Danger in the dark!

The role of visual experience in the spatial mapping of nociception: neuropsychological studies in congenitally blind and normally sighted individuals

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The role of visual experience in the spatial mapping of nociception: neuropsychological studies in congenitally blind and normally sighted individuals

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Thèse présentée en vue de
l'obtention du grade de Docteure en
Sciences psychologiques et de
l'Education

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Collection de thèses de l'Université catholique de Louvain, 2020

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Couverture: illustration réalisée par Pablo Boulanger.

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Abstract

This thesis was aimed to investigate how the position of a nociceptive stimulus applied on the body is coded in the brain and what is the role of visual experience in the development of these localization mechanisms. This was investigated by comparing the abilities of normally sighted people to those of people who never experienced vision, i.e. congenitally blind, in perceiving and localizing radiant-heat stimuli applied on two separate body parts. We showed that sighted participants localize nociceptive stimuli according to both their position on the body surface but also according to the location of the stimulated body part in external space. On the contrary, although congenitally blind participants are also able to use a spatial external coordinate system, they preferentially rely on the location of the stimuli according to their position on the body. This suggests that the way we perceive and localize nociceptive stimuli is shaped by visual experience.

Résumé

Cette thèse avait pour objectif d'étudier comment le cerveau code la position d'un stimulus nociceptif sur le corps et le rôle des expériences visuelles dans ces mécanismes de localisation. Ces questions ont été abordées en comparant les capacités de personnes voyantes à celles de personnes qui n'ont jamais eu d'expérience visuelle (aveugles congénitaux) à percevoir et localiser des stimuli nociceptifs présentés sur deux parties distinctes du corps. Nous avons montré que les voyants localisaient les stimuli nociceptifs selon leur position sur la surface du corps, mais aussi selon la position de la partie du corps stimulée dans l'espace externe. Au contraire, les aveugles congénitaux, bien qu'ils soient capables d'utiliser un système de coordonnées basé sur l'espace externe, localiseraient les stimulations préférentiellement selon leur postion sur le corps. Cela suggère que la manière dont nous percevons et localisons les stimuli nociceptifs dépendrait de nos expériences visuelles.

Acknowledgments

Ce n'est pas sans une certaine émotion que cette fin de thèse arrive, et je voudrais ici prendre l'espace nécessaire pour remercier tous ceux qui, de près ou d'un peu plus loin, ont contribué à la réalisation de ce travail.

Avant tout, je souhaite remercier mon promoteur de thèse, le Prof. Valéry Legrain, de m'avoir donné l'occasion d'entamer ce travail. Merci pour ta confiance, ta disponibilité, nos discussions et tes conseils. Merci d'avoir cru en mes compétences académiques et de m'avoir toujours poussée à plus de rigueur dans mon travail.

Je voudrais également remercier ma co-promotrice, la Prof. Anne de Volder, pour son aide précieuse lors du recrutement des participants non-voyants, ainsi que les Prof. Olivier Collignon et Martin Edwards, pour m'avoir accompagnée et conseillée pendant ces 4 années. Merci également à ce dernier d'avoir accepté de présider le jury de cette thèse.

I would also like to thank the members of my thesis jury, Prof. Virginie Crollen, Elena Azañón and Irene Ronga, for having accepted to read and discuss this manuscript. Thank you for your time, your questions and valuable insights on this work.

Cette thèse n'aurait jamais vu le jour sans la participation des nombreux participants, voyants et non-voyants, aux différentes expériences qui la composent. Je remercie chacun de vous pour la confiance que vous m'avez accordée. Merci également aux étudiants et mémorants pour leur aide précieuse lors des longues journées de testing.

Je voudrais aussi remercier Leïla, Véronique et Cathy pour leur travail administratif remarquable au sein de l'Institut.

Merci également à tout le groupe NOCIONS dont l'ambiance est légendaire. Grâce à vous, ces quatre années ont été enrichissantes tant sur le plan scientifique que social. Merci pour votre aide et vos encouragements lors de ces derniers mois. Un merci plus spécial à André Mouraux pour son aide précieuse lors de la réalisation des scripts de mes expériences. Merci aussi au Prof. Léon Plaghki et à Arthur pour leurs éclaircissements à propos de la méthode adaptative.

Un merci tout particulier à mes collègues et amies, les Valérettes. Lieve, aucun mot ne pourrait exprimer toute la gratitude et l'admiration que j'ai pour toi. Cette thèse ne serait pas ce qu'elle est aujourd'hui sans ta contribution inestimable à chaque étape de ce parcours. Merci pour ton écoute, tes relectures et excellents conseils, ainsi que pour ta capacité incroyable à gérer les situations de stress et de doute au sein de notre petit groupe. Merci pour ta présence et ta bienveillance sans limite. Charlotte et Roxane, merci de m'avoir si bien accueillie et intégrée parmi vous, merci pour ces instants de bonheur au labo ou en dehors, ces rires, ces larmes, et tout ce que nous avons pu partager d'extrême et de moins extrême pendant ces années de thèse. Louise, avoir une amie qui vient se doubler d'une collègue a été une expérience formidable. Merci pour ta disponibilité, ton soutien inconditionnel, ton écoute si attentive et ton implication sincère dans chacune de nos discussions quotidiennes. À toutes, merci pour votre présence à mes côtés tout au long de ces quatre années, merci pour cette amitié qui nous lie et que je chéris.

Un tout grand merci également à mes parents de m'avoir permise de faire mes études, de m'avoir épaulée et d'avoir cru en moi. Papa, merci pour ton implication, ton écoute et tes bons conseils de ces derniers mois. Maman, merci pour ton soutien et ta confiance en moi. Merci aussi à Antoine et Jonathan d'être les frères extraordinaires que vous êtes, et d'avoir cette capacité de me faire rire dans n'importe quelle situation. Sarah, Gaëlle, merci pour cette sororité qui nous lie envers et contre tout, votre soutien et votre bienveillance.

Enfin, un immense merci à ma seconde famille, mes ami·e·s Alix, Chanael, Charly, Chacha, Joachim, Paloma, Pablo, Charlotte, Roxane, Louise, Charlie, Clémence, Chloé, Christel, Juliette, Louis, Stéphanie. A tous, merci d'être les ami·e·s incroyables que vous êtes. Merci pour votre soutien inestimable, en particulier lors de ces derniers mois. Merci à ceux d'entre vous qui sont venus me soutenir jusqu'à Valence où j'ai rédigé la majeure partie de ce travail. Un merci plus particulier à toi, Alix, pour notre profonde amitié et ton accompagnement quotidien dans ce long parcours de thèse, en particulier lors de mon séjour à Valence. Merci pour ton écoute et ta bienveillance sans limite et si réconfortante, merci de croire en moi et d'être toujours présente, dans mes moments de joie comme dans mes moments de doute. Merci à Chlo, Jo et Palo d'avoir suivi cette fin de thèse même à l'autre bout du monde, et d'avoir toujours été là pour me faire rire et m'encourager. Merci également à Pablo d'avoir accepté de me prêter son talent et d'avoir pris le temps de dessiner la couverture de cette thèse.

Bruxelles, Mars 2020

Camille

This work was supported by the Fonds de la Recherche Scientifique – FNRS.

General Introduction

Acting in the external world around the body such as, for example, chasing away a fly that is annoyingly tingling our shoulder while we are sitting outside, or withdrawing our arm from a cigarette that is burning our skin in a crowd of people, are responses that occur so automatically that we are not even fully aware of doing them. In reality, these behaviors result from a sequence of finely tuned processes and integration mechanisms working in concert from the activation of the corresponding sensory receptors to the execution of the motor response, such as an orchestra whose conductor would be the brain. While the body's integrity is not threatened by the fly, the burning of the cigarette has the potential to damage the body, conferring to this somatic input an additional warning function prompting protective behavior. This example illustrates the importance of somatic sensations, since they are triggering a cascade of events ending up in an adequate and effective behavioral response. It also emphasizes the crucial role of painful stimuli, whose role would be to warn the brain about an impending threat in the environment, and adequately guide defensive actions aiming at preserving the integrity of the body.

Accordingly, localizing painful inputs on the body would be of primary importance for survival. However, since our body limbs constantly move in external space, solely locating the pain on the body surface would not be sufficient to allow us to initiate a defensive action towards the threatening stimulus in contact with the body. Indeed, in order to determine the origin of the pain and adequately orient the defensive action, the brain also needs to take the position of the stimulated limb in external space into account. Therefore, pain should be coded according to multiple spatial representations. In spite of the behavioral and functional relevance of such spatial representations of pain, this topic has received little attention in previous pain research. Instead, previous studies have mainly focused on the ability to localize painful stimuli on the surface of the body, neglecting their spatial perception according to a coordinate system that would take external space as reference. In contrast, previous literature on the perception of innocuous tactile stimuli has extensively studied this topic. Moreover, these studies have suggested a role of early visual experience in the spatial representations underlying the localization of tactile stimuli. Indeed, vision has been demonstrated to play a key role in calibrating spatial perception in general.

Therefore, the aim of this thesis was twofold. A first objective was to provide evidence for the existence of multiple spatial coordinate systems to code the position of painful stimuli. A second objective was to investigate the role of early visual experience in shaping such spatial representations of pain.

This general introduction will be composed of several theoretical chapters. In a first section, I will define the concepts of nociception and pain and the difference between the two. The functioning of the nociceptive system and the neural mechanisms underlying the

experience of pain will be quickly reviewed before emphasizing the functional aspect of nociception and pain.

The second chapter will describe in details the frames of reference for the localization of tactile stimuli. The neurophysiological mechanisms underlying the spatial coding of touch will be presented, as well as some developmental aspects.

The third chapter will review the few studies having addressed the question of the spatial frames of reference for coding the position of nociceptive stimuli on the body. Other studies having shown an impact of the posture of the body on pain perception will be presented and a link with multisensory interactions between nociception and vision will be made.

The fourth and final theoretical chapter of the general introduction will focus on spatial perception abilities in congenitally blind individuals. Existing differences between congenitally blind and normally sighted people regarding the somatosensory processing in the tactile and nociceptive modality will be first described. The ability of congenitally blind individuals to localize auditory inputs in external space will be quickly reviewed, before emphasizing differences with sighted people regarding the spatial processing of tactile stimuli. Finally, I will quickly review their capacities to integrate stimuli from somatic (i.e. tactile) and other sensory modalities presented in external space, such as auditory stimuli.

This theoretical introduction will be followed by the experimental part of this thesis. This section will be separated in five chapters corresponding to the five studies conducted within the general context of investigating the role of visual experience in the spatial mapping of nociceptive stimuli. The first study aimed at validating a new methodological approach that has been used in the second and third studies. Studies 2 and 3 aimed at comparing the abilities of congenitally blind and normally sighted people to code nociceptive stimuli according to multiple frames of reference. The fourth study investigated the potential influence of body posture on the perception of pain in congenitally blind and normally sighted individuals. In the fifth and last study, we addressed the question of the time course of the spatial mapping of nociceptive inputs in normally sighted people by comparing brain responses to nociceptive and non-nociceptive stimuli.

In a general discussion, the main findings of the experimental part will be presented, before being interpreted and integrated with the existing literature. Potential limitations of our studies will be discussed, and perspective for future research will be proposed. I will finish by concluding remarks.

1. Nociception and pain

1.1. The nociceptive system

The nociceptive system can be seen as a system enabling the brain to rapidly detect the presence of a potential danger, and act consequently. Accordingly, the nociceptors, i.e. the sensory receptors present in the skin or the viscera responding to nociceptive inputs, are characterized by high activation thresholds, indicating that they are activated by high intensity and potentially noxious stimuli (Belmonte & Viana, 2008). A stimulus is considered as noxious as soon as it is potentially harmful for the body tissue, representing a potential or real threat for its integrity. Therefore, nociception can be defined as the ensemble of the neural processes that are specifically devoted to the coding, the transmission and the processing of information regarding potentially noxious stimuli (Kandel, Schwartz, Jessell, Siegelbaum, & Hudspeth, 2013).

At the peripheral level of the nervous system, while tactile information is transmitted through the mechanoreceptors associated with largely myelinated Aβ fibers, nociceptive information is mostly coded and transmitted by free nerve endings associated to thinly myelinated Aδ and unmyelinated C fibers (Kandel et al., 2013). These nociceptors are considered as polymodal since the majority of them can be activated by thermal, mechanical as well as chemical inputs (Belmonte & Viana, 2008). The difference in terms of myelin results in different conduction velocities associated with these types of fibers. Indeed, as compared to Aβ fibers (30-120 m/s), the conduction velocity of the Aδ fibers is slower (4-30 m/s) and that of the C fibers is considered as ultra-slow (0,4-2 m/s) (Le Bars & Plaghki, 2009). In addition, Aδ nociceptive fibers are characterized by high activation thresholds, e.g. thermal stimuli of approximately 46°C or higher, and C fibers are generally activated by stimuli of lower intensities, i.e. thermal stimuli ≥40°C (Churyukanov, Plaghki, Legrain, & Mouraux, 2012). Given the lower activation thresholds of C-, as compared to Aδ fibers, high-intensity stimuli activating Aδ fibers have high chances to concomitantly activate C fibers. This conjoint activation generally results in a double sensation of pain. The first pain sensation, associated with Aδ fibers activation, is brief, well localized and usually described as pricking. The subsequent second sensation, reflecting C fibers activation, is generally felt as a prolonged and diffuse burning, and is thus more difficult to precisely localize (Le Bars & Plaghki, 2009).

The nociceptive fibers conduct the nociceptive information to the spinal cord, in which the message is relayed by the corresponding neurons in the dorsal horn. While tactile information is transmitted through the posterior cordonal pathway, the nociceptive signal is then afferently projected through the anterolateral pathway, mainly composed of the spinothalamic, the spinoreticular and the spinotectal tracts (Figure 1; Le Bars & Plaghki, 2009; Tracey & Mantyh, 2007). After thalamic relays, nociceptive inputs are sent to a wide array of subcortical and cortical areas, such as the primary (SI) and secondary (SII) somatosensory cortices, the anterior cingulate cortex (ACC) and the insular cortex (IC) (see Bushnell & Apkarian, 2006; Garcia-Larrea, Frot, & Valeriani, 2003; Tracey & Mantyh, 2007 for reviews). While tactile and thermo-nociceptive inputs are coded and transmitted by anatomically segregated systems at the peripheral and spinal levels, nociceptive stimuli generate activity in a cortical network that largely overlaps with that activated by tactile stimuli (see section 1.2). However, it seems that the spatial-temporal pattern of cortical activity generated by somatosensory inputs might be different between touch and nociception. Cortical projections of nociceptive inputs appeared indeed more parallely and bilaterally distributed than that of tactile inputs. For instance, while SI, and especially the Brodmann area 3b, represents an important early relay for tactile cortical processing (e.g. Hsiao & Yau, 2008), its contribution seems less important for nociceptive processing (e.g. Lenoir, Huang, Vandermeeren, Hatem & Mouraux, 2017).

Noteworthy, the activation of the nociceptive system does not necessarily result in experiencing pain (e.g. Lee, Mouraux, & Iannetti, 2009; Ostrowsky et al., 2002). Pain is defined as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (IASP, 1994, p. 210). Therefore, the terms of nociception and pain need to be dissociated, with pain being one out of many possible responses to the activity of the nociceptive system and containing emotional and cognitive components, resulting in a subjective and conscious experience. For instance, a stimulus that activates nociceptive fibers would not always elicit a painful sensation, depending of the sensibility of each. On the contrary, phantom pain that amputees can experience represents a perception in the limb that is not physically present, and, therefore, not directly stimulated (despite the fact that it is debated whether phantom pain might be partially generated by neural activity in the stump) (Nikolajsen & Jensen, 2006).

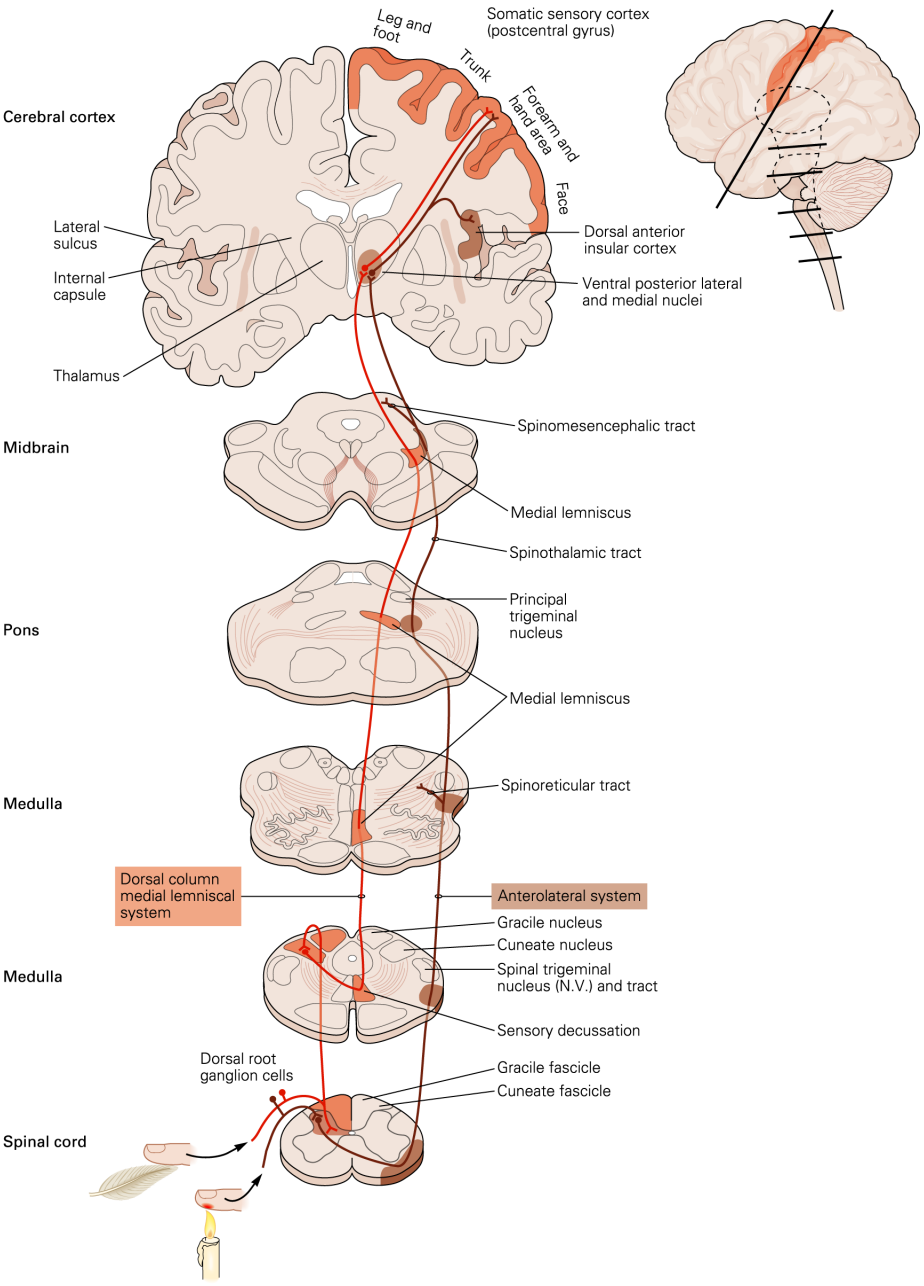
Leg and foot
Somatic sensory cortex (postcentral gyrus)
Trunk
Forearm and hand area
Face
Cerebral cortex
Lateral sulcus
Internal capsule
Thalamus
Dorsal anterior insular cortex
Ventral posterior lateral and medial nuclei
Midbrain
Spinomesencephalic tract
Medial lemniscus
Spinothalamic tract
Pons
Principal trigeminal nucleus
Medial lemniscus
Medulla
Spinoreticular tract
Dorsal column medial lemniscal system
Anterolateral system
Gracile nucleus
Cuneate nucleus
Medulla
Spinal trigeminal nucleus (N.V.) and tract
Sensory decussation
Dorsal root ganglion cells
Gracile fascicle
Cuneate fascicle
Spinal cord

Figure 1. Illustration of the afferent pathways and neuro-anatomical projections of tactile and nociceptive inputs*. Tactile information reaches the brain by means of the dorsal column system (in orange), while nociceptive information is transmitted through the anterolateral system (in brown). An important difference between the two pathways is that, after a first relay in the spinal dorsal horn, the decussation of nociceptive pathways directly occurs at the segmental level of the spine, whereas the transmission of tactile information is relayed and the decussation occurs in the medulla, before the signal is projected through the medial lemniscus. Adapted from Kandel et al. (2013).*

1.2. From the "pain matrix" towards a "saliency detection system"

Since pain is undeniably an important public health issue, a considerable part of previous research in this field has been dedicated to investigating the existence of specific mechanisms through which pain would emerge at the cortical level from the initial nociceptive information, i.e. cortical correlates of pain perception in the human brain. Hence, studies have tried to find a direct, objective and quantifiable measure of pain experience by using various techniques enabling to assess brain activity during the application of nociceptive and painful stimuli, such as electroencephalography (EEG), magnetoencephalography (MEG), positron emission tomography (PET), and functional magnetic resonance imaging (fMRI). Such studies have massively emerged in pain research by showing that nociceptive stimuli perceived as painful recurrently elicited brain responses in opercula-insular and cingulate areas, in spite of diverse experimental designs and techniques. In addition, the magnitude of the activity in these same structures was shown to be (1) correlated with the perceived intensity of pain reported by the participants (e.g. Coghill, Sang, Maisog, & Iadarola, 1999; Iannetti, Zambreanu, Cruccu, & Tracey, 2005) and (2) modulated by the same factors modulating pain perception (e.g. Hofbauer, Rainville, Duncan, & Bushnell, 2001; Rainville, 2002). This brain network was therefore considered as "the cerebral signature" of the experience of pain, or the so-called "pain matrix" (e.g. Peyron, Laurent, & García-Larrea, 2000; Tracey & Mantyh, 2007).

Nonetheless, a wealth of studies has emerged and challenged the idea that this cortical network was specifically involved in experiencing pain. First, it was shown that cortical responses within the so-called "pain matrix" could be actually dissociated from the perceived pain intensity (e.g. Iannetti, Hughes, Lee, & Mouraux, 2008; Lee et al., 2009; Mouraux &

Plaghki, 2007). In addition, brain responses in these regions have been shown to be modulated by factors independent of the intensity of the nociceptive inputs (e.g. Legrain, Guérit, Bruyer, & Plaghki, 2002; Legrain, Perchet, & Garcia-Larrea, 2009). Finally, and most importantly, operculo-insular and cingulate responses have been demonstrated to be evoked by non-nociceptive and non-painful stimuli, including non-somatic stimuli such as visual and auditory inputs (see Iannetti & Mouraux, 2010; Legrain, Iannetti, Plaghki, & Mouraux, 2011 for reviews; Liberati et al., 2016; Lui et al., 2008; Mouraux, Diukova, Lee, Wise, & Iannetti, 2011; Mouraux & Iannetti, 2009). These findings have led the researchers to conclude that the cortical activity classically sampled by neuroimaging and neurophysiological techniques in response to nociceptive stimuli would therefore rather reflect a network involved in detecting and reacting to any sensory inputs that are meaningful for the integrity of the body, regardless of the sensory modality through which they are conveyed and regardless of whether they are perceived as painful (Iannetti & Mouraux, 2010; Legrain et al., 2011). Nociceptive stimuli being the archetype of physical threat, the nociceptive system would be seen as part of a broader system involved in homeostasis (Legrain et al., 2011). Accordingly, pain could be seen as a warning signal, whose functional role would be confined to prioritize the detection, localization, and reaction to stimuli that could constitute a threat to the physical integrity of the body (Legrain & Torta, 2015). This view emphasizes three important cognitive processes underlying nociception: (1) *selective attention* through which the processing of stimuli that are the most relevant for the integrity of the body are prioritized based on their saliency and the ongoing cognitive goals, (2) *spatial perception* allowing to map the accurate position of these stimuli on the body and in external space, and (3) *action selection* enabling the preparation of the most appropriate motor response to the nociceptive stimuli (Legrain & Torta, 2015). This PhD work will be centered around the spatial perception of nociceptive inputs, and more specifically, the mechanisms at play when the brain localizes such stimuli on the body.

1.3. Spatial perception of nociceptive inputs: a focus on somatotopy

Being able to localize nociceptive stimuli is of primary importance for one to identify which part of the body is potentially being threatened or damaged. Localization processes also enable to define the position of the harmful stimulus, i.e. the potential cause of the damage, in external space and guide defensive motor actions towards this threat. For this behavioral response to be effective, the brain has to coordinate the representation of the body space and that of external space. Since the body limbs are constantly moving in space, spatial information about the relative position of the stimulated body part needs to be updated and integrated in this process (Legrain & Torta, 2015).

Accordingly, the position of somatosensory information is coded according to different frames of reference in the brain (Vallar & Maravita, 2009). A frame of reference can be defined as a coordinate system defining a specific position on a map. Hence, one type of reference frames used to localize somatic inputs is body-based and anatomically maps the location of the event on the body surface in the cortex, which contains a spatially organized representation of the sensory receptors of the skin. For instance, such somatotopic organization has been found for touch in the primary somatosensory and motor cortices and is referred to as the *Homonculus*, representing the whole cutaneous surface of the body proportionally to the amount of skin receptors and the size of the receptive fields of each body part (Penfield & Boldrey, 1937; Penfield & Rasmussen, 1950). The other type of reference frames through which somatic inputs would be mapped is based on the position of the stimulated body part in external space, in interaction with proprioceptive information, i.e. the relative position of the body limbs in space (Legrain & Torta, 2015; Vallar & Maravita, 2009). Such spatiotopic representations would be of great importance for nociception since, using external space as coordinate system, they would provide the brain with a common spatial framework allowing and facilitating interactions between somatic inputs and sensory information from other modalities, coding stimuli from external (i.e. extra-somatic) space. In other words, spatiotopic frames of reference could be seen as an interface between the location of the noxious event on the body and the position of the object in external space that could be responsible for such sensation, in order to prompt adequate and effective defensive behavior and avoid further damage. In line with studies in the tactile modality (Driver & Spence, 1998), we use the term *spatial remapping* to define the mechanisms through which spatial locations are updated based on other reference systems, integrating various sources of information, such as proprioception and kinesthesia.

In spite of the apparent importance of spatiotopic frames of reference in the localization mechanisms underlying an effective protective response of the organism against a potential threat, little interest has been given to such processes in pain research. Instead, most of the studies have focused on the search in the brain of a somatotopic organization that would be comparable to that of touch. Indeed, it has been shown that human subjects were able to localize noxious stimuli on the body with high accuracy (e.g. Mancini, Longo, Iannetti, & Haggard, 2011; Moore & Schady, 1995; Schlereth, Magerl, & Treede, 2001). These findings have led the researchers to hypothesize that an accurate somatotopic representation for pain localization in the brain must exist. By using fMRI, PET and intracerebral electrical stimulations, such somatotopic organization depending on the stimulation site and broadly similar to that observed for the tactile system has been found in the lateral thalamus (Lenz et al., 1994), the putamen (Bingel, Glascher, Weiller, & Buchel, 2004; Brooks, Zambreanu, Godinez, Craig, & Tracey, 2005), SI (Andersson, 1997; Bingel, Lorenz, et al., 2004; Mancini, Haggard, Iannetti, Longo, & Sereno, 2012), SII (Bingel, Lorenz, et al., 2004), and the insular cortex (Baumgärtner et al., 2010; Brooks et al., 2005; Henderson, Gandevia, & Macefield,

2007; Mazzola, Isnard, Peyron, Guenot, & Mauguiere, 2009). While most of these studies highlighted a gross somatotopy of nociceptive stimuli by showing that distinct areas within these brain structures were responsive to stimulations of the hand, the foot or the face, Mancini et al. (2012) succeeded to demonstrate the existence of fine-grained nociceptive maps organized in a somatotopic fashion for each digit within the hand area of SI. Moreover, in this study, the regions activated by the nociceptive and tactile stimuli were highly aligned, despite the poor nociceptive innervation density relative to the abundance of tactile receptors on the digits (e.g. Kelly, Terenghi, Hazari, & Wiberg, 2005; Lauria, 1999). This might suggest that the perceived location of a nociceptive input on the skin surface might result from complex interactions between tactile and nociceptive central projections (Mancini et al., 2012), as well as interplays between afferent inputs and higher-order structural representations of the body surface, such as a *supramodal representation of the body structure* (Mancini, Longo, Iannetti, et al., 2011). Noteworthy, a recent fMRI study has evidenced the existence of even more precise somatotopic representations of nociception within each digit, not in SI, but in the intraparietal sulcus (Mancini, Sereno, Lee, Iannetti, & Tracey, 2019). However, no evidence of such within-digit representations were found for tactile inputs in the same region, suggesting that the somatotopic representations of touch and nociception at least partly differ from each other (Mancini et al., 2019).

These studies emphasize what has been defined as the *interoceptive* function of nociception, i.e. "the sense of the physiological condition of the body" (Craig, 2002). Indeed, the interoceptive system is a homeostatic afferent pathway that conveys signals about the physiological status of all tissues of the body. In that sense, it is intimately related to the maintenance of the body's integrity, informing the brain about a potential risk of tissue damage (Craig, 2002, 2003). However, the way we perceive our body is undoubtedly shaped by the surrounding environment. Hence, taking such external information into account appears to be crucial for survival. The *exteroceptive* function of pain could be defined in such terms, monitoring the space around the body and guiding defensive behaviors towards external threats that might impact the physical integrity of the body (Haggard, Iannetti, & Longo, 2013; Legrain, 2017). Since spatiotopic representations of pain can be seen as an interface between the body and external space, they would play an important role in this exteroceptive function of pain. Nevertheless, in spite of its great relevance for survival, such spatiotopic representation of nociception remains poorly understood. However, any somatic event could be relevant for the body's integrity. Nociception and touch both being somatic systems informing the brain about the physical state of the body, they are believed to share, at least partially, the same spatial organization. The following section will therefore be dedicated to describe the spatial representations underlying the localization of tactile events, with the aim of better understanding that of nociceptive inputs.

2. Spatial representations of touch

Unlike nociception, the spatial representations underlying the perception and localization of tactile inputs has been extensively studied. Indeed, the sense of touch is intricately connected to the grasp and manipulation of objects in the external world, but also to the perception of pain, enabling to orient defensive behaviors towards noxious stimuli entering in contact with the body.

Here, I will review the scientific work that has been done with the aim of understanding how the location of a touch is mapped in the brain in order to interact with other sensory modalities and trigger the most appropriate motor response.

2.1. Frames of reference for localizing tactile inputs

As soon as an object enters in contact with the body, the brain will code the position of the touch on the body surface according to somatotopic frames of reference. Since our body parts are constantly moving in space, the brain also needs to take into account the position of the body limbs in external space in order to effectively respond to this stimulus. Hence, the location of the touch is *remapped* according to spatiotopic coordinates, allowing the brain to associate the touch with the location of the object that is actually responsible for the touch in external space. This process is referred to as *tactile spatial remapping* (Driver & Spence, 1998; Vallar & Maravita, 2009).

2.1.1. Evidence from patient studies

Initially, evidence of the existence of such *spatiotopic remapping* of tactile events came from studies with right brain damage patients showing somatosensory extinction (e.g. Smania & Aglioti, 1995; Aglioti, Smania, & Peru, 1999). Extinction is observed after the lesion of one cortical hemisphere, most often the right one, and is defined as an inability to report a stimulus delivered to the side contralateral to the damaged hemisphere when it is concomitantly presented with a stimulus on the ipsilesional side, whereas it is normally well perceived when presented alone (e.g. Brozzoli, Demattè, Pavani, Frassinetti, & Farne, 2006; Farnè, Meunier, Hadj-Bouziane, Brozzoli, & Jacobs, 2011). Regarding the tactile modality, Smania and Aglioti (1995) observed that, when the patients with tactile extinction crossed

their hands over the body midline such as the left hand was in the right part of space and vice versa, the detection rate for tactile stimuli significantly improved (see **Figure 2**). This indicates that the perception of tactile stimuli did not only depend on the hand on which the stimulus was applied, but also on the position of that hand in external space. The same results were obtained when the patients crossed their hands while they were both placed in one single hemispace relative to their body midline (Aglioti et al. 1999), or when different fingers of the same hand were stimulated while that hand was placed in various positions (e.g. palm up/down; in front or behind the back) (Tinazzi, Ferrari, Zampini, & Aglioti, 2000). For instance, the stimulation delivered to the left-sided finger, i.e. the little finger of the left hand in palm down orientation or the thumb in the palm up hand orientation, was extinguished by a stimulus simultaneously applied to the right-sided finger, i.e. the thumb in palm down orientation but the little finger in palm up orientation, suggesting that the position of one body part relative to another also matters when perceiving and localizing tactile inputs, and not only the general position of the limbs in space according to the body midline (Aglioti et al., 1999; Tinazzi et al., 2000). Interestingly, alongside with a better tactile perception on the contralesional body limbs, crossing the arms and the legs has been shown to also have a detrimental effect on the detection of stimulations applied on the ipsilesional side of the body in these patients, even when two non-homologous body parts were stimulated, e.g. the hand and the knee (Bartolomeo, Perri, & Gainotti, 2004).

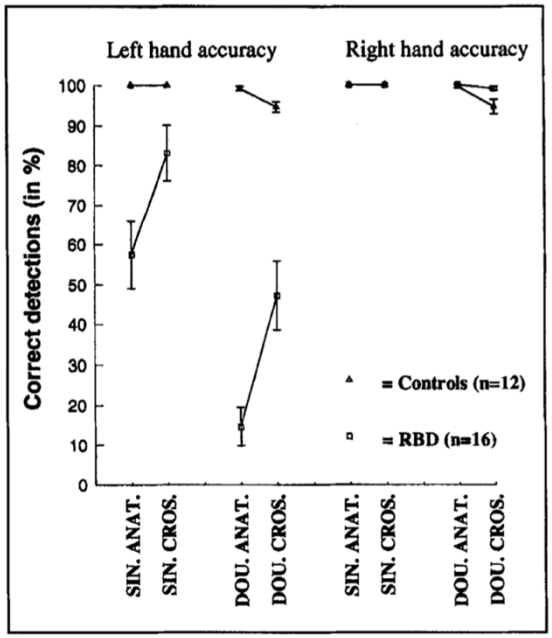

Figure 2. *Correct detections of stimuli (in percentage) for right brain damaged patients and controls in the study of Smania & Aglioti (1995). Error bars represent standard errors. SIN = single stimulation, DOU = double stimulation; ANAT = hands in uncrossed position; CROS = hands in crossed position. The detection rate on the left hand improved in the crossed posture for both single and double stimulation conditions. Adapted from Smania & Aglioti (1995).*

2.1.2. Evidence from studies in healthy volunteers

In healthy volunteers, crossing the limbs while performing various types of detection or discrimination tasks has also been largely used to study the spatial representations of touch and dissociate the somatotopic from the spatiotopic reference frames. The most common experimental paradigm that has been used for that purpose is probably the temporal order judgement (TOJ) task performed with the limbs onto the tactile stimuli are applied in an uncrossed vs. a crossed posture (Heed & Azañón, 2014).

Temporal order judgement studies

In a typical somatosensory TOJ task, participants are presented with two stimuli in rapid succession, usually one on each hand. The two stimuli are separated by various time intervals, i.e. stimulus onset asynchronies (SOA), and the participants have to report which stimulus of the pair they perceived as having been presented first, usually by reporting on which hand it occurred. Crucially, the task is performed while the arms are placed in a normal uncrossed posture, or crossed over the body midline such as the left hand is placed in the right part of space and vice versa. The crossed posture is intended to create a mismatch between the somatotopic and spatiotopic reference frames (**Figure 3**). Indeed, stimuli applied on the left hand are projected to the contralateral right hemisphere, irrespective of the position of the hand is external space. Therefore, the somatotopic frame of reference does not change as a function of the posture, i.e. whether the hand is placed in the left or in the right hemispace. However, the spatiotopic coordinates of the stimuli applied to the left hand change as a function of its position in external space (the posture). Thus, when the hands are crossed, stimuli applied to the left hand are coded as *left* according to somatotopic frames of reference, but as *right* according to spatiotopic reference frames, creating a conflict between the two representations. Therefore, crossing the hands enables to investigate the involvement of spatiotopic frames of reference while localizing tactile inputs.

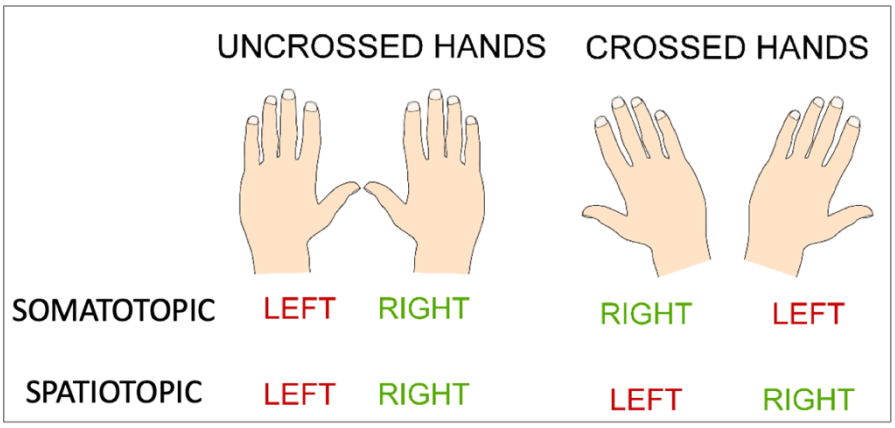

Figure 3. ***Illustration of the conflict emerging from the crossed hand posture****. When the hands are uncrossed, the somatotopic and spatiotopic coordinates of each hand are aligned. When the participants crossed the hands, while the left hand is still coded as "left" according to somatotopic coordinates, it is now coded as "right" according to spatiotopic coordinates which take the relative position of the body limbs in external space into account. Thus, a mismatch between the two coordinates system emerges from this posture.*

Data from such TOJ tasks are generally plotted by taking the probability of responding one of the hands as having been perceived as first stimulated (e.g. left-first responses) as function of the different SOA. On the x-axis, the SOA are usually represented from the larger ones at the extremities of the axis to the smaller ones being represented more centrally (see **Figure 4**). By convention, negative SOA values indicate that the left hand was stimulated first and positive SOA values mean that the right hand was stimulated first. Participants' responses are then fitted according to the different SOA by means of sigmoid or straight line functions (see **Figures 4.A and 4.B, respectively**) (Heed & Azañón, 2014). The performance in TOJ tasks can be depicted by various parameters, such as the slope of the psychometric function fitting participants' responses. The steeper is the slope, the better is the performance, since this indicates that the participants were able to accurately discriminate the temporal order of the two stimuli even with shorter time intervals (SOA). From the slope can be

measured the time interval needed between the two stimuli for the participants to correctly discriminate their order of appearance in a certain amount of trials. This measure is the most commonly used to assess participants' performance and is referred to as the *just noticeable difference* (JND). The smaller is the JND, the better is the performance (see Study 1 for more details regarding the methods, analyses and graphical representations of TOJ data). Hence, an impact of the posture on participants' performance is usually illustrated by lower slope values, that is graphically represented by a flattening of the slope (**Figure 4**), and higher JND values, i.e. higher time interval needed between the two touches to be able to correctly order the stimuli in most of the trials (Heed & Azañón, 2014; Heed, Backhaus, & Röder, 2012).

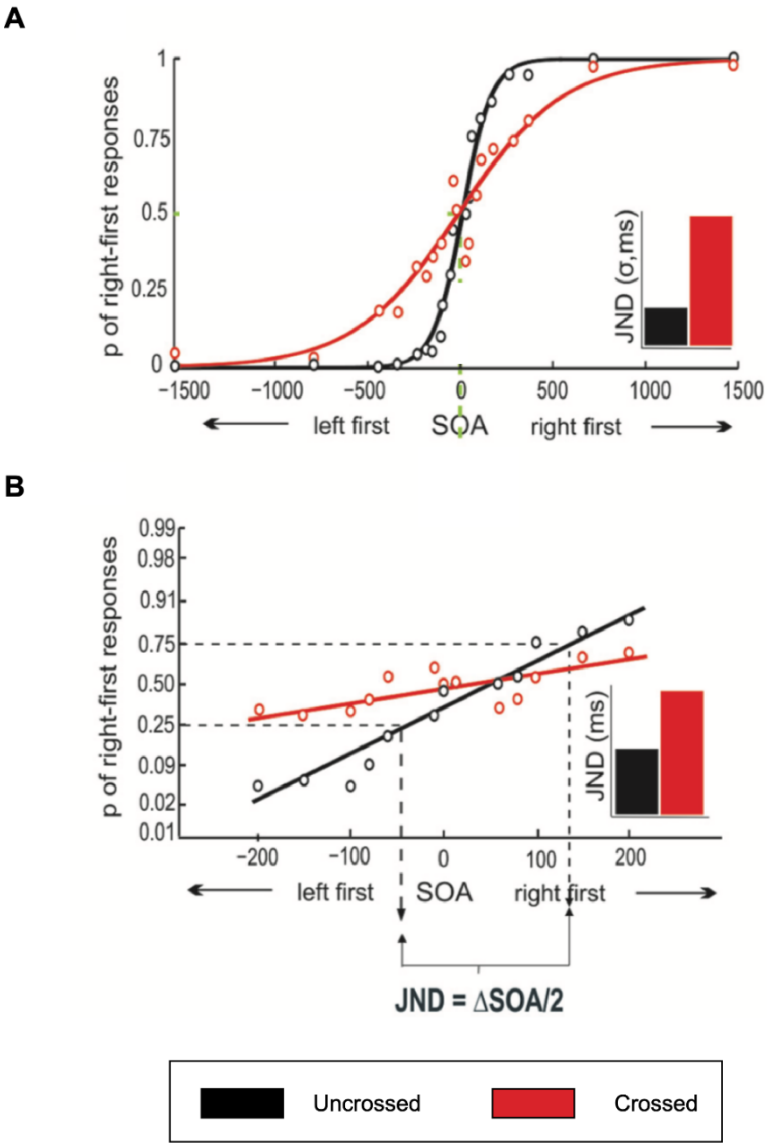

Figure 4. *Example of tactile TOJ data in uncrossed (black) and crossed (red) posture, fitted with sigmoid functions* **(A)** *and straight lines* **(B)**. *The y-axis represents the proportion of right-first responses from 0 to 1. The x-axis represents the different SOA in milliseconds. Negative values indicate that the left hand was stimulated first while positive values mean that the right hand was stimulated first. The slope of both the psychometric curve and the*

straight line is steeper with uncrossed (black) as compared to crossed (red) hands. Adapted from Heed & Azañón (2014).

Temporal discrimination is generally relatively good with the hands uncrossed, as participants are normally capable of correctly ordering two stimuli separated in time by 30 to 70 ms. In contrast, their performance dramatically decreases as soon as they cross their hands over the body midline (JND values from 120 to 300 ms), as evidenced by multiple studies having used this paradigm (e.g. Sambo et al., 2013; Shore, Spry, & Spence, 2002; Yamamoto & Kitazawa, 2001a). In addition to impair TOJ performances, crossing the hands has also been shown to increase reaction times associated with the participants' responses (Heed et al., 2012; Shore et al., 2002; Yamamoto & Kitazawa, 2001a). Because spatiotopic representations of the stimuli are actually irrelevant to perform the task (i.e. participants have to report on which hand they perceived the first stimulus of the pair irrespective of the position of the hands in external space), the detrimental effect of crossing the hands on TOJ performance has been interpreted as indexing an automatic remapping of tactile inputs into spatiotopic coordinates, taking the position of the stimulated limbs in space into account (Heed & Azañón, 2014). In other words, the crossing hands effect would emerge from the conflicting information provided by the two frames of reference when they are mismatching, whilst both representations normally bring consistent information when the hands are uncrossed, the somatotopic and spatiotopic coordinates of the stimuli being aligned and merging to allow better performance (Shore et al., 2002). Accordingly, it has been recently suggested that the frequent occurrence of tactile information in particular spatial location might promote the emergence of *visual spatial priors.* For instance, touches on the right hand would originate more often from objects in the right side of space than from the opposite side of space. Therefore, one could preferentially expect the source of the right-hand tactile stimulus as originating from the right hemispace, because it constitutes the most plausible configuration considering past experiences. Similarly, the frequent occurrence of touches while adopting a particular body posture would promote the emergence of *canonical postural priors*, that is*,* stored prototypical postural configurations containing the most plausible body configuration for a given touch. Together, these frequent associations (i.e. co-occurrence of tactile-visual or tactile-postural sensory signals) would be used as a reference for localizing tactile events, providing accurate performance. However, when the body adopts an unusual configuration, such as when the hands are crossed over the body midline, the reliance on these priors would be inefficient. Indeed, in this situation, the spatial priors (i.e. the visual space where the hand normally is and from which one could expect the source of the stimulus to come) would mismatch the online tactile-proprioceptive information. This mismatch would result in impaired tactile localization (Tamé, Azañón, & Longo, 2019).

This crossing hands effect has been demonstrated to be very reliable and stable across studies, in spite of various differences in the experimental designs. Indeed, although variable in amplitude, a robust effect of limb crossing was found no matter the response mode (motor response with the stimulated finger e.g. Shore et al. (2002); or with another finger of the stimulated hand e.g. Sambo et al. (2013); with foot pedals e.g. Kobor, Furedi, Kovacs, Spence, and Vidnyanszky (2006); verbally e.g. Pagel, Heed, and Röder (2009); by eye saccade e.g. Overvliet, Azañón, and Soto-Faraco (2011)). Such effects seem also independent on the gender (Cadieux, Barnett-Cowan, & Shore, 2010) and the handedness of the participants (Wada, Yamamoto, & Kitazawa, 2004). It was even evidenced with small distance between the stimulated crossed hands (e.g. only 7 cm in Heed et al., 2012). Moreover, crossing the limbs has been shown to deteriorate participants' performance when the stimuli differed in terms of frequency (e.g. Badde, Röder, & Heed, 2015), or when two non-homologous body limbs were stimulated, such as two different fingers from the two hands or belonging to the same hand (Heed et al., 2012), or when the stimulated arm was crossed over the contralateral stimulated leg (Schicke & Röder, 2006). Crossing hands effects were not only observed when the hands were placed in the space in front of the body, but also when the hands were crossed behind the back of the participants, even though the effect was considerably reduced in the latter situation (Kobor et al., 2006). Interestingly, it has also been shown that movement planning could modulate performances of tactile TOJ tasks. Indeed, planning to change the posture from an uncrossed to a crossed arm posture impaired TOJ performance, while the reverse improved participants' performance (Hermosillo et al; 2011; Heed et al 2015). This was also true when performing the movement change during the stimulations were applied (Heed et al, 2015). In addition, Azañón, Stenner, Cardini, and Haggard (2015) showed that while frequently changing the posture from uncrossed to crossed and vice versa resulted in decreased TOJ performances as soon as the crossed position was adopted, blocking the participants in the crossed posture could rapidly improve their performance over few trials. However, this gain in performance was almost immediately abolished when the participants changed to the uncrossed and then changed back to the crossed posture. Taken together, the results of all these studies indicate that spatiotopic frames of reference were always taken into account when participants localized tactile events on the body, indexing that touch is remapped from somatotopic representations to spatial external coordinates binding cutaneous and proprioceptive signals.

Interestingly, Yamamoto and Kitazawa (2001a) manipulated the orientation of the hands by asking their participants to perform the TOJ task while their hands were placed in six different positions from uncrossed to crossed defined as if the hands were rotating along a circle. They showed that only the positions in which one arm crossed the other gave rise to a significant impairment of performance. This is in line with the findings of Heed et al. (2012) who showed that placing one hand on top of the other along the body midline affected the temporal order judgements of two tactile stimuli applied on the index fingers but not on the

fourth digits. Indeed, whereas both hands share the same spatial location (i.e. in front of the body trunk), the fourth digit of the right hand is placed at the right relative to the fourth digit of the left hand, just as when the hands are uncrossed in their respective hemispace. In contrast, when one hand is placed on top of the other, the right index finger is positioned at the left of the index finger belonging to the left hand, just as in the crossed hands posture. This indicates that TOJ performance is impaired only when there is a conflict between the two spatial reference frames of the stimulated body parts, while manipulating the posture without creating any mismatch does not seem to influence the performance. In addition, the same authors demonstrated a reduced effect of crossing the hands when the stimulated little fingers were crossed back to their normal hemispace, as compared to a fully crossed posture (i.e. the "normal" crossed hands posture), suggesting that the localization of tactile stimuli on a finger was determined by its external location in space but also by the spatial coordinates of the hand to which it belongs, probably converging through integration mechanisms (Heed et al., 2012). Following the same idea, it has been shown that making TOJ about vibrations presented at the tips of sticks held in a crossed posture while the hands are maintained uncrossed impacted the performance of the participants. Similarly, TOJ performance was decreased when holding L-shape sticks so that the tips of the sticks were positioned in the opposite side of space (Yamamoto & Kitazawa, 2001b; Yamamoto, Moizumi, & Kitazawa, 2005). Conversely, crossing the hands while holding vibrating sticks crossed back in the normal hemifields diminished the crossing effect (Yamamoto & Kitazawa, 2001b). These studies emphasize the flexibility of the representation and integration processes of touch localization. Indeed, this suggests that the tools (i.e. sticks) were integrated with the representation of the body as if it was an extension of its boundaries in external space, illustrating the plasticity of body representation and thereby of the spatial representation of tactile inputs applied to the body (Martel, Cardinali, Roy, & Farne, 2016).

Other experimental procedures

Although TOJ tasks has been used as a privileged paradigm to investigate the spatial remapping of touch, other studies succeeded to evidence the integration of somatotopic and spatiotopic reference frames during the localization of tactile inputs using other paradigms (e.g. Azañón, Camacho, & Soto-Faraco, 2010; Azañón & Soto-Faraco, 2008a, 2008b; Overvliet et al., 2011; Shore, Gray, Spry, & Spence, 2005; Soto-Faraco, Ronald, & Spence, 2004; Tamé, Farne, & Pavani, 2011).

For instance, Azañón and Soto-Faraco (2008a) used a cueing paradigm in which tactile stimuli were applied on one of the two participants' hands and cued the possible location of the forthcoming lateralized visual stimuli. The participants were asked to respond as quickly as possible to the position of the visual stimuli while their hands were placed in a crossed

posture. The results showed that the perception of visual stimuli was facilitated by the occurrence of tactile cues applied on the hand congruent to the visual targets according to external space. For example, the perception of a visual stimulus presented in the left hemispace was facilitated by a tactile cue having been applied to the hand that was placed in the left hemispace, i.e. the right hand. Therefore, this indicates that these spatial-cueing effects were driven by spatiotopic coordinates of the tactile stimuli instead of their somatotopic coordinates. This suggests that tactile events are remapped from somatotopic towards spatiotopic coordinates, using external space as a reference frame.

Similarly, Soto-Faraco et al. (2004, experiment 3) asked their participants to make elevation judgements (i.e. up vs. down) about the location of vibrotactile stimuli presented to the index finger or the thumb of one hand while ignoring vibrotactile stimulations presented to either location on the other hand (i.e. distractors). Importantly, they varied the posture of the hands (i.e. the two hands placed palms up or palms down or one hand palm up and the other palm down). Thus, the distractors could be presented at spatially congruent or incongruent locations relative to the target stimuli in terms of somatotopic coordinates (i.e. the same/different two body parts, i.e. index or thumb, were stimulated irrespective of the posture of the hands) or regarding external space (i.e. the target and distractor stimuli are presented to same/different external locations, irrespective of the stimulated body part) (**Figure 5**). They found that the perception of the tactile target stimuli was facilitated by the occurrence of a tactile distractor applied on the other hand at the same location (i.e. congruency effect) in terms of external space. For instance, the localization of a stimulus on the thumb was facilitated by the presence of a stimulus on the thumb of the other hand when the hands were both placed palms up or palms down, but was facilitated by the occurrence of a stimulus presented on the index finger of the other hand when one hand was placed palm up and the other palm down. Conversely, participants' performance in judging the location of the target stimuli was decreased by the occurrence of distractors presented at incongruent locations according to external space, even though they were congruent in terms of somatotopic frames of reference. For example, the localization of a tactile target on the thumb was impacted by a tactile distractor presented on the thumb of the other hand when the two hands were placed in different positions). This indicates that the participants based their judgements on external locations (i.e. spatiotopic coordinates) of the stimuli, suggesting that the tactile stimuli were remapped into spatiotopic coordinates taking the position of the stimulated fingers in external space into account.

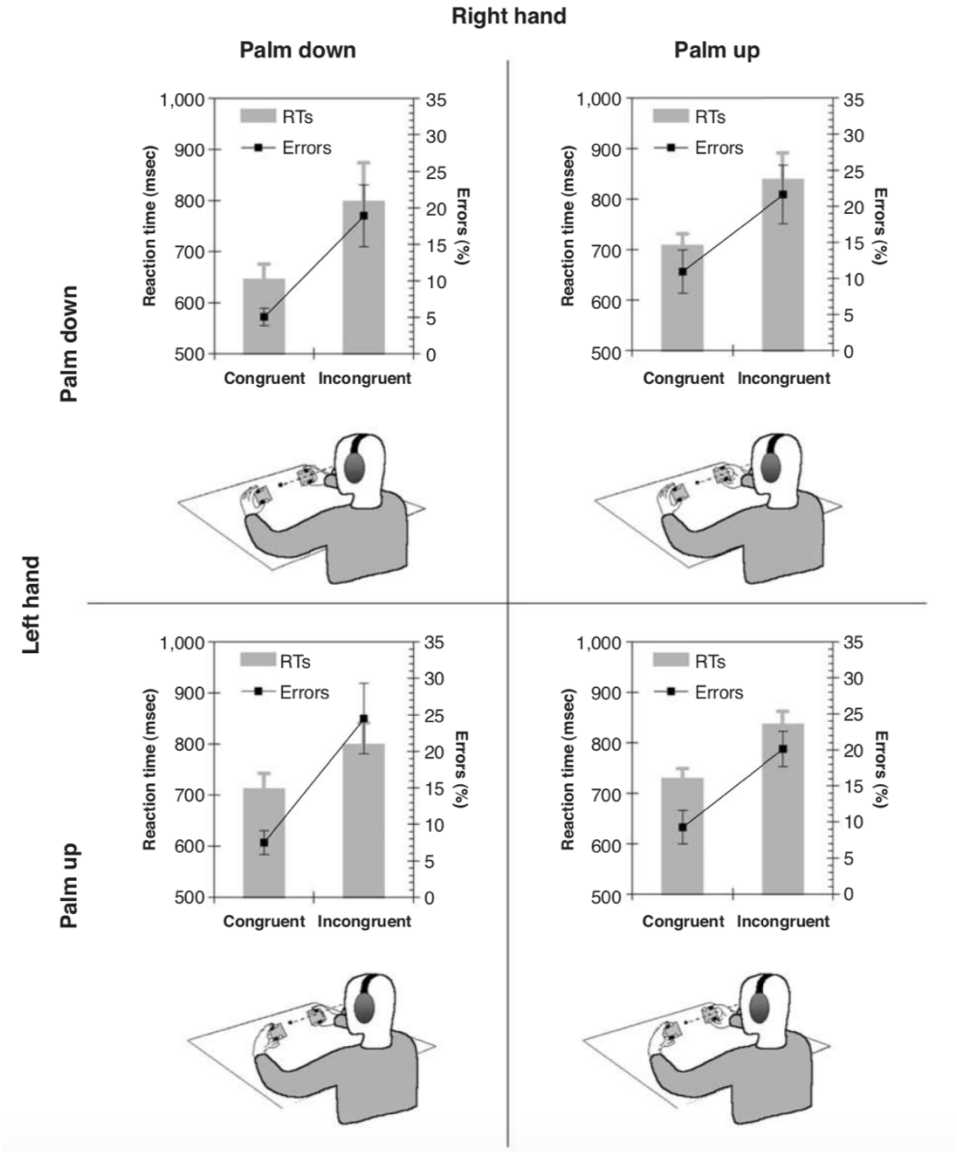

Figure 5. *Results of the vibrotactile elevation discrimination task as a function of target-distractor congruency for the four different postures tested in the experiment 3 of Soto-Faraco et al. (2004). The bars represent the mean reaction times (RTs). The filled squares connected by solid lines represent the percentages of errors. The perception of the target*

stimuli was facilitated by the occurrence of a tactile distractor on the other hand at the same location according to external space. Conversely, participants' judgements and reaction times were negatively impacted by the occurrence of tactile distractors presented in incongruent locations relative to the target stimuli in terms of external space. Adapted from Soto-Faraco et al. (2004).

The importance of spatiotopic representations in tactile perception has also been demonstrated through studies that manipulated the posture of the hands, but without having crossed them. Indeed, manipulating the distance between the two hands has been shown to influence tactile localization by both using TOJ tasks (Gallace & Spence, 2005; Roberts, Wing, Durkin, & Humphreys, 2003; Shore et al., 2005), and congruency-effects (Soto-Faraco et al., 2004, experiment 4). In these studies, the hands were placed either close together or far apart. In the TOJ studies, participants' judgements were less accurate in the close, as compared to the far hands posture. In the cueing paradigm, the congruency effects (i.e. smaller/larger error rate in localization judgements when the target and the distractor had congruent/incongruent spatial locations) was larger for the close as compared to the far posture, indicating a greater effect of the distractors when the hands were placed close together (Soto-Faraco et al., 2004). Hence these results suggest that the position of the stimulated hands in external space was taken into account and impacted localization performances even when somatotopic and spatiotopic reference frames were still aligned. It is however worth noting that, using TOJ tasks, we did not succeed to replicate the detrimental effect of gathering the two hands close together on TOJ performance (see **Appendix 1**).

Interestingly, an effect of the perceived distance between the hands has been observed by creating the illusion that the hands were placed close together or far apart by means of a mirror reflection, while the real position of the hands in external space was actually unchanged (Gallace & Spence, 2005; Soto-Faraco et al., 2004, experiment 5). Strikingly, similar results than the above-mentioned studies having manipulating the real position of the hands were obtained: TOJ performance was disturbed when the hands were seen close together as compared to when they were seen further apart. Furthermore, these findings suggest that TOJ performance in such experimental design was mostly driven by the visual perception of the body posture, and less by proprioceptive feedback about its actual position. In the same vein, it has been shown that after having created the illusion of the ownership of fake rubber hands (Botvinick & Cohen, 1998), seeing the uncrossed rubber hands while performing a tactile TOJ task with the hands crossed considerably alleviated the effect of crossing the arms on tactile localization, suggesting complex interactions between

spatiotopic representations of touch and visual information regarding the position of the hands in external space (Azañón & Soto-Faraco, 2007).

2.2. A flexibly weighted balance between reference frames: the *relative* role of context

Because remapping tactile inputs into spatiotopic coordinates seem to occur even when taking body posture into account is irrelevant to correctly perform the task, such as in tactile TOJ tasks (Heed & Azañón, 2014) or when space is made irrelevant in the task context (e.g. Azañón, Camacho, et al., 2010), this process has been hypothesized to be highly automatic. Nevertheless, several studies have manipulated in various way the context in which the participants were asked to localize tactile events, in order to determine how flexible the activation of such spatiotopic representations of touch is.

For example, Gallace, Soto-Faraco, Dalton, Kreukniet, and Spence (2008) used the same spatial congruency task than previously mentioned (Soto-Faraco et al., 2004) and showed that asking the participants to localize the tactile stimuli according to anatomical responses (i.e. thumb vs. index finger) instead of spatial responses (i.e. up vs. down) resulted in slightly reducing the spatial congruency effect (i.e. the fact that participants' judgements were influenced by the externally-defined location of the tactile distractors on the other hand), but not in abolishing it. Later on, Schubert and colleagues (2017) also demonstrated that the task instruction determined the direction of the congruency effect (Schubert, Badde, Röder, & Heed, 2017), with anatomical instruction leading to better performance when the distractor and the target tactile inputs were presented at anatomically congruent locations, and conversely regarding spatial instructions. This would suggest that task demands could affect the importance accorded to spatiotopic frames of reference during localization processes, emphasizing the flexibility of the spatial representations of touch. However, it is worth mentioning that during TOJ tasks, simply changing task instructions to stress external space did not lead to a significant modulation of the crossing hands effect (Cadieux & Shore, 2013; Crollen, Spruyt, Mahau, Bottini, & Collignon, 2019).

Instead of modifying task instructions, a group of researchers, in a series of experiment, manipulated body posture during TOJ tasks performed in the frame of a dual task paradigm. For instance, they manipulated the cognitive load by combining TOJ tasks with a secondary task relying on verbal or spatial working memory abilities (Badde, Heed, & Röder, 2014). In another study, they manipulated the task context by coupling the TOJ with a subsequent secondary judgement task (Badde et al., 2015). In the first study, they showed that the

crossing hands effect in the TOJ task was systematically reduced by the processing load of the working memory task, independently of its type (i.e. verbal or spatial). Moreover, this effect was modulated by the difficulty of the working memory task, the higher the difficulty level, i.e. the cognitive load, the smaller the detrimental effect of crossing the hands (Badde et al., 2014). This suggests that distracting the participants from the tactile localization task, by asking them to perform a difficult memory task, would result in reducing the conflict between the somatotopic and spatiotopic coordinates of the tactile stimuli, probably by reducing the importance accorded to spatiotopic representations. In the second study, the secondary task was intended to stress either anatomical reference frames (i.e. after having responded to the TOJ task, the participants reported which was the color of the box containing the hand on which was presented the stimuli with the higher frequency while the boxes moved with the hands in the crossed posture) or external frames (i.e. the participants reported which was the color of the box containing the hand who received the stimuli with the higher frequency while the boxes remained at the same spatial locations). The authors showed that the effect of crossing the hands in the TOJ primary task was reduced when the secondary judgement task emphasized anatomical reference frames but not when the secondary task stressed external coordinates, indicating that their results could not be solely attributed to the fact of being engaged in a secondary task (Badde et al., 2015). Therefore, the better TOJ performance of the participants under these task-irrelevant contexts has been attributed to a reduced influence of external coordinates under high cognitive load or when somatotopic coordinates were stressed. Together, these findings suggest that the spatiotopic representations of touch are subject to influences from contextual demands, such as task complexity or instruction, through top-down regulations, rather than being fully automatic (Badde et al., 2014; Badde et al., 2015).

Nonetheless, although the importance of spatiotopic frames of reference could be attenuated under certain circumstances, thereby reducing the underlying conflict between the two spatial codes, none of these studies has succeeded to completely abolish the implication of spatiotopic representations in touch localization. This suggests that even if not needed, this spatial reference frame remains always available even though to a lesser extent. Nevertheless, Roberts and Humphreys (2008) found no evidence of disrupting effect of crossing the hands on participants' performance when temporal judgements were made about non-spatial touch characteristics (i.e. discriminating stimuli of different duration or frequency) instead of stimuli location, even when the response mode was of a "*go/no go*" type (i.e. only responding when the target order is presented, e.g. *longer stimulus was presented first*). Similarly, crossing the hands does not seem to affect performance in simultaneity judgement tasks (i.e. deciding whether or not the stimuli presented to the two hands occurred at the same time) (e.g. Geffen, Rosa, & Luciano, 2000). These findings would rather suggest that the automaticity with which the spatiotopic remapping occur might depend on the processes at play, with stimuli location processes automatically triggering a

spatiotopic remapping of these inputs, whereas processing other characteristics of the stimuli might not (e.g. Forster & Eimer, 2004 for evidence of independent processing of spatial and non-spatial attributes of tactile inputs in a task using selective attention). Therefore, to reconcile these findings, it has been hypothesized that spatial perception of touch implies a genuine spatial remapping process that would be automatically initialized, followed by an integration process of the multiple frames of reference during which the respective weight given to somatotopic and spatiotopic coordinates can be modulated by relevant (e.g. Gallace et al., 2008) or irrelevant (e.g. Badde et al., 2015) contextual factors (Badde & Heed, 2016; Badde, Heed, & Röder, 2016). According to this view, the impaired performance observed in limb crossing studies would be the result of conflicting information trying to be integrated in order to derive the final location estimate of the stimuli. More widely, this integration account would explain the variations in the amplitude of posture effects encountered in the touch remapping literature (Badde & Heed, 2016; Badde et al., 2016).

So far, we have seen that although the remapping of tactile events from somatotopic towards spatiotopic coordinates would be automatically initiated during tactile localization, the weight accorded to the spatiotopic representations could be modulated to a certain extent according to ongoing cognitive goals during integration processes. However, one could wonder when, during tactile processing, the somatotopic coordinates of tactile stimuli would be remapped into spatiotopic representations, and in which brain areas somatotopic and spatiotopic representations of the stimuli would be integrated. The next sections will be devoted to review these topics.

2.3. Time course of spatial remapping of touch

Initially, some authors have put forward that while tactile stimuli would be remapped from somatotopic towards spatiotopic coordinates, they would be first *consciously* perceived according to external space, and somatotopic representations of the stimuli would be subsequently available to consciousness. In other words, this space-to-body account assumes that a tactile stimulus is first perceived according to spatiotopic coordinates, that brings up the conscious perception of the event, before being projected back onto its location on the body surface (Kitazawa, 2002; Yamamoto & Kitazawa, 2001a). According to this view, the two tactile stimuli presented in TOJ tasks would create an illusory motion percept, and the participants would base their judgement on the direction of the motion in external space. Hence, when the arms are crossed, each stimulus location according to external space would be projected to the wrong hand, resulting in impaired performance (Kitazawa et al., 2008; Takahashi, Kansaku, Wada, Shibuya, & Kitazawa, 2013).

However, it is most commonly accepted that the location of a touch is originally coded according to skin-based somatotopic reference frames before being relatively quickly remapped according to spatiotopic coordinates considering body posture in external space. Hence, the location of the tactile stimulus would be first only available in somatotopic coordinates. Subsequently, these coordinates would be transformed into spatial external location (i.e. spatiotopic coordinates), creating a conflict when the two frames of reference are not aligned (e.g. when the hands are crossed). The resolution of this conflict would require a cognitive effort that would be responsible for performance impairment in limb crossing studies. Evidence of such time course has been provided by behavioral as well as EEG studies. Originally, Yamamoto and Kitazawa (2001a) suggested that the remapping process would be completed around 300 ms after stimulus presentation, because TOJ performance in the crossed posture, although impaired in trials with short SOA, was considerably improved when the SOA increased up to 300 ms. Later on, studies having used cueing paradigms succeeded to demonstrate that tactile remapping into spatiotopic coordinates would start from 60 ms after the presentation of the tactile stimulus (Azañón & Soto-Faraco, 2008a, 2008b). As a reminder, in these studies, participants were asked to discriminate the location of visual stimuli presented in either the left or right part of space. Each visual target was preceded by a tactile cue presented to one of the hands placed in a crossed posture. Crucially, the time interval between the tactile cues and the visual stimuli varied from 30 to 360 ms (**Figure 6.A & 6.B**). The results revealed that, at time intervals shorter or equal to 60 ms, the perception of visual targets was facilitated (i.e. reaction times were faster) by tactile cues previously applied on the hand spatially congruent to the visual stimuli according to somatotopic coordinates. For instance, visual stimuli occurring in the left hemispace were faster perceived when preceded by a tactile cue applied on the left hand, even though that hand was placed in the right side of space. On the contrary, when the interval between the tactile cue and the visual target was longer than 60 ms (i.e. 180 and 360 ms), the perception of visual stimuli was facilitated by tactile cues presented to the hand congruent to the visual targets according to external space, e.g. left visual targets were faster perceived when preceded by tactile cues presented in the left hemispace (applied on the right hand that was placed in the left hemispace) (**Figure 6.C**). These results thus indicate that the cueing effects changed as a function of the time intervals separating the tactile and visual stimuli, showing that these effects were first driven by somatotopic frames of reference at shorter time intervals while they were driven by spatiotopic coordinates of the tactile stimuli at longer time intervals. This suggests that tactile stimuli are first coded according to somatotopic representations only, before being transformed into spatiotopic coordinates between 60 and 180 ms after the onset of the stimulation (Azañón & Soto-Faraco, 2008a). Accordingly, in some studies having used saccadic movement to localize tactile inputs (e.g. Groh & Sparks, 1996; Overvliet et al., 2011) it was occasionally observed that, when the hands were crossed, the saccade towards tactile stimuli started in the wrong direction (i.e. towards the side of space in which the stimulated hand normally resides when the hands are uncrossed) and was corrected after a

certain time. Considering the time needed for motor preparation of the saccade, the authors suggested that an external representation of touch would become available around 190 ms (Overvliet et al., 2011).

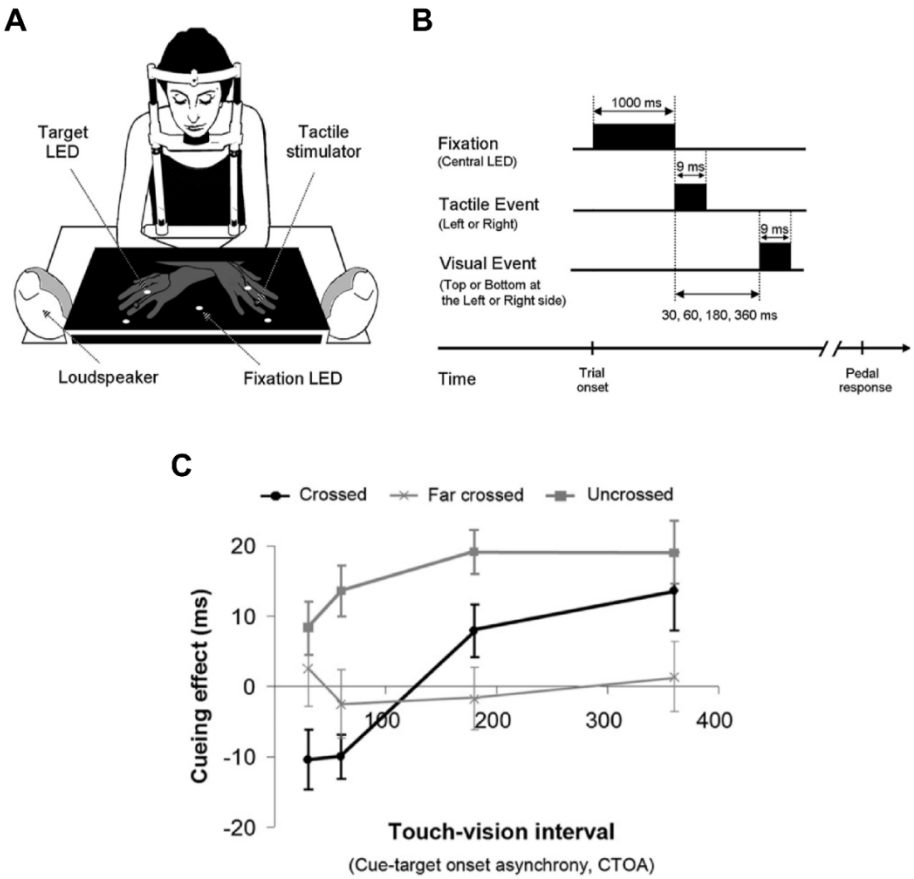

Figure 6. ***Experimental setup, sequence trial and results of the behavioral study of Azañón & Soto-Faraco (2008)***. ***(A)*** *Frontal view of the setup used for the experiment. Participants' hands were crossed over the body midline and occluded beneath a black cardboard screen. The light emitting diodes (LEDs), constituting the visual targets, were placed above each hand at two locations: top vs. bottom. The tactile stimuli (cues) were presented to the dorsal surface of the middle phalanx of each ring finger. A central LED served as fixation point. Two loudspeakers played white noise throughout the experiment.*

(B) *Trial sequence. In a typical trial, after 1 s fixation, a tactile irrelevant stimulus (cue) was delivered to one of the hands and followed by a brief visual flash (target) from one of the two LEDs (top or bottom) placed above one of the hands (same or different from the one having received the tactile cue with equal probability). Four possible time intervals separated the tactile cues from the visual targets: 30, 60, 180, and 360 ms. Participants were asked to respond as quickly as possible to the location of the LED in the vertical dimension (top vs. bottom).* ***(C)*** *Results of the experiment. The graph represents the mean spatial cueing effects (difference between RTs from trials in which the tactile and visual stimuli were presented in opposite hemispace and from trials in which they were presented in the same hemispace) as a function of the time intervals between the tactile cue and the visual target (CTOA). A positive cueing effect indicates faster performance for trials in which visual events occurred in the same hemispace than the tactile cues as compared to trials in which the tactile and visual stimuli were presented in opposite hemispace. A negative cueing effect indicates the reverse. The results of the main experiment in which the participants' hands were crossed over the body midline are represented by the thick black line. They indicate that the cueing effects were driven by somatotopic reference frames when the time intervals were shorter than 100 ms. For longer time intervals, the pattern of results reversed, i.e. the cueing effects were driven by the location of the tactile stimuli according to external space (spatiotopic coordinates). Noteworthy, a control experiment was run in which the participants' hands were uncrossed. The results of this experiment are represented by the thick grey line. The thin grey line corresponds to the results of another control experiment in which the authors introduced a physical distance (28 cm) between the tactile cues and the visual targets (far-crossed experiment). Adapted from Azañón and Soto-Faraco (2008).*

Studies having used electroencephalography to record brain responses elicited by tactile stimuli applied to either uncrossed or crossed hands corroborate the above-mentioned behavioral results. For instance, Soto-Faraco and Azañón (2013) showed that the earliest effect of the body posture (i.e. uncrossed vs. crossed) on the brain responses to tactile stimuli occurred at about 70 ms after the onset of the stimuli, as reflected on the magnitude of the event-related brain potentials (ERPs) elicited by the tactile stimuli. In this experiment, the participants were presented with tactile stimuli applied on one of the two hands. Once in a while, a second tactile stimulus was applied on the other hand and the participants were asked to perform TOJ on the two tactile stimuli. EEG recordings on single tactile trials revealed that the crossed posture led to a significantly greater amplitude of the tactile ERPs, characterized by a negative shift in this condition, as compared to the uncrossed condition. This difference of ERPs magnitude was evidenced as early as 70-90 ms after the onset of the stimulus, and was observed over fronto-temporal electrodes at earlier stages, extending to

temporo-parietal electrodes at around 170 ms post stimulus (see **Figure 7**). Hence, tactile ERPs evoked at latencies earlier than 70 ms were unaffected by the posture. These results therefore suggest that spatiotopic representations would not be taken into account in the very beginning of tactile processing, and would become available from 70 ms onward. In addition, in this study, the amplitude of the posture effect on the tactile ERPs correlated with the size of the posture effect on interweaved TOJ trials, indicating that the more the participants were impaired in the temporal order judgements during the crossed posture, the more important was the difference between the ERPs elicited in the crossed as compared to the uncrossed posture condition. Hence, this could potentially suggest that the modulation of the ERPs in the crossed posture might reflect the emerging conflict between the somatotopic and spatiotopic frames of reference when the latter spatial code becomes available. Similarly, in a study in which participants regularly changed the arm posture (uncrossed vs. crossed) while being presented with unpredictable tactile stimuli, effects of crossing the hands on tactile ERPs, characterized by a greater amplitude of the ERPs elicited in the crossed as compared to the uncrossed posture condition, were evidenced around 130 ms when the sight of the hands was available, and around 150 ms post stimulus when the hands were hidden. These results suggest that the vision of the stimulated hands can influence the encoding of tactile stimuli according to spatiotopic frames of reference (Rigato et al., 2013).

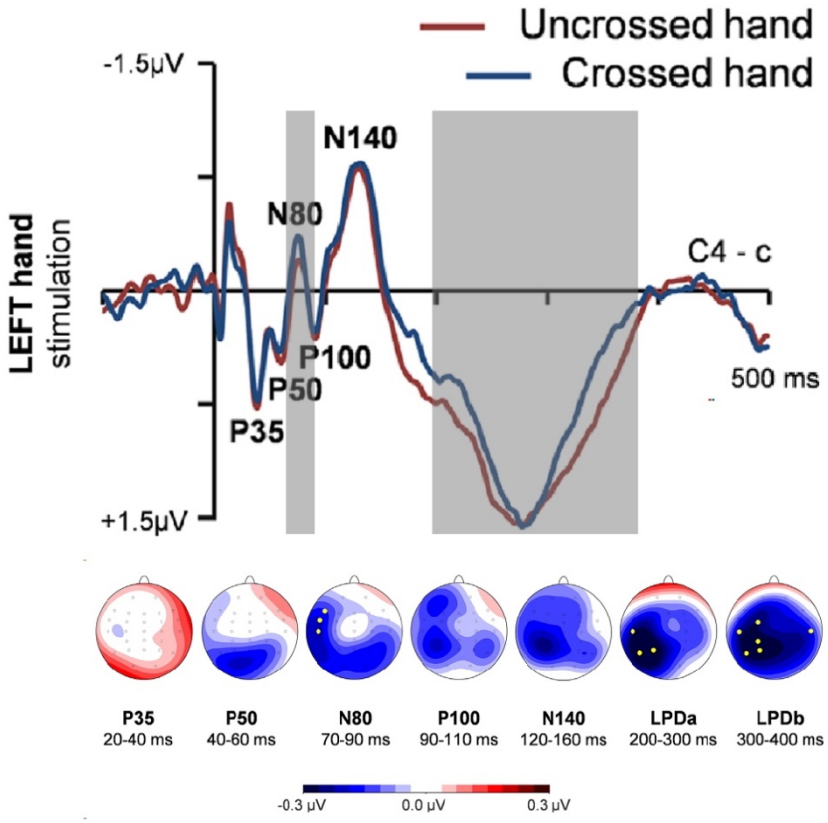

Figure 7. ***Time course of the spatiotopic remapping of tactile inputs using ERPs***. *Illustration of the results of one of the experiments from the study of Azañón & Soto-Faraco (2013). Top panel: Grand-averaged event-related potentials elicited by tactile stimuli presented to the left hand of the participants taken at the central electrode contralateral to the stimulated hand (i.e. C4). Blue and red lines represent the crossed and the uncrossed hands postures, respectively. The main somatosensory components are illustrated on the graph. The earliest difference between the postures was observed during the N80 component, i.e. between 70-90 ms (outlined in grey), while earlier ERP components were unaffected by hands posture. Bottom panel: topographical maps showing the average voltage difference between crossed and uncrossed postures (crossed-uncrossed subtraction) for each of the temporal windows used in the study. Blue is negative and red is positive. Electrodes in which significant differences between postures were highlighted are marked in yellow. Adapted from Azañón & Soto-Faraco (2013).*

In the same line, EEG experiments that manipulated attentional processes have also shown a modulation of tactile ERPs by spatiotopic coordinates at a latency range of 70-140 ms post stimulus (Heed & Röder, 2010; Ley, Steinberg, Hanganu-Opatz, & Röder, 2015). For instance, in the study of Heed and Röder (2010), participants received tactile stimuli on one of the two hands or on one of the two feet, always placed close to the hands, while attending one of the four limbs. The hands were either uncrossed or crossed in order to vary the distance between each hand and each foot. The EEG recordings revealed that the ERPs measured at centro-parietal electrodes were more positive between 100 and 140 ms post stimulus when the attended limb (e.g. left foot) belonged to the same hemibody (anatomically congruent) than the stimulated limb (e.g. left hand), irrespective of the hands posture. In addition, tactile evoked potentials were also more positive when the distance between the attended and stimulated limbs was small (e.g. left foot attended and left/right hand stimulated in the uncrossed/crossed posture respectively), as compared to a large distance (e.g. left foot attended and right/left hand stimulated in the uncrossed/crossed posture respectively). This indicates that spatiotopic coordinates were taken into account at that latency range.

Taken together, these findings across studies suggest that spatiotopic coordinates of tactile stimuli would be available around 100 ms after stimulus presentation. It has initially been suggested that once the remapping completed, the somatotopic coordinates would have been abandoned to the benefit of external coordinates, prompting interactions with other sensory modalities in external space (e.g. Azañón & Soto-Faraco, 2008a). However, considering the relative flexibility of spatial representations of touch, these electrophysiological studies would rather suggest that both somatotopic and spatiotopic representations are maintained after the completion of the remapping, and remain available to be weighted according to the context (Badde & Heed, 2016; Badde et al., 2016; Heed & Röder, 2010; Ley et al., 2015). For instance, Heed and Röder (2010) have observed a modulation of tactile ERPs by both anatomical and external frames of reference at 100-140 ms after stimulus presentation. Moreover, Ley et al. (2015) found that the influence of visual stimuli on tactile perception was concomitantly modulated by somatotopic and spatiotopic reference frames at latencies earlier than 250 ms, but predominantly by somatotopic coordinates at later latencies, possibly because their task involved a stronger weighting of somatotopic coordinates. Furthermore, studies in spatial attention that analyzed data from EEG or MEG in the frequency domain have associated responses corresponding to oscillatory activity in specific frequency ranges with each type of spatial representation (Buchholz, Jensen, & Medendorp, 2011, 2013; Schubert et al., 2015; Takahashi & Kitazawa, 2017). While somatotopic reference frames have been related to central responses in the beta frequency range (i.e. frequencies of 15-30 Hz), modulation of more posterior activity in alpha frequency range (i.e. frequencies of 7-14 Hz) has been reported to reflect spatiotopic coordinates of tactile stimuli. For instance, the alpha-band oscillatory activity associated with the effect of orienting attention to one hand has been found to be modulated by crossing the

hands, while beta-band related activity was not (Schubert et al., 2015). Importantly, both types of responses were observed in parallel at the same latency range, suggesting that both representations of touch were concurrently active (Heed, Buchholz, Engel, & Röder, 2015).

2.4. Neural correlates of spatial remapping of touch

Combining the location of a tactile stimulus on the skin with information about the relative position of the body parts in space would enable the brain to derive the external location of the stimulus. In that sense, the ultimate goal of the spatiotopic remapping would be to allow multisensory interactions between somatic and extrasomatic (e.g. visual) stimuli to occur, and guiding oriented actions in the external world, especially in the space directly surrounding the body and within which we can directly interact with objects (e.g. grasping) or defend the body (e.g. chasing a wasp away), i.e. the *peripersonal space* (Brozzoli, Ehrsson, & Farne, 2014). Such multisensory interactions are thought to be based on a cortical network of interconnected multimodal areas (e.g. di Pellegrino & Làdavas, 2015; Graziano, Gross, Taylor, & Moore, 2004; Làdavas, 2002; Maravita, Spence, & Driver, 2003). In non-human primates, these areas have been found to contain multimodal neurons, i.e. neurons that are able to respond to sensory inputs from different sensory modalities. For instance, such neurons that respond to tactile stimuli applied on a certain body part but also to visual stimuli occurring close to that body part have been found in the ventral premotor cortex (PMv) (Graziano & Gross, 1998; Graziano, Hu, & Gross, 1997; Graziano, Yap, & Gross, 1994; Rizzolatti, Fadiga, Fogassi, & Gallese, 1997; Rizzolatti, Scandolara, Matelli, & Gentilucci, 1981) and ventral intraparietal sulcus (VIP) (Duhamel, Colby, & Goldberg, 1998). Crucially, the visual receptive field (RF) was shown to be anchored to the associated tactile RF for some of these neurons, i.e. it was limited to the portion of space directly adjacent to the tactile RF. Thus, considering the tactile RF of the hand, when the hand moves in external space, the visual RF of these bimodal neurons does not move with eye movements (i.e. retinotopic coordinates) but moves with the tactile RF, indicating that the position of the limbs in space is taken into account by continuously adjusting the visual RF associated with tactile events.

Therefore, these brain areas, and more generally the posterior parietal cortex (PPC), has been suggested to be a good candidate to subserve the remapping of touch in external coordinates as well. Indeed, premotor and posterior parietal areas have been repeatedly associated with the spatiotopic representations of touch by means of transcranial magnetic stimulation (TMS), allowing to artificially and transitory disrupt cortical activity at the targeted location (Azañón, Longo, Soto-Faraco, & Haggard, 2010; Bolognini & Maravita, 2007; Ruzzoli & Soto-Faraco, 2014) and fMRI techniques (Crollen, Lazzouni, et al., 2017; Lloyd, Shore, Spence, & Calvert, 2003; Takahashi et al., 2013; Wada et al., 2012). For

instance, Ruzzoli and Soto-Faraco (2014) applied rhythmic TMS (rTMS) at a frequency of 10 Hz over the intraparietal sulcus (IPS) of their participants with the aim of increasing the sensitivity in the ipsilateral hemibody and lowering the sensitivity in the contralateral one. The participants were asked to make two-alternative forced choice (target/non-target) about events composed of a vibrotactile stimulus followed by a white-noise mask (target events) or of white noise only (non-target events). The vibrotactile stimuli of the target events were presented unpredictably to the left or right index finger. They found, as expected, that, as compared to stimulation over SI as a control condition, 10-Hz rTMS over the IPS had a negative impact on tactile detection on the contralateral hand but resulted in enhanced performance on the ipsilateral hand. Crucially, when the hands were crossed, TMS induced reversed effects, that is, detection performance was enhanced on the contralateral hand placed in the ipsilateral side of space, and deteriorated on the ipsilateral hand that was placed in the contralateral hemispace. This indicates that the effect produced by the modulation of IPS on the detection of tactile stimuli did not depend on the position of the vibrotactile stimuli on the body according to somatotopic reference frames, but depended on the position of the stimulated hand in external space, i.e. their spatiotopic coordinates. Hence, these modulatory effects of TMS according to body posture suggests that IPS is involved in the spatiotopic mapping of tactile inputs. Similarly, in another study, Azañón, Longo, et al. (2010) showed that applying single pulses of TMS over the right PPC at the location of the IPS disrupted the participants' ability to judge the position of tactile stimuli according to external space. In this study, the participants were asked to position their forearm in three different postures along the vertical axis (**Figure 8**). They were asked to discriminate the location of tactile stimuli presented at different locations on their forearm. More specifically, they had to judge whether the tactile stimuli applied on their forearm was higher or lower than a tactile stimulus previously applied on different possible location on their face. Since the forearm was placed in different positions relative to the face, only relying on somatotopic frames of reference was not sufficient to correctly perform the task, and spatiotopic reference frames of tactile stimuli applied on the forearm also needed to be taken into account. Therefore, the fact that participants' performance in this discrimination task after TMS over the IPS was impaired, whereas TMS over a control site (i.e. vertex) had no influence on their performance, suggests that this brain area is involved in remapping tactile stimuli into spatiotopic frames of reference (**Figure 8**). Essentially, control experiments were performed to respectively assess the effect of TMS over IPS and vertex locations on proprioceptive localization of the arm in space, and on tactile localization on the face and on the arm alone. The results of these control experiments allowed the authors to put forward that TMS over IPS had a disrupting effect on the processing of touch localization in external space, i.e. the integration of somatotopic and spatiotopic information, rather than on one of these processes individually (Azañón, Longo, et al., 2010). Hence, they concluded that PPC, and more specifically the IPS, might play a crucial role in remapping touch into spatiotopic representations taking body posture into account. Accordingly, using fMRI, Lloyd et al. (2003) observed enhanced activity in IPS, amongst other parietal structures, when participants received tactile stimuli while their hands

were crossed as compared to uncrossed, confirming the important role of this structure in considering spatiotopic coordinates of tactile events. Moreover, crossing the hands while performing tactile TOJ tasks has been related to increased brain activity in a large cortical network, including premotor and posterior parietal areas (Crollen, Lazzouni, et al., 2017; Takahashi et al., 2013; Wada et al., 2012). In addition, the TOJ performance of the participants was negatively correlated to the amplitude of their brain responses in this network. Thus, the more the participants struggled to realign somatotopic and spatiotopic coordinates of tactile stimuli to perform the task when the hands were crossed, the greater the activation of these brain areas was observed (Wada et al., 2012).

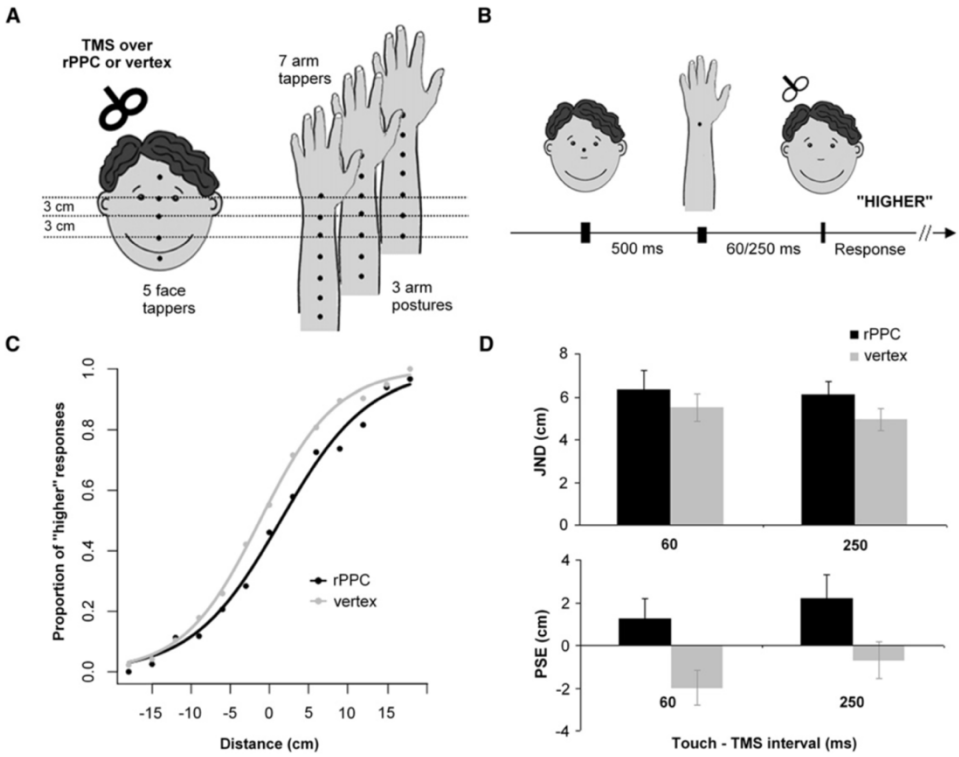

Figure 8. ***Experimental setup and results of the study of Azañón et al. (2010).*** *(A) schematic frontal view of the 3 arm postures of the experiment. Black dots represent the possible locations of the tactile stimuli on the face and on the forearm. (B) time course of a typical trial in the experiment. A 30 ms touch was delivered on the face, followed, 500 ms later, by a touch at one possible location on the forearm. After either 60 or 250 ms, one single transcranial magnetic stimulation (TMS) pulse was applied over the right PPC (rPPC) or the vertex (in different blocks). Then, participants were asked to report as quickly as possible whether the touch on the arm was higher or lower than the touch on the face (motor responses by pressing response keys with the index and middle fingers of the dominant hand). (C) Mean proportion of "higher" responses as function of touches disparity. The logistic fitting lines represent the group average data. The black line represents the TMS over rPPC condition while the grey line represent the control condition (i.e. TMS over the vertex). (D) Mean just noticeable difference (JND) and point of subjective equality (PSE). Black bars represent data from the rPPC TMS condition and gray bars represent the vertex TMS condition. Error bars represent the standard error of the mean. Participants' performance was decreased by 20% (increased JND values) in the TMS over rPPC as compared to TMS over vertex condition, independently of the time interval between the touch on the forearm and the TMS stimulation. Adapted from Azañón et al. (2010).*

Hence, in the previous section, we have seen that during tactile processing, somatotopic frames of reference were first activated, before spatiotopic representations of the stimuli become available from 70 ms after the onset of the stimulation onward. Taken together with the above-mentioned studies, this could suggest that the location of tactile events would be first coded according to a somatotopic fashion in the contralateral SI before being remapped into spatiotopic coordinates considering body posture in premotor and posterior parietal areas. The two spatial reference frames would be integrated and maintained in these associative cortical areas for a certain time in order to be integrated with other sensory modalities with the ultimate aim of preparing an adequate response to the stimulation. In accordance with this hypothesis, MEG studies having used electrical (i.e. tactile) stimulations have shown an early activation of contralateral SI (e.g. 20-60 ms), whereas ipsilateral SI as well as other association areas in premotor cortex and the PPC were not activated before 70-140 ms (e.g. Inui et al., 2003; Mauguière et al., 1999). Furthermore, premotor and posterior parietal areas have also been shown to participate in multisensory interactions within the peripersonal space close to the body (e.g. Avillac, Deneve, Olivier, Pouget, & Duhamel, 2005; Brozzoli, Gentile, Petkova, & Ehrsson, 2011; Graziano et al., 1997; Makin, Holmes, & Zohary, 2007), emphasizing the role of this cortical network in the representations of somatic and extra-somatic events according to external space.

2.5. Developmental aspect

In spite of the evident importance of touch remapping in everyday life, this process seems to be acquired during early sensory experiences in life, rather than being completely innate (Bremner, Holmes, & Spence, 2008). Although researchers have observed early signs of tactile coding into spatiotopic coordinates in young infants, i.e. between 6 and 10 months of age (Begum Ali, Spence, & Bremner, 2015; Bremner, Mareschal, Lloyd-Fox, & Spence, 2008; Rigato, Begum Ali, van Velzen, & Bremner, 2014), TOJ studies have provided evidence of the emergence of an automatic tactile remapping only from the age of 5 to 6 years old onward (Azañón, Camacho, Morales, & Longo, 2017; Pagel et al., 2009). Inter-individual differences among the tested children suggest that the ability to rely on spatiotopic representations to localize touch develops during an extended period of time before becoming completely automatic (Pagel et al., 2009). Once it is available, however, the automatic spatial remapping of touch not only impaired performances on TOJ crossed hands trials, but also improved the performance of the children on trials with the hands uncrossed over time, emphasizing the increasing role of spatiotopic representations in facilitating tactile localization by the integration of information from different spatial codes and, therefore, in facilitating multisensory interactions between somatic and extra-somatic inputs, which has also been shown to develop as a function of age (e.g. Lewkowicz, 1999).

Interestingly, electrophysiological findings indicated that crossing the hands modulated tactile ERPs of 10 months old infants, but only if they could see their arms, suggesting that it is primarily the vision of the limb posture that would modulate somatosensory processing at that age (Rigato et al., 2014). Additionally, the authors observed posture-related modulations of somatosensory ERPs in 8 months old infants, but only for those who had the capacity and tendency to make spontaneous reaching movements that cross the body midline, suggesting an influence of the development of sensorimotor functions in the emergence of spatiotopic representations of touch. Importantly, alongside with sensorimotor experience, early visual experience has been demonstrated to play a key role in the development of this automatic spatiotopic mapping of somatosensory stimuli. Indeed, the TOJ performance of congenitally blind participants is usually not affected by changes in posture (e.g. Crollen, Albouy, Lepore, & Collignon, 2017; Röder, Rösler, & Spence, 2004), whereas a crossing hands deficit is noticeable in late blind participants (i.e. individuals who lost sight later in life) (Röder et al., 2004). More specifically, studies having tested participants who were born

blind and recovered sight at different time points in life[1] suggest the existence of a sensitive period between 5 months and 2 years of life. Indeed, blind individuals whose sight was recovered within the first 5 months of age showed similar performances in tactile TOJ than normally sighted controls, i.e. crossing the hands yielded to impaired performance indexing the presence of a spatiotopic remapping (Azañón et al., 2017). In contrast, single cases of two participants, one who has been operated at 2 years and the second one at 7 years old have both been reported to be unaffected by crossing the hands in TOJ tasks, just as the congenitally blind participants (Azañón et al., 2017; Ley, Bottari, Shenoy, Kekunnaya, & Röder, 2013). These studies emphasize the importance of early visual experience in the development of the automatic remapping of touch into spatiotopic coordinates, although the very early visual experiences appear to have a minor, or a non-, influence. Noteworthy, this question will be further discussed in a following section of this manuscript, which is specifically dedicated to the review of the literature regarding the spatial representations of somatosensory inputs in early blind participants (see section 4).

[1] People who were born blind due to the presence of bilateral dense cataracts, that is, the formation of a cloudy area in the lens of the eye by the accumulation of proteins that prevents the lens from sending clear images to the retina, offer such possibility of investigation since cataracts can be removed by means of surgery at different moments during life.

3. Spatiotopic representations of nociception

The noxious character of nociceptive stimuli confers to these inputs a naturally high level of relevance, warning the brain about the occurrence of a potential danger it should take care of in order to avoid tissue damage. Before initiating a potential motor response intended to protect the body's integrity, however, the brain should also map nociceptive stimuli into spatiotopic frames of reference taking the position of the body limbs in external space into account. Indeed, this would enable deriving the position of the potentially threatening object entering in contact with the body in external space. In addition, this would allow to choose the most adequate effector to perform the defensive action. Indeed, often, when a stimulus is perceived in a certain limb, this same limb cannot be used to act towards the stimulus. Furthermore, spatiotopic representations of nociception would provide the brain with a common spatial framework to integrate sensory information from different modalities (e.g. nociceptive and visual), allowing it to picture the whole situation before reacting to the input. In that way, the resulting behavior can be adequately oriented and efficient.

As mentioned in the first section of this PhD work, most studies in spatial perception of nociception have concentrated on somatotopic representations of nociceptive inputs. However, some studies have brought into focus the importance of spatiotopic frames of reference in localizing nociceptive stimuli, or in perceiving pain more generally. For instance, studies in stroke patients suffering from hemispatial neglect, a neuropsychological condition characterized by the inability to detect, attend and respond to contralesional stimuli whereas abilities to process stimuli in the ipsilesional hemispace are spared, emphasized the importance of spatial processes in pain perception. Indeed, Liu et al. (2011) applied thermal hot and cold nociceptive stimuli on the hands of patients with hemispatial neglect. They evidenced in these patients signs of extinction, as some of the thermal stimuli applied on the contralesional hand were not detected when they were simultaneously presented with another stimulus on the ipsilesional hand, whereas they were well detected when presented alone. Accordingly, in another study, hemineglect patients seemed to omit more painful pinprick stimuli on the contralesional hand, as compared to the ipsilesional hand (Vizzari et al., 2017). This indicates that the detection of somatic stimuli, even when they are painful and thereby relevant to take into account in order to avoid tissue damage, depended on their spatial location on the body. Strikingly, in the study of Liu et al. (2011), when the contralesional thermal stimuli were correctly detected, they were however often mislocalized as having occurred on the ipsilesional hand, or misidentified as being cold instead of hot (or the reverse). Therefore, these results emphasize the importance of localization processes in the perception of noxious stimuli.

3.1. Spatial remapping of nociception

As for touch, even though to a much lesser extent, some studies have investigated the spatiotopic remapping of nociceptive events by means of TOJ tasks. Indeed, Sambo et al. (2013) asked their participants to perform TOJ tasks with either tactile or nociceptive stimuli applied on the hands placed either in a crossed or an uncrossed posture. The nociceptive stimuli consisted of intra-epidermal electrical (IES) stimulations. The results showed that the localization of stimuli from both modalities were similarly impacted by crossing the hands, as indicated by an effect on JND values. Indeed, JND values were larger in the crossed as compared to the uncrossed posture, irrespective of the stimuli modality (**Figure 9**). This suggests that the processing of tactile and nociceptive stimuli would rely on similar spatial representations. In the same vein, in the context of a cueing paradigm, De Paepe, Crombez, and Legrain (2015) presented to their participants a TOJ task to perform on nociceptive IES slightly preceded by lateralized visual cues. Visual cues were presented close to one of the two stimulated hands and were irrelevant for the TOJ tasks. Crucially, the hands were placed in an uncrossed or crossed posture. The results showed that participants' judgements in the TOJ task were biased towards the hand that was placed in the side of space in which the visual cue occurred, independently of hands posture (uncrossed vs. crossed). In other words, the perception of the nociceptive stimuli applied on the hand placed in the same side of space as the visual cue was prioritized. Hence, this suggests that nociceptive stimuli were mapped according to spatiotopic reference frames in order to interact with visual stimuli. Importantly, regardless of the cueing effect, they found decreased performances in the temporal discrimination of the nociceptive stimuli in the crossed, as compared to the uncrossed posture. However, this effect was significantly evidenced only in one of the two experiments performed in this study.

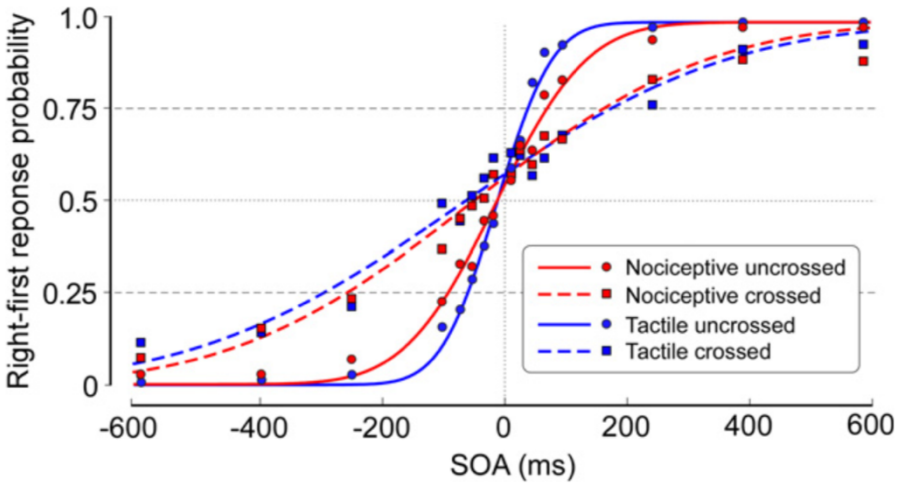

Figure 9. *Data from the experiment of Sambo et al. (2013) fitted with psychometric curves (i.e. Gaussian cumulative function). The solid lines represent participants' data in the uncrossed posture of the tactile (blue) and nociceptive (red) TOJ tasks. The dashed lines represent participants' data in the crossed posture for tactile (blue) and nociceptive (red) stimuli. The y-axis indicates the probability of right-first responses. The x-axis represents the different stimulus onset asynchronies (SOA) used in this study. The steepness of the curve reflects the performance, with steeper the curve, better the performance. Here, the participants' performance was decreased in the crossed posture as compared to the uncrossed posture, irrespective of the stimuli modality. Adapted from Sambo et al. (2013).*

Using EEG, Moayedi et al. (2016) have used another paradigm in which three nociceptive laser stimulations were successively presented to the participants on their hand and/or foot. In one condition, the three stimuli were all presented at the same location on the body (the hand, i.e. HHH condition). In a second condition, the two first stimuli were applied on the same body location (the foot) and the third one was presented to a different location (the hand, i.e. FFH condition). Importantly, the participants were asked to adopt two body postures intended to manipulate the spatial distance between the hand and the foot. Hence, the two body limbs were either placed far from each other, or were placed close together. The authors recorded laser-evoked ERPs associated with each of the three stimuli and

compared the magnitude of the potentials elicited by the third stimuli of the train according to the posture condition. First, they observed a decrease in the cortical responses elicited by the second and third laser stimuli, as compared to the first one, when they were all applied on the same body location, indexing habituation of the cortical responses. However, when the location of the third stimulus of the train changed, its evoked cortical response significantly increased again (i.e. dishabituation due to the novel character of the stimuli). Secondly, and most importantly, they found that these effects of novelty on the brain responses elicited by the third stimuli were dependent on the spatial distance between the limb on which the third stimulus was applied, and that on which the first and the second ones were applied. Indeed, dishabituation (i.e. increase of the magnitude of the ERPs elicited by the stimulus that has changed of location) was only evidenced when the third stimulus was applied on a limb placed at a greater distance than the other limb, as compared to when the two limbs were placed close together (**Figure 10**). Therefore, these results suggest that the effect produced by the novelty of the stimulus location was driven by the distance between the stimulated limbs, and thus, their position according to spatiotopic frames of reference, confirming the existence of dual spatial representations for nociception.

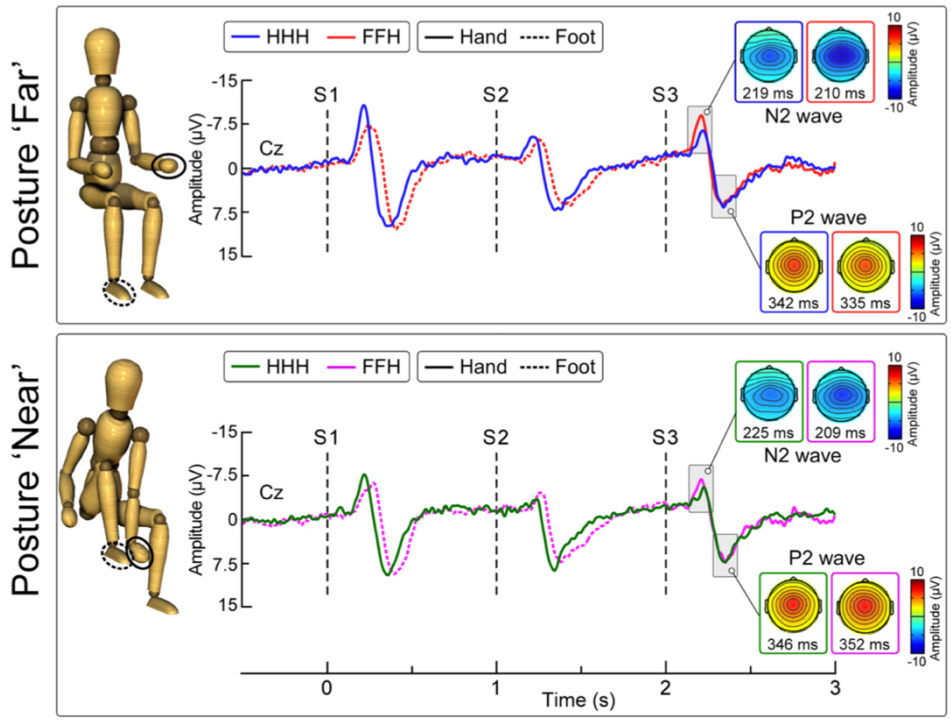

Figure 10. *Results of the study of Moayedi et al. (2016). Effect of stimulus location change and posture on laser-evoked potentials. Group-level average waveforms elicited by trains of three laser stimuli (S1-S2-S3). The signals displayed in the figure are recorded from the vertex (Cz electrode, nose reference). S1 and S2 were always delivered to the same body location (hand (H) or foot (F)). S3 was always applied to the hand. Therefore, S3 was either delivered on the same body location as S1 and S2 (HHH condition, no location change) or on a different body part (FFH condition, location change). During the experiment, the participants held two postures: far (with the hand and foot ~100 cm apart, top panel of the figure), and near (with the hand and foot next to each other, ~10 cm apart, bottom panel of the figure). The x-axis represents the time (s). The y-axis represents the amplitude (μV). Scalp maps were obtained at peak latency of the N2 and P2 waves and show the vertex potentials elicited by S3. The amplitude of the N2 peak elicited by S3 in the FFH condition was significantly greater than in the HHH condition in the far posture, but not in the near posture. Adapted from Moayedi et al. (2016).*

These results indicate that nociceptive events are mapped according to both somatotopic and spatiotopic reference frames, and suggest similarities in the spatial organization underlying the localization of tactile and nociceptive stimuli. However, the characteristics of the spatiotopic mapping of nociception have been poorly studied, as compared to touch, and a lot of questions remain to be answered. The following sub-sections will be devoted to present previous scientific work that has been done regarding the spatial perception of nociception, such as effects of the posture on pain perception, and how nociceptive stimuli can interact with inputs from other modalities, in order to gain more insight on the spatial representation of nociceptive inputs.

3.2. Effects of posture on pain perception

Intriguingly, some studies have evidenced an impact of the body posture on the perception of pain intensity. For instance, Moseley, Gallace, and Iannetti (2012) asked patients suffering from a chronic pain condition generally affecting one of the upper limbs (i.e. complex regional pain syndrome: CRPS) to cross their painful limb over the body midline for several minutes so that it was placed in the side of space where the unaffected limb normally resides. They observed that this resulted in a reduction of the perceived pain on the affected limb.

This effect of alleviating pain by crossing the hands has been encountered in healthy participants as well, with the crossed posture being associated with lower perceived intensity of pain induced by laser- induced heat stimuli (Gallace, Torta, Moseley, & Iannetti, 2011; Valentini, Koch, & Aglioti, 2015), as well as by pinprick mechanical stimuli (Torta et al., 2013). Interestingly, this was also true for the perceived intensity of tactile stimuli (Gallace et al., 2011) (**Figure 11.A**). This effect has been associated with a decreased amplitude of late latency responses of laser evoked potentials (LEPs), i.e. N2-P2 components, whereas early components (i.e. N1) were unaffected by the posture (**Figure 11.B**). Gallace et al. (2011) interpreted this effect as reflecting a disruption of the nociceptive processing in the brain, characterized by an abolishment of privileged connections involved in the spatial perception of these stimuli when the hands are placed in an unusual posture (i.e. when the hands are crossed), as compared to when the body posture match a more usual (i.e. default) body posture. As a result, the decreased cortical responses associated with this crossed posture would impede the processing of the intensity of nociceptive stimuli. In the same line, the effect of crossing the hands on perceived pain intensity has been related, using fMRI, to increased activity in the ACC and the insula, but also in the medial frontal gyrus (Torta et al., 2013). Because of the apparent involvement of the frontal lobe in this effect, and that modulations of frontal activity have often been associated with attentional effects, it has been

alternatively hypothesized that this crossing effect on perceived pain intensity might rather reflect a greater cognitive load associated with the crossed hands posture. As a result, limited cognitive resources would be left available to process the other characteristics of the stimulus such as its intensity, leading to a decreased intensity perception when the hands are crossed (Torta et al., 2013). In accordance with this attentional account, in an ERP study, the participants were presented with painful electrical stimuli applied randomly on the left or on the right hand while the participants' arms were either uncrossed or crossed over the body midline. The painful stimuli were preceded by cues regarding the location of the upcoming stimulus. These cues (arrows) were either congruent to the actual location of the following stimulus (e.g. the arrow pointed towards the left and the hand that was place in the left hemispace received the painful stimulus), or incongruent (the arrow pointed towards the left and the stimulated hand was placed in the right hemispace). The results showed that the amplitude of the brain responses elicited by the painful stimuli at the P3 peak latency (250-400 ms) was significantly greater for the incongruent - as compared to the congruent - trials. Importantly, the amplitude of the difference between the incongruent and the congruent conditions was significantly reduced in the crossed as compared to the uncrossed posture, suggesting that crossing the hands modulated (i.e. decreased) cueing attentional effects (Świder, Wronka, Oosterman, van Rijn, & Jongsma, 2017). Moreover, Vizzari et al. (2017) evidenced an effect of crossing the hands on the perceived intensity of nociceptive stimuli in brain damaged patients without hemispatial neglect, whereas the intensity ratings of patients with hemispatial neglect were unaffected by the posture. This suggests that the reduced perceived intensity of nociceptive stimuli when adopting a crossed posture would depend on the integrity of the cortical structures involved in spatial attentional processes.

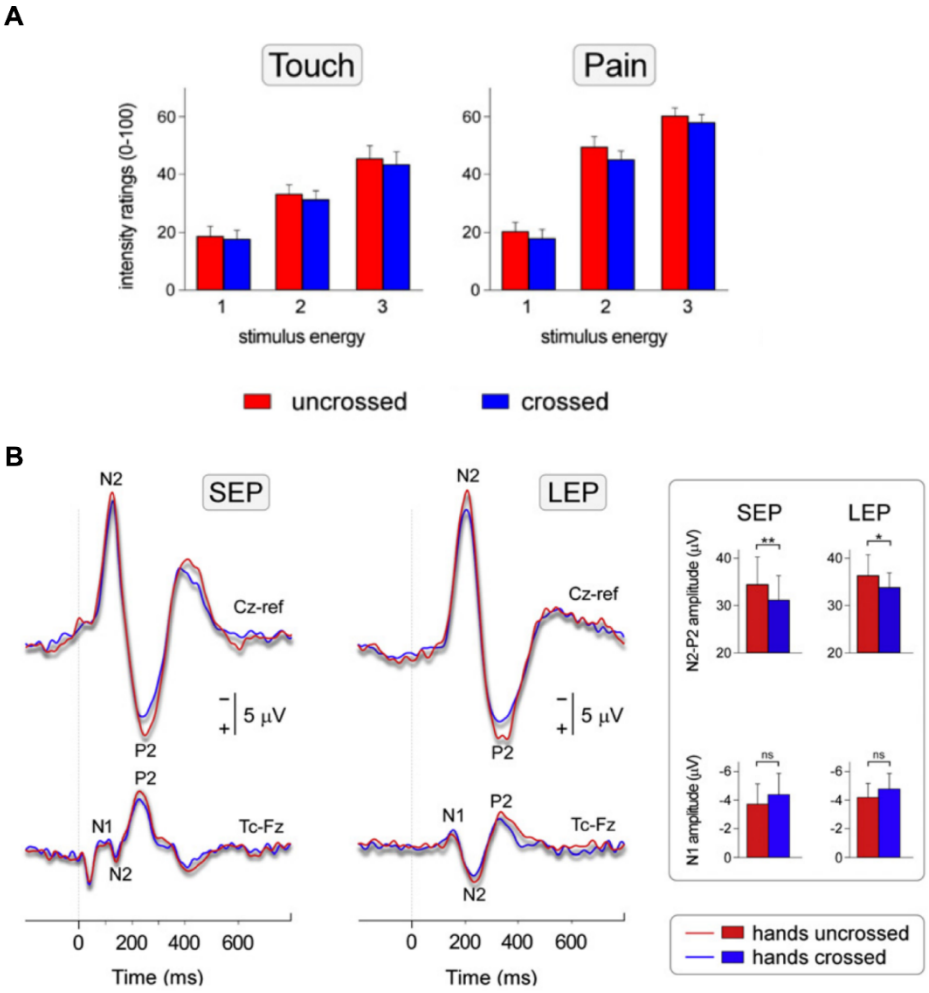

Figure 11. **(A)**. *Behavioral results of the study of Gallace et al. (2011). The left graph represents the intensity of the sensations evoked by tactile stimuli in the uncrossed (red) and crossed (blue) posture. The right graph illustrates the participants ratings from 0 to 100 elicited by the nociceptive laser stimuli in the uncrossed (red) or crossed (blue) posture. Three energies of both types of somatosensory stimuli were used. Crossing the arms significantly reduced the intensity of the sensation evoked by the stimuli, regardless of their sensory modality.* **(B)**. *Electrophysiological results of the study of Gallace et al. (2011). Grand-average waveforms showing the early N1 and the N2-P2 waves elicited by electrical (tactile) stimuli (SEPs, left panel), and nociceptive laser stimuli (LEPs, right panel) delivered*

to the hand dorsum while the hands were either uncrossed (red) or crossed (blue). Crossing the arms significantly reduced the peak amplitude of the N2-P2 wave, regardless of stimulus modality, whereas it has no influence of the amplitude of the N1 wave. Adapted from Gallace et al. (2011).

Therefore, considering the impairment of nociceptive inputs localization when crossing the hands (De Paepe et al., 2015; Sambo et al., 2013), it might be hypothesized that the increased load associated with crossing the limbs while evaluating the intensity of nociceptive inputs would be due to the spatiptopic remapping of nociceptive stimuli. In that sense, the effect of crossing the hands on the perceived intensity of pain might reflect the effort that the brain has to make in order to integrate the somatotopic and spatiotopic reference frames of the stimuli that are mismatching (i.e. in conflict). This possible explanation will be further discussed in the experimental section of this PhD thesis (see Study 4).

3.3. Multisensory interactions involving nociception

As already mentioned regarding touch localization, the ultimate goal of remapping somatic events into spatial external coordinates would be to facilitate multisensory interactions with extra-somatic events. This integration of sensory information from different sensory modalities allows accurate and efficient behaviors to be prepared and initiated. In the context of nociception and pain, these multisensory interactions appear even more relevant, enabling us to protect the body's integrity against potential threatening stimuli occurring in external space. Noteworthy, vision is a crucial sense, if not the dominant one, in multisensory interactions, since it should allow us to rapidly detect the presence of a threat in the environment. Therefore, several studies in pain multisensory research have been dedicated to describe and characterize visual-nociceptive interactions.

3.3.1. Effects of vision on pain perception

In this context, several studies have investigated the effect of vision on the perception of pain. For instance, it has been shown that looking at one's hand on which nociceptive stimuli are applied, directly or through a mirror, resulted in decreasing the perceived intensity of pain (Longo, Betti, Aglioti, & Haggard, 2009; Longo, Iannetti, Mancini, Driver, & Haggard,

2012; Mancini, Longo, Canzoneri, Vallar, & Haggard, 2013) as well as the magnitude of cortical responses elicited by the nociceptive stimuli (Longo et al., 2009; Torta, Legrain, & Mouraux, 2015). In the same vein, another study has shown that looking at the stimulated hand increased pain tolerance to heat stimuli (Mancini, Longo, Kammers, & Haggard, 2011). In addition, using fMRI, this effect has been associated with an increasing functional connectivity between brain areas generally activated during painful stimuli (i.e. such as SII, ACC and the insula) and posterior parietal structures (Longo et al., 2012). In contrast, the intensity ratings of tactile stimuli were unaffected by the vision of the hand on which they were applied (Mancini et al., 2013). Moreover, when tactile stimuli were applied, vision of the stimulated limb decreases the magnitude of ERPs, whereas nociceptive stimuli elicited ERPs with greater amplitude when the stimulated limb was seen (Mancini et al., 2013; Torta et al., 2015). This suggests that vision of the stimulated body part differentially affected the cortical processing of nociceptive and non-nociceptive stimuli. However, the robustness of this effect has been questioned since Torta et al. (2015) failed to replicate any effect of vision of the hands on pain intensity ratings. In addition, Valentini et al. (2015) did replicate this effect on pain reports as well as on ERPs amplitude elicited by laser stimuli only when the stimulated hands were crossed, and not when they were placed in an uncrossed posture. Moreover, Beck, Làdavas, and Haggard (2016) found that watching the body decreased the ability to discriminate between two intensities of heat painful stimuli, suggesting that vision of the body could also affect the sensory discriminative aspects of nociception. However, they observed that participants generally judged the intensity of the medium heat-pain stimuli as being perceived as high-pain stimuli in the situation in which vision of the hand was available. Thus, watching the body seemed to result in increased perceived intensity, conversely to the above-mentioned studies. Therefore, albeit the mechanisms underlying the modulatory effect of seeing the body part on which nociceptive stimuli are applied remain unclear, all these studies emphasize the presence of close interactions between visual information about the body, pain perception, and much likely proprioceptive information as well (Valentini et al., 2015).

3.3.2. Visual-nociceptive interactions

The influence of vision on pain perception is not limited to visual information about the body, as it has been demonstrated that visual stimuli occurring in space surrounding the body can intimately interact with nociceptive stimuli, and influence their perception when the visual stimuli occurred near the limb on which the nociceptive stimuli were applied. For instance, Filbrich et al. (2019) showed that the probability of perceiving nociceptive stimuli delivered at very low intensities, that is, at an intensity corresponding to individual absolute perceptual threshold, was influenced by the co-occurrence of visual stimuli. More specifically, it was increased when the visual stimuli occurred near the stimulated hand, and

decreased when they occur near the opposite hand. In another study, De Paepe, Crombez, and Legrain (2016) showed that participants were faster at responding to nociceptive stimuli when dynamic visual stimuli approached the stimulated hand, as compared to when they were receding from it.

Following similar ideas, several other studies used TOJ tasks to better characterize the factors influencing these visual-nociceptive interactions (De Paepe et al., 2015; De Paepe, Crombez, & Legrain, 2017; De Paepe, Crombez, Spence, & Legrain, 2014; Filbrich, Alamia, Blandiaux, Burns, & Legrain, 2017; Filbrich, Alamia, Burns, & Legrain, 2017; Filbrich, Halicka, Alamia, & Legrain, 2018; Manfron, Legrain, & Filbrich, 2019; Vanderclausen, Filbrich, Alamia, & Legrain, 2017). These studies mostly relied on the evaluation of the point of subjective simultaneity (PSS), the other measure used to characterize participants' performance in this kind of tasks. The PSS refers to the SOA at which the two stimuli are perceived as occurring first equally often. This parameter allows to investigate the presence of potential bias promoting the processing of one of the stimuli to the detriment of the other (see Filbrich, Torta, Vanderclausen, Azañón, & Legrain, 2016). In these studies, TOJ were performed on pairs of stimuli from one sensory modality (e.g. on two lateralized visual stimuli, or on two nociceptive stimuli, one applied on each hand). Crucially, each pair of target stimuli was shortly preceded by a stimulus of the other modality presented to one side only (e.g. a nociceptive stimulus on one hand during visual TOJ, and a visual stimulus in one side of space during nociceptive TOJ). The rationale underlying these studies was to characterize the conditions under which the preceding cueing stimulus would impact the judgements about the target stimuli from the other modality and presented in the same side of space. For instance, in the studies of De Paepe and colleagues, TOJ were performed on nociceptive intra-epidermal electrical stimuli applied on each hand dorsum, preceded by lateralized visual stimuli. They showed that participants' judgements during TOJ tasks were biased to the advantage of the nociceptive stimuli applied on the hand that was placed in the same side of space as the visual cue (De Paepe et al., 2014). Importantly, such crossmodal effects were maximized when the visual stimuli were presented in the close vicinity of the stimulated hand, independently of the position of the hands in external space and irrespective of the distance of the visual stimuli from the main axes of the participant's body such as the trunk (**Figure 12**) (De Paepe et al., 2015; De Paepe et al., 2017).

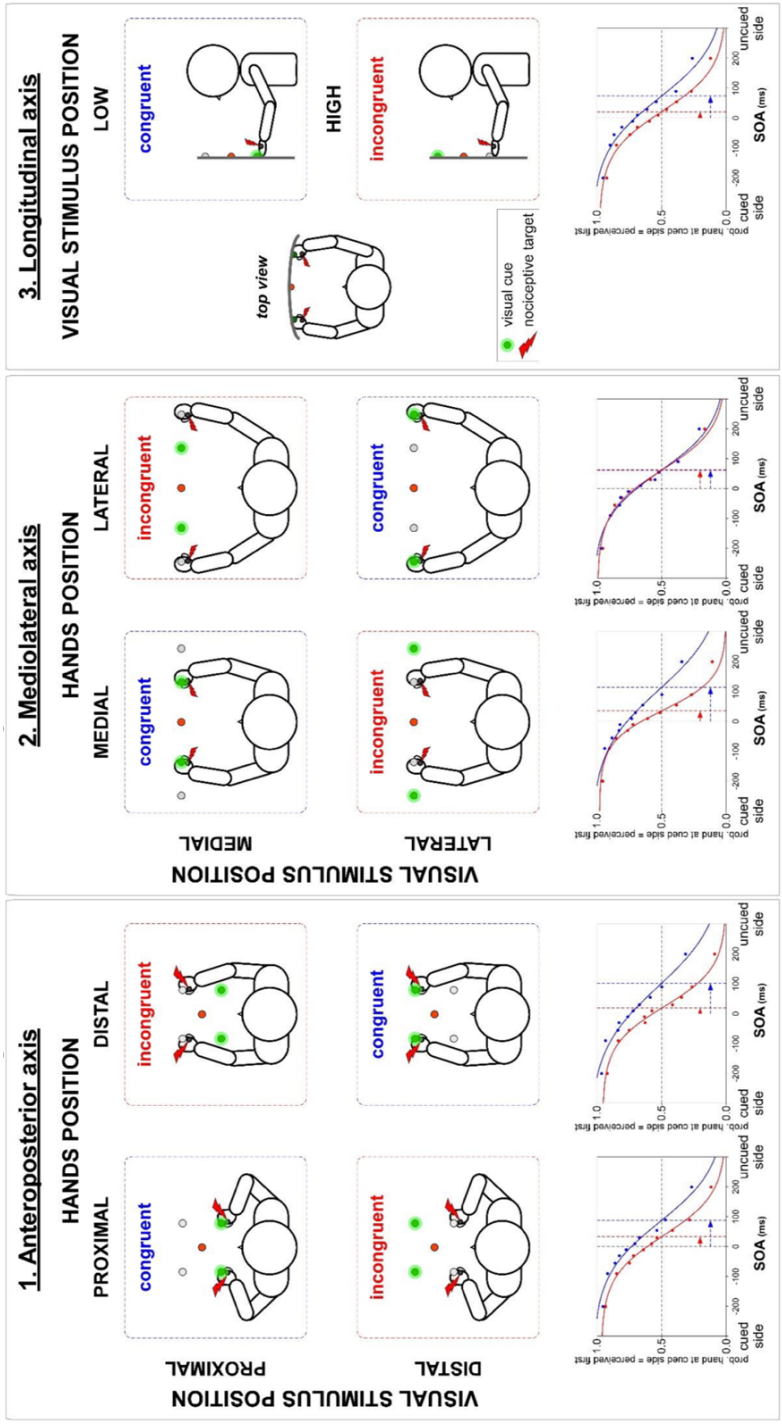
1. Anteroposterior axis
HANDS POSITION
PROXIMAL
DISTAL
congruent
incongruent
VISUAL STIMULUS POSITION
PROXIMAL
DISTAL
2. Mediolateral axis
HANDS POSITION
MEDIAL
LATERAL
congruent
incongruent
VISUAL STIMULUS POSITION
MEDIAL
LATERAL
3. Longitudinal axis
VISUAL STIMULUS POSITION
LOW
HIGH
congruent
incongruent
top view
visual cue
nociceptive target
prob. hand at cued side = perceived first
cued side
uncued side
SOA (ms)

Figure 12. *Experimental set-up and results of the three TOJ experiments of the study of De Paepe et al. (2017) from left to right, respectively.* ***(1)*** *Visual stimulus position was manipulated according to the anteroposterior axis, and hands were positioned at a congruent or incongruent position relative to the visual stimuli. The figure illustrates the fitted curves from cumulative data from 24 participants. Trials were either associated with visual stimuli at a proximal position (left graph) or at a distal position (right graph), and with the visual and nociceptive stimuli occurring at congruent (blue) vs. incongruent (red) locations. Data are plotted as the mean proportion of cued hand first responses (on the y-axis), as a function of the SOA (on the x-axis). On the x-axis, negative values indicate that the cued hand was stimulated first while a positive value means that the uncued hand was stimulated first. The vertical dashed lines correspond to the PSS values in each condition. All curves were shifted towards the uncued side, indicating that the nociceptive stimulus on the uncued hand had to be presented several milliseconds before the stimulus on the cued hand to have an equal chance to be perceived first. Crucially, this bias was larger when hands position was congruent to the visual stimulus position, irrespective of the distance of the visual stimulus to the body trunk.* ***(2)*** *Visual stimulus position was manipulated according to the mediolateral axis, and hands were positioned at a congruent or incongruent position relative to the visual stimuli. The figure illustrates the fitted curves from cumulative data from 22 participants. Trials were either associated with visual stimuli at a medial position (left graph) or at a lateral position (right graph), and with the visual and nociceptive stimuli occurring at congruent (blue) vs. incongruent (red) locations. Data are plotted as the mean proportion of cued hand first responses (on the y-axis), as a function of the SOA (on the x-axis). On the x-axis, negative values indicate that the cued hand was stimulated first while a positive value means the reverse. The vertical dashed lines correspond to the PSS values in each condition. All curves were shifted towards the uncued side, indicating that the nociceptive stimulus on the uncued hand had to be presented several milliseconds before the stimulus on the cued hand to have an equal chance to be perceived first. Importantly, this bias was larger when hands position was congruent to the visual stimulus position. Moreover, the difference in PSS values between the congruent and incongruent hand positions was larger when visual stimuli were presented medial as opposed to lateral.* ***(3)*** *Visual stimulus position was manipulated according to the longitudinal axis, so that the visual stimulus was either at a congruent or incongruent position with respect to the hands. The figure illustrates the fitted curves from cumulative data from 23 participants. Trials were either associated with visual stimuli at a congruent (blue) or incongruent (red) position. Data are plotted as the mean proportion of cued hand first responses (on the y-axis), as a function of the SOA (on the x-axis). On the x-axis, negative values indicate that the cued hand was stimulated first while a positive value means the reverse. The vertical dashed lines correspond to the PSS values. All curves were shifted towards the uncued side, indicating that the nociceptive stimulus on the uncued hand had to be presented several milliseconds before the stimulus on the cued hand to have an equal chance to be perceived first. Crucially, this bias was larger when the visual stimulus position was congruent as opposed to incongruent to the hands. As the distance of the visual*

stimuli to the body trunk was kept constant, it is unlikely that this influenced the results. Adapted from De Paepe et al. (2017).

Similar results were obtained when TOJ were performed on pairs of visual stimuli shortly preceded by nociceptive stimuli applied on one of the two hands. Indeed, participants' judgements were biased in favor of the visual stimuli presented near the hand on which the nociceptive cue was applied, irrespective of the position of the visual stimuli in external space (Filbrich, Alamia, Blandiaux, et al., 2017). In order to further investigate the role of the specific vicinity of the stimulated body part in these crossmodal interactions, Vanderclausen et al. (2017) placed participants' hands and visual targets along the participant's anteroposterior axis in front of them, at proximal and more distal positions from the body trunk (**Figure 13**). As such, the authors got rid of any spatial position with reference to the main axes of the body considered as a whole. It was shown that nociceptive stimuli positively biased the perception of visual stimuli presented near the stimulated hand, irrespective of their position on participants' anteroposterior axis and, thus, of the distance from the body. In addition, Filbrich et al. (2018) further demonstrated the crucial importance of the relative distance between extra-somatic i.e. visual stimuli and the body part on which nociceptive stimuli were applied by changing gaze direction during the TOJ task. They showed similar effects of the close spatial proximity between the nociceptive and the visual stimuli, regardless of the hemifield in which the stimulated hand and the visual stimuli were seen. Finally, it has been shown that such impact of nociceptive stimuli on the perception of visual stimuli in the surrounding of the stimulated hand was decreased when the vision of the hands was disrupted by a mask, suggesting that visual feedback about hand's position is an important factor for crossmodal interactions between nociceptive and visual stimuli (Manfron et al., 2019).

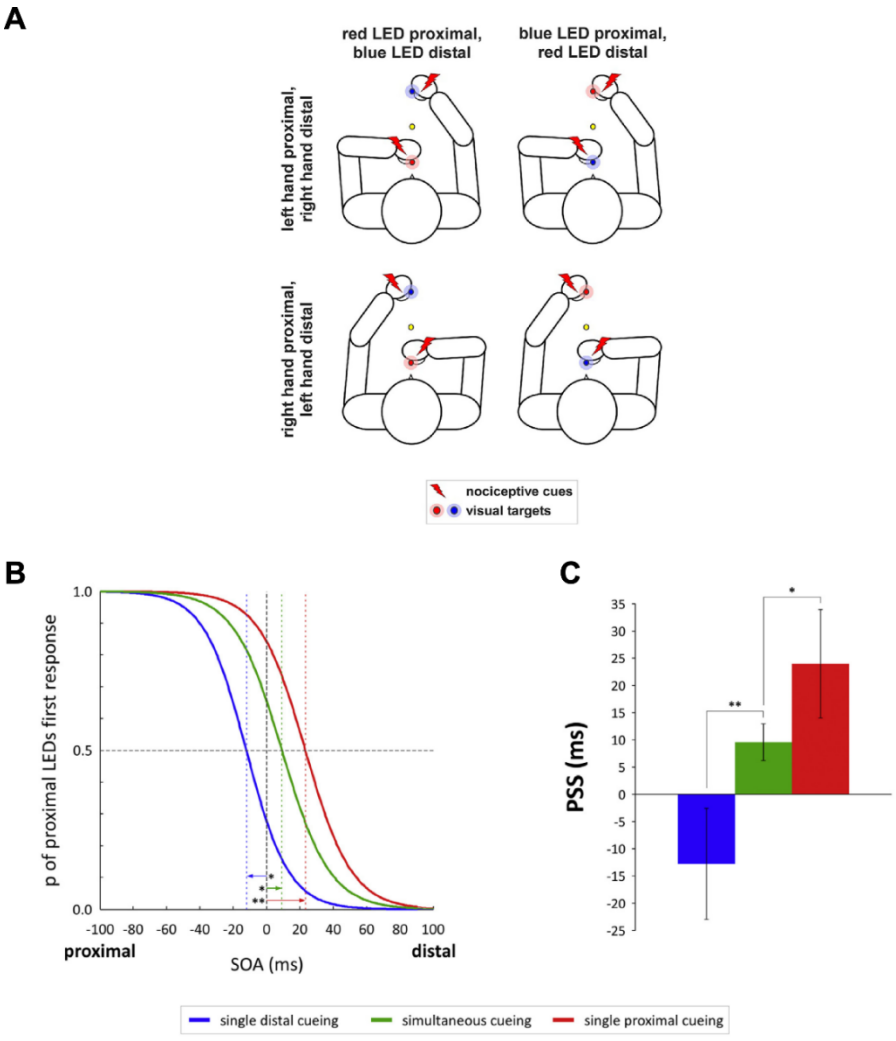

Figure 13. *Experimental procedure and results of the study of Vanderclausen et al (2017)* **(A)** *Experimental set-up. Participants performed a temporal order judgment task on two colored LEDs (i.e. red and blue), placed equidistantly from a yellow fixation LED along the participants' anterioposterior body axis. Participants placed each hand close to one of the target LEDs, so that both the hands and the targets LEDs were positioned at a proximal vs. distal location. Slightly before the presentation of visual stimuli, nociceptive stimuli (represented by red flashes) were applied either on both hands simultaneously or on one single hand.* **(B)** *Fitted curves of the psychometric function from the data of the 16*

participants according to the cueing conditions. The x-axis represents different possible SOAs. Negative values indicate that the proximal visual stimulus was presented first, and positive values that the distal visual stimulus was presented first. The y-axis represents the proportion of trials in which the proximal visual stimulus was perceived as occurring first. The sigmoid curves fit respectively the data of the single distal cueing condition (blue), the simultaneous cueing condition (green), and the single proximal cueing condition (red). The respective points of subjective simultaneity (PSS) were obtained by deriving the x-values of the points of the fitted curves with (x, 0.5) as coordinate. **(C)** *Mean values of the PSS for the single proximal cueing condition (red), the simultaneous cueing condition (green) and the single distal cueing condition (blue). Results show that participants' judgments were biased in favor of the visual stimuli presented in the same part of space of the hand that received a nociceptive cue, irrespective of its position from the body trunk. Adapted from Vanderclausen et al. (2017).*

Hence, this body of studies emphasize the existence of reciprocal influences between visual and nociceptive events, especially when they occur in the same spatial location in external space. Therefore, it has been suggested that these visuo-nociceptive interactions rely on peripersonal reference frames, a coordinate system that would integrate spatial information from somatic events, proprioceptive information regarding body posture in external space, and spatial information from extra-somatic events occurring close to the body into a multisensory representation of space allowing to optimize the preparation of adequate and efficient defensive behaviors (Brozzoli et al., 2014; Graziano & Cooke, 2006). In that sense, the remapping of nociceptive stimuli into spatiotopic coordinates could be seen as an interface for multisensory interactions between nociceptive and extra-somatic (e.g. visual) stimuli, providing the brain with a common spatial framework which would facilitate the integration of spatial information from different sensory modalities.

4. Spatial perception and early visual deprivation

Vision appears to be the dominant sense regarding spatial perception (e.g. Eimer, 2004). Indeed, visual information rapidly provides reliable information regarding the position of objects in external space. Therefore, it could be hypothesized that lacking of visual information can impact the ability to localize and adequately react to threatening stimuli in the environment to defend the body's integrity. The study of people with early visual deprivation offers a unique opportunity to investigate the role of vision in the development of cognitive abilities. Indeed, performance differences between sighted and blind people in tasks testing particular cognitive skills suggest that the development of these skills is shaped by predominant visual experience in sighted people. Accordingly, the role of early visual experiences in shaping the spatial representations of somatosensory stimuli can be investigated by comparing spatial abilities of congenitally blind individuals to those of normally sighted participants.

The brain is plastic by nature. While developing during gestation, some parts of it are pre-programmed to primarily process sensory information from certain type of inputs, e.g. somatosensory, visual or auditive. When one type of sensory information is lacking, the part of the brain set up to process this sensory information is not left out. For instance, it has been shown that the deprived visual cortex of congenitally blind individuals remains active (De Volder et al., 1997; Veraart et al., 1990). Instead, the loss of one sensory modality usually results in the cortical reorganization of the brain areas normally recruited to process information from that sensory modality, in order to make these cortical regions contributing to the processing of the remaining intact senses. This phenomenon is commonly referred to as *crossmodal plasticity,* or *functional plasticity,* reflecting the brain's ability to move functions to other parts of the cortex as well. In congenitally blind people, occipital cortical areas, normally activated during the processing of visual information, have been observed to be recruited to process tactile or auditory inputs, but also various cognitive abilities (Collignon, Voss, Lassonde, & Lepore, 2009; Frasnelli, Collignon, Voss, & Lepore, 2011; Kupers & Ptito, 2014). This cortical reorganization is related to the fact that people who were born blind must rely on the remaining intact senses, such as touch and audition, to compensate in the best possible way the lack of visual information. I will here mainly focus on the processing of somatosensory inputs in congenital blindness since this thesis is articulated around the spatial representations of nociception, but I will subsequently present some work having investigated their capacities to localize auditory information in external

space as well, in order to have a global overview of their spatial abilities. Indeed, if early visual deprivation influences the spatial processing of auditory inputs, which are coded by default in external space, it might also have an impact on the spatiotopic representations of somatosensory stimuli.

4.1. Somatosensory processing

By almost exclusively apprehending their environment through tactile sensations, blind individuals can acquire an expertise in the processing of tactile inputs over the years (Wong, Gnanakumaran, & Goldreich, 2011). As a result, they often display enhanced abilities in touch perception as compared to their sighted counterparts. More specifically, they have been shown to outperform normally sighted participants in several difficult tactile discriminative tasks, such as 2 dimensions haptic angle or grating orientation discrimination tasks involving the fingertips (e.g. Alary et al., 2008; Goldreich & Kanics, 2003; Legge, Madison, Vaughn, Cheong, & Miller, 2008). However, they do not always show better abilities than the sighted in simpler threshold tasks (Alary et al., 2009), or in orientation, motion or shape discrimination tasks involving a non-overused body part, i.e. the tongue (Matteau, Kupers, Ricciardi, Pietrini, & Ptito, 2010; Ptito et al., 2012; Ptito, Moesgaard, Gjedde, & Kupers, 2005). This suggests that these superior abilities in tactile spatial acuity would be driven by their stronger reliance on the sense of touch and their specific sensory experiences, for instance in braille reading (Wong et al., 2011). Accordingly, blindfolding normally sighted participants for a prolonged period (i.e. one week) has been shown to enhance their tactile acuity, an effect that lasted several days after having removed the mask (Zubek, Flye, & Aftanas, 1964). Alongside crossmodal plasticity, *intra-modal somatosensory plasticity*, i.e. the enlargement of the somatosensory cortical representations of a specific body part that is intensively used, such as the index fingers for braille reading (Sterr et al., 1998; Sterr, Müller, Elbert, Rockstroh, & Taub, 1999), has been suggested to mediate such tactile acuity enhancement in the blinds (Wong et al., 2011).

Regarding nociception, only few studies have investigated the impact of visual deprivation on pain perception (see review in Mancini, 2013). Nonetheless, it has been reported, for example, that blindfolding normally sighted participants for one week not only led to enhanced tactile acuity but also resulted in increased sensitivity to heat and pain (Zubek et al., 1964). Therefore, in a series of studies, a group of researchers has suggested that congenital blindness could lead to a hypersensitivity to pain. Indeed, lower heat and cold pain thresholds have been observed in congenitally blind (Slimani et al., 2013) - but not in late blind (Slimani, Danti, Ptito, & Kupers, 2014) – individuals, as compared to normally sighted participants. This suggests a specific role of early visual experience in the perception of pain.

The ratings associated with stimulations at suprathreshold levels were also higher in congenitally blinds relative to sighted controls, with warm and cold stimuli being judged as more painful in the blind group (Slimani et al., 2013). Conversely, the temperatures needed to elicit pain in congenitally blinds have been shown to be on average four degrees lower than in their sighted peers (Holten-Rossing, Slimani, Ptito, Danti, & Kupers, 2018). In line with this hyperresponsiveness to nociceptive stimuli, it has been further evidenced that congenitally blinds showed enhanced abilities to discriminate small changes in temperature (Slimani, Ptito, & Kupers, 2015). In this study, congenitally blind participants, as compared to sighted ones, showed higher accuracy in detecting small increases of temperature among warm nociceptive stimuli. In addition, they were more prone to spatial summation effects of heat, that is, extending the size of the stimulation surface resulted in improved discrimination performance, corroborating the idea of an increased sensitivity to heat stimuli.

This hypersensitivity has been hypothesized to be associated with a more efficient central processing of C fiber mediated nociceptive inputs (Slimani, Plaghki, Ptito, & Kupers, 2016). Indeed, while the detection thresholds of C- and Aδ- fibers mediated sensations did not differ from the sighted neither from late blind participants (see also Slimani et al., 2013), the reaction times associated with the stimulations conveyed by C-, but not Aδ- fibers, were faster in congenitally blinds (Slimani et al., 2016). Moreover, congenitally blind participants detected more stimuli conveyed by nociceptive C fibers as compared to their sighted counterparts, reflected by an overall higher detection rate in this population. In contrast, the blinds did not differ from sighted controls regarding the processing of more intense Aδ fibers mediated stimuli, but one possible explanation put forward by the authors was that reaction times of such intense stimuli are already so fast that differences between groups may be difficult or impossible to evidence.

Together, these results might reflect the need in congenitally blind individuals, in order to prevent thermal injuries, of a more efficient (i.e. faster) low intensity thermal processing because small and/or rapid increases in temperature may be indicative of an impending painful and potentially harmful stimulus (Slimani et al., 2016; Slimani et al., 2015). Alternatively, or rather complementarily, the apparent hypersensitivity in congenitally blind individuals has also been suggested to be related to an overall hypervigilance associated with the lack of visual information regarding painful encounters (Holten-Rossing et al., 2018; Slimani et al., 2013). In accordance with this hypothesis, higher scores of anxiety associated with higher pain ratings were found in congenitally blinds in situations of uncertainty regarding the intensity of the upcoming noxious stimulations, whereas only the anxiety ratings increased in people with sight (Holten-Rossing et al., 2018).

4.2. Spatial processing of auditory stimuli

Besides the apparent increased sensitivity in touch and thermal processing, congenitally blind people have also been shown to display equally good, or even better performances in localizing extra-somatic stimuli in external space such as sounds (Collignon, Voss, et al., 2009; Frasnelli et al., 2011; Kupers & Ptito, 2014). For instance, better temporal discrimination was evidenced in early blind (i.e. people who became blind after birth but never had functional sight) as compared to sighted participants in auditory TOJ tasks (Stevens & Weaver, 2005). More specifically, early blind participants have been found to localize horizontally presented sounds similarly than their sighted peers under binaural condition but outperformed them in situations in which one ear was obstructed (i.e. monaural condition) (e.g. Lessard, Pare, Lepore, & Lassonde, 1998). Similarly, comparable performances of congenitally blind and normally sighted participants were found when localizing sounds centrally in the frontal space whereas better abilities of the blinds were highlighted when the sounds were presented peripherally (Röder et al., 1999; Voss et al., 2004). These results were associated, using ERPs recordings, with a greater effect of spatial attention on early auditory processing in the blinds as compared to sighted participants when attending to peripheral spatial locations (Röder et al., 1999). By also manipulating spatial attention, it was shown that congenitally blind participants were faster to detect non-visual (i.e. tactile and auditory) targets under both selective or bimodal divided attention conditions, as opposed to normally sighted participants, suggesting better spatial attention abilities in this population (Collignon & De Volder, 2009; Collignon, Renier, Bruyer, Tranduy, & Veraart, 2006). Yet, the superior or normally good abilities of the blinds in spatially perceiving sounds would not be true in all circumstances, since poorer performances were observed, relative to sighted controls, when blind participants localized sounds according to the vertical, instead of horizontal plane. However, this was observed only under noisy background conditions (Zwiers, Van Opstal, & Cruysberg, 2001) or for some but not all of the tested early blind participants (Lewald, 2002).

Taken together, these studies might suggest that blind individuals can map an accurate representation of the external space by relying on auditory cues (Collignon, Voss, et al., 2009). Accordingly, enhanced capacities in echolocation, i.e. the fact of scanning the environment by producing a sound (e.g. with a cane, the voice or the foot) and listen to the returned sound waves to estimate an object distance, size, or density (Griffin, 1944), have been highlighted in the blinds (Dufour, Despres, & Candas, 2005; Schenkman & Nilsson, 2010). Nevertheless, it is worth mentioning that these studies involved relatively simple localization of sounds in space. In contrast, it has been shown that congenitally blind individuals are severely impaired when estimating and comparing the relative position of

different sound's sources in space (Gori, Sandini, Martinoli, & Burr, 2014). In this study, while the abilities of the blinds in simpler tasks (e.g. pointing to a sound) were similar to those of the sighted controls, they were in severe difficulty while performing a three sounds spatial bisection task (i.e. reporting whether the second sound was spatially closer to the first or the third one), suggesting the importance of the visual system in calibrating more complex auditory spatial representations. Therefore, it has been hypothesized that blind individuals might have more difficulties than their sighted peers in the processing of spatial information when *allocentric* frames of reference are required, i.e. estimating the location of an object in space with respect to the position of other objects in the environment, as opposed to when the task requires them to rely on *egocentric* coordinates, that is, the object location with respect to the position of the observer (Pasqualotto & Proulx, 2012).

4.3. Spatial representations of somatosensory stimuli

Estimating with accuracy the location of a touch on the body in order to adapt our behavior would be logically easier when sight is available, since visual information about the object in contact with the skin and about body posture is of greater reliability than proprioceptive information alone. More specifically, since it was suggested that vision plays a role in calibrating spatial perception (Eimer, 2004; Gori et al., 2014), it has been inferred that the ability to localize somatosensory inputs according to spatiotopic representations might be impacted in people with congenital blindness.

Indeed, as previously described in the section of this work dedicated to the developmental aspects of touch localization (see section 2.5), the detrimental effect of crossing the hands on tactile TOJ tasks has not been observed in congenitally blind subjects, suggesting that the spatiotopic remapping of touch is at least partially dependent on early visual experience (e.g. Crollen, Albouy, et al., 2017; Röder et al., 2004). Using fMRI, these behavioral results were replicated and associated with a differentially activated brain network when the hands were crossed in congenitally blind and normally sighted participants (**Figure 14**; Crollen, Lazzouni, et al., 2017). Indeed, while crossing the hands elicited enhanced activity in premotor and parietal areas in the sighted, i.e. the cortical network that was associated with the remapping of tactile inputs into spatiotopic coordinates (see section 2.4), this was not the case in congenitally blind participants. Instead, the crossed hands posture led to an increased functional connectivity between dorsal frontal and parietal regions (Crollen, Lazzouni, et al., 2017). Interestingly, in line with above-mentioned results regarding tactile acuity, better performances of the blind participants relative to their sighted peers were systematically observed in these tactile TOJ tasks. In addition, Röder, Focker, Hotting, and Spence (2008) have manipulated the hand posture during a tactile spatial attention task and

recorded the brain responses by means of EEG. In this study, both congenitally blind and normally sighted participants were asked to attend to one of the two hands while receiving tactile stimuli on both hands. Importantly, the participants held their hands in an uncrossed or crossed posture. They were instructed to detect deviant stimuli (double touch) occurring on the attended hand, and to ignore both deviant stimuli occurring to the unattended hand and standard stimuli (single touch) presented to either hand. The results showed an effect of orienting attention on the ERPs elicited by tactile stimuli characterized by an attention negativity in both congenitally blind and normally sighted participants. However, crossing the hands modulated (i.e. decreased) this effect only in normally sighted participants. Moreover, sighted participants displayed decreased performances in the crossed as compared to the uncrossed condition. This indicates that the effect of spatial attention did not only depend on the hand that was stimulated (attended vs. non attended), but also on the position of the hands in external space (i.e. spatiotopic coordinates) in the sighted. In contrast, changing the posture had no influence neither on behavioral performance nor on the brain responses of congenitally blind participants. This suggests that whereas spatiotopic frames of reference appear to be automatically taken into account in the sighted, this was not the case in congenitally blind participants. Similarly, analyses of the oscillatory activity of these data revealed that alpha-band activity, which is thought to reflect the spatiotopic mapping of tactile stimuli (Buchholz et al., 2011, 2013), was modulated by the posture of the hands in the sighted but not in the congenitally blind participants (Schubert et al., 2015). Thus, although the effects of tactile attention reflected in oscillatory activity was globally similar in the two groups of participants, this effect varied as function of the posture only in the sighted. Moreover, alpha-band activity in parieto-occipital areas has been found to be generally reduced in congenitally blind individuals relative to their sighted counterparts in tactile discrimination, but also in spatial imagery tasks (e.g. Kriegseis, Hennighausen, Rosler, & Röder, 2006).

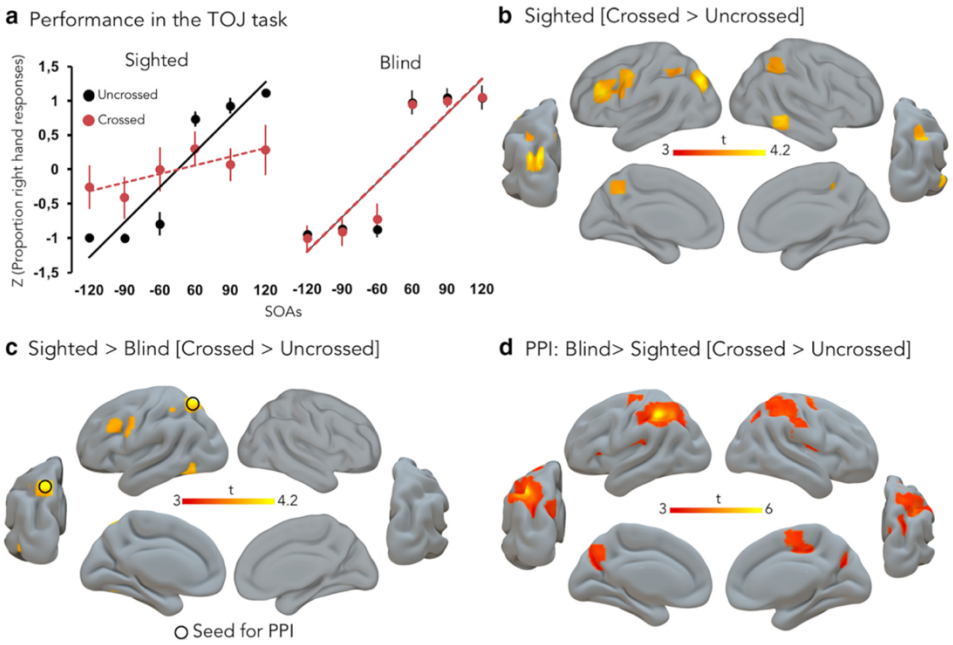

Figure 14. *Results of the tactile TOJ and associated brain responses in the study of Crollen et al. (2017). (**a**) Results of the tactile TOJ task. Standardized z-score equivalents of the mean proportions of right-hand responses and best-fitting linear regression lines for the uncrossed (black lines) and crossed (red lines) postures for sighted (SC) and congenitally blind (CB) individuals. Error bars represent standard errors. While the slope of the regression line of the crossed (red) posture is flatter than the slope of the line corresponding to the uncrossed (black) posture in the SC group, reflecting a decreased performance in the crossed condition, the two lines are superimposed in the CB group showing that posture did not affect performance in this group. (**b**) Results of analyses of the whole brain probing brain activity obtained from the contrast testing regions that are specifically dedicated to the external remapping process in SC participants (crossed>uncrossed). The crossed posture, as compared to the uncrossed posture, elicited brain responses including the left superior parietal gyrus, the right PPC, the left precuneus, the left precentral gyrus, the left dorsolateral prefrontal cortex, and the right middle temporal gyrus. The same contrast in CB participants did not reveal any significant result. (**c**) Regions selectively more active in the SC as compared to the CB group in the crossed over the uncrossed posture (crossed>uncrossed), i.e. the left precuneus, the left medial intraparietal area, the left dorsolateral prefrontal cortex, and the right middle temporal gyrus. The CB group did not show more activity than the SC group for this contrast in any region. (**d**) functional*

*connectivity changes revealed by means of psychophysiological interaction (PPI) analyses aiming at identifying brain regions showing a significant change in the functional connectivity within identified seed regions, i.e. the left precuneus and the left medial intraparietal area (encircled in figure (**c**)). The results revealed that the seed regions showed an increased connectivity with an extended bilateral frontoparietal network when the CB group performed the TOJ tasks in the crossed over uncrossed posture. Adapted from Crollen et al. (2017).*

Therefore, it has been initially suggested that congenitally blind individuals might exclusively rely on somatotopic coordinates to localize tactile inputs on the body (Röder et al., 2008; Röder et al., 2004). Nonetheless, it has been demonstrated that congenital blindness does not prevent spatiotopic representations to be accessible when such coordinates are required to be used for the ongoing task. Indeed, under certain circumstances, such as when motor coordination is involved, early blind individuals have been shown to be able to efficiently rely on external coordinates. For instance, Heed and Röder (2014) asked their participants to perform tapping or oscillation movements with the fingers while manipulating the instruction and the position of the hands so that the movements were either guided by anatomical or external reference frames. The results indicated that both congenitally blind and normally sighted participants were similarly biased towards the use of spatiotopic reference frames while performing bimanual coordinated movements. Similarly, Crollen, Albouy, et al. (2017) showed that congenitally blind, just like their sighted peers, were able to reproduce a learned sequence of movements with the fingers under spatial instruction, that is, keeping the same spatial locations on the keyboard onto which the sequence was played while it was turned upside down, forcing the participants to transfer the sequence from somatotopic towards spatiotopic coordinates. Furthermore, it has been shown that performing an action in external space could influence touch localization in people with congenital blindness. Indeed, changing the arm posture from an uncrossed towards a crossed posture had a detrimental effect of tactile TOJ performance when the stimuli were presented during the movement in both congenitally blind and normally sighted participants (Heed, Möller, & Röder, 2015).

Even more surprisingly, simply changing task instruction in tactile TOJ tasks has been shown to be sufficient to evidence the use of external spatial reference frames in congenitally blind subjects. In their study, Crollen et al. (2019) asked their participants to judge the temporal order of two touches either according to the stimulated hand (i.e. anatomical instruction), as it had commonly been done in previous TOJ studies (Heed & Azañón, 2014), or according to the side of space in which the stimulated hand was placed (i.e. spatial external

instruction). The results revealed that crossing the hands led to impaired TOJ performances in both early blind and sighted participants under spatial instructions, whereas the posture did not affect the performance of the blinds under anatomical instruction, in line with previous findings (Crollen, Albouy, et al., 2017; Röder et al., 2004). Accordingly, a study that has manipulated spatial attention by asking the participants to attend to one of the two hemispaces showed a modulation of spatial attention effects by crossing the hands in both congenitally blind and normally sighted participants (Eardley & van Velzen, 2011) . Indeed, they showed that the attention negativity observed on tactile ERPs, reflecting attentional control processes, was reversed in polarity and delayed when the hands were crossed as compared to uncrossed in the two groups of participants. This suggests that these effects of tactile spatial attention were affected by both somatotopic and spatiotopic coordinates of the stimuli, irrespective of early visual experience (Eardley & van Velzen, 2011). Importantly, this contrasts with the results of Röder et al. (2008) previously described, in which the participants were instructed to attend to one of the two hands instead of one of the two side of space. This would suggest that when external space is task-relevant, both congenitally blind and normally sighted participants would remap tactile events into spatiotopic representations. Noteworthy, however, the modulatory effect of the posture on the tactile evoked potentials was smaller in the congenitally blind participants, as compared to the sighted. Similar results were obtained in a recent behavioral study having manipulated both task instruction (anatomical vs. external) and posture of the hands (i.e. palms down vs. one palm up and one palm down). Just like in the sighted, external instructions modulated tactile spatial congruency effects as a function of the posture in congenitally blind participants, indicating that spatiotopic coordinates of tactile stimuli can be used by the blind when it is relevant for the ongoing task (Schubert et al., 2017).

Hence, as a result of visual deprivation, a preferential reliance on somatotopic representations for congenitally blind people in touch localization has been observed. However, spatiotopic representations remain available when such reference frames are relevant for task requirements, which might indicate that both congenitally blind and normally sighted would integrate somatotopic and spatiotopic representations of touch, but according to a different weighting scheme, with lower default weights for spatial external coordinates in the blinds (Crollen & Collignon, 2012; Crollen et al., 2019; Schubert et al., 2017). Although the spatial remapping of tactile events appears to be greatly automatic in people with sight, it would be more context-dependent in people with congenital blindness. Accordingly, early visual experience might play a crucial role in shaping the neural circuitry generating the automatic recoding of touch in external space (Crollen, Lazzouni, et al., 2017; Schubert et al., 2015).

4.4. Multisensory processing

On the one hand, the literature has evidenced an apparent role of visual experience in automatically mapping somatosensory inputs according to spatiotopic coordinates. On the other hand, it has been assumed that spatiotopic representations would facilitate interactions between somatic and extra-somatic events. Therefore, vision has been supposed to play a key role in the development of efficient multisensory integration. For instance, although the multisensory neurons found in the monkey brain are present from birth, they would acquire their integration capacities (i.e. additional responses to sensory events from different modalities occurring at same spatial location) in the first months of life through visual experiences (e.g. Wallace & Stein, 2001). Moreover, no evidence of multisensory integration between auditory and somatosensory inputs could be found in cats reared in the dark (Wallace, Perrault, Hairston, & Stein, 2004). In humans, the study of patients having been operated from cataracts and regained vision later in life have revealed that these patients did not show the same beneficial effect from integrating visual and auditory events as compared to sighted controls (Putzar, Goerendt, Lange, Rosler, & Röder, 2007; Putzar, Hötting, & Röder, 2010).

Accordingly, it has been suggested that interactions between inputs from intact sensory modalities, e.g. touch and audition, might be impacted by congenital blindness. Indeed, in an EEG study, congenitally blind and sighted control participants focused their attention on a given hemispace (i.e. left or right) and on a given modality (i.e. tactile or auditory) while detecting deviant stimuli within the selected location and modality and ignoring all irrelevant events. The results revealed a modulation of the early ERPs elicited by inputs of both the attended and unattended modalities occurring at the relevant spatial location in the sighted participants, i.e. crossmodal attention effect. However, such early crossmodal effect was absent in the blind participants (Hötting, Rösler, & Röder, 2004). Similarly, Hötting and Röder (2004) found that the influence of task irrelevant auditory inputs on touch perception (i.e. the number of task-irrelevant tones biased participants' judgements about the number of tactile events when presented simultaneously) was reduced in congenitally blind subjects as compared to normally sighted, suggesting a diminished multisensory integration in this population. Moreover, Collignon, Charbonneau, Lassonde, and Lepore (2009) asked their participants to localize tactile, auditory, or audiotactile stimuli by pressing the corresponding response key while their hands were either uncrossed or crossed over the body midline. In the crossed posture, while the performance of the sighted participants was decreased for the localization of tactile stimuli, that of congenitally blind participants was deteriorated for the auditory and audiotactile conditions. Thus, they had more difficulties than their sighted peers to efficiently integrate the location of a sound in external space, presented alone or

accompanied by a tactile stimulus at the same location, with the position of the responding (or stimulated in audio-tactile stimulation condition) hand when the hands were crossed. Using a similar paradigm, Röder, Kusmierek, Spence, and Schicke (2007) found that although sighted participant's performance improved when the location of a sound matched the location of the corresponding response key as compared to when the sound and the response key were at opposite locations in space, irrespective of whether the hands were hold in an uncrossed or crossed posture (i.e. *simon effect*), this effect was reversed in congenitally blind participants under the crossed condition. Hence, in the crossed posture, the blinds performed better when the sound's location (e.g. left hemispace) matched the position of the corresponding hand (e.g. left hand placed in the right hemispace over the right response key) instead of the corresponding response key placed in the same hemispace than the sound (i.e. left). These results extend the preferential reliance of congenitally blinds on somatotopic representations for the localization of touch to the localization of sounds in external space, and indicate that this default mode may impact multisensory processing. However, it is worth noting that Crollen et al. (2019) did not replicate these results, showing similar *simon effects* in congenitally blind and normally sighted participants irrespective of the posture. Thus, the *simon effect* was driven by external coordinates in both groups. Intriguingly, Occelli, Spence, and Zampini (2008) designed a crossmodal audiotactile TOJ task in which the participants were asked to judge which modality was presented first. Whereas sighted participants' performance was not affected by the relative spatial position from which the two stimuli were presented (i.e. same vs. different), early blind participants performed better at the task when the touch and the sound originated from different locations in space (e.g. the touch on the left hand and the sound from the right loudspeaker), as compared to when they were presented at the same location, suggesting that they were more sensitive than the sighted to the spatial separation between the auditory and tactile stimuli.

Therefore, it appears that early visual experience, in addition to shape spatial perception of somatosensory events, might play a critical role in the emergence of multisensory functions as well (Hötting & Röder, 2009).

All the studies presented in the present section shed more light on the differences that might exist between congenitally blind and normally sighted participants regarding somatosensory and spatial processing. First, we have seen that congenitally blind individuals might display an increased sensitivity in the processing of somatosensory inputs, suggesting more finely tuned tactile and nociceptive systems, as compared to their sighted peers. In contrast, while they are able to correctly perceive and localize sounds in external space with respect to their body, they might be in difficulty when it comes to more complex spatial representations of sounds. Accordingly, it was shown that they mostly perceive and localize tactile events according to somatotopic frames of reference, even though they are able to rely

on spatiotopic coordinates when it is relevant for the ongoing activity. Taken together, this suggests an important role of visual experience in the development of spatial perceptual abilities.

5. Aims and hypotheses

Being able to localize somatic inputs is essential to inform the brain about the physical state of the body and adapt behaviors. Spatiotopic representations of nociceptive stimuli considering the spatial position of the body limbs would be crucial in that sense that it would enable to localize the source of the stimulation in external space, and initiate an adequate and effective reaction towards this object in order to protect the body from being damaged.

The previous sections of this dissertation indicate that somatosensory stimuli, including nociceptive ones, are highly likely to be mapped in such frames of reference, in addition to be coded according to somatotopic coordinates. This suggests that the mechanisms underlying the spatial perception of tactile and nociceptive stimuli are, at least partially, shared by the two modalities. Studies conducted in congenitally blind people suggest a critical role of early visual experience in the development of an automatic remapping of touch from somatotopic into spatiotopic reference frames. Nonetheless, the importance of early vision in shaping spatiotopic representations of nociception has never been considered. Therefore, the general aim of this work was to investigate how early visual deprivation can impact the spatial perception of nociceptive inputs, in order to understand to what extent visual experience is necessary for the integration of the different spatial codes underlying the localization of nociception.

We used two main approaches to investigate this question. First, the spatiotopic remapping of nociceptive inputs was assessed by means of different tasks, in which the participants had to localize radiant heat stimulations applied on the hands' dorsa through two CO_2 infrared laser stimulators. Indeed, previous studies having investigating the spatial perception of nociception have used low intensities electrical stimulations conveyed through small electrodes touching the skin (De Paepe et al., 2015; Sambo et al., 2013). In contrast, the present technique, by applying heat which only penetrates the superficial layers of the skin, enables to target nociceptive C and Aδ fibers without concomitantly activate heat-insensitive tactile Aβ fibers which are localized in deeper layers (Plaghki & Mouraux, 2005). Thus, this type of stimulation allows us to specifically investigate the spatial perception of nociceptive inputs without any contribution of tactile afferents. Second, the role of early visual experience in the spatial perception of nociception was investigated by comparing the abilities to localize such stimuli according to spatiotopic frames of reference of congenitally blind individuals to that of normally sighted participants. Hence, we used early visual deprivation as a tool to study how spatial representations of somatosensory inputs are shaped by vision in the normal brain. We hypothesize that the spatiotopic remapping of nociceptive

events is shaped by early visual experience, just as that of tactile stimuli. Furthermore, given the importance of coding somatic events in spatiotopic representations, and especially nociceptive ones, to be able to defend the body against a potential threatening object in contact with the body, we hypothesize that visual deprivation should not prevent from efficiently map nociceptive stimuli into spatiotopic coordinates when it is relevant for the context.

In the first three studies, we tested these hypotheses by means of TOJ tasks, in which two tactile (study 1) or nociceptive (study 2 and 3) stimuli were presented in rapid succession to the participants' hands placed in an uncrossed or crossed posture. Importantly, in the context of this thesis, these tasks were adapted with an adaptive procedure, i.e. the *adaptive psi method* (see Kontsevich & Tyler, 1999). In most of the existing somatosensory TOJ studies, the method of constant stimuli was used (e.g. Crollen, Albouy, et al., 2017; Sambo et al., 2013; Shore et al., 2002). With this method, a predefined sample of SOA (i.e. time intervals) is chosen and each of them is presented several times to the participants during the experiment. The disadvantage of this method is that it can be time-consuming and tedious as many trials have to be presented for each SOA in order to reliably derive the parameters of interest (Kingdom & Prins, 2010). Moreover, previous studies have highlighted a better temporal sensitivity of early blind participants, as compared to sighted ones, in tactile TOJ tasks. This was indexed by smaller JND values in this population, suggesting that they are capable of correctly performing in the task within a smaller range of SOA than the sighted. Therefore, in order to cover both sighted and blind performances in TOJ tasks, a large number of SOA should be tested. In contrast, with the adaptive procedure, the presented SOA are adjusted to the participant's performance in the task, allowing us to estimate the parameters of interest without probing extensively all the possible SOA. This enables to significantly reduce the experiment duration by reducing the number of trials, which is of special interest when using laser stimulations because it allows to avoid skin overheating or habituation, in addition to refrain confounding effects associated with extended experiment duration, such as fatigue.

In **Study 1**, we firstly investigated whether adapting the tactile TOJ task with the adaptive *psi* method replicated the results of previous research having used the method of constant stimuli. To this aim, congenitally blind and matched normally sighted participants performed tactile TOJ tasks with 11 different possible SOA ranging from 5 ms to 400 ms, presented according to the adaptive procedure adjusting the SOA to each participant's performance. Crucially, they performed the task with their hands either uncrossed or crossed over the body midline. We hypothesized that crossing the hands would lead to impaired performance in the sighted group, but not in the early blind group, as compared to the uncrossed posture condition. In addition, we hypothesized that early blind participants would

show better performances than their sighted peers throughout the task, irrespective of the posture.

In **Study 2**, we investigated the role of early visual experience in the spatial representations of nociceptive stimuli. To this aim, early blind and matched normally sighted participants performed nociceptive TOJ tasks with pairs of laser stimulations applied on the hands' dorsa. Again, participants performed the task with the hands either uncrossed or crossed over the body midline in order to dissociate the somatotopic and the spatiotopic frames of reference. We hypothesized that nociceptive stimuli would be automatically remapped into spatiotopic coordinates taking body posture into account in sighted participants, indexed by decreased performances in the crossed as compared to the uncrossed posture. In contrast, we would expect early blind's performance to be unaffected by the posture. However, because of the higher relevance of nociception, as compared to touch, in terms of survival and the underlying crucial role of its spatial representation, we could also expect that early blind participants would show indications of a spatiotopic remapping for nociceptive stimuli. This would suggest that the spatial perception of nociceptive stimuli would be less dependent on external factors, such as visual experience, than that of tactile events.

In **Study 3**, we further investigated the importance of early visual experience in shaping the spatiotopic representations of nociceptive inputs. More specifically, we tested the role of task demands in the activation of such representations in sighted and blind individuals. To do so, nociceptive TOJ tasks were performed by early blind and matched normally sighted participants in an uncrossed and crossed arm posture. Crucially, we manipulated the instruction at the task, in order to stress either somatotopic (i.e. *which hand was stimulated first?*) or spatiotopic (i.e. *from which side of space came the first stimulus?*) frames of reference. We hypothesized that under *somatotopic instructions*, a crossing hands deficit would emerge in the sighted but not in early blind participants. In contrast, under *spatiotopic instruction*, we expected that crossing the hands would lead to decreased performances as compared to the uncrossed condition in the early blind as well as in the normally sighted participants. This would indicate that the spatiotopic remapping of nociceptive stimuli in early blind participants would depend on contextual factors such as task demands.

In **Study 4**, we investigated whether remapping nociceptive stimuli into spatiotopic frames of reference could impact the perception of the intensity of these stimuli. Indeed, it has been suggested that the ability to discriminate the temporal order of two nociceptive stimuli is impaired when the stimulated hands are crossed over the body midline, because this posture would create a conflict between the somatotopic and spatiotopic reference frames which are no longer aligned with each other. Crossing the hands has also been shown to

reduce the perceived intensity of nociceptive stimuli (Gallace et al., 2011; Torta et al., 2013). Therefore, the aim of this study was to investigate the involvement of the spatiotopic remapping of nociceptive stimuli in the effect of crossing the hands on the perceived intensity of nociceptive stimuli. More specifically, we tested the hypothesis according to which this effect on intensity would reflect the cognitive effort that the brain has to make in order to integrate somatotopic and spatiotopic representations of nociceptive stimuli when the two reference frames are mismatching, such as when the hands are crossed. Consequently, this would leave less neural resources available to process the intensity of the stimulations, resulting in decreased perceived intensity of pain. To test this, normally sighted and early blind participants were presented with laser stimulations applied unpredictably onto the left or right hand while the participants placed their arms either in an uncrossed or crossed posture. Participants reported intensity ratings after each stimulus. Congenitally blind people have been shown to preferentially rely on somatotopic frames of reference during the perception of somatosensory stimuli (e.g. Crollen, Albouy, et al., 2017; Röder et al., 2004). Consequently, if the effect of crossing the hands on pain perception can be explained by the automatic spatiotopic remapping of nociceptive stimuli, crossing the hands should lead to decreased perceived intensity of nociceptive stimulations in normally sighted participants but not in the early blind. In addition, given the presumed increased sensitivity to painful stimuli in congenitally blind individuals (e.g. Holten-Rossing et al., 2018; Slimani et al., 2013), we hypothesized that the pain ratings would be higher in early blind as compared to normally sighted participants, regardless of the posture.

In **Study 5**, we explored the time course of the spatiotopic remapping of nociceptive stimuli in healthy subjects using electroencephalography. More specifically, we compared the time courses of the spatiotopic mapping of tactile and nociceptive stimuli. To this aim, we recorded event-related brain potentials (ERPs) elicited by non-nociceptive vibratory tactile and nociceptive laser-induced heat stimuli while the participants adopted an uncrossed or crossed arm posture. The goal of the experiment was to identify the earliest time window at which a difference between the postures would be observed on the ERPs in each modality. We hypothesized that such effect of posture would indicate at which latency range spatiotopic representations of the stimuli would be taken into account, and thereby would reveal the time course of the remapping of these stimuli. Because the stimulation parameters of tactile and nociceptive stimuli were matched in order to be compared, and because ERP components of somatosensory stimuli at very early latencies can only be observed by stimulating at a high frequency (Cruccu et al., 2008), transcutaneous electrical stimuli were also used in order to potentially highlight very early effects of the posture on tactile processing.

Experimental Part

Study 1

Measuring the sensitivity of tactile temporal order judgments in sighted and blind participants using the adaptive *psi* method

Abstract

The perception of somatosensory stimuli on the body implies the use of different reference frames. It was shown that they were not only mapped according to a somatotopic reference frames, but also remapped according to spatial external coordinates. However, it has also been shown that this spatiotopic remapping would be mainly shaped by early visual experience. These findings have been generally evidenced using temporal order judgment (TOJ) tasks in which participants had to discriminate the temporal order of two tactile stimuli, one applied on each hand, with their hands placed either in an uncrossed or crossed posture, in order to dissociate the different frames of reference. Indeed, the crossed posture creates a mismatch between somatotopic and spatiotopic representations, given that the left hand is placed in the right part of space and vice versa. Importantly, in most of previous tactile TOJ studies, the stimuli were presented according to the method of constant stimuli, that is, a sample of stimulus onset asynchronies (SOA) separating the two stimuli was chosen and each of them was presented a certain number of times. However, several disadvantages of using this method might be noted, such as the important number of trials needed in order to obtain reliable data, or when it comes to compare different groups of participants that vary regarding their task performances. Therefore, this study aimed to calibrate tactile TOJ tasks with a new method, allowing to circumvent these problems, i.e. the adaptive *psi* method. This method adapts the SOA presented in each trial according to the participant's performance in all the previous trials, enabling to precisely estimate the temporal sensitivity of the participants within a task in which the stimulus levels are adapted to their respective discrimination threshold. The results showed that whereas sighted participants performed better with their hands uncrossed, as compared to the crossed posture, early blind's performance was not affected by the posture. These results replicate previous findings regarding the critical role of early visual experience in shaping spatial representations of touch, and therefore validate the use of the adaptive *psi* method for tactile TOJ tasks in investigating the spatial frames of reference underlying the localization of somatosensory inputs.

1. Introduction

Our body is constantly moving in space, adopting various postures as a function of the ongoing activity. Therefore, in order to adapt our behavior to a somatic stimulus received at a certain moment on a given part of the body, it is crucial to consider the current position in space of this stimulated body part, since it would allow deriving the probable location in external space of the object responsible for such somatic event. Accordingly, the perception and localization of somatosensory stimuli is underlined by different coordinate systems. Number of studies have demonstrated that they are not only mapped according to somatotopic frames of reference, i.e. anatomical representations based on the ordered projection of the receptor fields to spatially segregated groups of neurons in the primary somatosensory cortex (Penfield & Boldrey, 1937), but are also remapped according to spatiotopic frames of reference, taking the position of the stimulated limb in external space into account (Azañón & Soto-Faraco, 2008a; Driver & Spence, 1998; Graziano et al., 1997; Shore et al., 2002; Smania & Aglioti, 1995; Yamamoto & Kitazawa, 2001a).

This spatiotopic remapping of somatosensory inputs has been evidenced for both non-noxious tactile and nociceptive stimuli, among other tasks, by means of temporal order judgement (TOJ) tasks (e.g. Crollen, Albouy, et al., 2017; De Paepe et al., 2015; Heed & Azañón, 2014; Heed et al., 2012; Kobor et al., 2006; Pagel et al., 2009; Röder et al., 2004; Sambo et al., 2013; Shore et al., 2002; Yamamoto & Kitazawa, 2001a). In a typical TOJ task, participants are presented with two successive stimuli separated by various time intervals between their respective stimulation onsets (i.e. SOA standing for stimulus onset asynchrony). More particularly, two somatosensory stimuli are applied one on each hand and participants are asked to discriminate the order of appearance of the two stimuli by reporting which one they perceived as being presented first. Crucially, in order to dissociate the somatotopic and spatiotopic frames of reference, the task is usually performed in different body postures, i.e. with the arms placed either in an uncrossed canonical posture or crossed over the body midline. In fact, the crossed posture is intended to create a mismatch between the somatotopic and spatiotopic representations, given that the left hand is placed in the right part of space and vice versa. One critical parameter depicting participants' performance during TOJ tasks is the just-noticeable difference (JND) that characterizes the minimal amount of time needed for the participants in order to be able to discriminate the temporal order between the two stimuli at a specified level of performance, e.g. giving rise to a certain percentage of correct responses (Spence & Parise, 2010). JND values are derived from the slope of the psychometric function used to fit participants' responses (see Heed & Azañón, 2014 for a review). It has been recurrently shown that crossing the hands increases JND values, suggesting that participants needed more time to discriminate the temporal order of

the two somatosensory stimuli with the hands crossed than with the hands uncrossed (e.g. Sambo et al., 2013; Shore et al., 2002; Yamamoto & Kitazawa, 2001a). This decrease of the performance during the crossed hands posture can be denoted by a flattening of the slope of the function used to regress the data in this condition. Such effect of crossing the hands on the TOJ performance has been imputed to confusion regarding stimuli location that would result from the conflict between the somatotopic and spatiotopic reference frames which are no longer aligned with each other when the arms are crossed. Hence, this indicates that spatiotopic coordinates of the stimuli were automatically taken into account, even though it was actually irrelevant for the task, i.e. participants were instructed to report on which hand they perceived the first stimulus of the pair (Heed & Azañón, 2014). Noteworthy, the ability to automatically remap somatosensory stimuli according to spatiotopic representations has been suggested to be shaped by early visual experience, since crossing the hands does not affect performances of newborns (Begum Ali et al., 2015; Bremner, Holmes, et al., 2008; Bremner, Mareschal, et al., 2008) and adult with congenital visual deprivation (Crollen, Albouy, et al., 2017; Röder et al., 2004; Vanderclausen, Bourgois, De Volder, & Legrain, 2020).

Importantly, most of these findings have been evidenced with TOJ tasks during which stimuli were presented by means of the method of constant stimuli (Crollen, Albouy, et al., 2017; Kobor et al., 2006; Röder et al., 2004; Shore et al., 2002; Yamamoto & Kitazawa, 2001a). Accordingly, a sample of SOA was selected and presented randomly to the participants a fixed amount of times. In other words, all SOA conditions have to be tested in order to estimate the parameters of the TOJ task. While the method of constant stimuli has the advantage that participants cannot predict what level of stimulus will be tested at each trial, its main disadvantage is that a large number of stimulus levels must be tested to correctly estimate the parameters of interest. As a consequence, the number of trials can be considerably high when several conditions are interleaved, which can result in a significant increase in experiment duration (e.g. Crollen, Albouy, et al., 2017; De Paepe et al., 2015; Heed et al., 2012; Kobor et al., 2006; Sambo et al., 2013; Yamamoto & Kitazawa, 2001a) and can lead the researchers to face problems of performance degradation or loss of data (see e.g. De Paepe et al., 2015). Conversely, testing few trials in order to preserve a reasonable duration of experimentation can reduce the quality of the psychometric function and its derived parameters of interest. An additional problem arising from that method is related to the comparison of conditions that actually requires different stimulus levels in order to be correctly performed, or to the comparison of groups of participants that differ according to their respective ability to perform the task. For instance, healthy participants can correctly judge the time interval between two tactile stimuli even at very short SOA (i.e. from ~30 to ~75 ms) with the hands uncrossed. However, when crossing the hands, some participants inverted their judgements at longer intervals (i.e. between ~100 and ~300 ms) while they again correctly judged the temporal order at very long SOA (i.e. over ~500 ms) (Yamamoto

& Kitazawa, 2001a). In other words, a large sample of different SOA was needed in this study to cover participants' performances during the two posture conditions. Similarly, De Paepe et al. (In preparation) reported that chronic pain patients could not perform TOJ tasks with the range of SOA within which healthy volunteers could achieve very satisfactory performances, suggesting that the chosen SOA were not similarly adapted for both groups. The problem might thus lead to floor effects in one of the subgroups, giving rise to uninterpretable data or mask results of potential interest.

One way to circumvent these problems is to present the different time intervals by means of an adaptive procedure during which the SOA presented at each trial is selected based on the participant's individual performance in the previous trials. Among the different adaptive methods used for testing temporal discrimination (e.g. Stelmach & Herdman, 1991; Sternberg, Knoll, & Gates, 1971; Zampini, Guest, Shore, & Spence, 2005), TOJ tasks have been recently adapted using the *psi* method (Kingdom & Prins, 2010; Kontsevich & Tyler, 1999). This method relies on a Bayesian framework adopted by the algorithm. The ultimate goal is to estimate the posterior probability of the parameters of interest without probing extensively all the conditions, i.e. the SOA. The core idea is to minimize the expected entropy of the posterior distributions of the parameters trial by trial, by selecting the most appropriate condition at each trial such that the response of the participant provides the most information about the distribution of the parameters. Notably, the distributions are shaped during the experiment considering all the previous trials, thus exploiting an adaptive approach. The method offers several advantages. Mainly, it allows adapting the tested conditions to each participant's own performance in each experimental condition. Thus, different populations or experimental conditions in which the performance is known to - or can - differ can be compared with avoiding ceiling or floor effects. In addition, it enables to increase the validity and the reliability of the measures by allowing to test a wide range of different SOA with a lower number of trials (i.e. without probing extensively all the possible SOA), therefore minimizing the risk that task-independent factors related to extended experiment duration, such as fatigue or sustained attention difficulties, influence the data. Finally, the *psi* method allows to estimate during the same experiment the two main parameters of the psychometric function fitting participant's performance, that is the slope and the inflection point, characterizing respectively the sensitivity of judgment and the sensory or discrimination threshold.

The adaptive *psi* method has already been implemented to investigate temporal discrimination of visual (Filbrich, Alamia, Blandiaux, et al., 2017; Filbrich, Alamia, Burns, et al., 2017; Filbrich et al., 2018; Legrain, Manfron, Garcia, & Filbrich, 2018; Manfron et al., 2019; Vanderclausen et al., 2017) tactile (Filbrich, Alamia, Verfaille, et al., 2017), and nociceptive stimuli (Vanderclausen, Bourgois, et al., 2020; Vanderclausen, Manfron, De

Volder, & Legrain, 2020). However, for the visual and tactile modalities, the main purpose was to study spatial cognitive bias by means of the point of subjective simultaneity (PSS), characterized by the threshold parameter of the function. The PSS actually refers to the SOA at which the participants report the two stimuli as occurring first equally often (Spence & Parise, 2010). It thus usually stays around 0 when there is no bias. In contrast, when the perception of one of the stimuli is prioritized over the other one, the PSS corresponds to the SOA by which one stimulus has to precede the other one in order for both stimuli to be perceived as occurring at the same time. For instance, Filbrich, Alamia et al. (2017), by means of TOJ tasks adapted with the *psi* method, succeeded to demonstrate the existence of a privileged interaction between nociceptive and visual stimuli when the visual stimulus occurred in the peripersonal space of the body part on which the nociceptive stimulus was applied.

Regarding the issue of the remapping of somatosensory inputs, we are interested in estimating the slope parameter of the psychometric function fitting participants' performance, as it characterizes the participants' sensitivity in the task, i.e. the precision of their performance (Kingdom & Prins, 2010; Kontsevich & Tyler, 1999). Therefore, the main goal of the present studies was to investigate the impact of body posture on early blind and normally sighted participants' sensitivity in tactile temporal order judgments by means of the adaptive *psi* method. Such topic was already investigated regarding the perception of nociceptive stimuli (Vanderclausen, Bourgois, et al., 2020; Vanderclausen, Manfron, et al., 2020). The objective of Experiment 1 was to calibrate the adaptive *psi* method for tactile temporal order judgment tasks in order to validate the use of such paradigm for the investigation of the spatial representations underlying the perception of tactile inputs. To this aim, young healthy participants were asked to perform a tactile TOJ task in which the SOA were presented according to the *psi* method with either their hands uncrossed or crossed over the body midline. The objective of the Experiment 2 was to test whether we could replicate previous findings according to which tactile inputs would be automatically remapped into spatiotopic coordinates in sighted but not in congenitally blind individuals while adapting the task to each group's sensitivity with the adaptive *psi* method. To do so, early blind and matched normally sighted participants were asked to perform the exact same task than in Experiment 1.

2. *Methods*

2.1. Participants

Eleven healthy volunteers took part in Experiment 1 (4 women, 24.5 years of mean age (*SD*=3.7) ranging from 20 to 34). There was one left-handed according to the Flinders Handedness Survey (Nicholls, Thomas, Loetscher, & Grimshaw, 2013). Participants had normal or corrected-to-normal vision, and did not report any prior history of neurological, severe psychiatric and chronic pain disorders, serious traumatic injury of the upper limbs within the 6 months preceding the experiment, regular use of psychotropic drugs and intake of analgesic drugs (e.g. NSAIDs and paracetamol) within the 12 h preceding the experiment.

Eighteen congenitally blind individuals as well as 21 normally sighted participants took part in Experiment 2. Inclusion/exclusion criteria for sighted participants were the same as those of Experiment 1. Four sighted participants were excluded from Experiment 2 because they couldn't achieve task requirements properly (see paragraph 2.5). The remaining 17 sighted participants had a mean age of 35.82 years (*SD*=10.85, ranging from 20 to 63, 5 women) and there were 3 left-handed according to the Flinders Handedness Survey (Nicholls et al., 2013). Inclusion/exclusion criteria were the same for blind participants excepting for the sight. Early blind participants were recruited according to blindness attributed to peripheral deficits with no additional neurological problem (see Table 1 for a detailed description of blind participants). They were totally blind or had only rudimentary sensitivity to brightness but no ability for pattern perception. They were all considered as totally blind since birth. One early blind participant was excluded because of a residual vision of 1/50 of dioptry in both eyes. The remaining 17 blind participants had a mean age of 36.12 years (*SD*=10.71), ranging from 18 to 65 years (5 women, 2 left-handed and 1 ambidextrous). One early blind participant was epileptic (participant EB7) and was under medication for that reason (Levetiracetam: 1750 mg and Oxcarbazepine: 1500 mg daily). The epileptic focus is located in the left temporo-occipital border of the cortical brain. Nevertheless, this participant was not excluded from the study as there was no evidence of cognitive impairment or somatosensory perception deficit. Another one, participant EB1, because of a genetic disease, became totally blind at 3 months of life, but was still considered as early blind since his visual acuity was very poor in the first months of life. The participants of the sighted group were matched to the blind participants in terms of age, gender and level of education.

Written informed consents were obtained for all participants and all experimental procedures were approved by the local ethics committee and conformed to the Declaration of Helsinki. All participants received financial compensation for their participation.

Participant	Gender - Age	Handedness	Profession / Educational level	Visual Perception	Onset of blindness	Cause of blindness	Braille	Cane	Musical Instrument	Musical experience	Other
EB1	M 65	R	College degree	None	<18 months	Bilateral retinoblastoma	Yes	Yes	Organ	>9 years	/
EB2	M 49	R	College degree	None	Birth	Leber congenital amaurosis	Yes	Yes	Piano	3 years	/
EB3	M 31	L	Some college	None	Birth	Hereditary retinal dysplasia (*)	Yes	Yes	Guitare	>4 years	Slight auditory loss
EB4	F 43	L	College degree	None	Birth	Retinopathy of prematurity	Yes	Yes	Piano/Flute/Drums	7 years	/
EB5	M 39	R	College degree	None	Birth	Leber congenital amaurosis	Yes	Yes	Piano/ Organ	5 years	Torball
EB6	M 39	R	Teacher/ College degree	None	Birth	Anterior chamber cleavage syndrome (Peters syndrome)	Yes	Yes+ Dog	Piano/Flute/Drums	>5 years	Hearing aids
EB7	F 39	R	Interpreter/ College degree	None	Birth	Severe retinal dystrophy– congenital pigmentary retinitis with macular perforation	Yes	Yes	Piano	>5 years	/
EB8	M 31	R	Some college	None	Birth	Persistent hyperplastic primary vitreous involving both eyes	Yes	Yes	Musical keyboard	>10 years	/
EB9	F 38	R	Official High School	None	Birth	Retinopathy of prematurity	Yes	Yes	Used to sing in a choir	2 years	/
EB10	M 36	R	College degree	None	Birth	Genetic eye disorder (*)	Yes	Yes+ Dog	Piano/ Drums/ Harmonica	>10 years	/
EB11	F 35	R	Phone sale/ Official High School	None	Birth	Severe corneal dysplasia (*)	Few	Yes+ Dog	Drums	Only few months	/
EB12	M 29	R	College degree	None	Birth	Leber congenital amaurosis	Yes	Yes	/	/	Various spoart activities
EB13	M 22	R	Some college	None	Birth	Congenital cause (*)	Yes	Yes	/	/	/
EB14	M 25	A	Official high school	None	Birth	Leber congenital amaurosis	Yes	Yes	Drums/piano/ guitar/harmon -ica	>5years	ADHD syndrome
EB15	F 38	R	College degree	None	Birth	Leber congenital amaurosis	Yes	Yes	/	/	/
EB16	M 37	R	Specialized school until 6th grade	None	Birth	Incubator accident resulting in the burning of both retinas	Yes	Yes	Piano	2 years	/
EB17	M 18	R	High school (inferior degree)	None	Birth	Norri Syndrome	Few	Yes	Accordion	>6 years	/

Table 1. Description of the early blind participants of Experiment 2.

***Note**: EB: early blind; Age in years; F= female; M= male; R= right; L= left; (*): no additional details available. ADHD=attentional deficit and hyperactivity disorder. As subject EB1 had very poor vision from birth and underwent a bilateral eye enucleation by the age of 18 months, he was considered early blind. Torball is an indoor sport for the blind participants.*

2.2. Stimuli and apparatus

Vibrotactile stimuli were generated by means of two vibrotactile transducers driven by standard audio amplifiers (TL-002-14R Haptuator Redesign, Tactile Labs, Inc., Montreal, Canada). The duration of the vibration was 10 ms and the stimulation was delivered at 440 Hz. Participants held the two vibrotactile transducers slightly above the table, one in each hand, between the thumb and the index finger. Two of the normally sighted participants from Experiment 2 held the transducers between the thumb and the medium finger because of the presence of a minor injury on the tip of the index finger on the day of the experiment. The two transducers were hold at a distance of ~30 cm between them and a distance of ~30 cm from the edge of the table. All the participants were familiarized with the vibrotactile stimulations and the experimental set-up before starting the experiment. The intensities of the stimulations were matched between both hands and, if necessary, it was individually adapted so that the perceived intensity and sensation were identical on the left and the right hand for each participant. The intensity had to be slightly adapted for two blind participants (EB7 and EB11) in two out of the four experimental blocks, because the perceived intensity was no longer judged as equivalent between both hands. Vibrotactile stimulations were remotely controlled using Matlab 2012.

2.3. Procedure

The procedure was exactly the same for both Experiment 1 and Experiment 2. The participants were sitting on a chair in front of the table. Participants' arms were placed in an uncrossed posture in half of the experimental blocks. In the other half, we asked them to cross their arms over the sagittal body midline. Participants' heads were placed in a chin-rest at an individually adapted level, in order to minimize head movement during the experiment. Noises from experimental devices were covered by means of a white noise played through earphones. The sighted participants were blindfolded.

During each block of stimulation, on each trial, the participants were presented with two vibrotactile stimuli, one on each hand, separated in time by 22 possible stimulus onset asynchronies (SOAs): ±5, ±10, ±15, ±30, ±45, ±60, ±75, ±90, ±145, ±200, ±400 ms. Negative values indicate that the first stimulus of the pair was applied on the left hand, and the second one on the right hand. Positive values indicate that the right hand was stimulated first. The stimuli were presented using the adaptive *psi* method (see measures). The participants had to report verbally after each trial which one of the two hands they perceived as being stimulated

first in one half of the stimulation blocks, and as being stimulated second in the other half, by saying '*left'* or *'right'*. These two different response conditions were used to prevent that any potential response bias could influence our data (Filbrich et al., 2016; Spence & Parise, 2010). The response was encoded by the experimenter by pressing a key of the keyboard triggering the next trial that started 2000 ms later. The task was unspeeded and no specific instruction was given to the participants regarding the speed of their responses but they were told to be as accurate as possible. They didn't receive any feedback on their performance in the task.

The experiment started with a practice session of 4 blocks of 10 trials each, one block per condition (hand posture: *uncrossed* vs. *crossed*, and response modality: '*which is first*' vs. '*which is second*'), with only two among the largest SOAs (±145, ±200 ms). In the experimental session per se, participants were presented with 4 blocks of 40 trials each, one per condition. The order of the blocks was counterbalanced across participants regarding the posture (half of the participants started the experiment with their hands uncrossed while the other half started it in the crossed posture), as well as which of the two arms was crossed above the other one (half of the participants crossed their left arm on the right one and the other half did the reverse). The order of the experimental blocks was randomized concerning the response modality. The whole experiment lasted about 30 minutes.

2.4. Measures

For all experimental conditions, the proportion of left stimuli having been reported as presented first was plotted as a function of SOA. Data were fitted online during the experiment with a logistic function, i.e. i.e. $f(x) = 1/(1+\exp(-\beta(x-\alpha))$, from which the parameters of interest (α, the threshold, and β, the slope) were derived (see Filbrich, Alamia, Burns, et al., 2017). The main parameter of interest in the present experiments was the β parameter, characterizing the slope of the logistic function. It describes the noisiness of the participant's responses and corresponds to the precision of these responses during the experiment (i.e. their sensitivity in the task). It was thus considered as a measure of the participant's performance (Kingdom & Prins, 2010). The α parameter is the threshold of the function and refers to the point of subjective simultaneity. Although the contribution of the α parameter to current data was less important, that parameter was also measured in order to assess the possible presence of biases that could affect the estimation of the slope (see Filbrich, Alamia, Blandiaux, et al., 2017; Filbrich, Alamia, Burns, et al., 2017; Vanderclausen et al., 2017). To estimate the logistic function, the adaptive *psi* method was used (Kontsevich & Tyler, 1999). Hence, the psychometric curve and its parameters were estimated at each trial, the final parameter estimates corresponding to the last update computed by the algorithm of the adaptive procedure (Kingdom & Prins, 2010; Kontsevich

& Tyler, 1999). Thus, this method adapts the experimental procedure and the presented SOA according to individual performance in all the previous trials in order to target the estimation of both the threshold and the slope with similar accuracy (Kingdom & Prins, 2010). Based on previous trials, it picks the condition (i.e. SOA) the most informative to estimate the joint distribution of the parameters, which minimizes the expected entropy, i.e. uncertainty, of the posterior distribution trial by trial, so that the response of the participant at each trial provides the most information about the distribution of the parameters. Hence, the distributions are shaped during the experiment, based on all the previous trials. At each trial, the *psi* method finds the best-fitting psychometric function to the participant's responses collected so far (Kingdom & Prins, 2010). Since this procedure is based on a Bayesian approach, a prior probability distribution needed to be postulated. We used a prior distribution of 0±20 to estimate the α parameter, since no bias towards one of the two hands was expected (e.g. Filbrich, Alamia, Blandiaux, et al., 2017; Filbrich, Alamia, Burns, et al., 2017). Based on pilot experiments performed with healthy volunteers, 0.06±0.6 was chosen as a prior distribution to estimate the β parameter. This range of values is indeed large enough to consider the difference of performance between the two experimental conditions (i.e. postures) as well as possible inter-individual differences. Noteworthy, prior values were also postulated for the lapse and guess rates. Lapse rate (λ parameter) is defined as the probability of incorrect response independently of stimulus intensities (i.e. SOA), such as related to vigilance or response errors (i.e. participants answered "left" but meant "right") (Kingdom & Prins, 2010; Prins, 2012). It was set at 0.02 and the guess rate (γ parameter) was set at 0 for all conditions, as recommended by Kingdom and Prins (2010).

Since we used an adaptive method, all the participants were not presented with the same sequence of SOA during the experiment, as it was adapted to individual performance. Therefore, a third but non-standard parameter was derived a posteriori from the present data: the mode of the presented SOA. This corresponds to the value of the SOA, among all the possible SOA, that was the most frequently presented to a given participant during a particular condition of the experiment. A significant difference between the modes of the two experimental conditions would illustrate that the participants needed different ranges of SOA between the experimental conditions in order to be able to correctly perceive the temporal order between the stimuli with a satisfactory level of performance. In other words, a larger mode value in one condition relative to the other would indicate that the task was more difficult to perform in this condition as compared to the other one. The mode of the presented SOA was therefore used as a complementary index of participants' performance.

2.5. Analyses

Data were excluded from further statistical analyses if the slope of the psychometric function couldn't 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), indexing that their performance was too inconsistent and below chance level. Before statistical analyses, data from the two response modalities ('*which is first*' and '*which is second*') were merged. In order to examine the presence of possible biases towards one of the two sides, one sample t-tests were performed to compare the PSS values to 0 for each condition of *hand posture* (i.e. uncrossed vs. crossed) and for each group. Next, the PSS, slope and mode values of Experiment 1 were compared by means of an analysis of variance (ANOVA) for repeated measures with *posture* (i.e. uncrossed vs. crossed) as a within-participant factor. For data from Experiment 2, the same ANOVA were performed, adding *group* (i.e. blind vs. sighted) as a between-participants factor.

Greenhouse-Geisser corrections of the degrees of freedom and contrast analyses were used if necessary. Effect sizes were measured using partial Eta squared for ANOVAs and Cohen's d for t-tests. Significance level was set at $p \leq .05$.

3. Results

3.1 Experiment 1

The curves of the fitted psychometric functions are illustrated in Figure 1.a. The t-tests revealed that none of the PSS values were significantly different from 0 (uncrossed: $t(10)=-1.312$, p=.219, d=.395.; crossed: $t(10)=0.940$, $p=.369$, d=.283). The ANOVA didn't reveal any significant effect of the hand posture on PSS values ($F(1,10)=3.628$, $p=.086$, $\eta^2p=.266$). These results confirm the absence of any spatial bias during the TOJ.

Regarding the slopes, the ANOVA revealed a significant effect on the hands posture ($F(1,10)=23.669$, $p=.001$, $\eta^2p=.703$). The slope values were significantly smaller when the participants performed the tactile TOJ with the hands in a crossed posture (M±SD= 0.021±0.016) as compared to the uncrossed posture (M±SD=0.090±0.038) (Figure 1.b).

The same pattern of results were observed for the mode of the presented SOA as the ANOVA revealed a significant effect of the hand posture ($F(1,10)=8.937$, $p=.014$, $\eta^2p=.472$). Participants' performances were adapted using greater SOA values when the task was performed with the hands in the crossed posture (M±SD=245.910±180.724) than with the hands in the uncrossed posture (M±SD=84.550±156.100) (Figure 1.c).

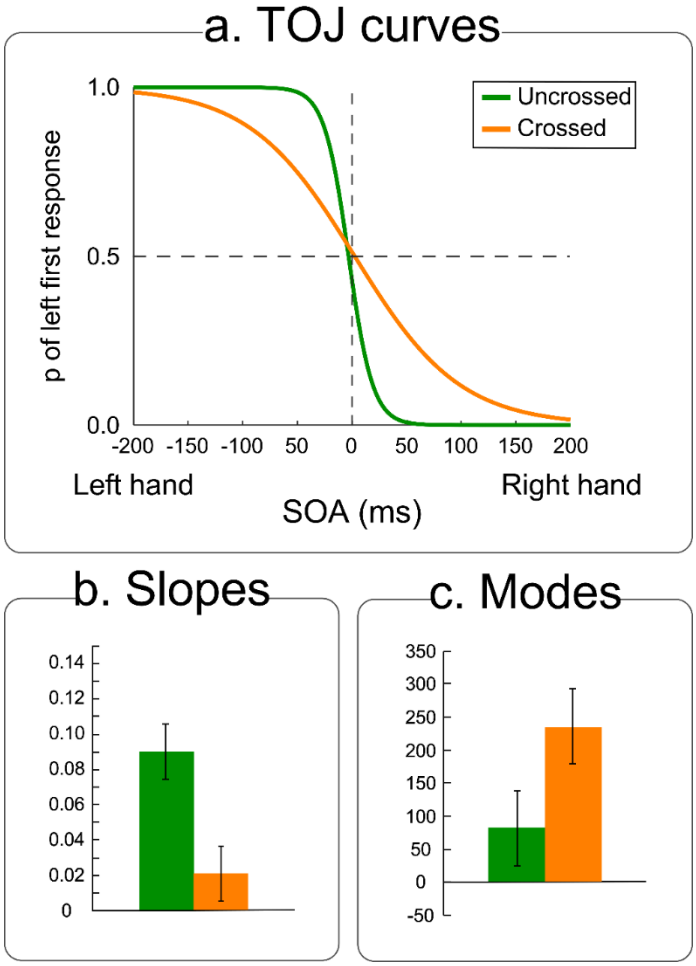

Figure 1. ***Tactile temporal order judgments (TOJs) in experiment 1.*** *(A) Fitted curves of the psychometric function from the data of the 11 participants according to the hands posture condition. The x-axis represents different possible SOA. A negative value indicates that the left hand was stimulated first and a positive value indicates that the right hand was stimulated first. The y-axis represents the proportion of trials in which the vibrotactile stimulus applied on the left hand was perceived as being presented first. The lines represent the fitted curves for the uncrossed posture condition (green) and the crossed posture condition (orange), respectively. (B) Mean slope values for each posture condition. The slope value of the crossed posture condition was significantly lower than the slope value corresponding to the uncrossed posture condition (C) Mean mode values of the presented*

SOAs in millisecond for each posture condition. The averaged mode in the crossed posture condition was significantly higher than the mean mode value of the uncrossed posture condition. Error bars represent confidence intervals calculated according to Cousineau's method for within-subject designs (Cousineau, 2005).

3.2. Experiment 2

Curves of the fitted psychometric functions are illustrated for the two groups in Figure 2.a. None of the t-tests revealed PSS values significantly different from 0 in the sighted group (all t(16)≤1.059, all p≥.305, all d=.257). However, both the PSS values of the uncrossed and crossed posture conditions appeared to significantly differ from 0 in the early blind group (uncrossed: t(16)=2.352, p=.032, d=.570 ; crossed: t(16)=3.977, p=.001, d=.964). This indicates that judgements of the participants in this group were slightly biased towards the left hand. Overall, the stimulus applied on the right hand had to precede the stimulus presented to the left hand by 3.736 ms (SD=6.549) for the uncrossed posture and by 8.496 ms (SD=3.967) for the crossed posture in order for both to be perceived as occurring at the same time. Nevertheless, the ANOVA did not show any significant effect of the posture (F(1,32)=.386, p=.539, η^2p=.012), of the group (F(1, 32)=.630, p=.433, η^2p=.019), and of significant interaction between the two factors (F(1,32)=3.961, p=.055, η^2p=.110). This suggests that the PSS values observed for blind participants were not significantly different from each other, neither from the ones observed in the sighed participants.

Regarding the slope values, the ANOVA revealed a significant main effect of the posture (F(1,32)=12.802, p=.001, η^2p=.286) and a significant main effect of the group (F(1,32)=12.190, p<.001, η^2p=.276). Importantly, the interaction between the posture and the group factors also reached significance level (F(1,32)=4.166, p=.050, η^2p=.115). Contrast analyses revealed a significant effect of the posture in the sighted group (t(16)=3.844, p=.001, d=.932), the averaged slope value being larger in the uncrossed (M±SD=0.062±0.039) as compared to the crossed posture condition (M±SD=0.024±0.017). In contrast, such difference was not significant in the early blind group (t(16)=1.126, p=.277, d=.273; M±SD uncrossed=0.113±0.080; M±SD crossed=0.102±0.071). Besides, the averaged slope value was significantly greater for the early blind than for sighted participants for both the uncrossed (M±SD blind=0.113±0.080; M±SD sighted=0.062±0.039; t(32)=2.346, p=.025, d=.402) and the crossed (M±SD blind=0.102±0.071; M±SD sighted=0.024±0.017; t(32)=4.449, p=.000, d=.763) posture conditions (Figure 2.b). Individual slope values are illustrated in the Figure 3, showing that a crossing-hand effect on

the slope values is almost systematically present in the normally sighted participants of Experiment 1 and 2, whereas it is much more inconsistent in the blind participants.

Regarding the mode of the presented SOAs, the ANOVA revealed a significant main effect of the posture ($F(1,32)=16.477$, $p<.001$, $\eta^2p=.340$), a significant main effect of the group ($F(1,32)=18.254$, $p<.001$, $\eta^2p=.363$), and a significant interaction between the two factors ($F(1,32)=15.198$, $p<.001$, $\eta^2p=.322$). Contrast analyses revealed a significant effect of the posture in the sighed participants ($t(16)=-3.990$, $p=.001$, $d=.968$), whereas such a difference was not significant for the blind participants ($t(16)=-1.083$, $p=.295$, $d=.263$). The sighted participants used lower SOA values to perform the TOJ task with the hands uncrossed (M±SD=34.120±19.222) than with the hand crossed (M±SD=208.82±187.471), whereas the blind participants seemed to be able to use a similar range of SOA to perform the task in both posture conditions (M±SD uncrossed=17.350±12.884, M±SD crossed=20.880±14.815). In addition, early blind participants appeared to perform the TOJ task overall with smaller SOA than the sighted both in the uncrossed (M±SD blind=17.35±12.884; M±SD sighted=34.12±19.222; $t(32)=-2.987$, $p=.005$, $d=.512$) and the crossed (M±SD blind=20.880±14.815; M±SD=208.82±187.471; $t(32)=-4.121$, $p=.001$, $d=.707$) posture conditions.

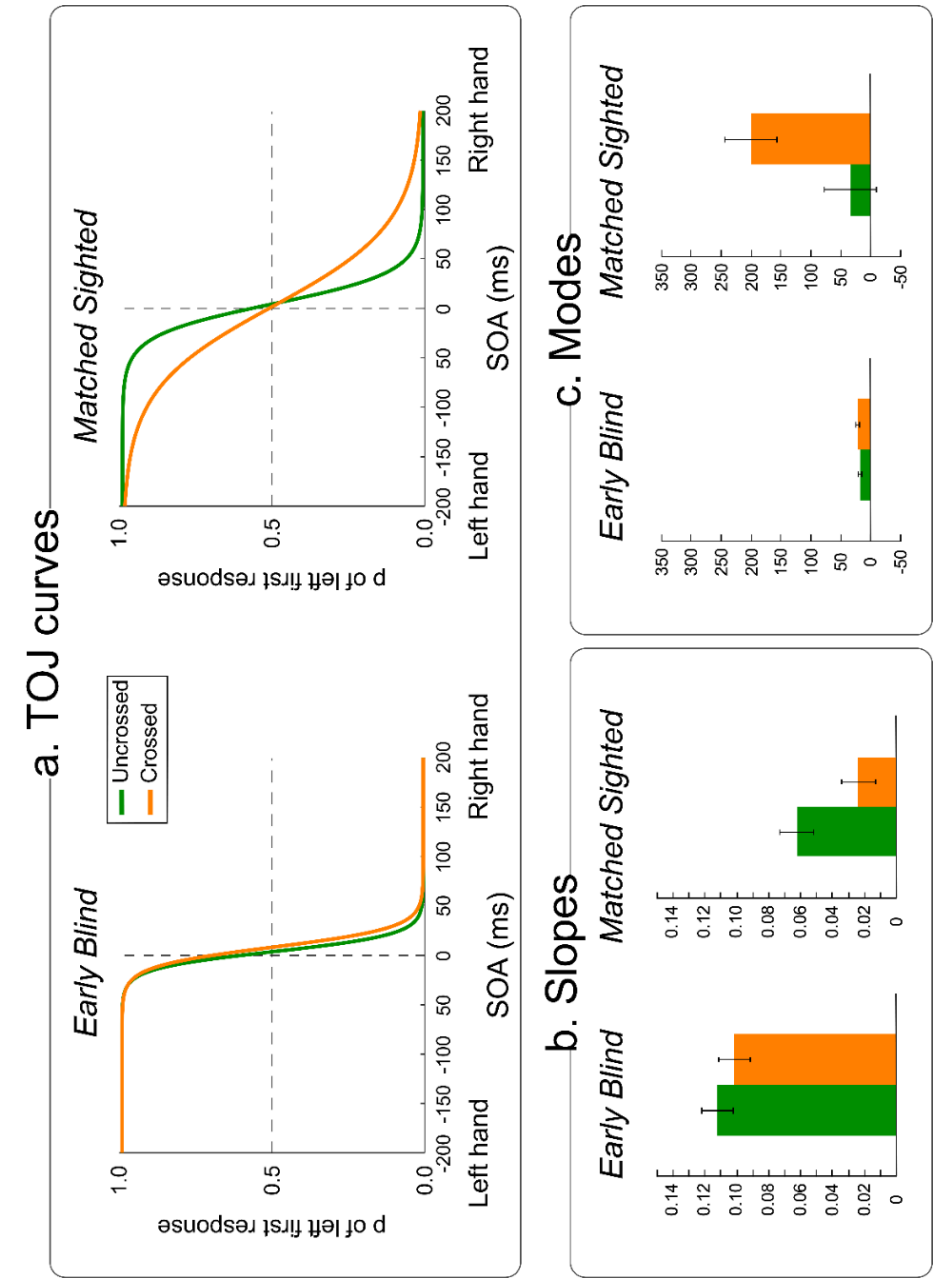
a. TOJ curves
Early Blind
Matched Sighted
Uncrossed
Crossed
p of left first response
1.0
0.5
0.0
-200 -150 -100 -50 0 50 100 150 200
Left hand
Right hand
SOA (ms)
b. Slopes
c. Modes
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0
350
300
250
200
150
100
50
0
-50

Figure 2. ***Tactile temporal order judgments (TOJs) in experiment 2.*** *(A) Fitted curves of the psychometric function from the data of the 17 early blind and the 17 normally sighted participants according to the hands posture condition. The x-axis represents different possible SOA. A negative value indicates that the left hand was stimulated first and a positive value indicates that the right hand was stimulated first. The y-axis represents the proportion of trials in which the vibrotactile stimulus applied on the left hand was perceived as being presented first. The lines represent the fitted curves for the uncrossed posture condition (green) and the crossed posture condition (orange) for the early blind group and the normally sighted group, respectively. (B) Mean slope values for each posture condition and according to each group. The slope value of the crossed posture condition was significantly lower than the slope value of the uncrossed posture condition for the sighted group but not for the blind group. Additionally, the averaged slope value of the early blind group was significantly greater than the mean slope value of the normally sighted group, independently of the posture. (C) Averaged mode values of the presented SOAs in millisecond for each posture condition and each group. The averaged mode in the crossed posture condition was significantly higher than the averaged mode value of the uncrossed posture condition in the normally sighted group but not in the early blind group. In addition, the averaged mode of the presented SOA was smaller in the blind, as compared to the sighted group, irrespective of the posture. Error bars represent confidence intervals calculated according to Cousineau's method for within-subject designs (Cousineau, 2005).*

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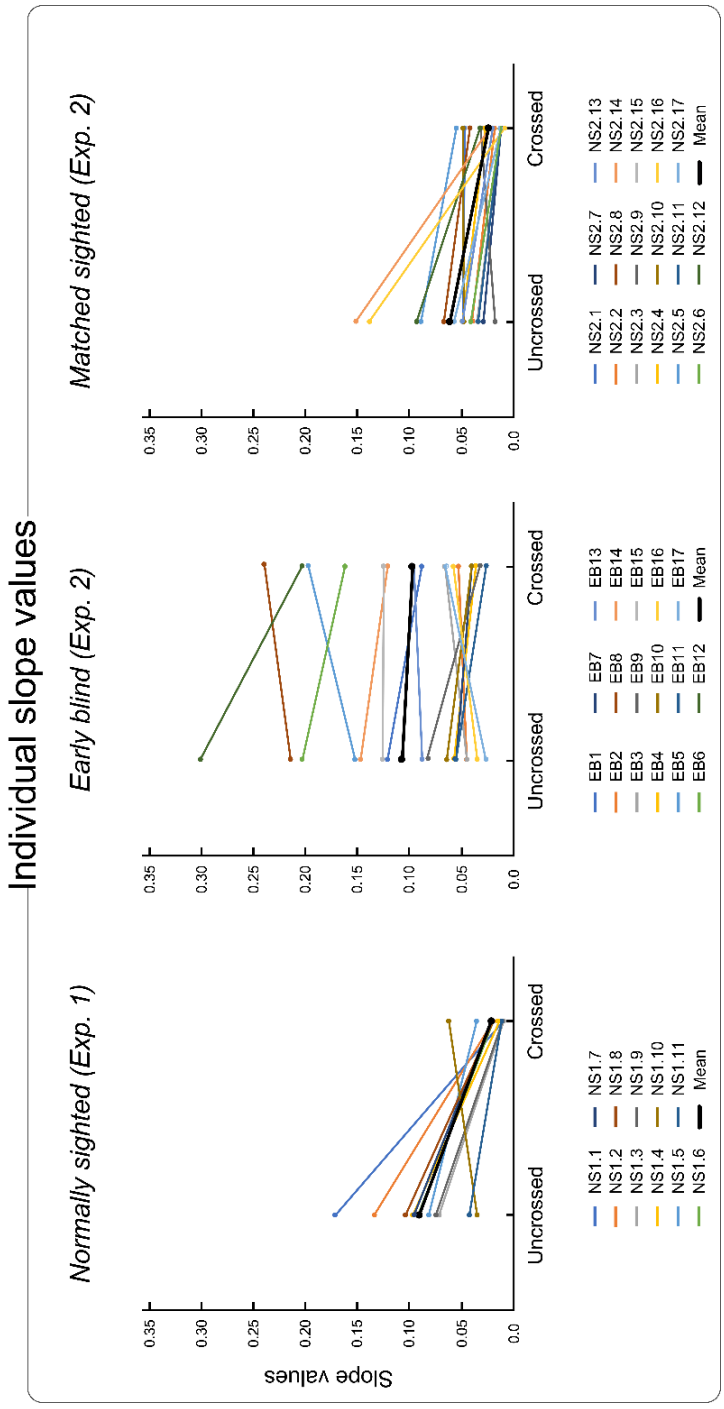


Figure 3. *Individual data from experiment 1 and 2.* *Individual slope values corresponding to the uncrossed and crossed posture conditions for each sighted observer that participated in the experiment 1, as well as each early blind and matched normally sighted participants of experiment 2. Mean slope values for each experiment and each group are represented in black.*

4. Discussion

The present study was aimed to investigate the spatial representations underlying the localization of tactile stimuli in both early blind and matched normally sighted participants by using a new paradigm allowing to adapt the parameters of the stimuli to each participant's sensitivity during TOJ tasks. Indeed, to investigate the spatial frames of reference of touch by means of TOJ tasks with posture manipulation, most of previous studies have used the method of constant stimuli, in which each SOA is presented a fixed number of times (e.g. Crollen, Albouy, et al., 2017; Röder et al., 2004; Shore et al., 2002; Yamamoto & Kitazawa, 2001a). However, when it comes to compare different experimental conditions or groups of people within which the performance is expected to vary, i.e. different ranges of SOA are needed to correctly discriminate the order of the stimuli (e.g. De Paepe et al., In preparation; Yamamoto & Kitazawa, 2001a), the stimulus levels (SOA) to be tested should be adapted in order to maximize the accuracy of the parameter estimates while avoiding floor or ceiling effects which could potentially mask an effect of the experimental variable(s). Here, we calibrated tactile TOJ tasks with the adaptive *psi* method, a procedure that allows adapting the presented SOA according to each participant's performance in each experimental condition. This method enabled us to investigate the spatial representations underlying touch perception with a high level of precision, and compare performances of early blind and normally sighted participants while performing TOJ task at their respective level of sensitivity, without extending the experiment duration by testing all the possible SOA. This paradigm has already been successfully implemented for experiment having tested TOJ of visual (Filbrich, Alamia, Blandiaux, et al., 2017; Filbrich, Alamia, Burns, et al., 2017; Filbrich et al., 2018; Legrain et al., 2018; Manfron et al., 2019; Vanderclausen et al., 2017), nociceptive (Vanderclausen, Bourgois, et al., 2020; Vanderclausen, Manfron, et al., 2020) and tactile stimuli (Filbrich, Alamia, Verfaille, et al., 2017). However, most of these studies focused on the estimation of the PSS while the estimation of the slope was out of the scope regarding the question addressed in these experiments. Only Vanderclausen et al. (2020) specifically targeted the estimation of the slope values during nociceptive TOJ (Vanderclausen, Bourgois, et al., 2020; Vanderclausen, Manfron, et al., 2020). The experiments presented here constitute the first study during which the slope of TOJ psychometric function was estimated in an adaptive procedure to test the ability of participants from distinct groups to represent spatial location of tactile stimuli under different posture conditions. All previous studies have indeed tested tactile TOJ with constant stimulation procedure (Cadieux et al., 2010; Crollen, Albouy, et al., 2017; Crollen et al., 2019; Heed et al., 2012; Kobor et al., 2006; Pagel et al., 2009; Röder et al., 2004; Sambo et al., 2013; Schicke & Röder, 2006; Shore et al., 2002; Wada et al., 2004; Yamamoto & Kitazawa, 2001a).

In the first experiment, the results of the tactile TOJ in young normally sighted participants revealed decreased performances in the crossed as compared to the uncrossed posture condition, which is completely in accordance with previous findings that used the method of constant stimuli (e.g. Cadieux et al., 2010; Shore et al., 2002; Wada et al., 2004; Yamamoto & Kitazawa, 2001a). Moreover, the adaptive character of the method allowed us to derive a second estimation of the participants' performance, which is the mode of the presented SOA, i.e. the most frequently presented SOA to a given participant in each posture condition during the adaptive procedure. Results indicated that the participants were presented with higher time intervals in the crossed as compared to the uncrossed posture. This indicates that they needed larger time intervals to be able to correctly judge the order of the two tactile stimuli when their hands were crossed relative to the canonical uncrossed posture, corroborating the findings on the slope values. These results emphasize the presence of an automatic spatiotopic remapping of tactile inputs, taking the position of the stimulated limbs in external space into account.

Regarding the second experiment, we found that crossing the hands did not affect the ability to discriminate the temporal order of the two tactile stimuli in early blind participants, while the crossed posture impacted performance of their matched normally sighted control participants' performance as in the first experiment. These results were reflected in both the slope and the mode values. Indeed, results on the SOA values indicated that early blind participants were presented with the same range of SOA values to perform the task irrespective of the posture adopted, whereas normally sighted participants were globally presented with larger SOA in the crossed as compared to the uncrossed posture. These results are in accordance with previous tactile TOJ studies having used the method of constant stimuli (Crollen, Albouy, et al., 2017; Crollen et al., 2019; Röder et al., 2004). Hence, we successfully replicated the findings of previous research with the use of an adaptive procedure which allows to enhance the accuracy of the parameter estimates by choosing the most appropriate range of stimulus levels according to each participant's sensitivity. These findings can also be related to recent studies having observed the same pattern of results through an adaptive procedure with the *psi* method but with stimuli having selectively activated cutaneous nociceptive receptors (Vanderclausen, Bourgois, et al., 2020; Vanderclausen, Manfron, et al., 2020). This suggests that similar mechanisms are involved in the spatial representations of innocuous and noxious somatosensory inputs respectively transmitted through lemniscal and extral-lemniscal pathways.

It is therefore suggested that our tactile TOJ task adapted with the adaptive *psi* method is a valid and reliable tool to investigate the complexity of spatial representations underlying touch localization, even when a limited number of stimuli are used. Given that all participants were not presented with the same sequence of SOA, and consequently with the exact same

task, one could argue that data of each participant cannot be compared with the results of the other ones. However, in our opinion, it appears way more relevant to compare data provided by a task that is adapted to individual performance, since the parameters would reflect a similar level of difficulty across participants, reflecting each participant's discrimination ability of TOJ sensitivity. Notably, the use of the adaptive method allowed us to obtain reliable data, provided by an algorithm that searched within a large range of different SOA those that were the most suitable for each participant within each experimental condition, without extending the experiment duration which can result in increasing fatigability of the observers.

It is worth noting that, regardless of the posture condition, we found that blind participants displayed overall better performances as compared to their sighted counterparts. This was indicated by higher slope values and smaller discrimination thresholds as reflected by the mode of the presented SOA in this group. This better sensitivity of the early blind in tactile TOJ tasks could be explained by increased tactile acuity (e.g. Alary et al., 2008; Goldreich & Kanics, 2003; Legge et al., 2008), and/or enhanced spatial resolution of touch in blind individuals possibly resulting from a stronger reliance on the sense of touch in this population (Wong et al., 2011). Moreover, and quite interestingly, the use of an adaptive method in our experiment highlighted greater inter-individual differences among early blind participants than it could be observed within the two groups of normally sighted participants (see Figure 3). This higher level of variability regarding performance of the blinds could be due to diverse levels of expertise in everyday life activities involving the tactile modality (e.g. braille reading) and diversity in strategies used to compensate for the lack of visual inputs among the early blind individuals tested in this study.

In conclusion, using a new paradigm combining tactile TOJ tasks with the adaptive *psi* method, the present study allowed us to confirm previous outcomes of the literature regarding the spatial remapping of touch in both early blind and normally sighted people by providing accurate and reliable data while maintaining a reasonably short experiment duration. We therefore encourage future studies willing to compare either populations that might differ in terms of performance (e.g. patients with specific pathologies) or experimental conditions that can impact the participants' sensitivity in the task to consider using this method, since it seems suitable for the investigation of the spatial representation of somatosensory stimuli in such situations (see **Studies 2** and **3**).

Interim summary

In this first study, we showed that the adaptive *psi* method represents a suitable procedure to investigate the spatial representations underlying the localization of tactile stimuli and we successfully replicated the results of previous studies with this new method. Present and previous results have demonstrated that early blind individuals do not seem to rely automatically on a spatiotopic frame of reference to localize tactile stimuli during temporal order judgement of tactile stimuli applied on different body locations. On the contrary, normally sighted participants seem to be confused by the spatiotopic representation of tactile inputs when they have to localize them on their body.

Given the greater relevance of mapping nociceptive stimuli according to external space, as compared to tactile ones, for defensive purposes, the next study we conducted was intended to investigate the spatial representations of nociceptive stimuli in both early blind and matched sighted participants. We took advantage of the adaptive *psi* method to reduce the number of trials and compare both populations. Reducing the total number of stimuli is of special interest when using heat nociceptive stimuli, as in the next study, because it allows minimizing such effects as skin overheating or habituation associated with stimuli repetition on a small skin surface which could potentially impact the data.

Study 2

Testing the exteroceptive function of nociception: the role of visual experience in shaping the spatial representations of nociceptive inputs[2]

Abstract

Adequately localizing pain is crucial to protect the body against physical damage and react to the stimulus in external space having caused such damage. Accordingly, it is hypothesized that nociceptive inputs are remapped from a somatotopic reference frame, representing the skin surface, towards a spatiotopic frame, representing the body parts in external space. This ability is thought to be developed and shaped by early visual experience. To test this hypothesis, normally sighted and early blind participants performed temporal order judgment tasks during which they judged which of two nociceptive stimuli applied on each hand's dorsum was perceived as first delivered. Crucially, tasks were performed with the hands either in an uncrossed posture or crossed over body midline. While early blinds were not affected by the posture, performances of the normally sighted participants decreased in the crossed condition relative to the uncrossed condition. This indicates that nociceptive stimuli were automatically remapped into a spatiotopic representation that interfered with somatotopy in normally sighted individuals, whereas early blinds seemed to mostly rely on a somatotopic representation to localize nociceptive inputs. Accordingly, the plasticity of the nociceptive system would not purely depend on bodily experiences but also on crossmodal interactions between nociception and vision during early sensory experience.

[2] Based on: Vanderclausen, C., Bourgois, M., De Volder, A. & Legrain V. (2020). Testing the exteroceptive function of nociception: the role of visual experience in shaping the spatial representations of nociception, *Cortex 126,* 26-38.

1. Introduction

Pain is as an unpleasant sensory and emotional experience associated with actual or potential tissue damage (IASP, 1994). It usually results from the activation of nociceptors, sensory receptors characterized by high activation thresholds, i.e. by the capacity to respond – at least under normal conditions – to stimuli of high intensity and potentially noxious (Belmonte & Viana, 2008). Pain has therefore an interoceptive function of warning the brain about the occurrence of sensory events having the potential to damage the body (Craig, 2003).

Among other functions of pain, its localization on the skin or in the viscera is of primary importance because it helps to identify which part of the body is being damaged. Conversely to the classical view (e.g. Kandel et al., 2013), nociceptive inputs can provide detailed and accurate spatial information, suggesting finely-tuned mapping systems for pain (Moore & Schady, 1995). Surprisingly, studies having investigated the mapping organization of nociceptive inputs in the brain (Andersson, 1997; Baumgärtner et al., 2010; Bingel, Lorenz, et al., 2004; Henderson et al., 2007; Mancini et al., 2012) only focused on the somatotopic organization characterized by anatomical representations of the body surface based on the ordered projection of the receptor fields to spatially segregated subgroups of neurons (Penfield & Rasmussen, 1950). However, it has been repeatedly shown that innocuous tactile inputs can be recoded according to spatiotopic representations, i.e. representations that use external space as reference frame, taking the relative position of the limb on which a given stimulus is applied into account (Azañón & Soto-Faraco, 2008a; Graziano et al., 1997; Heed & Azañón, 2014; Iwamura, Tanaka, Sakamoto, & Hikosaka, 1993; Shore et al., 2002; Smania & Aglioti, 1995; Yamamoto & Kitazawa, 2001a). While somatotopic maps allow coding the position of contacts on the skin surface, spatiotopic maps provide an appropriate readout for the brain allowing to identify the object in external space that is in contact with the body, and therefore planning an adequate spatially guided action towards that object (Brozzoli et al., 2014). Such complex ability to represent somatic information appears even more crucial for nociceptive and painful stimuli since it allows to detect and appropriately react against noxious stimuli that threathen the physical integrity of the body (Legrain & Torta, 2015). Demonstrating the brain's ability to map nociceptive inputs according to spatiotopic representations would provide evidence for the exteroceptive function of nociception (Haggard et al., 2013), whose role would be to optimize the monitoring of space around the body and react to potential danger (Legrain, 2017).

Spatiotopic mapping of touch has been repeatedly demonstrated using temporal order judgment (TOJ) tasks during which participants judge the order of occurrence of two successive tactile stimuli, one applied to each hand, and separated by different temporal delays (Heed & Azañón, 2014). It is noteworthy that TOJ tasks are performed with the hands either in a normal uncrossed posture or crossed over the midsagittal plane of the body.

Participants' judgements are typically less accurate when their hands are crossed, and such an effect is accounted by the fact that the somatotopic representation ("*Which hand is stimulated?*") mismatches the spatiotopic representation ("*Where is the stimulated hand?*") (Shore et al., 2002; Yamamoto & Kitazawa, 2001a). This indicates that, when judging the position of a tactile stimulation on the body, its position is automatically recoded according to spatiotopic frames of references (Azañón & Soto-Faraco, 2008a; Heed & Azañón, 2014). Importantly, it has been suggested that spatiotopic representations of touch are not innate but instead develop during infancy (Azañón et al., 2017; Pagel et al., 2009). Accordingly, hand posture does not affect the performance of people with early and complete visual deprivation, suggesting that the ability to remap touch according to external frame of reference is, at least partially, shaped by early visual experiences (Crollen, Albouy, et al., 2017; Röder et al., 2004).

The first aim of the present experiments was to test the hypothesis according to which nociceptive inputs are automatically coded according to spatiotopic reference frames. Normally sighted participants performed temporal order judgment tasks on thermal stimuli specifically and selectively activating skin nociceptors. Stimuli were applied on each hand dorsum and tasks were performed with the hands either uncrossed or crossed. We expected a decrease of performance in the crossed posture as compared to the uncrossed posture. The second aim was to test the hypothesis of the role of early visual experience in the development of the spatiotopic representation of nociception. We therefore compared the ability of early blind participants and matched blindfolded sighted controls in discriminating the temporal order of nociceptive stimuli. Considering that touch and nociception share the same spatial representation (Legrain & Torta, 2015), we would expect early blind participants to be unaffected by hand posture, indicating that their judgements mostly rely on somatotopic representations of nociception. However, due to the higher relevance of nociception in terms of survival and the underlying fundamental role of its spatial representation, we could also expect that early blind participants would be affected by the conflict between somato- and spatiotopic representations during crossed hand posture. In this line, the spatial mapping of nociceptive stimuli would be less dependent on external factors, such as early visual experience, than that of tactile inputs.

2. Methods

2.1. Participants

Thirteen healthy volunteers took part in Experiment 1. Sample size has been determined based on previous studies on similar topics (De Paepe et al., 2015; Filbrich, Alamia, Burns, et al., 2017; Filbrich et al., 2018; Sambo et al., 2013). Inclusion/exclusion and data exclusion criteria were established prior to data analysis, and we report all manipulations and measures. One participant was excluded because he could not achieve task requirements properly (see Procedure). The mean age of the 12 remaining participants (7 women) was 25.00 ± 2.63. Nine participants were right-handed and three of them were left-handed according to the Flinders Handedness Survey (Nicholls et al., 2013). The participants had normal to corrected-to-normal vision. They did not report any prior history of severe neurological, psychiatric or chronic pain disorders. They did not suffer from a traumatic injury of the upper limbs within the six months nor any cutaneous lesion on the hands' dorsum. The regular use of psychotropic drugs or the intake of analgesic drugs (e.g. NSAIDs and paracetamol) within the twelve hours preceding the experiment were also considered as exclusion criteria.

Thirteen early blind as well as 15 normally sighted individuals participated in Experiment 2. Inclusion/exclusion and data exclusion criteria were applied as in Experiment 1. The number of blind participants has been determined based on previous studies on the same topic (e.g. Crollen, Albouy, et al., 2017; Röder et al., 2004). One of the early blind and three of the normally sighted participants were excluded from the data set because they could not achieve the task requirements properly (see Procedure). Among the 12 remaining early blind participants (7 women, 36.67 ± 10.98 years of mean age), there were 9 right-handed, 1 ambidextrous and 2 left-handed participants (Nicholls et al., 2013). The 12 remaining sighted participants (36.08 ± 10.73 years) were matched individually to the early blind participants in terms of age, sex, and level of education. The inclusion and exclusion criteria for sighted participants were similar as for Experiment 1. In addition, the early blind participants were recruited according to blindness attributed to peripheral deficits without additional neurological problems (see Table 1 for a detailed description of blind participants). They were all considered as totally blind since birth. One of them, participant EB5, because of a genetic disease, became totally blind at 3 months of life, but was still considered as early blind since his visual acuity was very poor in the first months of life. The participant EB9 of the blind group suffered from epilepsy and was under medication for that reason (Levetiracetam 1750 mg and Oxcarbazepine 1500 mg daily). The epileptic focus was located in the left temporo-occipital border of the brain. Nevertheless, this participant was not excluded from the study since there was no evidence of cognitive impairment or somatosensory perception deficit. The participant EB12 suffered from attention deficit and

hyperactivity disorder but his medication (methylphenidate) was interrupted at the moment of the experiment.

All experimental procedures were approved by the local ethics committee and conformed to the Declaration of Helsinki. Written informed consents were obtained for all participants before starting the study.

Partic-ipant	Sex/ Age	Hande-dness	Profession/Edu-cational level	Visual perception	Onset of blindness	Cause of blindness	Braille	Cane	Musical instrument	Musical experience	Other
EB1	M 40	R	College degree	None	Birth	Leber congenital amaurosis	Yes	Yes	Piano/ Organ	5 years	Torball
EB2	F 39	R	Official High School	None	Birth	Retinopathy of prematurity	Yes	Yes			
EB3	F 35	R	Phone sale until 2006/ Official High School	None	Birth	Severe corneal dysplasia (*)	Few	Yes+Dog	Drums	Only few months	
EB4	M 32	R	Some college	None	Birth	Persistent hyperplastic primary vitreous involving both eyes	Yes	Yes	Clavier	>10 years	
EB5	M 65	R	College degree	None	<18 months	Bilateral retinoblastoma	Yes	Yes	Organ	>9 years	
EB6	M 39	R	Teacher/ College degree	None	Birth	Anterior chamber cleavage syndrome (Peters syndrome)	Yes	Yes+Dog	Piano/Flute/Drums	>5 years	Hearing aids
EB7	M 32	L	Some college	None	Birth	Hereditary retinal dysplasia (*)	Yes	Yes	Guitare	>4 years	Slight auditory loss
EB8	F 43	L	College degree	None	Birth	Retinopathy of prematurity	Yes	Yes	Piano/Flute/Drums	7 years	
EB9	F 39	R	Interpreter/ College degree	None	Birth	Severe retinal dystrophy/ congenital pigmentary retinitis with macular perforation	Yes	Yes	Piano	>5 years	Epilepsy
EB10	M 29	R	College degree	None	Birth	Leber congenital amaurosis	Yes	Yes	No		Various sport activities
EB11	M 22	R	Some college	None	Birth	Congenital cause (*)	Yes	Yes	No		
EB12	M 25	Ambi	Receptionist	None	Birth	Leber congenital amaurosis	Yes	Yes	Drums, piano, harmonica, guitar	>5 years	ADHD syndrome

Table 1. Profile of the blind subjects.

Note: *EB= early blind; F= female; M= male; Age in years; R= right handed; L= left handed; Ambi=ambidextrous; (*): no additional details available. Regarding the onset of the blindness, participant EB5 was not blind from birth. However, because he had very poor vision from birth and underwent a bilateral eye enucleation at the age of 18 months, he was considered as early blind. His data were nevertheless in the range of those observed for the other blind participants (see Figure 2). Torball is an indoor sport for the blind.*

2.2. Stimuli and apparatus

Nociceptive stimulations consisted of radiant heat stimuli delivered onto the skin of the hands' dorsa by means of two identical infrared CO_2 laser stimulators (wavelength 10.6 μm; Laser Stimulation Device, SIFEC, Ferrières, Belgium). This technique is known to selectively and specifically activate thermo-sensitive cutaneous nociceptors associated to thinly myelinated and unmyelinated fibers (Plaghki & Mouraux, 2005). The power of the output stimulation was regulated using a feedback control based on an online measurement of the skin temperature at the site of stimulation by means of a radiometer whose field of view was collinear with the laser beam. This allows defining specific skin temperature profiles (see Churyukanov et al., 2012). The laser beams were conducted through 10-m optical fibers. Each fiber ended with a head containing the optics used to collimate the laser beam to 6 mm diameter at the target site. Each laser head was hold upon each participant's hand by means of articulated arms attached to a camera tripod system (Manfrotto, Cassola, Italy). Each laser head was fixed into a clamp attached to a 3-way head allowing displacements of the target site of the laser beam perpendicularly oriented to the hand dorsum by means of several sliders in all directions. During threshold measurements and during the experiments, laser beams were displaced after each stimulus using the sliders. Stimulus duration was 100 ms with a 10-ms heating ramp to reach the target temperature, followed by a 90-ms plateau after which heating was stopped. The target temperature was determined for each participant's hand according to individual activation threshold of nociceptive thinly myelinated Aδ fibers. Thresholds were estimated by means of an adaptive staircase procedure using reaction times (RTs) to discriminate detections triggered by Aδ fiber inputs (RT < 650 ms) from detections triggered by C-fiber inputs (RT ≥ 650 ms) (Churyukanov et al., 2012). Indeed, Aδ fibers have faster nerve conduction velocity than unmyelinated C fibers (~10 m/s vs. ~1 m/s), while Aδ-fibers are known to have higher thermal activation thresholds than C-fibers (Plaghki & Mouraux, 2005). Concretely, the participants were asked to press a button with the non-stimulated hand as soon as they felt something on the stimulated hand. Any RT equal or superior to 650 ms leaded to a temperature increase of 1°C for the next stimulus. On the contrary, any RT inferior to 650 ms leaded to a decrease in temperature of 1°C. The procedure started at 46°C and lasted until four reversals were encountered. The mean value of the four temperatures that leaded to a reversal was considered as the threshold. This procedure allowed us to specifically target responses of Aδ nociceptors, more particularly rapidly-adapting type II Aδ-mechano-heat-sensitive nociceptors (Churyukanov et al., 2012; Treede, Meyer, Raja, & Campbell, 1995). For the stimuli used during the experimental phase, 5°C were added to that value, and if necessary, the temperature was slightly adapted for each hand and across experimental blocks so that stimuli were always perceived as equally intense between the two hands. View of the hands was prevented in sighted participants during threshold estimation. Stimuli at such temperature values were perceived as pricking and elicited a slightly painful sensation. Before starting and during the experiment, elicited sensations were tracked using a list of words to be chosen (not perceived, light touch, tingling, pricking, warm, burning). Subjective intensity was measured for each hand using a

numerical rating scale (NRS) from 0 (no sensation) to 10 (strongest sensation imaginable). This was made to ensure that stimuli were still perceived as pricking and equally intense between the two hands. Stimuli temperatures were then adapted if necessary.

2.3. Procedure

The procedure was exactly the same for Experiments 1 and 2. The participants were sitting on a chair in front of a table. Their hands rested on the table palms down, with a distance of ~30 cm between the two index finger tips. Participants' head was placed in a chin-rest in order to minimize head movement during the experiment. The participants were asked to perform the task with their hands either uncrossed or crossed over the body midline. Noises from experimental devices were covered by means of a white noise played through earphones during the whole experiment. The sighted participants were blindfolded with an eye mask.

Participants were presented with four blocks of 40 trials each. During two blocks, the task was performed with the hands in an uncrossed posture, whereas in the two other blocks it was performed with the hands crossed over the sagittal midline of their body (the order of these two conditions was counterbalanced across participants). Each trial consisted in pairs of nociceptive stimuli, one applied on each hand, separated in time by 24 possible stimulus onset asynchronies (SOA) : ±10, ±15, ±30, ±45, ±60, ±75, ±90, ±150, ±200, ±400, ±500, ±600 ms. Negative values indicated that the first stimulus of the pair was applied on the left hand, and the second one on the right hand. Positive values indicated that the right hand was stimulated first. Within each block and for each trial, the presented SOA was determined online based on participants' performance on all previous trials according to the PSI method (Kingdom & Prins, 2010; Kontsevich & Tyler, 1999), implemented through the Palamedes Toolbox (Prins & Kingdom, 2009). Based on a Bayesian framework, this adaptive procedure estimates the posterior distribution of the parameters of interest and minimizes its expected entropy (i.e. uncertainty) trial by trial, considering all the previous trials. In other words, at each trial, the algorithm infers which condition (i.e. SOA) is the most informative to estimate the distribution of the parameters of interest. This method thus allowed us to estimate the parameters of interest without probing extensively all the possible SOAs, which would be time consuming (Filbrich, Alamia, Burns, et al., 2017). After each trial, the participants had to report verbally which one of the two stimuli they perceived as being presented first in half of the experimental blocks ('which is first'), and which one they perceived as being presented second in the other half ('which is second'), by saying 'left' or 'right' aloud. The order of these instructions was randomized within each posture condition. The aim of using two response modalities was to prevent the data from being influenced by a potential response bias (Filbrich et al., 2016; Spence & Parise, 2010). Participants' responses were encoded by the experimenter by using a keyboard, and the next trial started 2000 ms later. The time interval between two trials varied from 5 to 10 seconds. Laser beams were displaced after each trial between the heating offset and encoded experimenter's response, which triggered

the next trial. The task was unspeeded but the participants were told to be as accurate as possible. They did not receive any feedback on their performance in the task.

Experiments were preceded by a practice session of 4 blocks of 5 trials each, one block per hand posture (i.e. uncrossed vs. crossed) and response condition (i.e. 'which is first' vs. 'which is second'), but only with two different SOA, i.e. ±150 and ±200 ms. During the experiment, to avoid overheating of the skin and habituation, a 10 minutes break was imposed to the participants between the blocks. One block lasted 10 to 15 minutes. The whole study, including the threshold measurement, the training session and the experiment lasted two to three hours. No part of the study procedures was pre-registered prior to the research being conducted.

2.4. Measures

Aδ fiber activation thresholds and stimulation intensities (corresponding to the averaged intensity used for each hand across all experimental blocks (i.e. approximately 5°C added to the Aδ fiber activation threshold) were measured in degree Celcius (°C). Regarding temporal order judgment (TOJ) performance, for all experimental conditions, the proportion of left stimuli having been reported as presented first was calculated as a function of SOA. For each participant, data were fitted online during the experimental block with the logistic function, i.e. $f(x) = 1/(1+\exp(-\beta(x-\alpha))$, from which the parameters of interest were computed (Filbrich, Alamia, Burns, et al., 2017). These parameter estimates corresponded to the last update computed by the algorithm of the adaptive procedure (Kontsevich & Tyler, 1999). They characterized respectively the threshold (α) and the slope (β) of the function. In the present experiments, the parameter of interest was the β parameter, describing the noisiness of the participants' responses, i.e. the precision of their responses during the experiment (Kingdom & Prins, 2010). The β is classically used to derive from TOJ performances the just noticeable difference (JND) that denotes the SOA needed for the participants to correctly perceive the order of the two stimuli in a certain percentage of trials (e.g. Crollen, Albouy, et al., 2017; Röder et al., 2004; Shore et al., 2002). Although the contribution of the α parameter was out of the scope of the present study, it was taken into account in order to assess the presence of potential biases which could influence the estimation of the slope in the frame of the adaptive *psi* method (Kingdom & Prins, 2010). The α is the threshold of the function and refers to the point of subjective simultaneity (PSS), defining the SOA at which the participants report the two stimuli as occurring first equally often. In other words, in the present experiments, the α corresponded to the SOA at which the proportion of trials during which the stimuli applied to the left hand were reported as presented first reaches 0.5. Since the *psi* method is based on a Bayesian approach, a prior probability distribution needs to be postulated, based on previous knowledge regarding the values of the parameter of interest (Filbrich, Alamia, Burns, et al., 2017; Kingdom & Prins, 2010). In the present experiments, we used a prior distribution of 0 ±20 for the α parameter and 0.06 ±0.6 for the β parameter, based on previous

studies in the tactile modality (e.g. see Study 1). Lapse rate, which is defined as the probability of incorrect response independently of stimulus intensities (i.e. SOA), such as related to vigilance or response errors (i.e. participants answered "left" but meant "right") (Filbrich, Alamia, Burns, et al., 2017; Kingdom & Prins, 2010; Prins, 2012) was set at 0.02 and guess rate at 0 for all conditions, as recommended by Kingdom and Prins (2010). Because the adaptive *psi* method was used, a third parameter was computed and corresponded to the mode of the presented SOAs, i.e the value of the SOA that was the most frequently presented to each participant during each adaptation procedure. This measure can be considered as indexing the participant's adaptation during the task, with the idea that smaller is the mode, better is the performance, and larger it is, worse is the performance because this indicates that, overall, the participant needed higher SOAs to be able to discriminate between the two stimuli.

2.5. 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. Since different responses were used to minimize potential response biases, the data from the two response conditions ('which is first' and 'which is second') were merged (i.e. averaged).

Analyses were first performed on the Aδ fiber activation threshold and stimulation intensity values, to ensure that no difference was found between the two hands regarding these parameters that could have influenced the results in any way. In Experiment 1, comparison between activation thresholds and stimulation intensities was made using paired t-tests with the *hand* as factor (left vs. right). In Experiment 2, we used an analysis of variance (ANOVA) for repeated measures with adding the group as the second factor (sighted vs. blind).

Regarding the TOJ tasks, in order to examine the presence of potential perceptual biases towards one of the two sides of space, one-sample t-tests were performed to compare the PSS values to 0 for each condition of the posture factor (uncrossed vs. crossed) and for each of the three groups separately. Next, PSS, slope and mode values were compared using an ANOVA for repeated measures with the *posture* (uncrossed vs. crossed) as a within-participant factor in Experiment 1, and using the *posture* and the *group* (early blind vs. normally sighted) respectively as within- and between-participant factors in Experiment 2. Greenhouse-Geisser corrections and contrast analyses were used if necessary. Effect sizes were measured using partial Eta squared for ANOVA and Cohen's d for t-tests. Significance level was set at $p \leq .05$. No part of the study analyses was pre-registered prior to the study being conducted. Study data are archived in a publicly accessible repository, including brief explanation of the content and variables (https://osf.io/n9kbx/).

3. Results

3.1. Experiment 1

Threshold and intensity values

Aδ-fiber activation threshold values were on average 48.08±2.02°C for the left hand and 47.58±2.11°C for the right hand. These values are compatible with responses from type II AMH fibers (Churyukanov et al., 2012; Treede et al., 1995). The difference between the hands was not significant ($t(11)=0.88$, $p=.400$, $d=0.25$). Similarly, there was no significant difference between the left (M=53.63±1.58) and the right (M=53.33±1.76) hands for the stimulation intensity values ($t(11)=.77$, $p=455$).

TOJ values

The fitted psychometric curves are illustrated in Figure 1a. The one sample t-tests revealed that the PSS value in the crossed posture condition (M=-0.30±14.11ms) was not significantly different from 0 ($t(11)=-0.07$, $p=.943$, $d=0.02$). But, surprisingly, PSS was slightly but significantly different from 0 in the uncrossed posture condition ($t(11)=2.37$, $p=.037$, $d=0.68$). With a mean value of 8.86ms (SD=12.95), it indicated a slightly biased judgment toward the left hand in this posture condition.

Comparison of the posture conditions revealed no significant effect on the PSS values ($F=4.49$, $p=0.580$, $\eta^2_p=.29$), suggesting that the bias observed in the uncrossed posture condition was marginal. Regarding the slope values, the ANOVA revealed a significant effect of the posture ($F(1,11)=13.13$, $p=.004$, $\eta^2_p=.54$), showing that the slope value was significantly lower in the crossed posture (M=0.011±0.006) than in the uncrossed posture condition (M=0.021±0.009) (Figures 1b & 2). Similarly, analysis of the mode of the presented SOAs revealed a significant effect of the posture ($F(1,11)=8.82$, $p=.013$, $\eta^2_p=.45$). The mode of the presented SOAs was significantly larger in the crossed posture condition (M=402.50±259.13ms), as compared to the uncrossed posture condition (M=157.50±211.28ms) (Figure 1c).

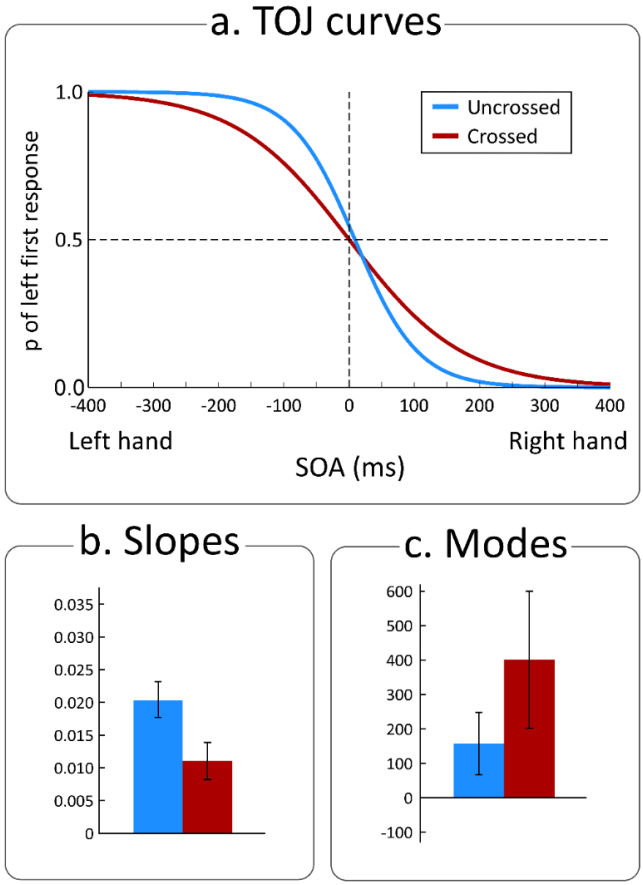


Figure 1. ***Nociceptive temporal order judgments in Experiment 1***. *(a) Fitted curves of the psychometric function from the data of the 12 sighted participants according to the hands posture condition. The x-axis represents the different possible SOAs. A negative value indicates that the left hand was stimulated first and a positive value indicates that the right hand was stimulated first. The y-axis represents the proportion of trials in which the nociceptive stimulus applied on the left hand was perceived as being presented first. The lines represent the fitted curves for the uncrossed posture condition (blue) and the crossed posture condition (red), respectively. (b) Mean of the slope values for each posture condition. The slope value of the crossed posture condition was significantly lower than the slope value corresponding to the uncrossed posture condition. (c) Mean of the mode values of the presented SOAs in millisecond for each posture condition. The averaged mode in the crossed posture condition was significantly higher than the mean mode value of the uncrossed posture condition. Error bars represent the 95% confidence intervals estimated for each measure according to the Cousineau's method (Cousineau, 2005).*

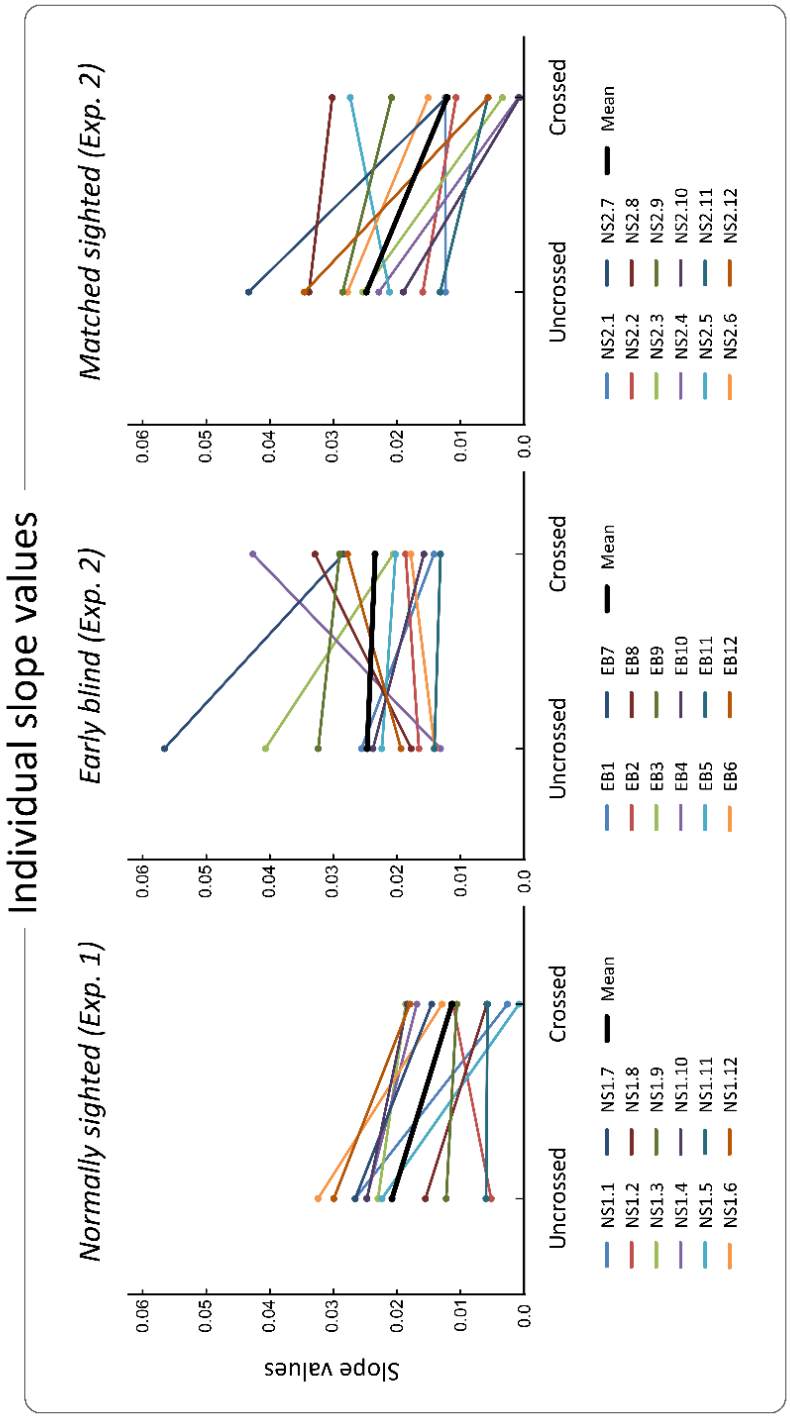


Figure 2. *Individual data in Experiments 1 and 2.* *Individual slope values corresponding to the uncrossed and crossed posture conditions for each sighted observer that participated in the Experiment 1, as well as each early blind and matched sighted participants from Experiment 2. The averaged slope values for each experiment, each group and each posture condition are represented by the thick black lines. The data of participants EB5, EB9 and EB12 are in the range of the group values.*

3.2. Experiment 2

Threshold and intensity values

Analyses of the Aδ fibers activation thresholds showed no significant effect of the hand ($F(1,22)=1.12$, $p=.302$, $\eta^2_p=.05$), no significant effect of the group ($F(1,22)=1.30$,$p=.267$, $\eta^2_p=.06$), and no significant interaction between the two factors ($F(1,22)=0.17$, $p=.689$, $\eta^2_p=.01$). Early blind participants had a similar activation threshold ($M=48.25\pm2.18°C$) than the normally sighted participants ($M=49.21\pm1.94°C$). Similar results were obtained for the stimulation intensity, as the ANOVA revealed neither significant main effect of the hand ($F(1,22)=1.71$, $p=.205$, $\eta^2_p=.07$) nor of the group ($F(1,22)=0.94$, $p=.344$, $\eta^2_p=.04$), nor significant interaction between the two factors ($F(1,22)<0.01$, $p=.949$, $\eta^2_p<.01$).

TOJ values

The fitted psychometric curves are illustrated for both groups in Figure 3a. The one sample t-tests performed for each group and for each posture separately showed that none of the PSS values were different from 0 (all $t(11)\leq-1.35$, all $p\geq.204$).

The ANOVA performed on the PSS values revealed no significant difference between the posture conditions ($F(1,22)=0.01$, $p=.922$, $\eta^2_p<.01$), no significant difference between the groups ($F(1,22)=0.77$, $p=.389$, $\eta^2_p=.03$) and no significant interaction between the two factors ($F(1,22)=0.20$, $p=.657$, $\eta^2_p=.01$). On the contrary, the ANOVA performed on the slope values revealed a significant main effect of the posture ($F(1,22)=6.33$, $p=.020$, $\eta^2_p=.22$) and an almost significant interaction with the group factor ($F(1,22)=4.25$, $p=.051$, $\eta^2_p=.16$). The main effect of the group was not significant ($F(1,22)=3.09$, $p=.092$, $\eta^2_p=.12$). Contrast analyses revealed a significant effect of the posture in the normally sighted group ($t(11)=3.76$, $p=.003$, $d=1.08$), the slope value of the crossed condition ($M=0.012\pm0.010$) being lower than that of the uncrossed condition ($M=0.025\pm0.009$). Conversely, in the blind group, such a difference was not significant ($t(11)=0.29$, $p=.779$, $d=0.08$), the slope value of the crossed condition ($M=0.023\pm0.008$) being comparable to that of the uncrossed condition ($M=0.024\pm0.013$) (Figures 2 and 3b). Regarding the mode of the presented SOAs (Figure 3c), the results corroborated those of the slope values, as the ANOVA revealed an almost significant main effect of the posture ($F(1,22)=4.12$, $p=.055$, $\eta^2_p=.16$) and a significant interaction with the group factor ($F(1,22)=15.34$ $p=.001$, $\eta^2_p=.41$), while there was no significant main effect of the group ($F(1,22)=3.03$, $p=.096$, $\eta^2_p=.12$). Contrast analyses revealed a significant difference between the two postures in the normally sighted group ($t(11)=-3.79$, $p=.003$, $d=1.10$), the mode of the presented SOAs being larger in the crossed

posture condition (M=329.17±284.49ms) as compared to the uncrossed posture condition (M=32.92±42.13ms). The difference (crossed posture: M=36.67±45.19ms; uncrossed posture: M=130.83±222.77ms) was not significant in the early blind group ($t(11)=1.53$, $p=.156$, $d=0.44$) (Figure 3c).

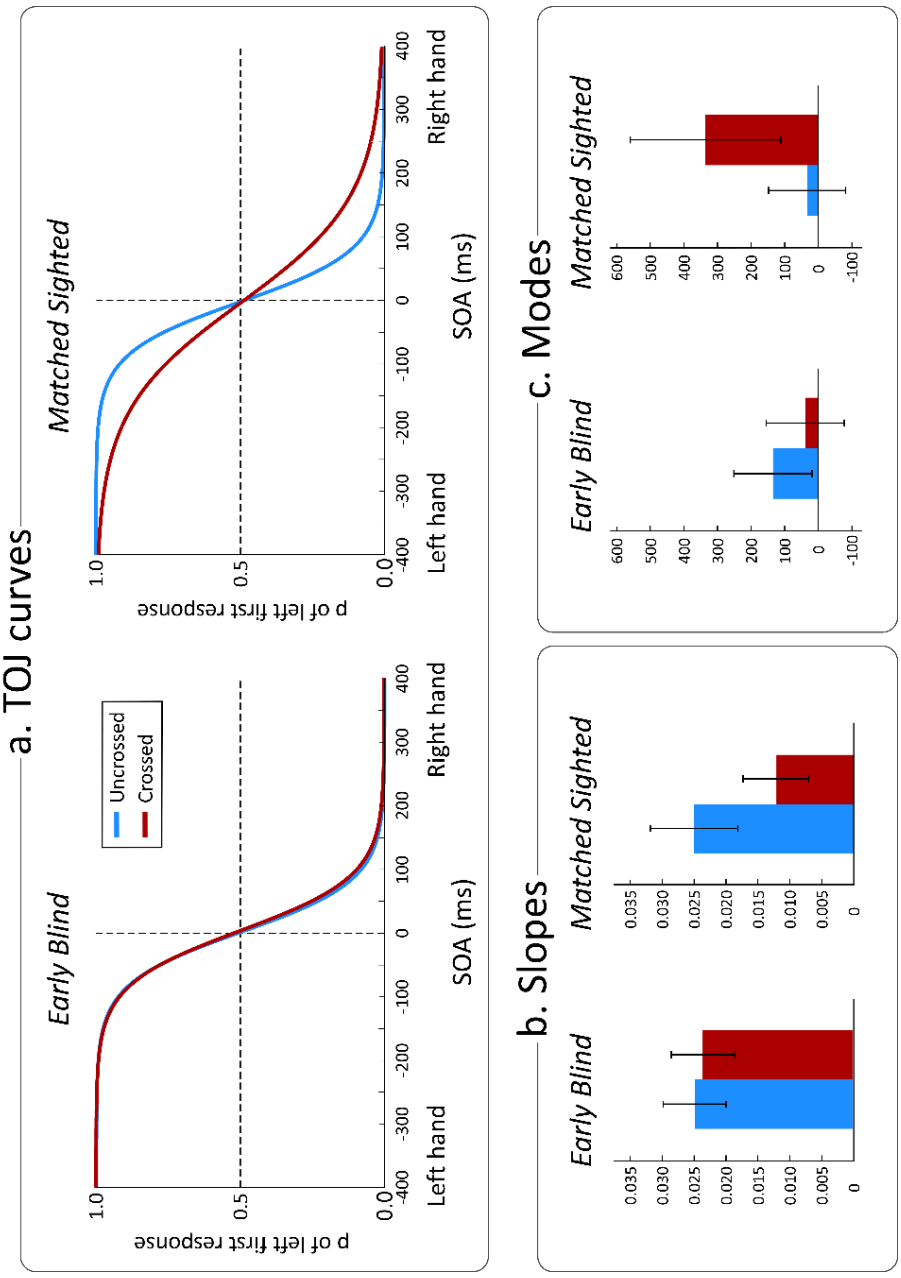

a. TOJ curves
Early Blind
Matched Sighted
Uncrossed
Crossed
p of left first response
1.0
0.5
0.0
-400
-300
-200
-100
0
100
200
300
400
Left hand
Right hand
SOA (ms)
b. Slopes
c. Modes
0.035
0.030
0.025
0.020
0.015
0.010
0.005
0
600
500
400
300
200
100
-100

Figure 3. ***Nociceptive temporal order judgments in Experiment 2.*** *(a) Fitted curves of the psychometric function from the data of the 12 early blind and the 12 matched sighted participants according to the hands posture condition. The x-axis represents the different possible SOAs. A negative value indicates that the left hand was stimulated first and a positive value indicates that the right hand was stimulated first. The y-axis represents the proportion of trials in which the nociceptive stimulus applied on the left hand was perceived as being presented first. The lines represent the fitted curves for the uncrossed posture condition (blue) and the crossed posture condition (red) for the early blind group and the matched sighted group, respectively. (b) Mean of the slope values for each posture condition for each group. The slope value of the crossed posture condition was significantly lower than the slope value of the uncrossed posture condition only in the sighted group. In the early blind participants, the averaged slope in the crossed and uncrossed posture conditions were not significantly different from each other. (c) Mean of the mode values of the presented SOA in millisecond for each posture condition and each group. The averaged mode in the crossed posture condition was significantly higher than the averaged mode value of the uncrossed posture condition in the sighted group but such difference was not found significant for the early blind group. Error bars represent the 95% confidence intervals estimated for each measure according to the Cousineau's method (Cousineau, 2005).*

4. Discussion

The goals of the present study were to characterize the spatial representations of nociceptive stimuli and the role of early visual experience in shaping these representations. To this aim, two experiments were conducted by means of TOJ tasks during which participants discriminated the temporal order of two nociceptive stimuli, one applied on each hand placed in either an uncrossed or crossed posture. While early blind participants' performance was not affected by the posture, the performance of the two groups of blindfolded sighted participants decreased in the crossed condition as compared to the uncrossed condition. As the crossed posture is aimed to generate a mismatch between the somatotopic and the spatiotopic representations of somatic inputs (Heed & Azañón, 2014), the results indicated that when normally sighted people had to localize a nociceptive stimulus on their body, its position was automatically mapped into a spatiotopic representation and interfered with the somatotopic map.

Since the same pattern of results was observed with innocuous tactile stimuli (Shore et al., 2002; Yamamoto & Kitazawa, 2001a), it is assumed that the perception and localization of touch and nociception, although being processed through two segregated afferent pathways, share similar spatial representations (Legrain & Torta, 2015). These results are in line with the study of Sambo et al. (2013) who showed a crossing-hands effect in sighted participants during TOJ tasks using intra-epidermal electrical stimulation (IES). While the selective activation of nociceptors by IES depends on a strict stimulation procedure (Mouraux, Iannetti, & Plaghki, 2010), we replicated here these results by using radiant heat stimuli delivered by means of two CO_2 laser stimulators, a technique that allows undoubtedly specific and selective activation of skin nociceptors (Plaghki & Mouraux, 2005). More specifically, the staircase procedure based on participants' reaction times allowed us to target nociceptors associated to Aδ fibres (Churyukanov et al., 2012).

The most novel result of the present study comes from the comparison between normally sighted and early blind participants. These results showed that early blind participants were unaffected by the posture of the hands as they performed the TOJ tasks similarly in the crossed and uncrossed conditions, a result that completely matches those observed for touch (Crollen, Albouy, et al., 2017; Röder et al., 2004). Moreover, this outcome parallels other findings suggesting that somatosensory perceptual abilities of early blind people mostly rely, at least in similar tasks, on somatotopic reference frames (Collignon, Charbonneau, et al., 2009; Crollen & Collignon, 2012; Röder et al., 2008). Therefore, it can be suggested that, despite the great relevance of the spatial representation of nociceptive painful stimuli in terms of behavioural adaptation, the ability to map nociceptive inputs according to spatiotopic reference frames is not innate but would rather be shaped by visual experience during development.

Given the assumed similarities between the spatial representations of touch and nociception (Gallace et al., 2011; Legrain & Torta, 2015; Torta et al., 2013), the present data support the importance of other sensory modality inputs such as visual inputs for the development of the nociceptive system. Our results are indeed in line with studies that demonstrated a close interaction between nociceptive and visual stimuli occurring near the body (De Paepe et al., 2015; De Paepe et al., 2017; De Paepe et al., 2014; Filbrich, Alamia, Blandiaux, et al., 2017; Filbrich et al., 2018). Furthermore, seeing the limb on which nociceptive stimuli are applied and the posture of the limb have been shown to affect the brain responses elicited by nociceptive stimuli, the evaluation of their intensity and the perception of pain (Gallace et al., 2011; Longo et al., 2009; Mancini, Longo, Kammers, et al., 2011; Torta et al., 2013).

It is worth noting that our data shed more light on the reasons underlying the impact of body posture on the perception of pain (Gallace et al., 2011; Torta et al., 2013). Indeed, it has been suggested that the decreased performance during somatosensory TOJ tasks with crossing hands reflects the cost of the automatic spatiotopic remapping, and the resources needed to solve the conflict between the different spatial representations in order to adequately localize the relevant stimulation (Shore et al., 2002). The influence of the posture on the subjective intensity might therefore reflects the additional cognitive load associated with the necessity to realign the spatiotopic map with the somatotopic one when the hands are crossed, resulting in limited neural resources available to process intensity feature (Torta et al., 2013). While further studies are needed to better characterize the relation between those two aspects, the afore-mentioned and the present data highlight the importance of the spatial representations of nociceptive inputs for the perception of pain. Being able to adequately defend the body against potential physical threats requires both coding somatosensory inputs and representing the body limbs according to their relative location in external space. This is requested for planning spatially-guided actions against those threats. In that sense, spatiotopic mapping of somatosensory inputs might be conceptualized as a premise of multisensory integration, facilitating interactions between somatic and non-somatic (e.g. visual) inputs. Spatiotopic mapping therefore offers a multimodal reference frame shared by the different sensory modalities.

Nociceptive stimuli have been shown to interact with visual stimuli, especially with those occurring in the proximity of the limb on which the nociceptive stimuli are applied (De Paepe et al., 2015; De Paepe et al., 2017; De Paepe et al., 2014; Filbrich, Alamia, Blandiaux, et al., 2017; Filbrich et al., 2018; Vanderclausen et al., 2017). Accordingly, nociceptive stimuli are coded according to a peripersonal reference frame (Legrain & Torta, 2015), that is a representation integrating spatial information from the body space and spatial information from the external space immediately surrounding the body (Vallar & Maravita, 2009). Since the peripersonal reference frame is assumed to play an important role in shaping interactions between the body and external objects in contact with the body (Brozzoli et al., 2014), it is hypothesized that spatiotopic mapping of nociceptive stimuli represents an

important process to integrate physical threats in peripersonal representations of the body, therefore optimizing defensive behaviours to protect the body against potential damages (Haggard et al., 2013; Legrain & Torta, 2015).

Based on the present data, we can hypothesize an involvement of premotor and posterior parietal areas in nociception and pain. These cortical regions have been indeed demonstrated to play a role in coding tactile inputs according to spatiotopic reference frames (Azañón, Longo, et al., 2010; Bolognini & Maravita, 2007; Crollen, Lazzouni, et al., 2017; Lloyd et al., 2003; Takahashi et al., 2013; Wada et al., 2012) and in participating in crossmodal interactions within peripersonal frames of reference (Avillac et al., 2005; Brozzoli et al., 2011; Graziano et al., 1997; Makin et al., 2007). Premotor and posterior parietal areas have also been shown to be activated by nociceptive and painful stimuli (Apkarian, Bushnell, Treede, & Zubieta, 2005). However, because their activity was interpreted as related to pain epiphenomena (Apkarian et al., 2005), they received much less attention than other activated cortical areas (Legrain et al., 2011). For instance, a source modelling study of the magnetic fields elicited by nociceptive stimuli suggests a response in the posterior parietal cortex evoked in the same latency range than responses in primary and secondary somatosensory cortices (Nakata et al., 2008). Therefore, considering that the cortical areas classically observed in response to nociceptive and painful stimuli, such as cingulate and operculo-insular cortices, are often seen as belonging to a brain network involved in the detection of any sensory stimuli that might have an impact on the body's integrity (e.g. Legrain et al., 2011), we might hypothesize that premotor and posterior parietal areas are associated to that network with the purpose of mapping physically threatening objects into external space and preparing spatially guided actions in order to protect the body.

The difference in spatially representing nociceptive inputs between early blind and normally sighted people illustrates the neuroplasticity of the nociceptive system and supports the idea that nociception might develop along different tracks, depending on sensory experience through the available sensory systems. This would lead to qualitatively different ways of processing threatening information and perceiving pain. Accordingly, several studies have assumed that early blind people might display differences in their sensitivity to pain as compared to normally sighted individuals (Slimani et al., 2014; Slimani et al., 2015). However, further reports suggested that hypersensitivity to pain in early blindness might be restricted to changes in the processing of C-fibre inputs (Slimani et al., 2016) and would be related to differences in anxiety levels and attention between blind and sighted participants (Holten-Rossing et al., 2018). In the present study, we did not find any difference between the groups of participants regarding Aδ fibre detection thresholds, and blind and sighted participants perceived the nociceptive stimuli similarly. Nonetheless, further studies are needed to better characterize the influence of cross-modal plasticity of the nociceptive system on the perception of pain.

In conclusion, the present experiments emphasized the exteroceptive function of nociception by highlighting the importance of the spatial representations of nociceptive inputs and the role of vision for the development of the nociceptive system. The present study also indicates that visual deprivation can impact the organization of the cortical network underlying nociception, potentially leading to differences in pain processing in early blind people.

Interim summary

In this second study, we showed that even though remapping nociceptive stimuli into spatiotopic coordinates appears crucial to efficiently defend the body against potential threats in external space, this process seems to depend on visual experiences since early blind participants do not seem to rely on such representations when localizing nociceptive stimuli. Early blind participants were indeed insensitive to the posture of the limbs on which nociceptive stimuli were applied during temporal order judgement of radiant heat stimuli.

However, in these previous TOJ tasks, participants had to report the hand that was perceived as being stimulated first. This response mode emphasizes the reliance on somatotopic frames of reference, whereas spatiotopic coordinates are irrelevant to correctly perform the task. Therefore, it might be that the difference between early blind and matched sighted participants would be accounted for by different weight given to the different reference frames in early blind and normally sighted participants based on past sensory experience and/or ongoing cognitive goals. The underlying idea is that the spatiotopic reference frame could be underweighted in early blind participants, consecutive to early visual deprivation, but still used by these participants when the ongoing task stresses its relevance. The next study was thus intended to test such hypothesis. More specifically, we investigated the role of cognitive goals in the spatial representations of nociceptive stimuli in early blind and normally sighted participants by manipulating task instructions so that either the somatotopic or the spatiotopic frame of reference was task-relevant.

Study 3

The influence of visual experience and cognitive goals on the spatial representations of nociceptive stimuli[3]

Abstract

Localizing pain is crucial as it allows detecting which part of the body is being hurt and identifying in its surrounding which stimulus is producing the damage. Nociceptive inputs should therefore be mapped according to somatotopic ("which limb is stimulated?") and spatiotopic representations ("where is the stimulated limb?"). Since the body posture constantly changes, the brain has to realign the different spatial representations, for instance when the arms are crossed with the left hand in the right space and vice versa, in order to adequately guide actions towards the threatening object. Such ability is thought to be dependent on past sensory experience and contextual factors. We compared performances of early blind and normally sighted participants during temporal order judgement tasks. Two nociceptive stimuli were applied, one on each hand, with the hands either uncrossed or crossed. Participants reported which stimulus they perceived as first presented, according to either its location on the body or the position of the stimulated hand, respectively prioritizing anatomy or external space as task-relevant reference frame. Relative to the uncrossed posture, sighted participants' performances were decreased when the hands were crossed, whatever the instruction. Early blind participants' performances were affected by crossing the hands during spatial instruction, but not during anatomical instruction. These results indicate that nociceptive stimuli are automatically coded according to both somatotopic and spatiotopic representations, but the integration of the different spatial reference frames depends on early visual experience and ongoing cognitive goals, illustrating the plasticity and the flexibility of the nociceptive system.

[3] Based on: Vanderclausen, C., Manfron, L., De Volder, A., & Legrain, V. (2020). The influence of visual experience and cognitive goals on the spatial representations of nociceptive stimuli. *Pain 161*, 328-337.

1. Introduction

One of the most relevant yet unresolved questions in pain research is how the brain localizes pain on the body (Legrain & Torta, 2015). Most research so far focused on the ability to localize nociceptive stimuli based on the somatotopic organization of the brain (Andersson, 1997; Baumgärtner et al., 2010; Bingel, Lorenz, et al., 2004; Brooks et al., 2005; Henderson et al., 2007), anatomically mapping the body surface from the ordered projections of receptive fields (Penfield & Rasmussen, 1950). However, since the position of the body limbs in external space constantly changes, such a spatial representation might be inefficient to appropriately localize the harmful stimulus around the body (Legrain & Torta, 2015). The spatiotopic representation considers the relative position of the body part receiving the stimulus in external space (Vallar & Maravita, 2009). Using external space as reference frame, it allows the brain to identify the object in contact with the body, and spatially guide actions towards this object (Brozzoli et al., 2014), such as defensive behaviors (Haggard et al., 2013; Legrain & Torta, 2015).

The spatiotopic representation was evidenced, both for touch and nociception, using temporal order judgment (TOJ) tasks (Badde et al., 2014; Badde et al., 2015; Crollen, Albouy, et al., 2017; Crollen, Lazzouni, et al., 2017; Crollen et al., 2019; De Paepe et al., 2015; Heed & Azañón, 2014; Röder et al., 2004; Sambo et al., 2013; Shore et al., 2002; Yamamoto & Kitazawa, 2001a), during which participants determined the order of appearance of two successive somatosensory stimuli, one applied on each hand. TOJ are typically less accurate when their arms are crossed, as compared to an uncrossed posture, when reporting which hand is perceived as having been stimulated first. That effect is accounted for by the fact that the somatotopic representation mismatches the spatiotopic one (when crossed, a contact on the left hand is coming from the right part of space) (Yamamoto & Kitazawa, 2001a). The sensitivity of TOJ to posture indicates that nociception and touch, in addition to the somatotopic coding, are automatically coded according to spatiotopic coordinates taking into account the location of the hands in external space (Heed & Azañón, 2014). Additionally, crossing the hands decreases the perceived intensity of nociceptive stimuli (Gallace et al., 2011; Torta et al., 2013), highlighting the crucial role of spatial representations in pain processing. Interestingly, this automatic and default spatiotopic coding of somatic stimuli is not innate but shaped by early visual experience (Heed & Azañón, 2014). Accordingly, tactile TOJ performance of congenitally blind individuals is not affected by crossing the hands (Crollen, Albouy, et al., 2017; Crollen, Lazzouni, et al., 2017; Röder et al., 2004), witnessing their preferential reliance on somatotopic representations to localize somatosensory inputs (Crollen & Collignon, 2012). However, recent data showed that tactile TOJ of congenitally blind individuals can be affected by body posture when spatiotopic coordinates are relevant according to the goal of the task (Crollen et al., 2019).

Using TOJ tasks, we investigated the role of (1) past visual experience - by comparing performances of sighted and congenitally blind participants – and (2) ongoing cognitive goals - by manipulating spatial coordinates' priorities through task instructions - in shaping the spatial representations of nociceptive stimuli. Participants responded to the nociceptive stimuli according to either their anatomical location or the spatial location of the stimulated hand. It was hypothesized that body posture would decrease sighted participants' performances whatever the response condition, whereas blind participants' performance would only be affected under spatial instruction. Present data highlight the role of multisensory interactions in shaping nociceptive processing, and suggest that the spatial representations of nociceptive inputs are not fixed, but rather plastic and flexibly adjusted to contextual priorities.

2. Methods

2.1. Participants

Sixteen normally sighted participants took part in Experiment 1. One participant was excluded because she could not properly achieve task requirements (see Analyses). The remaining 15 participants (12 women) had a mean age of 24 years old (*SD*=2.6). Twelve of these participants were right-handed, according to the Flinders Handedness Survey (Nicholls et al., 2013). Ten early blind participants (mean age=38, SD=13; 1 woman; 8 right-handed, 1 ambidextrous) took part in Experiment 2. Ten normally sighted participants were recruited as controls and matched to blind participants according to age and gender (Mean age=37, SD=13; 1 woman, 8 right-handed). None of the participants reported prior history of severe neurological, psychiatric or chronic pain disorders, traumatic injury of the upper limbs in the last six months, cutaneous lesion of the hands' dorsa, regular use of psychotropic drugs, as well as intake of analgesic drugs (e.g. NSAIDS and paracetamol) within the 12 hours preceding the experiment. Normally sighted participants had normal or corrected-to-normal vision, meaning that some of them had mild visual deficits (e.g. mild myopia) completely corrected by glasses or contact lenses. Early blind participants were recruited according to blindness attributed to peripheral deficits (see Table 1 for a complete description of blind participants). They were all considered as totally blind from birth. One of them (participant EB6) had very poor vision from birth and became definitively and totally blind consecutive to enucleation of the eyes at 18 months; he was therefore considered as early blind. Written informed consents were obtained for all participants and all experimental procedures were approved by the biomedical local ethics committee (Comité d'Ethique hospitalo-facultaire, Saint-Luc University Hospital & Université catholique de Louvain, approval number: B403201214265) conformed to the Declaration of Helsinki. All participants received financial compensation for their participation.

Particip-ant	Gend-er; Age	Hande-dness	Profession/ Educational level	Visual percept-ion	Onset of blindness	Cause of blindness	Braille	Cane	Musical instrument	Musical experience	Other
EB1	M;29	R	College degree	None	Birth	Leber congenital amaurosis	Yes	Yes	No	/	Various sport activities
EB2	M;23	R	Some college	None	Birth	Congenital cause (*)	Yes	Yes	No	/	/
EB3	M;41	R	College degree	None	Birth	Leber congenital amaurosis	Yes	Yes	Piano/ organ	>5 years	Torball
EB4	M;41	R	Teacher/ College degree	None	Birth	Anterior chamber cleavage syndrome (Peters syndrome)	Yes	Yes + Dog	Piano/Drums/Flute	>5 years	Hearing aids
EB5	M;32	L	Some college	None	Birth	Hereditary retinal dysplasia	Yes	Yes	Guitar	>4 years	Slight auditory loss
EB6	M;66	R	College degree	None	18 months	Bilateral retinoblastoma	Yes	Yes	Church organ	>9 years	/
EB7	F;36	R	Phone sale until 2006/ Official high school	None	Birth	Severe corneal dysplasia	Few	Yes + Dog	Drums	Only few months	/
EB8	M;33	R	Some college	None	Birth	Persistent hyperplastic primary vitreous involving both eyes	Yes	Yes	Musical keyboard	>10 years	/
EB9	M;50	R	College degree	None	Birth	Leber congenital amaurosis	Yes	Yes	Piano	>3 years	/
EB10	M;26	Ambi	Receptionist/ Official high school	None	Birth	Leber congenital amaurosis	Yes	Yes	Drums, piano, harmonica, guitar	>5 years	ADHD syndrome

Table 1. Description of the early blind participants.

Note: EB: early blind; Age in years; F= female; M= male; R= right; L= left; Ambi=ambidextrous; (*): no additional details available.

2.2. Stimuli and apparatus

Nociceptive stimulations consisted of radiant heat stimuli delivered onto the skin of the hands' dorsa by means of two infrared CO_2 laser stimulators (wavelength 10.6 μm) (Laser Stimulation Device; SIFEC, Ferrières, Belgium). The power of the output stimulation was regulated using a feedback control based on an online measurement of the skin temperature at the site of stimulation by means of a radiometer whose field of view was collinear with the laser beam (see (Churyukanov et al., 2012)). This allows defining specific skin temperature profiles. The laser beams were conducted through 10-m optical fibers. Each fiber ended with a head containing the optics used to collimate the laser beam to 6 mm diameter at the target site. Each laser head was hold upon each participant's hand by means of articulated arms attached to a camera tripod system (Manfrotto, Cassola, Italy). Each laser head was fixed into a clamp attached to a 3-way head affording displacements of the target site of the laser beam perpendicularly oriented to the hand's dorsum by means of several sliders going in all directions (see Figure 1). Laser beams were displaced after each stimulus. Stimuli duration was 100ms. Stimuli were composed of a 10-ms heating ramp dedicated to reach the target temperature, followed by a 90-ms plateau during which the skin temperature was maintained at the target temperature. Heating was then stopped. The target temperature was determined for each participant's hand according to individual activation threshold of nociceptive thinly myelinated Aδ fibers. Thresholds were estimated by means of an adaptive staircase procedure using reaction times (RTs) to discriminate detections triggered by Aδ-fiber inputs (RT < 650 ms) from detections triggered by C-fiber inputs (RT ≥ 650 ms) (Churyukanov et al., 2012). Participants were asked to press a button with the non-stimulated hand as soon as they felt something on the stimulated hand. Any RT equal or superior to 650ms leaded to a temperature increase of 1°C for the next stimulus. On the contrary, any RT inferior to 650ms leaded to a decrease in temperature of 1°C. The procedure started at 46°C and lasted until four reversals were encountered. The mean value of the four temperatures that leaded to a reversal was considered as the threshold. View of the hands was prevented during threshold estimation in sighted participants. Next, 5°C were respectively added to the threshold values of the left and right hands to determine the target temperatures of the experimental stimuli. In order to avoid unbalanced intensity perception between the two hands, and, consequently, attentional shift and perceptual bias towards stimuli of one of the hands (see De Paepe et al., 2015), stimuli temperatures were adapted so that stimuli were perceived as equally intense between the two hands. To these aims, pairs of laser stimuli were delivered, one on each hand, and participants were then asked to report if the stimulations on the two hands were perceived as equally intense and if the sensation elicited on the two hands was similar. If not, temperatures were slightly increased or decreased until similar perceived intensity between the left and the right hands was reached. Such adaptation was needed for 5 of the early blind and 7 of the normally sighted participants, and temperatures were adapted by maximum 2 °C as compared to the initial target values (i.e. threshold + 5°C). Stimuli at such temperature values elicited a clear and vivid pricking sensation perceived as slightly painful. During the

experiment, after each block of stimuli, participants were asked to describe the overall sensation of the stimuli using a list of word descriptors (*not perceived*, *light touch*, *tingling*, *pricking*, *warm*, *burning*), and to rate their overall intensity using a numerical scale (from 0 (*no sensation*) to 10 (*strongest sensation imaginable*)). The list of words was visually presented to the sighted participants and read out loud to the blind participants. Sensation evaluation and intensity rating were only intended to ensure that stimuli were still perceived as pricking and equally intense between the two hands; they were not further analyzed. If necessary, stimuli temperatures were adapted for the upcoming block. Such adaptation was made for only 2 early blind and 5 normally sighted participants using an increase of maximum 1 °C as compared to the initial values.

2.3. Procedure

The same procedure was used for Experiments 1 and 2. Participants were sitting on a chair, hands' palms laying down on a table in front of them. During the uncrossed hands posture condition (see below), the tips of the two index fingers were separated by a distance of ~30cm. During the crossed hands posture condition, the same distance separated the tips of the two forth fingers. Reference fingers were chosen in order to ensure similar distance between the hands during the two posture conditions. Distance between the reference fingers and the edge of the table was of ~40cm (Figure 1). Participants' head was placed in a chin-rest in order to minimize head movement during the experiment. Noises from experimental devices were covered by a white noise played through earphones that the participants wore during the whole experiment. The sighted participants were blindfolded with an eye mask.

Participants were presented with four blocks of 40 trials each. Each trial consisted in pairs of nociceptive stimuli, one applied on each hand, separated by 24 possible stimulus onset asynchronies (SOA): ±10, ±15, ±30, ±45, ±60, ±75, ±90, ±150, ±200, ±400, ±500, ±600ms. Negative values indicated that the left hand was stimulated first, positive values indicated that the right hand was stimulated first. Within each experimental block, the presented SOA for a given trial was selected according to the participant's performance in all the previous trials, using the adaptive *psi* method (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 SOA (see Filbrich, Alamia, Burns, et al., 2017 for further details about the use of the *psi* method in the frame of TOJ tasks). Two of the 4 blocks were performed with the hands in an uncrossed posture and the two other blocks in a crossed posture (i.e. arms crossed over the body midline). Within each posture condition, participants performed one block in which they had to respond according to an anatomical instruction ("*Which hand was stimulated first?*") and one block in which a spatial instruction was used ("*From which side of space came the first stimulus?*"). The order of the *posture* and

instruction conditions was counterbalanced across participants. Participants had to verbally report either on which hand they felt the first stimulus or from which side of space came the first stimulus of the pair, by saying "*left*" or "*right*" out loud. Participants' responses were encoded by the experimenter on a keyboard triggering the next trial 2000 ms later. Time interval between two trials varied from 5 to 10 seconds. During that time interval, the two laser beams were displaced on the participant's hands to avoid skin overheating or habituation. The task was unspeeded but the participants were instructed to be as accurate as possible. No feedback was available regarding their performance in the task.

A practice session preceded the experiment and consisted of 4 blocks of 5 trials each, one block per hand posture and per instruction condition (i.e. uncrossed vs. crossed, and "which hand" vs. "which side of space"). Only two SOA were presented during this practice session, i.e. ±150 and ±200 ms. One block lasted between 10 and 15 minutes. A ten minutes break was imposed to the participants between the experimental blocks. The whole experiment lasted two to three hours, including the threshold measurement, the training session and the experiment per se.

2.4. Measures

Aδ-fiber activation thresholds and stimulation intensities (corresponding to the averaged intensity used for each hand across the experimental blocks, i.e. approximately 5°C added to the Aδ-fiber activation thresholds) were measured in degrees Celcius (°C).

Regarding TOJ performances, the proportion of left stimuli perceived as being presented first was computed as a function of SOA for each experimental condition. To allow comparisons between the different conditions, responses during the crossed hands posture with spatial instruction were coded according to the stimulated hands. For each participant, data were fitted online with the logistic function, i.e. $f(x) = 1/(1+\exp(-\beta(x-\alpha))$, used to derive the measures of interest: the threshold (α) and the slope (β) of the function, estimated trial by trial. The final estimates of the measures thus correspond to the last update of the parameter estimation (Kontsevich & Tyler, 1999). In the present experiments, we were especially interested in the β parameter, which described the noisiness of the participants' responses, i.e. the precision of their responses during the experiment (Kingdom & Prins, 2010). In previous TOJ studies classically using the method of constant stimuli (i.e. each of the SOA is presented a fixed number of times), the slope was used to derive the just noticeable difference which denotes the minimal SOA value needed for the participants to correctly perceive the order of the two stimuli in a certain percentage of trials (see De Paepe et al., 2014; Heed & Azañón, 2014). The slope and other derived measures are classically used to index the impact of posture on TOJ performances both in sighted and blind participants: steeper is the fitted function, better is the participants' performance in the task (Badde et al.,

2014; Badde et al., 2015; Crollen, Albouy, et al., 2017; Crollen, Lazzouni, et al., 2017; Crollen et al., 2019; De Paepe et al., 2015; Heed & Azañón, 2014; Röder et al., 2004; Sambo et al., 2013; Shore et al., 2002; Yamamoto & Kitazawa, 2001a). The α is the threshold of the function and corresponds to the SOA at which the participants reported the two stimuli as occurring first equally often (i.e. the probability of 0.5). Accordingly, this measure corresponds to the point of subjective simultaneity (PSS) defining the amount of time (in milliseconds) with which one of the stimuli has to precede or follow the other one in order for the two stimuli to be perceived as occurring simultaneously (De Paepe et al., 2014). Although this parameter was not relevant for our research questions, it was taken into consideration in order to investigate the presence of potential biases towards the perception of the stimuli applied to one of the hands, which could have influenced the estimation of the slope. Indeed, in the frame of the adaptive *psi* method, the measures of the threshold and the slope are not completely independent and a large PSS value, indicating a bias in the perception of one of the two stimuli, could reduce the noisiness of the participant's responses because of the predictability of these responses. Since the *psi* method was based on a bayesian approach, a prior probability distribution needed to be postulated, based on previous knowledge regarding the values of the parameter of interest. For the present experiments, the prior distributions were set at 0 ±20 and 0.06±0.6 for the α and the β parameters, respectively (Filbrich, Alamia, Burns, et al., 2017).

Since we used an adaptive method, all the participants were not presented with the same sequence of SOA during the experiment, as it was adapted to each participant's performance. Therefore, a third non-standard parameter was derived a posteriori from the present data: the mode of the presented SOA. This corresponded to the value of the SOA, among all the possible SOA, that was the most frequently presented to a given participant during a particular condition of the experiment (in milliseconds). The mode of the presented SOA characterizes the probability distribution of the SOA values that were actually chosen for each participant and how this probability distribution was influenced by the experimental variables during the adaptation procedure of the method. Indeed, a significant difference between the modes of two experimental conditions would indicate that the SOA the most frequently presented to the participant was larger in one condition relative to the other for the participant to be able to correctly determine the temporal order of the stimuli. In this case, a larger mode value would indicate that the task was more difficult to perform in this condition as compared to the other one. As such, the mode of the presented SOA was used as complementary index of participants' performance.

2.5. Analyses

Participants' data were excluded from statistical analyses if the threshold and slope of the psychometric function could not be reliably estimated during the 40 trials of one or several experimental conditions (i.e. their respective estimates did not converge on a stable

value on the last trials), indexing that their performance was too inconsistent and below chance level. Analyses were first performed on the Aδ-fibers activation threshold and stimuli intensity values, to ensure that no difference between hands or groups regarding these factors could have influenced the results. In Experiment 1, comparison of activation thresholds and stimulation intensities was made using paired t-tests with *hand* as the factor (left vs. right). In Experiment 2, we used an analysis of variance (ANOVA) for repeated measures with adding the group as second factor (sighted vs. blind).

Regarding TOJ values, one-sample t-tests were first performed to compare the PSS values to 0 for each condition of the *posture* and *instruction* factors, and each of the three groups, in order to examine the presence of potential biases. Next, the effects of the different factors on the PSS, slope and mode of the SOAs values were compared by means of analyses of variance (ANOVA) for repeated measures. For Experiment 1, *posture* (uncrossed vs. crossed) and *instruction* (anatomical vs. spatial) were used as within-participants factors. For Experiment 2, *group* (early blind vs. normally sighted) was added as a between-participants factor. Greenhouse-Geisser corrections were used if necessary. Contrast analyses were conducted to detail significant interactions between two or more factors. Effect sizes were measured using partial Eta squared for ANOVA and Cohen's d for t-tests. Significance level was set at $p \leq .050$.

3. Results

3.1. Experiment 1

Threshold and intensity values

Paired sample t-tests revealed no difference between the Aδ-fiber activation threshold values of the left (M=47.80°C, SD=1.52°C) vs. the right hand (M=47.40°C, SD=1.77°C) in the sighted participants in Experiment 1 (t(14)=0.72, p=.442, d=.26). Similarly, no difference were found regarding the mean intensity of nociceptive stimuli between the left (M=52.55°C, SD=1.98°C) and the right (M=52.34°C, SD=1.98°C) hands (t(14)=0.39, p=.702, d=0.26).

TOJ values

Results of Experiment 1 are illustrated in Figure 2. The t-tests showed that none of the PSS values from each posture and instruction conditions was significantly different from 0 (all t(14)≤.977, p≥.345, d≤.25). The ANOVA performed on the PSS values revealed neither a significant main effect of the posture (F(1,14)=.01, p=.941, η^2_p<.01), nor of the instruction (F(1,14)=.56, p=.468, η^2_p=.04), nor significant interaction between the two factors (F(1,14)<.01, p=.970, η^2_p<.01).

The analysis of the slope values showed a significant main effect of the posture (F(1,14)=37.34, p<.001, η^2_p=.73) with no significant effect of the instruction (F(1,14=1.54, p=.235, η^2_p=.10) and no significant interaction between both factors (F(1,14)=.33, p=.577, η^2_p=.02). This indicated that the slope values in the crossed posture (M=.01, SD=.01) was significantly lower than those in the uncrossed posture (M=.03, SD=.01), irrespective of the instruction.

The analysis of the mode values did not reveal any significant effect of the posture (F(1,14)=2.01, p=.178, η^2_p=.13), of the instruction (F(1,14)=.01, p=.921, η^2_p<.01), nor any significant interaction between the two factors (F(1,14)=.08, p=.781, η^2_p<.01).

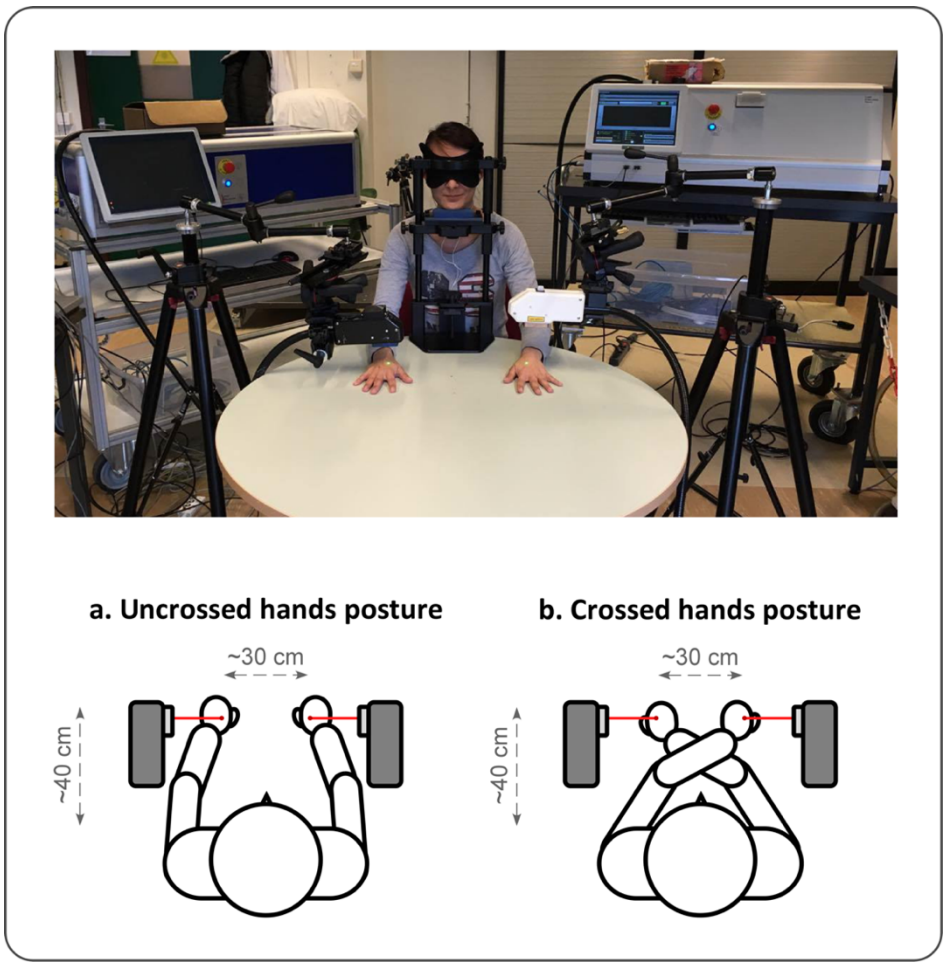


Figure 1. ***Experimental design of Experiments 1 and 2.*** *Two temperature-controlled CO_2 laser stimulators were used to activate Aδ-fibers. Laser beams were displaced after each trials on the hands' dorsa using camera tripod systems. Temporal order judgement tasks were performed with the hands in either an uncrossed (A) or a crossed (B) posture. Sighted participants performed the tasks blindfolded. Permission for publishing was obtained from the participant appearing in this picture.*

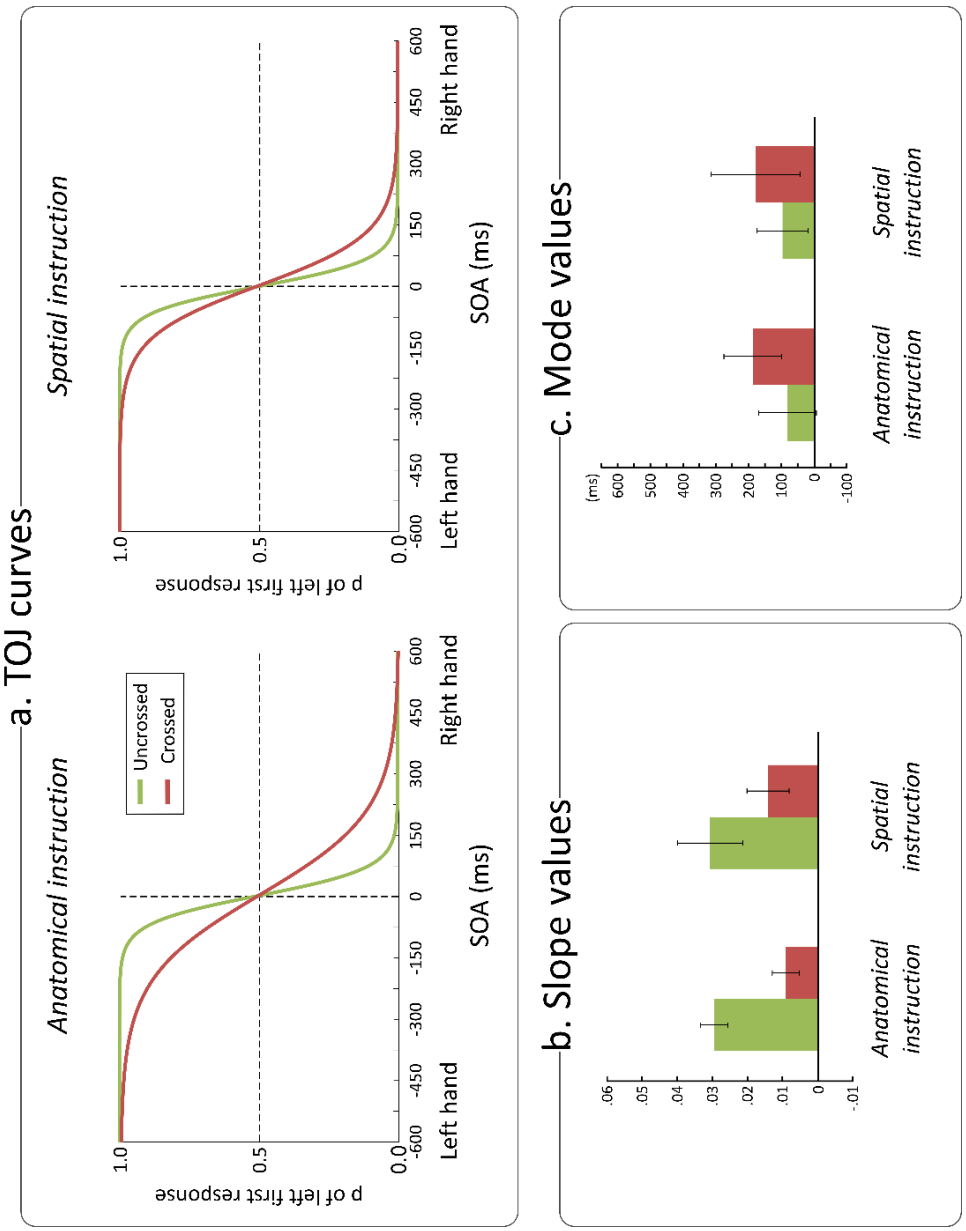

a. TOJ curves
Anatomical instruction
Spatial instruction
Uncrossed
Crossed
p of left first response
1.0
0.5
0.0
-600
-450
-300
-150
0
150
300
450
600
Left hand
Right hand
SOA (ms)
b. Slope values
c. Mode values
(ms)
Anatomical instruction
Spatial instruction

Figure 2. ***Nociceptive TOJ tasks of Experiment 1.*** *(a) Fitted curves of the psychometric functions from the data of 15 normally sighted participants according to the posture (i.e. uncrossed vs. crossed) and according to the instruction (i.e. anatomical vs. spatial) conditions. The x-axis represents the different possible SOAs. A negative value indicates that the left hand was stimulated first and a positive value indicates that the right hand was stimulated first. The y-axis refers to the proportion of trials in which the nociceptive stimulus applied on the left hand was perceived as being presented first. The lines represent the fitted curves computed by the adaptive algorithm for the uncrossed (green) and crossed (red) conditions respectively. (b) Averaged slope values for each posture and instruction condition. The mean of the slope values was significantly lower in the crossed as compared to the uncrossed condition, whatever the instruction condition. (c) Averaged mode values of the presented SOA according to each posture and instruction condition. Error bars represent confidence intervals calculated according to Cousineau's method for within-subject designs (Cousineau, 2005).*

3.2. Experiment 2

Threshold and intensity values

The ANOVA performed on the Aδ-fibers activation thresholds did not show significant effect of the hand ($F(1,18)=.74$, $p=.400$, $\eta^2_p=.04$), of the group ($F(1,18)=0.33$, $p=.574$, $\eta^2_p=.02$), nor any significant interaction between the two factors ($F(1,18)=.24$, $p=.628$, $\eta^2_p=.01$). Early blind participants thus had a similar Aδ-fibers activation threshold (M=49.75°C, SD=3.91°C) than the sighted participants (M=50.55°C, SD=2.06°C). Similar results were obtained regarding the stimulation intensities since the analyses showed neither significant effect of the hand ($F(1,18)=2.04$, $p=.171$, $\eta^2_p=.10$), nor significant effect of the group ($F(1,18)=.85$, $p=.369$, $\eta^2_p=.01$), or significant interaction between the two factors ($F(1,18)=.17$, $p=.688$, $\eta^2_p=.01$). The averaged stimulation intensity used for the early blind group (M=54.77°C, SD=2.77°C) was comparable to that for the sighted group (M=55.73°C, SD=1.79°C).

TOJ values

Results of Experiment 2 are illustrated in Figures 3 and 4. None of the PSS values were significantly different from 0 in the early blind group (all $t(9)\leq-.54$, all $p\geq.224$, $d\leq.17$). In the sighted group, most of the PSS values were not significantly different from 0 (all $t\leq-1.91$, $p\geq.088$, $d\leq.60$), except for the PSS value in the uncrossed posture with anatomical instruction ($t(9)=-7.02$, $p<.001$, $d=2.22$). With an averaged value of -10.12 ms (SD=4.56 ms), this

indicated that their judgments were slightly biased towards the right hand in this condition. The ANOVA did not reveal significant main effect neither of the posture ($F(1,18)=2.22$, $p=.154$, $\eta^2_p=.11$) nor of the instruction ($F(1,18)=1.96$, $p=.179$, $\eta^2_p=.10$). In contrast, this analysis showed a significant effect of the group ($F(1,18)=6.25$, $p=.022$, $\eta^2_p=.26$), indicating that the PSS values of normally sighted participant were more negative (M=-5.60ms, SD=7.60ms) that those of the early blind participants (M=1.68ms, SD=10.32ms). In addition, a significant interaction between the *posture* and the *instruction* factors was observed ($F(1,18)=5.60$, $p=.029$, $\eta^2_p=.24$). Contrast analyses showed that during the uncrossed posture, the PSS value in the anatomical instruction condition (M=-6.05ms, SD=9.57ms) was larger than that of the spatial instruction condition (M=-0.80ms, SD=10.70ms; $t(19)=-2.15$, $p=.045$, d=.48). Such difference was not significant during the crossed posture ($t(19)=.54$, $p=.593$, d=.12). None of the other possible interactions was significant (all $F(1,18)\leq.22$, all $p\geq.643$, $\eta^2_p\leq.01$).

Regarding the slope values, the ANOVA showed a significant main effect of the group ($F(1,18)=4.80$, $p=.042$, $\eta^2_p=.21$), a significant main effect of the posture ($F(1,18)=27.15$, $p<.001$, $\eta^2_p=.60$), a significant main effect of the instruction ($F(1,18)=4.68$, $p=.044$, $\eta^2_p=.21$), and a significant interaction between *posture* and *instruction* ($F(1,18)=7.23$, $p=.015$, $\eta^2_p=.29$). We also observed a significant triple interaction between all factors ($F(1,18)=6.47$, $p=.020$, $\eta^2_p=.26$). None of the other interactions was significant (all $F(1,18)\leq.21$, all $p\geq.653$, $\eta^2_p\leq.01$). Next, analyses were run separately in each group of participants with *posture* and *instruction* as within factors. For the early blind participants, we observed a significant main effect of the posture ($F(1,9=6.45$, $p=.032$, $\eta^2_p=.42$), a significant interaction between the *posture* and *instruction* factors ($F(1,9)=8.27$, $p=.018$, $\eta^2_p=.48$), but no significant effect of the instruction ($F(1,9)=2.26$, $p=.167$, $\eta^2_p=.20$). Contrast analyses revealed no significant difference between the two postures in the anatomical instruction condition ($t(9)=-1.00$, $p=.343$, d=0.22; M±SD uncrossed=0.03±0.01, M±SD crossed=0.03±0.02). On the contrary, such difference was significant in the spatial instruction condition ($t(9)=3.08$, $p=.013$, d=0.68). Slope values were indeed smaller in the crossed posture (M=0.01, SD=0.01) than in the uncrossed posture conditions (M=0.04, SD=0.03) in the early blind group. In contrast, in the normally sighted group, only a significant main effect of the posture was observed ($F(1,9)=64.82$, $p<.001$, $\eta^2_p=.88$) with neither significant effect of the instruction ($F(1,9)=2.44$, $p=.150$, $\eta^2_p=.21$) nor significant interaction between the two factors ($F(1,9)=.03$, $p=.87$, $\eta^2_p<.01$). For the normally sighted participants, the slope values in the crossed posture condition (M=0.01, SD=0.00) were significantly lower than those in the uncrossed posture condition (M=0.02, SD=0.01). To summarize, results showed that the posture affected performances of the normally sighted participants whatever the instruction condition, whereas early blind participants' performance was only affected by the crossed posture when a spatial response was required.

Finally, the ANOVA performed on the mode of the presented SOA values showed a significant main effect of the posture ($F(1,18)=34.3$, $p<.001$, $\eta^2_p=.66$), a significant main effect of the group ($F(1,18)=14.26$, $p=.001$, $\eta^2_p=.44$) and a significant interaction between

these two factors ($F(1,18)=10.95$, $p=.004$, $\eta^2_p=.38$). None of the other comparisons was significant (all $F(1,18)\leq1.46$, all $p\geq.243$, all $\eta^2_p\leq.08$). Analyses were then run separately in each group. In the early blind group, the ANOVA showed neither significant effect of the posture ($F(1,9)=3.13$, $p=.11$, $\eta^2_p=.26$), nor of the instruction ($F(1,9)=3.19$, $p=.11$, $\eta^2_p=.26$). The interaction between these two factors was just a bit above significance level ($F(1,9)=4.01$, $p=.070$, $\eta^2_p=.31$). In the sighted group, a significant effect of the posture was observed ($F(1,9)=43.67$, $p<.001$, $\eta^2_p=.83$), the mode value in crossed posture being higher (M=420.50ms, SD=137.24ms) than that in the uncrossed posture condition (M=136.25ms, SD=122.24ms). The effect of the instruction did not reach significance ($F(1,9)=.01$, $p=.920$, $\eta^2_p<.01$), neither the interaction between the two factors ($F(1,9)=.02$, $p=.900$, $\eta^2_p<.01$).

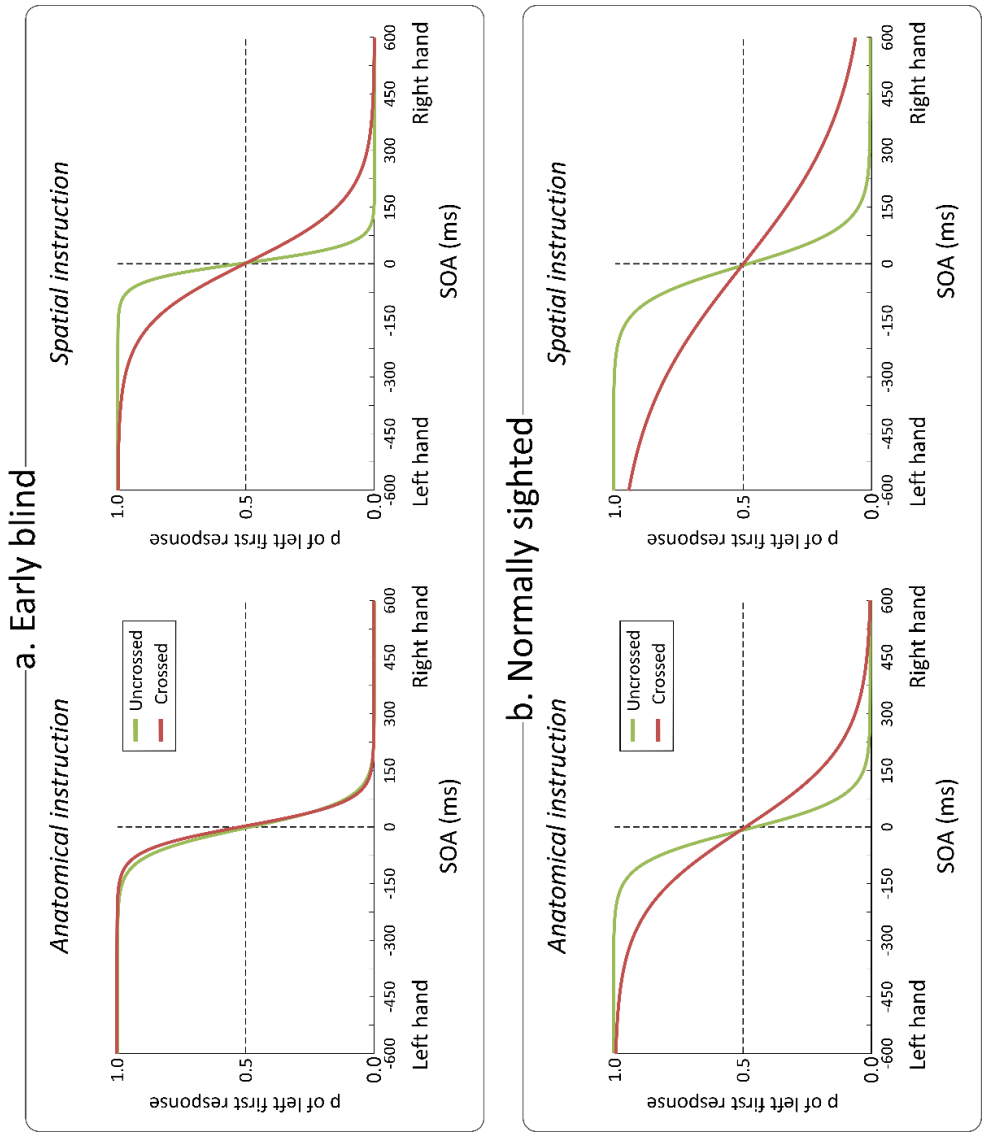

a. Early blind
b. Normally sighted
Anatomical instruction
Spatial instruction
Uncrossed
Crossed
p of left first response
1.0
0.5
0.0
-600
-450
-300
-150
0
150
300
450
600
Left hand
Right hand
SOA (ms)

Figure 3. ***Nociceptive TOJ tasks of Experiment 2.*** *The figure illustrates the fitted curves of the psychometric functions from data of 10 early blind (a.) and 10 sighted participants (b.) according to the posture (uncrossed in green vs. crossed in red) and the instruction conditions (anatomical on the left vs. spatial on the right side of the figure). The x-axis represents the different possible SOAs. A negative value indicates that the left hand was stimulated first and a positive value indicates that the right hand was stimulated first. The y-axis refers to the proportion of trials in which the nociceptive stimulus applied on the left hand was perceived as being presented first.*

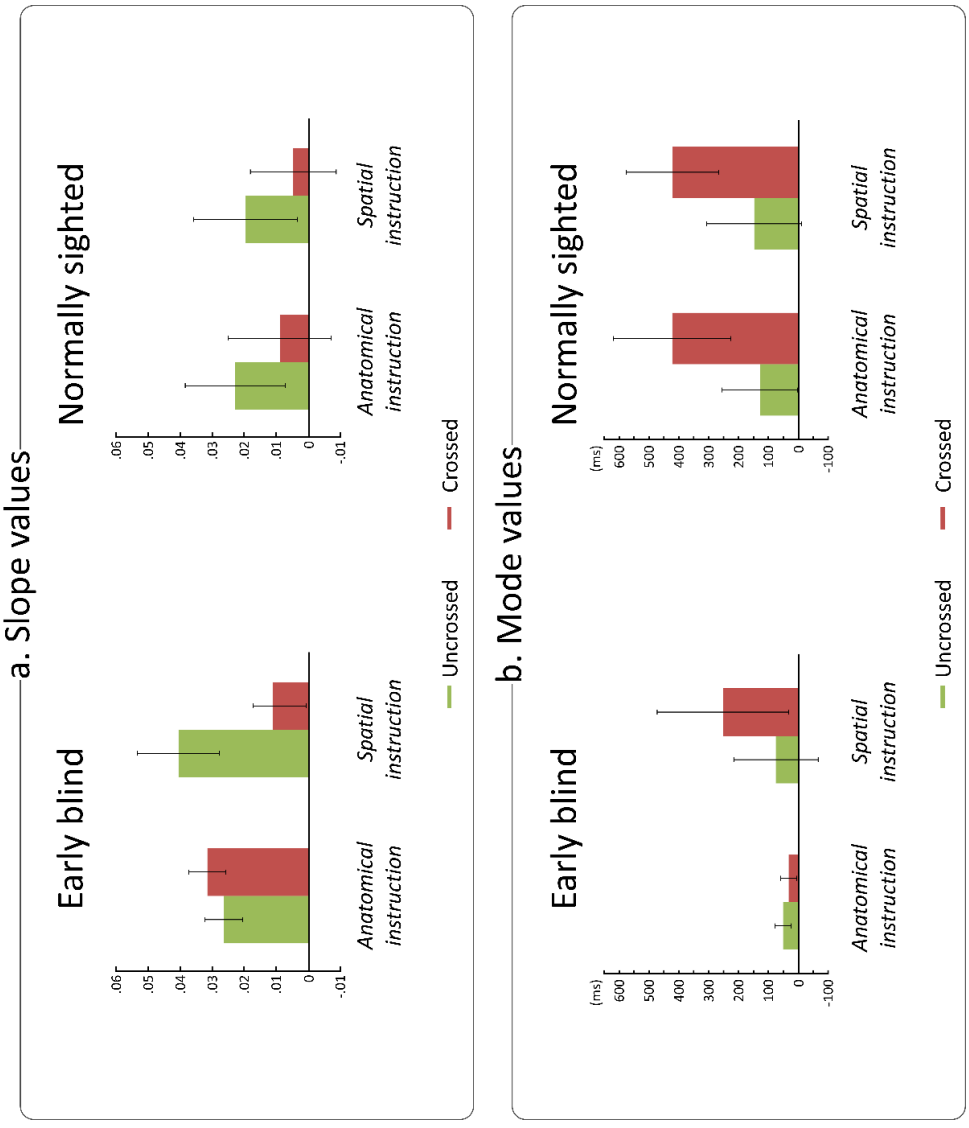

a. Slope values
Early blind
Normally sighted
.06
.05
.04
.03
.02
.01
0
-.01
Anatomical instruction
Spatial instruction
Uncrossed
Crossed
b. Mode values
Early blind
Normally sighted
(ms)
600
500
400
300
200
100
0
-100
Anatomical instruction
Spatial instruction
Uncrossed
Crossed

Figure 4. ***Slope and mode values of the nociceptive TOJ tasks of Experiment 2.*** *(a) Mean slope values for each posture (uncrossed in green vs. crossed in red) and instruction conditions (anatomical on the left vs. spatial on the right part of the graphs) for respectively the early blind (left) and normally sighted participants (right). In the early blind group, a lower averaged slope value was found in the crossed as compared to the uncrossed posture condition in the spatial instruction condition, whereas the performance of this group did not significantly differ according to the posture in the anatomical instruction condition. Conversely, in the sighted group, the averaged slope value was significantly lower in the crossed as compared to the uncrossed posture condition, whatever the instruction condition. (b) Mean values of the mode of the presented SOA for each posture (uncrossed in green vs. crossed in red) and instruction conditions (anatomical on the left vs. spatial on the right part of the graphs) for respectively the early blind (left) and normally sighted participants (right). Whereas no significant difference between the conditions was evidenced in the blind group, significantly higher mode values were found in the sighted group in the crossed as compared to the uncrossed posture condition, irrespective of the instructions. Error bars represent confidence intervals calculated according to Cousineau's method for within-subject designs (Cousineau, 2005).*

4. Discussion

The objectives of the present experiments were to investigate the role of visual experience and cognitive goals in shaping the spatial representations of nociceptive stimuli. To this aim, we compared performances of normally sighted and early blind participants during temporal order judgments of nociceptive stimuli, during which instructions favoured to use either an anatomical or a spatial representation. Importantly, TOJ tasks were performed with the hands either uncrossed or crossed over body midline, the latter condition being intended to generate a mismatch between somatotopic and spatiotopic representations. Results showed that sighted participants' performances were decreased in the crossed hands posture independently of which reference frame was task-relevant. On the contrary, performances of early blind participants were only affected by crossing the hands when they were requested to use a spatial response, while their performance was insensitive to the posture under anatomical instruction.

Influence of crossing the hands during cognitive tasks has been recurrently described in normally sighted people for both tactile and nociceptive stimuli (Badde et al., 2014; Badde et al., 2015; Crollen, Albouy, et al., 2017; Crollen, Lazzouni, et al., 2017; Crollen et al., 2019; De Paepe et al., 2015; Heed & Azañón, 2014; Röder et al., 2004; Sambo et al., 2013; Shore et al., 2002; Yamamoto & Kitazawa, 2001a). Such an effect was interpreted as reflecting the ability of the brain to code the spatial location of somatosensory inputs according to spatiotopic reference frames (Heed & Azañón, 2014). Spatiotopic mapping has also been suggested to represent an important process, affording a common spatial framework for inputs from somatic and extra-somatic sensory modalities to be integrated in a peripersonal representation of the body (De Paepe et al., 2015; Filbrich et al., 2018). In this line, nociceptive and visual stimuli would optimize detection and reaction against physical threats around the body (Legrain & Torta, 2015). Together, this would suggest a default and major role of spatiotopic representations over somatotopic ones in the perception of somatosensory stimuli. However, the present data offers a new insight on this assumed dominance.

In normally sighted participants, results confirmed that nociceptive stimuli were mapped into spatiotopic representations taking body posture into account, in addition to be coded according to somatotopic representations (De Paepe et al., 2015; Sambo et al., 2013). Since TOJ performance was similarly impaired under the two different task instructions, this indicated that both somatotopic and spatiotopic representations might be co-activated by default during spatial localization processing of nociceptive inputs. Hence, adapting cognitive goals by changing task instruction to stress external space-based coordinates was not enough to give advantage to the spatiotopic frame of reference and attenuate the crossing hands deficit in our experiments (see Crollen et al., 2019 for similar results with tactile stimuli). On the contrary, studies on tactile processing suggested that spatial coding of somatosensory stimuli was actually weighted depending on task demands and cognitive goals

(Badde & Heed, 2016; Badde et al., 2014; Badde et al., 2015; Gallace et al., 2008). Specifically, the results of these experiments indicated that the weight accorded to the spatiotopic representation could be attenuated under some conditions, but externally defined coordinates still had a robust influence on the participants' responses during tactile processing. Accordingly, the present data suggest that nociceptive stimuli are automatically coded according to both somatotopic and spatiotopic reference frames, but that the weight respectively given to each reference frames during the localization processing of nociception would be more dependent on contextual factors such as cognitive goals (Badde et al., 2016; Badde et al., 2014).

Additionally, results in early blind participants indicated that the assumed more weighted activation of the spatiotopic reference frame of nociceptive stimuli might be driven by early visual experience. Indeed, a default advantage of somatotopic representations in congenitally blind people during touch localization had been recurrently suggested by means of behavioural as well as electrophysiological and neuroimaging data (Crollen & Collignon, 2012; Crollen, Lazzouni, et al., 2017; Röder et al., 2008). However, regarding nociception and pain, being able to consider the position of the limbs in external space is of primary importance to protect the body from potential physical threats. Then, any individual should be able to take such spatial information into account, if not automatically, at least when it is relevant for the ongoing situation. Accordingly, we observed that a crossing hands deficit emerged in early blind participants in the spatial instruction condition, confirming that early blind participants were able to activate and use spatiotopic representations. Indeed, this finding suggests that the spatial representations at play when localizing nociceptive events could be adapted according to the task requirements. We showed that making external space relevant by changing the instruction was sufficient to highlight the use of the spatiotopic reference frame in this group during TOJ tasks. These data are in line with a very recent study having shown the exact same pattern of results using a tactile TOJ task in early blind and normally sighted participants (Crollen et al., 2019). Other studies showed that, in tactile motor coordination tasks, spatial external coordinates were actually used by congenitally blinds when task demands prioritized the external space reference (Crollen, Albouy, et al., 2017; Heed & Röder, 2014). Taken together, these studies suggest a differential balance between the activation by default of the somatotopic and spatiotopic frames of reference in normally sighted and early blind participants during somatosensory perception (Crollen, Albouy, et al., 2017; Crollen, Lazzouni, et al., 2017; Crollen et al., 2019). Following this idea, early blind individuals might have better abilities to inhibit the spatial responses when it is irrelevant for the ongoing activity, while formatting responses according to external space would be resistant to inhibition in sighted people, even when irrelevant to current behavioural goals.

The present studies therefore suggest that early visual experience shapes the way spatiotopic mapping of nociceptive stimuli develops, resulting in qualitatively different ways

of processing nociception and pain in adulthood between early blinds and normally sighted individuals. Perhaps as a result, some quantitative differences were observed between congenitally blind and normally sighted individuals regarding the perception of pain. For instance, Slimani et al. (Slimani et al., 2013; Slimani et al., 2016) observed lower thresholds for heat and cold pain, as well as faster reaction times to stimulations mediated by C-, but not Aδ-, fibers in congenitally blinds as compared to sighted controls. These authors have linked this "*hypersensitivity*" to pain in this population to higher levels of anxiety and enhanced attention to painful stimuli (Holten-Rossing et al., 2018). Altogether, the present and previous experiments on early blindness highlight that the plasticity of the nociceptive system depends on early sensory experience from any sensory modalities, including non-somatic ones.

Our studies suggest that mechanisms underlying spatial representations of nociceptive inputs are similar to those evidenced for touch (Heed & Azañón, 2014). However, while the cortical substrates underlying the spatial representation of touch were extensively studied (Avillac et al., 2005; Azañón, Longo, et al., 2010; Bolognini & Maravita, 2007; Brozzoli et al., 2011; Crollen, Lazzouni, et al., 2017; Graziano et al., 1997; Lloyd et al., 2003; Soto-Faraco & Azañón, 2013; Takahashi et al., 2013; Wada et al., 2012), they are still poorly understood for nociception (Legrain & Torta, 2015; Torta et al., 2013). Premotor and posterior parietal brain areas have been largely shown to be involved in the spatial coding of tactile stimuli (Azañón, Longo, et al., 2010; Bolognini & Maravita, 2007; Crollen, Lazzouni, et al., 2017; Lloyd et al., 2003; Takahashi et al., 2013; Wada et al., 2012) and in visuo-tactile crossmodal interactions (Avillac et al., 2005; Brozzoli et al., 2011; Graziano et al., 1997; Lloyd et al., 2003; Makin et al., 2007). Nociceptive and painful stimuli were also shown to elicit brain activity in premotor and posterior parietal areas (see review in Apkarian et al., 2005). On the other hand, it was suggested that the cortical regions classically observed in response to nociceptive and painful stimuli, such as cingulate and operculo-insular cortices, were usually associated to a broader brain network involved in the detection of any sensory stimulus that might have an impact on the body's integrity (e.g. Legrain et al., 2011). Therefore, future studies should investigate the involvement of premotor and posterior parietal areas in mapping nociceptive inputs according to external spatial coordinates and in preparing spatially guided actions to protect the body's integrity.

The present data also offer a new insight on the so-called "*crossing hands analgesia*" according to which crossing the hands over the body midline decreases cortical responses to nociceptive stimuli and the perception of their intensity (Gallace et al., 2011; Torta et al., 2013). Gallace et al. (Gallace et al., 2011) interpreted this effect as reflecting a disruption of nociceptive processing in the brain. Accordingly, during unusual body posture such as when the arms are crossed, privileged connections with the nociceptive system would not be engaged, especially those involved in spatial perception, resulting in a decrease of the cortical responses, which would in turns impede the processing of the intensity and its perception. However, based on present results, we propose an alternative hypothesis according to which,

when the different reference frames are conflicting, the less accurate TOJ performance would reflect the effort that the brain has to make to prioritize the relevant reference frame and inhibit the irrelevant spatial code. We therefore hypothesize that the so-called analgesic effect observed during the crossed hands posture results from a lack of processing resources left out by the competition between the different spatial representations. In other words, resolving the conflict between the different reference frames and selecting the relevant spatial response requests attentional resources (Badde et al., 2014) that are less available to process other stimulus features such as its intensity. Manipulating the attentional load was indeed shown to modulate nociceptive processing (Legrain, Crombez, Plaghki, & Mouraux, 2013).

In conclusion, the present studies emphasize that localization of nociceptive stimuli is based on multiple mapping systems taking into account both the space of the body and external space. We showed that activating the different spatial reference frames is automatic but disentangling between the different spatial responses where there is a mismatch requires effort and depends on developmental and contextual weighting. Further experiments will be needed to disclose the cortical mechanisms underlying the spatial representations of pain and their impairments during pathological pain (Filbrich, Alamia, Verfaille, et al., 2017).

Interim summary

In this third study, we showed that early blind individuals, even though they seem to mostly rely on the somatotopic reference frame to localize nociceptive stimuli, are able to respond to the location of nociceptive stimuli according to a spatiotopic reference frame when it is relevant for the ongoing goal. This suggests that early visual deprivation impacts the default weight given to spatiotopic representations.

In the following study, we aimed to test whether the conflict generated by the different spatial representations of nociceptive stimuli when the posture of the body is changed could influence their perceived intensity. Indeed, it was shown in previous experiments that crossing the hands can change the painfulness induced by nociceptive stimuli, suggesting that cortical activity underlying spatial perception of nociceptive inputs represents important processing steps of the perception of nociceptive stimuli. However, we hypothesized that it is not the processing of the spatial features of the nociceptive stimuli per se that influences the subjective intensity ratings, but, instead, the cognitive effort put in resolving the conflict between the different spatial representations when the somatotopic and the spatiotopic reference frames are misaligned when the hands are crossed.

The next study was intended to test such hypothesis by taking advantage of the results that we observed in the previous studies of this thesis in both early blind and normally sighted people. Indeed, as early blind participants seem to be less sensitive to such conflict between the spatial representations, we assumed that an influence of body posture on subjective intensity ratings of nociceptive stimuli would be only observed in normally sighted participants but not in early blind participants.

Study 4

Investigating the effect of crossing the hands on the perceived intensity of pain in normally sighted and early blind individuals

Abstract

Considering the posture of a body in pain is crucial to be able to defend the body against the external threatening stimulus that caused the pain. Accordingly, nociceptive inputs have been shown to be automatically mapped into spatiotopic frames of reference taking the position of the stimulated body part in external space into account, in addition to their coding according to somatotopic coordinates. Such spatiotopic reference frames have, for instance, been evidenced by showing that crossing the hands over the body midline impairs the localization of nociceptive inputs applied on the hands, suggesting a conflict between the spatiotopic and somatotopic reference frames. Crossing the arms has also been associated with reduced cortical responses and decreased perceived intensity elicited by the nociceptive stimuli. In the present study, we investigated whether this latter effect could be accounted for by the cognitive effort associated with the realignment of the somatotopic and spatiotopic reference frames which are put into conflict (i.e. misaligned) when the hands are crossed. The idea is that this cognitive effort would leave less cortical resources available to process pain intensity. Previous studies have suggested that the spatiotopic remapping of nociceptive stimuli would depend on early visual experience. Therefore, we should not observe an effect of hands crossing on the intensity perception in early blind individuals. To test this, a first experiment was intended to replicate this effect in a group of healthy young volunteers, while a second experiment was dedicated to assess the presence of potential differences regarding this effect between early blind and matched sighted participants. While an effect of the posture on intensity ratings of nociceptive stimuli was observed in the first experiment, this finding was neither replicated in the normally sighted participants in the second experiment, nor in the early blind group. The discrepancy between the results of our two experiments could be partially explained by several factors related to the methodology of the present study, but mostly encourages future studies to investigate the potential factors underlying the variability of the effect of crossing the hands on the intensity perception of pain in order to better characterize this phenomenon.

1. Introduction

Pain is an unpleasant sensory and emotional experience usually triggered by the activity of the nociceptive system, a neural system involved in coding, transmitting and processing noxious information, that is, information about stimuli that have the potential to damage the body (IASP, 1994; Kandel et al., 2013). However, recent studies have shown that at the cortical level, painful nociceptive stimuli induce activity in a large-scale network that integrate different sources of sensory inputs, even those that are not conveyed through the nociceptive pathways, e.g. tactile and visual stimuli (e.g. Mouraux et al., 2011; Mouraux & Iannetti, 2009). Therefore, it was suggested that painful nociceptive stimuli are processed in a multimodal cortical system that is specifically involved in processing sensory stimuli that are the most meaningful for homeostasis in order to prompt adaptive behaviors (Iannetti & Mouraux, 2010; Legrain et al., 2011). Accordingly, it has been shown that cortical responses to nociceptive stimuli and the associated perception of pain are modulated by the body posture (i.e. proprioceptive information) (Gallace et al., 2011; Moseley et al., 2012; Torta et al., 2013; Valentini et al., 2015) and the vision of the body limb onto the nociceptive stimuli are applied (e.g. Longo et al., 2009; Longo et al., 2012; Mancini, Longo, Kammers, et al., 2011; Torta et al., 2015).

For instance, Moseley et al. (2012) have demonstrated that placing the affected (i.e. painful) limb of patients with complex regional pain syndrome in the other side of space (i.e. the side of the healthy limb) during 10 minutes reduced the pain felt in the affected limb. In healthy participant, reduced perceived intensity of tactile and nociceptive stimuli were observed when participants received the stimuli while crossing the hands, as compared to an uncrossed posture (Gallace et al., 2011; Torta et al., 2013). These results were associated with a decreased amplitude of the late-latency components of the event-related potentials (ERPs) elicited by tactile and laser stimuli (Gallace et al., 2011). Therefore, the authors interpreted their results as reflecting a disruption of the spatial processing of the somatosensory stimuli in the brain. More specifically, they assumed that because the somatotopic representation of the hand is often activated together with the corresponding space-based representation (i.e. a stimulation of the left hand often occurs in the left side of space in everyday life), processing somatic inputs when the posture of the body (i.e. proprioceptive information) matches a "default" mode would involve enhanced and highly effective connections. In contrast, when the body is in an unusual posture, such as when the hands are crossed and that a stimulation on the left hand occurs in the right part of space, such privileged connections would not be engaged, resulting in an impediment of the sensory signal which would be in turn responsible for the decreased perceived intensity of the stimuli (Gallace et al., 2011). Using fMRI, Torta et al. (2013) associated the effect of crossing the arms on the perceived intensity of nociceptive stimuli to an increased activity in the ACC, the insula, as well as the medial frontal gyrus. Therefore, because of the involvement of the frontal lobe, these authors alternatively hypothesized that the reduced intensity perception

would rather reflect a consequence of a greater cognitive load associated with the crossed hands posture. As a result, limited attentional resources would be left available to process other characteristics of the stimulus such as its intensity. In line with this attentional account, a recent ERP study manipulated selectively the orientation of spatial attention toward one of the hands on which painful electrical stimuli were applied. This study showed that crossing the hands reduced the impact of spatial attention on the magnitude of the somatosensory ERPs (Świder et al., 2017).

It is therefore suggested that processing spatial information of nociceptive inputs might involve complex cortical operations requiring attentional resources. Indeed, it has been shown that the spatial perception of somatic inputs implies the use of different coordinate systems (i.e. frames of reference). Since the body limbs constantly move in external space, the location of somatosensory stimuli is not only coded according to somatotopic coordinates (i.e. the position on the body surface), but is also remapped according to the position of the stimulated body part in external space, i.e. spatiotopic frames of reference. For instance, several studies have shown that, as compared to an uncrossed hands posture, crossing the hands dramatically impaired participants' performance during temporal order judgment (TOJ) tasks during which participants judged the order of appearance of two somatosensory, nociceptive or not, inputs presented in rapid succession. These results have been attributed to the presence of a conflict between somatotopic and spatiotopic reference frames providing mismatching spatial information when the hands are crossed (e.g. De Paepe et al., 2015; Sambo et al., 2013; Shore et al., 2002; Vanderclausen, Bourgois, et al., 2020; Vanderclausen, Manfron, et al., 2020; Yamamoto & Kitazawa, 2001a). More recent studies have suggested that, despite both spatial representations are automatically activated, disentangling between the different spatial codes during crossed hands posture might require effort to produce the correct response (Badde et al., 2015; Crollen et al., 2019; Vanderclausen, Manfron, et al., 2020). In order words, decreased performance during somatosensory TOJ would reflect the effort that the brain has to make in order to realign the somatotopic and spatiotopic reference frames which are concurrently active and mismatching when the hands are crossed.

Such spatiotopic representations would be of primary importance, especially for nociceptive stimuli, since it would allow the brain to bind the perception of the noxious sensory event with the identification of its source in the space surrounding the body. The ability to map nociceptive inputs according to space-based references is therefore thought to represent an important process that prompt and adequately orient defensive behaviors towards potential physical threats. However, it has been suggested that spatiotopic representations of nociceptive stimuli were not innate but would rather depend on early visual experience, since crossing the hands had no effect on the TOJ performance of congenitally blind participants (Vanderclausen, Bourgois, et al., 2020). Therefore, this was suggested that congenitally blind individuals would preferentially rely on somatotopic frames of reference to perceive and localize somatic events (Crollen, Albouy, et al., 2017; Crollen & Collignon, 2012; Crollen, Lazzouni, et al., 2017; Röder et al., 2004; Vanderclausen, Bourgois, et al.,

2020), unless they are forced to use spatiotopic coordinates (e.g. Crollen, Albouy, et al., 2017; Crollen et al., 2019; Vanderclausen, Manfron, et al., 2020). With regards to the interpretation of the crossing hands effect during somatosensory TOJ explained here above, insensitivity of congenital blind people to the limb posture would suggest that selecting body-based coordinates and inhibiting mismatching location provided by the spatiotopic representation would be less effortful for them (Vanderclausen, Manfron, et al., 2020).

Hence, it could be hypothesized that the reduced perceived intensity of painful stimuli when the hands are crossed could also be due to the cognitive effort associated with the spatiotopic remapping of nociceptive events when the hands are placed in such conflicting posture. We hypothesize that, in normally sighted participants, the cognitive resources allocated to realignment operations of the somatotopic and spatiotopic coordinates of nociceptive stimuli when the hands are crossed would limit the availability of cortical resources for processing stimuli intensity, resulting in reduced perceived intensity of pain. On the contrary, in congenitally blind participants, mostly relying on somatotopic representations, at least when task-relevant, realignment of the spatial coordinates should be less effortful, as the spatiotopic representation has less impact. Therefore, this would spare attentional resources for processing other features of nociceptive stimuli such as their intensity. We therefore hypothesize that, conversely to normally sighted participants, crossing the hands would not affect intensity ratings of early blind participants. In line with the literature (Holten-Rossing et al., 2018; Slimani et al., 2014; Slimani et al., 2013), we also expected generally higher pain intensity ratings in early blind participants, as compared to their sighted counterparts.

2. Methods

2.1. Participants

Twenty-nine normally sighted participants took part in Experiment 1 (15 women and 14 men ; mean age (M±SD) =23.34±1.91, ranging from 20 to 27 years old ; 21 right-handed, 5 left-handed and 3 ambidextrous according to the « Flinders Handedness Survey » (Nicholls et al., 2013). All the participants had normal to corrected-to-normal vision. None of them reported prior history of brain injury, severe psychiatric or chronic pain disorder, diabetes, skin disease, traumatic injury of the upper limbs within the last 6 months, cutaneous lesion of the hands' dorsa, regular use of psychotropic drugs, or intake of analgesic drugs (e.g. NSAIDS and paracetamol) within the twelve hours preceding the experiment.

Twelve early blind participants as well as twelve normally sighted participants matched in gender and age took part in Experiment 2 (blind group: two women; mean age (M±SD) =37±12.92 ranging from 18 to 67, 11 right-handed and 1 ambidextrous (Nicholls et al., 2013); sighted group: two women, mean age (M±SD) =37±12.53 ranging from 19 to 66 years old, 10 right-handed, 1 left-handed and 1 ambidextrous). Early blind participants were recruited according to blindness attributed to peripheral deficits with no additional neurological problem (see Table 1 for a detailed description of blind participants). They were totally blind or had only rudimentary sensitivity to brightness but no ability for pattern perception. They were all considered as totally blind since birth. One of them, participant EB2, because of a genetic disease, became totally blind at 3 months of life, but was still considered as early blind since his visual acuity was very poor in the first months of life.

All the participants from both Experiments had slept at least 6 hours the night preceding the experiment and were blinded to the aim of the study. Written inform consent were obtained for all participants and all experimental procedures were approved by the local biomedical ethics committee conformed to the Declaration of Helsinki. The participants received financial compensation for their participation in the experiment.

Partic-ipant	Sex/ Age	Hande-dness	Profession/Edu-cational level	Visual percept-ion	Onset of blindness	Cause of blindness	Brai-lle	Cane	Musical instrument	Musical experience	Other
EB1	M 40	R	College degree	None	Birth	Leber congenital amaurosis	Yes	Yes	Piano/ Organ	5 years	Torball
EB2	M 67	R	College degree	None	<18 months	Bilateral retinoblastoma	Yes	Yes	Organ	>9 years	/
EB3	F 39	R	College Degree	None	Birth	Leber congenital amaurosis	Yes	Yes	/	/	/
EB4	M 18	R	High School (inferior degree)	None	Birth	Norri syndrome	Yes	Yes	Accordion	>6 ans	Hearing aids
EB5	M 34	R	Some college	None	Birth	Persistent hyperplastic primary vitreous involving both eyes	Yes	Yes	Musical keyboard	>10 years	/
EB6	M 30	R	College degree	None	Birth	Leber congenital Amaurosis	Yes	Yes	No	/	Various sport activities
EB7	M 24	R	Some college	None	Birth	Congenital cause (*)	Yes	Yes	No	/	/
EB8	F 37	R	Phone sale until 2006/ Official high school	None	Birth	Severe corneal dysplasia	Few	Yes + dog	Drums	Only few months	/
EB9	M 51	R	College degree	None	Birth	Leber congenital Amaurosis	Yes	Yes	Piano	>3 years	/
EB10	M 37	R	Specialized school until 6th grade	None	Birth	Incubator accident resulting in the burning of both retinas	Yes	Yes	Piano	2 years	/
EB11	M 27	Ambi	Receptionist/ Official high school	None	Birth	Leber congenital amaurosis	Yes	Yes	Drums/ Piano/ Harmonica/ Guitar	>5 years	ADHD syndrome
EB12	M 42	R	Teacher/ College dgree	None	Birth	Anterior chamber cleavage syndrome (Peters syndrome)	Yes	Yes + dog	Piano/Drums/ Flute	>5 years	Hearing aids

Table 1. Profile of the early blind participants.

Note: *EB= early blind; F= female; M= male; Age in years; R= right-handed; L= left-handed; Ambi=ambidextrous; (*): no additional details available. Regarding the onset of the blindness, participant EB2 was not blind from birth. However, because he had very poor vision from birth and underwent a bilateral eye enucleation at the age of 18 months, he was considered as early blind. Torball is an indoor sport for the blind.*

2.2. Stimuli and apparatus

Nociceptive stimuli consisted of radiant heat stimuli delivered onto the skin of the hands' dorsa by means of two infrared CO_2 laser stimulators (wavelength 10.6 μm; Laser Stimulation Device, SIFEC, Ferrières, Belgium). The laser stimulating the left hand and that stimulating the right hand were alternated across participants to counterbalance the differences related to specific calibration of each laser device. Stimulation was remotely controlled by means of Matlab 2018 using data acquisition boards (NI 6343, National Instruments, Austin, TX). The power of the output stimulation was regulated using a feedback control based on an online measurement of the skin temperature at the site of stimulation by means of a radiometer whose field of view was collinear with the laser beam. This allows defining specific skin temperature profiles to generate sensory inputs that selectively activate thermo-sensitive cutaneous nociceptors associated to thinly myelinated Aδ- or unmyelinated C-fibers (see Churyukanov et al., 2012). The laser beams were conducted through 10-m optical fibers. Each fiber ended with a head containing the optics used to collimate the laser beam to 6 mm diameter at the target site. Each laser head was hold upon each participant's hand by means of articulated arms attached to a camera tripod system (Manfrotto, Cassola, Italy). Each laser head was fixed into a clamp attached to a 3-way head allowing displacements of the target site of the laser beam perpendicularly oriented to the hand dorsum by means of several sliders in all directions. Laser beams were displaced on each participant hand's dorsum using the sliders after each stimulus. Stimulus duration was 100 ms with a 10-ms heating ramp to reach the target temperature, followed by a 90-ms plateau after which heating was stopped.

The target temperatures were determined for each participant and each hand according to individual activation threshold of nociceptive Aδ-fibers. Participants' thresholds were estimated by means of an adaptive staircase procedure using reaction times (RTs) to disentangle detections triggered by thinly myelinated Aδ-fiber inputs (RT < 650 ms) from detections triggered by unmyelinated C-fibers inputs (RT ≥ 650 ms) (Churyukanov et al., 2012), since Aδ nociceptive fibers have faster nerve conduction velocity than C-fibers. Participants were asked to press a button with the non-stimulated hand as fast as possible as soon as they felt something on the stimulated hand. The procedure started at 46 degrees Celcius (°C). For each stimulus, any RT equal or superior to 650 ms led to a temperature increase of 1°C for the next stimulus. Conversely, any RT inferior to 650 ms conducted to a temperature decrease of 1°C for the next stimulus. The procedure lasted until 4 reversals were encountered; the threshold value was then considered as the mean value of the four temperatures that led to a reversal. View of the hands was prevented in all sighted participants during the threshold measurement. During each Experiment, the threshold measurement procedure was started with the left hand for half of the participants, while the procedure was started with the right hand in the other half of the participants.

Two target temperatures were used during the experimental testing. Low intensity stimuli were defined as the threshold value, as individually defined for each hand, to which 4°C were added. High intensity stimuli were defined as the threshold value + 8°C. Stimuli at both intensity ranges elicited a clear pricking sensation. If necessary (e.g. if the threshold value of a given participant was already quite high), target temperatures were slightly adapted so that the maximum target temperature for the higher intensity value did not out pass 60°C, for safety measures. This adaptation was made for one participant of Experiment 1, for whom 2.5 and 5°C were added to his threshold values for each hand instead of 4 and 8°C. In Experiment 2, such adaptation of target temperatures was needed for two of the early blind and 2 of the normally sighted participants, for whom 3 and 6 °C were added to the threshold values of each hand, instead of 4 and 8°C, for low and high intensities, respectively. In addition, to avoid unbalanced perceived intensity between the two hands, target temperatures were then tested to ensure that the stimuli were perceived as equally intense between the two hands for both the low and high intensity values. To this aim, pairs of laser stimuli were delivered, one on each hand, and participants were then asked to report if the stimulations on the two hands were perceived as equally intense as well as if the sensation elicited on the two hands was similar. This was made separately for the low and high intensity values. All participants from Experiment 1 and 2 reported the stimuli on the left and right hands as approximately equally intense both for the low and high intensities. Importantly, participants were not made aware that only two temperatures were actually used during the experiment. Before each experimental block, the elicited sensations were tracked using a list of words to be chosen (not perceived, light touch, tingling, pricking, warm, burning). At each trial, subjective intensity was measured using a numerical rating scale (NRS) from 0 (no sensation) to 10 (strongest sensation imaginable). Sighted participants from Experiment 2 were blindfolded with an eye mask.

2.3. Procedure

The procedure was almost identical for Experiment 1 and 2. Participants were sitting on a chair, hands' palms laying down on a table in front of them. During the uncrossed hands condition, the tips of the two index fingers were separated by a distance of ~30cm. During the crossed hands condition, the same distance separated the tips of the two forth fingers. Reference fingers were chosen in order to ensure similar distance between the hands during the two posture conditions. The reference fingers were placed at a distance of ~40cm from the edge of the table (Figure 1). In Experiment 1, participants were provided with a numerical scale printed on a sheet of paper (A4 format) placed in front of them, at ~40 cm from the edge of the table and just above each referenced finger. This page also contained a fixation cross, which was placed in the middle of the paper sheet, at 9,5 cm from the bottom of the page, and 14 cm from each side of the page. On this page, the NRS was placed 4 cm above the fixation cross (total length: 26 cm with steps of 2,5 cm for each scale level). The numbers from 0 to 10 were visible. In Experiment 2, since sighted participants were blindfolded with

an eye mask, the NRS was presented verbally at the beginning of the experiment. A chin-rest held the participants' head in order to minimize head movement during the experiment. Noises from experimental devices were covered by a white noise played through earphones that the participants wore during the whole experiment. The sighted participants from Experiment 1 were asked to maintain their gaze on the fixation cross.

After the threshold measurement phase, participants were presented with 4 experimental blocks, each of them being composed of 24 stimuli. Stimuli were randomly and equiprobably applied on the left and right hands. On each hand, 6 stimuli were applied with the lower intensity and 6 with the higher intensity. Directly after each stimulus, participants were asked to rate its intensity by reporting it verbally using the NRS. Each participant's response was encoded after the laser beam had been displaced by the experimenter by means of the numerical path of the keyboard. Key pressing triggered the next trial. Inter-stimuli time interval was of approximately 10 seconds. One experimental block lasted approximately 10 minutes. A small break was imposed to the participants after each block. In Experiment 1, half of the participants started the experiment with their hands in the crossed posture and the other half started with their hands uncrossed. The two blocks of the same posture condition were always consecutive, using a AABB/BBAA design. In Experiment 2, half of the participants started in the crossed posture while the other half started in the uncrossed posture as in Experiment 1. However, the participants changed the posture at the beginning of each block, using a ABAB/BABA design. This change in the design was made in order to ensure that any effect of the experimental variables could not be attributable to habituation of the nociceptive stimuli. In the crossed posture, half of the participants crossed the left arm over the right arm and the other half did the reverse in both experiments.

2.4. Measures

Threshold and intensity values were measured in °C. Ratings were averaged for each participant according to each hand (i.e. left vs. right), intensity (i.e. low vs. high), and posture (uncrossed vs. crossed) condition.

2.5. Analyses

Analyses were performed using IBM SPSS Statistics 25. Threshold and intensity values were first analyzed to ensure that no difference between hands or groups regarding these factors could have influenced the results. To this aim, analyses of variance (ANOVA) for repeated measures were run on the threshold values with *hand* (left vs. right) as a within factor in Experiment 1, and *hand* (left vs. right) and *group* (early blind vs. normally sighted) as within and between factors respectively in Experiment 2. For the intensity values, repeated

measures ANOVA were performed with *hand* (left vs. right) and *intensity* (low vs. high) for Experiment 1 and the same analysis with adding *group* (early blind vs. normally sighted) as a between factor was run for Experiment 2. Next, the effect of the experimental variables on the intensity ratings were tested by means of ANOVA for repeated measures with *hand* (left vs. right), *intensity* (low vs. high) and *posture* (uncrossed vs. crossed) as within factors. For Experiment 2, *group* (early blind vs. normally sighted) was added as a between factor. Greenhouse-Geisser corrections of the degrees of freedom and contrast analyses were used if necessary. Effect sizes were measured using partial Eta squared for ANOVA and Cohen's d for t-tests. Significance level was set at $p \leq .050$.

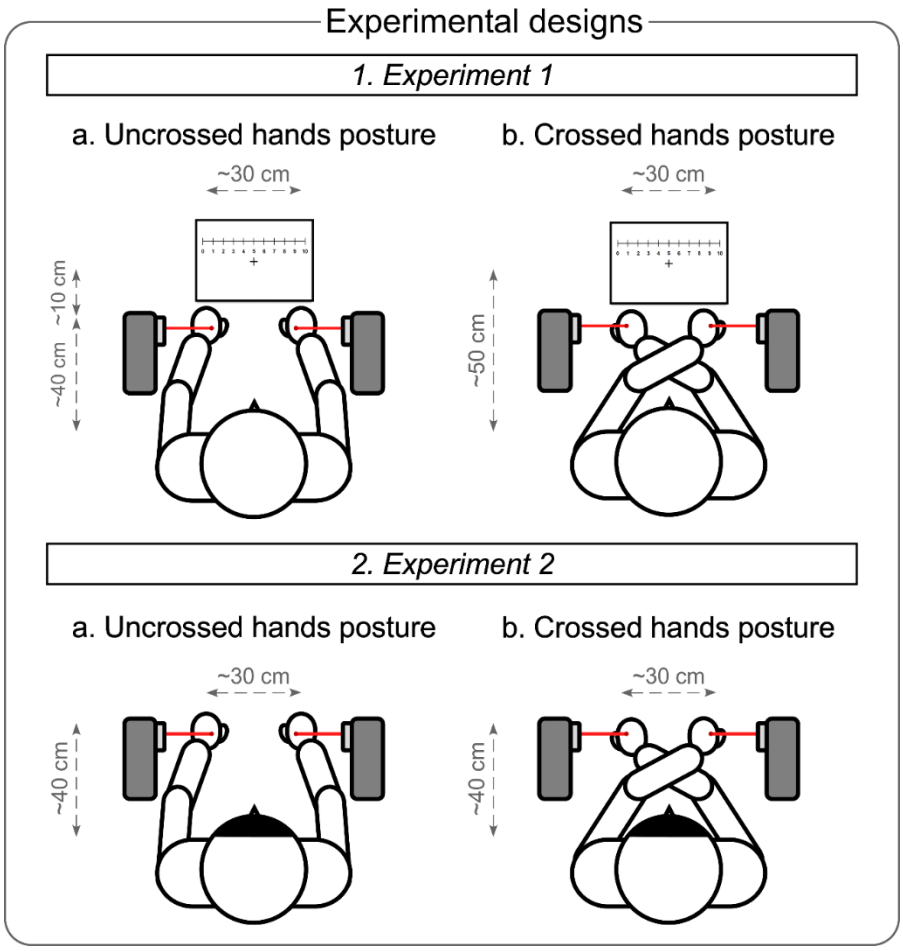


Figure 1. ***Experimental design of Experiment 1 (top) and 2 (bottom).*** *Two temperature-controlled CO_2 laser stimulators were used to activate Aδ-fibers. Laser beams were displaced after each trial on the hands' dorsa using camera tripod systems. Two different intensities were used (i.e. Aδ-fibers activation threshold +4°C and +8°C). Participants were asked to rate the stimuli applied either on the left or on the right hand after each trial with the hands either in an uncrossed (A) or a crossed (B) posture. In Experiment 1 (above), participants were presented with a physical numerical scale in front of them and were asked to maintain their gaze on the fixation cross placed in the middle of the numerical scale (i.e. at a distance of 50 cm from the edge of the table). In Experiment 2, sighted participants performed the task blindfolded.*

3. Results

3.1. Experiment 1

The ANOVA performed on the threshold values did not reveal any significant difference between the left (M±SD= 48.66±2.42) and the right (M±SD= 49.03±2.24) hands ($F(1,28)= 1.054$, $p=.313$, $\eta^2p=.036$). Regarding the intensity values, the analyses did not show any significant difference between the left and right hands neither for the low intensities (left: M±SD= 52.66±2.42; right: M±SD= 53.03±2.24; $F(1,28)=1.054$, $p=.313$, $\eta^2p=.036$), nor the high intensities (left: M±SD= 56.66±2.42, right: M±SD= 57.03±2.24; $F(1,28)=1.054$, $p=.313$, $\eta^2p=.036$).

Results of Experiment 1 are illustrated in Figure 2. The ANOVA performed on the averaged ratings of the participants revealed no significant effect of the hand ($F(1,28)=2.327$, $p=.138$, $\eta^2p=.077$), but a significant effect of the posture ($F(1,28=6.566$, $p=.016$, $\eta^2p=.190$), and a significant effect of the intensity ($F(1,28)=140.895$, $p=.000$, $\eta^2p=.834$). None of the interactions between the factors reached significance (all $F(1,28)\leq2.634$, all $p\geq.116$, all $\eta^2p\leq.086$). The ratings of the participants were on average lower in the crossed (M±SD=3.60±0.19) as compared to the uncrossed (M±SD=3.91±0.21) posture condition. Also, the ratings were lower in the low intensity (M±SD=2.95±0.17) as compared to the high intensity (M±SD=4.56±0.23) condition (see Figure 2).

In order to explore the possibility that the effect of the posture on the perceived intensity of the nociceptive stimuli could be accounted for by habituation of the stimulations throughout the experiment (i.e. decreased responses as a result of stimuli repetition), a new variable "*order*" considering the posture in which the participants started the experiment was introduced in the analyses as a between-participants factor. Adding this factor did not change the results of the main analyses, as a significant effect of the posture was still observed ($F(1,27)=6.349$, $p=.018$, $\eta^2p=.190$), as well as a significant main effect of the intensity ($F(1,27)=136.832$, $p=.000$, $\eta^2p=.835$). Importantly, there was no significant effect of the order ($F(1,27)=.862$, $p=.361$, $\eta^2p=.031$), neither a significant interaction between the posture and the order ($F(1,27)=.015$, $p=.904$, $\eta^2p=.001$). None of the other effect or interaction was significant (all $F(1,27)\leq2.716$, all $p\geq.111$, all $\eta^2p\leq.091$).

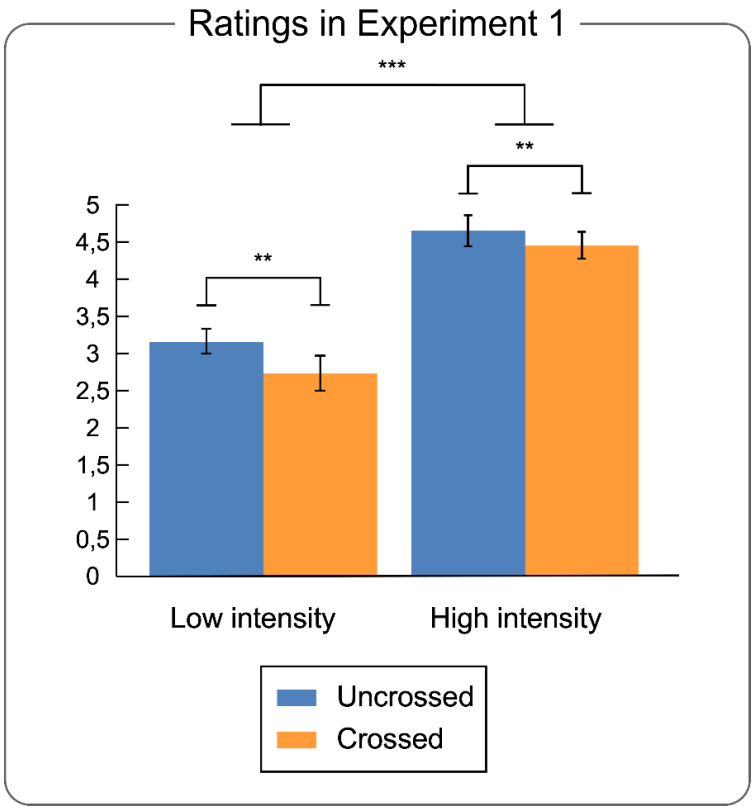


Figure 2. ***Ratings in normally sighted participants of Experiment 1.*** *Averaged ratings of 29 normally sighted participants as function of the posture (uncrossed vs. crossed) and the intensity (low vs. high) factors. Ratings in the crossed posture (light orange) were on averaged significantly lower as compared to the ratings in the uncrossed posture (blue), independently of the intensity (**=p<.05). Overall, the ratings in the low intensity condition were lower than the ratings in the high intensity condition, irrespective of the posture (***=p<.01). Error bars represent confidence intervals calculated according to Cousineau's method for within-subject designs (Cousineau, 2005).*

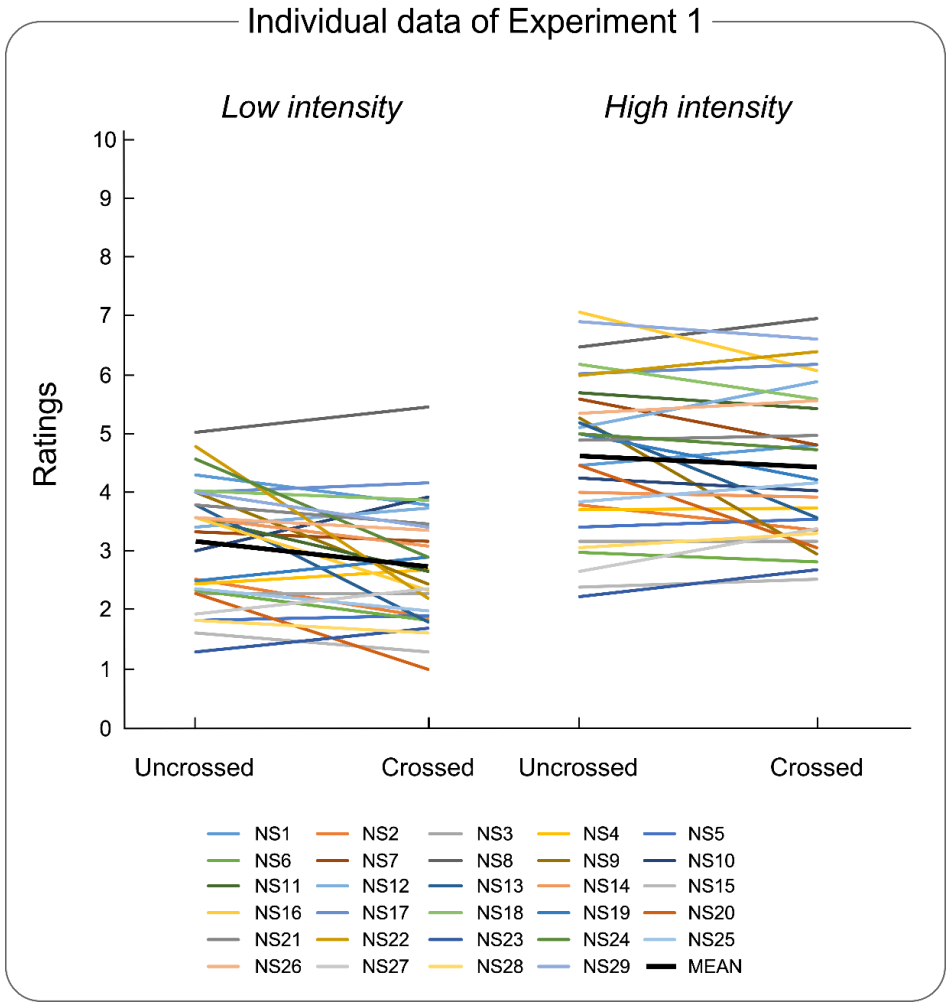


Figure 3. ***Individual data of Experiment 1.*** *Averaged ratings of each of the 29 normally sighted (NS) participants of experiment 1 according to the posture (uncrossed vs. crossed) and the intensity (low vs. high). The mean of each condition is indicated by a black thick line. Both for the low and high intensity, the ratings were on average lower in the crossed as compared to the uncrossed posture condition.*

3.2. Experiment 2

Analyses performed on threshold values showed no effect of the hand ($F(1,22)=2.328$, $p=.141$, $\eta^2p=.096$), no effect of the group ($F(1,22=.727$, $p=.403$, $\eta^2p=.032$), and no significant interaction between the hand and the group ($F(1,22)=.259$, $p=.141$, $\eta^2p=.012$). The threshold values of the early blind participants (left hand M±SD= 49.17±2.04; right hand M±SD= 49.25±2.45) did not significantly differ from the threshold values of the sighted participants (left hand M±SD=50.083±2.065; right hand M±SD=50.25±2.49). Regarding intensity values, the ANOVA on the low intensity values did not show any significant effect of the hand ($F(1,22)=2.252$, $p=.148$, $\eta^2p=.093$), neither of the group ($F(1,22)=1.268$, $p=.272$, $\eta^2p=.055$), nor a significant interaction between the hand and the group ($F(1,22)=0.490$, $p=.491$, $\eta^2p=.022$). The ANOVA on the high intensity values did not show any significant effect either (all $F(1,22) \leq 2.081$, all $p \geq .163$, all $\eta^2p \leq .086$). Thus, neither the low intensity values significantly differ between the early blind (left M±SD= 52.92±1.83; right M±SD= 53.00±2.17) and the sighted (left M±SD=53±1.810; right M±SD=54.17±2.167) participants, nor the high intensity values (blind left M±SD= 56.67±1.72; blind right M±SD= 56.75±1.96; sighted left M±SD =56.833±1.642 ; sighted right M±SD =57.917±1.782).

Results of Experiment 2 are illustrated in Figure 3 and 4. The repeated measures ANOVA revealed a significant effect of the intensity ($F(1,22)=127.080$, $p=.000$, $\eta^2p=.852$), and a marginally significant interaction between the intensity and the group factors ($F(1,22)=4.217$, $p=.052$, $\eta^2p=..161$). However, neither the effect of the posture ($F(1,22)=.661$, $p=.425$, $\eta^2p=.029$), nor that of the hand ($F(1,22=.465$, $p=.503$, $\eta^2p=.021$), of the group ($F(1,22)=3.534$, $p=.073$, $\eta^2p=.138$) or any other interaction (all $F(1,22) \leq 2.652$, all $p \geq .118$, all $\eta^2p \leq .108$) reached significance (see Figure 3).

In order to detail the marginally significant interaction between the intensity and the group, two ANOVA with the posture, the hand and the group as factors were run separately on the ratings of the low and high intensities respectively. The analyses revealed a significant effect of the group for the high intensities ($F(1,22)=4.360$, $p=.049$, $\eta^2p=.165$) whereas this effect did not reach significance for the low intensities ($F(1,22)=2.026$, $p=.169$, $\eta^2p=.084$). This indicates that early blind participants tended to rate the high intensity stimuli with higher values (M±SD= 5.046±1.484) as compared to the sighted participants (M±SD= 3.969±0.996) whereas the ratings were comparable across the groups for the low intensity stimuli (early blind M±SD= 3.207±0.990; normally sighted M±SD= 2.696±0.750) (see Figure 4). None of the other effect or interaction reached the significance level for the low intensity ratings (all $F(1,22) \leq 1.681$, all $p \geq .208$, all $\eta^2p \leq .071$) nor for the high intensity ratings (all $F(1,22) \leq 1.304$, all $p \geq .266$, all $\eta^2p \leq .056$).

Since the participants of Experiment 2 were on average older (M±SD= 37±12.92) than the participants who took part in Experiment 1 (M±SD= 23.34±1.91), we wondered whether

the age of the participants could explain the discrepancy in the results obtained between the first and the second experiments. We explored this hypothesis by dividing the participants of Experiment 2 into two groups of age. First, we performed an ANOVA on the threshold values with *hand* (left vs. right), *group* (early blind vs. normally sighted) and *Age* (< 35 vs. > 35 years old) as factors to look at potential differences at this level. This analysis did not show any difference on the threshold values according to the age of the participants ($F(1,20)=.676$, $p=.421$, $\eta^2p=.033$). The other variables did not reach significance either (all $F(1,20)=2.358$, $p=140$, $\eta^2p=.105$). Then, in order to test whether the age could explain the discrepancy in the posture effect on pain intensity ratings between Experiment 1 and 2, we run an ANOVA with *posture*, *hand*, and *intensity* as within factors, and *group* and *Age* as between factors. The ANOVA showed a main significant effect of the intensity ($F(1,20)=144.661$, $p=.000$, $\eta^2p=.879$), a significant interaction between the intensity and the group ($F(1,20=4.801$, $p=.040$, $\eta^2p=.194$), and a significant triple interaction hand*posture*age ($F(1,20)=6.845$, $p=.017$, $\eta^2p=.255$). None of the other effect or interaction reached significance (all $F(1,20)\leq3.724$, all $p\geq.068$, all $\eta^2p\leq.157$). In order to detail the triple interaction, ANOVAs were performed separately according to each of these variables. However, these analyses did not reveal anything significant. Indeed, the posture and the hand did not interact differently according to the age (all $F(1,10)\leq3.98$, all $p\geq.074$, all $\eta^2p\leq.285$). More specifically, the effect of the posture was not significant in the younger participants ($F(1,10)=.446$, $p=.519$, $\eta^2p=.043$), neither in the older participants ($F(1,10)=.218$, $p=.650$, $\eta^2p=.021$). The posture and the age did not interact differently according to the hand (all $F(1,10)\leq1.822$, all $p\geq.192$, all $\eta^2p\leq.084$), and the hand and the age did not interact differently according to the posture ($F(1,10)\leq1.070$, all $p\geq.313$, all $\eta^2p\leq.051$). The interaction between the group and the intensity was not further analyzed since it was also significant and detailed in the main analyses.

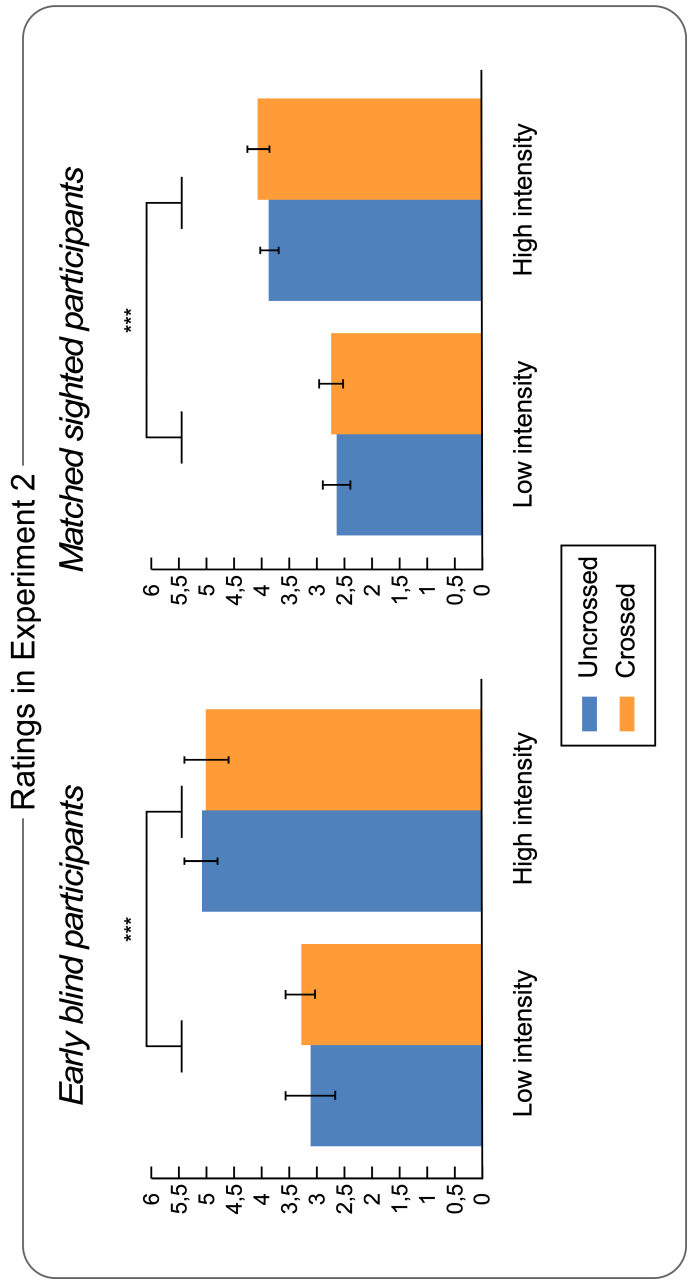


Figure 3. *Ratings in early blind and matched sighted participants of Experiment 2.* *Averaged ratings in 12 early blind and 12 matched normally sighted participants as function of the posture (uncrossed vs. crossed) and the intensity (low vs. high) factors. The ratings in the crossed condition (light orange) were not significantly different from the ratings in the uncrossed condition (blue), neither in the early blind nor in the normally sighted participants. Besides, the ratings in the low intensity condition were on averaged lower as compared to the ratings in the high intensity condition, irrespective of the group (***=p<.001). Error bars represent confidence intervals calculated according to Cousineau's method for within-subject designs (Cousineau, 2005).*

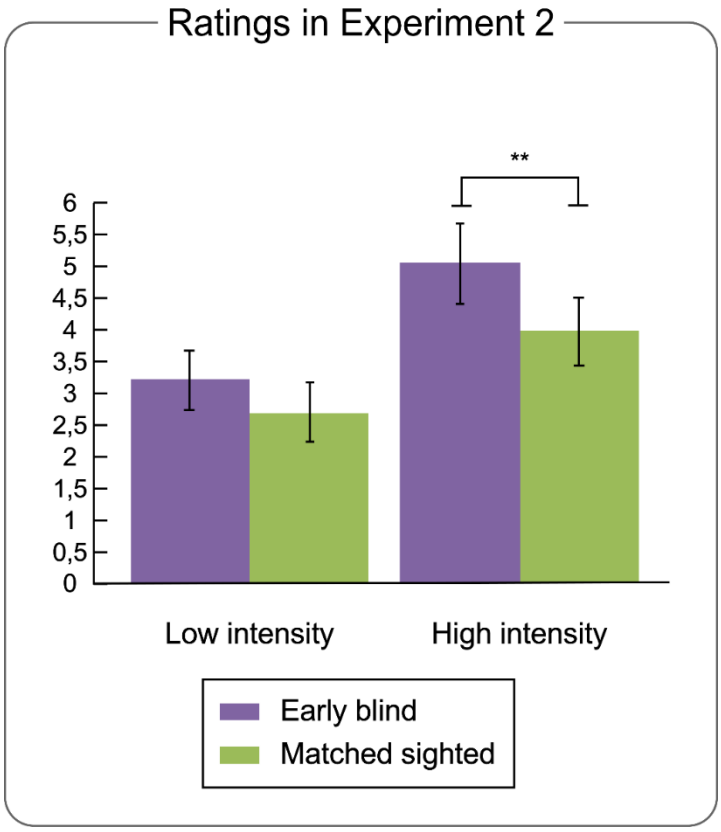


Figure 4. ***Ratings of early blind and matched sighted participants of Experiment 2.*** *Averaged ratings of 12 early blind (purple) and 12 normally matched sighted (light green) participants according to the intensity factor (low vs. high). The ratings in the high intensity condition were significantly higher in early blind participants as compared to normally sighted participants (**=p<.05). However, this difference did not reach significance for the low intensity condition. Error bars represent confidence intervals calculated according to Cousineau's method for within-subject designs (Cousineau, 2005).*

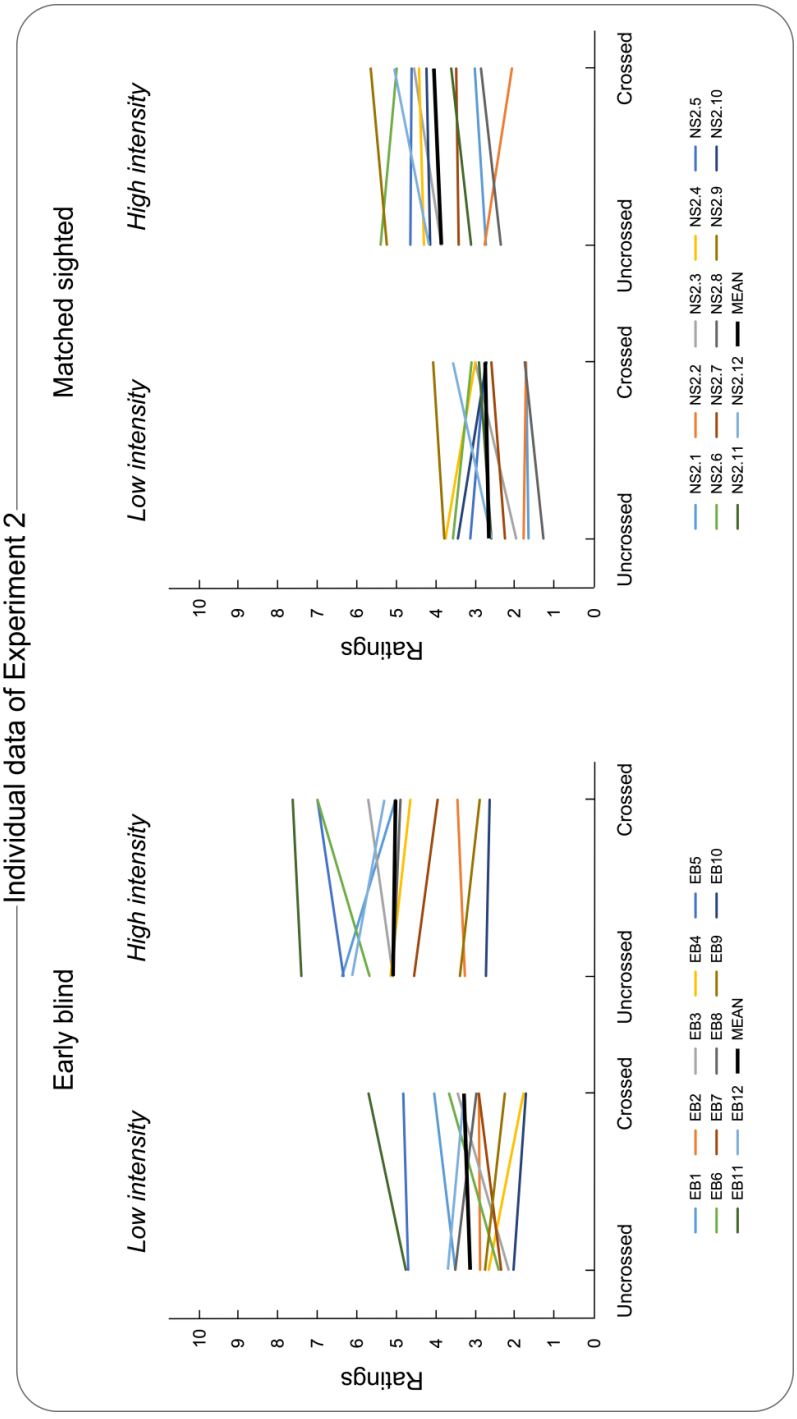


Figure 6. *Individual data of Experiment 2.* *Averaged ratings of each of the 12 early blind (EB) and each of the 12 matched normally sighted (NS2) participants who took part in experiment 2 according to the posture (uncrossed vs. crossed) and the intensity (low vs. high). The mean of each condition is indicated by a black thick line. The ratings were comparable between the crossed and the uncrossed posture in every intensity condition, irrespective of the group.*

4. Discussion

The goal of the present study was to reconsider the mechanisms underlying the modulation of the perceived intensity of pain induced by nociceptive stimuli applied on the hands in a crossed posture (Gallace et al., 2011; Torta et al., 2013). The reduced cortical activity and pain ratings observed when the hands are crossed over the body midline had been suggested to reflect a disruption of the processing of the nociceptive stimuli in the brain when the body adopts an unusual posture (Gallace et al., 2011), or had been explained as reflecting a greater attentional load associated with the crossed posture (Torta et al., 2013). Considering that (1) nociceptive stimuli are represented in the brain according to two spatial representations (De Paepe et al., 2015; Sambo et al., 2013; Vanderclausen, Bourgois, et al., 2020; Vanderclausen, Manfron, et al., 2020), and that (2) the realignment of these two spatial representations when they are conflicting (such as when the stimulated limbs are crossed) might be effortful (Vanderclausen, Manfron, et al., 2020), we hypothesized that the impact of the body posture on pain perception could be due to a lack of attentional resources to process stimuli intensity, as they are mainly used for the realignment of spatial coordinates. In addition, it has been shown that the spatial mapping of nociceptive inputs is less conflicting in early blind people, suggesting that their spatiotopic representation is less strongly activated and that the spatial realignment during the crossed hands posture should therefore be less effortful for them (Vanderclausen, Bourgois, et al., 2020; Vanderclausen, Manfron, et al., 2020). It was thus hypothesized that, in early blind people, when their hands are crossed, their attentional resources, being less solicited by the processing of spatial features of nociceptive inputs, would be more available to process other aspects of nociceptive stimuli such as their intensity. Thereby, it was expected that the impact of crossing the hands would be only observed in normally sighted individuals while early blind participants would give similar intensity ratings to the nociceptive stimuli irrespective of the posture of the limbs on which they are applied. To this aim, heat nociceptive stimuli of two different suprathreshold intensities were applied on the hands of young healthy participants in a first experiment and of early blind as well as a group of matched normally sighted participants in a second experiment. Participants of all three groups were asked to subjectively rate the intensity of the stimuli while their hands were placed either in an uncrossed or in a crossed posture. The results showed a reduction of the intensity ratings of the nociceptive stimuli in the crossed as compared to the uncrossed posture in Experiment 1, corroborating results of previous research (Gallace et al., 2011; Torta et al., 2013). However, in Experiment 2, the intensity ratings were not affected by the posture, neither in the early blind group, nor in the matched normally sighted group. Noteworthy, we did find a difference between the groups on the intensity ratings irrespective of the posture. Indeed, higher intensity ratings were observed in early blind participants as compared to their sighted peers, even though it was only true for the highest intensity stimuli.

The fact that we did observe an effect of crossing the hands on pain perception in the first but not in the second experiment could be attributed to some differences in our experimental design between the two studies. For instance, participants of the first experiment were asked to maintain their gaze on a fixation cross placed below a visible NRS in front of them, whereas participants of the second experiment were blindfolded, in order to be compared to early blind individuals. Therefore, the view of the NRS itself could have induced or promoted the emergence of an effect in Experiment 1, while multiple possible ways of representing the numerical rating scale across the participants from Experiment 2 could have potentially prevent the effect from emerging. In addition, although participants of Experiment 1 were not instructed to specifically look at their hands during the experiment, we cannot ensure that the vision of the hands in their peripheral field of view had no influence on the perceived intensity of the nociceptive stimuli. Indeed, several studies have demonstrated that the simple fact of seeing the part of the body that was receiving a painful stimulus resulted in reduced perception of pain (Longo et al., 2009; Longo et al., 2012; Mancini et al., 2013; Mancini, Longo, Kammers, et al., 2011; Torta et al., 2015). Moreover, proprioceptive information and vision of the stimulated body part have been shown to interact regarding their effect on perceived intensity of pain (Valentini et al., 2015). Accordingly, pain ratings were reduced when participants held their hands in a crossed posture and that they could see their hands, whereas only placing the stimulated hand in the contralateral side of space without looking at it or only directly look at the stimulated limb without crossing it over the body midline was not sufficient to significantly impact pain perception in this study (Valentini et al., 2015). Therefore, one could speculate that the effect of crossing the arms on the perception of pain in Experiment 1 could have been enhanced by the fact that vision of the stimulated hands was available. In that sense, the decreased perceived intensity observed in the crossed posture in Experiment 1 might simply reflect the combination of two distinct effects, each of them having a relative impact on the perception of pain. In contrast, it is possible that the fact that vision of the hands was made unavailable in Experiment 2 could have participated to the non-replication of the posture effect observed in Experiment 1, at least regarding the normally sighted participants of Experiment 2. However, it is worth noting that vision of the hands was prevented by means of a wooden board in the study of Gallace et al. (2011) and that the participants were asked to close their eyes in the study of Torta et al. (2013). Since they both succeeded to evidence a significant reduction of pain intensity ratings in the crossed posture without any visibility of the stimulated hands, it seems however quite unlikely that vision vs. non-vision of the hands could explain the discrepancies between the results of our two experiments.

Another difference in the experimental designs of the two experiments is to be found in the order of the posture variable across the experimental blocks. Indeed, since the participants of Experiment 1 performed the two blocks of a given posture in a row before changing towards the other posture condition (AABB/BBAA design), participants of Experiment 2 changed the posture of their arms at the beginning of each experimental block (ABAB/BABA design). Even though adding the order in the analyses of data from Experiment 1 did not

change the results, we cannot completely rule out the possibility that changing the design of the experiment across our two studies regarding the order of the posture condition could have influenced the results. For instance, in spite of the efforts put in both experiments to avoid this phenomenon from contaminating the data, it might be possible that the decreased perceived intensity of the nociceptive stimuli found in Experiment 1 would have been partly driven by habituation, that is a phenomenon referred to as a response decrement to the stimuli resulting from their repetition (Rankin et al., 2009; Thompson & Spencer, 1966). For example, stimulus repetition can result in decreasing the perception of the nociceptive stimuli over time. Indeed, it could be possible that habituation have occurred to a greater extent in several participants who had started the experiment in the uncrossed posture and ended it in the crossed posture condition, resulting in decreased perception of the stimulations over the last experimental blocks, which haphazardly corresponded to the two blocks of the crossed condition. As a result, this could have enhanced the effect of the crossed posture on the intensity ratings. However, it would be extremely difficult to disentangle whether the observed effect of the posture on the perception of pain in Experiment 1 would be due to the fact of crossing the arm or to habituation. This was in fact the main argument supporting the modification of the experimental design for Experiment 2.

Another possibility that might have explained the discrepancy between the results of our two experiments is related to the age of the participants. Indeed, participants of our second experiment were on average almost 15 years older than participants in the first experiment. It is worth mentioning that aging has been associated with a decreased pain sensitivity (Lautenbacher, Kunz, Strate, Nielsen, & Arendt-Nielsen, 2005), accompanied by decreased pain ratings and increased pain thresholds, as well as a reduction in the ability to discriminate different intensity levels of noxious stimulations (Gibson & Helme, 2001). These age-related changes have been linked to structural and functional modifications of the peripheral nociceptors (Chakour, Gibson, Bradbeer, & Helme, 1996; Verdu, Ceballos, Vilches, & Navarro, 2000) and the central nociceptive system (Tseng et al., 2013) in older adults. However, we did not observe any difference on the threshold values or on the intensity ratings between the younger (i.e. <35 years old) and older (i.e. >35 years old) participants of Experiment 2. In addition, we did not provide statistical evidence that the absence of an effect of the posture on the perceived intensity of the nociceptive stimuli in Experiment 2 could be related to the older age of the participants in this study by directly comparing the younger and older participants of this experiment.

More generally, one other possibility would be that the effect of crossing the hands on the perceived intensity of pain might be accounted for by other processes than the cognitive effort associated with realigning the spatial representations as we presently hypothesized. Indeed, the relevance of processing the spatial location of the stimuli might be questioned in the present task context. In fact, rating the intensity of nociceptive stimuli would not mandatorily imply to localize them on the body, on the contrary of, for instance, TOJ tasks, in which the spatiotopic remapping of the stimuli would be automatically triggered by the

spatial nature of the task, that is, localizing the inputs on the hands (Sambo et al., 2013; Vanderclausen, Bourgois, et al., 2020; Vanderclausen, Manfron, et al., 2020). Accordingly, several studies have shown a modulation of the weight accorded to spatiotopic reference frames of touch, depending on the relative relevance of these spatial reference frames for the ongoing task (Badde et al., 2016; Badde et al., 2015; Gallace et al., 2008; Roberts & Humphreys, 2008). This suggests that the integration of the somatotopic and spatiotopic reference frames can be flexibly adjusted to the contextual factors (Badde & Heed, 2016). For instance, it has been demonstrated that judging the temporal order of two tactile inputs based on the stimuli frequency or duration, instead of their location on the body, was unaffected by crossing the hands (Roberts & Humphreys, 2008). Therefore, the limited relevance of locating the stimuli while rating their intensity might have reduced the conflict between the somatotopic and spatiotopic frames of reference by giving lower weights to the spatiotopic representation, or by decreasing the relevance of resolving such conflict when giving a response based on the stimuli location is not required. In other words, while remapping nociceptive stimuli into spatiotopic coordinates would indeed involve a cognitive cost (Vanderclausen, Bourgois, et al., 2020; Vanderclausen, Manfron, et al., 2020), it might be possible that nociceptive stimuli were not remapped, or that spatiotopic representations were not weighted enough in the present task context to induce a conflict that would need cognitive resources to be resolved, given the limited relevance of the spatial location of the stimuli for judging their intensity. In this case, our hypothesis to explain the effect of crossing the arms on the intensity perception of nociceptive stimuli might not be relevant to test in such task context, and other potential mechanisms should be investigated in future studies. Importantly, this might reconsider the idea of a strictly automatic remapping of somatosensory stimuli into spatiotopic coordinates. This will be further discussed in the **General discussion** of the present thesis.

Interestingly, we observed higher intensity ratings in the early blind, as compared to the normally sighted participants, for the highest intensities. This finding seems to be in accordance with previous research on pain sensitivity in people with early visual deprivation. Indeed, higher pain ratings, but also lower pain thresholds, have been found in congenitally blind people, as compared to their sighted controls, suggesting a hypersensitivity to pain in the blind (Holten-Rossing et al., 2018; Slimani et al., 2013). However, the detection thresholds did not differ between the groups in the study of Slimani et al. (2013), which is also in line with our results. The fact that we observed a difference between the groups for the high but not for the low intensities, even though both types of stimuli were described as pricking by the participants and targeted the activation of Aδ nociceptive fibers, could suggest that the increased sensitivity of congenitally blind participants would be more prominent for more intense painful stimuli. This hyperresponsiveness to painful stimuli in congenitally blind people has been suggested to be related to excessive attention paid to painful encounters, since higher scores of anxiety have been associated with the higher pain ratings in these participants in a study having manipulated the uncertainty about the intensity of upcoming painful stimulations (Holten-Rossing et al., 2018). In addition, a study has

shown that heat nociceptive inputs were better and faster detected by congenitally blind, as compared to normally sighted participants, suggesting a more efficient central processing of nociception in this population. However, it is worth mentioning that these results were limited to C-fiber mediated stimuli, since the authors did not succeed to extend their results to the processing of more intense stimuli conveyed by Aδ nociceptive fibers, perhaps because of higher detection rate and lower reaction times associated with this type of stimuli, as compared to C-fiber mediated stimulations, making differences between groups more difficult to evidence (Slimani et al., 2016).

In conclusion, it is possible that a combination of several factors has contributed to the inconsistency of the effect of crossing the hands on the perceived intensity of pain in the present study. This would question the robustness of such an effect. Therefore, these results encourage future research to investigate more precisely the implication of factors potentially involved in modulating this effect, in order to better characterize the mechanisms underlying the influence of body posture on pain perception and thereby better understand the variability of such an effect across studies.

Interim summary

So far, we showed that nociceptive stimuli can be spatially coded according to both a somatotopic and spatiotopic frames of reference, similarly to what was already described and that we replicated in the first study for the innoucuous tactile stimuli. This was mainly evidenced by TOJ tasks in which the participants have to judge to position of nociceptive stimuli applied to two different body limbs according to their perceived temporal order of appearance, with the two stimulated limbs being crossed over the body midline.

Behavioral and neurophysiological studies of the spatial representation of touch have proposed that tactile inputs are initially coded according to a somatotopic reference frame and secondly remapped according to spatiotopic coordinates. Given that the spatial-temporal pattern of brain activation is not exactly the same between touch and nociception, the goal of the last experiment of this thesis was to track the time course in the brain of the spatial processing of nociceptive inputs and compare it to that of tactile inputs. To this aim, we used event-related brain potentials in normally sighted people.

Study 5

Investigating the time course of the spatiotopic mapping of tactile and nociceptive stimuli using event-related brain potentials in healthy volunteers

Abstract

To adapt our behavior to the occurrence of any somatosensory stimulus, it is not only essential to code its exact location on the body surface, but also to consider the position of the limb onto which the stimulus was applied in external space. Therefore, it has been shown that both tactile and nociceptive stimuli are spatially represented according to somatotopic as well as spatiotopic coordinates. However, it remains to determine whether the spatial perception of the two somatosensory modalities share the same mapping mechanisms at the cortical level. Tactile inputs have been suggested to be firstly mapped according to somatotopic coordinates before being remapped into spatiotopic representations at later stages of processing. However, the time course underlying the spatial representations of nociceptive stimuli has never been addressed. Taking advantage of the high temporal resolution of event-related brain potentials, the goal of the present study was to tag the earliest latency at which spatiotopic representations would be taken into consideration in each modality. To this aim, tactile and nociceptive evoked potentials were recorded while the participants adopted either an uncrossed or a crossed posture of the hands. The earliest difference between the postures on the elicited brain potentials was considered as indexing the activation of spatiotopic frames of reference in each modality. The results for tactile stimuli revealed effects of the posture at relatively early latencies. In spite of some inconsistencies between the two hands, these effects seem in agreement with previous research. However, no clear effect emerged in the nociceptive modality. Potential explanations for these inconsistencies are suggested to be related to some parameters of the present study. Alternatively, we propose that the cortical organization underlying the spatiotopic mapping of tactile and nociceptive inputs might differ.

1. Introduction

Localizing somatosensory stimuli applied on the body is an important function as it allows optimizing interactions with objects from our environment when these objects are innocuous and processed through the tactile system (Brozzoli, Cardinali, Pavani, & Farne, 2010) and triggering defensive reactions when they are noxious and activate the nociceptive system (Legrain & Torta, 2015). Both tactile and nociceptive inputs have been shown to be mapped according to the anatomical position of the stimuli in somatosensory neurons functionally organized based on the spatially ordered projection of the receptive fields (Andersson, 1997; Baumgärtner et al., 2010; Bingel, Glascher, et al., 2004; Bingel, Lorenz, et al., 2004; Brooks et al., 2005; Mancini et al., 2012; Mancini et al., 2019; Mazzola et al., 2009; Penfield & Boldrey, 1937). However, in order to adequately orient a potential action towards the object that enters in contact with the body, the brain needs to take the relative position of the stimulated body limb in external space into account. Indeed, numerous studies have shown that the position of both tactile and nociceptive stimuli are coded according to anatomical (i.e. somatotopic) and external space-based (i.e. spatiotopic) reference frames (e.g. Azañón & Soto-Faraco, 2008a; Graziano et al., 1997; Sambo et al., 2013; Shore et al., 2002; Smania & Aglioti, 1995; Vanderclausen, Bourgois, et al., 2020; Yamamoto & Kitazawa, 2001a).

Such dual spatial coding has been mostly evidenced by means of experimental procedures during which the posture of the limbs on which the somatosensory stimuli are applied is manipulated across conditions. For example, tactile or nociceptive stimuli are applied on both hands that are either uncrossed or crossed over the body midline. In these experiments, the crossed hands posture is intended to create a mismatch between the spatial responses respectively provided by the somatotopic and spatiotopic maps, the left hand being placed in the right part of space and vice versa. For instance, during temporal order judgment (TOJ) tasks testing the minimal amount of time between two successive stimuli, one applied to either hand, the participants need to accurately perceive their order of presentation, performance usually dramatically decreases when the task is performed with the hands crossed. These effects of hands posture on TOJ performance have been interpreted as reflecting an automatic activation of spatiotopic representations during the processing of somatosensory stimuli (Crollen, Albouy, et al., 2017; Sambo et al., 2013; Shore et al., 2002; Vanderclausen, Bourgois, et al., 2020; Vanderclausen, Manfron, et al., 2020; Yamamoto & Kitazawa, 2001a).

The location of tactile stimuli has been shown to be initially coded according to somatotopic coordinates before being remapped into spatiotopic reference frames. Accordingly, perceptual abilities to localize tactile stimuli seem unaffected by the spatial location of the stimulated hands within the first 60 ms of their processing, suggesting that spatiotopic remapping occurs at later stages of tactile processing (Azañón & Soto-Faraco,

2008a). In agreement with these behavioral data, an electrophysiological study has shown that the first cortical responses to tactile stimuli being impacted by the posture of the hands occur around 70 ms after stimulation onset, which corresponds to the time range of the N80 component of the somatosensory-evoked event-related potentials (ERPs), whereas earlier responses seemed unaffected by spatiotopic representations (Soto-Faraco & Azañón, 2013). This suggests that during early stages within the primary somatosensory cortex (SI), tactile inputs are only processed according to somatotopic reference frames, and are secondarily remapped into spatiotopic coordinates out of the SI area, during later processing stages within secondary somatosensory (SII) and/or posterior parietal (PPC) areas, probably by integrating proprioceptive information and extrasomatic cues (Azañón, Longo, et al., 2010; Bolognini & Maravita, 2007; Crollen, Lazzouni, et al., 2017; Lloyd et al., 2003; Takahashi et al., 2013; Wada et al., 2012).

Conversely to touch, the neurophysiological mechanisms underlying the spatial mapping of nociceptive inputs remains largely poorly explored. Despite evidence of a finely-tuned mapping system for nociception (Mancini, Longo, Iannetti, et al., 2011; Moore & Schady, 1995; Schlereth et al., 2001), most of the studies in this field only focused their investigation on the description of a somatotopic organization of nociceptive inputs in the brain (Andersson, 1997; Apkarian et al., 2005; Baumgärtner et al., 2010; Bingel, Lorenz, et al., 2004; Henderson et al., 2007; Mancini et al., 2012). However, behavioral studies have recently demonstrated an impact of crossing the hands on the temporal order judgements of nociceptive stimuli (De Paepe et al., 2015; Sambo et al., 2013; Vanderclausen, Bourgois, et al., 2020; Vanderclausen, Manfron, et al., 2020), suggesting that nociceptive inputs are spatially represented according to both somatotopic and spatiotopic reference frames, similarly to what was previously described for touch (e.g. Crollen, Albouy, et al., 2017; Crollen et al., 2019; Shore et al., 2002; Yamamoto & Kitazawa, 2001a). An ERP study has shown that crossing the hands on which laser-induced thermo-nociceptive stimuli were applied decreased the magnitude of the late-latency ERP components in the 200-400 ms latency-range (i.e. N2-P2), while the early-latency N1 component remained unaffected by the change of the posture (Gallace et al., 2011). Considering that N2-P2 components mostly reflect the activity of insular and cingulate areas elicited by nociceptive stimuli while the N1 is mostly evoked during the time range of the SI and SII responses (e.g. Garcia-Larrea et al., 2003; Legrain et al., 2011; Valentini et al., 2012), these results suggest that early stages of nociceptive processing within somatosensory cortices would be unaffected by body posture and that spatiotopic representations of nociceptive stimuli would be taken into account at later latencies. These findings were corroborated by a neuroimaging study having found that contrasting cortical activities elicited by nociceptive stimuli during uncrossed vs. crossed hands postures revealed an involvement of cingulate, insular and prefrontal areas when crossing the hands while responses within SI and SII areas were unaffected by the posture of the hands (Torta et al., 2013). Surprisingly, this study showed greater responses in PPC areas in the uncrossed as compared to the crossed posture condition, while previous studies on touch had shown greater activation of PPC areas when the participants crossed their hands

(Crollen, Lazzouni, et al., 2017; Lloyd et al., 2003; Takahashi et al., 2013; Wada et al., 2012). This difference might be related to the task that the participants were asked to perform while being scanned. Indeed, while the participants of Gallace's and Torta's studies were rating the perceived intensity of the nociceptive stimuli, those having participated to the tactile studies were judging the temporal order of two tactile stimuli successively applied on the two hands in several of these previous studies in touch (Crollen, Lazzouni, et al., 2017; Takahashi et al., 2013; Wada et al., 2012).

An important question that remains unanswered to date is whether touch and nociception share the same mapping mechanisms in the brain and whether spatial processes follow similar time courses for the two somatosensory modalities. While SI, and more specifically the Brodmann area 3b supporting the somatotopic coding of touch (Penfield & Boldrey, 1937), represents an early and important relay in the processing of tactile inputs in the cortex (Allison et al., 1989; Hsiao & Yau, 2008), it seems to be differently involved in nociceptive processing (Lenoir et al., 2017). For instance, a monkey study has suggested that SI does not constitute the main projection of the nociceptive pathways. Instead, the nociceptive afferents would essentially project the information to the operculo-insular and cingulate cortices (Dum, Levinthal, & Strick, 2009). Even though early contribution of SI to nociceptive processing has been evidenced in some studies (Nakata et al., 2008; Valentini et al., 2012), it does not seem to represent an important relay. Indeed, several studies have shown that responses to nociceptive stimuli in SI were not elicited at a significantly earlier latency than those in SII, motor and supplementary motor brain areas (Bastuji, Frot, Perchet, Magnin, & Garcia-Larrea, 2016; Frot, Magnin, Mauguière, & Garcia-Larrea, 2013; Kanda et al., 2000; Ohara, Crone, Weiss, Treede, & Lenz, 2004; Ploner, Schmitz, Freund, & Schnitzler, 1999), suggesting that those latter responses are not dependent on SI activity. Therefore, although the processing of nociceptive and tactile inputs has been shown to be processed in similar cortical areas (e.g. Mouraux et al., 2011; Mouraux & Iannetti, 2009), studies suggest that cortical projections of nociceptive inputs are more parallelly distributed, as compared to the tactile modality (Lenoir et al., 2017). We might thus expect that the spatial mapping processes of tactile and nociceptive inputs would occur following different time courses. Therefore, by taking advantage of the high temporal resolution of the event-related brain potentials, the aim of the present experiment was to compare in healthy humans the time courses of the activation of the spatial representations of somatosensory inputs elicited respectively by innocuous tactile and specific nociceptive stimuli.

To this aim, event-related potentials (ERPs) were recorded while participants received on their hands vibrotactile stimuli and CO_2 laser-induced radiant heat stimuli specifically activating skin nociceptors. Crucially, brain responses to these stimuli were recorded while participants' hands were placed either in an uncrossed or a crossed posture. Any noticeable difference between the ERPs elicited in the crossed as compared to the uncrossed posture condition within one modality was considered as likely reflecting the time windows during which somatotopic and spatiotopic representations would be concurrently activated. The

objective was to tag and compare the earliest latencies at which such effects of the posture would emerge across the tactile and nociceptive modalities. Therefore, we compared ERPs respectively elicited by vibrotactile stimuli and CO_2 laser stimuli delivered with the same stimulation parameters. Due to physical and physiological constraints, laser-evoked potentials are usually obtained in response to a small number of stimuli applied with relatively long and variable inter-stimuli intervals. However, such procedure hinders the observation of very early latency ERP components typically observed in response to non-nociceptive somatosensory stimuli (Mouraux et al., 2013). We therefore added a third recording session during which early latency ERP component were evoked by transcutaneous electrical stimulation of the medial nerve applied over the participants' wrists using a large amount of stimuli delivered at a short and constant time interval (Cruccu et al., 2008).

2. Methods

2.1. Participants

Twenty healthy young participants (14 men/6 women; mean age of 24.45 years old (SD=1.93) took part in the study. Seventeen of these participants were right-handed and three of them were left-handed according to the Flinders Handedness Survey (Nicholls et al., 2013). None of the participants reported prior history of severe neurological (i.e. brain injury, meningitis, prolonged state of unconsciousness), psychiatric or chronic pain disorders, diabetes, migraine, heart attack, traumatic injury of the upper limbs in the last six months, cutaneous lesion of the hands' dorsa, regular use of psychotropic drugs, or intake of analgesic drugs (e.g. NSAIDS and paracetamol) within the twelve hours preceding the experiment. Having a pacemaker and a very dark skin were also considered as exclusion criteria and are respectively related to the use of electrical and laser stimulations (see Stimuli). All participants had normal or corrected vision, had slept at least 6 hours the night preceding the experiment and were blinded to the aim of the study. Written inform consent were obtained for all participants and all experimental procedures were approved by the local biomedical ethics committee conformed to the Declaration of Helsinki. The participants received financial compensation for their participation in the experiment.

2.2. Stimuli

Three different stimulation modalities were used in this study. All stimulations were remotely controlled using Matlab 2018.

Nociceptive stimuli consisted of radiant heat stimuli delivered onto the skin of the two hands' dorsa by means of two CO_2 laser stimulators (wavelength 10.6 μm) (Laser Stimulation Device; SIFEC, Ferrières, Belgium). The power of the output stimulation was regulated using a feedback control based on an online measurement of the skin temperature at the site of stimulation by means of a radiometer whose field of view was collinear with the laser beam (see Churyukanov et al., 2012). This allows defining specific skin temperature profiles. The laser beams were conducted through 10-m optical fibers. Each fiber ended with a head containing the optics used to collimate the laser beam to 6 mm diameter at the target site. Each laser head was hold upon each participant's hand by means of articulated arms attached to a camera tripod system (Manfrotto, Cassola, Italy). Each laser head was fixed into a clamp attached to a 3-way head affording displacements of the target site of the laser beam perpendicularly oriented to the hand's dorsum by means of several sliders going in all directions. Laser beams were displaced after each stimulus in order to avoid nociceptor

habituation and/or sensitization. Stimuli duration was 100 ms. Stimuli were composed of a 10-ms heating ramp dedicated to reach the target temperature, followed by a 90-ms plateau during which the skin temperature was maintained at the target temperature. Heating was then stopped. The temperature used for the experiment was set at 60°C on both hands by default, which is intended to specifically target Aδ nociceptive fibers responses, more particularly rapidly-adapting type II Aδ-mechano-heat-sensitive nociceptors (Churyukanov et al., 2012; Plaghki & Mouraux, 2005; Treede et al., 1995). If necessary, this temperature was slightly adapted (i.e. lowered) for one of the hands when the participant reported the stimulations as unequally intense between the two hands, or for both hands when the pain elicited by the stimulations was considered unbearable by the participant for the duration of the whole experimental block (i.e. 10 to 15 minutes). Whether they were adapted or not, the intensities were unchanged between the two experimental blocks (Mean±SD left hand: 59.35±1.18 °C; right hand: 59.6±1.0.82 °C). Stimuli at such temperature values were perceived as pricking and relatively painful. After each block of stimulation, sensations were tracked using a list of words to be chosen (*not perceived*, *light touch*, *tingling*, *pricking*, *warm*, *burning*) in order to ensure that the stimuli were still well perceived as pricking by the participants.

Innocuous vibrotactile stimuli were generated by means of two vibrotactile transducers driven by standard audio amplifiers (TL-002-14R Haptuator Redesign, Tactile Labs, Inc., Montreal, Canada). The duration of the stimuli was 40 ms and the vibration frequency was of 250 Hz. Participants held the two vibrotactile transducers slightly above the table, one in each hand, between the thumb and the forefinger. The stimuli were perceived as equally intense for all participants and the sensation elicited was a clear and brief vibration.

Transcutaneous electrical stimuli of the median nerve were used in order to investigate a potential effect of the posture on the early-latency cortical responses elicited by non-nociceptive somatosensory inputs ascending through the lemniscal pathway (Cruccu et al., 2008). These stimuli were applied on the two wrists using constant-current square-wave (.5-ms duration) electrical pulses generated by two DS7 stimulators (Digitimer, Letchworth, UK), one for each arm, and were delivered by means of two pairs of adhesive electrodes (Covidien Kendall Disposable Surface EMG/ECG/EKG, Mansfield, MA). The electrodes were positioned over the superficial branch of median nerves and were separated by a distance of ~2 cm. The anode electrode was placed proximal relative to the cathode electrode. The adhesive electrodes were not displaced between the two experimental blocks. The intensity of stimulation (Mean ± SD left hand: 3.41±1.13 mA; right hand: 3.66±1.69 mA) was adapted at individual motor threshold for each arm. The experimenter started to stimulate the wrist at 2.5 mA with a humidified felt electrode (a device composed of two small electrodes separated by ~2 cm) at several locations over the median nerve on the wrist in order to find the position of the electrode eliciting the best response (i.e. a clear electrical current felt in the thumb and the index finger). Then, the intensity of the current was increased by step of 0.5 mA until the intensity of the stimulus elicited a clear, consistent and visible

twitch of the thumb for several trials in a row at the same intensity. Afterwards, the felt electrodes were replaced by the adhesive electrodes that were placed at the same emplacements on the wrist. After having done the same procedure for both arms, intensities were then slightly adapted if necessary, so that the participants perceived the stimulations of both arms as equally intense. These final intensities were then kept for the experiment and were unchanged between the two blocks. Stimuli were felt as nonpainful tingling sensations. In total, 2 blocks of 600 stimuli each, equally distributed and randomized between the two hands, were run at a stimulation frequency of 4 Hz. Therefore, one experimental block lasted approximately 3 minutes.

2.3. Procedure

Participants sat on a chair, the hands laying down on a table in front of them, on which a red cross that served as gaze fixation mark was placed at a distance of ~60 cm from their body trunk. They were presented with 6 experimental blocks of stimulation, two blocks for each stimulation modality (i.e. laser, vibrotactile, electrical). For each modality, participants were asked to uncross their arms during one block, and to cross them over their body midline during the other block. Half of the participants put the left arm over the right arm, and the other half did the reverse. The order of the blocks was counterbalanced across participants with the restriction that the two blocks of the same modality with the two different posture conditions were always presented one after the other. Within each stimulation modality, half of the participants started with the uncrossed posture and the other half started with the crossed posture. Participants' hands were placed on the table with reference to two marks separated by a distance of 30 cm, placed equidistantly from the gaze fixation mark. During the blocks of laser stimuli, the hands were placed palms down on the table. Index fingers were positioned on the marks in the uncrossed posture while the fourth fingers were used in the crossed posture to ensure a similar distance between the two hands in both posture conditions. During the blocks of vibrotactile stimuli, the participants were asked to hold the two transducers between the thumb and the forefinger slightly above the table at the location of the marks in both posture conditions. During the blocks of electrical stimuli, the hands' dorsa were placed on the table palms up at the location of the marks for both posture conditions.

During the laser and vibrotactile stimulation blocks, participants received 60 stimuli during each block during which stimuli were randomly and equiprobably applied on the two hands, i.e. 30 stimuli on the left and 30 stimuli on the right hand. Stimuli were triggered by the experimenter by pressing a key of the keyboard, using a inter-stimuli intervals that varied from 5 to 10 seconds. Between two laser stimuli, laser beams were displaced on the stimulated hands before the next trial was triggered. During the transcutaneous electrical stimulation blocks, 600 stimuli, 300 on each of the two wrists, were delivered at a constant 250 ms inter-stimuli time interval during each block. Stimuli were applied randomly and

equiprobably on each wrist. Therefore, each participant received on each hand and for each posture condition 30 laser stimuli, 30 vibrotactile stimuli and 300 transcutaneous electrical stimuli. The duration of a stimulation block was approximately 10 minutes for laser and vibrotactile stimuli and approximately 3 minutes for electrical stimuli.

During the EEG recording, participants were instructed to maintain their gaze fixed on the red fixation cross and to remain as relaxed as possible. In order to maintain a satisfying level of participants' arousal for the EEG recording and encourage them to focus their attention on the stimuli locations, during the laser and vibrotactile stimulations blocks, stimulation sequence was interrupted two times at a trial randomly chosen by the experimenter and participants were asked to verbally report which of the two hands they felt as the last stimulated (i.e. left or right). During transcutaneous electrical stimulation block, participants were asked to report which one of the wrists was stimulated only on the last trial of the block. A small break was proposed to the participants after each stimulation block. White noise was played through earphones during the whole experiment in order to cover noises from experimental devices.

2.4. Measures

The EEG was recorded using 64 Ag-AgCl electrodes placed on the scalp according to 10-10 system (Waveguard cap, Cephalon A/S, Denmark). The two mastoid electrodes were replaced by two extra-cephalic electrodes placed on the left and right earlobes. Eye movements and blinks were monitored by an electrooculogram (EOG) by means of two adhesive electrodes placed on the beginning of the eyebrow and on the cheek next to the left eye. Electrode impedances were kept below 5 kΩ. EEG and EOG signals were recorded and digitized using a sampling rate of 4000 Hz (ASA-LAB EEG system; Advanced Neuro Technologies, The Netherlands).

Offline analyses were done using Letswave6 (http://nocions.org/letswave/). EEG signals recorded during laser and vibrotactile stimulation blocks were down-sampled by 4, filtered using a FFT 50-Hz multi-notch filter, and next using a 0.3-30-Hz bandpass Butterworth filter, and then segmented in 2500-ms duration epochs extending from -500 to +2000 ms relative to the onset of the stimuli. For laser related epochs, trials in which the CO_2 laser did not shoot properly (e.g. due to a bad inclination of the laser beam on the hand) were deleted. Artefacts related to eye blinks or eye movements were removed using an independent component analysis (FastICA, Hyvärinen and Oja (2000)). Signals were next re-referenced to averaged earlobe channels and baseline-corrected using the pre-onset period. Epochs with a signal amplitude exceeding ±100 μV were rejected. Finally, artefact-free epochs were averaged for each participant, separately according to the modality of stimulation (i.e. laser, vibrotactile and transcutaneous electrical), the stimulated hand (i.e. left

and right) and the posture (i.e. uncrossed and crossed). Regarding laser-evoked ERPs, the baseline-to-peak amplitudes and latencies of three ERP components were extracted and analysed (Kunde & Treede, 1993; Legrain et al., 2013; Plaghki & Mouraux, 2005). N2 was first identified at Cz electrode as the most negative deflection peaking 150-250 ms after stimulus onset. P2 was next identified at Cz as the most positive deflection directly following N2 in the 300-400 ms time window. Finally, early-latency N1 was identified at 100-200 ms post-stimulation after having re-referenced ERP signals to Fz at the temporal electrode contralateral to the stimulated hand, i.e. T7 for ERPs elicited by right hand stimulation and T8 for ERPs elicited by left hand stimulation. For one of the participants, because N1 was not identifiable at T7 and T8 electrodes, it was extracted from C5 and C6 instead. For ERPs evoked by vibrotactile stimuli, N2 and P2 were similarly identified at Cz electrode in the 80-150 ms and 150-200 ms time windows, respectively (Legrain et al., 2013; Lenoir et al., 2017; Soto-Faraco & Azañón, 2013). The earlier latency components N60 and P100 were next identified at Cz electrode during the 50-70 ms and 90-110 ms time windows, respectively. No earlier peak component was identified on these ERP waveforms.

EEG signals recorded during transcutaneous electrical stimuli were first corrected for electrical stimulation artefact using a linear interpolation of the signals recorded from -1 to +4 ms relative to the stimulus onset. EEG signal was next bandpass filtered with FFT multinotch filter at 50 Hz and a Butterworth filter of 0.5-250 Hz, segmented into 200-ms duration epochs ranging from -50 to 150 ms, baseline corrected using the -50-0 ms time windows and re-referenced to Fz. Finally, epochs were averaged for each participant, separately according to the stimulated hand (i.e. left and right) and the posture (i.e. uncrossed and crossed). Five different components were identified from the averaged waveforms all at the parietal electrode contralateral to the stimulated hand, i.e. at P4 following stimulation of the left hand, P3 for the right hand. N20 was the earliest component identified as a negative deflection at 17-23 ms after the onset of the stimulation (Cruccu et al., 2008; Lenoir et al., 2017). P30 and P40 components were next identified as two consecutive positive deflections peaking between 25 and 45 ms after stimulus onset, followed by N60, a negative deflection in the 50-70 ms time window, and P80, a positive deflection in the 80-100 ms time window.

2.5. Statistical analyses

Statistical analyses were performed using Matlab 2018 and SPSS Statistics 24 (IBM Corp., Armonk, NY, USA). Analyses were first performed on the peak amplitudes and latencies of the identified ERP components to compare the effects of the manipulated variables. To this aim, amplitudes and latencies of each component at the target electrode were compared using analyses of variance (ANOVA) with hand (left vs. right) and posture (uncrossed vs. crossed) as within factors. For laser- and vibrotactile-evoked ERPs, these analyses were also performed on the amplitude difference between the N2 and the P2 peaks. Greenhouse-Geisser corrections were used if necessary. Contrast analyses were conducted

by means of paired-sample t-tests to detail significant interactions between two or more factors. Effect sizes were measured using partial Eta squared for ANOVA and Cohen's d for t-tests. Significance level was set at $p \leq .050$.

Next, in order to explore potential effects of the variables of interest on ERPs amplitude at any sampled time point and over the whole scalp, point-by-point comparisons by means of 2-way repeated measures ANOVAs with hand (left vs. right) and posture (uncrossed vs. crossed) as within factors were performed independently for each stimulation condition (i.e. electrical, vibrotactile, laser), using Letswave6. In order to reduce the probability of type 1 error due to multiple comparisons, non-parametric cluster-based permutation tests were used, with 500 hundred permutations per analysis (Maris & Oostenveld, 2007). Before performing these analyses, the datasets containing the averaged ERPs elicited by laser nociceptive and tactile stimuli were down-sampled by 2, corresponding to a sampling rate of 500 Hz. This was done because of an extremely important computation time related to the size of these datasets. The cluster-based permutation testing first compared the waveforms of each condition (i.e. posture: uncrossed vs. crossed, hand: left vs. right, and the interaction between the two factors) obtained at each electrode by means of point-by-point comparisons. Then, samples above the critical *F*-value that were adjacent in time were identified as clusters. An estimate of the magnitude of each cluster was then computed by taking the sum of the absolute *F*-value constituting each cluster (cluster-level statistic). Next, the permutation testing (500 times) was used to obtain a reference distribution of maximum cluster magnitude. Finally, the proportion of random partitions that resulted in a larger cluster-based statistic than the observed one (i.e. *p*-value) was calculated. Clusters in the observed data that had a magnitude exceeding the threshold of the 95th percentile of the permutation distribution (i.e. critical alpha-level of 0.05) were considered as significant (see van den Broeke, Lambert, Huang, & Mouraux, 2016). The same procedure was used for post-hoc analyses, which were performed by means of paired-sample t-tests, with the exception than 1000 permutations per comparison were used instead of 500.

3. Results

3.1. Component peak analyses

The grand averages of the ERPs elicited by nociceptive laser stimuli are illustrated in Figure 1. The ANOVA performed on the amplitude of N1 indicated a significant main effect of the hand ($F(1,19)=4.368$, $p=.050$, $\eta^2p=.187$), but no significant effect of the posture ($F(1,19)=.011$, $p=.917$, $\eta^2p=.001$) nor significant interaction between both factors ($F(1,19)=.007$, $p=.934$, $\eta^2p=.000$). N1 amplitude was larger following right hand stimuli (M±SD=-7.525±4.452) than left hand stimuli (M±SD=-5.837±3.136), irrespective of the posture condition. Analyses of N2 amplitude also revealed a significant main effect of the hand ($F(1,19=14.868)$, $p=.001$, $\eta^2p=.439$), but no effect of the posture ($F(1,19)=.384$, $p=.543$, $\eta^2p.020$) and no significant interaction between the two factors ($F(1,19)=.1.420$, $p=.248$, $\eta^2p.070$). N2 amplitude was larger following left hand stimuli (M±SD=-13.487±8.925) than right hand stimuli (M±SD=-11.334±7.446), irrespective of the posture condition. Analyses of P2 amplitude showed neither a significant effect of the hand ($F(1,19)=.004$, $p=.952$, $\eta^2p.000$) nor significant effect of the posture ($F(1,19)=.653$, $p=.429$, $\eta^2p.033$), but a significant interaction between the two factors ($F(1,19)=5.660$, $p=.028$, $\eta^2p=.230$). Laser stimuli applied on the left hand seem to have elicited P2 of slightly larger magnitude in the uncrossed hands posture (M±SD=19.830±9.921) than in the crossed hands posture condition (M±SD=17.100±10.688). However, the difference did not reach significance level ($t(1,19)=1.828$, $p=.083$, $d=.409$). Right hand stimuli elicited P2 of the same magnitude in the uncrossed (M±SD=18.108±10.815) and the crossed (M±SD=18.903±11.333) hands posture conditions ($t(1,19)=-0.604$, $p=.553$, $d=.135$). The analysis of the N2-P2 peak-to-peak amplitude revealed no significant effect of the hand, neither of the posture, nor significant interaction between the two factors (all $F(1,19)\leq2.579$, all $p\geq.125$, all $\eta^2p\leq.120$).

Analyses of the latencies of laser-evoked ERP components only revealed a significant main effect of the stimulated hand on P2 latencies ($F(1,19)=5.884$, $p=.025$, $\eta^2p=.236$) indicating that P2 peaked at earlier latencies when elicited by left hand stimuli (M±SD=0.401±0.040) relatively to right hand stimuli (M±SD=0.413±0.047). None of the other comparisons were significant (all $F(1,19)\leq.793$, all $p\geq.228$, all $\eta^2p\leq.040$).

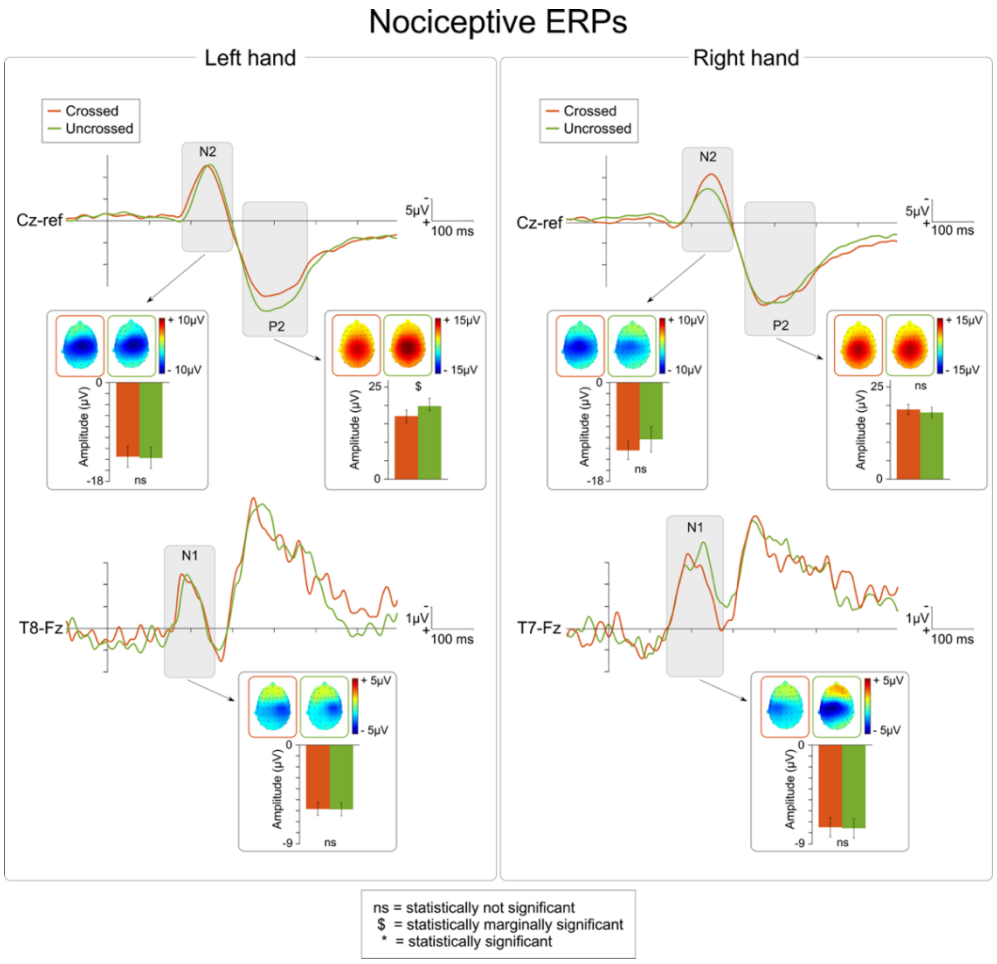


Figure 1. ***Nociceptive event-related potentials according to the hand and the posture.*** *The superimposition of orange and green waveforms represents the ERPs elicited by the nociceptive stimulations during the crossed and the uncrossed hands posture, respectively. The left part of the figure illustrates the ERPs elicited by left hand stimulations and the right part of the figure the ERPs elicited by right hand stimulations. The figure on top represents ERPs recorded from the vertex electrode (Cz referenced to earlobes). The figure on the bottom illustrates ERPs recorded from the contralateral electrodes T8 and T7 (re-referenced to Fz). The vertical lines define the onset of the nociceptive stimulations. The three identified ERP components, corresponding to N1, N2 and P2, are outlined by the grey boxes. The averaged amplitudes of these ERP components are also represented in the bar graphs around the figures. Error bars represent confidence intervals calculated according to Cousineau's method for within-subject designs (Cousineau, 2005). Scalp topographies*

(top-view maps above each bar-graph) were taken at the maximum negativity or positivity of each ERP component. None of the identified ERP components elicited by nociceptive stimulations gave rise to a significant effect of the posture. However, a marginally significant difference between the postures was observed for the P2 component in the nociceptive ERPs elicited by left hand stimulations, the amplitude of the P2 component tending to be larger in the uncrossed as compared to the crossed posture (the symbol "$" means 0.050<p<0.10).

The grand averages of the ERPs elicited by non-nociceptive tactile stimuli are illustrated in Figure 2. Data from two participants were excluded from the analyses due to technical problems during EEG recordings making signals unusable. Data from a third participant were disregarded for the analyses performed on the N60 component because this peak was non identifiable at the expected time window. The ANOVA performed on the data of the remaining 17 participants on the magnitude of the N60 component revealed a significant main effect of the hand ($F(1,16)=10.174$, $p=.006$, $\eta^2p=.389$), no effect of the posture ($F(1,16)=.972$, $p=.339$, $\eta^2p=.057$) and a significant interaction between hand and posture factors ($F(1,16)=5.233$, $p=.036$, $\eta^2p=.246$). Contrasts analyses revealed a significant difference between the two posture conditions for right hand stimuli ($t(1,16)=-2.171$, $p=.045$, $d=.527$), the N60 amplitude being greater in the uncrossed (M±SD=-1.511±1.951) than in the crossed (M±SD=-0.130±1.578) posture condition. Such difference between the postures was not significant for left hand stimuli ($t(1,16)=.760$, $p=.459$, $d=.184$). The ANOVA run on P100 amplitude showed no effect of the hand ($F(1,17)=1.423$, $p=.249$, $\eta^2=.077$) and no effect of the posture ($F(1,17)=1.296$, $p=.271$, $\eta^2=.071$), but revealed a marginally significant interaction between the two factors ($F(1,27)=3.781$, $p=.069$, $\eta^2=.182$). Although it was a marginal effect, we conducted paired sample t-tests, which revealed a slightly but not significant difference between the two postures consecutive to right hand stimuli ($t(1,17)=-1.966$, $p=.066$, $d=.463$; M±SD crossed =6.839±3.671; M±SD uncrossed =5.232±4.245)), while such amplitudes were comparable when the left hand was stimulated ($t(1,17)=.004$, $p=.997$, $d=.001$; M±SD uncrossed=5.182±3.412 M±SD crossed=5.179±3.882). The ANOVAs performed on the N2 and P2 components did not show any significant effect neither of the hand (all $F(1,17)\leq.536$, all $p\geq.474$, all $\eta^2p\leq.031$), nor of the posture (all $F(1,17)\leq1.311$ all $p\geq.268$, all $\eta^2p\leq.072$), nor significant interaction effect between both factors (all $F(1,17)\leq.1.855$, all $p\geq.191$, all $\eta^2p\leq.098$). Finally, the analysis performed on the N2-P2 peak-to-peak amplitude indicated no significant effect of the hand ($F(1,17)=.218$, $p=.646$, $\eta^2p=.013$), nor of the posture ($F(1,17)=1.363$, $p=.259$, $\eta^2p=.074$), but a marginally significant interaction between both factors ($F(1,17)=3.556$, $p=.077$, $\eta^2p=.173$). Comparisons revealed that N2-P2 tended to be larger in the uncrossed (M±SD=26.054±7.025) as compared to the crossed (M±SD=23.232±8.506) posture condition, but only for right hand stimuli ($t(1,17)=1.978$, $p=.064$, $d=.466$), and not for left hand stimuli ($t(1,17)=.244$, $p=.810$, $d=.058$; M±SD uncrossed=24.476±0.097, M±SD crossed=24.083±7.905).

No significant effects were found for analyses of the vibrotactile ERP latencies (all $F \leq 2.695$, all $p \geq .119$, all $\eta^2 p \leq .137$).

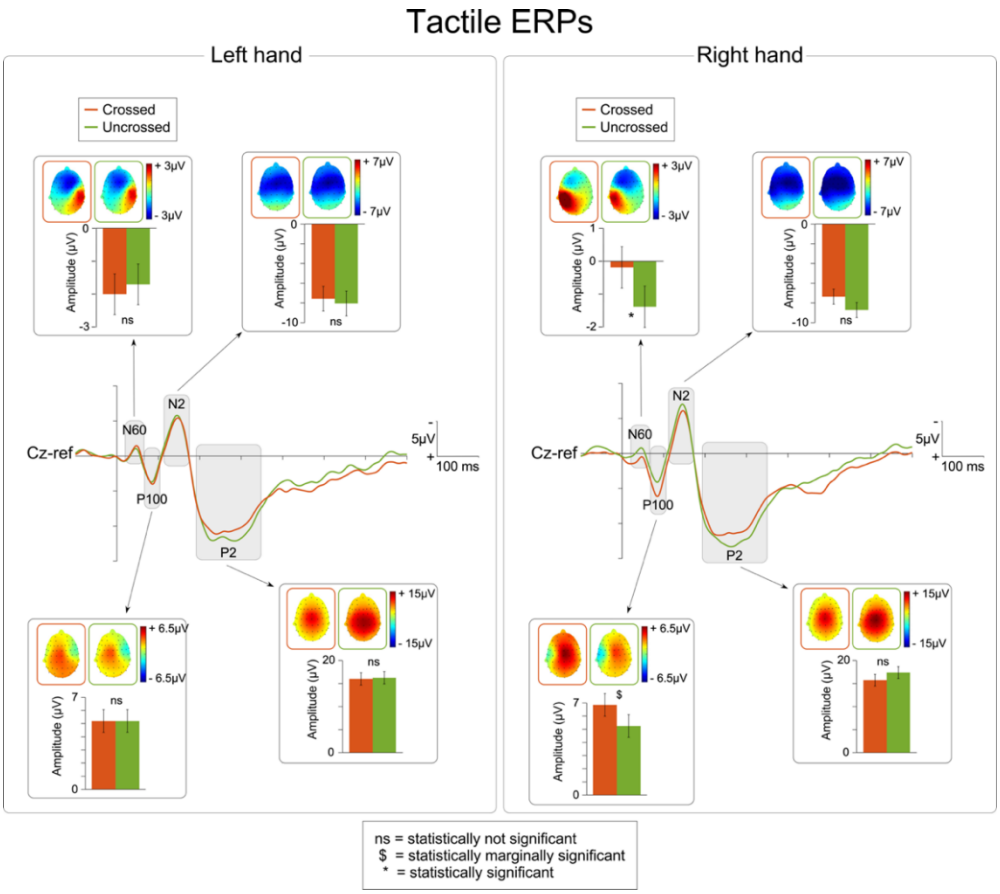


Figure 2. ***Tactile event-related potentials according to the hand and the posture.*** *The superimposition of orange and green waveforms represents the ERPs elicited by the vibrotactile stimulations during the crossed and the uncrossed hands posture, respectively. The left part of the figure illustrates the ERPs elicited by left hand stimulations and the right part of the figure the ERPs elicited by right hand stimulations. The figure represents ERPs recorded from the vertex electrode (Cz referenced to earlobes). The vertical lines define the onset of the electrical stimulations. The four identified ERP components, corresponding to N60, P100, N2 and P2 are outlined by the grey boxes. The averaged amplitudes of these ERP components are also represented in the bar graphs around the figure. Error bars represent confidence intervals calculated according to Cousineau's method for within-subject designs*

(Cousineau, 2005). Scalp topographies (top-view maps above each bar-graph) were taken at the maximum negativity or positivity of each ERP component. The amplitude of the early component N60 was larger in the uncrossed as compared to the crossed posture, but only for right hand stimulations. The statistically significant symbol "" means p<.050. In addition, the amplitude of the P100 ERP component tended to be larger in the crossed as compared to the uncrossed posture for right hand stimulations, but it was only marginally significant (the symbol "$" means 0.05<p<0.10). Finally, the amplitude of the N2-P2 complex also tended to be larger in the uncrossed as compared to the crossed posture condition, also with a marginally significant associated p-value. No significant difference between the postures was observed among the other ERP components of tactile stimulations.*

The grand averages of the ERPs elicited by transcutaneous electrical stimuli are illustrated in the Figure 3. One participant was removed from the analyses because of an artefact making the EEG recordings non exploitable for this modality. P40 was not identifiable in one additional participant. For the remaining participants, analyses performed on the peak amplitudes revealed no significant effect for N20, P30, P40, N60 and P80 components, neither for the effect of the hand (all $F(1,18)\leq1.187$, all $p\geq.290$, all $\eta^2p\leq.062$), nor for that of the posture (all $F(1,17;1,18)\leq.2.978$, all $p\geq.103$, all $\eta^2p\leq.149$). The analyses of the interaction between the two factors did not revealed significant results either (all $F(1,18)\leq2.639$, all $p\geq.122$, all $\eta^2p\leq.128$), with the exception of P80 for which the stimulated hand and posture factors slightly interacted together but still at a non-significant level ($F(1,18)=3.555$, $p=.076$, $\eta^2p=.165$). Given the exploratory nature of the study, post-hoc analyses were run even though the significance level was not reached. It seems that P80 amplitude was larger in the uncrossed (M=6.490±3.068) than in the crossed posture (M±SD=5.610±2.974) but only when the left hand was stimulated ($t(1,18)=2.109$, $p=.049$, d=.484). Indeed, such difference was absolutely not significant when the right hand was stimulated ($t(1,18)=.408$, $p=.688$, d=.094; M±SD uncrossed=5.489±2.908; M±SD crossed=5.366±2.674).

No significant effects were found for analyses of the transcutaneous electrical ERP latencies (all $F(1,17)\leq3.558$, all $p\geq.076$, all $\eta^2p\leq.173$).

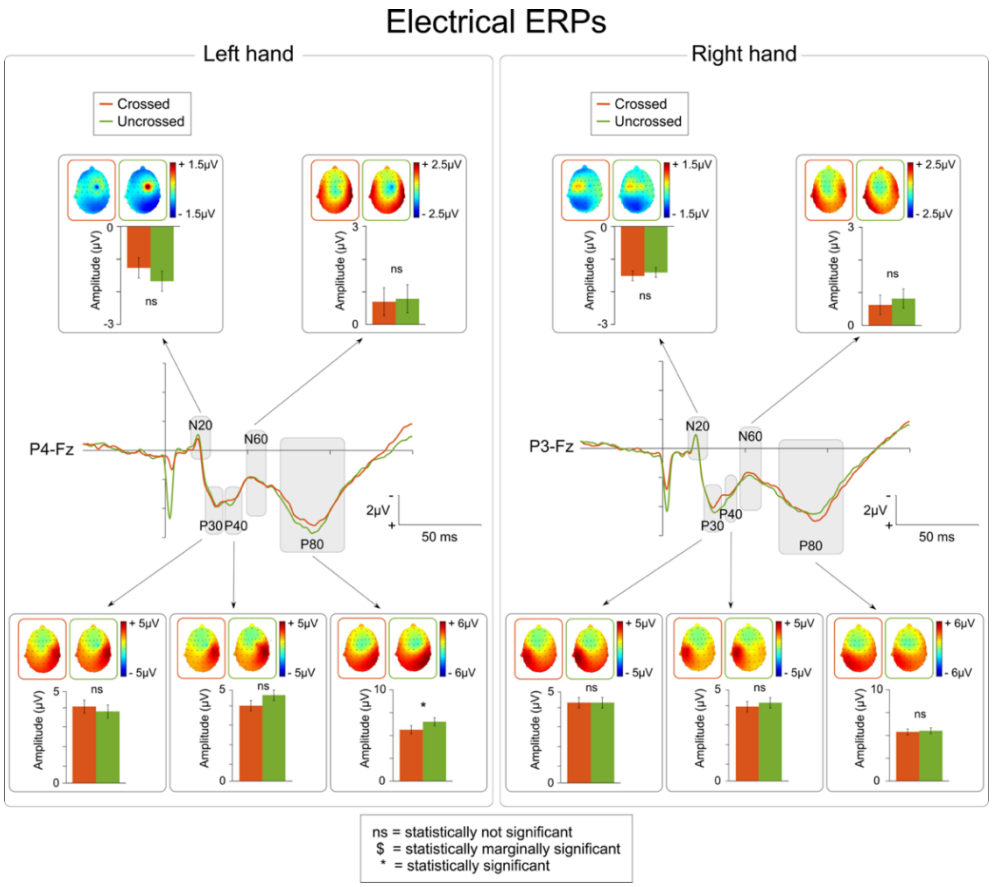


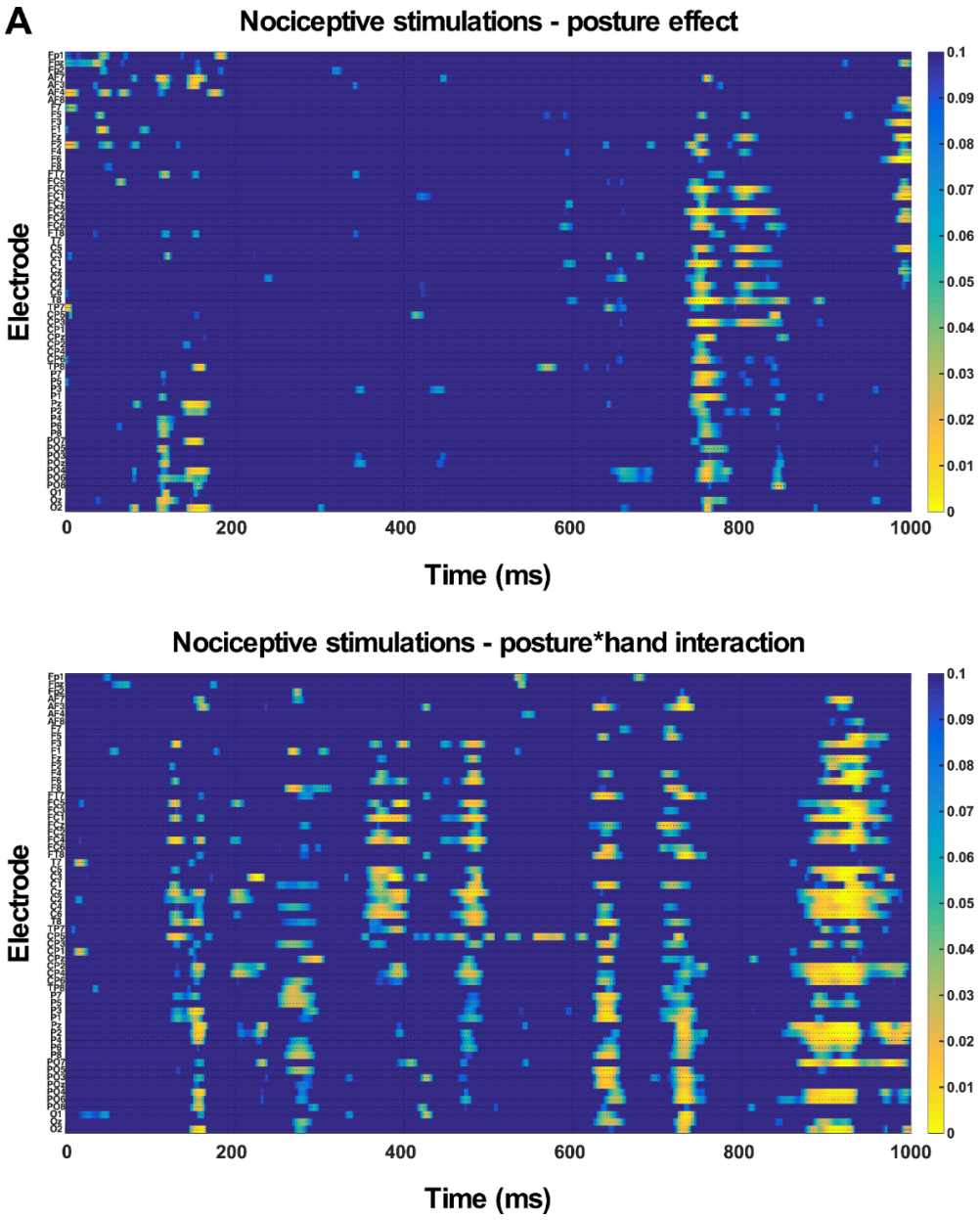
Figure 3. ***Electrical event-related potentials according to the hand and the posture.*** *The superimposition of orange and green waveforms represents the ERPs elicited by the electrical stimulations during the crossed and the uncrossed hands posture, respectively. The left part of the figure illustrates the ERPs elicited by left hand stimulations and the right part of the figure the ERPs elicited by right hand stimulations. The figure represents ERPs recorded from the P4 and P3 contralateral electrodes (re-referenced to Fz) for the left and right hand stimulations, respectively. The vertical line defines the onset of the electrical stimulations. The five identified ERP components, corresponding to N20, P30, P40, N60 and P80 are outlined by the grey boxes. The averaged amplitudes of these ERP components are also represented in the bar graphs around the figure. Error bars represent confidence intervals calculated according to Cousineau's method for within-subject designs (Cousineau, 2005). Scalp topographies (top-view maps above each bar-graph) were taken at the maximum negativity or positivity of each ERP component. An small but significant effect of the posture was found on the late P80 component, the amplitudes of this component being larger in the uncrossed as compared to the crossed posture, but only for ERPs elicited*

by left hand electrical stimulations. The statistically significant symbol "" means p<.050. No significant difference between the postures was observed among the earlier ERP components of electrical stimulations.*

3.2. Time analysis by means of point-by-point comparisons

For the sake of clarity, only differences considered as relevant regarding the main question of this study, i.e. effects of the posture, are reported in this section. The Figure 4A represents a colormap of the p-values resulting from the point by point repeated measures ANOVA performed on ERPs elicited by nociceptive laser stimuli. P-values are displayed, as a function of time and electrode, for the comparison of the posture condition on the top of the figure and for the interaction between the posture and the hand factors on the bottom of the figure. The first reliable significant difference between the two posture conditions that survived the cluster-based permutation testing was observed between 100 and 200 ms after stimuli onset mainly over the posterior parietal and occipital scalp. However, the presence of significant interactions between the posture and the hand factors within the same latency range suggests that this effect might depend on the stimulated hand. Another significant effect of the posture could be noted between 750 and 850 ms at various electrode sites over the whole scalp. Regarding the interaction effects between the posture and the hand, several clusters at intermediate latencies between 200 and 750 ms reached significance, as well as a late latency cluster between 900 and 1000, all over various sites of the scalp. Post-hoc analyses by means of paired-sample t-tests were performed to compare the effect of the posture between left- and right- hand stimulations in order to detail the observed interactions. This revealed clearly significant effects of the posture within the 140-170 ms time window for right hand stimuli at several posterior parietal electrodes, whereas these effects seemed much more inconsistent and reduced at the same latency range for left hand stimuli. Similarly, significant effects of the posture over multiple electrodes were elicited by right hand stimulations at intermediate latency around 650 and around 750 ms after stimulus onset, whereas no significant effect of the posture emerged at these same latencies for left hand stimulations. Regarding the late latency time window (900-1000 ms), post-hoc analyses showed that both left- and right- hand stimulations elicited effects of the posture within this time range. However, the significant cluster for right hand stimulations was observed at earlier latencies (i.e. around 900 ms) than the one elicited by left hand stimulations (i.e. around 950-1000 ms). The remaining significant clusters on the interaction posture*hand (between 300 and 500 ms) were disregarded since these interactions did not seem to be explained by differential effects of the posture according to the stimulated hand (see Figure 6A).

The Figure 4B represents a colormap of the p-values resulting from the point by point repeated measures ANOVA performed on ERPs elicited by non-nociceptive tactile stimuli, displayed exactly as for the illustration of the laser-evoked ERPs and using the same time scale. The first observable effect of the posture having survived the cluster-based permutation testing arose around 100 ms, and was quite largely distributed over the scalp electrodes. The presence of interaction effects between the posture and the hand at similar latencies suggest that this posture effect might, once again, depend on the stimulated hand. Other significant differences between the two posture conditions seemed to emerge between 250 and 400 ms after the onset of the stimulation, first distributed over frontal electrodes and next more posteriorly. This seems to correspond to the latency range of the P2 peak (see component peak analyses, a marginally significant effect of the posture was observed on the N2-P2 peak amplitudes). Next, differences emerged around 500 ms at central and posterior electrodes. Significant interaction effects between the posture and the hand arose at multiple electrodes widely distributed over the scalp between 700 and 1000 ms after stimulus onset. Post-hoc analyses by means of paired-sample t-tests performed separately for each hand were conducted in order to explain the observed interactions between the posture and the hand. This revealed that only right hand stimulations gave rise to significant effects of the posture within the first 100 ms after stimulation onset, at various sites over the scalp, whereas such effects were not observed for left hand stimulations. The latency range of these posture effects seems to correspond to the time window of the N60 and P100 peak components, on which a significant- and marginally significant- differences between the postures, respectively, were observed for right hand stimulations (see peak component analyses). At late latencies between 700 and 1000 ms, both left- and right- hand stimulations elicited significant effects of the posture. However, these effects seemed mainly distributed over frontal electrodes for right hand stimulations whereas they were more prominent over posterior electrodes for left hand stimulations (see Figure 6B).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Nociceptive stimulations - posture effect
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Nociceptive stimulations - posture*hand interaction
Electrode
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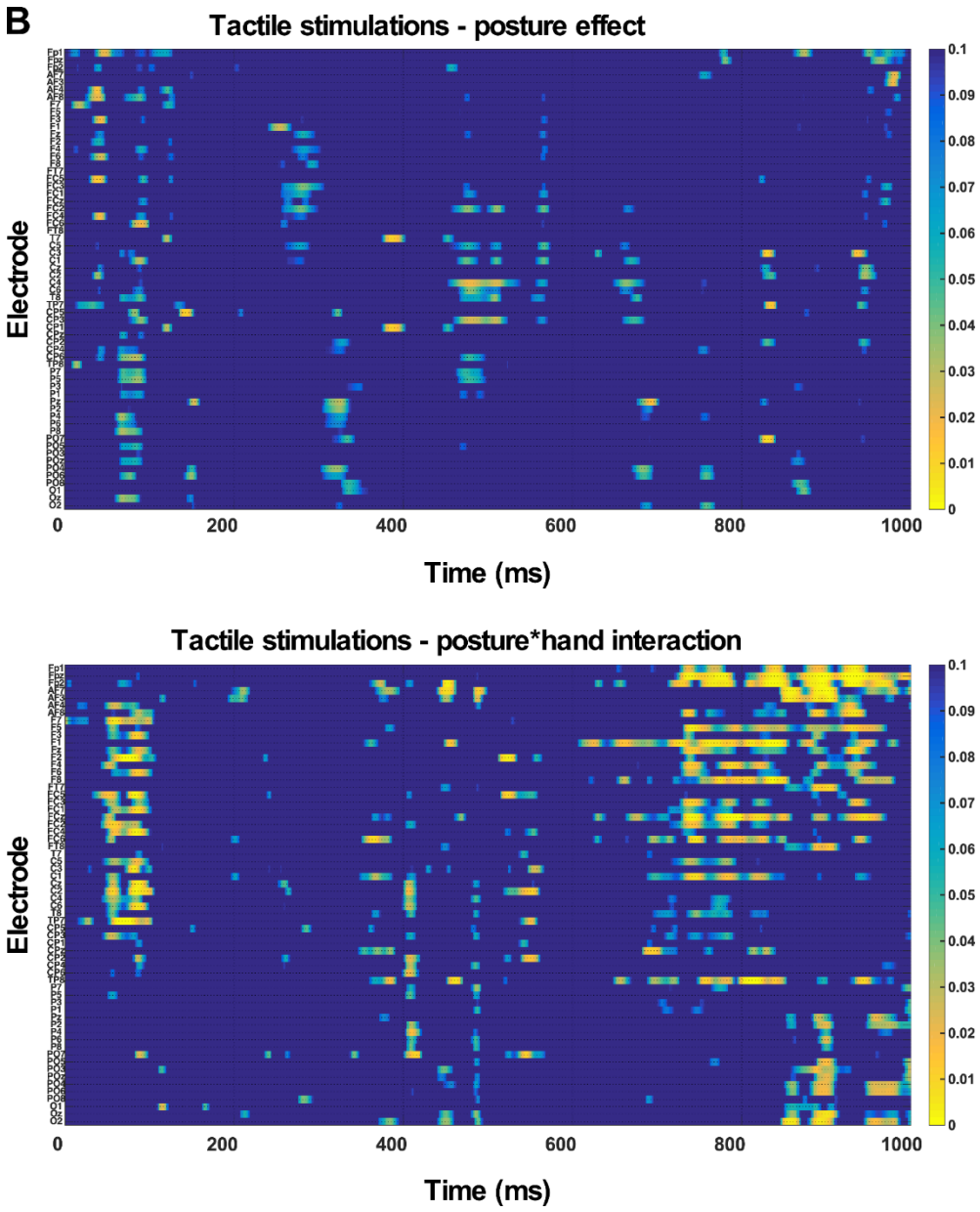
B
Tactile stimulations - posture effect
Electrode
Time (ms)
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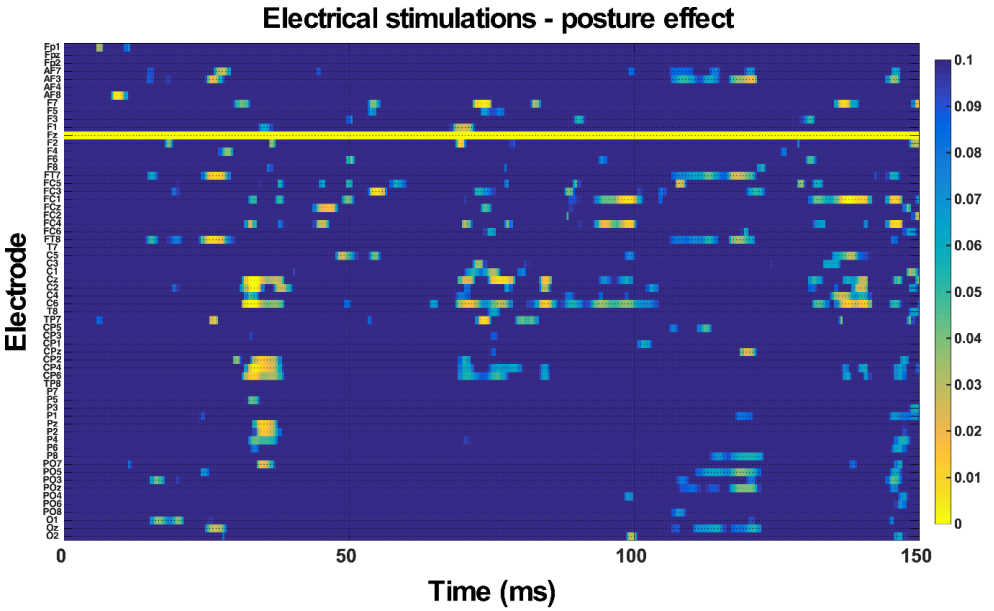
0
Tactile stimulations - posture*hand interaction
Electrode
Time (ms)

Figure 4. *Time by electrode significance maps corresponding to the comparison between nociceptive laser **(A)** and non-nociceptive tactile **(B)** event-related potentials in the crossed and the uncrossed postures (top panel) and for the interaction between the posture (uncrossed vs. crossed) and the hand (left vs. right) factors (bottom panel) obtained from the repeated measures two-way ANOVA. Different colors represent p-values from 0 to 0.1 (significance level was set at p<.05, see colour key) after having applied non-parametric cluster-based permutation tests (Maris & Oostenveld, 2007). Electrodes are grouped according to laterality from top (frontal) to bottom (occipital) following the order: left – central – right, and by proximity.*

The Figure 5 represents a colormap of the p-values resulting from the analyses of the ERPs elicited by non-nociceptive electrical stimuli in the same conditions as previous illustrations but within the 0-to-150 ms time window only. The earliest significant effect of the posture that survived the cluster-based permutation tests was observed between 25 and 50 ms after stimuli onset, mainly at central and posterior electrodes. Since an interaction between the posture and the hand could be noted at the same electrodes and latency range, post-hoc analyses by means of paired sample t-tests were conducted independently for each hand in order to see whether this effect of the posture was dependent on the hand that was stimulated. These analyses revealed that neither left- nor right- hand stimulations seemed to give rise to significant effects of the posture within this narrow 25-30 ms time window, suggesting that the interaction between the posture and the hand could not be explained by differential effects of the posture according to the stimulated hand. The next significant cluster of the main effect of posture was observed between 80 and 100 ms, which seems to correspond to the P80 time window, at the peak on which a significant difference between the uncrossed and crossed postures was evidenced for left hand stimulations (see component peak analyses). However, this cluster was mostly observed for the posture*hand interaction on the posterior part of the scalp (see Figure 6, below panel). Post-hoc analyses showed that neither left- nor right-hand stimulations seemed to elicit clear significant effects of the posture within this time window, suggesting that this interaction could not be explained by differential effects of the posture according to the stimulated hand (see Figure 7).


Electrical stimulations - posture effect
Electrode
Time (ms)
0
50
100
150
0.1
0.09
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0

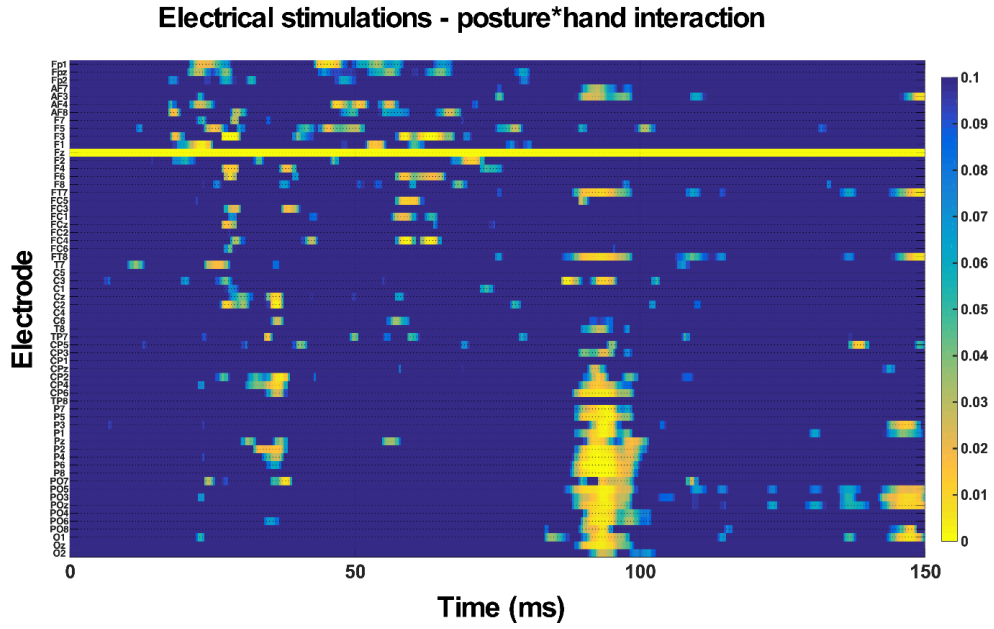
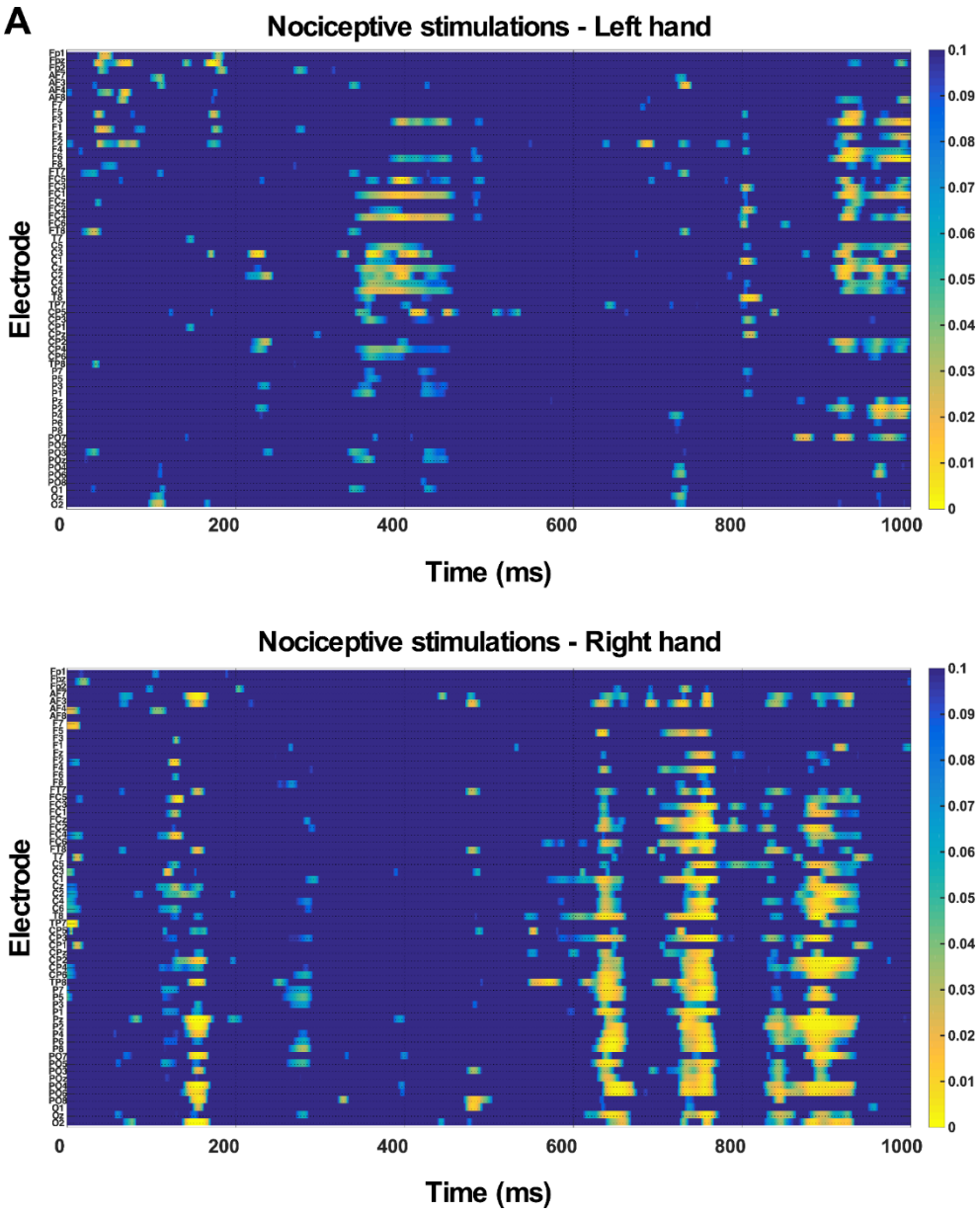

Electrical stimulations - posture*hand interaction
Electrode
Time (ms)
0
50
100
150
0.1
0.09
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0

Figure 5. *Time by electrode significance maps corresponding to the comparison between non-nociceptive electrical event-related potentials in the crossed and the uncrossed postures (top panel) and for the interaction between the posture (uncrossed vs. crossed) and the hand (left vs. right) factors (bottom panel) obtained from the repeated measures two-way ANOVA. Different colors represent p-values from 0 to 0.1 (significance level was set at p<.05, see color key) after having applied non-parametric cluster-based permutation tests (Maris & Oostenveld, 2007). Electrodes are grouped according to laterality from top (frontal) to bottom (occipital) following the order: left – central – right, and by proximity. The yellow line at Fz electrode indicates that the datasets for this stimulation modality were re-referenced to Fz.*


A
Nociceptive stimulations - Left hand
Electrode
Time (ms)
0
200
400
600
800
1000
0.1
0.09
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0
Nociceptive stimulations - Right hand
Electrode
Time (ms)

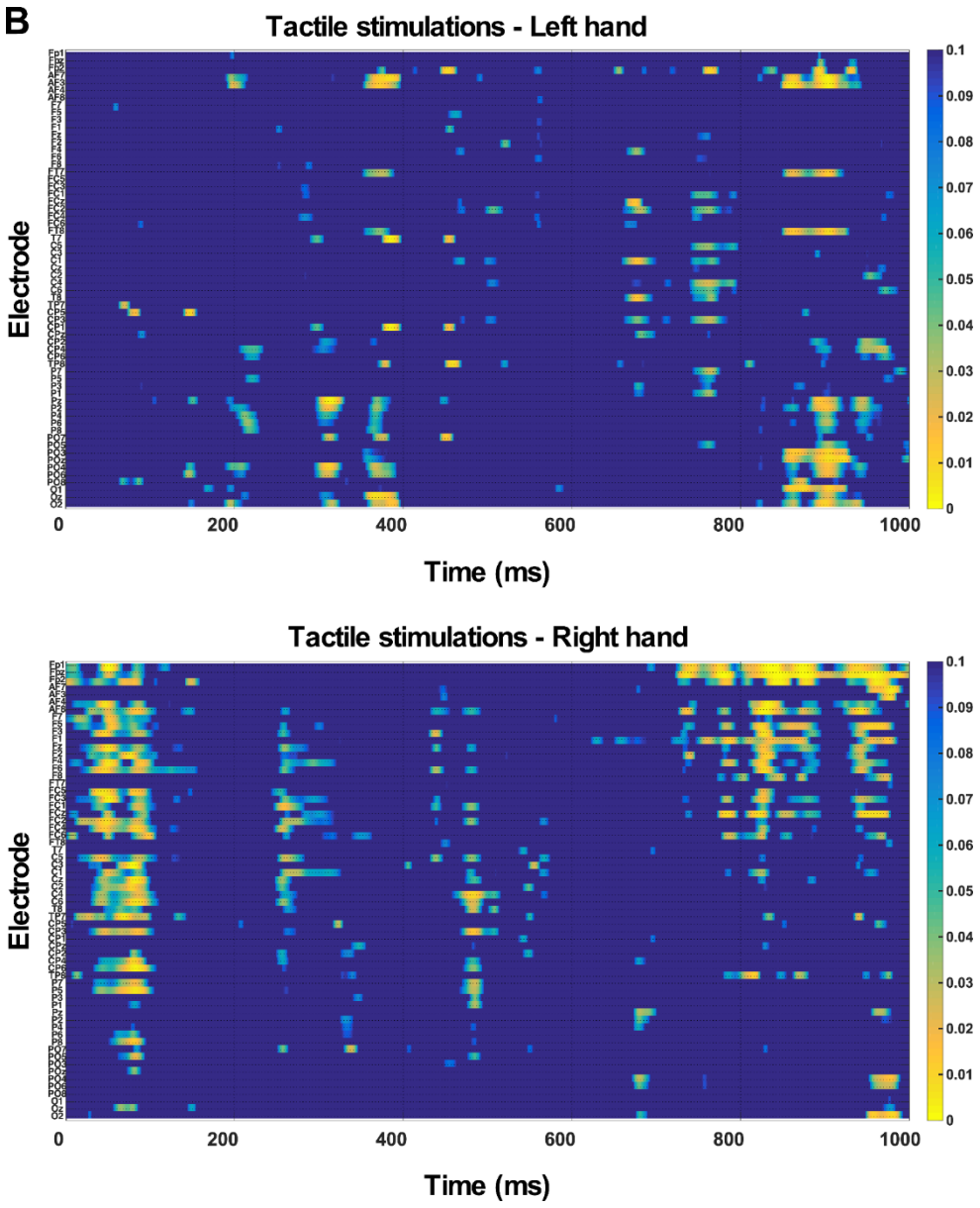
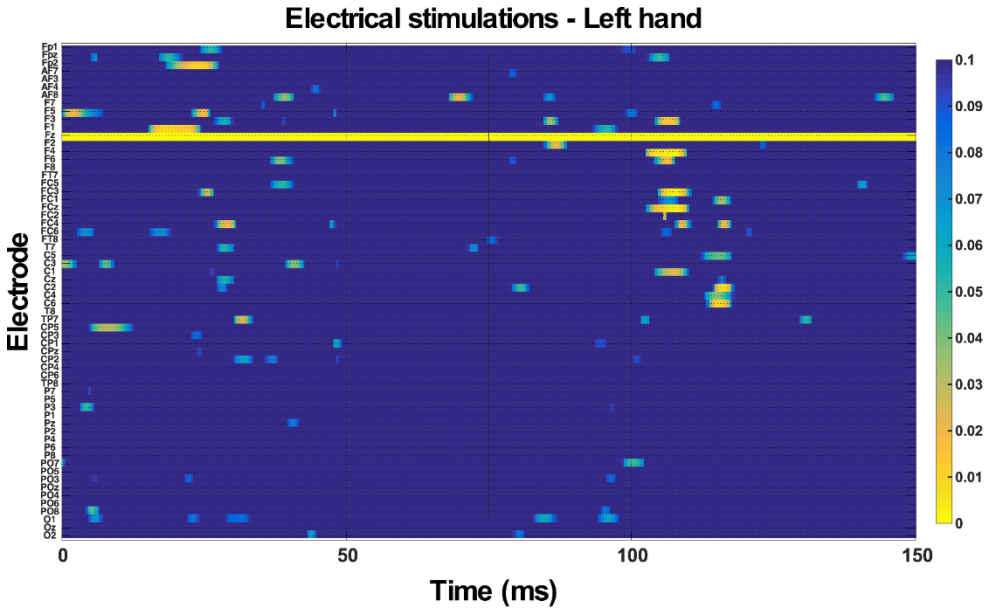

B
Tactile stimulations - Left hand
Electrode
0
200
400
600
800
1000
Time (ms)
0.1
0.09
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0
Tactile stimulations - Right hand
Electrode
0
200
400
600
800
1000
Time (ms)
0.1
0.09
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0

Figure 6. *Time by electrode significance maps corresponding to the comparison between nociceptive laser **(A)** and non-nociceptive tactile **(B)** event-related potentials in the crossed and the uncrossed postures for left (top panel) and right (bottom panel) hand stimulations. Different colors represent p-values from 0 to 0.1 (significance level was set at $p<.05$, see color key) after having applied non-parametric cluster-based permutation tests (Maris & Oostenveld, 2007). Electrodes are grouped according to laterality from top (frontal) to bottom (occipital) following the order: left – central – right, and by proximity.*


Electrical stimulations - Left hand
Electrode
Time (ms)
0
50
100
150
0.1
0.09
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0

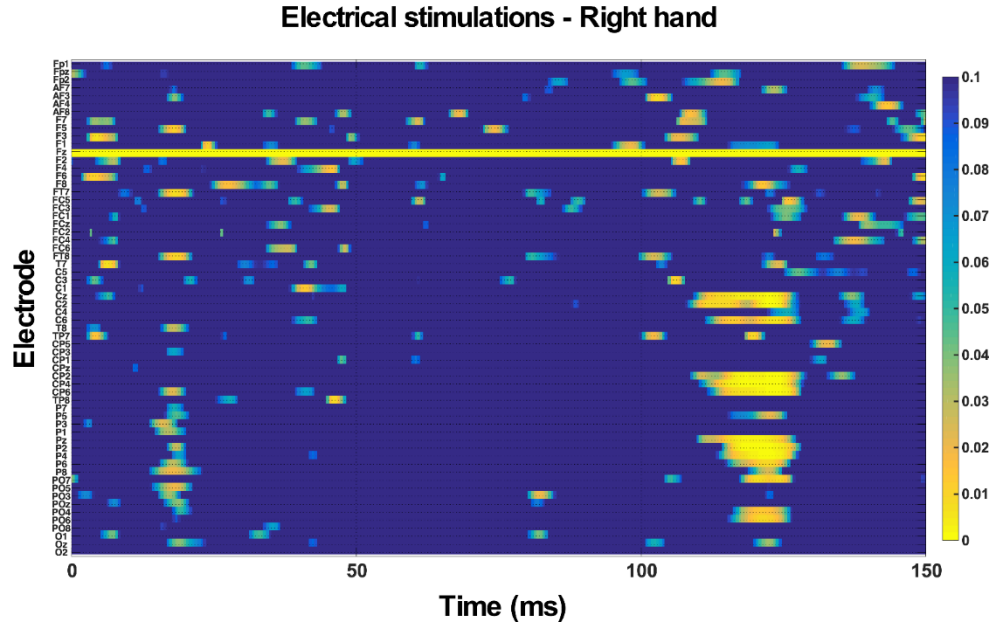

Electrical stimulations - Right hand
Electrode
Time (ms)
0
50
100
150
0.1
0.09
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0

Figure 7. *Time by electrode significance maps corresponding to the comparison between non-nociceptive electrical event-related potentials in the crossed and the uncrossed postures for the left (to panel) and righ (bottom panel) hand stimulations. Different colours represent p-values from 0 to 0.1 (significance level was set at p<.05, see colour key) after having applied non-parametric cluster-based permutation tests (Maris & Oostenveld, 2007). Electrodes are grouped according to laterality from top (frontal) to bottom (occipital) following the order: left – central – right, and by proximity. The yellow line at Fz electrode indicates that the datasets for this stimulation modality were re-referenced to Fz.*

4. Discussion

The aim of the present study was to compare the time courses of the spatial representations of tactile and nociceptive stimuli. More specifically, we compared the impact of the body posture on the ERPs evoked by somatosensory stimuli applied on the hands that were either crossed or uncrossed. ERPs were elicited by the activation of cutaneous mechanoreceptors (by means of vibrotactile and electrical stimuli) or nociceptors (by means of radiant heat stimuli). By comparing the magnitude of the ERPs elicited in the two hand postures, we explored the earliest time window at which somatotopic and spatiotopic representations would be concurrently activated and impact somatosensory processing in the brain.

To summarize the main findings of the present study, differences between the uncrossed and the crossed postures were not evidenced before the 140-170 ms latency range for laser nociceptive stimuli, during which relatively small and sparse effects of the posture emerged, but only consequently to stimulation of the right hand. This time window seems to correspond to the N1 component. However, these results were not corroborated by the analyses on the N1 peak magnitude, since no significant difference between the two posture conditions was found for the N1 peak. Regarding the tactile modality, the earliest significant difference between the uncrossed and the crossed postures was evidenced within the first 100 ms after stimulus onset. This was corroborated by a significant effect of the posture on the peak amplitude of the N60 component, peaking between 50 and 70 ms after the onset of the stimuli. This effect was characterized by a decreased peak amplitude for the crossed, as compared to the uncrossed condition. However, this difference was, once again, only significantly observed for right hand stimulation. Non-nociceptive electrical stimulation did elicit a small effect of the posture on the N80 peak amplitude, in the 70-90 ms latency range, characterized by a decreased amplitude of the N80 peak for the crossed as compared to the uncrossed posture. Noteworthy, this was significant for left- but not right- hand stimulations and only roughly reflected in the point-by-point comparison analyses. Importantly, no modulation of the ERPs' amplitude according to the posture could be evidenced at earlier latencies.

Therefore, our results in the tactile modality, even though limited to the ERPs elicited by right hand stimuli, seem to be in line with previous electrophysiological (Soto-Faraco & Azañón, 2013) and behavioral (Azañón & Soto-Faraco, 2008a) studies having suggested that the spatiotopic representation of tactile inputs would be taken into consideration from ~70 ms after the onset of the stimulation onward. Indeed, Soto-Faraco & Azañón (2013) have shown a modulation of the cortical activity by the posture as early as the 70-90 ms time window whereas cortical responses in earlier latency ranges, such as in the 40-60 ms time window, remained unaffected by the posture. Noteworthy, the effect of the posture in the study of Soto-Faraco & Azañón (2013) was characterized by an increased amplitude in the

crossed, relative to the uncrossed hands posture, similarly to the effects found by another tactile ERP study but at later latencies (i.e. 130-180 ms) (Rigato et al., 2013). However, the present results rather tended to show the reverse, i.e. a decreased peak amplitude in the crossed, as compared to the uncrossed condition.

Conversely to touch, such effects of the posture could not be reliably evidenced for nociceptive stimuli. Indeed, apart from some small and short-lasting differences at relatively early latencies and for right hand stimulations only, no evidence of posture effect could be highlighted on the peak amplitudes of three identified ERP components, namely N1, N2 and P2. This contrasts with the study of Gallace et al. (2011), who have shown that crossing the hands over the body midline resulted in a significant reduction of the N2-P2 peak-to-peak amplitude elicited by laser stimuli. However, an important difference to be noted is that the participants of the present study were not involved in any specific task, unless reporting the hand that was last stimulated two times during each experimental block, while Gallace's participants were rating the intensity of the somatosensory stimuli applied on their hands. Therefore, one possible explanation could be that different processes would be involved in rating the intensity of nociceptive stimuli and locating these stimuli. However, it was shown that being involved in a task focusing either on stimuli intensity or stimuli location did not differently affect the N2-P2 components elicited by nociceptive laser stimulations (Torta, Ninghetto, Ricci, & Legrain, Submitted).

Importantly, the sparse character of the present findings, especially in the nociceptive modality, prevents us from interpreting these data with a high degree of confidence. Several explanations could be proposed in order to account for such results. A first possible explanation to account for the fact that our results are not so clear-cut, both within and between stimulation modalities, could be related to the parameters of our experimental design. For instance, even in the tactile modality, none of the reported posture effects could be observed for both left- and right- hand stimulations. This lack of consistency between the stimulated hands might highlight an important limitation of the present study. Indeed, the impact of crossing the hands on the ERP amplitudes have been evidenced with relatively small effects, at least for the tactile modality (Rigato et al., 2013; Soto-Faraco & Azañón, 2013). Therefore, a very good signal to noise ratio should be necessary in order for such effects to clearly emerge at the level of ERP magnitudes. For instance, as compared to previous studies who used a large amount of stimulation trials to average ERPs (e.g. Rigato et al., 2013; Soto-Faraco & Azañón, 2013), few trials were used in each experimental condition of the present experiment. However, this limitation is inherent to the use of laser stimulations. Indeed, for safety measures (i.e. avoiding burning risks), the stimulation spot needs to be changed after each stimulus. In addition, increasing the number of stimulations and/or the stimulation frequency would have resulted in raising the transient inflammatory reaction of the skin consecutive to high-intensity laser stimuli, which might lead to skin overheating or habituation and impact the perception of the stimuli. Finally, increasing the

number of trials would logically extend the experiment's duration, which can also result in increasing the participants' fatigability, and, in turn, affects the EEG signal.

Another possibility to be found in our experimental procedure could be related to the fact that our participants were not engaged in any specific spatial task. More specifically, although they were asked to maintain their attention on stimuli location because it could be asked them to report the hand that was last stimulated at any trial during the experiment, it remained to occur at rare occasions (i.e. two times per block). Therefore, we cannot ensure that the spatial perception of the stimuli was clearly made relevant during the experiment. In contrast, in the tactile ERP study of Soto-Faraco & Azañón (2013), trials were interweaved in between the single stimulation trials during which two stimuli were applied, one on each hand, and participants judged the temporal order of these two stimuli. Even though these trials were excluded from the ERPs analyses, this indicates that the participants could expect, at each trial, being presented with two stimuli and having to provide a response based on the location of the two stimuli. This experimental context might be more effortful as compared to simply reporting one single stimulated hand at very rare occasion in the present study. Accordingly, it is possible that such contextual factors have triggered, or enhanced, the activation of spatiotopic representations of tactile stimuli. In contrast, the circumstances of our experiment might not have been focused enough on spatial features of the stimuli for a conflict between the two spatial maps to emerge in the crossed posture, and thereby to be clearly reflected in the evoked potentials. This interpretation would suggest that the spatiotopic representations of somatosensory stimuli might not be so strictly automatically activated, and could rather depend on whether the spatial perceptual aspects of the stimuli are task-relevant or not. In accordance with this idea, a behavioral study has shown that when the participants underwent temporal order judgment tasks in which they were asked to judge the order of appearance of two tactile stimuli based on non-spatial characteristics, such as their duration of frequency, crossing the hands had no influence on their performance (Roberts & Humphreys, 2008). An alternative hypothesis could be that spatiotopic representations of somatosensory stimuli would be automatically taken into account, but would be reflected by crossing effects only when a conflict between the somatotopic and spatiotopic representations would emerge. Most importantly, such conflict between the two maps would be triggered by - or proportional to – the relevance of spatial location of the stimuli for the ongoing activity.

In spite of these quite scarce results, the present study appears to reveal the presence of more pronounced effects of the posture for the tactile, as compared to the nociceptive modality. A possible account that might be proposed in discreet terms would be that the spatiotopic mapping would follow different time courses for touch and nociception. Indeed, the time course of the spatiotopic remapping has been suggested to be sequential for tactile inputs, the location of the touch being originally represented according to somatotopic coordinates in the primary somatosensory cortex (SI) (Penfield & Boldrey, 1937) before being remapped into spatiotopic representations taking body posture into account (Azañón

& Soto-Faraco, 2008a; Overvliet et al., 2011; Soto-Faraco & Azañón, 2013), much likely in posterior parietal areas (Azañón, Longo, et al., 2010; Bolognini & Maravita, 2007; Crollen, Lazzouni, et al., 2017; Lloyd et al., 2003; Takahashi et al., 2013; Wada et al., 2012). Notably, the absence of any effect of the posture on very early (e.g. N20) and early latencies, thought to reflect activity confined to Brodmann area 3b of SI (Allison et al., 1989; Mauguière et al., 1999), observed in the present study, whereas some differences emerged at later latencies, would be in accordance with this hypothesis. However, SI has been suggested to be differentially involved in nociception. For instance, it would not represent an important relay to the nociceptive information, conversely to touch (Dum et al., 2009; Lenoir et al., 2017). Therefore, considering that nociceptive events usually evoke brain activity in a non-specific widely distributed network of brain structures, among which SI and SII have sometimes been observed to be activated at the same latency range (Bastuji et al., 2016; Frot et al., 2013; Kanda et al., 2000; Ohara et al., 2004; Ploner et al., 1999), it could be proposed that the cortical organization underlying the spatial perception of nociceptive stimuli might differ from that of tactile inputs. More specifically, nociceptive stimuli might be co-mapped into somatotopic and spatiotopic coordinates parallelly, instead of being sequentially mapped according to somatotopic, followed by spatiotopic representations. Following this idea, if we consider that the modulation of tactile ERPs by crossing the hands would reflect the conflict between the somatotopic and spatiotoic maps once spatiotopic coordinates become available (Soto-Faraco & Azañón, 2013), no effect of the posture should be highlighted on ERPs elicited by nociceptive inputs. Indeed, in this instance, both spatial codes would be available from the beginning of the processing, or at very early stages. This could explain the lack of results in the nociceptive modality while more obvious effects of the posture on tactile ERPs could be evidenced in the present study.

In conclusion, while the present results seem to partly replicate previous literature regarding the timing of spatial remapping of touch, they would also give some indications about potential differences between the time course of such spatiotopic mapping for tactile and nociceptive stimuli. Therefore, our findings, even though lacking of robustness, would constitute a good start and would provide useful directions for future research aiming at testing this hypothesis with a suitable experimental design.

General Discussion

Localizing somatic input that might be of potential harm to our body is of primary importance to adapt our behavior and prevent body tissues from being damaged. In order to efficiently react to such nociceptive stimuli, it is thus not only crucial to identify which part of the body is potentially being harmed, but also its position in external space at the moment of the stimulation. Taking such spatiotopic frames of reference into account would indeed allow deriving the position of the potentially harming stimulus in external space that is in contact with the body. Therefore, coding the position of nociceptive stimuli according to spatiotopic representations would enable to efficiently orient a defensive action towards the threatening object.

Since the visual system allows us to rapidly detect the source of a felt and potentially noxious stimulus, vision would thereby facilitate defensive actions. Therefore, it could be logically assumed that lacking of such reliable visual information would influence the way of spatially perceiving nociceptive events and/or the efficiency to initiate adequate protective behaviors. The present thesis work was aimed to investigate the impact of visual deprivation on the spatial representation of nociception, with the more general objective of characterizing the role of early visual experiences in shaping the brain's ability to localize nociceptive inputs according to spatiotopic frames of reference.

In this general discussion, the main findings of the different experiments performed to investigate this question will be reviewed. Then, the results of these studies will be interpreted and integrated with the existing literature. Finally, potential limitations of these studies will be discussed and perspectives for future research on this topic will be proposed.

1. Main findings

Study 1 was designed to calibrate tactile TOJ tasks, in which participants judge the temporal order of pairs of tactile stimuli, with the adaptive *psi* method. In previous research, TOJ tasks performed with the limbs crossed over body midline have been extensively used to demonstrate that tactile inputs are not only mapped according to somatotopic frames of reference, but are also remapped into spatiotopic representations taking body posture into account. Notably, these studies have used the method of constant stimuli. The aim of the present study was therefore to investigate the spatial representations of tactile inputs in both early blind and matched normally sighted participants by using a new paradigm allowing to adapt the parameters of the task to each participant's sensitivity, which, in addition, enables to significantly reduce the number of trials. To this aim, congenitally blind and matched normally sighted participants were asked to discriminate the temporal order of two tactile stimuli in an uncrossed or crossed hands posture, with the presented SOA (i.e. time intervals) being adapted to their individual performance in each experimental condition. The results have shown that while crossing the hands resulted in decreased performances in the sighted participants, early blind individuals' sensitivity was not affected by the posture. This suggests that spatiotopic representations of tactile stimuli were automatically taken into account in normally sighted participants but not in the blind, indicating that early visual experience plays an important role in the spatial remapping of tactile events. Thus, we successfully replicated previous findings with our new paradigm. Most importantly, we showed that using this method could provide valid and reliable data while maintaining a reasonably low number of trials, which is of special interest when it comes to using laser-induced heat nociceptive stimuli, as in the following studies.

In **Study 2**, we firstly investigated the spatial representations of nociceptive stimuli by using TOJ tasks with pairs of nociceptive CO_2 laser stimuli applied on sighted participants' hands with the different SOA between the two stimuli being presented according to the adaptive *psi* method. The participants performed the task with their arms uncrossed or crossed over the body midline. They were asked to report on which hand they perceived the first stimulus of the pair. The results showed that participants' ability to discriminate the temporal order of the two nociceptive stimuli was affected by crossing the hands, suggesting that nociceptive inputs are automatically mapped according to spatiotopic representations considering the position of the stimulated body limbs in external space. In a second experiment, we investigated the role of early visual experience in this spatiotopic remapping. To this aim, early blind participants and matched normally sighted participants were asked to perform the exact same task. The results revealed that the performance of early blind participants, on the contrary to that of the sighted, was unaffected by the posture of the hands. Therefore, these findings suggest that early visual experience might play a crucial role in shaping the spatiotopic representations of nociceptive stimuli.

In **Study 3**, we investigated both the influence of early visual experience and cognitive goals on the spatial frames of reference underlying the localization of nociceptive stimuli. To this aim, early blind and normally sighted participants were asked to perform nociceptive TOJ tasks with pairs of laser stimuli presented on each of the two hands according to the *psi* method, while placing their hands either in an uncrossed or crossed posture. Crucially, the influence of cognitive goals was tested by manipulating the task instruction. The participants were asked to report which stimulus of the pair they perceived as having been presented first, according to either its location on the body (left or right hand) or the position of the hand onto which it was applied (left or right side of space), thereby stressing anatomy (i.e. somatotopic coordinates) or external space (i.e. spatiotopic coordinates) as task-relevant reference frame. A first experiment was intended to investigate this question in sighted participants only, while a second experiment using the exact same task and instruction manipulation was intended to compared early blind and matched normally sighted participants. The results have shown that, in sighted participants, crossing the hands led to decreased performances in discriminating the temporal order of the two stimuli, irrespective of task instruction, and thus, of which reference frame was task-relevant. In the early blind participants, the results revealed that, while the posture had no effect on their performance in the task under anatomical instruction, crossing the hands resulted in performance decrement under the spatial instruction. This suggests that the weight accorded to spatiotopic representations of nociceptive stimuli would be more dependent on contextual factors in early blind individuals, as compared to normally sighted people. Taken together, these findings suggest that nociceptive stimuli are automatically coded according to both somatotopic and sapatiotopic frames of reference, but that the integration of these two spatial representations would be weighted according to early visual experience and ongoing cognitive goals.

In **Study 4**, we tested whether the remapping of nociceptive inputs into spatiotopic frames of reference when the hands are crossed could also influence the perception of the intensity of nociceptive stimuli when such conflicting posture is adopted. Indeed, when the somatotopic and spatiotopic maps are misaligned, the two spatial representations must be realigned, which would be effortful and would require cognitive resources. We hypothesized that this cognitive load would leave limited resources available to process stimuli intensity, resulting in reduced perceived intensity of nociceptive stimuli. Therefore, considering that early blind participants mostly rely on somatotopic representations to spatially perceive nociceptive inputs, such conflict between the two spatial representations should be reduced and no additional cognitive cost should be involved in the spatiotopic remapping of the stimuli. Thus, we expected that crossing the hands would lead to reduced perception of pain in normally sighted but not in early blind participants. To test so, two experiments were conducted. A first experiment was intended to see whether we could replicate the effect of crossing the hands on the perceived intensity of nociceptive stimuli. Healthy participants were asked to rate the intensity of nociceptive stimuli of two different intensities while adopting an uncrossed or crossed posture. The results showed reduced intensity ratings in the crossed as compared to the uncrossed posture condition for both intensities. A second

experiment using a similar procedure was performed in order to compare the effect of the posture on the intensity ratings in early blind and matched normally sighted participants. In this second experiment, we did not find any effect of crossing the hands on the perceived intensity of nociceptive stimuli, in none of the groups. Therefore, we could not provide evidence in favor of our hypothesis. However, we did observe differences between the two groups, that is, higher intensity ratings in early blind, as compared to normally sighted participants for the highest intensity condition, independently of the posture. This suggests a greater sensibility to pain in early blind, relative to normally sighted people.

In **Study 5**, we explored the time course of the spatial mapping of nociceptive stimuli in healthy participants, and compared it to that of tactile stimuli which have been suggested to be initially coded in somatotopic representations before being remapped according to spatiotopic frames of reference. To this aim, we recorded event-related brain potentials elicited by non-nociceptive tactile and nociceptive laser stimuli applied on the hands with the same stimulation parameters. The participants' hands were placed either in an uncrossed or crossed posture. To investigate the time course of the activation of spatiotopic representations in each modality, we looked at earliest differences between the crossed and the uncrossed posture condition on the event-related brain potentials elicited by tactile and nociceptive stimuli, respectively. In order to explore potential effects of the posture at very early latencies, sustained non-nociceptive electrical stimuli were also applied on the participants' wrists with a high stimulation frequency. Although only significant for right hand stimulations, the results in the tactile modality showed effects of the posture at a latency range that seem consistent with previous studies, suggesting that spatiotopic representations would become available around 70 ms after stimulus onset. No difference between the postures could be evidenced at earlier latencies. For the nociceptive modality, the results were not very conclusive. We observed some minor differences between the two postures but these effects lacked of consistency across the stimulated hands and the analyses. These findings thus need to be clarified by future research.

2. *Interpretation and theoretical implications*

2.1. *How* does the brain map nociceptive stimuli into spatiotopic representations?

Whereas the spatial representation of innocuous tactile inputs has been extensively studied over the past years (Badde & Heed, 2016; Heed & Azañón, 2014; Tamé et al., 2019), the mechanisms underlying the localization of noxious events on the body has received much less attention. Beside several studies having focused their research on the existence of somatotopic representations of nociceptive stimuli in the brain (e.g. Andersson, 1997; Baumgärtner et al., 2010; Bingel, Lorenz, et al., 2004; Brooks et al., 2005; Henderson et al., 2007; Mancini et al., 2012; Mazzola et al., 2009), only very few studies specifically addressed the question of their representation according to external space (De Paepe et al., 2015; Sambo et al., 2013). These past studies suggested that the spatial perception of nociceptive stimuli might be grounded on the same mechanisms than those of tactile inputs, by demonstrating that nociceptive intra-epidermal electrical stimuli were spatially perceived according to both somatotopic and spatiotopic frames of reference. While these results appreciably extended previous studies in the tactile modality, the specificity (i.e. the selective activation of nociceptive Aδ fibers without concomitantly activating tactile Aβ fibers) of the stimulation technique could not be thoroughly assured in the sense that these stimuli were conveyed by small electrodes in contact with the skin. Therefore, an activation of tactile Aβ fibers could not be excluded with 100% confidence. In addition, whereas the brain's ability to automatically remap tactile inputs into spatiotopic coordinates has been shown to be shaped by early visual inputs (Azañón et al., 2017; Crollen, Albouy, et al., 2017; Crollen, Lazzouni, et al., 2017; Crollen et al., 2019; Röder et al., 2004), the role of visual experience in the spatial representations of nociceptive stimuli had never been investigated so far. In **Studies 2 and 3**, we successfully demonstrated, using a technique that allowed us to selectively and specifically target skin nociceptors, that localizing heat laser-induced nociceptive stimuli on the body automatically implies that its position on the body surface is remapped according to spatiotopic frames of reference considering the position of the stimulated body parts in external space. Taken together with previous research in the tactile modality (Heed & Azañón, 2014) as well as the results of **Study 1** according to which tactile stimuli would be automatically remapped into spatiotopic representations, these findings suggest that the tactile and nociceptive systems would share the same spatial representation. Interestingly, these similarities are observed despite the fact that the inputs from the two modalities are conveyed through two segregated afferent pathways (Kandel et al., 2013). However, conversely to touch, the function underlying the spatiotopic remapping of nociceptive stimuli would be defined by the potentially noxious character of this modality, and thereby potentially harmful for the body's integrity. Indeed, the role of taking spatiotopic representations of any somatic stimulus into account would be to facilitate their integration

with extra-somatic inputs with the purpose of adequately and efficiently adapting our behavior (Legrain & Torta, 2015). Crucially, when it comes to signal a possible danger that might inflict damage to the body, inputs conveyed by the nociceptive system would constitute stimuli of greater relevance to consider and locate, as compared to tactile inputs, in order to protect the body from such potentially damaging stimulus. Therefore, we provided evidence of the exteroceptive function of pain, whose role would be to monitor the space around the body and optimize defensive actions (Legrain, 2017). In that vein, spatiotopic representations of nociceptive stimuli could be seen as a premise of the integration of those stimuli with inputs from other sensory modalities occurring in external space, such as visual or auditory inputs, allowing them to interact and protective actions to be planned. Such multisensory interactions between nociceptive and visual stimuli have been demonstrated to rely on a peripersonal representation, integrating somatic and extra-somatic inputs to build a coherent representation of the body space and the space directly surrounding the body (De Paepe et al., 2015; De Paepe et al., 2017; De Paepe et al., 2014; Filbrich, Alamia, Blandiaux, et al., 2017; Filbrich, Alamia, Burns, et al., 2017; Filbrich et al., 2019; Filbrich et al., 2018; Manfron et al., 2019; Vanderclausen et al., 2017). The spatiotopic mapping of nociceptive events would thus constitute an important preliminary step allowing to integrate physical threats in peripersonal representations of the body and react to the potential danger.

Therefore, the present work complements previous knowledge regarding the spatial perception and representation of pain, by filling the previously existing gap between research on the somatotopy of pain, and research having focused on multisensory interactions between nociceptive and extra-somatic visual stimuli. However, it remains to study whether these principles also apply equally to interactions between nociceptive inputs and other sensory modalities defined in external space, such as auditive stimuli, whose relevance in terms of survival might also be of potential interest.

Strikingly, the findings of **Studies 2 and 3** also offer new insights regarding the importance of visual inputs, in the development of the mechanisms underlying the spatial representation of nociception. Our results highlighted the existence of differences between early blind and normally sighted participants in spatially perceiving nociceptive stimuli. In **Study 2**, we found that, in spite of the great relevance of spatiotopic representations of nociceptive inputs in terms of survival, early blind participants mostly rely on somatotopic frames of reference to localize nociceptive stimuli. This suggests a default advantage of somatotopic representations during the spatial processing of somatosensory stimuli, including nociceptive ones, in visually deprived individuals. This contrasts with the automatic spatiotopic remapping of somatosensory stimuli observed in normally sighted participants. However, in **Study 3**, we successfully demonstrated that despite this embodied default mode of perceiving somatic inputs, early blind participants were able to activate spatiotopic representations of nociceptive stimuli when it was relevant for the ongoing cognitive goal, i.e. when task demands specifically required the participants to use external space as reference frame. From these results, two hypotheses could be proposed. The first

one would assume that nociceptive stimuli are automatically coded according to spatiotopic representations in normally sighted participants, irrespective of the relevance of taking such spatial coordinates into account for the ongoing task. On the contrary, early blind people would only map nociceptive stimuli into spatiotopic representations when it is required for the ongoing activity. This would imply that the genuine automatic process of remapping would depend on early visual experience. The second hypothesis would propose that nociceptive inputs are automatically remapped according to spatiotopic representations in both early blind and normally sighted subjects, but that somatotopic and spatiotopic representations would then be integrated following a different weighting scheme. In the tactile modality, spatial perception has been suggested to be composed of two steps. Tactile stimuli would first be automatically remapped into spatiotopic frames of reference. In a second phase, somatotopic and spatiotopic representations would be integrated and, to a certain extent, flexibly adjusted according to the task demands in people with sight (Badde & Heed, 2016; Badde et al., 2016; Badde et al., 2015). Applying this idea to the present topic, this might suggest that the default weight respectively given to somatotopic and spatiotopic coordinates of nociceptive stimuli in the integration phase would depend on visual experience. It is worth mentioning that this was already hypothesized for touch (Crollen, Albouy, et al., 2017; Crollen & Collignon, 2012; Crollen, Lazzouni, et al., 2017; Crollen et al., 2019). Our results therefore suggest that the tactile and nociceptive systems would be similarly affected by early visual deprivation. In this line, early blind people would have lower default weight accorded to spatiotopic frames of reference of somatic inputs, independently of their modality. Therefore, the conflict between somatotopic and spatiotopic representations that arises when the hands are placed in a crossed posture might be reduced by this default weighting scheme. As a result, early blind participants would have better abilities to solve this conflict when the spatiotopic representation is irrelevant, i.e. to select the response provided by the relevant representation (i.e. somatotopic) and inhibit the response from the irrelevant frame (i.e. spatiotopic). This would account for the results in **Study 2** and **Study 3** under anatomical instructions. However, when external space is made relevant (**Study 3** under spatial instruction), the weight given to spatiotopic representations of nociceptive stimuli would increase, rendering the conflict more important, and resulting in decreased performances in discriminating the location of the stimuli during TOJ tasks, performances that were then comparable to that of people with sight. In that sense, the activation of spatiotopic representations in early blind individuals would be more dependent on contextual factors, while a greater importance would be attributed to spatiotopic representations in the sighted in any case. In other words, the important default weight accorded to spatiotopic representations of nociception, which would be considered as adaptive given the underlying defensive function of the remapping process, would be driven by early visual experiences.

In any case, considering the importance of visual inputs in shaping the spatial perception of nociceptive inputs, and therefore more generally in the preparation and orientation of defensive behaviors, it might be suggested that visually deprived individuals would have

lessened abilities to efficiently protect the body from potential threats. Indeed, vision allows us to rapidly detect the presence of a potentially harmful stimulus in the space close to the body, or approaching the body. Such visual information is meaningful in the sense that it enables us to adapt our behavior, by, for instance, avoiding the object before being hurt by it. Crucially, normally sighted people would know what kind of objects to avoid because they have learned, by associating somatic and visual information, which ones can potentially be painful or harmful for the body's integrity. For example, almost everyone has already associated the sharp shape of a kitchen knife with the painful sensation and the bleeding of a finger cut. This association is stored in the brain and can be transferred to other sharp objects. If, later on, we visually encounter an object with a similar shape, the information that this type of shape can be harmful is retrieved and can be used to adapt our behavior (e.g. avoiding to put the finger on the sharp side of the object). Similarly, the smoke and red color of a fire can be associated with the sensation of burning pain. As a result of this stored association, the vision of smoke in subsequent situations is sufficient to warn us about the potentially burning character of the object and prevents us from being hurt by adequately adapting our behavior. In addition, seeing other people being hurt by certain types of objects would also inform us about the harmful aspect of some situations. This learning by associating visual and nociceptive information would be essential for survival, or at least, would protect us from many injuries and painful experiences. In contrast, lacking of such meaningful and useful visual information would render congenitally blind people more prone to experience pain and to face all kind of injuries more often than sighted people. Indeed, the main feedback that they would benefit from in order to learn what kind of objects or situations they should avoid in future situations is somatic, i.e. by entering in contact with those objects, and thus by often experiencing pain or being hurt. Following this idea, they would rely more on their nociceptive system to be able to adequately adapt their behaviors, while the sighted can, in various situations, rely on their visual system instead. Therefore, in the same way that experiencing their surrounding space mainly through tactile sensations would result in enhanced tactile acuity in the blind (e.g. Wong et al., 2011), one might suggest that congenitally blind individuals would also have a more efficient nociceptive system from being more confronted to these inputs, which would allow them to compensate for the lack of vision. Accordingly, it was shown that congenitally blind subjects are better in discriminating small changes in the temperature of heat nociceptive stimuli, as compared to sighted controls (Slimani et al., 2015). Moreover, Slimani et al. (2016) have shown that low intensity heat nociceptive stimuli were more often and faster detected in early blind than in sighted participants. This apparent enhanced efficiency in processing nociceptive inputs might explain the findings according to which congenitally blind individuals would be more sensitive to nociceptive and painful stimuli, as compared to their sighted peers (Slimani et al., 2014; Slimani et al., 2013). In **Study 4**, we corroborated this hypersensitivity to pain in the early blind, by showing that their intensity ratings to high intensity laser stimuli were significantly higher, as compared to the sighted. However, this finding was not consistent across all our experimental conditions, since we did not observe this difference for lower intensity stimuli. One element that is worth noting is that evidence of enhanced nociceptive processing in the blind was shown for low intensity stimuli, much likely conveyed by C-

fibers (Slimani et al., 2016; Slimani et al., 2015), whereas we used two intensities above the activation threshold of Aδ fibers in **Study 4**.

Nevertheless, the reverse pattern, that is, the availability of visual inputs without any nociceptive feedback, would not be sufficient either in order to efficiently protect the body's integrity. For instance, children with congenital analgesia (i.e. the inability to feel pain), are often depicted as individuals who hurt themselves a lot (Melzack & Wall, 1996). Indeed, they usually display multiple and serious injuries, probably because they cannot efficiently associate the harmful object with the unpleasant or painful sensation that it induces to avoid body damage. This would emphasize the importance of the integrity of both the visual and nociceptive systems in order to develop adequate protective behaviors to avoid tissue damage.

As for tactile stimuli, we hypothesize that the spatial perception of nociceptive stimuli would depend on early visual experience, but also on cognitive goals. Even though the present work (i.e. **Study 3**) only provided evidence of a modulation of the weight accorded to spatiotopic representations of nociceptive stimuli as a function of the task instruction in early blind participants, it might be suggested that the importance of the activation of spatiotopic representations might also be flexibly adjusted to contextual factors in normally sighted subjects. Indeed, while mapping somatic stimuli according to spatiotopic coordinates appears to be a relatively automatic process in the sighted (e.g. Azañón, Camacho, et al., 2010; Heed & Azañón, 2014; Sambo et al., 2013; Shore et al., 2002; Vanderclausen, Bourgois, et al., 2020; Yamamoto & Kitazawa, 2001a), it was also shown, at least for the tactile modality, that the activation of such spatiotopic representations could be attenuated under certain circumstances. For example, reduced influence of spatiotopic representations was evidenced in behavioral tasks (e.g. TOJ or spatial congruency tasks) when the relevance of coding the stimuli according to somatotopic frames of reference was accentuated, and thus that the assumed weight given to spatiotopic coordinates of the stimuli in the integration of the two spatial codes was reduced (e.g. Badde et al., 2015; Gallace et al., 2008; Schubert et al., 2017). Importantly, albeit to a lesser extent, spatiotopic representations of the stimuli still exerted an influence on participants' performance in these tasks, indicating that they were still automatically activated and suggesting that the conflict between somatotopic and spatiotopic coordinates, even though reduced, was still present. However, it is worth noting that in all these studies, participants were required to make judgments about stimuli location on the body. In other words, the relevance of spatially perceiving the stimuli was ensured by task demands, i.e. the stimuli had to be located, if not always explicitly according to external space, at least according to somatotopic frames of reference to perform the task.

Therefore, a question that remains incompletely answered is to what extent the spatiotopic remapping of somatosensory stimuli would be automatically triggered. More specifically, the question would be whether the detection of any somatosensory stimulus would automatically initiate its remapping into spatiotopic coordinates, or whether

processing spatial features of the stimuli, i.e. their location on the body, would be required to initiate such remapping. It might be possible that the relevance of locating the stimuli for the ongoing activity would determine the activation, or the importance of the activation, of spatiotopic representations. In that sense, the modulation of the weight given to spatiotopic coordinates of the stimuli would modulate the importance of the conflict between the somatotopic and spatiotopic representations when they are misaligned, such as when the hands are crossed. Considering that the conflict between the two spatial codes, and more specifically the cognitive resources needed to select the response from the relevant spatial representation while inhibiting the one from the irrelevant spatial code, would be responsible for performance decrement in somatosensory localization tasks with the hands crossed (Badde & Heed, 2016; Heed & Azañón, 2014), it could be assumed that in situations in which spatial information of the stimuli is not relevant for the task, the reduced or non-existent conflict would considerably reduce or abolish experimental effects of crossing the hands on participants' performance. The underlying idea would be that a task context in which a spatial response is required might be necessary to trigger the spatiotopic remapping, or to attribute spatiotopic representations enough weight for a conflict between the somatotopic and spatiotopic maps to emerge when the hands are crossed. As a result, experimental effects originating from such conflict and indexing a spatiotopic remapping of somatosensory stimuli, might be only/more easily observed in such context. For instance, it has been shown, in the tactile modality, that when participants were engaged in tasks in which localizing the stimuli was not a prerequisite to give the response, for example when judging the temporal order of two tactile stimuli based on their duration or frequency (Roberts & Humphreys, 2008) or whether or not the two tactile stimuli were presented at the same time (e.g. Geffen et al., 2000), no effect of crossing the hands, and thereby of spatioptopic representations on participants' performance, could be evidenced.

In the same vein, this hypothesis might account for the fact that we successfully observed an effect of crossing the hands on TOJ performance of sighted participants in **Studies 1 to 3**, but that our results appeared more inconsistent in **Studies 4 and 5**. For instance, in **Study 4**, participants had to evaluate the perceived intensity of nociceptive stimuli. It might therefore be possible that the limited relevance of locating the stimuli in such task context would have reduced the relevance of remapping the nociceptive stimuli into spatiotopic representations. As a result, a conflict between the two spatial representations might not have been elicited by the crossed posture because resolving such conflict to provide a spatial response might not have been relevant enough. Therefore, it might be that such context was not relevant to test our hypothesis according to which the intensity ratings would be reduced in the crossed posture because of the cognitive load associated with the realignment of the two spatial representations. Importantly, future research is needed to clarify the mechanisms underlying the effect of crossing the hands on the perceived intensity of pain and the potential factors that might be responsible for its variability across studies, such as observed in **Study 4**.

The relevance of spatial information of the stimuli for resolving the task could also be applied to electrophysiological studies. Indeed, in studies having shown an impact of crossing the hands on tactile ERPs, the participants were either asked to perform interweaved TOJ trials (Soto-Faraco & Azañón, 2013), or to detect deviant tactile stimuli on one attended hand (e.g. Eardley & van Velzen, 2011; Röder et al., 2008), which would also make stimuli location relevant for the task. In contrast, in the study of Rigato et al. (2013), participants were simply asked to alternatively cross and uncross their arms without any spatial task. Although these authors (Rigato et al., 2013) did observe a modulation of tactile ERPs by the posture, the effect was only found for later latencies (i.e. 130-150 ms), as compared to the study of Soto-Faraco & Azañón (2013) who succeeded to evidence a clear effect of the posture on an early latency range (i.e. as soon as 70 ms after stimuli onset). Therefore, the fact that our results were unclear in **Study 5** (e.g. inconsistencies between left- and right-hand stimulations) might also be related to the experimental context, in which the location of the stimuli was not made very relevant. Indeed, although the participants were asked to report the hand that was last stimulated, they were only required to do so on very rare occasion (i.e. one or two times per experimental block). Therefore, it might be that the spatial features of the stimuli were not stressed enough in our task to elicit a clear conflict between the two spatial representations in the crossed posture that could be clearly reflected in the EEG signal.

Notably, these considerations regarding the automaticity of the spatiotopic mapping of somatosensory stimuli would be worth mentioning in the sense that they could be useful to be taken into account for future studies aiming at investigating such topics as, for instance, characterizing the time course of the spatiotopic mapping of nociceptive stimuli or the brain areas involved in such process.

2.2. *When* does the brain map nociceptive stimuli into spatiotopic representations?

One question that has been addressed in the present work was related to the time course of the spatiotopic mapping of nociceptive stimuli. More specifically, we aimed at comparing the latency at which spatiotiopic representations of tactile and nociceptive stimuli would be taken into account. Indeed, **Studies 1-3** of the present thesis, alongside with previous behavioral research in touch (e.g. Crollen, Albouy, et al., 2017; Crollen et al., 2019; Heed & Azañón, 2014), suggest that the two modalities share the same spatial perceptual processes. However, it is completely unknown whether the spatial mapping of tactile and nociceptive inputs is operated through the same neurophysiological mechanisms. Unfortunately, the results of **Study 5** did not allow us to provide reliable evidence to answer this question, perhaps due to the aforementioned considerations regarding the relevance of the spatial features of the stimuli in triggering the spatiotopic mapping of somatosensory stimuli. Therefore, this topic remains to be further investigated, and we encourage future studies to

take these potential limitations into account when designing the experiment. However, from what we know from previous research, we could hypothesize that the physiological mechanisms underlying the spatiotopic mapping of tactile and nociceptive inputs might differ. Indeed, tactile inputs have been shown to be initially coded according to somatotopic frames of reference within the contralateral primary somatosensory cortex (SI) (Penfield & Boldrey, 1937) before being remapped into spatiotopic coordinates (Azañón & Soto-Faraco, 2008a; Overvliet et al., 2011; Soto-Faraco & Azañón, 2013) in other brain areas, much likely including the posterior parietal cortex (Azañón, Longo, et al., 2010; Bolognini & Maravita, 2007; Crollen, Lazzouni, et al., 2017; Lloyd et al., 2003; Takahashi et al., 2013; Wada et al., 2012). Accordingly, event-related potentials elicited by tactile stimuli have been shown to be unaffected by the posture of the hands at early latencies (e.g. 20-60 ms) thought to reflect activity confined to SI (Allison et al., 1989; Mauguière et al., 1999), whereas effects of the posture could be evidenced at later latencies (i.e. 70-90 ms) assumed to reflect activity outside of SI (Soto-Faraco & Azañón, 2013; see also results of Study 5). However, SI has been recently suggested to be differentially involved in tactile and nociceptive processing. For instance, Lenoir et al. (2017) applied high-definition transcranial direct current stimulation (HD-tDCS), which is a non-invasive technique used to modulate the brain activity of a targeted area, over the primary somatosensory cortex of their participants, before presenting them with tactile and nociceptive stimuli. They showed that this procedure had differential after-effects on the brain responses elicited by tactile and nociceptive stimuli. Indeed, HD-tDCS modulated the brain responses elicited by tactile stimuli at the contralateral hand not only at very early latencies (i.e. 20 ms), but also at intermediate latencies (i.e. 90-160 ms), suggesting that responses originating from outside of SI are dependent on the state of SI, which would make SI an obligatory relay between the projections from the thalamus and other higher order cortical areas. In contrast, HD-tDCS over SI did not modulate brain responses elicited by nociceptive stimuli at early latencies thought to partly reflect activity within SI. Although nociceptive and tactile stimuli have been shown to elicit activity in a similar non-specific cortical network (e.g. Legrain et al., 2011; Mouraux & Iannetti, 2009), SI might not constitute the main targeted projection of nociceptive afferents (Dum et al., 2009). In addition, the cortical responses to nociceptive stimuli would be more bilaterally and parallelly distributed (Haggard et al., 2013). For instance, in several studies, activity in SI has been observed within the same latency range than activity in SII, motor and supplementary motor areas (Bastuji et al., 2016; Frot et al., 2013; Kanda et al., 2000; Ohara et al., 2004; Ploner et al., 1999). Therefore, if similar brain areas would be responsible for the spatiotopic mapping of tactile and nociceptive stimuli, it might be hypothesized that nociceptive stimuli would be co-mapped simultaneously into somatotopic and spatiotopic representations at very early latencies, from the first cortical connections onward. Such an early parallel coding of nociceptive stimuli in both somatotopic and spatiotopic coordinates would be in line with the higher relevance of nociception, as compared to touch, in terms of survival (Legrain & Torta, 2015). Noteworthy, this prediction would not be in accordance with the results of Gallace et al. (2011), who found reduced amplitude of late-latency ERP components elicited by nociceptive stimuli by crossing the hands, while the early latency component (i.e. N1) was not affected by the posture. However, the participants were not

engaged in a task involving to process the spatial features of the stimuli, as they were asked to evaluate the intensity of the stimuli. Importantly, future research is needed in order to characterize the time course of the spatial mapping of nociceptive stimuli as well as the potential influence of contextual factors such as the task in which the participants are involved in the modulation of the nociceptive ERPs by the posture of the hands.

2.3. Theoretical implications beyond the present topic

Beside our specific research questions, our results could also shed a new light on some data from previous literature. Indeed, theories on peripersonal space perception have been sometimes used to explain findings of previous studies in the context of, for instance, chronic pain or behavioral responses aiming at protecting the body. However, spatial perception, and more specifically within the peripersonal space, has received little attention in previous pain research and the underlying mechanisms remain relatively unknown. Therefore, the present results might contribute to revisit some of these findings. For instance, several studies have investigated the integrity of the spatial representations of sensory inputs in chronic pain patients suffering from complex regional pain syndrome (CRPS) using TOJ tasks (De Paepe et al., in press; Filbrich, Alamia, Verfaille, et al., 2017; Moseley et al., 2012; Moseley, Gallace, & Spence, 2009). They showed, for instance, that these patients displayed biases in the spatial perception of tactile stimuli, as well as of visual stimuli presented in the space surrounding the body, i.e. the peripersonal space. Importantly, the direction of the observed biases in the tactile modality depended on the position of the stimulated hands in external space (spatiotopic representations) (Moseley et al., 2012; Moseley et al., 2009). These results thus illustrate that pain is a complex phenomenon that not only implies somatic sensations but also depend on the spatial representations of the body and of the space around the body. Intriguingly, in some of these studies, the authors evidenced that crossing the hands led to significantly decrease the TOJ performances of the patients, as compared to the uncrossed condition, just as in the healthy participants (De Paepe et al., in press; Moseley et al., 2012; Moseley et al., 2009). This would indicate that the patients, just as healthy participants, successfully remapped tactile stimuli into spatiotopic coordinates. More specifically, this would indicate that the processes underlying the recoding of a somatic information into external space would be intact in CRPS. Therefore, considering that (1) we have hypothesized from the experiments conducted in the context of this present thesis that the spatiotopic remapping of somatosensory inputs would constitute a prerequisite, in the sense of a preliminary step, for the integration of spatial information from somatic and extra-somatic stimuli, and that (2) the above-mentioned studies suggest that CRPS patients show deficits in the perception of tactile and visual stimuli in external space, but not in their ability to remap tactile events into external spatial coordinates, it could be hypothesized that the observed cognitive impairments in these patients might rely on spatial processing stages beyond the spatiotopic remapping. Taken together, this would illustrate that the spatial perception and representation of sensory events is not unitary but segregated into different

spatial processes that might be selectively impaired by chronic pain conditions. However, it is worth mentioning that another study did not succeed to demonstrate such crossing hands effects in CRPS patients (Filbrich, Alamia, Verfaille, et al., 2017).

Another interesting finding that could be reinterpreted in light of our results concerns the hand blink reflex. This involuntary and stereotyped motor response is defined as a contraction of the muscles of the eyes elicited by abrupt and intense stimuli in visual- or auditory- but also in the somatosensory- modalities (Berardelli, Cruccu, Kimura, Ongerboer de Visser, & Valls-Solé, 1999). It is basically considered as a general protective reflex. For instance, several studies have evidenced that the amplitude of such a reflex, elicited by electrical stimulation of the wrist, depended on the distance of the stimulated hand from the face. The closest the stimulated hand from the face, the stronger the reflex response (e.g. Sambo, Forster, Williams, & Iannetti, 2012; Sambo, Liang, Cruccu, & Iannetti, 2012; Wallwork, Talbot, Camfferman, Moseley, & Iannetti, 2016). Additionally, in one of these studies, they placed a wooden screen between the stimulated hand and the face, with the aim of changing the boundaries of the peripersonal space of the face. They showed that this procedure abolished the effect of the proximity between the hand and the face on the blink response (Sambo, Forster, et al., 2012). Therefore, the stronger hand blink reflex as a function of hand-face proximity has been interpreted as resulting from the occurrence of a threatening stimulus entering the peripersonal space of the face, providing evidence of the existence of a so-called *defensive* peripersonal space (Bufacchi & Iannetti, 2018; Sambo, Liang, et al., 2012). But most interestingly, while normally sighted and late blind participants have been shown to display similar modulation of blink responses as a function of hand-face proximity, this effect could not be evidenced in one early blind participant (Wallwork, Bufacchi, Moseley, & Iannetti, 2017). These results suggest the importance of a functional visual system in early life in the modulatory effects of the blink response to intense electrical stimuli. Therefore, considering our results and previous tactile data, the modulation of the hand blink reflex by the proximity of the stimulated hand to the face might be reinterpreted as reflecting the spatiotopic mapping of the electrical stimuli. Indeed, in sighted participants, this reflex appears to be modulated by the distance between the sensor (i.e. the hand) and the effector (i.e. the eyes). Hence, this might suggest that the amplitude of the motor response underlying this reflex would be tuned by the spatial representations of the stimulated hand, that is, its position in external space relative to the face. The finding that the early blind participant tested in the study of Wallwork et al. (2017) did not show any modulation of the blink reflex would support this hypothesis, considering that we have shown that the automatic spatiotopic remapping of somatosensory stimuli would depend on early visual experience.

3. Further limitations and perspectives for future research

Beyond the questions of *how* and *when* the spatial mapping of nociception would take place, an important yet unresolved issue concerns *where* in the brain spatiotopic representations of nociception would be processed. Once again, while the neural correlates of the spatiotopic coding has already been addressed for the tactile modality, the cortical areas involved in mapping nociceptive stimuli into spatiotopic coordinates remain hypothetical to this day and need to be investigated in future studies. Nevertheless, from what we know from previous research in touch and nociception, potential candidates could be proposed to play a role in the spatiotopic mapping of nociceptive stimuli. Indeed, as mentioned earlier in this general discussion, several studies have observed brain responses consecutive to nociceptive stimuli in SII within the same time window as activity in SI (Bastuji et al., 2016; Frot et al., 2013; Kanda et al., 2000; Ohara et al., 2004; Ploner et al., 1999). Given that SII is part of the network having been suggested to be involved in the spatiotopic mapping of tactile stimuli (e.g. Takahashi et al., 2013), and considering our assumption according to which nociceptive stimuli might be co-mapped into somatotopic and spatiotopic representations, a role of SII in the spatiotopic mapping of nociception could be first hypothesized.

More generally, we might hypothesize a role of the posterior parietal cortex (PPC) in this process for nociception. Indeed, although brain areas in the PPC have been repeatedly shown to be activated by nociceptive and painful stimuli (Apkarian et al., 2005), the role of these brain structures has often been neglected, as compared to other brain areas such as the insula or the cingulate cortex (Legrain et al., 2011; Tracey & Mantyh, 2007). However, the PPC, and more specifically the intraparietal sulcus (IPS), has been suggested to be involved in the pathophysiology of chronic pain, i.e. CRPS (Maihofner & Peltz, 2011). CRPS patients commonly experience autonomic, sensory and motor symptoms (Marinus et al., 2011), but may also develop cognitive symptoms regarding spatial perception, as explained in the first part of this thesis discussion (e.g. Filbrich, Alamia, Verfaille, et al., 2017). Interestingly, some of their motor impairments, i.e. altered grasping movements, have been associated with activity in the IPS, alongside an activation of the motor and supplementary motor cortices (Maihofner et al., 2007). Moreover, the PPC has been shown to play a role in crossmodal interactions between somatic (i.e. tactile) and extra-somatic (i.e. visual) stimuli within peripersonal frames of reference, emphasizing its role in spatial perception (Avillac et al., 2005; Brozzoli et al., 2011; Graziano et al., 1997; Makin et al., 2007). As a reminder, the cortical areas classically observed in response to nociceptive stimuli have been suggested to belong to a non-specific brain network involved in the detection of any salient sensory event (Iannetti & Mouraux, 2010; Legrain et al., 2011). Considerably, premotor and posterior parietal areas have been demonstrated to be implicated in the spatiotopic remapping of tactile stimuli (Azañón, Longo, et al., 2010; Bolognini & Maravita, 2007; Crollen, Lazzouni, et al., 2017; Lloyd et al., 2003; Takahashi et al., 2013; Wada et al., 2012). Furthermore, in a fMRI

study, Oshiro, Quevedo, McHaffie, Kraft, and Coghill (2007) asked their participants to judge the location of a painful thermal stimulus applied on the back of the leg relative to a previous one applied on the same or a different location on the other leg. This spatial discrimination task activated a widely distributed array of cortical and subcortical regions including, amongst other areas, the PPC. Taken together, these studies suggest that the importance of PPC in pain processing, and potentially in the spatial representation of pain, might have been under-estimated and would deserve more attention in future research, more specifically to determine its potential role in the spatiotopic mapping of nociception.

Finally, although the insular cortex has been shown to be non-specifically activated by nociceptive stimuli, its activity in response to noxious inputs has been shown to be recurrent across studies (Legrain et al., 2011; Tracey & Mantyh, 2007), suggesting an important role of this region in pain processing. However, its exact function remains to be elucidated (Evrard, 2019). A role in interoception, i.e. the representation of the ongoing physiological status of the organs and tissues of the body, has been imputed to the insula (Craig, 2002, 2003). Accordingly, some studies have found gross somatotopic representations of the foot, hand and face in this cortical area (e.g. Baumgärtner et al., 2010; Brooks et al., 2005; Henderson et al., 2007; Mazzola et al., 2009). Besides, the insula has been shown to be activated by nociceptive but also by visual stimuli coded by default in external space (Liberati et al., 2016). Moreover, it was recently suggested that the insula not only hosted the interoceptive function of the body, but also has a role in integrating interoceptive information with information from other modalities such as proprioceptive inputs, likely involved in object-directed behaviors (Evrard, 2019). Therefore, it might be also possible that the insular cortex, or some part of it, would be involved in the spatial representation of pain.

Noteworthy, the proposition of an involvement of SII, PPC and/or the insular cortex in the spatiotopic representations of pain remains speculative and needs to be tested in future studies, as well as the potential implication of other brain areas in such adaptive process for survival.

Another aspect that has been started to be studied in touch but remains to be further investigated in the nociceptive modality is related to the flexibility of the spatial representations of nociceptive stimuli. Indeed, we have illustrated the plasticity of the nociceptive system by showing that visual deprivation could affect the way of spatially perceiving nociceptive stimuli. More specifically, the lack of visual inputs during development would confer less default weight to spatiotopic-, as compared to somatotopic-, representations of nociceptive inputs. In addition, we have shown that the importance accorded to spatiotopic representations of nociceptive stimuli could be adjusted to task demands in early blind participants. Therefore, we have assumed that the spatial representations underlying the localization of nociceptive inputs might be flexible. Importantly, in the first part of this general discussion, several of the hypotheses put forward to explain and interpret our results are based on this speculation as well as previous work that

has been done in the tactile modality (e.g. Badde et al., 2015; Roberts & Humphreys, 2008), given the apparent similarities between the two systems regarding spatial representations. Therefore, we made the assumption that if the spatial representations of touch can be flexibly adjusted to cognitive goals, it would also be the case for nociception. However, evidence of such flexible spatial representations of nociception remains to be established in normally sighted people.

An interesting perspective that could be addressed in future research concerns the developmental aspects of the spatial representations of nociceptive stimuli. Indeed, considering the greater relevance of mapping nociceptive stimuli, as compared to tactile ones, into spatiotopic coordinates in terms of survival, one might wonder whether the two modalities would follow the same developmental line regarding their spatial representation. In the tactile modality, the ability to rely on spatiotopic frames of reference to localize tactile inputs has been shown to develop throughout an extending period from infancy to 5-6 years old, corresponding to the age at which the spatiotopic remapping of touch would become completely automatic (Begum Ali et al., 2015; Bremner, Mareschal, et al., 2008; Pagel et al., 2009; Rigato et al., 2014). More specifically, the importance of visual inputs during a sensitive period in early life in order to develop an automatic spatial remapping of tactile stimuli during localization tasks has been emphasized (Azañón et al., 2017). However, once this ability is acquired through early visual experience, it would remain automatic even when vision is no more available. Accordingly, late blind and normally sighted individuals are similarly impaired during tactile TOJ tasks performed in a crossed posture (Röder et al., 2004). Notably, it is worth mentioning that in the present experiments (**Studies 1-3**), we only compared normally sighted participants to subjects that were blind from birth, thereby disregarding people who lost sight later in life. Therefore, although we can assume from our findings that the ability to automatically map nociceptive stimuli into spatiotopic frames of reference is not completely innate but would rather be shaped by visual inputs, these results do not allow us to determine the existence of a sensitive period that would be crucial in shaping the spatial representations of nociception. Considering the correspondences between previous tactile and present nociceptive studies having investigated spatial perception mechanisms in congenitally blind and normally sighted people, we might assume relatively similar developmental aspects in the two modalities. Nevertheless, this remains to be tested in future studies. Also regarding the participants that we tested in **Studies 1-4** of the present work, another potential limitation would deserve to be mentioned. While the early blind participants were more or less the same throughout the four studies, most of the matched normally sighted participants of the control group changed in each study. The main reason why we tested the same blind participants is that congenitally blind people represent a rare population. Even though they were always naïve to the aims of the studies, they could not remain ignorant regarding the procedure throughout the experiments, such as the laser stimulations or the TOJ tasks. For instance, we cannot exclude an effect of learning in TOJ tasks for the early blind that have participated in the three first studies. However, approximately one year separated each experiment. Therefore, it appears quite unlikely that

this would have influenced our results in any way. In contrast, although we tried to keep the same normally sighted participants to match the participants from the blind group throughout the studies, it was not always possible, most often because they were no longer available. Hence, independently of our will, it was not possible to retain the exact same matched sighted people in participating in all our studies.

Another possible methodological limitation in **Studies 2-5** is related to the use of the laser to stimulate the hands of the participants on which the nociceptive stimuli were applied. Indeed, applying repetitive laser stimuli on a small area of the skin can induce habituation, which is defined as a behavioral response decrement to the stimuli resulting from their repetition (Rankin et al., 2009; Thompson & Spencer, 1966). For instance, stimulus repetition can result in decreasing their perception. Noteworthy, care has been taken to minimize the impact of habituation on the experimental data by, for example, having used an adaptive method which allowed us to considerably reduce the number of trials. In addition, the laser beams were carefully displaced after each stimulation and inter-stimuli intervals were intentionally kept long enough to avoid this phenomenon to occur to a significant extent. However, in spite of our efforts to take this potential issue into account in the present experiments, we cannot completely rule out the possibility that habituation could still had some influence on our results. While the contribution of habituation in our **first three studies** would have been minimized by the robustness of effects of crossing the hands on TOJ performance, a potential influence of this phenomenon on the results of **Studies 4 and 5** could have represented a greater problem. For instance, **Study 4** specifically focused on the perception of the stimuli intensity. Therefore, if habituation would have decreased the perceived intensity of the stimuli throughout the experiment, this could have been partly responsible for misinterpreting our results in the Experiment 1 of **Study 4** and/or for the observed inter-experiment variability regarding the effect of crossing the hands on the intensity perception of pain.

Finally, a potential issue specific to the methodology of the TOJ tasks has to be considered. Indeed, during TOJ tasks, participants can be unsure about the correct answer, especially when the SOA separating the two stimuli are very short. In such situations of uncertainty, participant may display response biases. This means that they will preferentially choose, often not explicitly, one of the two possible responses (Filbrich et al., 2016). For example, a given participant could be more prone to respond that the first stimuli of the pair occurred on the left hand when s·he is unsure about the correct order. Within the context of our adaptive procedure, these biases can represent a potential problem because the presence of large biases (i.e. threshold) can significantly impact the estimation of our main parameter of interest (i.e. the slope characterizing participants' performance in the task) (Kingdom & Prins, 2010). Therefore, to minimize the influence of such potential biases on our data, in **Study 1 and 2,** we used two response conditions. Participants were asked to either report the hand on which they perceived the first stimulus of the pair, or the hand on which they perceived the second stimulus of the pair, in separate experimental blocks and for each

posture condition. This allows to counterbalance the occurrence of such biases across the experimental conditions (Filbrich et al., 2016). Moreover, we excluded participants who showed large biases in at least one of the experimental conditions. However, in **Study 3**, we added one experimental variable (i.e. task instruction). Therefore, in order to avoid increasing the number of stimulations by additional experimental blocks, which can result in increasing stimuli habituation or fatigability, we left out the second response condition in this latter TOJ study. Hence, participants always reported the hand that was stimulated first. Nevertheless, we did exclude participants showing large biases towards one of the two hands in their responses. Therefore, it remains quite unlikely that not having included this variable in our third TOJ experiment had a significant impact on our results.

4. Possible applications and conclusions

The most relevant reason why it would be important to study the nociceptive system would be to better characterize pain perception in order to alleviate the unpleasant experience of pain. Indeed, better understanding the underlying mechanisms of the perception and processing of pain might allow future research to develop new techniques to relieve pain in, for instance, chronic pain conditions, which represent a really challenging issue for public health. More specifically, showing that the perception of pain does not only rely on somatic sensations but can also be influenced by spatial perception would help enlarging the field of possible ways to relief pain. In this vein, better understanding and characterizing the processes at play when, for instance, pain intensity perception is reduced by simply crossing the arms appears essential. Even though this effect was not always replicated, it would deserve future studies' attention.

Beyond the clinical aspect of chronic pain, similar principles could also be applied regarding the main topic of the present work, that is, the impact of visual deprivation on the spatial perception of pain. Indeed, the present findings suggest that the lack of visual inputs could impact the spatial representation of pain, by conferring more weight to somatotopic representations, as compared to spatiotopic frames of reference. Considering the importance of spatiotopic representations of pain for deriving the location of the threatening object in external space and adequately reacting to it, this weighting scheme might in turn affect the ability of congenitally blind people to efficiently adapt their behavior and avoid painful experiences and tissue damage. In this case, better understanding and characterizing how the nociceptive system develops when visual inputs are lacking, might allow developing techniques with the purpose of optimizing the abilities of the blind to adequately adapt their behavior and, most importantly, avoiding hurting themselves. For instance, in cane users, that is, most of the blind individuals, the cane helps to navigate in space and identify the presence of a wall or stairs by hitting the cane to the obstacle in external space. Blind people are thus used to rely on the tactile system, including tactile cues convey by the cane, to supplement the visual system for localizing objects in their peripersonal space. Therefore, one possibility would be to adapt the cues transmitted through the cane regarding the characteristics of the object in external space that they hit with the cane. In other words, the cane could transmit information about the potential harmful character of an object in external space in order to optimize protective behaviors. For example, the cane could conduct the heat of a burning object, or the shape of a sharp object (e.g. through a specific pattern of vibration) to warn the blind about the potentially damaging aspect of these objects and avoid to burn/cut themselves.

The experiments performed in the context of the present thesis work were aimed at investigating the mechanisms underlying the spatial perception and representation of nociceptive stimuli, as well as the role of visual experience in these processes. Efficiently

localizing nociceptive stimuli on the body is important as it allows identifying which part of the body is potentially being harmed. Moreover, being able to consider the external location of the stimulated body part would allow deriving the location of the potentially harmful stimuli in external space. Therefore, spatiotopic representations of nociceptive stimuli would be essential in order to adequately adapt our behavior to protect the body's integrity. Considering the importance of the visual system in spatial perception in general, the aim of this thesis was to investigate how visual experience would shape the spatial representations of nociceptive stimuli.

To this aim, we conducted several experiments comparing the abilities of congenitally blind and normally sighted participants in perceiving and localizing nociceptive stimuli on the body. Although we could not provide an answer to all the research questions addressed in the frame of this present thesis, we succeeded to demonstrate that the way of spatially perceiving nociceptive events depends on the availability of visual inputs during development. Indeed, visual experience would shape the default weighting scheme of the spatial representations of nociception. Accordingly, normally sighted participants seem to automatically map nociceptive stimuli into both somatotipic and spatiotopic representations. In contrast, early visual deprivation would confer more default weight to somatotopic representations. Our results therefore emphasize the plasticity of the spatial representations of nociception.

Appendix

Study 6

The distance between the hands does not influence performance during tactile temporal order judgment[4]

Abstract

Localizing somatosensory stimuli is an important process, since it allows to adequately adapt our behavior and spatially guide our actions in external space to interact with the object that entered in contact with the body. Accordingly, the position of tactile inputs on the body is not only coded according to somatotopic frames of reference, but also according to spatiotopic coordinates, taking the position of the stimulated limb in external space into account. Such spatiotopic representations have often been evidenced by means of temporal order judgment (TOJ) tasks in which the participants discriminate the order of appearance of two somatosensory stimuli presented in rapid succession while their hands are placed in an uncrossed or crossed posture. Crossing the hands has been recurrently associated with a decrease of participants' performance, because somatotopic and spatiotopic representations are mismatching in such conflicting posture. Other studies have suggested that the distance between the two stimulated hands could also modulate TOJ performance. Accordingly, participants' sensitivity to judge the temporal order of two tactile stimuli decreases when the hands are placed close together, as compared to farther apart. However, while crossing hands effects are robust and reliable effects, the influence of the distance between the stimulated hands on TOJ performance is more controversial. Moreover, some studies have suggested that postural effects such as crossing the hands might depend on the vision of the stimulated body parts. Therefore, the aim of the present experiment was to test the influence of seeing the hands on the modulation of tactile TOJ by the spatial distance between the stimulated hands. The results showed no influence of the distance between the stimulated hands on TOJ performance, independently of whether the hands could be seen or not. This result therefore questions the relevance of manipulating the distance between the stimulated limbs, as compared to the more classically used crossed hands paradigm, in investigating the spatial representations of tactile inputs.

[4] Based on: Manfron, L.*, Vanderclausen, C.*, & Legrain, V. (In preparation). The distance between the hands does not influence performance during tactile temporal order judgment.*These two authors contributed equally as first authors to the present study

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 but, also, defensive reaction to noxious external objects, that is, objects that have the possibility to damage the body.

Somatotopy represents almost a 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 and adapt behaviors to their true 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 (Azañón & Soto-Faraco, 2008a; Driver & Spence, 1998; Graziano et al., 1997; Shore et al., 2002; Smania & Aglioti, 1995; Yamamoto & Kitazawa, 2001a). It thereby represents a crucial spatial representation of somatic information as it anchors somatosensory perception in a stable representation of the body posture and limb movements in external world.

The process underlying the formation of a spatiotopic representation has been assessed both for touch and nociception using temporal order judgment (TOJ) tasks (Badde et al., 2014; Badde et al., 2015; Crollen, Albouy, et al., 2017; Crollen, Lazzouni, et al., 2017; Crollen et al., 2019; De Paepe et al., 2015; Heed & Azañón, 2014; Röder et al., 2004; Sambo et al., 2013; Shore et al., 2002; Vanderclausen, Bourgois, et al., 2020; Vanderclausen, Manfron, et al., 2020; Yamamoto & Kitazawa, 2001a). In a TOJ task, participants judge the order of two successive somatosensory stimuli (i.e. two tactile or two nociceptive stimuli), one applied to each hand, separated by different temporal delays. Participants' judgements 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 is dependent 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 taking the posture by default into account (e.g. Crollen, Albouy, et al., 2017; Crollen et al., 2019; Sambo et al., 2013; Shore et al., 2002; Vanderclausen, Bourgois, et al., 2020; Vanderclausen, Manfron, et al., 2020; Yamamoto & Kitazawa, 2001a). This ability to recode

somatosensory inputs from an initial skin-based representation to a more external space-based reference frame is termed somatosensory remapping (Driver & Spence, 1998).

Spatial representations of somatosensory stimuli have also been investigated using other experimental procedures (e.g. Azañón, Camacho, et al., 2010; Azañón, Longo, et al., 2010; Azañón & Soto-Faraco, 2008a; Moayedi et al., 2016; Overvliet et al., 2011; Smania & Aglioti, 1995; Soto-Faraco & Azañón, 2013; Soto-Faraco et al., 2004; Tamé et al., 2011). For instance, the ability to spatially code somatosensory inputs according to both somatotopic and spatiotopic reference frames have been evidenced by manipulating the distance between the limbs on which the somatosensory stimuli are applied (e.g. Driver & Grossenbacher, 1996; Gallace & Spence, 2005; Geffen et al., 2000; Kuroki, Watanabe, Kawakami, Tachi, & Nishida, 2010; Lakatos & Shepard, 1997; Roberts et al., 2003; Shore et al., 2005; Soto-Faraco et al., 2004). The rationale behind the manipulation of the limb distance is the following: as the somatotopic representations of the two stimulated skin areas do not change between the different postural conditions, differences in participants' performances can only be accounted by the metric distance between the stimulated limbs in external space. In other words, it shows that the tested cognitive abilities are dependent on *remapped spatial information* about somatic inputs. For instance, Shore et al. (2005) and Roberts et al. (2003) found that during tactile TOJ, participants had more difficulties to correctly judge the temporal order between the two tactile stimuli when their stimulated hands were placed close together, as compared to when they were far apart. Roberts et al. (2003) demonstrated significant distance effect on TOJ performances when the hands were either crossed or uncrossed. Similarly, other studies showed that discrimination of tactile stimuli applied on one hand was more sensitive to distraction from tactile stimuli applied on the opposite hand when the two hands were close together, as compared to further apart (Driver & Grossenbacher, 1996; Lakatos & Shepard, 1997; Soto-Faraco et al., 2004; However see Evans, Craig, & Rinker, 1992).

Gallace and Spence (2005) further demonstrated that simply raising in participants the visual illusion that the distance between the hands is changed, by changing the distance between one hand and its mirror-reflected image, can modify tactile TOJ performances while the real distance between the hands remains actually unchanged. This experiment illustrated the relevance of manipulating distance between the stimulated limbs by disentangling the respective roles of proprioceptive cues and visual feedback about body posture to study somatosensory remapping, and by stressing more generally the important role of vision on somatosensory perception (see also Botvinick & Cohen, 1998; Gallace & Spence, 2005; Pavani, Spence, & Driver, 2000; Soto-Faraco et al., 2004; Torta et al., 2015).

However, while crossing the hands during tactile and nociceptive TOJ 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 succeed to replicate their results when different fingers of the hands were stimulated. Similarly, Kuroki et al. (2010) showed that participant's

judgements were more sensitive to the anatomical distance between two stimulated skin areas than to the distance in external space between the two body parts. As suggested by Gallace and Spence (2005), the postural effect during tactile TOJ could depend on visual feedback about hands positions. Indeed, Cadieux and Shore (2013) showed that preventing vision of the stimulated hands reduced the crossing hands deficit during tactile TOJ (at least when task procedure minimized the use of spatiotopic coordinates). The aim of the present experiments was to test the influence of seeing the hands on the modulation of tactile temporal order judgements by changing the spatial distance between the stimulated hands.

2. Methods

2.1. Participants

Thirty volunteers participated in the study. Four participants were excluded from 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 et al., 2013), one participant was left-handed, one was ambidextrous, and all the others were right-handed. The local ethic committee in agreement with 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 the hands 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. Stimulations 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 stimulations 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 at ~30 cm from the edge of the table was used as a fixation point for the group of participants who could see the stimulated hands (see below).

2.3. Procedure

The experiment took place in a dimly illuminated testing room. Participants, seated on a chair, rested their arms on a table with their hands holding the transducers slightly above the table surface in order to avoid noise from the vibrations of the transducers against it. Participant's head was stabilized with a chinrest to minimize movement during the

experiment. Half of the participants wore a blindfold to prevent vision of their hands throughout the experiment. The other half of participants could see their hands and were asked to maintain their gaze on the fixation point (see Fig.1). The assignment of the participants to the groups (i.e. *vision* vs. *blindfolded*) was counterbalanced. The hands were equally distant from the reference tape on the table in two different postures. In the *close* posture, the hands were placed with a distance of 2 cm from each other as measured between the two vibrotactile transducers, while in the *far* posture the distance was 70 cm. Within each group, half of the participants started the experiment with their hands in the *close* posture and the other half in the *far* posture. The two vibrotactile stimuli of each trial pair were separated by one out of 22 possible time intervals (SOAs 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 stimulus was applied first). At each trial, the SOA presented to one participant was selected using the adaptive psi method (Kingdom & Prins, 2010) based on the participant's responses to all the previous trials (see Filbrich, Alamia, Verfaille, et al., 2017; Torta, Filbrich, Van Den Broeke, & Legrain, 2018; Vanderclausen, Bourgois, et al., 2020; Vanderclausen, Manfron, et al., 2020 for details regarding the use of the psi method for somatosensory TOJ tasks). Participants were asked to either judge, by verbally answering *'left'* or *'right',* which of the two tactile stimuli they perceived as having occurred first, or perceived as having occurred second, depending on the block (with the aim of minimizing response biases, see Filbrich et al., 2016; Shore, Spence, & Klein, 2001; Spence & Parise, 2010). Responses were unspeeded, and no feedback was given regarding their performance. Once the experimenter encoded the participant's response (by pressing a key on the computer), the next trial started 2000 ms later.

Before starting the experiment, participants completed a training phase to get familiarized with the vibrotactile stimuli and the experimental set-up. This training session consisted of 4 blocks of 10 trials each, one block per condition (hands posture: *close* vs. *far*, and response modality: *which is first* vs. *which is second*). Participants were next presented with the four experimental blocks, one per posture and response modality condition. Forty trials were administrated in each block. 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 including instructions and the training phase lasted about 30 minutes.

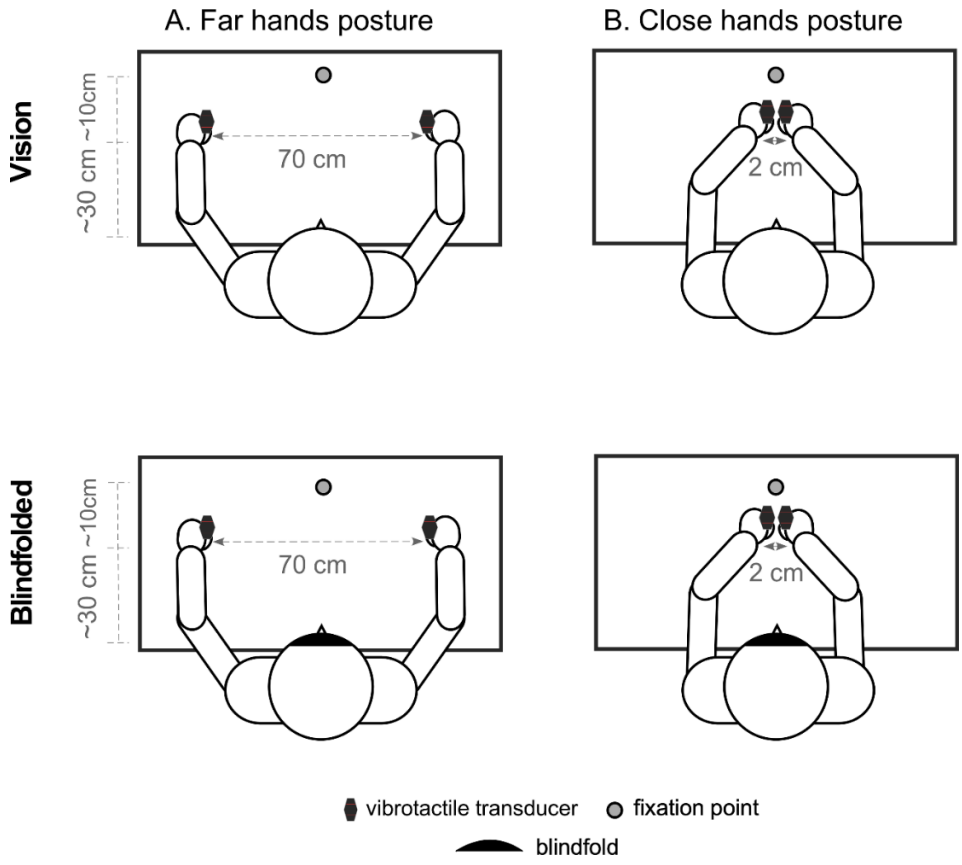


Figure 1. ***Design of the experiment.*** *Participants performed a temporal order judgement (TOJ) task on pairs of tactile stimuli by means of vibrotactile transducers (illustrated by the black diamond in the figure) held between the thumb and the forefinger of each hand. Hands were placed either close (~2cm) or far (~70cm) from each other. One group of participants was blindfolded during the task. In the other group, participants could see their hands. The fixation point (centrally placed and illustrated by the gray circle) served as fixation point for the vision group.*

2.4. Measures

The TOJ performances, i.e. the probability to perceive one of the two stimuli as occurring first according to the SOA, were 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. The α and the β values of the function were estimated at each trial, and, at the end of the stimulation block, the final values were taken as measures of the participant's performance. The main parameter of interest in this study is the β parameter (slope), describing the noisiness of the results (i.e. entropy). Therefore, this parameter reflects the precision of participants' responses during the experiment, i.e. their performance at the task (Kingdom & Prins, 2010; Kontsevich & Tyler, 1999). The slope of psychometric functions is often used to derive the just noticeable difference (JND) in typical TOJ experiments (Heed & Azañón, 2014; Spence & Parise, 2010). The α parameter is the threshold of the function and refers to the point of subjective simultaneity. Although the contribution of the α parameter to current data was less important, that 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, et al., 2017; Vanderclausen et al., 2017). Since the adaptive method was used, the logistic function and its parameters were estimated at each trial based on participants' performances on all the previous trials. Estimates at the last trial were used for analyses. We used a prior distribution of 0±20 to estimate the α parameter, since no bias towards one of the two hands was expected. Based on pilot experiments performed with healthy volunteers, 0.06±0.6 was chosen as a prior distribution to estimate the β parameter (e.g. Filbrich, Alamia, Blandiaux, et al., 2017; Filbrich, Alamia, Burns, et al., 2017). A third non-standard parameter was derived a posteriori to further characterize participants' performance. 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 (see Vanderclausen, Bourgois, et al., 2020; Vanderclausen, Manfron, et al., 2020).

2.5. Data analyses

Before statistical analyses, data from the two response modalities ('which is first' and 'which is second') were merged. One-sample t-tests were next 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.

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 factor and *group* (*vision* vs. *blindfolded*) as between-subject factor were performed on the

PSS, the slope and the mode values respectively. Greenhouse-Geisser corrections of the degrees of freedom, and contrast analyses were used when necessary. Effect sizes were measured by means of partial Eta squared for ANOVA and Cohen's d for t-tests. Significance level was set at $p \leq .05$. Statistical analyses were completed by Bayesian statistics (using Bayesian repeated measures ANOVA with JASP 0.9.2.0) performed on the PSS, mode and slope values respectively. To this aim, we computed a Bayes factor (BF_{10}, Cauchy prior = 0.707) to quantify the null hypothesis relative to the alternative hypothesis.

3. Results

3.1. Frequentist statistics

The psychometric curves fitting TOJ performances are illustrated in the Figure 2a.-The one sample t-tests comparing the PSS values to 0 did not reveal any significant results (all $t(12) \leq 0.741$, all $p \geq 0.125$), suggesting that there was no significant bias affecting one of the stimulated hand in none of the conditions and for none of the groups. This was further confirmed by the ANOVA of the PSS values that showed no significant effect neither for the *posture* ($F(1,24)=0.072$, $p=0.791$, $\eta^2_p =0.003$), nor for the *group* factors ($F(1,24)=0.142$, $p=0.709$,$\eta^2_p=0.060$) nor significant interaction between the two factors ($F(1,24)=2.182$, $p=0.153$, $\eta^2_p=0.083$).

Analyses of the slope values did not reveal any significant results for any condition. Results from the main effect of *posture* ($F(1,24)=0.788$, $p=0.384$, $\eta^2_p =0.032$), that of *group* ($F(1,24)=0.346$, $p=0.562$, $\eta^2_p =0.014$) and the interaction between the two factors ($F(1,24) = 0.062$, $p = 0.805$, $\eta^2_p = 0.003$) were not significant. It suggests that participants' performances during tactile TOJ were not hampered, neither by the distance between the stimulated hands, nor by the possibility to see or not the hands (Figure 2b).

Similar results were observed from the analyses on the mode of the SOA, as the ANOVA did not reveal any significant result of the *posture* ($F(1, 24)=0.477$, $p=0.496$, $\eta^2_p =0.019$), from *group* ($F(1,24)= 0.916$, $p=0.348$, $\eta^2_p =0.037$), and from the interaction between the two factors ($F(1,24)=0.477$, $p=0.496$, $\eta^2_p =0.019$) (Figure 2c).

3.2. Bayesian statistics

Bayesian analyses of the PSS values revealed moderate evidence in favor of the null hypothesis related to the effect of the *posture* ($BF_{10} = 0.275$, error = 0.819), and anecdotal evidences for the null hypotheses related to the main effect of the *group* ($BF_{10} = 0.488$, error = 1.465) as well as the interaction between the *posture* and the *group* ($BF_{10} = 0.832$, error = 1.126). Regarding the slope values, anecdotal evidence were shown for the null hypotheses related to the effects of the *posture* ($BF_{10} = 0.38$, error = 1.636) and the *group* ($BF_{10} = 0.54$, error = 1.556) as well as that of the interaction ($BF_{10} = 0.36$, error = 1.202). Finally, Bayesian analyses of the modes of the SOAs revealed moderate evidence in favor of the null hypothesis related to the main effect of the posture ($BF_{10} = 0.331$, error = 0.950), anecdotal evidences for the null hypotheses related to the main effect of the *group* ($BF_{10} = 0.57$, error = 0.981) as well as for the interaction between the *posture* and the *group* ($BF_{10} = 0.44$, error = 2.493).

These results seem to confirm that tactile TOJ performances were not affected neither by the spatial distance nor by the vision of the hands on which the tactile stimuli were applied.

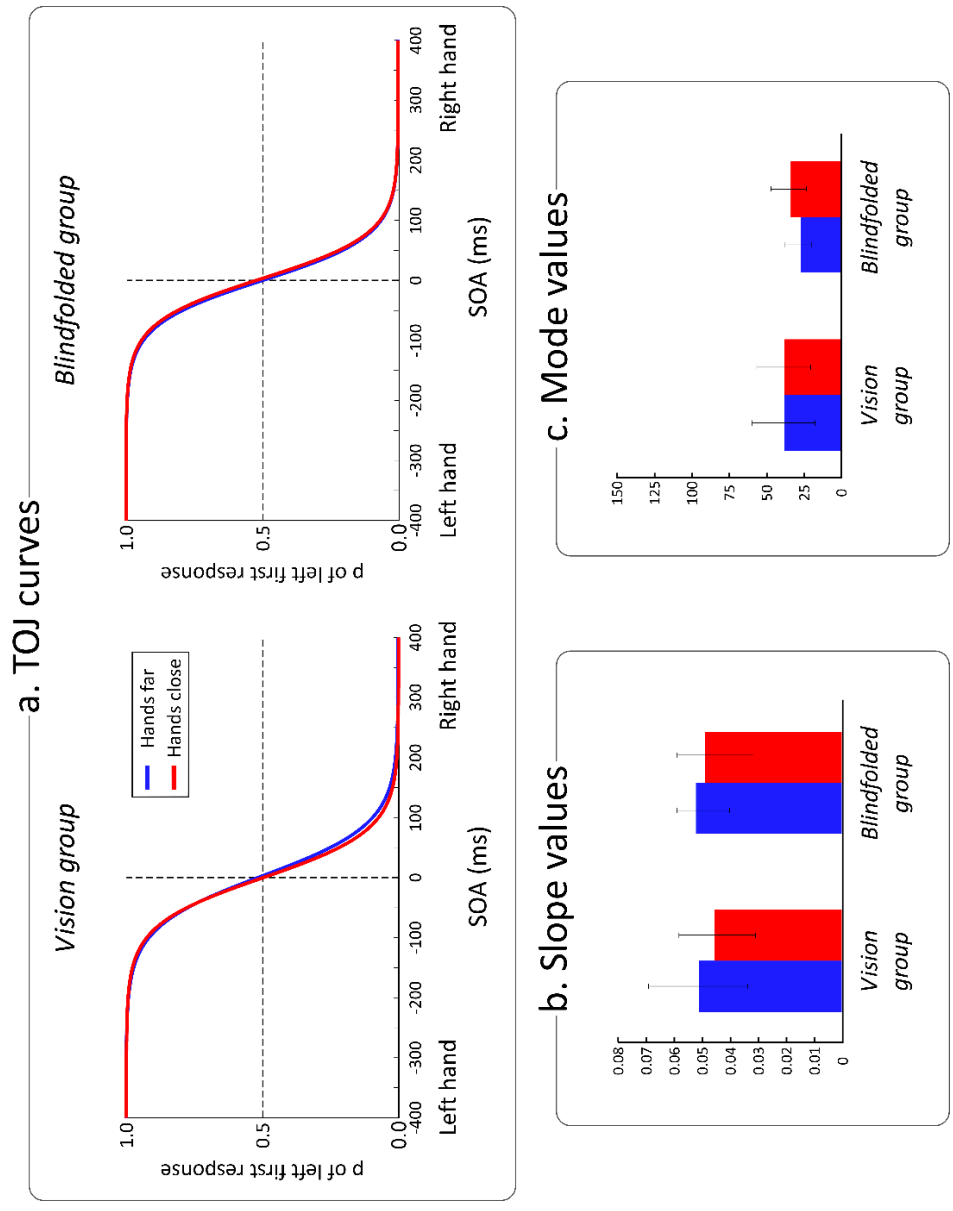

a. TOJ curves
Vision group
Blindfolded group
Hands far
Hands close
p of left first response
1.0
0.5
0.0
-400
-300
-200
-100
0
100
200
300
400
Left hand
Right hand
SOA (ms)
b. Slope values
0.08
0.07
0.06
0.05
0.04
0.03
0.02
0.01
0
Vision group
Blindfolded group
c. Mode values
150
125
100
75
50
25
0

Figure 2. Tactile temporal order judgments (TOJs). *(a) Fitted curves of the psychometric function from the data of 26 participants, divided in two groups: vision of the hands vs. blindfolded, according to the posture factor (i.e. close hands vs. far hands). The x-axis corresponds to the different possible SOAs (i.e. stimulus onset asynchronies). 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. The curves correspond to the fitted curves computed by the adaptive algorithm for the close hands (red) and far hands (blue) conditions. (b) Averaged slope values for each group and each posture condition. (c) Averaged mode values according to each group and each posture condition. None of the posture conditions significantly differed from each other neither in the blindfolded group, nor in the vision group, neither regarding the slope nor the mode values. Error bars represent confidence intervals that were calculated for each measure (slope and mode values) and for each group and posture conditions according to Cousineau's method for within-subjects designs (Cousineau, 2005).*

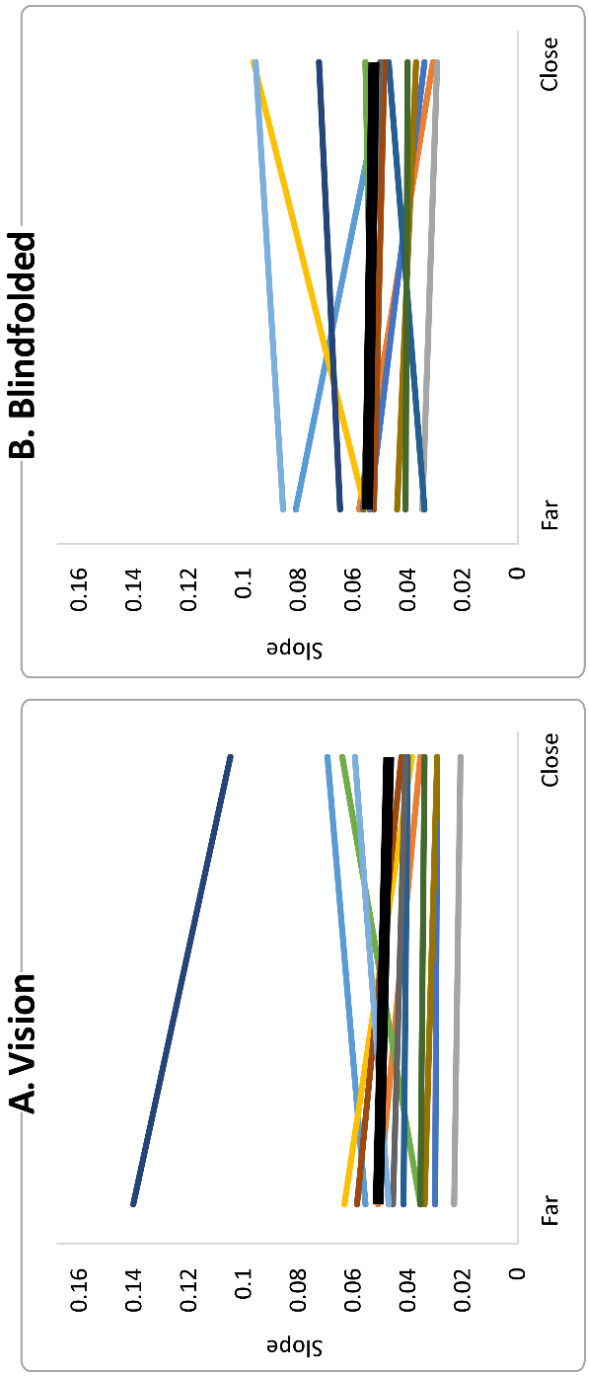


Figure 3. Individual slope values. *The left graph illustrates the slope values for the vision group, and the right graph the slope values for the blindfolded group. Within each graph, the left side illustrates the slope values of the tasks performed in the far posture, the right side those in the close posture. Each color line represents one of the 26 subjects who were involved in the experiment. The black line represents the averaged slope of each group.*

4. Discussion

The present study aimed to test the influence of the distance between two stimulated limbs in external space on the ability to discriminate the temporal order between two tactile stimuli, one applied on each limb. We also investigate whether such an effect could be modulated by the possibility of seeing or not the stimulated limbs. 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 (Gallace & Spence, 2005; Roberts et al., 2003; Shore et al., 2005). By corroborating recurrent 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, 2001a), these former studies showed that judgments were influenced by the spatial position of the hands, confirming that spatial representations of somatosensory inputs integrate information about the body posture. 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 evidences about the influence of limbs distance and their vision on tactile TOJ performances as none of our results reached statistical significance.

One of the main differences between present and previous experiments having tested the influence of hands distance on tactile TOJ 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 current 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 consisted of only 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, this is one of the main advantages of psychophysics adaptive methods over constant stimuli methods, as adaptive methods are known to allow more reliable estimation of the psychometric function even when a limited number of stimuli is used. Accordingly, using the same adaptive method as the one used in 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 et al., 2018; Legrain et al., 2018; Manfron et al., 2019; Torta et al., 2018; Vanderclausen et al., 2017) and the slope parameters (Vanderclausen, Bourgois, et al., 2020; Vanderclausen, Manfron, et al., 2020) of the TOJ-fitting psychometric function and to significantly measure changes in participants' judgments according to experimental manipulations. For instance, Vanderclausen, Manfron, et al. (2020) and Vanderclausen,

Bourgois, et al. (2020) have shown significant and reliable crossing hands effect during TOJ tasks with both tactile and nociceptive stimuli delivered using the *psi* procedure.

One of the main reasons why we failed to replicate the limb distance effect during somatosensory TOJ 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 was recurrently demonstrated during somatosensory TOJ tasks, the limb distance effect seems to be of smaller magnitude (Roberts et al., 2003) and not always replicated (Kuroki et al., 2010; Shore et al., 2005). Similarly, other studies failed to evidence significant effect of the distance between the two stimulated body parts during 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 while each hand remains in its hemispace, the somatotopic and spatiotopic representations remain aligned with each other, even when the hands are placed close together. In addition, somatosensory TOJ studies have suggested that somatotopic and spatiotopic representations of somatosensory inputs are automatically generated (e.g. Azañón, Camacho, et al., 2010; Badde & Heed, 2016; Badde et al., 2016), even if the spatiotopic representation is activated slightly later as compared to the initial somatotopic representation (e.g. Azañón & Soto-Faraco, 2008a, 2008b; Overvliet et al., 2011; Soto-Faraco & Azañón, 2013). Therefore, when the two representations are co-activated, they will provide 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 crossing hand 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. 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; 1988 for similar effect in the visual domain), such competition might be of lesser magnitude than that induced by crossing the hands. Therefore, it might not be reliably sampled during TOJ tasks.

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, studies having used tasks 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). In the same way, it might be instructing 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 than 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 stimulated limbs is less reliable than foreseen, and that crossing the hands is a more suitable technique to experimentally dissociate the respective contributions of the somatotopic and spatiotopic reference frames to the spatial representations of somatic stimuli.

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