Unimodal and crossmodal extinction of nociceptive stimuli in healthy volunteers

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ABSTRACT

Nociception, the physiological mechanisms specifically processing information about noxious and potentially painful stimuli, has the double function to warn about potential body damages (interoception) and about the cause of such potential damages (exteroception). The exteroceptive function is thought to rely on multisensory integration between somatic and extra-somatic stimuli, provided that extra-somatic stimuli occur near the stimulated body area. To corroborate this hypothesis, we succeeded to show in healthy volunteers that the perception of nociceptive stimuli applied on one hand can be extinguished, as compared to single presentation, by the simultaneous application of nociceptive stimuli on the opposite hand, as well as by the presentation of visual stimuli near the opposite hand. On the contrary, visual stimuli presented near the same stimulated hand facilitated the perception of nociceptive stimuli. This nociceptive extinction phenomenon indicates that the perception of noxious events does not merely rely on the specific activation of the nociceptive system, but also depends on other sensory experiences about the body and the space around it.

KEYWORDS

Nociception, vision, multisensory, crossmodal, extinction

INTRODUCTION

Pain relief, particularly concerning chronic pain, constitutes an important challenge for health professionals. The treatment of pain involves the ability to measure it. Pain usually results from the specific activity of a physiological sensory system, the nociceptive system, selectively encoding and transmitting neural information related to potentially harmful stimuli toward the cortical level (Belmonte & Viana, 2008; Le Bars & Plaghki, 2009). Therefore, most pain measurements are aimed at evaluating the integrity of the nociceptive system and mainly involve psychophysics (e.g. Backonia et al., 2013; Magerl et al., 2010; Rolke et al., 2006), sometimes completed by neurophysiological (e.g. Treede et al., 2003) and neuroimaging (e.g. Apkarian et al., 2015) assessment techniques. They generally consist in presenting a nociceptive stimulus and measuring the behavioral responses to it. Pain measurements have often been standardized for clinical purposes in such a way that the responses to a particular somatosensory stimulus are interpreted as being exclusively determined by the nature of the stimulus and the anatomical and functional integrity of specific somatosensory pathways. However, it is acknowledged that cortical activities observed in response to a nociceptive stimulus are not specific to nociceptive and pain processing (Mouraux et al., 2011; Mouraux & Iannetti, 2009) and that they involve various cognitive functions integrating information from different sensory sources (Legrain et al., 2011). Multisensory integration of nociceptive inputs with other sensory inputs, such as visual stimuli occurring near the body, is hypothesized to contribute to an extended cortical representation of the body, aiming to facilitate appropriate actions towards stimuli that are meaningful for homeostasis (Legrain et al., 2011). It seems thus unlikely that the responses to nociceptive stimuli are solely the result of transmission in the nociceptive pathways. Accordingly, the present study was aimed at demonstrating that responses to nociceptive stimuli also depend on the co-occurrence of other stimuli, including non-somatic ones, such as visual stimuli occurring near the body.

More specifically, we propose to challenge the specificity of the assessments of the nociceptive system by taking advantage of the phenomenon of extinction. Extinction is a pathological condition consecutive to a brain lesion, characterized by an inability to detect a stimulus presented on the side contralateral to the damaged cortical hemisphere, but only when it is presented simultaneously with a stimulus occurring on the ipsilateral side. Otherwise, the patient is able to detect the contralesional stimulus when presented alone (Brozzoli et al., 2006; Driver & Vuilleumier, 2001; Farnè et al., 2007; Jacobs et al., 2011). Extinction can be crossmodal (di Pellegrino et al., 1997; di Pellegrino & Làdavas, 2015; Farnè et al., 2005; Làdavas et al., 1998a, 1998b; Maravita et al., 2001; Mattingley et al., 1997): the perception of a touch applied on the contralesional hand is extinguished by a visual stimulus presented close to the ipsilesional hand (visual stimuli presented far from it have less influence). This suggests (1) that the cortical representation of the body space is competitive in nature and requires attention to localize the relevant stimulus and avoid interference from other stimuli, and (2) that this body representation is multisensory, in the sense that it extends slightly from the corporeal boundaries to external proximal space. Extinction is therefore considered as a valid tool to investigate multisensory integration and crossmodal spatial attention in humans (di Pellegrino & Làdavas, 2015; Farnè et al., 2007; Jacobs et al., 2011). However, this clinical approach is limited by the low availability of patients and by the fact that the presence of cortical lesions hampers detailed neurophysiological investigations of the phenomenon. Nevertheless, extinction can be simulated in healthy volunteers, by biasing their perception of tactile stimuli (Farnè et al., 2007). Indeed, it has been demonstrated in individuals without any brain lesion that the perception of low-intensity tactile stimuli applied on one hand can be extinguished by the simultaneous application of tactile stimuli on the opposite hand, as compared to single presentation. Here, we aimed to demonstrate that extinction in healthy participants can also extend to somatosensory stimuli that specifically activate the nociceptive pathways. Moreover, we hypothesized that it would be possible to impact the perception of nociceptive stimuli by the co-occurrence of visual stimuli, depending on their respective spatial locations. Demonstrating a phenomenon of nociceptive extinction induced by visual inputs will highlight the importance of

integrative mechanisms at the cortical level, whereas most of pain research classically focused on integrative mechanisms at the spinal level (e.g. Le Bars, 2002). Additionally, it will corroborate the usefulness of crossmodal extinction as a valid tool to investigate the influence of multisensory interaction on nociceptive processing and pain perception.

EXPERIMENT 1

Methods

Participants. The recruitment strategy consisted in enrolling healthy volunteers until approximately 20 participants fulfilled the selection criterion of perceiving at least 70% of the nociceptive stimulations applied singly (see Measures and Analyses section). The main data analyses testing specific hypotheses were performed only after data collection was deemed complete. Twenty-seven participants in total were recruited for the experiment. Three participants were excluded due to difficulties in determining stable and reliable sensory thresholds (see Procedure), and one for having responded at chance level during the experiment. The data of four additional participants were discarded from analyses because they did not fulfill the data inclusion criterion of the procedure (i.e. 70% correct hits in the single stimulation conditions). The remaining 19 participants, 17 women and 2 men, 17 right-handed and 2 left-handed (according to the Flinders Handedness Survey, Nicholls et al., 2013), were aged from 20 to 30 years (mean = 24 years). All participants had normal to corrected-to-normal vision and did not report any neurological, psychiatric or chronic pain problems. They did not experience upper limb trauma in the last 6 months, and did not regularly use psychotropic drugs. Taking of paracetamol, NSAID and acetylsalicylic acid was not allowed within the 12 hours before the experiment. The experimental procedure was approved by the local ethics committee and conform to the Declaration of Helsinki. The participants provided written informed consent prior to taking part in the study and received compensation for their participation.

Stimuli and apparatus. The nociceptive stimuli were delivered by means of intra-epidermal electrical stimulation (IES), using stainless steel concentric bipolar electrodes (Nihon Kohden, Japan). The electrodes consisted of a needle cathode of 0.1-mm length and 0.2-mm diameter surrounded by a cylindrical anode of 1.4-mm diameter. By gently pressing the device against the participant's skin, the needle was inserted into the epidermis of the dorsum of each hand, in the sensory territory of the superficial branch of the radial nerve. This method has been shown to selectively and specifically activate the free nerve endings of the nociceptive Aδ fibers without concomitant activation of the large Aβ fibers associated with tactile sensations, provided that electrical current is set at an intensity value no more than twice the absolute detection threshold (Mouraux et al., 2010). At higher intensity values, such a technique has been shown to co-activate Aβ mechanoreceptors (see Legrain & Mouraux, 2013). In the present experiment, current intensities were set at threshold values (see Procedure), in order to avoid ceiling effects of perceptual abilities and to increase competition between simultaneous stimuli (Farnè et al., 2007). Electrical stimuli were generated by constant current stimulators (DS7a stimulator, Digitimer Ltd, UK) and consisted of square wave single pulses of 0.5 ms of duration.

Procedure. The participants sat on a chair in a dimly illuminated room. They placed their arms on a table, palms downward, in front of them. During the experiment, their head was immobilized in a chin-rest and they placed their forearms through a small wooden gallows which was covered by a piece of blackout cloth to prevent the sight of the hands. The arms and the shoulders were covered by a dark cape. The distance between the two hands was 40 cm and the distance from the hands to the chin-rest was 30 cm, using the metacarpophalangeal joints of the little fingers as reference. The hands were equidistant from the body midline. A screen was placed in front of the participant to fix a light-emitting diode (yellow Multicomp SMD Super Bright LED, Farnell, UK; 1.34-cd luminous intensity at 20mA; 120° diffusion angle) which was used as fixation point during the experiment. This LED was positioned at 42 cm height from the table surface and 30 cm from the participants' forehead. Devices for remote control and experimenters were hidden behind an office screen.

142 The experiment started once the participants were informed and instructed, and comprised
143 two phases. During the first phase, each participant's absolute detection threshold to IES was
144 determined for each hand individually. Thresholds were always evaluated by the same experimenter
145 (S.B.). Whether the left or the right hand was tested first was alternated across participants. A first
146 stimulation at 1.00 mA was applied on the medial part of the hand's dorsum to familiarize the
147 participant with the sensation generated by IES. The intensity was then progressively decreased to
148 0.50, 0.30 and 0.20 mA. If the participant perceived the stimulus at 0.2 mA the electrode was attached
149 to the hand. If not, the electrode was displaced, the intensity set back to 1.00 mA and the procedure
150 restarted. Once the electrode attached, the threshold evaluation *per se* started, using an adaptive
151 staircase procedure (Churyukanov et al., 2012). Series of IES were applied using different intensities,
152 and for each trial the participant was asked to report whether or not the stimulus was perceived.
153 Stimulus intensity was determined by the participant's response to the previous one. If the stimulus
154 was perceived, the intensity of the following stimulus was decreased by 0.01 mA; if it was not
155 perceived, it was increased by 0.01 mA. The procedure was stopped after three consecutive reversals
156 between the same two values, and the highest of these values was considered as the threshold. If the
157 threshold could not be reliably determined at a value less than 0.50 mA, the procedure was restarted
158 (Favril et al., 2014).

159 During the second phase, the experimental phase, the participants were presented with 4
160 blocks of 25 trials each (computed using Matlab R2012b, MathWorks, MA). A trial started with the
161 illumination of the fixation LED that had to be fixated during the whole trial. The target stimulation
162 was delivered 500 ms later. The participant provided his/her response verbally (see below), which was
163 encoded by one of the experimenters and the fixation LED was switched off. The next trial started 2000
164 ms later. The duration of one block was approximately 3 minutes. Four types of stimulation were
165 randomly delivered within each block. In 20% of the trials, the IES was applied on the left hand only.
166 In 20% of the trials, the IES was applied on the right only. In 40% of the trials, simultaneous IES were
167 applied on both hands. Finally, in the remaining 20% of the trials, no stimulation was applied (catch

trials). In total, the participants received thus 20 trials of the single left stimulation condition, 20 trials of the single right stimulation condition, 40 trials of the double stimulation condition and 20 catch trials. Catch trials were introduced in order to prevent the participants from guessing whether the stimuli were present or not. In other words, the occasional presence of catch trials was intended to inform the participants that it was possible to not perceive a stimulus. For each trial, the participants were asked to report their perception, that is, whether they perceived a stimulus only on the left hand, only on the right hand, on both hands, or whether no stimulus was actually perceived. Before the start of each block, at least one pair of two consecutive IES was applied, one stimulus to either hand. The participants were asked to report if both stimuli were perceived. They were also asked to qualify the sensation and to judge whether they perceived the two stimuli as equally intense. If one of the two stimuli was perceived as more intense, currents were adapted, but only slightly. If at least one of the two IES was not perceived, or if the adapted intensities were too large (0.50 mA as limit), the threshold evaluation was restarted, to ensure threshold stability and perceptual equivalence between left and right IES intensity during the experiment. IES were perceived as tingling or pricking by all participants.

Measures and analyses. Individual data were only considered as valid for further analyses if the participants succeeded in correctly perceiving 70% of the single left stimuli and 70% of the single right stimuli. This was intended to exclude participants whose detection thresholds were not reliable enough to obtain stable intensity values during the experimental phase. To test whether stimulus intensities were similar for IES applied on the left and the right hand, we compared the values of the thresholds obtained for IES between both hands using a t-test for paired samples (left vs. right hand values). The same analysis was performed to compare the stimulus intensities of the IES actually used during the experiment. Because these intensities were adapted regularly through the experimental phase, the highest values used during the experiment were compared using t-test for paired samples.

Next, we compared the ability to perceive the nociceptive stimulus according to whether the stimulus was delivered alone or simultaneously with the same stimulus on the opposite hand. To this aim, the

performance of each participant was estimated for each stimulation condition (i.e. single left, single right, double) using binary measures. We estimated the number of omissions (i.e. the number of trials in which the participants failed to perceive the stimulus) and the number of correct hits (i.e. the trials in which the stimuli were correctly reported and localized). More specifically, in both the single left and the single right stimulation conditions, trials were considered as omissions when the participants reported the absence of any perception. They were considered as correct hits when they correctly reported the perception from the stimulated hand and no sensation was reported from the non-stimulated hand. Other types of responses (e.g. two sensations were reported while only one stimulus was delivered) were considered as mistakes. In the double stimulation condition, trials were considered as omissions when only one of the two stimuli was reported. Trials were considered as correct hits when the participants correctly reported two stimulations, one on each hand. Trials of the double condition with none of the two stimuli reported were considered as mistakes. Because in the double stimulation condition, the ability to report one stimulus is dependent on the perception of the stimulus applied on the opposite hand, we could not separately consider left-hand omissions (i.e. only the right stimulus is reported) and right-hand omissions (i.e. only the left stimulus is reported). Indeed, due to this particularity of the double stimulation condition, the two factors, i.e. the stimulated hand (i.e. left vs. right) and the stimulation condition (i.e. single vs. double) cannot be considered as independent. Left-hand and right-hand omissions in the double stimulation condition were estimated separately only for the purpose of descriptive data and illustrations. A Generalized Linear Mixed Model (GLMM) was used to analyze the binary responses (i.e. omissions vs. correct hits) with *stimulation condition* (single left vs. single right vs. double stimulation conditions) as a fixed main effect. A random intercept for participants was also included in the model in order to take into account the correlation between observations due to repeated measures. Mistakes were considered as missing values, and catch trials were discarded. Significance level was set at $p < 0.050$. When appropriate, tests of contrasts were used using sequential Bonferroni corrections of the p-values. The descriptive data and the

illustrations detail the number of omissions in percentage of the total amount of trials for each condition respectively.

Results

The mean detection thresholds were 0.12 ± 0.04 mA for the left hand and 0.13 ± 0.04 mA for the right hand, and were not significantly different from one another ($t(18) = 0.54$, $p = 0.595$). The highest intensities used during the experiment were 0.14 ± 0.06 mA and 0.13 ± 0.05 mA for the left and the right hand, respectively. This difference was also not significant ($t(18) = 0.34$, $p = 0.735$). These values correspond to those used in previous studies that selectively activated nociceptors (Mouraux et al., 2010, 2013). The absence of difference between left and right hand values shows that similar intensities were applied on both hands.

The GLMM revealed a significant main effect of *stimulation condition* ($F(2,1481) = 61.44$, $p < 0.001$). Contrast analyses showed significant differences between double and single left stimulation conditions ($t(1481) = 8.63$, $p < 0.001$, 95% CI = [0.17, 0.31]) and between double and single right stimulation conditions ($t(1481) = 8.74$, $p < 0.001$, 95% CI = [0.18, 0.31]). This suggests that the proportion of omissions was greater when the nociceptive stimulus was applied concomitantly with another stimulus on the opposite hand (31±13% in total, 19±12% left hand omissions, 12±8% right hand omissions) than when it was applied alone on one single hand (14±11% in total, 7±8% left stimulation omissions, 7±7% right stimulation omissions) (Figure 1). In the single stimulation conditions, there was no significant difference between the left and the right conditions ($t(1481) = 0.19$, $p = 0.850$, 95% CI = [-0.03, 0.04]).

EXPERIMENT 2

Methods

Participants. Recruitment conditions and selection criteria were the same as for Experiment 1. Twenty-eight healthy volunteers were recruited for the experiment. One participant was excluded due to difficulties in determining stable and reliable sensory thresholds. The data of 8 additional participants were discarded from analyses because they did not reach the data inclusion criteria of the procedure (i.e. 70% correct hits in the single stimulation conditions, see Measures and Analyses section). The remaining 19 participants, 15 women and 4 men, 18 right-handed and 1 left-handed (according to the Flinders Handedness Survey, Nicholls et al., 2013), were aged from 20 to 26 years (mean = 22 years).

Stimuli and apparatus. In addition to the nociceptive stimuli, visual stimuli were also used. Visual stimuli were presented by means of two white LEDs with a 17 lm luminous flux, a 6.40 cd luminous intensity, and a 120° diffusion angle (GM5BW97330A, Sharp Corporation, Japan). During the experiment, LEDs were illuminated for 5 ms.

Procedure. The procedure was similar to Experiment 1, except that participants could see their hands, which were placed near the LEDs. The LEDs were positioned ~30 cm from the participants' trunk, with 30 cm between them. Participants were asked to place their hands close to the LEDs so that the LEDs were seen between the metacarpophalangeal joint of the index finger and the thumb of each hand. The hands were placed equidistantly from the body midline. A black cross pictured on a white sheet, attached on a screen, was used a fixation point. The size of the cross was 6-cm high and 3-cm wide and positioned at a distance of 50 cm from participants' eyes (i.e. 6.86*3.43 visual angle).

After the measurement of the thresholds to IES, the participants were presented with 5 blocks of 28 trials each. A trial started with a verbal warning signal from the experimenter. The experimenter pressed at the same time a key that remotely triggered 500 ms later the first nociceptive stimulus of the block on one of the hands. Depending on the trial, this nociceptive stimulus was occasionally followed, by 50 ms, by a visual stimulus (see below). This 50-ms interval was used in order to take into account the differences in terms of distance and conduction velocity between the nociceptive and visual transmission pathways. This 50-ms onset asynchrony was estimated based on the expected

times for sensory inputs of each of the two modalities to reach their respective primary cortical targets (see Mouraux & Plaghki, 2007; Mouraux et al., 2010; Favril et al., 2014). Verbal responses of the participants were encoded by the experimenter and the next trial started approximately 2000 ms later. The approximate duration of one block was 4 minutes. During each block, 7 types of stimulation were presented equiprobably and randomly, so that, in total, the participants received 20 trials with IES only applied on the left hand (left hand stimulated, single condition), 20 trials with IES only applied on the right hand (right hand stimulated, single condition), 20 trials with left IES applied concurrently with a visual stimulus presented near the left hand (left hand stimulated, double ipsilateral condition), 20 trials with right IES applied concurrently with a visual stimulus presented near the right hand (right hand stimulated, double ipsilateral condition), 20 trials with left IES applied concurrently with a visual stimulus presented near the right hand (left hand stimulated, double contralateral condition), 20 trials with right IES applied concurrently with a visual stimulus presented near the left hand (right hand stimulated, double contralateral condition), and finally 20 trials without any stimulation (catch trials). After each trial, the participants were asked to report for each sensory modality respectively, that is, for both the visual and the nociceptive stimuli, if they were perceived, and, in case they were perceived, to report in which side of space. Again, they were informed about the occasional occurrence of the catch trials. As for Experiment 1, before the beginning of each block, perception of IES applied on each hand was controlled and stimulus intensities were adapted if necessary. IES were perceived as tingling or pricking.

Measures and analyses. Individual data were only considered as valid for further analyses if the participants succeeded to correctly perceive 70% of the single IES conditions. The values of the IES thresholds and the maximum intensity values used during the experiment were compared between the two hands using t-test for paired samples.

To test the influence of the visual stimuli and their location (i.e. ipsi- or contralateral to the stimulated hand) on the perception of the nociceptive stimuli, we analyzed the number of omissions

with regard to the number of correct hits according to the different stimulation conditions. Trials were considered as omissions if the nociceptive stimulus was not reported. Trials were considered as correct hits if the stimuli were perceived and correctly localized, including the visual stimuli in the double stimulation conditions. Were considered as mistakes trials in which the stimuli were not correctly localized (i.e. nociceptive stimulus perceived as applied on the opposite hand, visual stimulus perceived on the opposite side), trials with a single nociceptive stimulus during which a visual stimulus was reported (visual false alarms), and trials with double stimulations during which the visual stimulus was not reported (visual misses). Conversely to Experiment 1, all double stimulation conditions were independent. Therefore, a GLMM was run to analyze the number of nociceptive omissions relative to correct hits (binary responses) with *stimulated hand* (left vs. right hand) and *stimulation condition* (single vs. double ipsilateral vs. double contralateral) as fixed main effects, and the interaction between the two factors. The random intercept for participants was included. Significance level was set at $p < 0.050$. When appropriate, tests of contrasts were used using sequential Bonferroni corrections of the p-values. Omissions are reported in percentage for descriptive data and illustrations.

Results

The mean detection thresholds were 0.06 ± 0.03 mA for the left hand and 0.07 ± 0.04 mA for the right hand, and were not significantly different ($t(18) = 0.28$, $p = 0.776$) from one another. The highest intensities used during the experiment were 0.08 ± 0.04 mA and 0.09 ± 0.05 mA for the left and the right hand, respectively. This difference was also not significant ($t(18) = 0.84$, $p = 0.409$).

The participants made very few visual mistakes: 0.26% visual misses, 2.36% visual mislocations and 0.26% visual false alarms.

The GLMM revealed a significant main effect of *stimulation condition* ($F(2,2244) = 22.15$, $p < 0.001$). As compared to the single stimulation conditions (left hand omissions: 17±7%; right hand

omissions: 18±5%), participants omitted more often to report nociceptive stimuli when a visual stimulus was presented near the contralateral hand (left hand omissions: 20±13%; right hand omissions: 30±19%) ($t(2244) = 3.40$, $p = 0.001$, 95% CI = [0.03, 0.12]). Next, as compared to the single stimulation conditions, participants omitted to report nociceptive stimuli less often when the visual stimuli were presented near the ipsilateral hand, i.e. the hand on which the nociceptive stimulus was applied (left hand omissions: 9±11%; right hand omissions: 13±14%) ($t(2244) = 3.27$, $p = 0.001$, 95% CI = [0.02, 0.10]). Finally, the comparison between the two double stimulation conditions revealed more omissions when the visual stimulus was presented contralaterally than when presented ipsilaterally ($t(2244) = 6.06$, $p < 0.001$, 95% CI = [0.08, 0.19]). This suggests that the probability of perceiving the nociceptive stimulus was dependent on the presence and the location of the visual stimulus (Figure 2). The significant main effect of *stimulated hand* ($F(1,2244) = 10.15$, $p = 0.001$) suggests more omissions for nociceptive stimuli applied on the right hand as compared to stimuli applied on the left hand. The interaction did not reach significance level ($F(2,2244) = 2.22$, $p = 0.109$).

DISCUSSION

The aim of the present study was to evidence an extinction-like phenomenon to nociceptive stimuli in healthy participants. Usually observed in consequence to cortical lesions, extinction to double stimulation was described for almost all sensory modalities with the exception of nociception (Bellas et al., 1988; Berlucchi et al., 2004; Brozzoli et al., 2006; De Renzi et al., 1989; Driver & Vuilleumier, 2001; Maravita et al., 2001). Recently, Liu et al. (2011) investigated the ability to perceive painful heat and cold thermal stimuli in nine patients with post-stroke visual hemispatial neglect. While most of the patients *mislocalized* (i.e. transferred the sensation to the opposite hand) or *misinterpreted* (i.e. mixed heat and cold sensations) the thermal stimuli applied on the contralesional hand, two of them were not able to systematically report the perception of either the heat or the cold stimuli when a contact was produced simultaneously on the opposite hand. However, as continuous

contact heat stimuli were used, it is difficult to disentangle which somatosensory subcomponents of these somatic stimuli were actually neglected. In the present study, we used intra-epidermal electrical stimuli that have been shown to selectively and specifically activate capsaicin-sensitive Aδ nociceptive fibers (Mouraux et al., 2010) provided that stimulation is delivered at maximum twice the detection threshold (Legrain & Mouraux, 2013). The present study is the first systematic demonstration of an extinction-like phenomenon to specific nociceptive stimuli in healthy volunteers. Participants were asked to report and locate the perception of nociceptive stimuli. As compared to single hand stimulation, the ability to perceive the nociceptive stimulus was hampered by the co-occurrence of another stimulus presented in the opposite side of space, that is, by a nociceptive stimulus applied on the opposite hand and by a visual stimulus presented near the opposite hand. Conversely, the presence of visual stimuli near the stimulated hand facilitated the perception of nociceptive stimuli. These results extend those obtained by Farnè et al. (2007) who demonstrated extinction to double tactile stimulation in healthy volunteers, as well as the preliminary observation of tactile extinction due to concomitant visual stimulation (Jacobs et al., 2011). They are also in line with other studies having shown that visual stimuli occurring close to the body can influence the perception of near-threshold tactile stimuli (e.g. Salomon et al., 2017; Van der Biest et al., 2015).

Extinction is a phenomenon that reveals the competitive nature of perceptual abilities (Driver & Villeumier, 2001). Moreover, the crossmodal modulation of tactile extinction has been considered as a useful neuropsychological model to investigate the cognitive mechanisms – and their neural substrates – underlying the perception of peripersonal space, a spatial representation that integrates the body and its immediate surroundings (Farnè et al., 2007). For instance, the fact that the ability of these patients to perceive tactile stimuli depends on the position of the contralesional hand suggests that touch can be remapped from an initial anatomical representation of the body to a more spatial representation coding the tactile stimuli according to the location of the object in contact with the skin in external space (Bartolomeo et al., 2004; Smania & Aglioti, 1995). Additionally, crossmodal extinction between tactile and visual stimuli illustrates that the spatial representation of the body extends slightly

366 in external space and that it can be dissociated from the more distant extrapersonal space (di
367 Pellegrino & Làdavas, 2015; di Pellegrino et al., 1997; Farnè et al., 2005, 2007; Jacobs et al., 2011;
368 Làdavas et al., 1998a, 1998b; Mattingley et al., 1997). While multisensory influence on somatosensory
369 inputs in peripersonal space has been largely investigated for touch (Brozzoli et al., 2014; di Pellegrino
370 & Làdavas, 2015; Vallar & Maravita, 2009), data regarding nociception and pain are still sparse (Legrain
371 & Torta, 2015). Yet, the sensibility of nociceptive inputs to modulatory effects from extra-somatic
372 stimuli is of primary importance to understand the mechanisms underlying the processing of
373 nociceptive inputs and their transformation into a conscious perception of pain (Legrain et al., 2011).
374 Indeed, while crossmodal influence on touch can optimize the manipulation of innocuous objects
375 (Brozzoli et al., 2014), such an influence on nociception and pain is necessary to optimize defensive
376 behaviors against noxious stimuli (Dong et al., 1994; Graziano & Cook, 2006). It has indeed been
377 suggested that the brain's ability to perceive sensory stimuli according to a peripersonal frame of
378 reference can serve to shape defensive behaviors against physical threats (Graziano & Cook, 2006). It
379 appears therefore highly relevant to investigate the functional role of the peripersonal reference frame
380 through somatosensory stimuli that specifically activate the nociceptive system (Legrain et al., 2011).
381 The functional role of the nociceptive system is to warn the brain about potential body damage, as
382 well as to adapt behavior to protect the physical integrity of the body. Nociception has therefore a
383 double – interoceptive and exteroceptive – function (Haggard et al., 2013), that is, it provides
384 information about potential tissue damages and about external stimuli that can cause these damages.
385 The mechanisms underlying the interaction between the processing of nociceptive inputs and of
386 external stimuli that have the immediate potential to impact the body are thus inherent to the
387 exteroceptive function of nociception and pain (Legrain, 2017). The few studies that investigated
388 interactions between nociception and vision mostly used temporal order judgment (TOJ) tasks, in
389 which participants discriminate the order between two consecutive sensory events (De Paepe et al.,
390 2014, 2015, 2017; Filbrich et al., 2017a, 2017b, 2018; Vanderclausen et al., 2017). These studies
391 highlighted facilitation processes between nociceptive and visual stimuli, mainly when visual stimuli

were presented near the stimulated hands. Our study complements these findings, but also shows that a visual stimulus can, on the contrary, decrease the ability to perceive a nociceptive stimulus when the visual stimulus is presented near the opposite limb. In agreement with neurophysiological data in monkeys (Dong et al, 1994), this finding suggests that interactions between nociception and vision in humans take place in peripersonal representations of distinct body parts and that the processing of these representations is competitive.

It could be argued that the nociceptive stimuli used in the present studies are not ecological, since they were presented at the absolute detection threshold, while in everyday life nociceptive stimuli are generally perceived at higher intensities. Indeed, activation mechanisms of the nociceptors associated to the Aδ fibers are characterized by high activation thresholds (Belmonte & Viana, 2008) (for example, fast-adapting Aδ nociceptors respond to the onset of thermal stimuli with a threshold around 46° [Treede et al., 1995]). However, cutaneous electrical stimulation represents a method that bypasses the transduction and activation mechanisms of the nociceptors by directly activating axonal fibers. As the aim of the present study was to replicate the extinction phenomenon in healthy volunteers with stimuli that selectively activate nociceptors without co-activation of mechanoreceptors associated to tactile sensations, IES were used and presented at detection threshold to guarantee the selectivity of the stimulation method for nociceptive pathways (Mouraux et al., 2010). Furthermore, such low intensities were required to simulate extinction in participants without cortical lesion, hence, without any perceptual deficits (Farnè et al., 2007; Jacobs et al., 2011) and to reveal the competitive nature of somatosensory processing in the healthy brain. It is also worth noting that a main advantage of the present double stimulation paradigm is that it mimics standard assessments of somatosensory pathways as used in clinical settings. The Quantitative Sensory Testing method, for instance, consists of different techniques aimed at applying specific somatosensory stimuli (e.g. warm, cold, pinpricks, mechanical pressure, etc.) and measuring detection thresholds, to the purpose of assessing the integrity of each somatosensory pathway as well as of diagnosing selective impairments of these pathways, including chronic pain disorders (Backonia et al., 2013; Magerl et al.,

2010; Rolke et al., 2006). The present data suggest that the interpretation of these clinical evaluations might be biased if the potential influence of surrounding sensory stimuli is not controlled for. The present paradigm seems therefore highly suitable to be combined with psychophysical measures of the nociceptive pathways, in order to advance our knowledge as to the multisensory integration of nociceptive and extra-somatic stimuli in both healthy and pathological brains (Bultitude et al., 2017; Filbrich et al., 2017c; Vizzari et al., 2017). In the future, alternative methods with supra-threshold stimuli could be considered while increasing attentional competition by manipulating cognitive load for instance (e.g. Naert, Bonato, & Fias, 2018). Another limitation regarding the ecological value of the present study is that, in the second experiment, the appearance of the visual stimuli was delayed by 50 ms with regard to the onset of the nociceptive stimuli. Indeed, in everyday life the different sensory stimuli arising from a same perceptual object occur at the same time. Nevertheless, even with an onset asynchrony of 50 ms between nociceptive and visual stimuli – estimated based on the expected time for each modality input to reach their respective cortical targets (Mouraux & Plaghki, 2007; Mouraux et al., 2010; Favril et al., 2014) – we succeeded to observe an interaction between the two sensory modalities. This estimated delay is similar to the one described in Zampini et al. (2007), who observed, using temporal order judgment tasks, that a laser-induced nociceptive stimulus has to precede a visual stimulus by about 40 ms in order for the two stimuli to be perceived as occurring simultaneously.

Multisensory interactions between somatic (mostly tactile) and extrasomatic (e.g. visual or auditory) stimuli have been evidenced using different experimental procedures and by means of different behavioral responses (e.g. detection, reaction times) (e.g. Forster et al., 2002; Hartcher-O'Brien et al., 2010; Kennett et al., 2001; Legrain et al., 2018; Salomon et al., 2017; Serino et al., 2007; Spence et al., 2004; Van der Biest et al., 2015). Such multisensory effects between nociception and vision were rather tardily and less thoroughly studied (e.g. De Paepe et al., 2014, 2016; Favril et al., 2014). In order to understand the mechanisms governing interactions between nociceptive inputs and extrasomatic stimuli such as visual ones, the effects highlighted in the present experiments should thus be further investigated and replicated through different paradigms. For instance, it should be

addressed whether interactions between nociceptive and visual stimuli are operated through integrative or attentional mechanisms. In other words, it remains to be tested whether sensory inputs conveyed by different sensory pathways are combined to yield an unified perceptual experience of a noxious event inflicted on the body, or whether crossmodal interactions rather result from the attentional prioritization of all temporally and spatially aligned sensory stimuli. It should also be noted that the present data do not allow to disentangle whether modulation of the perception of the nociceptive stimuli is due to the occurrence of the visual stimuli inside the peripersonal space, or whether such interaction just resulted from the fact that visual stimuli were presented in the same vs. opposite side of space, independently of their distance from the body. Indeed, in the present study, the visual stimuli were presented close to the limb on which the nociceptive stimuli were applied, as well as close to the opposite homologous limb. In the future, the present experiments should be replicated using visual stimuli presented at different positions from the hands (see De Paepe et al., 2017; Filbrich et al., 2018).

The present findings about crossmodal influences of both somatic and extra-somatic stimuli on nociceptive processing are highly contributive to the long-lasting and still ongoing debate concerning the specificity of the somatosensory systems. Specificity theories consider that the different somatic sensations are generated through the activation, by specific stimuli, of anatomically and functionally segregated neurophysiological systems with their own receptors and pathways (see Moayedi & Davis, 2013 for a review). It is now more widely acknowledged that somatic sensations result from the convergence of sensory inputs from the different pathways. In particular, pain is described as a percept resulting from the brain's interpretation of a pattern of activities arising from different nerve fibers (Craig, 2003; Melzack et al., 2001). However, the neurophysiological investigation of such convergence has been so far mostly limited to the spinal level (e.g. Le Bars, 2002; Le Bars et al., 1979; Melzack & Wall, 1965). Data about integrative mechanisms at the cortical level still remain scarce. Moreover, studies so far have been limited to how nociceptive processing and pain can be modulated by the vision (or visual illusion) of the body or by postural changes (i.e. personal space)

(e.g. Boesch et al., 2016; Longo et al., 2009; Sambo et al., 2012; Wittkopf et al., 2017). On the contrary, very few studies investigated the influence of the representation of the space surrounding the body and of extra-somatic stimuli occurring nearby (i.e. peripersonal space) on nociceptive processing and pain perception (Legrain & Torta, 2015). This could be due to the fact that pain research mostly focused on the interoceptive role of nociception (e.g. Craig, 2002; Loeser & Treede, 2008). Yet, recent studies have shown that almost all of the cortical areas responding to nociceptive and painful stimuli are also able to respond to non-somatic, auditory and visual, stimuli (Mouraux et al., 2011; Mouraux & Iannetti, 2009). It has therefore been suggested that most of the cortical responses to nociceptive painful stimuli might reflect the activity of a multisensory system involved in locating and allocating processing priority to sensory inputs that are the most meaningful for homeostasis, independently of the sensory pathways through which these inputs are conveyed (Legrain et al., 2011). The present data further corroborate this hypothesis: the fact that the perception of nociceptive stimuli is influenced by the occurrence of visual stimuli clearly shows that the possible outputs of nociceptive processing depend on integrative mechanisms at the supra-spinal level.

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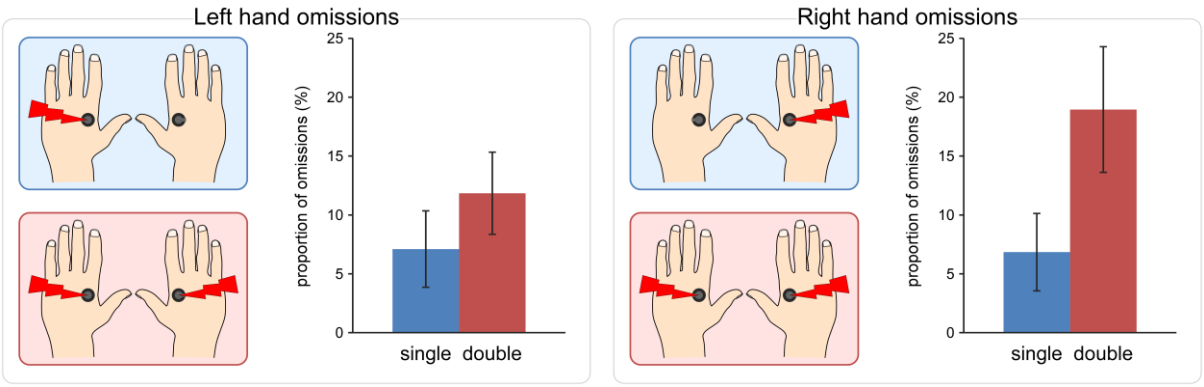
670

671 **FIGURE CAPTIONS**

672 

673 Figure 1. Design and results of Experiment 1. Participants were asked to report and locate the
674 perception of nociceptive intra-epidermal electrical stimulation delivered at the absolute detection
675 threshold. Nociceptive stimuli were applied either on one single hand (blue frames) or on both hands
676 simultaneously (red frames). The proportion of omissions was measured for each hand, that is, for
677 single stimulation conditions, the proportion of trials for which no perception was reported (blue bars),
678 and, for double stimulation conditions, the proportion of trials for which only the perception of the
679 nociceptive stimuli applied on the opposite hand was reported (red bars). Error bars represent 95%
680 confidence intervals estimated according to Cousineau (2005).

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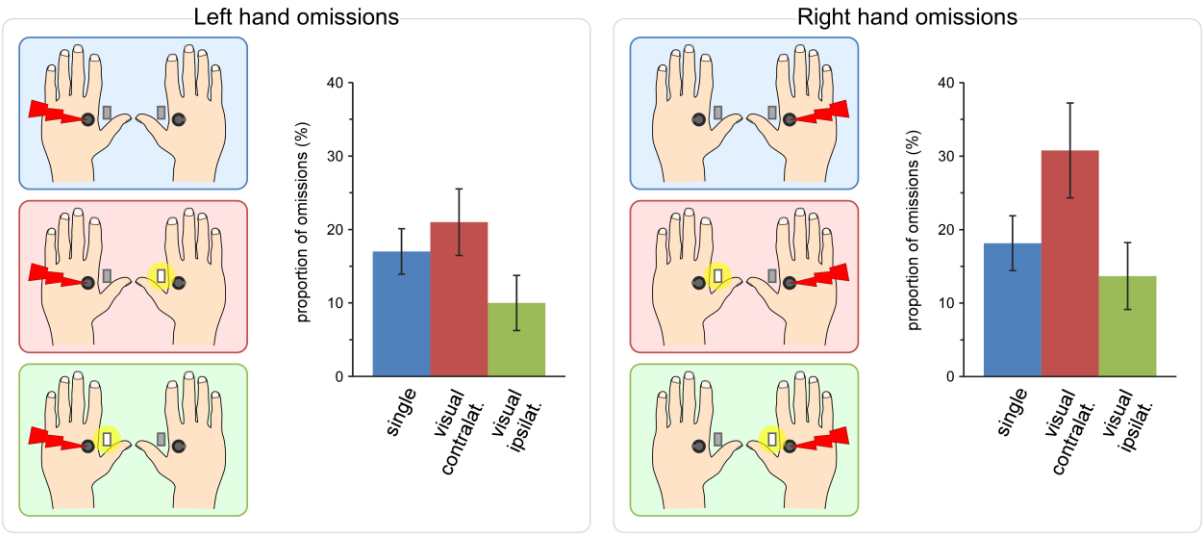

Figure 2. Design and results of Experiment 2. Participants were asked to report and locate the perception of visual stimuli and nociceptive intra-epidermal electrical stimulation delivered at the absolute detection threshold on one of the hands. Nociceptive stimuli were applied either alone (blue frames), or concomitantly with a visual stimulus delivered near the opposite hand (red frames) or near the same stimulated hand (blue frames). The proportion of omissions was measured for each hand, that is, for single stimulation conditions, the proportion of trials for which no perception was reported (blue bars), and, for double stimulation conditions, the proportion of trials for which only the perception of the visual stimuli delivered either in the contralateral (red bars) or the ipsilateral space (green bars) was correctly reported. Error bars represent 95% confidence intervals estimated according to Cousineau (2005).