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Remapping nociceptive stimuli into a peripersonal reference frame is spatially locked to the stimulated limb

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ABSTRACT

The localization of harmful stimuli approaching our body is essential for survival. Here we investigated whether the mapping of nociceptive stimuli is based on a spatial representation that is anchored to the stimulated limb. In three experiments, we measured the effect of unilateral visual stimuli on the perceived temporal order of nociceptive stimuli, applied to each hand. Crucially, the position of the hands and the visual stimuli was manipulated, so that visual and nociceptive stimuli occurred in an adjacent or non-adjacent spatial position. Temporal order judgments of nociceptive stimuli were biased in favor of the stimulus applied to the hand most adjacent to the visual stimulus, irrespective to their positions in space. This suggests that the ability to determine the position of a nociceptive stimulus on a specific body area is based on a peripersonal representation of the stimulated limb following it during limb displacement.

1. Introduction

The ability to localize somatosensory stimuli on the body is important to identify the impact of an external object on the body surface. It is also important to adapt purposeful behavior to that object, such as manipulation behaviors in the case of tactile inputs from a non-harmful object and protective behaviors in the case of nociceptive inputs from a potentially harmful object (Haggard et al., 2013; Legrain and Torta, 2015). The execution of adaptive behaviors towards objects approaching the body requires coordinating reference frames coding the body space with those coding external space. The peripersonal frames of reference are coordinate systems integrating representations of the body space and the external space closely surrounding the body (Cardinali et al., 2009; Rizzolatti et al., 1981; Spence and Driver, 2004) and within this space the location of somatosensory stimuli, the location of visual stimuli occurring close to the body and information about body posture are integrated. Animal studies suggest that such integrated spatial representations rely on neurons with multimodal receptive fields (RFs), mainly in the ventral parts of the premotor and intraparietal areas (Avillac et al., 2005; Graziano et al., 1994, 1997). More specifically, these neurons have been shown to be active in response to both tactile stimuli and visual stimuli occurring close to the stimulated body parts (Fogassi et al., 1996; Graziano et al., 1997). The visual RFs of these neurons are limited in size and are spatially locked to the tactile RFs, in the sense that these visual RFs follow the movements of the limb to which they are anchored in external space, independently of the retinal representation of the visual inputs. Dong et al. (1994) found similar multimodal neurons in area 7b in the inferior parietal lobe of monkeys. These neurons respond both to thermal nociceptive stimuli and to dynamical visual stimuli moving towards the RF of neurons or static visual stimuli presented in vicinity of the somatosensory RF.

Also in humans there is evidence for the use of peripersonal frames of reference for the localization of somatosensory stimuli. For the mapping of tactile stimuli, several studies have shown that crossmodal interactions between external (e.g. visual) stimuli and tactile stimuli are more efficient when the visual stimuli are presented close to the limb on which the tactile stimuli are applied, as compared to when they are presented further away (for a review, see Spence and Driver (2004)). For example, Làdavas et al. (1998) have shown that, in patients with brain lesions affecting various areas of the right hemisphere, the perception of a tactile stimulus applied to the hand contralateral to the lesion side is affected by the occurrence of a concomitant tactile stimulus applied to the opposite hand. Interestingly, such "extinction" phenomenon also occurs when a concomitant visual stimulus is applied to the opposite side, but only when that stimulus appears in the space

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near the opposite hand. Conversely, extinction is not observed when visual stimuli are presented far from the opposite hand or close to another body part (Làdavas et al., 1998). Recently, we extended these results to nociceptive stimuli. To this end, we used temporal order judgment (TOJ) tasks during which participants had to judge which of two nociceptive stimuli, one applied to each hand, was perceived as first delivered. Two pairs of light emitting diodes (LEDs) were placed on the horizontal plane, one pair close to the stimulated hands, the second pair further away, according the anteroposterior axis. When a visual stimulus was presented only in one of the two sides, nociceptive order judgments were biased in favor of the nociceptive stimulus applied to the hand ipsilateral to the visual stimulus. Importantly, this effect was largest when the visual stimulus appeared in close proximity of the stimulated hand, as opposed to when presented at the far position (De Paepe et al., 2014). Moreover, in a subsequent series of experiments, participants were required to perform the same task both in normal posture, and with hands crossed over the sagittal body midline (De Paepe et al., 2015). Results showed that visual stimuli prioritized the perception of nociceptive stimuli applied to the hand lying in the side of space where the visual stimulus was presented, irrespective of posture, providing evidence that processing nociceptive inputs uses space-based frames of reference, according to which the body posture is taken into account. Similar results were observed by Rossetti et al. (2014) who investigated the impact of approaching threatening stimuli on vegetative responses such as the skin conductance response (SCR) and showed that SCR was greater when the threatening stimulus was close to the body as compared to when it was far.

Unlike studies in monkeys (Fogassi et al., 1996; Graziano et al., 1997), studies investigating the mapping of nociceptive stimuli in a peripersonal frame of reference in humans have mainly focused on a representation of the peripersonal space of the whole body using the body's main axes, such as the midsagittal plane, splitting the body into two hemisides. Indeed, in the above mentioned studies either the position of the visual stimuli (De Paepe et al., 2014) or the position of the hands (De Paepe et al., 2015) was manipulated, leaving us unable to conclude whether the crossmodal interaction between visual and nociceptive stimuli is most effective in a spatial representation of the whole body or of the stimulated body part itself. Here we hypothesized that such interaction takes place in a perilimb spatial representation. Our hypothesis was tested using TOJ tasks with pairs of nociceptive stimuli applied to each hand, preceded by one visual stimulus presented either in the left or the right side of space. Crucially, the position of both the stimulated hand and the visual stimulus was manipulated so that the visual and the nociceptive stimuli occurred either at a close adjacent position or at a certain distance from each other, independently of their relative proximity from the body. Across blocks of stimulation, hands and visual lights were displaced according to the anteroposterior axis (i.e. in depth in front of the trunk, Experiment 1), the mediolateral axis (i.e. eccentricity relative to the body midline, Experiment 2), and the longitudinal axis (i.e. according to elevation positions, Experiment 3). We expected participants' judgments to be biased toward the side of space where the visual stimulus is presented and more importantly we expected this bias to be larger when the locations of the visual stimuli and the stimulated hands were congruent, irrespective of the relative distance of both the hands and the visual stimuli from the body as a whole.

2. Method

2.1. Participants

For each experiment, we aimed for a sample size of approximately 25 participants, in order to keep at least 20 participants for data-analysis. Depending on the availability of participants, and the cancellation of appointments, sample sizes varied across experiments. All participants had normal, or corrected-to-normal vision, did not report any neurological, psychiatric, upper limb trauma or chronic pain problems, and were currently not using any psychotropic and analgesic drugs, which were exclusion criteria. All participants were naïve to the purpose of the experiment, and did not participate before in any experiment on crossmodal interactions in the peripersonal space. Participants could only take part in one of the three experiments of the present study. The experimental procedure was approved by the local ethics committee. All of the participants provided written informed consent prior to taking part in the study.

2.1.1. Experiment 1

Twenty-six participants volunteered to take part in the study. Two male participants had to stop the experiment during the first block, because they were not able to feel the nociceptive stimuli despite repeated displacement of the electrodes (see section 2.2.). The mean age of the remaining 24 participants (20 female, 22 right-handed) was 23 years (ranging from 19 to 47 years).

2.1.2. Experiment 2

Twenty-two participants volunteered to take part in the study. The mean age of the participants (18 women, 20 right-handed) was 23 years (ranging from 18 to 29 years).

2.1.3. Experiment 3

Twenty-five participants volunteered to take part in the study. One participant was excluded due to the use of antidepressant medication at the time of the experiment. Another participant was excluded due to technical failure. The mean age of the remaining 23 participants (15 women, 20 right-handed) was 22 years (ranging from 18 to 26 years).

2.2. Stimuli and apparatus

The nociceptive stimuli were delivered by means of intra-epidermal electrical stimulation (IES) (DS7 Stimulator, Digitimer Ltd, UK), with stainless steel concentric bipolar electrodes (Nihon Kohden, Japan; Inui et al., 2006). The electrodes consisted of a needle cathode (length: 0.1 mm, Ø: 0.2 mm) surrounded by a cylindrical anode (Ø: 1.4 mm). By gently pressing the device against the participant's skin, the needle electrode was inserted into the epidermis of the dorsum of the hand in the sensory territory of the superficial branch of the radial nerve. Using IES at maximum twice the absolute detection threshold has been shown previously to selectively activate the free nerve endings of the Aδ fibers (Mouraux et al., 2010). The detection threshold was determined with a staircase procedure using single-pulse stimuli (0.5 ms square wave pulse) (Churyukanov et al., 2012). The intensity of the electrical currents were adapted individually, that is, increased or decreased in steps of 0.10 mA, depending on whether the participant reported having perceived the preceding stimulus. The staircase ended after four reversals in intensity direction. Threshold was defined as the mean of intensities at the four reversal levels. The detection threshold was established separately for each hand. Next, the stimulus intensity was set at twice the detection threshold. If necessary, the intensity of the stimuli was adjusted so that the stimuli delivered to each hand were perceived as being equally intense. During the course of the experiment, the stimuli consisted of trains of four consecutive 0.5 ms square-wave pulses separated by a 5-ms inter-pulse interval (Mouraux et al., 2014). Using a set of pain words from the Dutch McGill Pain questionnaire (Vanderiet et al., 1987), the stimuli have been found to be best described as pricking. After each experimental block, the participants were asked to estimate the intensity elicited by the nociceptive stimuli on a numerical graphic rating scale (10 cm) with the following labels selected from the Dutch McGill Pain questionnaire (Vanderiet et al., 1987): 0 = felt nothing, 2.5 = lightly intense, 5 = moderately intense, 7.5 = very intense, 10 = enormously intense. This scale was used in order to ensure that: (1) the stimuli were still perceived, and (2) the percept elicited by the IES delivered to each of the participant's hands