus is therefore influenced by information from other sensory modalities (e.g. Legrain et al., 2011), such as external stimuli that can have an immediate impact on the body's integrity (Legrain & Torta, 2015). Accordingly, studying a sensory system in interaction with information provided by other senses properly reflects most of the situations we are exposed to, on a daily basis. Multisensory research is thus a particularly relevant area of interest, which has been explored for the last century. In the context of nociception and pain, it is however a more recent topic of research, much of which still remains to be discovered, while pain represents a central societal challenge that generates considerable suffering for a significant part of the population.

Several cognitive functions allow the nociceptive system to fulfill its exteroceptive function, such as attention and spatial perception in order to adequately detect and localize the source of injury, and prepare motor actions to protect the integrity of the body (Legrain & Torta, 2015). The aim of this thesis was to deepen our understanding of the spatial and temporal mechanisms that govern visuo-nociceptive interactions and, specifically, of the detection of nociceptive inputs while interacting with visual stimuli. Previous studies about visuo-nociceptive interactions had mostly investigated the spatial representation underlying the localization of a nociceptive input, from the remapping of the somatotopic to the spatiotopic maps (Vanderclausen, Bourgois, et al., 2020; Vanderclausen, Manfron, et al., 2020) into a common, peripersonal, representation (De Paepe et al., 2014, 2015, 2016, 2017; Filbrich et al., 2017a,b; Filbrich et al., 2018; Vanderclausen et al., 2017). With regard to our objective, these studies highlighted the spatial factors that regulate visuo-nociceptive interactions, such as the spatial congruence of each stimulus, in order to examine the extent to which they can influence the detection thresholds of the nociceptive system.

Furthermore, interactions between different sensory inputs are also driven by their temporal proximity. However, most of the multisensory studies have examined the temporal relationships between visual and auditory or visual and tactile stimuli (e.g. Colonius & Diederich, 2004; Morein-Zamir, Soto-Faraco, & Kingstone, 2003; Spence et al., 2003; Stone et al., 2001; Sugita & Suzuki, 2003). Since each sensory system has its own conduction velocity and distance conveying the sensory information to the cortex and, that the nociceptive system is particularly slow as compared to other senses, prior to investigating the influence of visual stimuli on the detection of nociceptive stimuli, we examined the temporal factors that would optimize visuo-nociceptive interactions. This allowed us to set up new experimental paradigms, based on psychophysical adaptive methods that could be easily re-used in other contexts. Also, by using advanced stimulation techniques, we were able to dissociate the multisensory processes of the two different main types of fibers that compose the nociceptive system, the Aδ- and C-fiber afferents. Each experiment of this thesis was conducted with the common outline of studying step by step the spatial and temporal factors that govern visuo-nociceptive interactions, with the ultimate aim of examining the modulation of the detection thresholds of inputs transmitted through the nociceptive system by the presence of visual stimuli. Results of our experiments offer insights into how the interactions with our close surroundings may affect the activity of the nociceptive system.

This general discussion will critically discuss the main findings of the experiments that have been conducted throughout this thesis and outline avenues for further reflection.

1 MAIN FINDINGS

1.1 CHAPTER 1 "INVESTIGATIONS OF SPATIAL ASPECTS"

Study 1 focused on the sensory feedback that regulate the spatial alignment of visuo-nociceptive interactions in the peripersonal space of the stimulated limb. More specifically, we studied the extent to which visuo-nociceptive interactions could be mediated by the *visually* perceived proximity of the stimulated hand relative to the visual stimuli in external space. Indeed, they could also rely on other sensory feedback such as proprioception, that is, the sensation of *feeling* the stimulated hand close to the external visual stimuli. During a visual TOJ task, the temporal order judgment of visual stimuli was biased in favor of the cued side of space, that is, where the unilateral nociceptive cues were applied. But also, and above all, by manipulating the visual information about the location of the hands, these biases were greater in the condition in which the hands were seen (vision condition) as compared to the condition in which they were hidden by a wooden board (no-vision condition). As in this latter condition, the wooden board was placed above the hands, we investigated whether the significant difference between the vision and no-vision conditions was due to the presence of a barrier separating the stimulated hands from the visual stimuli rather than to the fact that the hands were not seen. To this aim, we used a third condition in which a translucent barrier was placed above the hands (vision through glass condition), to make any direct contact between the visual stimuli and the nociceptive cues impossible, in the same way as in the condition in which the hands were hidden by the wooden board. We hypothesized that the presence of the barrier could possibly provide additional protection to the body and, therefore, potentially decrease visuo-nociceptive interactions as compared to the condition without a barrier. The spatial biases induced by the nociceptive cues on the temporal order judgment of visual stimuli in that condition, as compared to a full sight of the hands, were not significantly different. This indicates that the presence of a barrier placed above the hands did not explain the significant differences observed between the condition in which the hands were seen and the condition in which sight of the hands was prevented. Finally, because the spatial biases induced by the nociceptive cues were still present when the sight of the hands was prevented, albeit to a lesser extent, the role of visual feedback in the regulation of visuo-nociceptive interactions could not really be dissociated from the role of proprioceptive feedback. However, these findings highlight the importance of visual feedback for determining spatial mapping of visuo-nociceptive interactions, which are thus optimized when visual information about the location of the stimulated limb, relative to the visual stimuli, is available. The results of this experiment ultimately show that, in order to optimize visuo-nociceptive interactions and in turn observe a potential modulation of the activity of the nociceptive system by the presence of external visual

stimuli, the visual stimulus should be presented spatially close to the nociceptive stimulus and that the stimulated limb should be seen.

1.2 Chapter 2 "Investigations of temporal aspects"

In addition to the importance of spatial congruence, multisensory interactions are also enhanced by the temporal co-occurrence of the different sensory inputs. Given that each sensory input is transmitted from the receptors to the cortex within its own sensory system, holding specific distances and conduction latencies, **Study 2** was designed to investigate the necessary asynchrony between a visual and a nociceptive stimulus to promote their perception of simultaneity. That asynchrony was estimated for each of the two main categories of fibers composing the nociceptive system, Aδ and C fibers. By using a TOJ task with pairs of stimuli composed by one visual and one laser input, we observed that, when applied on the hand dorsum, a laser stimulus eliciting Aδ-fiber responses needs to lead the visual stimulus on average by ~76 ms, while a laser stimulus activating only C-fiber afferents needs to lead the visual stimulus on average by ~577 ms to be perceived at the same time as the visual stimulus. Participants' performance during the task was more variable for C-fiber afferent than Aδ-fiber afferent stimulations, probably because of the different properties of each fiber type. Indeed, C-fiber stimulations induce diffuse sensations that might be less clear to detect than the pricking and localized sensations elicited by the activation of Aδ fibers. In general, the range of the PSS values, for each type of nociceptive fibers, was quite large, suggesting that there were important interindividual differences and that the Point of Subjective Simultaneity (PSS) would be observer-specific. Based on these results, we showed that, in order to maximize the perception of simultaneity of visual and nociceptive stimuli under laboratory conditions, it seems to be relevant to estimate and implement the individual PSS value of each participant, between the onset of each stimulus, with the ultimate aim of facilitating interactions between the visual and nociceptive stimuli.

1.3 Chapter 3 "Investigations of spatio-temporal aspects"

Study 3 is an in-depth continuation regarding the findings of Study 2. Since spatial and temporal factors are intimately connected during multisensory interactions, the impact of spatial congruence of visuo-nociceptive stimuli on their perception of simultaneity was examined. Participants performed a TOJ task composed of pairs of one visual and one laser stimulus but, this time, the visual stimulus could either be located next to the laser stimulus or on the other side of space, next to the non-stimulated hand.

One group of participants received stimulations related to C-fiber activations while another group received stimulations related to Aδ-fiber activations. We hypothesized that the PSS between visual and nociceptive stimuli would be smaller when the stimuli were spatially close as compared to an incongruent position. We also hypothesized that the spatial proximity between the stimuli would increase their interactions, producing a unity effect related to integrative mechanisms (‘*unity assumption*’), that would therefore decrease the accuracy of the participants to correctly judge the temporal order of each stimulus. For both fiber types, the PSS was significantly smaller when the visual stimulus was close to the laser stimulus, but no effect of spatial congruence on the performance of participants to correctly judge the temporal order of the stimuli was reported. Visuo-nociceptive interactions in the congruent position would thus possibly rely on attentional processes rather than on automatic integrative mechanisms. Finally, this study highlights the importance of combining the spatial and temporal components of the stimuli when studying visuo-nociceptive interactions under optimal conditions.

In **Study 4**, we investigated the effect of the spatial position of a visual stimulus on the detection threshold of inputs conveyed by thermo-nociceptive Aδ and C fibers. We hypothesized that the detection threshold of inputs conveyed by both types of fibers would be decreased when the visual stimulus is close to the hand stimulated by the laser stimulus (ipsilateral condition) as compared to a condition in which the visual stimulus is in front of the participant (control condition), in a farther space. A visual stimulus contralateral to the stimulated hand (contralateral condition) would increase the detection threshold of stimuli transmitted through the nociceptive fibers. Importantly, to maximize the likelihood of perceiving the two different stimuli at the same time and optimize their interactions, we predefined the individual PSS value of each participant before assessing their activation thresholds, based on the procedure developed in Study 2. In addition, to estimate participants’ threshold during each experimental condition, we implemented the *psi-marginal* adaptive method, known to decrease the potential biases of nuisance parameters on the estimation of the parameters of interest. Two different experiments were conducted. Oddly, results of the first experiment suggested that the visual stimuli that were contralateral to the stimulated hand decreased the detection threshold of stimuli conveyed by Aδ fibers as compared to a condition in which the thresholds were assessed without any visual stimulus. However, several methodological issues were identified, calling into question the reliability of these findings. The second experiment was therefore designed to reduce the methodological biases encountered during the first one, by changing the device used to record participants’ responses, the criterion used to dissociate the different types of fibers, the position and duration of the visual stimuli, as well as the instructions given to the participants. This time, results of the second experiment showed decreased thermo-nociceptive thresholds of Aδ-fiber afferents when visual stimuli were located close to the stimulated hand relative to a contralateral position, close to the non-stimulated hand. In other words, the necessary amount of energy transmitted through Aδ fibers required for the brain to detect the nociceptive input was

decreased by the visual stimuli presented in the peripersonal space of the stimulated hand. For the first time, we demonstrated that modulating the detection threshold of the nociceptive system using the sensory environment surrounding the body is feasible. In addition, participants' responses were more variable in the ipsilateral condition than in the contralateral condition, suggesting that the observed interactions may be mediated by integrative mechanisms. Finally, no significant interaction between the visual and the laser stimuli influenced the detection threshold of stimuli conveyed by C-fiber afferents. This could be related to the properties of the fibers and/or to the specific function they carry out in the nociceptive system, possibly making them less sensitive to multisensory interactions than Aδ fibers, at least when studied under identical conditions.

2 INTERPRETATIONS AND THEORETICAL IMPLICATIONS

2.1 PERCEPTION OF SIMULTANEITY BETWEEN VISUAL AND NOCICEPTIVE INPUTS: A CHALLENGE FOR THE BRAIN?

Spatial and temporal alignment of different sensory stimuli optimize their interactions. Electrophysiological studies at the single cell level in animals and behavioral studies in humans agree that multisensory interactions are possible in a defined time-window. However, the factors that determine that time-window, and thus the ability of the brain to resynchronize the arrival times of inputs from different sensory modalities, with different conduction velocities, are debated in the literature.

On the one hand, studies at the multisensory neuron's level suggest that the "interactive time-window" of different sensory inputs is related to the overlapping of the neuron discharge trains elicited by each input (Meredith et al., 1987), which are not determined by the conduction velocity of each sensory system. In the same vein, some behavioral studies afford that, among several stimulus onset asynchronies (SOAs) implemented between two different sensory inputs, the strongest interactions appear when the SOA is defined at zero, that is, when no asynchrony separates the inputs. For instance, Frassinetti, Bolognini, and Làdavas (2002) showed that the perception of visual stimuli presented below the detection threshold is increased by unrelated sounds only when these sounds are presented from approximately the same spatial location and at the same time, as compared to a 500 ms interval between the sound and visual inputs. Though, researchers have only compared the impact of two SOAs that were extremely different (0 ms vs. 500 ms). Since stimuli interact in a time-window, one could wonder whether other, smaller, SOAs could have also produced visuo-auditory interactions. Indeed, other researchers have shown that interactions take place when stimuli are presented at the same time, but also when they are presented successively. For instance, in a study examining the inhibition of painful stimuli by vibrotactile stimuli applied on the back, the interaction between the tactile and noxious stimuli occurred within a time-window ranging from –60 ms (nociceptive stimulus first) to 500 ms (tactile stimulus first). The maximal inhibition of the painful sensation by the tactile stimulus occurred when the two sensory stimuli were delivered at the same time or when the tactile stimulus was administered 20 to 40 ms after the nociceptive stimulus (Inui et al., 2006). The fact that maximal interactions are also observed when no asynchrony, respective to the conduction velocity of each system, is implemented between the stimuli is consistent with the fact that, in the environment, different sensory inputs elicited by the same sensory event occur at the same time and most of the time, individuals do not perceive the asynchrony. Under some conditions, the brain would resynchronize the respective arrival of each input (e.g. Morein-Zamir

et al., 2003; Spence & Squire, 2003; Sugita & Suzuki, 2003). This is corroborated by the phenomenon of "simultaneity constancy", characterized by the perception of simultaneity of two different sensory stimuli when they are delivered at the same time, despite differences in their respective latency (Kopinska & Harris, 2004).

On the other hand, some studies rather show that the implementation of a lag between the different inputs according to their respective conduction velocity induces the best chance that the two sensory inputs fall within a common interactive time-window, and thus interact together (e.g. Colonius & Diederich, 2004; Filbrich et al., 2019; Fujisaki et al., 2012; Lewald & Guski, 2003). For instance, when using basic stimuli (LEDs and burst sounds) to study the spatial ventriloquist effect, the best interactions occur when auditory stimuli are presented 50 to 100 ms after the visual stimuli (Lewald & Guski, 2003) and vanish if the auditory inputs are presented ~100 ms before the visual inputs (Slutsky & Recanzone, 2001).

However, the controversy between studies that report brain compensation for the asynchrony between the arrival times of each input and those that report the need to set a lag between the inputs from different senses to achieve simultaneity, and better multisensory interactions, remains unsettled to this date. According to Fujisaki et al. (2012), the ease with which the brain compensates for the difference between the *brain time* and the *subjective time* would depend on the specific combination of sensory modalities. Given that visuo-nociceptive interactions have a rarer occurrence in daily-life as compared to visuo-auditory or visuo-tactile interactions, and that the nociceptive system is extremely slow to transmit the sensory information to the cortex, an automatic temporal adaptation of the brain to process visuo-nociceptive inputs together is questionable, especially under laboratory conditions, with stimuli that are usually not related to each other.

In this regard, the study that reported significant visuo-nociceptive interactions on the detection of nociceptive stimuli introduced a lag between the onset of electrical stimuli, activating Aδ fibers at their threshold, and visual stimuli (Filbrich et al., 2019). To define the amount of time between the respective onset of each input in order for them to be perceived approximately simultaneously, the authors subtracted the latency of the first evoked potential of a visual input (~80 ms) from the latency of the first evoked potential of a nociceptive input activating Aδ-fiber afferents (~130 ms), as measured by previous studies (Michel et al., 2004; Mouraux & Plaghki, 2007). Interestingly, in a preliminary unpublished experiment inspired by the paradigm used in Filbrich et al. (2019), we did not replicate the visuo-nociceptive interactions that the authors reported after having removed the 50 ms asynchrony between the respective onsets of the visual and nociceptive inputs. However, the experimental procedure was slightly different as well, which prevented us from drawing any conclusion. In addition, Filbrich et al. (2017a) examined in which time-window the bias induced by a close nociceptive cue on the temporal order judgment of visual stimuli would be maximal. Their aim was not to optimize the perception of simultaneity between visual and

nociceptive stimuli, but to examine which time interval between the nociceptive cue and the visual stimuli induced the greatest bias on participants' judgments. To do so, they delivered the nociceptive cues either 600 ms, 400 ms or 200 ms before the pairs of visual stimuli. At each time interval, the temporal order judgment of visual stimuli was biased in favor of the cued side of space. However, the maximal interaction occurred when the cue was presented 200 ms before the visual stimuli. This supports that visuo-nociceptive interactions are maximized when the respective inputs are presented close together in time as compared to larger asynchrony situations. Interestingly, the authors also reported that during a pilot experiment, decreasing the asynchrony between nociceptive and visual inputs to 150 ms instead of 200 ms, led to visual stimuli being perceived before the nociceptive cues in some participants. Again, this observation illustrates the slower conduction velocity of the nociceptive system as compared to the visual system. Finally, Zampini et al. (2007) investigated the influence of attention on the perception of simultaneity of visuo-nociceptive stimuli. In their control condition, when attention was not manipulated, ~40 ms were necessary between the laser stimulus activating Aδ fibers and the visual input, both presented on the forearm, to achieve simultaneity.

The aforementioned studies about visuo-nociceptive interactions support the relevance of studying the specific time interval required between a thermo-nociceptive and a visual stimulus for them to be perceived at the same time, in order to desynchronize their respective onsets, optimize their perception of simultaneity, and maximize their interactions. In Study 2, we determined that the asynchrony between visual and thermo-nociceptive inputs eliciting Aδ-fiber responses was estimated around 76 ms for both stimuli to be perceived simultaneously. Crucially, the necessary asynchrony between visual and thermo-nociceptive inputs selectively activating C fibers was not comparable to any other modality, with an average amount of time of *half a second*. This huge discrepancy is an additional argument that questions the ability of the brain to automatically resynchronize the arrival times of each sensory stimulus. However, a nuance can be provided by the results of Study 3, according to which the asynchrony between the different stimuli is reduced when they are spatially congruent as compared to when they are located on opposite sides of space, regardless of the stimulated fibers. This suggests that the challenge for the brain to resynchronize different sensory inputs would be less demanding when the visual and nociceptive stimuli are close with regard to each other, because they would be more likely to arise from the same sensory event (e.g. Welch, 1999). Finally, in Study 4, if no asynchrony between the thermo-nociceptive and visual stimuli had been implemented, participants would have most likely always perceived the visual stimulus earlier than the thermo-nociceptive stimulus. Although perception of simultaneity cannot always be guaranteed for all pairs of stimuli (because of the different temperatures delivered to assess the activation threshold of the nociceptive fibers), since visuo-nociceptive interactions were reported for stimuli eliciting Aδ-fiber responses, this suggests that the visual and

thermo-nociceptive stimuli probably occurred within the same time-window of interactions.

In conclusion, we do not argue that exact perception of simultaneity is necessary to observe visuo-nociceptive interactions, nor do we rule out the possibility that the brain is able to compensate for the different arrival times of a visual and a thermo-nociceptive stimulus, under natural conditions. However, the information collected throughout our different studies seems to indicate that the issue might be different under experimental conditions. If one wants to study the exteroceptive function of nociception to understand how the detection of nociceptive inputs is affected by external visual information, under laboratory conditions, using basic stimuli, we recommend to artificially resynchronize the arrival times of each stimulus. Otherwise, it is very likely that the visual stimulus would be systematically perceived as occurring first.

2.2 Modulation of thermo-nociceptive thresholds by other senses

The study of the temporal relationships between visual and nociceptive stimuli allowed us to set up optimal conditions for exploring the influence of the spatial position of a visual stimulus on the detection threshold of inputs conveyed by the different types of fibers that compose the nociceptive system. In Study 4, we were therefore able to show that multisensory interactions with our close environment would affect the activity of the nociceptive system. Spatially congruent visual stimuli presented in the peripersonal space of the limb on which laser stimuli were applied decreased the detection threshold of inputs conveyed by Aδ fibers, as compared to an incongruent position. Such facilitation effect induced by the presence of a visual stimulus had been previously reported on the ability to perceive and correctly localize vibrotactile stimuli (Van der Biest et al., 2016) and on the number of detections of nociceptive stimuli, delivered on the hand dorsum, at an intensity activating Aδ fibers at their threshold (Filbrich et al., 2019). The added value of our findings is that we achieved to modulate the detection threshold itself, by solely presenting extra-somatic inputs in the peripersonal space. From a functional point of view, to survive, humans must be more sensitive to impending threats that can potentially reach their body. The decrease of the detection threshold of inputs transmitted through Aδ-fiber afferents could be interpreted as a final warning provided by the brain to prompt individuals to initiate effective reactions before risking more serious injuries. As a reminder, the function of the PPS would be to integrate somatic inputs with extra-somatic inputs occurring close to the stimulated limb, in order to prioritize the processing of meaningful or potentially harmful stimuli for the integrity of the body (Graziano & Cooke, 2006; Legrain & Torta, 2015). In this sense, the near visual stimulation would increase the perceived threat induced by the thermo-nociceptive stimulation. This hypothesis could potentially also explain why, when the visual stimulus was located

close to the non-stimulated hand, no clear modulation of the detection threshold of inputs conveyed by Aδ-fiber afferents was observed. When different sensory inputs are not spatially congruent, their interactions are decreased, even more when the extra-somatic input is not in the PPS of the stimulated limb (De Paepe et al., 2017; Filbrich et al., 2017b). Since the two inputs would interact less, the danger that the nociceptive input may represent would also be reduced.

In addition, the selective activation of C fibers allowed to investigate for the first time the influence of external visual stimuli on the processing of a thermo-nociceptive input only transmitted by C-fiber afferents. No effect of the visual stimulus position on the thermo-nociceptive threshold of C fibers was however observed. Possibly, this might suggest that the exteroceptive function of the nociceptive system that informs the brain about the potential cause of body damages is mainly carried by Aδ-fiber afferents. Since Aδ fibers convey information from higher temperature intensities than C fibers, eliciting pricking or burning sensations as compared to warm and diffuse sensations (Plaghki & Mouraux, 2005), it could be hypothesized that the information conveyed through Aδ fibers inform the cortex about a danger that is potentially more severe than information conveyed by C fibers. Their potential need to interact with other sensory stimuli might therefore be of greater importance for survival. In addition, Aδ fibers could require less attentional resources to be detected and therefore could more automatically interact with extra-somatic information. Nevertheless, it could also be that information conveyed by C-fiber afferents interact with visual stimuli under different conditions than Aδ-fiber afferents, especially considering that the profile of stimulations of the CO_2 laser used to selectively activate C-fiber afferents in the present studies, did not allow selectively activating the different subtypes of C units (see below).

Finally, it is important to emphasize that the modulation of the perceived intensity of a nociceptive input has previously been investigated by manipulating the visual information about the stimulated hand itself. Visual analgesia describes the phenomenon under which visual information about the stimulated hand can reduce the perception of noxious stimuli applied on the hand dorsum, such as their pain intensity ratings (Longo et al., 2009; Longo et al., 2012; Mancini et al., 2013) or pain threshold (Mancini et al., 2011), and modulate their cortical processing (Longo et al., 2009; Longo et al., 2012; Mancini et al., 2013). At first glance, visual analgesia appears conflicting with our results. However, since in the context of the visual analgesia phenomenon, no visual stimulus appears in the PPS around the stimulated hand, visual analgesia and our study might illustrate distinct adaptive functions of the nociceptive system. In addition, although the authors agree on the fact that vision of the stimulated hand during laser-induced stimuli modulates the cortical processing of the nociceptive stimuli, some studies have questioned the robustness of this effect on the modulation of their perceived intensity (Torta et al., 2015; Valentini et al., 2015).

2.3 MULTISENSORY INTEGRATION VS. ATTENTION

The previous section addressed the extent to which the function of the nociceptive system and the PPS may explain the modulation of the detection threshold of inputs conveyed by Aδ fibers by the presence of visual stimuli in the surrounding space. The potential multisensory mechanisms that mediate such visuo-nociceptive interactions will now be discussed according to integrative and attentional processes[7]. The degree to which each mechanism is involved in a given situation, however, remains a matter of debate (Macaluso et al., 2016).

As a reminder, multisensory integration can refer to automatic processes integrating spatially and temporally congruent stimuli together (e.g. Meredith & Stein, 1993), independently of attention and awareness. An example of such bottom-up multisensory integrative phenomenon would be the activity of the multisensory neuron of the superior colliculus of the cat (Meredith et al., 1987).

Multisensory integration can, in turn, enhance the saliency of the sensory event and therefore capture the organism's attention (e.g. Aller et al., 2015; Macaluso et al., 2016). Attention would boost the initial processing of the sensory event in a top-down fashion. Importantly, attention is either bottom-up or top-down and can also facilitate interactions without initial integrative processing. For example, in the case of spatial attention, the processing of a sensory input from one modality draws (bottom-up) attention to its location, which facilitates the processing of another subsequent input from another modality (Spence et al., 2004), such as the effect of the unilateral nociceptive cues on the biased temporal order judgments of pairs of visual stimuli, in favor of the cued side of space, in Study 1.

Last but not least, there are top-down modulations on bottom-up integrative mechanisms that does not necessarily involve attention. This refers to the 'unity assumption' concept, defined as the *"observer's assumption or belief that two or more unisensory cues belong together"* (Chen & Spence, 2017, pp.1). The unity assumption maximizes the possibility for the brain to bind stimuli from different sensory channels together in a unified representation (Welch, 1999). As a consequence, the different stimuli are less easy to discriminate. That mechanism would explain the effect of spatial congruence on the decreased performance of participants in judging which of two different sensory inputs occurred as first in visuo-auditory TOJ tasks (e.g. Spence et al., 2003; Zampini et al., 2003).

[7] In the following description, it is important to distinguish 'bottom-up' and 'top-down' fashions for integrative mechanisms from 'bottom-up' and 'top-down' attentional mechanisms, since they do not relate to the same processes (e.g. Chen & Spence, 2017).

In summary, bottom-up integrative mechanisms do not necessarily result in top-down processing, there can be top-down modulation on integrative mechanisms that does not necessarily involve attention and, attention does not necessarily emerge after bottom-up integrative mechanisms. Each process can potentially affect the level of multisensory interactions. Even if this debate is necessary to nourish our reflections, we have to consider that in most of sensory contexts, multisensory integration and attention go hand in hand to process multisensory events (Macaluso et al., 2016). Since the nature of a given task influences the level of interaction between inputs (see Figure 1), it is more than likely that the tasks conducted throughout this thesis recruited one or several of these processes in different proportions (Chen & Spence, 2017; Fujisaki et al., 2012; Macaluso et al., 2016).

To support this argument, we can compare the results of Study 3 and 4. In Study 3, when we examined the effect of the spatial congruence between the visual and the thermo-nociceptive stimulus on their perception of simultaneity, the Point of Subjective Simultaneity (PSS) was affected, but not the slope of the psychometric function, regardless of the fiber type activated. The slope illustrates the noise in participants' performance to accurately judge the temporal order between the two different inputs. Previous intermodal TOJ tasks in visuo-tactile and visuo-auditory modalities report that an effect of spatial congruence on the slope – or on the JND that is derived from the slope – is an index of unity assumption, that relates to top-down integrative mechanisms (e.g. Spence et al., 2003; Zampini et al., 2003). However, since participants' performance did not seem to be decreased by the spatial congruence of the visual and thermo-nociceptive inputs in Study 3, it was hypothesized that attentional processes rather than integrative mechanisms regulated the interactions observed during the TOJ task.

On the contrary, in Study 4, in addition to the effect of the spatial congruence between the visual and thermo-nociceptive stimuli on the detection threshold of thermo-nociceptive inputs transmitted through Aδ fibers, we observed an effect on the slope. In this case, the slope indicated the noise during the assessment of the thermo-nociceptive threshold. Indeed, at a given temperature, participants' responses were more variable when the visual stimulus was located next to the hand receiving the thermo-nociceptive stimulus as compared to the contralateral condition. Given that the visual and thermo-nociceptive stimuli appeared at approximately the same location, and perceived at approximately the same time, their interactions may arise from integrative mechanisms in a bottom-up fashion. In turn, top-down modulation by the *unity assumption* would have increased the uncertainty of participants' responses in having detected or not the thermo-nociceptive stimuli, but would also have compensated for the potential lag between the arrival times of each stimulus to the cortex, by facilitating their connection. Indeed, although we implemented the individual PSS between the stimuli during the assessment of the thresholds to maximize their perception of simultaneity, it is possible that they were not always perceived at the

same time (see above). As mentioned by Chen & Spence (2017) "*The unity assumption certainly serves as one of the key mechanisms by which the human brain solves the crossmodal binding problem; that is, how signals from the different senses are encoded into a unified object/event representation".*

In addition, in Study 3, the PSS between the visual and thermo-nociceptive stimuli eliciting C-fiber responses was significantly smaller when the spatial position of each input was congruent. In a way, information from C fibers can therefore interact with external visual stimuli when attentional processes are involved. Regarding study 4, no effect of the position of visual stimuli was reported neither on the detection threshold of inputs selectively conveyed by C-fiber afferents, nor on the slope of participants' responses. Since about *half a second* is necessary between a visual and a laser stimulus activating C-fiber afferents to achieve simultaneity (as shown in Study 2 and in Study 3), in contrast to Aδ fibers, C fibers would not be able to automatically integrate with visual stimuli, even when there is an artificial resynchronization of their respective arrival times to the cortex. In brief, the confrontation of the results of Study 3 and Study 4 suggests that C fibers can interact with extra-somatic information, but perhaps under attentional mechanisms rather than under integrative mechanisms.

In conclusion, interactions between visual and thermo-nociceptive stimuli eliciting Aδ-fiber responses would emerge from both automatic integration and attentional processing, according to the situation. Interactions between visual and thermo-nociceptive stimuli selectively activating C-fiber afferents appear to be less automatic and thus, if observed, could rather result from attentional processes. Finally, whether attentional or integrative processes mediated the observed visuo-nociceptive interactions, participants had to recruit their general attentional resources to perform each experiment.

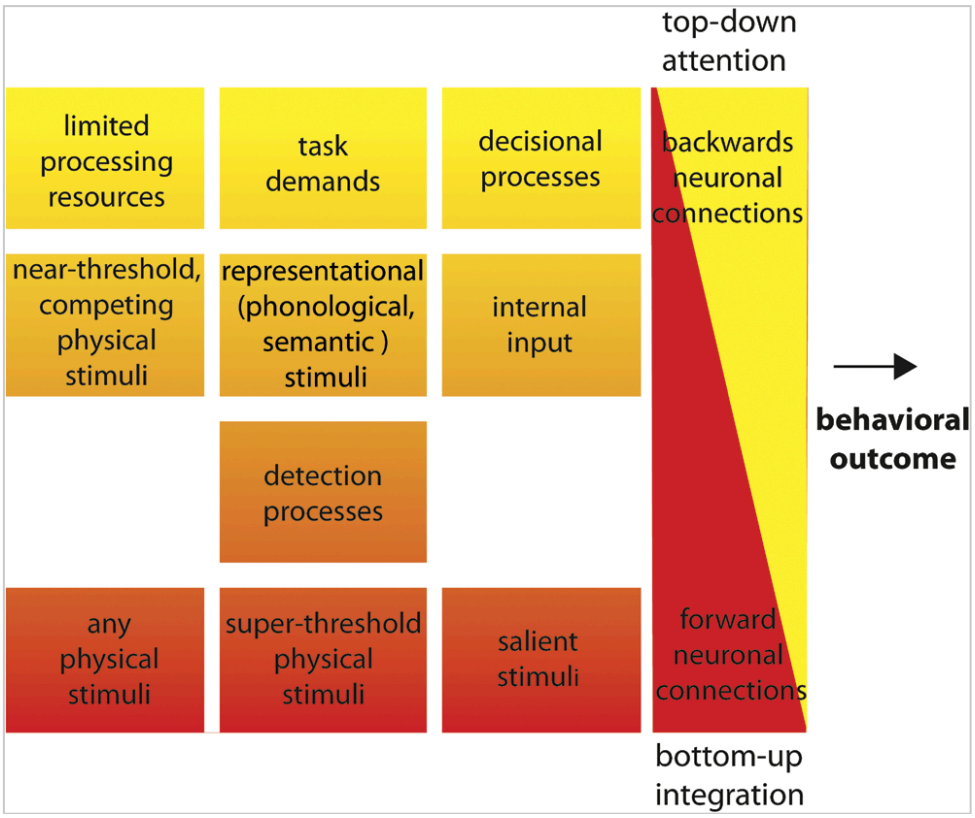

Figure 1. Top-down attention vs. bottom-up integration. This schema intends to explain the influence of different factors on the recruitment of *multisensory integrative mechanisms* vs. *attention* for a given sensory context. According to Macaluso et al. (2016), the mutual influence of multisensory integration and attention is determined by the sensory input, the task and the cognitive state of the individual. Based on this schema, in Study 3, the decisional processes to discriminate the temporal order between visual and thermo-nociceptive inputs would have recruited top-down attentional mechanisms. During the threshold assessment in Study 4, detection processes were involved to react to laser stimuli, and some supra-threshold stimuli were delivered using the *psi-marginal* adaptive procedure. Thus, integrative mechanisms could have regulated the interactions between the close visual stimuli and laser stimuli during Aδ-fiber stimulations. However, as illustrated in the figure, top-down attention and integrative mechanisms often regulate multisensory interactions together. *Adapted from Macaluso et al. (2016), pp. 12.*

3 LIMITATIONS AND CHALLENGES FOR FUTURE RESEARCH

Although we have investigated many questions that had remained unanswered so far about how visual stimuli can affect the detection threshold of the nociceptive system, there are still areas of shadows that need to be cleared up. Moreover, the experiments that have been conducted are not without flaws. Some avenues for improvement and reflections for future research will also be addressed in this section.

3.1 VISUAL VS. PROPRIOCEPTIVE FEEDBACK?

Based on the first study of this thesis, visuo-nociceptive interactions would be particularly enhanced when visual information about the position of the stimulated hand with regard to the visual stimuli is available, as compared to a situation in which vision of the stimulated hand is prevented. However, when visual information about the spatial proximity between the stimulated hand and the visual stimuli was not available, the spatial bias induced by the unilateral nociceptive cues on the temporal order judgment of visual stimuli was still significant. Therefore, we could not conclude that determining spatial congruence in interactions between nociceptive and visual stimuli mainly relies on visual feedback or that proprioception is less important, especially because we did not test a condition in which no proprioceptive feedback was available. It might be that the combination of both visual *and* proprioceptive feedback about the proximity between the hand receiving the nociceptive stimuli and the visual stimuli in external space optimizes their interactions. While it might be experimentally challenging to suppress any proprioceptive feedback, it could be interesting to manipulate proprioceptive feedback by experimentally induced illusions and see whether vision can actually overrule proprioceptive feedback, based on studies that have been proposed in the context of visuo-tactile interactions (e.g. Pavani et al., 2000). More specifically, participants would perform a visual TOJ task on pairs of LEDs placed on a table, with nociceptive cues applied unilaterally or bilaterally on the hands, which would be occluded from view by the table. The visual stimuli would thus be presented well above the hands. In half of the conditions, two rubber-hands would be placed on the surface of the table, spatially aligned with the real participants' hands, that would still be hidden under the table. Each rubber hand would be located close to one of the visual stimuli of the pair. In this situation, the visual information provided by the rubber-hands would raise the illusion that they were the participants own, as an integrated part of the participants' body (see rubber-hand illusion, Botvinick and Cohen, 1998). Visually, the visual stimuli would thus be located next to the nociceptive stimuli (nociception mislocated to the rubber hands), while in reality they would be located farther away from the nociceptive stimulation, that is, the unseen real hands, as

specified proprioceptively. If the biases induced by the close unilateral nociceptive cues on the temporal order judgment of visual stimuli during the 'rubber-hand' condition are more important than in the condition without the rubber-hands, this would suggest that visual feedback about limb position can overrule proprioceptive feedback if the two are mismatching, as shown for visuo-tactile interactions (Pavani et al., 2000).

3.2 Temporal congruence or Perception of simultaneity?

The open debate about the factors that determine the time-window of multisensory interactions in humans brings us to the following questions: (1) *can visuo-nociceptive interactions also be observed, under laboratory conditions, when there is no specific temporal delay between the respective administrations of each input* and, (2) *do visual and nociceptive systems follow the same temporal rules of interactions than other sensory systems?*

One way to answer the first question would be to replicate the second experiment of Study 4 without implementing any asynchrony between the administration of the thermo-nociceptive and visual stimuli. On the one hand, if interactions between the close visual and thermo-nociceptive stimuli on the detection threshold of inputs transmitted through Aδ fibers are still observed or, even, manifest in a larger extent, this would suggest that the time-window of interactions for visuo-nociceptive modalities is large enough for the brain to resynchronize both inputs, given illusion of "*simultaneity constancy*"(Kopinska & Harris, 2004, see above). Alternatively, this could also indicate that perception of simultaneity between visual and nociceptive stimuli is not indispensable for observing significant interactions. However, in this latter case it could be that the visual stimulus acts as a warning signal before the detection of the thermo-nociceptive stimulus, maximizing the involvement of attentional rather than integrative mechanisms to mediate the potential visuo-nociceptive interactions. On the other hand, if the facilitation effect disappears, this would support the need to artificially resynchronize the arrival times of each input, to examine visuo-nociceptive interactions under laboratory conditions.

Next, to respond to our second question, the same experiment could also be replicated with visuo-tactile modalities, with one condition in which the individual PSS between visual and tactile inputs would be implemented and another condition in which no time interval between the respective onsets would be set. The aim would be to compare the 'temporal' condition leading to optimized visuo-tactile interactions and the one leading to optimized visuo-nociceptive interactions (cfr. the experiment suggested above). This would help establishing whether the specific function and comparably slow conduction velocities of the nociceptive system with regard to the tactile system imply different temporal rules to optimize its interaction with visual

stimuli or whether visuo-nociceptive interactions are governed by similar "temporal rules" than those that regulate visuo-tactile interactions.

On another note, across our studies, we considered that the value of the PSS between a thermo-nociceptive and a visual stimulus was constant over time. Indeed, Stone et al. (2001) showed that the PSS of their participants between visual and auditory inputs during a first experimental session was significantly correlated with their PSS during a second experimental session, performed a few days later. However, we did not verify this assumption about visuo-nociceptive modalities. It would therefore be interesting to measure the PSS of visuo-nociceptive stimuli selectively eliciting C-fiber responses and Aδ-fiber responses across, at least, two testing sessions. If the results corroborate those of Stone and colleagues, this will give an additional argument in favor of measuring the individual PSS of visuo-nociceptive inputs in each participant to optimize their interactions.

To conclude on the temporal aspects of multisensory interactions, there are several factors, such as spatial congruence, distance between the multisensory event and the body, attentional resources, stimulus intensity, modality combination, causal association, individual variance, task type and context that can affect the perception of simultaneity between different sensory inputs, in their own way (Colonius & Diederich, 2004; Fujisaki et al., 2012; Meredith et al., 1987; Stein & Meredith, 1993). This makes it very difficult to establish a defined interactive time-window that can be generalized to any situation. Apprehending each factor separately and understanding their impact on each sensory system in a systematic way would be an interesting approach to advance our understanding of the perception of multisensory time in humans.

3.3 Multisensory integration vs. attention?

In order to understand to what extent, the effect of the ipsilateral visual stimulus on the detection threshold of inputs transmitted through Aδ-fiber afferents is mediated by attentional mechanisms and/or multisensory integrative processes in a 'pre-attentive' manner, one could replicate the experimental paradigm used in the second experiment of Study 4 by adding a condition in which participants' attention is manipulated. This approach has already been applied to other multisensory phenomena such as the spatial ventriloquist or the McGurk effects (e.g. Spence & Driver, 2004, pp. 207). The ventriloquist effect, on the one hand, which is characterized by mislocalizing sounds towards temporally correlated visual events (e.g. Slutsky & Recanzone, 2001) is unaffected by the direction of participants' spatial attention toward different positions of the visual stimuli during a secondary task (Bertelson, Vroomen, De Gelder, & Driver, 2000). The McGurk illusion, on the other hand, which is characterized by the influence of a seen lip-movement on the perception of speech-sound, such as hearing "ba-ba"

while at the same time the lips move according to the sound "ga-ga" and the actual pronounced sound is "da-da" (McGurk & McDonald, 1976), is attenuated when participants orient their attention to another visual stimulus than the lips movement (Tiippana et al., 2004) or when participants perform a concurrent task (Alsius, Navarra, Campbell, & Soto-Faraco, 2005). These studies suggest that ventriloquism is determined by automatic 'pre-attentive' sensory integration whereas the McGurk effect is subject to attentional demands. In our case, if the effect of the ipsilateral visual stimulus on the thermo-nociceptive threshold of Aδ fibers is still present, while attention of the individual is divided between several tasks or oriented toward another unrelated spatial location/stimulus, this would confirm our hypothesis that pre-attentive multisensory integration plays a key role on the observed visuo-nociceptive interactions. On the contrary, if the effect is not replicated during the 'attentional' condition, this would indicate that attentional mechanisms regulate the facilitation effect of the ipsilateral visual stimulus on the Aδ-fiber thermo-nociceptive threshold.

As the effect of the close visual stimulus on the detection threshold of the inputs transmitted through Aδ-fiber afferents has been assumed to mainly result from integrative mechanisms, one could estimate the influence of the *unity assumption* effect (i.e., top-down multisensory integration) on the observed visuo-nociceptive interactions, in order to potentially provide an additional factor that maximizes interactions between visual and nociceptive stimuli. To do so, the instructions given to the participants during the threshold assessment could be manipulated. According to the factors involved in the unity assumption phenomenon, the level of interactions between the ipsilateral visual stimulus and the thermo-nociceptive stimulus could potentially be influenced by explicitly asking to the participants to assume that both sensory inputs originate from the same sensory event (see Harrar & Harris, 2005; Sugita & Suzuki, 2003 for examples of experiments that used similar strategies in visuo-tactile and visuo-auditory modalities, respectively). Although such a condition is not specifically required to observe unity assumption effects, it could optimize the 'connection' between both inputs, maximizing their interactions (e.g. Chen & Spence, 2017).

3.4 Do thermo-nociceptive inputs conveyed by C fibers can interact with visual stimuli?

In the present thesis, the possibility that C fibers interact with surrounding extra-somatic inputs has been investigated for the first time. It is however important to note that the profile of stimulations of the CO_2 laser and the staircase procedure/adaptive methods we used during our experiments, although being able to selectively stimulate C-fiber afferents dissociated from Aδ-fiber afferents, did no differentiate between the

subtypes of C-fiber units sensitive to heat. For instance, the polymodal C-fiber mechano-heat nociceptors (CMHs) are either fast-adapting (high peak discharge with the onset of the stimulus) or slow-adapting (uniform discharge rate throughout the stimulation). Slow-adapting unmyelinated fibers preferentially respond to sustained stimulation profiles (Schepers & Ringkamp, 2010; Treede et al., 1995). By delivering laser inputs during 100 ms (10 ms-heating ramp; 90 ms-plateau) with a 6 mm laser beam in the present studies, fast-adapting C units were probably targeted most of the time. In everyday life, however, multisensory interactions can occur between stimuli with longer durations than those delivered to our participants. Consequently, we cannot exclude that if we had selectively activated slow-adapting C fibers by using sustained stimulation profiles, we might have observed an impact of the position of a visual stimulus on the detection threshold of the fibers. Indeed, related to the "interactive time-window" theory of the multisensory neurons of the superior colliculus of the cat (Meredith et al., 1987), in the case of the selective activation of slow-adapting C fibers, the discharge trains of the neuron elicited by each sensory input might overlap better as compared to selectively activating fast-adapting CMHs, which could potentially result in better interactions between the thermo-nociceptive and visual stimuli. In this case, it would also be relevant to match the duration of the visual stimulus to the (prolonged) duration of the laser stimulus to increase the chance that the two stimuli interact, based on the observation that the more different sensory stimuli share the same features, such as their duration, the more these stimuli should interact (Welch, 1999).

4 POTENTIAL IMPLICATIONS

Several avenues for future experiments have now been considered to overcome some of the limitations of our studies. Before concluding, the current section will highlight some thoughts that may be relevant for researchers, but also clinicians.

The main advantage of studying visuo-nociceptive interactions under laboratory conditions is to be able to precisely control the conditions of experimentation and in turn obtain a detailed and fundamental overview of the ins and outs regarding our research topic. This allowed us, for example, to highlight that the number of information processing steps to meet the requirements of a task influences the standard criterion usually used to dissociate the selective activation of the different fiber types of the nociceptive system. While Churyukanov et al. (2012) estimated that the cut-off, dissociating the RTs in response to the selective activation of C fibers from those of Aδ fibers, was at 650 ms during simple detection tasks, results of Experiment 1 and 2, Study 4, suggested that this cut-off was delayed by ~100 ms when additional information needed to be processed to react to the laser stimuli. Therefore, when using standardized procedures based on criteria that have been defined in a specific context, it is important to ensure that the context in which these procedures are re-used is similar to the initial context. If this is not the case, it might be necessary to carry out preliminary experiments in order to see to what extent the novel conditions have an impact or not on the predefined criteria.

Similarly, the fact that the presence of a visual stimulus in the space close to the stimulated limb is capable of lowering the detection threshold of inputs conveyed by Aδ-fiber afferents, corroborates the idea that the perception of nociceptive stimuli is not only the outcome of the transmission of the nociceptive input from the skin receptors to the cortex, but is also affected by interactions with information from several perceptual modalities. Therefore, whether this is done in a research or clinical context, the integrity of the nociceptive system needs to be assessed in a controlled environment, identical for each examination, especially when the examinations are carried out repeatedly in the same person. In a previous study, Van der Biest et al., (2016) showed that dynamical visual stimuli approaching the hand on which tactile stimuli were applied, increased the sensitivity to the tactile stimuli. Based on these observations, authors proposed that the results of somatosensory testing during medical examination (such as Quantitative Sensory Testing (QST) in patients with neuropathic pain) could be affected by the sensory environment around the patient. Our research supports this statement and extends it to the specific study of the nociceptive system. In addition, based on the results of Van der Biest et al. (2016) and on the results of our last study, multisensory interactions between visual and somatosensory stimuli could be used to alleviate patients from pain using the sensory discrimination training (SDT) program. Indeed, changes in the cortical representation

of the painful limb in the somatosensory cortex have been reported in patients suffering from chronic low back pain, phantom limb pain and CRPS. This cortical reorganization is associated with increased pain sensations and decreased tactile discrimination (Moseley, Zalucki, Wiech, 2008; Kälin, Rausch-Osthoff, Bauer, 2016). Therefore, by training discrimination and sensorimotor functions with detection and localization of non-painful tactile stimuli, SDT aims to normalize the cortical representation of the painful limb, leading to decreased painful sensations (Kälin et al., 2016). In this vein, it might be relevant to study the effect of close visual stimuli on the detection threshold, localization and discrimination of tactile stimuli. If close visual stimuli modulate tactile perception, adding visual stimuli in the procedure of SDT could boost the benefits of the training, and therefore, improve in a larger extent the cortical reorganization of SI and SII, and decrease the associated pain in this clinical population.

On a different note, the investigation about the asynchrony between the arrival times of a nociceptive input and a visual input (Study 2 and 3) allowed us to set-up an efficient procedure based on temporal order judgments using an adaptive method. That procedure could be easily re-used by other researchers, with the main benefit that adaptive methods decrease the time of testing as compared to a method of constant stimuli (Filbrich, Alamia, Burns, et al., 2017; Vanderclausen et al., accepted; Vanderclausen, Manfron, et al., 2020), which consequently also decreases habituation risks to the stimuli. Related to our comment in the first paragraph, the definition of the SOA values and of the prior of the parameter estimates would however need to be adapted, based on the conduction velocities of the sensory systems that are assessed, and on the hypotheses of the given experiment.

Regarding the theoretical framework about the processing of nociceptive and potentially painful sensations in the brain, it was underlined in the Introduction of this dissertation that the cortical areas usually activated by nociceptive and painful stimuli, mainly operculo-insular and cingulate areas, are also activated by any salient sensory events that are not specifically processed through the nociceptive system. This supports the view that this cortical network constitutes a multisensory network integrating inputs from different sensory systems (e.g. Legrain et al., 2011). Accordingly, we hypothesized that the detection thresholds of nociceptive stimuli conveyed by C and Aδ fibers to the cortex would also depend on the information conveyed by other senses, such as visual stimuli. However, in our last study, contrasting with the impact of proximal visual stimuli on the detection threshold of inputs conveyed by Aδ-fiber afferents, visual stimuli and their spatial position do not seem to have modulated the detection of inputs selectively transmitted through C-fiber afferents. In addition to the fact that C-fiber inputs would not interact with visual stimuli as automatically as Aδ-fiber inputs (see above), these findings could alternatively suggest that the stimuli we used to activate C fibers were not salient enough to generate multisensory interactions with visual stimuli. It has indeed been proposed that stimulus salience, that is, its ability to stand out relative to other surrounding stimuli, is an important determinant of

multisensory interactions (e.g. Talsma et al, 2010). As briefly mentioned in the previous section, using stimulation parameters that allow to selectively activate other subtypes of C-fiber units with higher temperatures (e.g. Lenoir, Plaghki, et al., 2018), could have generated C-fiber inputs of greater salience and promoted visuo-nociceptive interactions.

To end this section, it is important to emphasize the fact that the manifold terminologies used to describe the same multisensory phenomenon as well as the use of the same terminology to refer to different multisensory processes, are undoubtedly a source of confusion in multisensory research. As already pointed out by Stein et al. (2010) and Talsma et al. (2010), there is the need for a universal consensus regarding the definition of all the concepts and tasks addressed in the multisensory literature. This would certainly facilitate advances in cognitive neurosciences and help clarifying the nuances that distinguish different multisensory phenomena and, thus, their underlying mechanisms.

5 CONCLUSION

The studies conducted in the context of this thesis have deepened our understanding of the conditions under which the nociceptive system interacts with extra-somatic inputs present in the close surrounding. For the first time, the modulation of the activity of the nociceptive system by the presence of visual stimuli has been investigated. We showed that, in addition to affecting our ability to localize nociceptive stimuli on the body, visual stimuli occurring in the peripersonal space of the stimulated limb are able to decrease the detection threshold of Aδ fibers. This phenomenon might be adaptive, in the sense that the increased perception of nociceptive stimuli when visual stimuli are spatially close to the stimulated limb would serve as a final warning by the brain to prompt individuals to implement effective reactions before risking serious injuries. Since the detection threshold of C fibers does not seem to be affected by the presence of visual stimuli, C fibers would consequently rather play a role in the interoceptive function of nociception, that is, warning the brain about a potential damage on the body, than in its exteroceptive function, that is, detecting, localizing and reacting to the source of the potential damage.

To observe the modulation of the activity of the nociceptive system by visual stimuli, it was necessary to first study the *spatial* and *temporal* factors that would optimize visuo-nociceptive interactions. We showed that, in addition to being enhanced by the spatial proximity between the different stimuli, visuo-nociceptive interactions are maximized when the visual information about the position of the stimulated limb with regard to the visual stimuli is available. Based on the multisensory literature established in other sensory modalities, we hypothesized that visuo-nociceptive interactions would also be optimized when the respective stimuli are perceived at approximately the same time. We observed however an important asynchrony between the onset of each input for them to be perceived at the same time, due to the respective conduction velocities of the visual and nociceptive systems, especially for the selective activation of C fibers. This asynchrony was later used to adapt the respective onsets of visual and nociceptive stimuli. Finally, we combined temporal and spatial factors, showing that the spatial congruence between a visual and a thermo-nociceptive stimulus, by improving their interactions, reduced the necessary asynchrony between both inputs to achieve simultaneity.

These findings pave the way for further studies on the possible multisensory interactions that could modulate the activity of the nociceptive system. By using the knowledge about the multisensory integrative and attentional mechanisms that mediate such interactions, it might be interesting to investigate whether extra-somatic inputs can *increase* the detection threshold of the nociceptive system, with the perspective of a multisensory environment that would attenuate pain.

Appendix

Study 5: No evidence for an effect of the distance between the hands on tactile temporal order judgments[8]

Abstract

Localizing somatosensory stimuli is an important process, since it allows us to spatially guide our actions towards the object entering in contact with the body. Accordingly, the positions of tactile inputs are coded according to both somatotopic and spatiotopic representations, the latter one considering the position of the stimulated limbs in external space. The spatiotopic representation has often been evidenced by means of temporal order judgment (TOJ) tasks. Participants' judgments about the order of appearance of two successive somatosensory stimuli are less accurate when the hands are crossed over the body midline than uncrossed, but also when participants' hands are placed close together as compared to farther away. Moreover, these postural effects might depend on the vision of the stimulated limbs. The aim of this study was to test the influence of seeing the hands, on the modulation of tactile TOJ by the spatial distance between the stimulated limbs. The results showed no influence of the distance between the stimulated hands on TOJ performance and prevent us from concluding whether vision of the hands affects TOJ performance, or whether these variables interact. The reliability of such distance effect to investigate the spatial representations of tactile inputs is questioned.

[8] This study is published as:
Manfron, L., Vanderclausen, C., & Legrain, V. (2021). No evidence for an effect of the distance between the hands on tactile temporal order judgments. *Perception*, 0301006621998877.

1. Introduction

Mapping somatosensory stimuli on the body surface is an important function as it helps to identify which part of our body is in contact with external stimuli, but also to locate these stimuli in the surrounding space. Ultimately, somatosensory mapping helps to translate spatially-located perception of bodily contacts into spatially-guided motor behaviors in order to finely tune manipulation with innocuous objects and, also, defensive reaction to noxious external objects (Brozzoli, Ehrsson, & Farnè, 2014; Graziano & Cooke, 2006).

Somatotopy represents an almost point-by-point readout for the brain of the spatial arrangement of the somatosensory receptors in the skin and in internal organs. More exactly, it corresponds to the ordered projection of the afferent responses from the receptors to spatially segregated groups of neurons in the brain (Penfield & Boldrey, 1937). However, as the body limbs, and consequently the somatosensory receptors, are constantly moving in external space, such a spatial representation might be inefficient to appropriately localize the contacting objects in external space and orient behaviors towards their location. Therefore, the spatiotopic representation uses external space as reference frame and considers the relative position of the body part on which the stimulus is applied (e.g. Azañon & Soto-Faraco, 2008; Driver & Spence, 1998; Graziano, Hu, & Gross, 1997; Shore, Spry, & Spence, 2002; Smania & Aglioti, 1995; Yamamoto & Kitazawa, 2001). It thereby represents a crucial spatial representation of somatic information as it anchors somatosensory perception in a representation of the body posture and limb movements in external world, with the purpose of interacting with objects in the environment close to the body (Brozzoli et al., 2014).

The ability to code somatosensory (tactile or nociceptive) information according to spatiotopic reference has been assessed, among others, using temporal order judgment (TOJ) tasks (Badde, Heed, & Röder, 2014; Badde, Roder, & Heed, 2015; Crollen, Albouy, Lepore, & Collignon, 2017; Crollen, Lazzouni, et al., 2017; Crollen, Spruyt, Mahau, Bottini, & Collignon, 2019; De Paepe, Crombez, & Legrain, 2015; Heed & Azañón, 2014; Röder, Rösler, & Spence, 2004; Sambo et al., 2013; Shore et al., 2002; Vanderclausen, Bourgois, De Volder, & Legrain, 2020; Vanderclausen, Manfron, De Volder, & Legrain, 2020; Yamamoto & Kitazawa, 2001). In these tasks, participants judge the temporal order of two successive somatosensory stimuli, one applied to each hand, separated by different temporal delays. Participants' judgments are typically less accurate when their hands are crossed, as compared to an uncrossed posture. Such an effect is accounted for by the fact that the somatotopic representation mismatches the spatiotopic representation (e.g. when crossed, a stimulus applied on the left hand is coming from the right part of space). The fact that TOJ performance depends on the location of the hands in external space suggests that nociception and touch, in addition

to the somatotopic coding, are automatically coded according to a spatiotopic reference frame, a process called *somatosensory remapping* (Driver & Spence, 1998).

Spatiotopic coding of somatosensory information has also been investigated using other experimental procedures (e.g. Azañón, Camacho, & Soto-Faraco, 2010; Azañón, Longo, Soto-Faraco, & Haggard, 2010; Azañon & Soto-Faraco, 2008; Moayedi et al., 2016; Overvliet, Azañón, & Soto-Faraco, 2011; Smania & Aglioti, 1995; Soto-Faraco & Azañón, 2013; Salvador Soto-Faraco, Ronald, & Spence, 2004; Tame, Farnè, & Pavani, 2011) such as manipulating the distance between the limbs to which the somatosensory stimuli were applied. The rationale is that, as the somatotopic representations of the two stimulated skin areas do not change between the different postural conditions, potential differences in participants' performance between two conditions can only be attributed to the metric distance between the stimulated limbs in external space. Studies have indeed shown that the discrimination of tactile stimuli applied on one hand was more sensitive to distraction induced by tactile stimuli applied on the opposite hand when the two hands were close together, as compared to when they were further apart (Driver & Grossenbacher, 1996; Evans, Craig, & Rinker, 1992; Lakatos & Shepard, 1997; Salvador Soto-Faraco et al., 2004). During tactile TOJ tasks, judgments are more difficult with decreasing the distance between the hands (Roberts, Wing, Durkin, & Humphreys, 2003; Shore, Gray, Spry, & Spence, 2005). Such an effect was also shown when distance manipulation was made through mirror-reflected images of the hands while their physical distance was unchanged (Gallace & Spence, 2005).

However, while crossing the hands during tactile and nociceptive TOJ tasks has provided very robust and reliable effects across the different studies, results from the studies having manipulated the distance between the stimulated limbs are very small and less consistent. For instance, Shore et al. (2005) did not replicate the distance effect between arms when different fingers of the hands were stimulated. Similarly, Kuroki, Watanabe, Kawakami, Tachi, and Nishida (2010) showed that participants' judgments were more sensitive to the anatomical distance between two stimulated areas on the skin surface than to the distance in external space between the two body parts. As suggested by the study of Gallace and Spence (2005), the postural effect during tactile TOJ could depend on visual feedback about hand positions. The data of that study indeed illustrate the important role that vision of the body plays in somatosensory perception, sometimes taking priority over proprioceptive cues (see also Botvinick & Cohen, 1998; Gallace & Spence, 2005; Pavani, Spence, & Driver, 2000; Soto-Faraco et al., 2004; Torta, Legrain, & Mouraux, 2015). Accordingly, Cadieux and Shore (2013) showed that preventing vision of the stimulated hands reduced the crossed hands deficit during tactile TOJ (at least when the task procedure minimized the use of spatiotopic coordinates). The aim of the present study was therefore to test the influence of seeing the hands on the modulation of tactile temporal order judgments induced by changing the spatial distance between the two stimulated hands.

Participants performed a TOJ task with vibrotactile stimuli delivered to their fingertips with the hands placed according to two postures: close *vs.* far distance from each other. One group of participants could see their hands during the experiment while another group was blindfolded. It was hypothesized that, because visual information about position of the limbs in external space was prevented, participants would mostly rely on anatomical representations. We therefore expected reduced distance effects in blindfolded participants, as compared to those who could see their hands. In other words, we expected to observe significant differences in TOJ sensitivity between the two hand postures in the group of sighted participants, while such a difference would be reduced in the blindfolded group.

2. Methods

2.1. Participants

Based on the sample size of our previous studies (e.g. Filbrich, Alamia, Blandiaux, Burns, & Legrain, 2017; Filbrich, Alamia, Verfaille, et al., 2017; Vanderclausen, Filbrich, De Volder, & Legrain, accepted), 30 volunteers participated in the study. Four participants were excluded from the analyses due to unreliable performances during the task (see analyses section). The mean age of the remaining 26 participants (15 women) was 23.88 years old (*SD*=3.54, range=18–36). Inclusion criteria were: normal or corrected-to-normal visual acuity, no prior history of severe neurological, psychiatric, or chronic pain disorder, no traumatic injury of the upper limbs within the last six months, no regular use of psychotropic drugs, no intake of analgesic drugs (e.g. NSAIDs, paracetamol) within the 12 hours preceding the experiment. According to the Flinders Handedness Survey (Flanders) (Nicholls, Thomas, Loetscher, & Grimshaw, 2013), one participant was left-handed, one was ambidextrous, and all the others were right-handed. The local ethic committee in agreement with the sixth revision (2008) of the Declaration of Helsinki approved the experimental procedure. All volunteers signed an informed consent before starting the experiment and received financial compensation for their participation.

2.2. Stimuli and materials

Vibrotactile stimuli were applied on each hand by means of two vibrotactile transducers (TL-002-14R Haptuator, Tactile Labs, Canada) driven by standard audio amplifiers, and lasting 10 ms at 440 Hz (interruption of the last cycle did not affect stimulus perception). Stimuli were remotely controlled using Matlab 2014. Participants held the vibrotactile transducers at ~30 cm from the edge of the table, one in each hand

between the thumb and the forefinger. The intensities of the vibrotactile stimuli were matched between the two hands, in order for the stimuli to be perceived as equally intense. If necessary, they were adapted before or during the experiment when this criterion was not met anymore. A small strip of tape pasted on the table along the participant's midsagittal plane at 40 cm from the edge of the table (i.e. at ~10 cm above the hands) was used as a fixation point for the group of participants who could see the stimulated hands (see below).

2.3. Procedure

The experiment consisted of a TOJ task performed on two tactile stimuli, one applied to each hand. More exactly, for each pair of left and right stimuli, participants were asked to discriminate the order of temporal succession between the two stimuli. They responded verbally by saying aloud 'left' or 'right', which of the two tactile stimuli they perceived either as having occurred first ('which is first' response condition), or as having occurred second ('which is second' response condition), depending on the experimental blocks (with the aim of minimizing response biases, see Filbrich, Torta, Vanderclausen, Azañón, & Legrain, 2016; Shore, Spence, & Klein, 2001; Spence & Parise, 2010). Verbal responses were encoded by the experimenter (by pressing one of two keys on the computer, which triggered the next trial 2000 ms later). No instruction regarding the speed of their responses nor any feedback regarding the accuracy of their performance was given to the participants during the task. The participants were pseudo-randomly assigned to one of two groups of equal size. In one group, the participants could see their hands and were asked to maintain their gaze on a fixation point (vision group). In the other group, they wore a blindfold to prevent vision of their hands throughout the experiment (blindfolded group). The blindfolding was manipulated between participants, instead of within, to avoid extending the duration of the experiment that might have impacted their ability to focus on the task. For each group, the task was performed under two posture conditions, either with the hands close to each other or further apart (see below for more details).

The experiment took place in a dimly illuminated testing room. Participants were seated on a chair and rested their arms on a table while holding the transducers in their hands slightly above the table surface in order to avoid noise from the vibrations of the transducers against it. Their head was stabilized with a chinrest to minimize movement during the experiment. Participants' hands were always equally distant from their midsagittal plane. In the far posture, the hands were placed at a distance of 70 cm from each other, as measured between the two vibrotactile transducers, while in the close posture the distance was of 2 cm. Before starting the experiment, participants completed a practice session to get familiarized with the vibrotactile stimuli and the experimental set-up. This practice session consisted of 4 blocks of 10 trials each, one block for each combination of posture (close vs. far hands) and the response conditions

(which is first vs. which is second). During this practice phase, only two SOA were used, i.e. ±145, ±200. Participants performance was not recorded during practice blocks and no feedback was given to them.

During the experiment, each participant was presented with 4 blocks of 40 trials each. During two blocks, the participants' hands were placed according to the close posture condition, while they were placed in the far posture in two other blocks. Each participant started the experiment with two blocks of the same posture condition, and then continued with the two blocks of the other condition; the order of the posture condition was counterbalanced across participants of the same group. For each block of the same posture condition, one was performed with the 'which is first' instruction, the other with the 'which is second' instruction; order of the response conditions was randomized. Noises from experimental devices were covered by means of a white noise played through earphones. Each block lasted approximately 5 minutes and the entire experiment lasted approximately 30 minutes, including instructions and the practice session.

For each pair of stimuli, the two vibrotactile stimuli were separated by one out of 22 possible time intervals (SOA for stimulus onset asynchronies): ±5, ±10, ±15, ±30, ±45, ±60, ±75, ±90, ±145, ±200, ±400ms (negative values indicate that the vibrotactile stimulus on the left hand was applied first, positive values that the right hand stimulus was applied first). At each trial, the presented SOA was selected using the adaptive psi method (Kingdom & Prins, 2010) based on the participant's responses in all the previous trials (see Filbrich, Alamia, Verfaille, et al., 2017; Vanderclausen, Bourgois, et al., 2020; Vanderclausen, Manfron, et al., 2020 for details regarding the use of the psi method for TOJ tasks). More specifically, the algorithm adopts a Bayesian framework with the ultimate goal of estimating the posterior probability of the parameters of interest (i.e. the α (PSS) and the β (slope)) without probing extensively all the SOAs. The core idea is to minimize the expected entropy (i.e. uncertainty) of the posterior distribution trial by trial, such as the response of the participant at each trial provides the most information about the distribution of the parameters. In other words, the algorithm, given all the information collected so far in the previous trials, infers which condition (i.e. SOA) is the most informative in the next trial in order to estimate the joint distribution of the parameters.

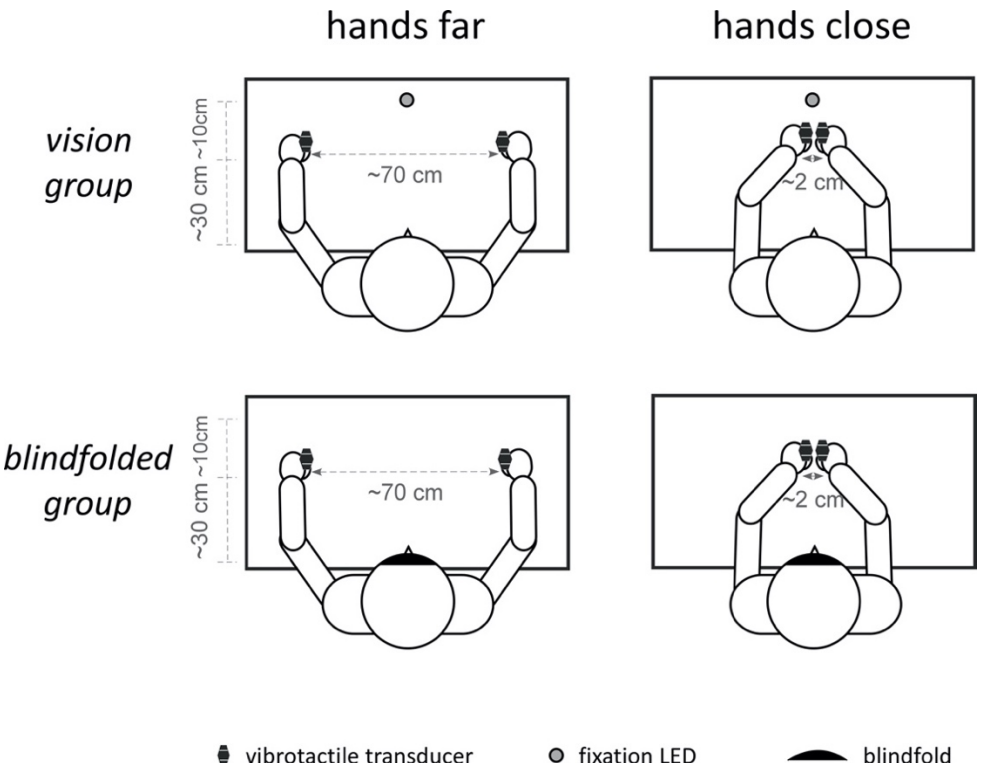

Figure 1. Design of the experiment. Participants performed a temporal order judgment task on pairs of tactile stimuli applied one to each hand by means of vibrotactile transducers (illustrated by the black diamonds) held between the thumb and the forefinger. Hands were placed so that the vibrotactile transducers were held at a distance of either ~70cm (hands far; left) or ~2cm (hands close; right) from each other. One group of participants could see their hands during the task (vision group; top) while participants of the other group were blindfolded (blindfolded group; bottom). The participants of the vision group were asked to maintain their gaze on a central point at ~40 cm in front of them (illustrated by the grey circle).

2.4. Measures

The TOJ performance, i.e. the probability to perceive one of the two stimuli as occurring first as a function of the SOA, was fitted online for each participant and each condition using the logistic function $f(x)=1/(1+exp(-\beta(x-\alpha)))$ (Kingdom & Prins, 2010; Kontsevich & Tyler, 1999). Here, the proportion of left first responses was plotted as a function of SOA. Since the adaptive method was used, the α and the β values of the function were estimated at each trial and, at the end of the stimulation block, the last estimates were taken as measures of the participants' performance. The β parameter characterizes the slope of the psychometric function and describes the noisiness of the results (i.e. entropy). Therefore, this parameter reflects the precision of the participants' responses during the experiment, i.e. their performance at the task (Kingdom & Prins, 2010; Kontsevich & Tyler, 1999). It constitutes the main parameter of interest in this study, as the slope is often used to derive the just noticeable difference (JND) in typical TOJ experiments (Heed & Azañón, 2014; Spence & Parise, 2010) and was shown to be affected by the distance between the hands during tactile TOJ (Roberts et al., 2003; Shore et al., 2005). The α parameter is the threshold of the function and refers to the point of subjective simultaneity (PSS). Although the contribution of the parameter to current data was less relevant, this parameter was also measured in order to assess the presence of possible biases that could affect the estimation of the slope (see Filbrich, Alamia, Blandiaux, et al., 2017; Filbrich, Alamia, Burns, & Legrain, 2017; Vanderclausen, Filbrich, Alamia, & Legrain, 2017). A third non-standard parameter was derived a posteriori to further characterize participants performances. Based on all trials presented for each condition, we computed the mode of the presented SOA to index which of the time interval values was the most often presented to a given participant (see Vanderclausen, Bourgois, et al., 2020; Vanderclausen, Manfron, et al., 2020).

Because the adaptive psi method is based on a Bayesian framework, priors had to be postulated (Kingdom & Prins, 2010). We used a prior distribution of 0±20 ms to estimate the α parameter, since no bias towards one of the two hands was expected. Based on previous experiments performed with healthy volunteers, 0.06±0.6 was chosen as a prior distribution to estimate the β parameter (Filbrich, Alamia, Verfaille, et al., 2017; Vanderclausen et al., accepted). Two other parameters, the λ and γ were fixed in advance for all participants and not used for analyses. The λ corresponds to the lapse rate, i.e. the probability of giving an incorrect response independently of stimulation variables, and the γ to the guess rate, i.e. the probability of giving a correct answer whereas the stimulus has not been detected (Prins, 2012). As suggested by Kingdom and Prins (2010), the λ was set at 0.02 and the γ at 0.

2.5. Data analyses

Data were excluded from further statistical analyses if the slope of the psychometric function could not be reliably estimated during the 40 trials within one condition (i.e. the parameter estimate did not converge on a stable value on the last trials). Before statistical analyses, data from the two response conditions ('which is first' and 'which is second') were averaged together for each group and for each posture condition.

One-sample t-tests were used to examine the potential presence of biases towards one of the two hands by comparing the averaged PSS values of each condition to 0. Next, in order to assess the influence of experimental manipulations on participants' TOJ performances, analyses of variance (ANOVA) with posture (far vs. close) as within-subject variable and group (vision vs. blindfolded) as between-subject variable were performed separately on the PSS, the slope and the mode values. Effect sizes were measured by means of partial Eta squared for ANOVA and Cohen's d for t-tests. Significance level was set at p≤.05. Finally, classic frequentist statistical analyses were complemented by Bayesian statistics (using Bayesian repeated measures ANOVA with JASP 0.9.2.0, University of Amsterdam, The Netherlands) performed on the PSS, slope and mode values respectively. To this aim, we computed a Bayes factor to quantify the alternative hypothesis (HA) relative to the null hypothesis (H0) (BF10, Cauchy prior = 0.707). Interpretations are based on the classification scheme established by Lee and Wagenmakers (2013); Wagenmakers et al. (2017).

3. Results

The psychometric curves fitting TOJ performances are illustrated in Figure 2. Individual data and their means are displayed on Figure 3. Analyses of the slope values did not reveal any significant results neither for the main effect of posture ($F(1,24)=0.788$, $p=0.384$, $\eta^2p=0.032$), nor for that of group ($F(1,24)=0.346$, $p=0.562$, $\eta^2p=0.014$), nor for the interaction between the two variables ($F(1,24)=0.062$, $p=0.805$, $\eta^2p=0.003$). Regarding Bayesian analyses, anecdotal evidences were shown in favor of H0 for the posture (BF_{10} = 0.38, error = 1.636) and group factors (BF_{10} = 0.54, error = 1.556) and for their interaction as well (BF_{10} = 0.36, error = 1.202). This suggests that there is no sufficient evidence allowing us to draw conclusions about the effect of the distance between the stimulated hands or the possibility to see them, on TOJ performances.

The one sample t-tests comparing the PSS values to 0 did not reveal any significant results (all $t(12)\leq1.648$, all $p\geq0.125$), suggesting that there was no significant bias affecting the perception of the stimuli applied to one of the two hands in none of the conditions and for either group. The ANOVA performed on the PSS values showed no

significant effect either for the posture (F(1,24)=0.072, p=0.791, η^2p=0.003) or for the group variables (F(1,24)=0.142, p=0.709 ,η^2p=0.060), or for the interaction between the two variables (F(1,24)=2.182, p=0.153, η^2p=0.083). Bayesian ANOVA analyses revealed moderate evidence in favor of H0 related to the effect of posture (BF_{10} = 0.275, error = 0.819), and anecdotal evidences in favor of H0 for to the main effect of group (BF_{10} = 0.488, error = 1.465) and the interaction between posture and group as well (BF_{10} = 0.832, error = 1.126).

The ANOVA analyses about the mode of the SOA did not reveal any significant effect of the posture (F(1, 24)=0.477, p=0.496, η^2p =0.019), of the group (F(1,24)= 0.916, p=0.348, η^2p =0.037), nor significant interaction between the two variables (F(1,24)=0.477, p=0.496, η^2p =0.019) (Figure 2c). Finally, Bayesian analyses revealed moderate evidence in favor of H0 for the main effect of posture (BF_{10} = 0.331, error = 0.950), anecdotal evidences in favor of H0 for the main effect of group (BF_{10} = 0.57, error = 0.981) and for the interaction between posture and group as well (BF_{10} = 0.44, error = 2.493).

Overall, it appears that tactile TOJ performances were not affected by the spatial distance between the stimulated hands. However, results from Bayesian statistics prevent us from concluding on the role of vision on these performances, or on the interaction between posture and group variables.

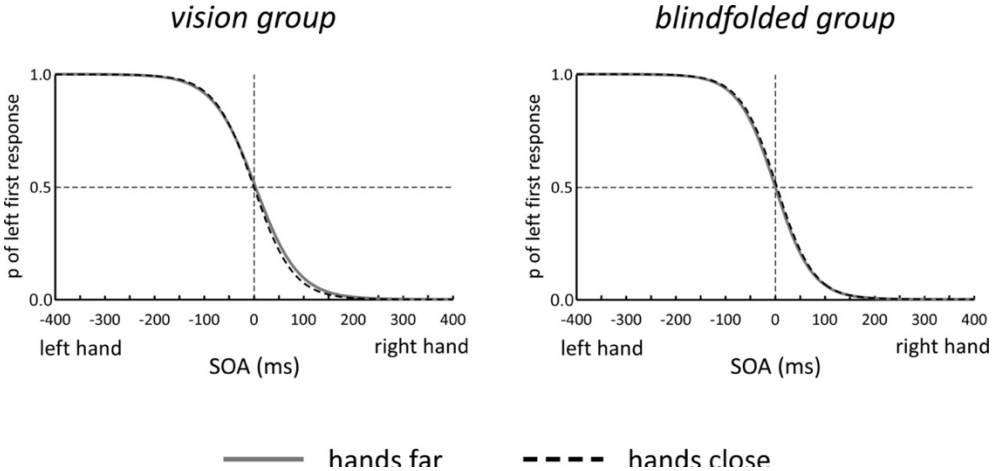

Figure 2. TOJ curves. The figure illustrates the curves of the psychometric function, based on group averaged data, from the fitted responses of the *vision* group participants (left) and of the *blindfolded* group participants (right) separately, when performing the task with the hands placed either in a far (solid grey lines) or in a close (dotted black lines) posture. The x-axis corresponds to the different possible stimulus onset asynchronies (i.e. SOA). Negative values indicate that the left hand was stimulated first and positive values that the right hand was stimulated first. The y-axis refers to the proportion of trials in which the tactile stimulus applied on the left hand was reported as being perceived first.

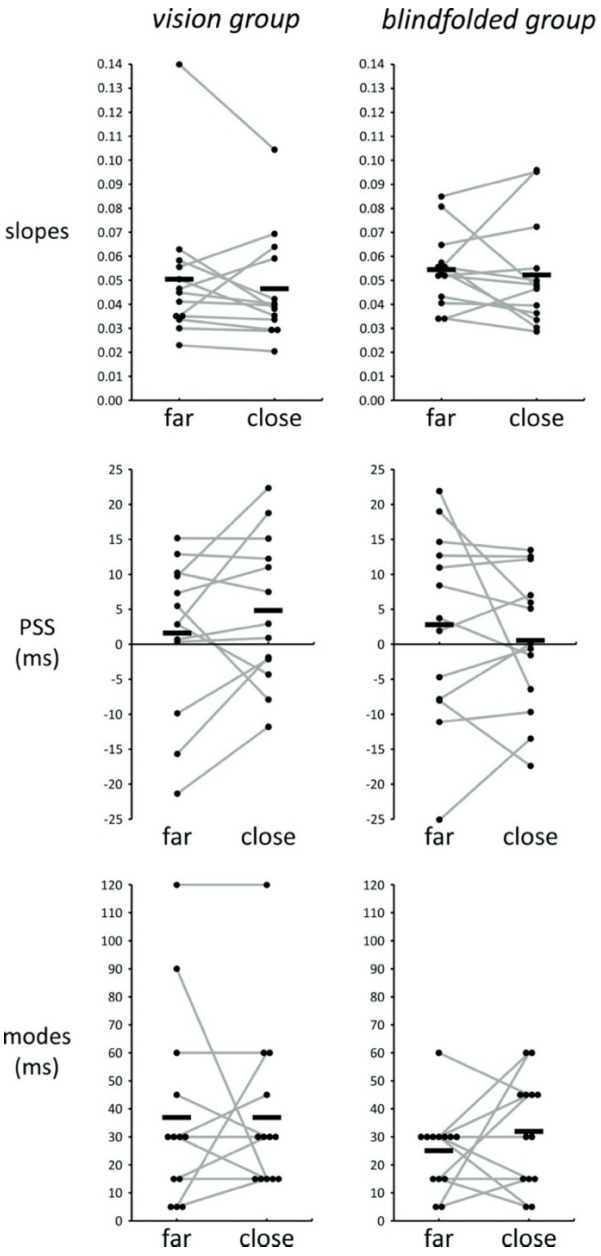

Figure 3. TOJ parameters. The figure shows scatter plots displaying individual data (black dots) and their means (black strips) respectively for the slopes and PSS values of the TOJ task as well as the modes of the SOA used during the adaptive procedure. The data are plotted according to the group (*vision* group: left; *blindfolded* group: right) and the experimental condition (hands in the *far* posture: left inner-sections; hands in the *close* posture: right inner-sections). Data of the same participant are linked by the grey lines.

4. Discussion

The present study aimed to test the influence of the distance in external space between two body limbs on the ability to discriminate the temporal order between two tactile stimuli, one applied to each of those limbs. We also investigated whether such an effect could be modulated by the possibility of seeing or not the limbs on which tactile stimuli were applied. Previous experiments reported decreased performances in judging the order of appearance of two tactile stimuli when the hands are positioned close together as compared to when they are placed farther away, as indexed by higher JND values in the close posture (Gallace & Spence, 2005; Roberts et al., 2003; Shore et al., 2005). These studies confirm that spatial processing of somatosensory inputs integrates information about the relative posture of the body limbs in external space, in line with the results from the studies having tested tactile TOJ performance with the hands in a crossed posture (e.g. Crollen, Lazzouni, et al., 2017; Crollen et al., 2019; Heed & Azañón, 2014; Röder et al., 2004; Shore et al., 2002; Yamamoto & Kitazawa, 2001). It was also suggested that these effects might be mostly driven by the actual vision of the limbs position (Cadieux & Shore, 2013; Gallace & Spence, 2005). However, in the present study, we did not succeed to provide reliable evidence in favor of the influence of the distance between the stimulated limbs, and its modulation by actual vision of the limbs, on tactile TOJ performances.

One of the main differences between the present and previous experiments having tested the influence of hands distance on tactile TOJ performance, relies on the fact that the different time intervals (i.e. SOA) between the two consecutive stimuli were administrated by means of an adaptive procedure in the present experiment while previous studies used methods of constant stimuli (Gallace & Spence, 2005; Roberts et al., 2003; Shore et al., 2005). In these previous studies, each SOA condition was repeated 8 to 15 times in block of 80 to 90 stimuli, whereas the stimulation blocks of the present experiment only consisted of 40 trials selected among 22 possible SOA conditions. It is therefore possible that our experimental procedure did not succeed to fully sample the psychometric function fitting participants' responses and did not properly measured limb distance effect during somatosensory TOJ tasks. However, this seems unlikely as, on the contrary, one of the main advantages of psychophysics adaptive methods over constant stimuli methods is to allow more reliable estimation of the parameters of the psychometric function even when a limited number of stimuli is used (Filbrich, Alamia, Burns, et al., 2017; Kontsevich & Tyler, 1999). Accordingly, using the same adaptive method as the one used in the present experiment, previous studies succeeded to reliably estimate both the threshold (Filbrich, Alamia, Blandiaux, et al., 2017; Filbrich, Alamia, Burns, et al., 2017; Filbrich, Alamia, Verfaille, et al., 2017; Filbrich, Halicka, Alamia, & Legrain, 2018; Legrain, Manfron, Garcia, & Filbrich, 2018; Manfron, Legrain, & Filbrich, 2020; Torta, Filbrich, Van Den Broeke, & Legrain, 2018; Vanderclausen et al., 2017) and the slope parameters (Vanderclausen, Bourgois, et al., 2020; Vanderclausen

et al., accepted; Vanderclausen, Manfron, et al., 2020) of the TOJ-fitting psychometric function and to significantly measure changes in participants' judgments according to experimental manipulations such as the posture of the stimulated limbs. For instance, Vanderclausen and colleagues (Vanderclausen, Bourgois, et al., 2020; Vanderclausen et al., accepted; Vanderclausen, Manfron, et al., 2020) have shown significant and reliable crossing hands effects during TOJ tasks with somatosensory (vibrotactile or radiant heat) stimuli delivered using the adaptive *psi* procedure.

Therefore, one of the most probable reasons why we failed to replicate the limb distance effect during somatosensory TOJ tasks could rely on the fact that such an effect is weaker than that observed when the stimulated limbs are crossed over the body midline. Indeed, while the crossing hands effect has been recurrently and robustly demonstrated during somatosensory TOJ tasks, the limb distance effect seems to be of smaller magnitude (Roberts et al., 2003). For example, in Shore et al. (2005), the averaged difference between the JND of close and far postures, when the hands are uncrossed, ranges from 9 to 20 ms. Furthermore, the distance effect varies according to the use of temporal order judgment (Kuroki et al., 2010; Shore et al., 2005) or simultaneity judgment tasks (Axelrod, Thompson, & Cohen, 1968; Kuroki et al., 2010). Conversely to the manipulation of crossing the hands over the body midline, when the distance between the stimulated limbs is manipulated, each hand remains in its hemispace, and, therefore, the somatotopic and spatiotopic representations remain aligned with each other, even when the hands are placed close together. Indeed, TOJ studies suggest that spatiotopic representation of tactile inputs can be automatically generated and overlaps in times with that of the somatotopic one, at least at the time scale of TOJ experimental designs (e.g. Azanon, Camacho, et al., 2010; Badde & Heed, 2016; Badde, Heed, & Roder, 2016). Therefore, their co-activation generates mismatching responses when the limbs are crossed as the left hand is in the right part of space and vice versa. It has been suggested that decreased TOJ performances during the crossed hands posture might actually reflect the effort that the brain has to make in order to inhibit the response from the irrelevant spatial representation and select the relevant one (Crollen et al., 2019; Vanderclausen, Manfron, et al., 2020). By comparison, although decreasing spatial distance between two stimuli might actually induce more attentional competition between the two stimuli (see for instance Mangun & Hillyard, 1987 for similar effect in the visual domain; 1988), such competition might be of lesser magnitude than that induced by crossing the hands. Therefore, it might not be reliably sampled during TOJ tasks manipulating the distance between the stimulated limbs.

As a consequence, the possibility to evidence reliable effects of the spatial positions of the stimulated body parts could depend on the cognitive goals manipulated by the task instruction and on the associated attentional requirements. For instance, experiments involving fine discrimination of tactile stimuli did evidence significant effect of the spatiotopic distance between the stimulated body parts (Driver & Grossenbacher, 1996; Lakatos & Shepard, 1997; Soto-Faraco et al., 2004). Accordingly,

it might be instructive to compare the results of the temporal judgment studies based on whether participants are asked to judge the order between the stimuli or whether they are simultaneous or not. It has been indeed suggested that simultaneity judgments are less demanding in terms of attentional resources that temporal order judgments (Fujisaki, Kitazawa, & Nishida, 2012). However, Kuroki et al. (2010) did not evidence any significant distance effect during neither temporal order nor simultaneity judgment tasks. Further studies will be needed to disclose and describe the conditions under which reliable effect of manipulating the spatial distance between the body parts on which somatosensory stimuli are applied might be observed during perceptual tasks.

In conclusion, it seems that changing the spatial distance between the stimulated limbs is less reliable than foreseen in aiming to highlight the complex cognitive processes used to spatially represent somatosensory stimuli. On the contrary, crossing the hands is a more suitable technique to experimentally dissociate the respective contributions of the somatotopic and spatiotopic reference frames underlying the spatial representations of somatic stimuli.

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