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BODY, SPACE AND PAIN

Topic Editors
Diana M. Torta, Jörg Trojan, Martin Diers
and Camila Valenzuela-Moguillansky

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BODY, SPACE AND PAIN

Topic Editors:
Diana M. Torta, University of Turin, Italy
Jörg Trojan, University of Koblenz-Landau, Germany
Martin Diers, Central Institute of Mental Health, Germany
Camila Valenzuela Moguillansky, Instituto de Sistemas Complejos de Valparaíso, Chile

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Body, space, and pain

Jörg Trojan[1,2], Martin Diers[2], Camila Valenzuela-Moguillansky[3] and Diana M. E. Torta[4]*

[1] Department of Psychology, University of Koblenz-Landau, Landau, Germany
[2] Department of Cognitive and Clinical Neuroscience, Central Institute of Mental Health, Medical Faculty Mannheim / Heidelberg University, Mannheim, Germany
[3] Institute of Complex Systems of Valparaíso, Valparaíso, Chile
[4] Department of Psychology, University of Turin, Turin, Italy
*Correspondence: trojan@uni-landau.de

Edited and reviewed by:
Hauke R. Heekeren, Freie Universität Berlin, Germany

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THEORETICAL BACKGROUND

Chronic pain is accompanied by a variety of alterations in body perception. Pain patients often exhibit distortions in the perception of limb positions and sizes: back pain patients have problems in delineating the outline of their backs and their body image is distorted in the painful area (Moseley, 2008). Patients with Complex Regional Pain Syndrome (CRPS) suffer from intense pain in their affected hand and often perceive it as being larger than it actually is (Moseley, 2005). Amputees often report pain in their amputated limb and the amount of pain seems to be related to distorted spatial perception of the limb (Grüsser et al., 2001). Results from CRPS patients show that not only the perception of the body is affected, but that pain leads to a distorted perception of the peripersonal space surrounding the body (Reinersmann et al., 2011). At a more fundamental level, sensory changes associated with chronic pain states cannot be explained by peripheral deficits alone, rather, cortical representations seem to be involved as well.

Research on how body perception and pain are linked to each other has been conducted from different and possibly overlapping perspectives. One line of research highlights the importance of attentional biases toward or away from the location of pain. Another approach underlines the role of multisensory representation of our body and the surrounding space in the perception of pain and nociceptive stimuli. Extending this latter view, there is also work focusing in particular on the complex interplay between motor action and pain perception.

Experimental studies on the relationship between body perception and pain are contributing to our understanding of clinical findings and the development of new treatment approaches: nociceptive stimuli draw attention to their locations (Van Damme et al., 2007) and pain stimuli are perceived as less intense if attention is drawn away from their location (Van Ryckeghem et al., 2011). Vision of stimulated body parts reduces pain perception (Longo et al., 2009; Diers et al., 2013) and the larger the perceived size of a limb, the stronger is the effect (Mancini et al., 2011). Ongoing nociceptive input alters somatosensory localization (Trojan et al., 2009) and conflicts between frames of reference onto which somatosensory stimuli are localized modulate the perception of the stimuli (Gallace et al., 2011; Torta et al., 2013). Studies about the relationship between somatosensory inputs and motor planning suggest that visual–motor feedback leads to "peculiar" (and sometimes painful) sensations (McCabe et al., 2005).

OVERVIEW OF THE ARTICLES IN THIS RESEARCH TOPIC

In this Research Topic, three studies focused on the effect of painful or nociceptive stimulation on body representation and postural control. Bouffard et al. (2013) applied pain to the right arms of healthy participants and observed that the subjective body midline shifted to the right; non-painful vibration applied to the left arm also led to a right-shift. The pain-specific shift toward the stimulated side might be functionally beneficial to protect the painful area of the body. Steenbergen and collaborators assessed the agreement of spatial perceptual maps for touch and nociception and proposed that a common internal body representation can underlie spatial perception of touch and nociception (Steenbergen et al., 2012). Lelard and collaborators showed that imagining being in a painful situation induces changes in postural control and leg muscle activation, thus resulting in an increased stiffness compared to non-painful situations (Lelard et al., 2013). Anelli and colleagues did not study the effect of pain directly but explored the effect that potentially dangerous approaching stimuli have on motor responses: static neutral objects triggered faster responses compared to static dangerous ones (Anelli et al., 2013). Responses to dynamic objects were instead affected by the direction of the movement of the object.

Two studies addressed the question of how changes in body representations affect pain processing. In a virtual reality study, Martini and colleagues demonstrated that pain thresholds could be top-down modulated by changing the color of a seen arm (Martini et al., 2013). Pia and collaborators showed that right-brain damaged patients could feel pain in response to a stimulus produced in a foreign arm that was subjectively experienced as their own (Pia et al., 2013).

The interplay between movement, sensory feedback, and pain was specifically addressed by two studies. Foell and collaborators used a mirror setup in order to clarify the impact of sensory motor incongruence on pain perception (Foell et al., 2013). The results revealed that sensorimotor conflict affected perceived body integrity but was not sufficient to trigger substantial pain experiences in healthy volunteers. Meulders and colleagues induced pain-related fear of movements in healthy participants and demonstrated that this fear could be generalized to similar movements (Meulders et al., 2013). These findings may yield a better understanding of the role of fear and avoidance in chronic musculoskeletal pain.

Four studies were conducted on clinical populations. Preißler et al. (2013) looked for the influence of prosthesis use in upper limb amputees on phantom limb pain and cortical thickness and suggested a relationship between prosthesis use and cortical plasticity of the visual stream. This plasticity might present a brain adaptation process to new movements and coordination patterns needed to guide an artificial hand. Riquelme and colleagues showed that administration of a somatosensory therapy could reduce pressure pain sensitivity in adults with cerebral palsy, without affecting other abilities such as texture recognition or tactile sensitivity (Riquelme et al., 2013). Turton and colleagues presented a new method to report body perception disturbances, targeted at patients with CRPS (Turton et al., 2013). Patients could manipulate a variety of features of an avatar on a computer screen, yielding 3-D representations of their symptoms. Wallwork and colleagues aimed at dissociating the ability to judge the rotation of the neck as compared to the rotation of the hand in dizzy people and observed that those patients show generally slower responses independently of to the task (Wallwork et al., 2013).

Finally, broadening the focus to social neurosciences, Krahé and collaborators proposed three factors playing a major role in pain perception: (1) the relationship between the person in pain and the social partner; (2) the possibility of the person in pain to understand the social partner's intentions; and (3) the degree to which the person in pain sees the social partner's possibility to act (Krahé et al., 2013).

CONCLUSION

The findings presented here demonstrate that the subjective experience of pain can only be understood in a larger framework of body representations and peripersonal space. The relationship between pain and these spatial representations is bidirectional, but the underlying neurophysiological mechanisms are not yet known. Regardless of this present lack of knowledge, the results reported in this Research Topic clearly bear clinical significance: future pain diagnostics and treatment approaches will benefit from putting more stress on body perception.

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Effect of painful and non-painful sensorimotor manipulations on subjective body midline

Jason Bouffard[1,2†], Martin Gagné[1†] and Catherine Mercier[1,2*]

[1] Centre Interdisciplinaire de Recherche en Réadaptation et en Intégration Sociale, Québec, QC, Canada
[2] Département de Réadaptation, Faculté de Médecine, Université Laval, Québec, QC, Canada

Edited by:
Martin Diers, Central Institute of Mental Health, Germany

Reviewed by:
Donatella Spinelli, Università di Roma "Foro Italico," Italy
Johan W. Vlaeyen, University of Leuven, Belgium

****Correspondence:***
Catherine Mercier, Centre Interdisciplinaire de Recherche en Réadaptation et Intégration Sociale, 525 Boul. Hamel, Québec, QC G1M 2S8, Canada.
e-mail: catherine.mercier@rea.ulaval.ca

[†]Jason Bouffard and Martin Gagné have contributed equally to this work.

Patients with chronic pain often show disturbances in their body perception. Understanding the exact role played by pain is however complex, as confounding factors can contribute to the observed deficits in these clinical populations. To address this question, acute experimental pain was used to test the effect of lateralized pain on body perception in healthy subjects. Subjects were asked to indicate the position of their body midline (subjective body midline, SBM) by stopping a moving luminescent dot projected on a screen placed in front of them, in a completely dark environment. The effect of other non-painful sensorimotor manipulations was also tested to assess the potential unspecific attentional effects of stimulating one side of the body. SBM judgment was made in 17 volunteers under control and three experimental conditions: (1) painful (heat) stimulation; (2) non-painful vibrotactile stimulation; and (3) muscle contraction. The effects of the stimulated side and the type of trial (control vs. experimental condition), were tested separately for each condition with a 2 × 2 repeated measures ANOVA. The analyses revealed a significant interaction in both pain ($p = 0.05$) and vibration conditions ($p = 0.04$). *Post hoc* tests showed opposite effects of pain and vibration. Pain applied on the right arm deviated the SBM toward the right (stimulated) side ($p = 0.03$) while vibration applied on the left arm deviated the SBM toward the right (not stimulated) side ($p = 0.01$). These opposite patterns suggest that the shift in SBM is likely to be specifically linked to the stimulation modality. It is concluded that acute experimental pain can induce an SBM shift toward the stimulated side, which might be functionally beneficial to protect the painful area of the body. Interestingly, it appears to be easier to bias SBM toward the right side, regardless of the modality and of the stimulated side.

Keywords: body perception, spatial attention, neuropathic pain, neglect, egocentric frame of reference

INTRODUCTION

Patients with chronic pain often show disturbances in their body perception. For example, alterations in the perceived size or shape of the painful body parts have been reported in complex regional pain syndrome (CRPS) patients (Moseley, 2005; Lewis et al., 2007, 2010; Peltz et al., 2011) and low back pain patients (Moseley, 2008). In a hand size estimation task, CRPS patients judge their affected hand to be larger than its actual size (Moseley, 2005; Peltz et al., 2011). When asked to place their spine on a drawing of a back, patients with low back pain tend to draw it toward the painful side (Moseley, 2008). Deafferentation, as in the case of amputation, is also associated with altered body perception. Most amputees continue to feel the presence of their amputated limb (phantom limb) but its size, posture, and integrity are often altered (Giummarra et al., 2010). In addition to these persistent sensations of their lost limb, most amputees also experience pain in their missing limb (Ephraim et al., 2005).

As amputation is an extreme case of sensorimotor alteration, more subtle abnormalities in sensorimotor processing are observed in other chronic pain populations. Alteration of complex tactile functions such as tactile acuity (Moseley, 2008; Wand et al., 2010; Peltz et al., 2011), graphesthesia (Wand et al., 2010), or tactile stimuli localization (Forderreuther et al., 2004) have been demonstrated. Similarly, proprioception can be impaired as illustrated by poorer performance in a limb positioning task in various chronic pain populations (Pinsault et al., 2008; Lewis et al., 2010; Anderson and Wee, 2011). Furthermore, chronic pain patients tend to move more slowly (Schilder et al., 2012). Even their ability to imagine movements, a process known to at least partially solicit the same brain areas as those involved in movement production, is impaired, as illustrated by their performance in the laterality judgment task (Schwoebel et al., 2001, 2002; Moseley, 2004, 2008; Coslett et al., 2010a,b; Mercier, 2012). Together, these observations suggest that pain is related, to some extent, to perturbations in sensorimotor processing and may lead to a distortion of body representations. Neurophysiological data support this view, as pain intensity has been shown to be linked to the extent of reorganizations in the primary sensorimotor cortex in different population of patients with chronic pain (Flor et al., 1995; Karl et al., 2001; Lotze et al., 2001; Schwenkreis et al., 2009; Wrigley et al., 2009; Henry et al., 2011).

In a recent study, Moseley et al. (2009) showed that, in order to perceive tactile stimulations on both arms as simultaneous, CRPS patients have to receive the stimulation on the affected arm a few milliseconds before the stimulation on the unaffected arm. This observation was interpreted as neglect of the affected arm. However, when the same procedure was tested while patients had their arms crossed the stimulation had to be applied a few milliseconds earlier on the unaffected arm to be perceived as simultaneous. Thus, it suggests that the neglect is not related to the affected arm *per se* but to the hemispace where the painful limb normally lays. In other words, it suggests that the association between altered sensorimotor processing and pain is not related (or at least not exclusively related) to an altered somatotopical body representation, as plastic changes observed in the primary sensorimotor cortices might suggest. Rather, it seems to imply broader, multimodal information processing related to the egocentric framing of space (Legrain et al., 2012).

A series of studies by Sumitani et al. (2007a,b) and Uematsu et al. (2009) supports this view. They asked CRPS patients to align the position of a luminescent dot on their perceived body midline (subjective body midline, SBM) in a dark environment. They showed that patients systematically judged their SBM toward their painful side. This illustrates that the alignment of the proprioceptive and visual maps, which is important in maintaining the integrity of the egocentric frame of reference, is altered in these patients.

However, research with clinical pain populations may involve confounding factors, not associated directly with pain (for example disuse), that have the potential to influence sensorimotor processing. Although, as observed in pathologic pain, experimental pain has been shown to influence body perception (Gandevia and Phegan, 1999), other behavioral observations showed some discrepancies between clinical and experimental pain (Moseley et al., 2005). The objective of the present study was to evaluate the effect of acute experimental pain on the perception of body midline, which strongly relies on the proper integration of somatosensory and visual inputs. According to Sumitani's studies with CRPS patients (Sumitani et al., 2007a,b; Uematsu et al., 2009), we hypothesized that SBM should deviate toward the stimulated side in the presence of experimental pain. The effect of other non-painful sensorimotor manipulation was also tested to assess for potential unspecific attentional effects of stimulating one side of the body.

MATERIALS AND METHODS

SUBJECTS

Seventeen subjects participated in the study (nine females; mean age 26.9, SD 5.6). All were right handed according to the Edinburgh handedness questionnaire (Oldfield, 1971) and all had normal or corrected to normal vision. All subjects gave their written informed consent prior to participating in the experiment, which was approved by the Ethics Committee of the Institut de Réadaptation en Déficience Physique de Québec and conformed to the ethical aspects of the *Declaration of Helsinki*.

EXPERIMENTAL PROCEDURE

The SBM was tested in a dark environment to ensure that subjects had no visual spatial reference. A schema of the set-up is shown in **Figure 1**. Subjects sat in front of the experimental device and stared at a black screen. The subject was seated in a hydraulic chair (allowing vertical and lateral positioning). Once in place, the subject's head was restrained from movement in a headrest, fixed on the center of the experimental device (see **Figure 1**). A pointing laser mounted on a rotating motor projected a red dot onto the black screen. The width of the screen was 1.15 m, which corresponds to 60° of eccentricity (both lateral edges at 30° of eccentricity). The center of the screen was given the position 0°

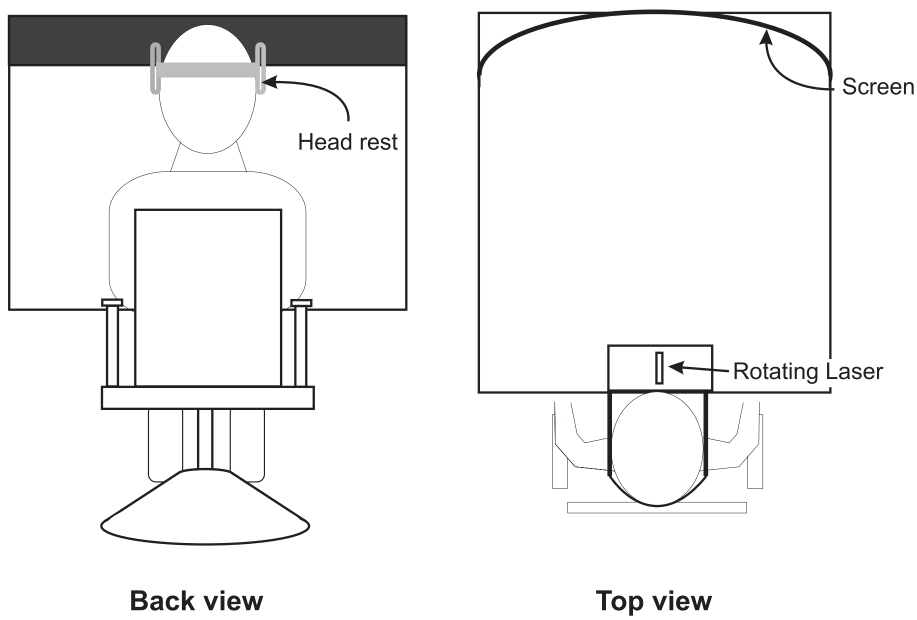

FIGURE 1 | Experimental set-up used to test the subjective body midline. Note that the screen on which the laser was projected was curved to ensure that the speed of the projected laser dot remained constant.

flanked with positive values on the right and negative values on the left. To judge the SBM, the pointer lit up and a red dot appeared on the screen. For each trial, the initial dot position was randomly determined. It was located at eye level, either on the right or on the left of the screen's center, between 15° and 25° of eccentricity. In the same conditions, half of the trials started from the right and the other half started from the left, with symmetrical positions. After its apparition, the red dot started moving toward the center at a constant speed of 3°/s. Subjects indicated their perceived SBM by stopping the red dot with a verbal command, consisting in briefly blowing in a microphone positioned immediately before the subject's mouth. The microphone signal was interfaced with the laser controlling system. To determine the SBM, the onset of the voice signal was identified and the position of the red dot at that moment was assessed by monitoring the rotation of the shaft on which the pointing laser was mounted. The signal from an optical encoder, detecting the shaft rotation, and the microphone were fed through an analog-to-digital converter (CED 1401 interface; Cambridge Electronic Design, Cambridge, UK) and then sent to a personal computer. Data were compiled with Spike 2 (Cambridge Electronic Design, Cambridge, UK).

CONDITIONS

The effect of pain and of two non-painful sensorimotor manipulations, vibrotactile stimulation and muscle contraction, on the SBM was tested on both sides of the body. Each condition was tested in a separate block (for a total of six experimental blocks; three conditions × two sides). At the beginning of each block, the subject's head was positioned in the headrest and the shoulders were aligned parallel to the screen. The subject was prompted to remain as still as possible throughout the block. Sixteen trials were tested in each block. No stimulation was applied in the first six trials and they served as controls for that particular block. In the remaining 10 trials (test trials), the appropriate stimulation was applied during each trial. Each trial was separated by 30 s. The effect of all three conditions on SBM judgment were first tested on one arm and then tested on the other arm. The order in which each arm was tested was counter-balanced across subjects as well as the order of tested conditions on each arm.

The pain condition consisted in applying a controlled thermal stimulation via a 30 × 30 mm thermode (Pathway Model ATS, Medoc advanced medical system, Israel) placed on the ventral face of the forearm. Before beginning the SBM assessments, we determined the pain threshold for each arm. To do this, the thermode temperature was initially set at 33°C and gradually increased at a rate of 1.5°C/s. The subject was instructed to push a button to stop the thermal stimulation when he/she felt that the stimuli switched from a sensation of warmth to a sensation of pain. This procedure was repeated three times and the mean of the temperature measured at each button press was calculated and considered as the pain threshold. The default stimulation temperature used in the SBM measurement trials was set at 0.5°C above measured threshold. In these trials, the thermode temperature started at 33°C and rose up at a rate of 3.5°C/s until it reached the stimulation temperature, plateaued for 10 s, and fell back to 33°C at a rate of 8°C/s. The pain sensation had to be considered as moderate by the subject across the whole 10 s. In a few subjects, it has been necessary to slightly re-adjust the temperature to obtain a moderate pain level over the 10-s period. For the SBM judgment, the red dot appeared on the screen at the moment the painful stimulation temperature was reached. The duration of the painful stimulus was not influenced by the subject's response time.

In the vibration condition, a custom made vibrator was fixed on the ventral face of the midportion of forearm with a Velcro strap. The vibration frequency was set at 25 Hz. It is important to note that such parameters do not induce illusions of movement (typically induced while vibrating the tendons at frequencies between 60 and 80 Hz (Roll and Vedel, 1982). During a trial, vibration started 4 s before the red dot appeared on the screen and ended when the subject stopped the laser.

The muscle contraction condition consisted in supporting a weight (conventional dumbbell) with the forearm in a neutral position with the elbow flexed at about 90°. Before beginning the experimental procedure, each biceps maximal voluntary contraction was measured by means of surface electromyographic (EMG) recordings during an isometric contraction. The subject was then required to hold different weights and the weight generating an EMG corresponding to 15% (±5%) of the maximal contraction was retained for the experimental task. During the muscle contraction condition, the weight was lifted for 4 s before the red dot was presented and started moving on the screen. The subject was instructed to hold the weight until the SBM judgment was completed and to rest afterward. The rational for applying vibration and to lift the weight about 4 s before starting the trials was to match the rise time of the temperature in the painful condition.

DATA ANALYSIS

In each block of trials, the mean of the 6 control trials and the mean of the 10 test trials were calculated for statistical analysis. In order to avoid a potential bias that could have been introduced by a slight difference in the head placement across blocks, the SBM measured during a painful/non-painful sensorimotor manipulation in one block was always compared to the SBM measured during control trials of the same block. As the aim of the study was to assess the individual effect that each sensorimotor manipulation had on the SBM, rather than to quantitatively compare the effect of each manipulation relative to the others (as it is impossible to match the intensity of a muscle contraction or of a non-painful stimuli to that of a painful stimuli), a distinct analysis was performed for each condition. As such, for each experimental condition, the effect of the stimulated side (right vs. left) and the effect of the type of trial (control vs. test) were tested with a 2 × 2 (side × trial type) repeated measures ANOVA computed with SPSS 13.0 software (without correction for multiple testing, given that a different set of data was employed for each analysis). When a significant interaction effect was found, paired t-tests [corrected for multiple testing using a Hochberg procedure (Olejnik et al., 1997)] were used for pre-planned comparisons between control and test trials measured on the same tested body side.

In order to compute group descriptive statistics on the effect of each experimental condition, normalized SBM was calculated for each subject in each experimental block. This was done by subtracting, for each block, the mean SBM measured in control trials from the mean SBM measured in test trials (°test − °control).

Thus, a normalized SBM with a positive value indicates that the sensorimotor stimulation shifted the SBM to the right and conversely, a negative value indicates a shift to the left.

RESULTS

The mean stimulation temperature used during the SBM judgment was 47.2˚C (SD 1.9) on the right arm and 47.5 (SD 1.5) on the left which is not statistically different [$t_{(16)} = -0.97, p = 0.35$].

Group means of the normalized SBM positions for each condition are presented in **Figure 2**. In the pain condition, the ANOVA revealed an interaction effect [$F_{(1,16)} = 4.466$, $p = 0.05$]. T-tests showed that when the painful stimulus was applied over the right arm, the SBM was significantly deviated to the right when compared to control trials [$t_{(16)} = -2.473$, $p = 0.03$]. No such effect was found when the stimulus was applied over the left arm [$t_{(16)} = 0.148$, $p = 0.90$]. An interaction effect was also detected with the ANOVA in the vibration condition [$F_{(1,16)} = 5.046$, $p = 0.04$]. T-tests revealed that vibrations applied to the left arm deviated the SBM to the right when compared to control trials [$t_{(16)} = -3.003$, $p = 0.01$]. The effect was not found when the stimulus was applied over the right arm [$t_{(16)} = 0.785$, $p = 0.4$]. Finally, in the contraction condition, there was no significant effect (whether main effect or interaction effect) detected by the ANOVA [$F_{(1,16)} = 1.380$, $p = 0.26$]. Individual results obtained in conditions that yield significant effects indicated that 76% of the subjects had their SBM deviated toward the right when stimulated with pain on their right side and 82% were deviated to the right when vibrotactile stimuli were applied to their left side (see **Figure 3**).

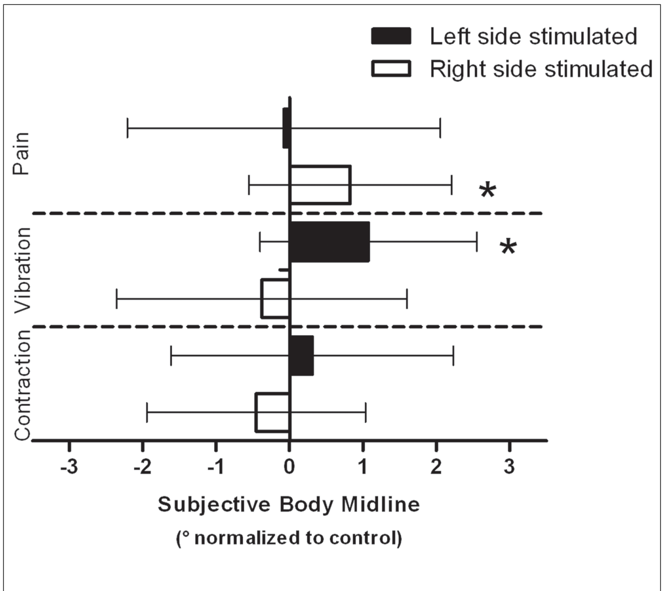

FIGURE 2 | Group data for each modality are presented. Data are normalized to their respective controls (see Materials and Methods). Negative values indicate a shift of the SBM position toward the left and conversely, a positive value indicates a shift toward the right. Error bars indicate the standard deviation on the mean normalized data. *Indicates a statistically significant difference between the test SBM (e.g., with pain/vibration/contraction) and the control SBM measured in the same block.

DISCUSSION

The primary objective of the present study was to evaluate the effect of acute experimental pain on the perception of body midline, which strongly relies on the integration of somatosensory and visual inputs. Vibrotactile stimulation and muscle contraction were used to control for the effect of non-specific sensory inputs. The results show that both painful and vibrotactile stimulation influence the judgment of the SBM. Importantly, these two stimulation modalities induced opposite effects on the SBM judgment. Indeed, both produced a deviation of the SBM to the right, but this effect was only observed if (a) pain was applied to the *right* side of the body and (b) vibrotactile stimulation was applied to the *left* side of the body. This suggests that the observed deviation in the perceived body midline is modality specific and not simply an unspecific perceptual bias caused by sensory input whatever the stimulation modality used. These results are consistent with those of a few studies reporting that acute pain can interfere with tasks involving multimodal sensory processing. For example, altered perception of the size of the thumb (Gandevia and Phegan, 1999) and perturbations in laterality recognition (Moseley et al., 2005) have been shown when acute nociceptive stimulation is applied to the hand.

Results of clinical studies showed that patients with chronic neuropathic pain (CRPS) tend to judge their body midline toward their painful side (Sumitani et al., 2007b), consistent with our observations in experimental acute pain. Interestingly, they

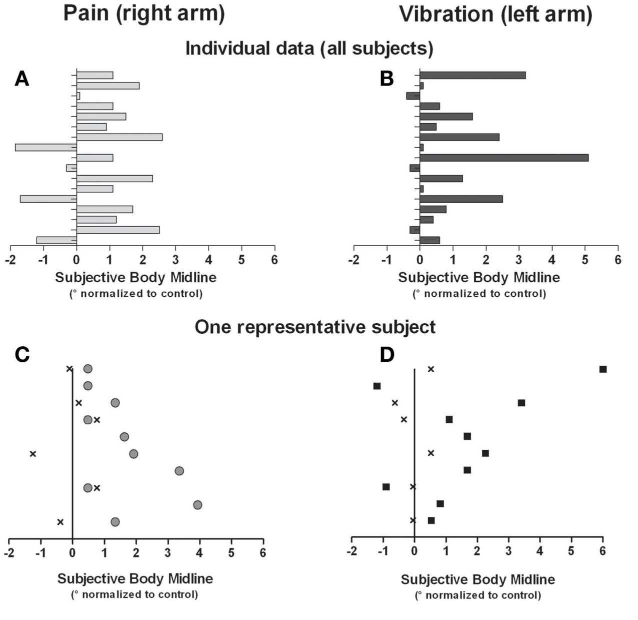

FIGURE 3 | Individual data for all subjects are shown for the right pain condition (A) and the left vibration condition (B). In addition, data from one subject in the right pain condition **(C)** and the left vibration **(D)** are shown. Data in C and D were each obtained in a single block, and each dot represents a single trial. "X" indicates trials in the control condition (i.e., no stimulation, trials 1–6 of a given block), gray circles in right pain condition, and black squares in left vibration condition (respectively trials 7–16 of a given block). All data are normalized against the average SBM obtained in the control condition.

showed that using adaptation to prismatic deviation in these CRPS patients [an "unconscious" way to re-align the distorted visuomotor and proprioceptive maps (Rossetti et al., 2005)] can reduce pain intensity (Sumitani et al., 2007a). This further supports the idea that pain and multimodal sensory processing have mutual interactions. However, the observation that subjective SBM is deviated toward the painful side might appear to be in contradiction with other studies suggesting that patients tend to neglect the side of their body affected by pain (Lewis et al., 2007) and exhibit slower sensorimotor processing on that side. Indeed, CRPS patients have longer reaction time to judge the laterality of pictures corresponding to the affected limb when compared to the unaffected limb (Schwoebel et al., 2001; Moseley, 2004; Moseley et al., 2008; Reinersmann et al., 2010). Another study, with the help of a tactile temporal order task, showed that CRPS patients felt cutaneous stimulations applied over both forearms as simultaneous when the affected arm was actually stimulated first. This apparent discrepancy might reside in part in the nature of the tasks studied. In the latter studies, the experimental manipulations might constitute a "threat" to the painful limb as motor imagery has been shown to increase pain in CRPS patients (Moseley et al., 2008). Also, normally inoffensive tactile stimulation might provoke painful sensations (allodynia) in neuropathic pain populations (Gierthmuhlen et al., 2012). It was proposed that the delayed processing of the sensory information on the painful body part might be a way to protect oneself against painful threats (Moseley, 2004; Moseley et al., 2009). In contrast performing a SBM task does not impact on pain which might explain why in this condition the perception appears to be biased toward the painful side.

Both pain and vibrotactile stimulations led to a rightward deviation of the SBM. This rightward deviation of the SBM is similar to what is observed in patients with a neglect of the left hemispace following a brain lesion (Farne et al., 1998). Indeed, chronic neglect was reported to be three times more frequent in right brain damaged than in left brain damaged patients (Ringman et al., 2004). Thus, dominance might be a factor in the effect we observed (i.e., a deviation of the SBM only toward the right side of the body). Studies in healthy subjects tend to support that right handers showed a systematic bias toward the left side in tasks such as line bisection (Jewell and McCourt, 2000), a phenomenon that was termed pseudoneglect. The presence of such pseudoneglect may hinder the possibility of sensorimotor manipulations to further deviate the SBM toward the left (Kline et al., 2009), or at least make it easier to deviate SBM toward the right.

Voluntary contraction did not induce a shift of the SBM. This might be explained by the fact that when a movement is self-produced, its sensory consequences can be accurately predicted by an internal model (Wolpert et al., 1995). It has been proposed that this prediction can be used to attenuate the sensory effects of the movement (Blakemore et al., 1998) and therefore might cancel the potential impact of sensory feedback on the SBM. Alternatively negative results might also be attributable to limitations related to the methodology. It needs to be kept in mind that all the sensory manipulations were tonic (e.g., stimulation/contraction was maintained for several seconds) because of the time needed to perform the SBM judgment. As such this method does not allow the measurement of the time-course of the effect of a given condition. It can therefore not be excluded that the effect of contraction is too short-lived to be observed using that method. Similarly the effects of pain/vibration on the SBM might vary depending upon the duration of the stimulation. Finally the variability of the SBM measure in the baseline condition might also have led to some negative results, especially given that shifts induced in SBM in healthy subjects are expected to be small. Some of this variability is probably associated to the fact that the subjects had to produce a verbal command in order to stop the moving dot when it was crossing their perceived SBM. Now that we have an estimate of the range of shift of the SBM that can be induced using sensorimotor manipulations, other psychophysical methods, such as two-alternative forced choice for example, might provide a way to improve both the spatial and temporal resolution of the SBM measurement.

CONCLUSION

In line with the results of studies in patients with chronic pain, the results of this study indicate that body representation can be influenced by acute painful sensations. They show that acute experimental pain can rapidly shift the SBM bias toward the stimulated side, a phenomenon that might potentially be functionally beneficial to protect the painful body region. This effect was found to be specific to painful stimuli, as the effect of vibration was in the opposite direction. Interestingly, it appears to be easier to bias SBM toward the right side, regardless of the modality and of the stimulated side.

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Subject-level differences in reported locations of cutaneous tactile and nociceptive stimuli

Peter Steenbergen[1]*, Jan R. Buitenweg[1], Jörg Trojan[2], Bart Klaassen[1] and Peter H. Veltink[1]

[1] Biomedical Signals and Systems, Mira Institute for Biomedical Technology and Technical Medicine, University of Twente, Enschede, Netherlands
[2] Department of Cognitive and Clinical Neuroscience, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany

Edited by:
Diana M. Torta, University of Turin, Italy

Reviewed by:
Matthew R. Longo, Birkbeck, University of London, UK
Vanessa Harrar, Oxford University, UK

****Correspondence:***
Peter Steenbergen, Biomedical Signals and Systems, University of Twente, Zuidhorst, Room ZH211, Drienerlolaan 5, Postbus 217, Enschede, Netherlands.
e-mail: p.steenbergen@utwente.nl

Recent theoretical advances on the topic of body representations have raised the question whether spatial perception of touch and nociception involve the same representations. Various authors have established that subjective localizations of touch and nociception are displaced in a systematic manner. The relation between veridical stimulus locations and localizations can be described in the form of a perceptual map; these maps differ between subjects. Recently, evidence was found for a common set of body representations to underlie spatial perception of touch and slow and fast pain, which receive information from modality specific primary representations. There are neurophysiological clues that the various cutaneous senses may not share the same primary representation. If this is the case, then differences in primary representations between touch and nociception may cause subject-dependent differences in perceptual maps of these modalities. We studied localization of tactile and nociceptive sensations on the forearm using electrocutaneous stimulation. The perceptual maps of these modalities differed at the group level. When assessed for individual subjects, the differences localization varied in nature between subjects. The agreement of perceptual maps of the two modalities was moderate. These findings are consistent with a common internal body representation underlying spatial perception of touch and nociception. The subject level differences suggest that in addition to these representations other aspects, possibly differences in primary representation and/or the influence of stimulus parameters, lead to differences in perceptual maps in individuals.

Keywords: perceptual map, touch, nociception, electrocutaneous stimulation, localization, body representations, primary representations

INTRODUCTION

A number of reviews recently discussed the involvement of multimodal body representations in spatial perception of touch (Longo et al., 2010; Medina and Coslett, 2010; Serino and Haggard, 2010). Information from primary sensory representations with different reference frames is projected to these body representations, which allows, for instance, localizing cutaneous stimuli in space and integrating cues from different senses which are related to the body. Central processing of nociception and touch differs and these modalities may have different primary representations (Mancini et al., 2011). If this is indeed the case, there may be differences in spatial perception between these modalities.

For identifying the location of a stimulus on the body surface, somatosensory information needs to be referenced to models of body form and body surface (Longo et al., 2010; Medina and Coslett, 2010). In order to perform a pointing movement task to report the perceived location of the stimulus, this information needs to be translated into an external reference frame. This involves representations of body posture, which contain information about the position of body parts in space. There is evidence that these body representations are not perfectly matched; humans have been shown to exhibit systematic distortions in identifying the locations of landmarks in their hand, which indicates that representations of body shape differ from the physical shape of the body (Longo and Haggard, 2010, 2012). Furthermore, the relation between the reference frames of body form and body posture representations is variable, since the location of body parts in space is variable, while the shape of the body is constant. There is evidence that sensory information about the orientation of the head on the body and the eyes in the head are involved in aligning these representations (Pritchett and Harris, 2011; Pritchett et al., 2012). This alignment is not perfect, as is illustrated by the finding that tactile stimuli are mislocalized in the direction of gaze (Harrar and Harris, 2009).

Although much information is available on the cortical primary sensory structure of touch, the cortical representation of nociception is still a matter of debate. It has been suggested that SI is responsible for spatial perception of nociception as well as touch (Bushnell et al., 1999; Ogino et al., 2005). Activation patterns in SI differ for these modalities, with mechanical stimuli mainly activating areas 3b, 1 and 2, and heat pain stimuli additionally involving area 3a (Tommerdahl et al., 1998; Chen et al., 2009, 2011). Furthermore, touch and nociception may not lead to activity in the same cortical columns, analogous to the differences in activation between different tactile submodalities (Mountcastle, 1997; Friedman et al., 2004). Several researchers have argued that the somatotopy of cortical maps is fundamental to their functioning [see for instance Kaas (1997)], which is supported by a recent finding that experimental manipulations of the cortical topography of fingers affects reaction times in a decision task involving spatial perception (Wilimzig et al., 2012). Therefore, if SI is indeed involved in spatial perception of both touch and nocicepion, differences in cortical representation of these modalities may lead to differences in spatial perception. Alternatively, it has been suggested that the primary sensory cortex for nociception is located in the posterior insular-opercular region (Garcia-Larrea, 2012). Regardless of whether the primary sensory cortex for touch and nociception is the same or different, it is likely that the cortical representations for these modalities differ, which may lead to differences in spatial perception of these modalities. This supports the idea put forward by Mancini et al. (2011) that these modalities may have their own primary representations, which are mapped to the same multimodal internal body representations.

When humans localize a cutaneous stimulus, the reports generally deviate from the veridical stimulus site. When repeatedly stimulating various sites of a body part and asking a subject to localize these stimuli, a somatosensory perceptual map can be constructed which relates the localizations to the veridical stimulus sites (Trojan et al., 2006). Studies using this procedure in combination with mechanical and laser stimulation on the lower arm have shown that somatosensory perceptual maps deviate from the veridical stimulus locations for both touch (Trojan et al., 2010) and nociception (Trojan et al., 2006). The maps varied between participants: compared to the veridical stimulus locations, subjects exhibited overall biases and scaling of the area over which they reported. In a recent study we showed that somatosensory perceptual maps of non-painful electrocutaneous stimuli have highly reproducible features, which supports the idea that these maps measure a stable property of spatial perception and may therefore reflect internal body representations (Steenbergen et al., 2012b). Mancini et al. (2011) addressed the question whether the same body representations underlie spatial perception of the various cutaneous sensory modalities by comparing perceptual maps of tactile, heat and nociceptive stimuli on the hand. They found some significant differences in perceptual maps between stimulus modalities on the group level, but perceptual maps of the three modalities had similar features, from which the authors concluded that common internal body representations are involved in spatial perception of the modalities studied.

Multimodal body representations and primary representations in SI reflect each individual's own body. Differences between tactile and nociceptive SI representation may therefore vary between subjects. As a consequence, a resulting difference in somatosensory perceptual maps would also be subject-dependent and these individual differences therefore do not necessarily contribute to a difference at the group level. Therefore, we conducted a study in which we assessed agreement of tactile and nociceptive perceptual maps at the group level, as well as their differences at the subject level.

We conducted a study in which we compared perceptual maps of tactile and nociceptive electrocutaneous stimuli on the lower arm. Using stimulation electrodes designed for this study (Steenbergen et al., 2012a), we applied nociceptive and tactile stimuli at four sites. Based on the results by Mancini et al. (2011), we expected to find a small difference at the group level, but also to find some level of agreement between perceptual maps of the two modalities. Two topics which we were interested in were not addressed by Mancini et al. (2011). The first one was that we wanted to quantify the agreement between perceptual maps of the different modalities. We assessed this by calculating Intraclass Correlation Coefficients of the regression parameters fitted to the data of individual subjects. The second topic concerned differences between tactile and nociceptive localization in individuals rather than on the group level. We had no clear hypothesis on what type of differences to expect. We therefore tested for these differences in a way which required minimal assumptions about the data by conducting separate tests for all electrode sites and subjects.

MATERIALS AND METHODS

SUBJECTS

Eighteen subjects from the population of students and employees of the University of Twente volunteered to participate in this study and gave informed consent prior to the experiments. One subject was excluded because he did not detect any of the nociceptive stimuli. The mean (M) age of the remaining seventeen subjects was 23.8 years with standard deviation (SD) of 2.7 years (range 19–28 years). Seven subjects were female. The arm length of the subjects was 27.2 ± 1.63 (M $\pm$ SD) cm, with the shortest being 24 cm and the longest 29 cm. The protocol was approved by the Medical Ethical Board Twente (file number NL35875.044.11).

STIMULATION METHOD

Tactile and nociceptive electrocutaneous stimuli were applied using the compound electrode arrays we presented in an earlier paper (Steenbergen et al., 2012a); this electrode is presented in **Figure 1**. The devices consist of an array of disc and needle electrodes which are capable of eliciting a tactile or nociceptive sensation, the strength of which can be varied using pulse train modulation.

Four compound electrodes were placed on the left lower arm along a line connecting the distal end of the ulna and proximal end of the radius. The most proximal electrode was placed 10 cm from the proximal end of the radius, the most distal one 4 cm from distal end of the ulna. The remaining two electrodes were placed with equal distance between all four electrodes. A Protens 9×5 cm rectangular TENS electrode served as anode and was placed at the wrist (see **Figure 2**). The electrodes were fixed using tape. The stimuli were applied using 8-channel stimulators with a common anode which were similar to stimulators in previous studies by our group (van der Heide et al., 2009; Roosink et al., 2011; Steenbergen et al., 2012a; van der Lubbe et al., 2012). All stimuli were monophasic cathodic pulses with a pulsewidth of 0.21 ms.

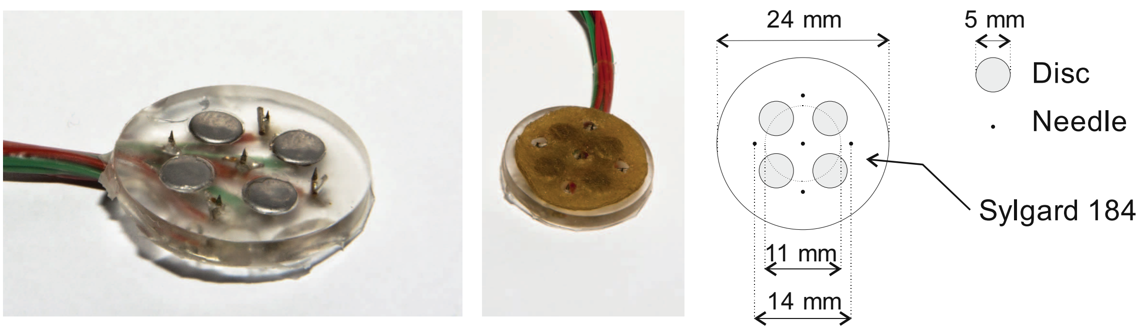

FIGURE 1 | One of the compound electrode arrays which were used in the experiments. Each compound electrode consists of four disc electrodes and five needle electrodes. During experiments, the disc electrodes were covered with a conducting pad which did not touch the needle electrodes. The left and middle panels show the compound electrode without and with this pad. A schematic diagram of the compound electrodes is presented in the right panel.

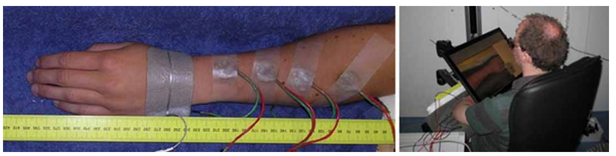

FIGURE 2 | Left: The arm of a subject with four compound electrodes (green and red wires) and a reference electrode on the hand. **Right:** A subject seated using the tablet screen setup. The arm with electrodes is obscured from the subject's view by the monitor, which shows a photograph of the subject's own arm without electrodes.

REPORTING METHOD

Subjects performed the localization task on a 46 × 29 cm tablet monitor displaying a photograph of their own arm (see **Figure 2**). The monitor was placed over their arm, thus preventing visual information about the electrode positions from interfering with the experiment. When the electrodes were attached, subjects were prevented from seeing their arm by this same tablet monitor. The photograph was taken before the electrodes were placed, after which it was scaled in such a way that subjects reported that size and position matched the real arm. During the experiments, subjects reported the perceived stimulus locations by tapping the monitor using a pen, after which they tapped a ready button.

SENSATION THRESHOLDS

Sensation thresholds for the two electrode types were determined for each of the four sites using an adaptive psychophysical threshold determination method. The method consisted of applying a series (10 in this experiment) of stimuli of ascending amplitude. Based the estimated threshold and its uncertainty, the starting point and increment of the series was adjusted. The sensation threshold was defined as the current at which a subject has a 50% chance of detecting a stimulus. This point was determined using a logistic regression fit. Details of this method are presented in Steenbergen et al. (2012a). The sensation thresholds for the needle and disc electrodes were 0.62 ± 0.30 (M ± SD) mA and 2.76 ± 1.10 mA respectively.

STIMULI

During the remainder of the experiments, the stimuli were pulse trains of five monophasic cathodic pulses, each of which had a pulse width of 0.21 and 5 ms between the onsets of the pulses. The amplitude of the stimuli was equal to the sensation threshold as determined for each site and electrode type combination.

QUALITATIVE VERIFICATION OF STIMULI

We verified the quality of the eight stimuli which were to be used during the remainder of the experiment by using the quality visual analogue scale (VAS) which is described in Steenbergen et al. (2012a). The VAS was presented horizontally with left side being labeled as *dull* and the right side as *sharp*. The ratings were converted to numbers ranging from 0 (dull) to 10 (sharp). Reports lower than 5 were interpreted as tactile sensations, and higher than 5 as nociceptive. If the reported quality scores of an electrode were higher than 5 for the discs or lower than 5 for the needles, the electrode was moved to another spot on the skin. This was followed by a re-determination of the sensation thresholds and a new quality judgment. For the stimuli which were used in the localization experiments, subjects reported quality scores lower than five (dull halve of the scale) in 60 out of 68 stimulus sites.

EXPERIMENT PROCEDURE

After giving informed consent, subjects were seated in a chair. They placed their left forearm in a comfortable armrest which was placed before them. A photograph was taken of the arm in the armrest. Next, their view of the arm was obscured by placing a tablet monitor, which was later used for reporting tasks during the experiments, between their head and arm. After this, the electrodes were placed as described above, following which the tablet monitor was lowered over the arm. This was followed by the sensation threshold and quality verification procedures. After this, the main experiment started. The localization experiment consisted of two blocks, a tactile and a nociceptive one, the order of which was randomly balanced over the subject population. 15 stimuli for each site were applied in each block, leading to a total of 120 stimuli. The localization procedure lasted approximately 30 min. At the end of the experiment, a photograph was taken of the subject's arm with electrodes and placed in the armrest.

DATA PREPARATION OF LOCALIZATION TRIALS

The following procedures were performed in Matlab (version 7.13.0. Natick, Massachusetts: The MathWorks Inc., 2011).

Localization data: The reports which were generated by the tablet screen setup were in the form of x-y coordinates in pixels. This two-dimensional data was reduced to a single dimension by applying principal component analysis on the data of each subject separately and retaining the first principal component. After this, outliers were detected separately for each subject by site by modality condition and discarded. Outliers were defined as being 1.5 times the interquartile distance removed from the median.

Electrode locations: The photographs of the arms with electrodes were scaled to match the representation of the arm which was presented to the subjects during the experiments. In this scaled figure, the electrode locations were manually identified. These localizations were subsequently projected obliquely on the first principal component of the data.

As a final step, the data and electrode locations projected on the first principal component were normalized to the subjects' arm length by using information about the electrode placement in relation to the anatomy.

GROUP LEVEL ANALYSIS: LINEAR MIXED MODEL

The dataset with all trials was analyzed using the linear mixed model (LMM) in SPSS 18.0 using the default settings. LMM's have several advantages compared to a repeated measures ANOVA. The method accounts for inter subject differences, which, as discussed in the introduction, are considerable in the case of localization data. Also, the model allows the inclusion of correlated data points, therefore we could include all localization trials in the analysis, rather than the mean of each condition as would be the case in a repeated measures ANOVA. The model contained fixed main effects for *Stimulus type* (categorical with levels Tactile, for the disc electrode stimuli, and Nociceptive, for the needles electrode stimuli), *Electrode site* (a covariate ranging from 0 at the elbow to 1 at the wrist) and for the *Stimulus type* × *Site* interaction effect. A random intercept for subjects was modeled, as well as random effects for *Stimulus type* and *Electrode site*. A variance components covariance structure was used for modeling the random effects.

SUBJECT LEVEL ANALYSIS

In order to determine whether differences in localization are present at the subject level, we assessed each electrode site separately for each subject. For each site, a two-sided t-test was performed (using the Matlab t-test2 procedure) on the localizations of the tactile and nociceptive stimulus conditions. In addition, the magnitude of the difference in means was assessed. If this difference was larger than the maximum distance between disc and needle electrodes (1.5 cm), the difference was considered relevant. The reason for this cut-off value was that since each electrode array contains multiple electrodes of each type, there is a possibility that a single disc and a single needle are responsible for the stimuli because of differences in electrical contact between the component electrodes in each array. The maximum difference in stimulus site caused in this way in one compound electrode is 1.5 cm.

Performing separate t-tests for each site and subject means that 68 t-tests were performed for the whole dataset. In order to find out whether these differences were caused by false positives we counted the number of subjects which had one or more significant t-test result. This number was tested against the false positive rate using a binomial test. If we take the significance level for the t-tests of $p = 0.05$ as a worst case estimation for the probability of a false positive, the chance of any subject having one or more sites turn out positive by chance is $1–0.95^4 = 0.186$. The binomial distribution used for testing the number of subjects with significant t-tests was therefore B(17,0.186).

In addition to the tests of separate electrode sites, a separate regression model was fitted to the tactile and nociceptive localization datasets of each subject using the Matlab glmfit function. Trials were weighted such that each electrode site contributed equally to the regression fits. The intercepts and slopes of each were stored for analysis.

AGREEMENT BETWEEN STIMULUS MODALITIES

In order evaluate the agreement between perceptual maps of the tactile and nociceptive experiment conditions, we calculated intraclass correlation coefficients [*ICC(1,k)*, see (Shrout and Fleiss, 1979)] of slopes and offsets of the subject and modality dependent regression fits on the localization data. As a reference to compare these values with, we also calculated the within-modality reproducibility by splitting the data of each modality in two parts over time. This split was performed separately for each electrode in each subject to prevent unequal numbers of trials in the two halves. The difference between the split data ICCs and the between-modality ICCs was tested using Konishi-Gupta modified Z-tests (Donner and Zou, 2002).

RESULTS

The results of the localization experiments projected on the subjects' own arms are presented in **Figure 3**. The top panels show the arms with electrodes, the middle and lowers panels the nociceptive and tactile localizations respectively. The localizations of each electrode are color coded to match the top panels. The localizations are drawn as means and SDs in two directions. The grey lines indicate the first principal component of the data of each subject to which the data was projected for further analysis. **Figure 4** presents this reduced localization data as a function of the actual electrode positions, along with the linear regression fits for each stimulus type. These regression models showed the same features which were previously identified by Trojan et al. (2006): subjects showed contractions/expansions (slope larger/smaller than 1) and distal and proximal displacements (intercept smaller/larger

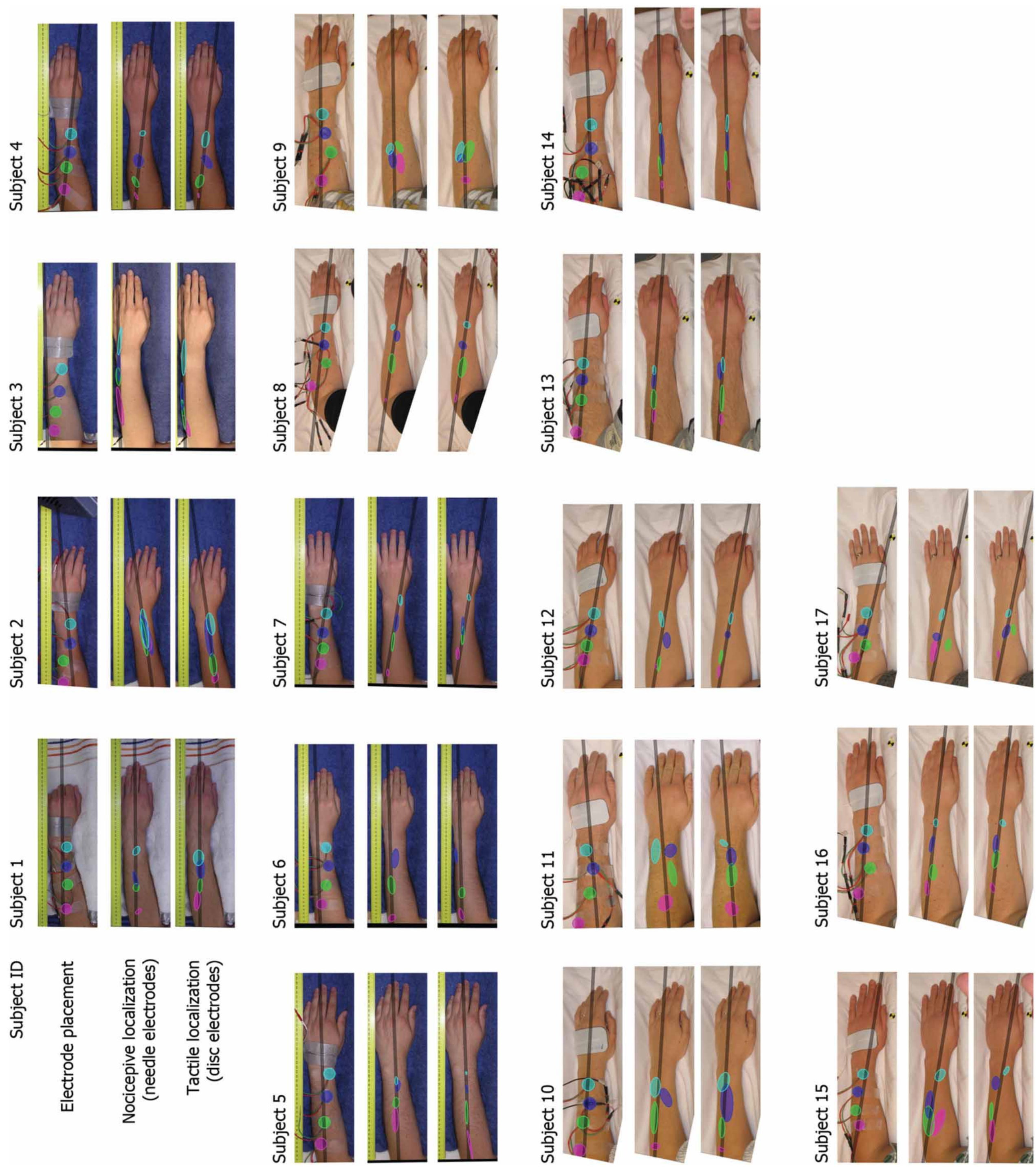

FIGURE 3 | Electrode placements and localizations plotted on the subjects' arms. The localizations are plotted as means with standard deviations in two directions (the orientation of the ellipses was determined by applying a principal component analysis on all separate electrodes). The grey bar represents the first principal component of all data of each subject, this was the line on which all data is projected for further analysis.

than 1). In 12 out of 17 subjects at least one stimulus site showed a significant difference between localizations of tactile and nociceptive stimulus conditions which exceeded the electrode array diameter 1.5 cm (see **Figure 4**). Comparing this frequency of 12 out of 17 to a false positive rate 0.186 using a one-tailed binomial test showed that this number is significant ($p < 0.001$).

The agreement of the tactile and nociceptive regression parameters was $ICC(1,k) = 0.66$ [0.09–0.88 confidence interval (CI)]

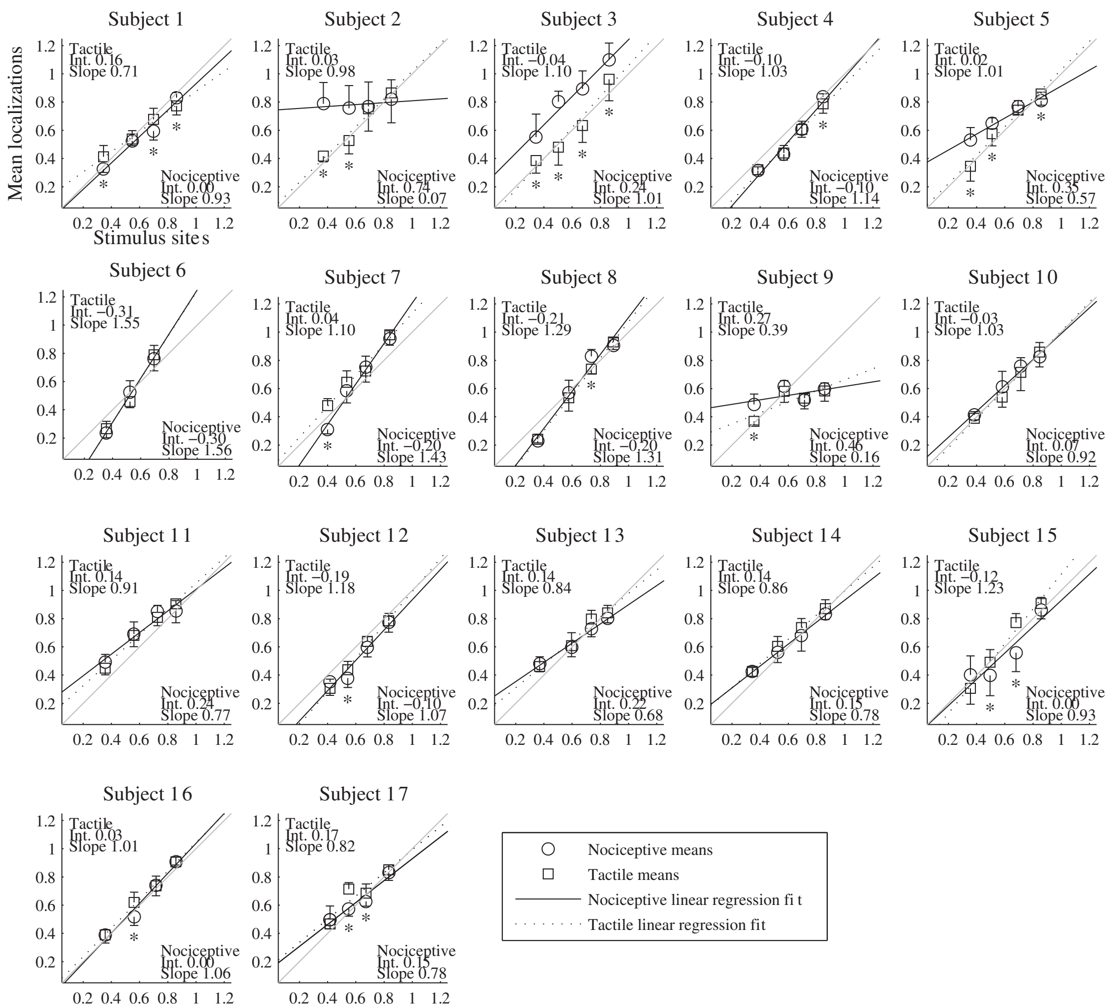

FIGURE 4 | Results of the localization experiments as a function of the stimulus site for each subject. The localizations (vertical axis) are plotted as function of the sites (horizontal axis); both localizations and sites are shown as fraction of each subject's arm length, with 0 being the elbow and 1 the wrist. Each marker represents the mean localization of one site for either the nociceptive (circle) or the tactile (square) stimulus condition. The bristles indicate the standard deviations; these are plotted to one side only. The lines show the fitted regression models, solid for the nociceptive stimulus condition and dashed for the tactile condition. As a reference, a grey line is included in each panel which indicates the relation of perfect correspondence (i.e., intercept = 0 and slope = 1). The coefficients of the regression models are printed in the corners of each plot. Asterisks mark the sites for which (1) the localizations of the two types differed significantly and (2) the differences of the means were larger than the electrode diameter of 1.5 cm.

for the intercept and 0.76 [0.37–0.91 CI] for the slope. The ICCs for the slopes of the split data was 0.96 [0.90–0.99 CI] for the nociceptive and 0.98 [0.94–0.99 CI] for the tactile localizations. These ICCs were significantly higher than the between-modality ICC of the slopes (Konishy–Gupta modified Z-test: $T_{ZM} = 3.67$, df = 32, $p < 0.001$ and $T_{ZM} = 4.48$, df = 32, $p < 0.001$ respectively). For the intercepts, the split data ICCs were 0.97 [0.91–0.99 CI] for the nociceptive and 0.96 [0.90–0.99 CI] for the tactile localizations, which in both cases was significantly higher than the between-modality ICC of the intercepts ($T_{ZM} = 4.47$, df = 32, $p < 0.001$ and $T_{ZM} = 4.41$, df = 32, $p < 0.001$).

The results of the LMM group level analysis are presented in **Table 1**. Significant effects were found for *Stimulus type*, *Electrode site* and for the interaction between these. The regression models fitted by the LMM on the tactile and nociceptive localizations of the whole study population are presented in **Figure 5**. Both the stimulus sites and localizations are represented as a fraction of the arm length, with 0 being at the elbow and 1 at the wrist.

Table 1 | Linear mixed model fixed effects results for the normalized localizations.

Factor	df[a]	*F*	*p*
Stimulus type	1/40.1	16.00	<0.001*
Electrode site	1/15.8	178.06	<0.001*
Type × Site	1/1825.0	30.79	<0.001*

$^*p < 0.05$, [a]Numerator/denominator degrees of freedom.

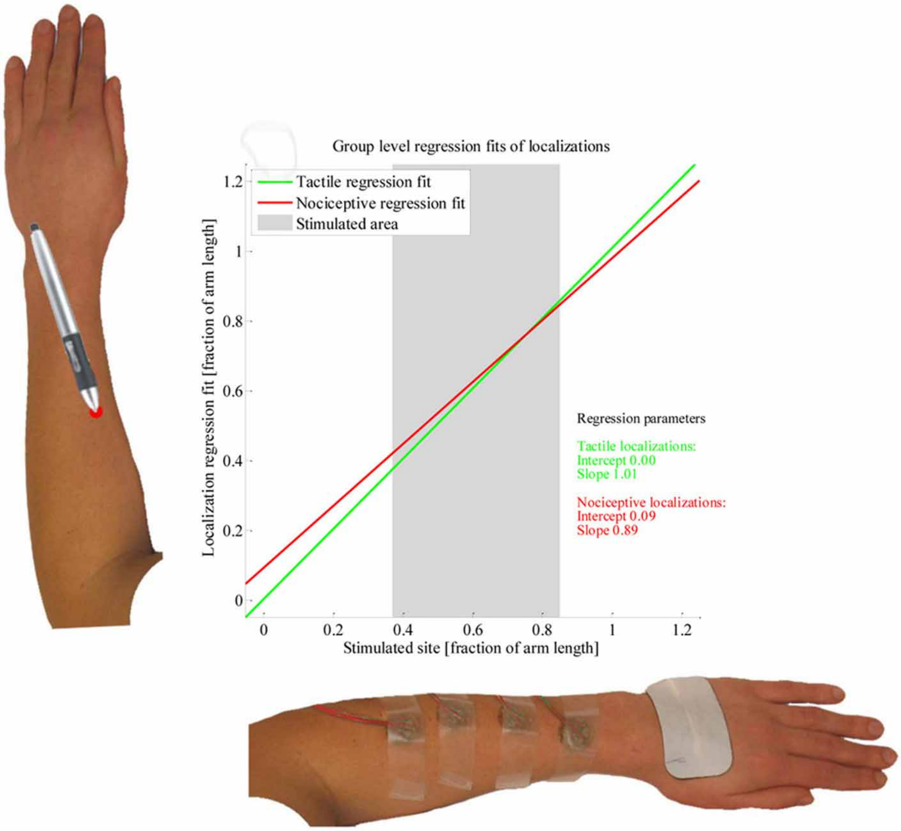

FIGURE 5 | Linear mixed model fit of the localization data. The two lines present the group-level regression fits of the tactile (green) and nociceptive (red) localizations; the regression parameters are presented as well. Two example arms are presented along the axes. The average length over which subjects were stimulated is presented by a grey block.

DISCUSSION

Our aim was to determine whether there are differences between tactile and nociceptive perceptual maps at the subject level and whether the perceptual maps of these modalities are in agreement for the whole subject population. In a series of experiments, tactile and nociceptive sensations were elicited on the lower arm using electrocutaneous stimulation. Subjects repeatedly reported the perceived location of stimuli of both types applied at four sites. When assessed for each separate electrode, the localizations of the tactile and nociceptive conditions differed for most subjects, but in a manner which varied between subjects. Despite these differences, linear regression fits of the data of each separate modality and subject showed some measure of agreement. This agreement was lower than the within modality ICCs we obtained by splitting the data in two halves.

The subject-level differences that we found between tactile and nociceptive localization occurred at different sites and do not seem to follow a common pattern for all subjects. In some subjects, no difference in localization between the two modalities was found. Nevertheless, from the magnitude of the differences and their frequent occurrence we conclude that these differences in localization are the result of an actual difference in perceived location and not a chance occurrence. From our data we cannot conclude what causes these differences. Possibly they reflect the columnar organization of the primary sensory cortices for touch and nociception.

At the group level, we found the regression fits of the tactile and nociceptive stimuli to differ, with the regression fit of the nociceptive localizations being contracted while the fit of the tactile localizations was close to veridical. This matches the results by Mancini et al. (2011), who found group-level perceptual maps of painful laser stimuli on the dorsal and volar hand to be more contracted than perceptual maps of tactile stimuli. However, since the regression fits for individual subjects show large differences, performing the same experiment in a new population is likely to yield different group level results.

The moderate agreement we found between tactile and nociceptive perceptual maps is consistent with a common body representation underlying perception of these modalities, which supports the conclusions by Mancini et al. (2011). However, this agreement was less than the agreement within each modality as calculated by splitting the data of each subject in two over time. Also, there were significant differences between modalities in most subjects. This indicates that common body representations and the physical location of the stimuli together do not fully account for the differences in perceptual maps between modalities. Another factor is responsible for these differences, possibly a difference in primary representations in the somatosensory cortex. Thus our findings are consistent with a projection of information from slightly different primary representations to common body representations. Differences in perception between touch and nociception are unlikely to be noticeable in daily life. Multisensory integration processes have been demonstrated to be able to integrate spatially disparate information from different modalities into a single percept (Alais and Burr, 2004; Block and Bastian, 2009). In any real life situation, information from various cutaneous senses generally arises in conjunction, therefore a difference in spatial perception between touch and nociception due to a difference in primary representations would not be noticeable due to these integration processes. Making a difference in spatial perception between touch and nociception observable requires eliminating or minimizing the integration of nociceptive information with tactile cues, for which we used electrocutaneous stimulation.

Although we found significant differences in tactile and nociceptive localization, other stimulus parameters than modality could have contributed to these. Very little information is available about the effect of stimulus intensity (both physical and perceived) and stimulus duration on localization. Hamburger (1980) reported an increase in localization accuracy with increasing force of mechanical stimulation, but it is unknown whether this difference is due to a reduction in the stochastic component of localizations or to effects on the perceptual map. Since touch and nociception are different modalities, perceived strength of these cannot be directly compared. Concerning physical stimulus strength, we already demonstrated in the previous publication that varying the physical strength of electric stimuli using pulse train modulation has a different effect on perceived intensity for preferential stimulation of touch and nociception (Steenbergen et al., 2012a). Therefore a possible effect of stimulus intensity on localization is likely to differ between these modalities.

In conclusion, we found perceptual maps of electrically elicited nociceptive and tactile stimuli to differ. We suggest that differences in primary representations between the modalities may be responsible for these differences. We also found moderate agreement between perceptual maps of both modalities, which is consistent with the involvement of common underlying internal body representations. Further research will have to point out whether the differences we found are indeed due purely to a difference in stimulus modality, or whether another stimulus parameter contributed to this.

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Postural correlates with painful situations

Thierry Lelard[1,2], Benoît Montalan[1,2,3], Maria F. Morel[1,2], Pierre Krystkowiak[1,2,4], Said Ahmaidi[2,5], Olivier Godefroy[1,2,4] and Harold Mouras[1,2]*

[1] EA 4559, Laboratoire de Neurosciences Fonctionnelles et Pathologies, UFR de Médecine, Université de Picardie Jules Verne, Amiens, France
[2] Structure Fédérative de Recherche en Santé CAP-Santé, Université de Picardie Jules Verne, Amiens and Université de Reims-Champagne-Ardennes, Reims, France
[3] Laboratoire ICONES (EA4699), Normandie Université, U.F.R. des Sciences de l'Homme et de la Société, 76821 Mont-Saint-Aignan Cedex, France
[4] Service de Neurologie, CHU Amiens, Amiens, France
[5] EA 3300, Adaptations Physiologiques à l'Exercice et Réadaptation a l'Effort, UFR des Sciences du Sport, Université de Picardie Jules Verne, Amiens, France

Edited by:
Camila V. Moguillansky, University Pierre et Marie Curie, France

Reviewed by:
Stefano Sandrone, Vita-Salute San Raffaele University and Institute for Advanced Study IUSS–Pavia, Italy
Adam Safron, Northwestern University, USA

****Correspondence:***
Harold Mouras, EA 4559, Laboratoire de Neurosciences Fonctionnelles et Pathologies, Site d'Amiens, UFR de Médecine, Université de Picardie Jules Verne, 3 Rue des Louvels, 80000 Amiens, France.
e-mail: harold.mouras@u-picardie.fr

Background: Emotional context may play a crucial role in movement production. According to simulation theories, emotional states affect motor systems. The aim of this study was to compare postural responses assessed by posturography and electromyography when subjects were instructed to imagine themselves in a painful or a non-painful situation.

Methods: Twenty-nine subjects (22.3 ± 3.7 years) participated in this study. While standing quietly on a posturographic platform, they were instructed to imagine themselves in a painful or non-painful situation. Displacement of the center of pressure (COP), leg muscle electromyographic activity, heart rate, and electrodermal activity were assessed in response to painful and non-painful situations.

Results: The anteroposterior path was shorter ($p < 0.05$) when subjects imagined themselves in a painful situation ($M = 148.0 \pm 33.4$ mm) compared to a non-painful situation (158.2 ± 38.7 mm). Higher tibialis anterior (TA) activity (RMS-TA $= 3.38 \pm 1.95\%$ *vs.* $3.24 \pm 1.85\%$; $p < 0.001$) and higher variability of soleus (SO) activity (variation coefficient of RMS-SO $= 13.5 \pm 16.2\%$ *vs.* $M = 9.0 \pm 7.2\%$; $p < 0.05$) were also observed in painful compared to non-painful situations. No significant changes were observed for other physiological data.

Conclusion: This study demonstrates that simulation of painful situations induces changes in postural control and leg muscle activation compared to non-painful situations, as increased stiffness was demonstrated in response to aversive pictures in accordance with previous results.

Keywords: empathy for pain, posturography, embodiment, socioaffective neuroscience, affiliation

INTRODUCTION

The interrelation between the motor and affective components of behavior has been studied for a long time. For example, one of the first attempts to study the human mind was conducted by Plato using one of his philosophical models, the tripartite structure of the soul, which had a profound influence on psychology research. As noted by Popper (1968), "Plato's structure of the soul is characterized by an unstable equilibrium—indeed a schism—between its upper functions, the instincts or appetites." As part of this history, Charles Darwin also made a major contribution by arguing that an emotion induces adaptation of behavioral responses according to the environmental context that triggered this emotion (Darwin, 1872). Thus, the automatic responses triggered by emotional stimuli play a central role for survival of the species and reproduction (Campbell et al., 1997) and can be viewed as instinctual responses (Panksepp and Biven, 2012).

Some studies suggest that emotions influence motor processes (Michalak et al., 2009; Schmidt et al., 2009; Naugle et al., 2011; Coombes et al., 2012). Several authors have tried to explain behavior by means of a biphasic model in which emotional stimuli should be considered as appetitive or defensive (Lang et al., 2008) and might result in approach-withdrawal responses. The corresponding hypothesis is that emotion shapes behavior so that pleasant events should trigger approach whereas unpleasant events should trigger withdrawal.

This interrelation between behavior and emotion is also supported by neuroanatomical data regarding the interface between limbic and motor neural circuits. For example, the basal ganglia are involved in involuntary movements (such as gait and posture), but also in the physiological expression of emotions (Kandel et al., 2000).

Posturography determines displacement of the center of pressure (COP) and is appropriate to demonstrate postural changes and quantify body movements accompanying approach-withdrawal behaviors (Gurfinkel, 1973; Winter et al., 1990). In recent studies, this method was used to record motor responses-induced by emotional stimuli while subjects remained in bipedal and/or unipedal stance. Presentation of emotional pictures [International Affective Picture System (IAPS); Lang et al., 2008] has been shown to induce an approach-withdrawal behavior

(Hillman et al., 2004) or freezing responses (Hillman et al., 2004; Azevedo et al., 2005; Facchinetti et al., 2006; Stins and Beek, 2007). These postural responses were recorded in response to negative stimuli such as disgusting aversive pictures depicting mutilation and can be defined as "instinctual responses."

Pain includes a subjective experience triggered by activation of a mental/neural representation of actual or potential tissue damage supporting the affective component of pain and inducing aversion that motivates termination or reduction of behavior, or induces escape behavior to avoid exposure to the noxious stimulation (Price, 2000).

Simulation of another subject's behavior or imagination of a visual situation experienced by ourselves involve simulation processes and activation of internal models (Zahavi, 2008). The ability to simulate a situation explains the mechanism by which we can understand another person's actions and the induction of the bodily expression of emotion. Simulation of one's own behavior is based on the ability of an individual to simulate actions, to simulate perception and to anticipate (Hesslow, 2002, 2012). During simulation processes, the subject may replay her own past experience in order to extract from it pleasurable, motivational, or strictly informational properties (Dokic and Proust, 2002). According to the embodiment theories, experiencing emotional states affects motor systems (Giummarra et al., 2008; Michalak et al., 2009; Kiefer and Pulvermuller, 2012). Simulation of a situation is supported by the discovery of mirror neurons (Gallese et al., 1996; Rizzolatti et al., 1996; Thioux and Keysers, 2010), responding both during action production and observation of the same action performed by another person. Hutchison et al. (1999) have shown that there are pain-related neurons in the anterior cingulate cortex (ACC) that respond both to thermal stimulation and also to the observation of the same thermal stimulation delivered to another individual (Hutchison et al., 1999).

An individual who is imagining a situation involve representational characters rather than instinctual characters (Giummarra et al., 2008; Michalak et al., 2009; Kiefer and Pulvermuller, 2012). For instinctual characters, emotional propensities arise out of subcortical structures and activate quite automatic-visceral and bodily outputs. On the other hand, for representational characters, emotional propensities arise out of cortical structures. For example, similar fronto-parietal network is activated in pianist participants when they played music and when they imagined playing the same music (Meister et al., 2004).

According to the perception-action model (Preston and De Waal, 2002), empathy activates somatic and autonomic responses. Simulation of a painful situation may therefore be an efficient functional context involving emotional information processing associated with the promotion of protective or recovery visceromotor and behavioral responses. The ability to experience the emotion observed in others implies a physiological synchrony between the observer and the observed individual (Levenson and Ruef, 1992). The automatic coupling mechanism between perception and action would be used to predict and understand the other person's behavior (Rizzolatti et al., 2001). This ability to simulate another person's emotional response in a particular situation could be the basis for the development of empathic skills (Meltzoff and Decety, 2003). The instruction to adopt another person's perspective modulates pain rating according to the affective link between the observer and the individual experiencing the outcome (Singer et al., 2006; Penner et al., 2008). To address the question of whether motor response is modulated by perspective taking, it must be determined whether differential motor responses are observed when viewing pictures depicting painful situations compared to non-painful situations.

The aim of this study was therefore to record differential postural responses as measured by posturography and electromyography when subjects were instructed to imagine themselves in a painful or non-painful situation within the functional context of empathy for pain.

Visual pain stimuli and instructions to embody the displayed situation were hypothesized to induce postural adaptation variations that could be quantified by changes in the trajectory of the body's COP. Considering the inverted pendulum model, in quiet standing, an ankle strategy applies in the antero-posterior direction (Winter et al., 1990). Leg muscles activation (tibialis anterior and soleus) reflect forward or backward leaning of the whole body. Carpenter et al. (2001) also reported changes in TA or SOL activation during a postural threat condition that was attributed to a freezing response (Carpenter et al., 2001).

MATERIALS AND METHODS

PARTICIPANTS

Thirty participants (13 males; mean age and SD $= 22.3 \pm 3.7$) were included with (1) no history of visual or motor impairment, (2) no prior or current treatment for psychiatric or neurological disorders. All participants signed an informed consent form. The experimental procedures were in accordance with the ethical standards of the Helsinki declaration and were approved by the local ethics committee (CPP Nord Ouest 2).

STIMULUS MATERIALS

Ten pictures depicting painful or non-painful situations involving the hands or feet were selected from a larger database validated in previous studies (e.g., Jackson et al., 2005). Participants were instructed to imagine that they had experienced the situations that they were about to see. Stimuli presentation was controlled by a computer running E-Prime software (Psychology Software Tools, Inc., Pittsburgh, PA, USA).

POSTUROGRAPHY AND PHYSIOLOGICAL DATA ASSESSMENTS

Posturography and physiological data were recorded using a Biopac MP150 system (Biopac Inc., Santa Barbara, CA). Movements of the COP were recorded during the rest stance by a posturographic platform (Satel, Blagnac, France). Analogue data from three strain gauges were recorded and movements of the COP in the anteroposterior (AP) and mediolateral (ML) directions were computed by AcqKnowlege software (Biopac Inc., Santa Barbara, CA).

Electromyography (EMG), electrocardiography (ECG), and electrodermal activity (EDA) were recorded at a rate of 1000 Hz by a MP-150 Biopac System. Heart rate (HR) was recorded with a standard Lead-II electrocardiogram using three disposable electrodes (EL503). EDA was recorded with two Ag/AgCl electrodes (GSR100C, Biopac Inc., Santa Barbara, CA) filled with an isotonic paste attached to the volar surface of the index and middle fingers of the subject's hand. A constant-voltage device was used to pass 0.5 V between electrodes. EMG activity of leg muscles was recorded with disposable electrodes (EL503). The electrodes were fixed (2 cm apart center to center) over the tibialis anterior (TA) and soleus (S) muscle bellies.

Respiratory activity was recorded via a transducer (TSD201) recording chest circumference variations.

PROCEDURE

Firstly, participants stood barefoot in the middle of the force plate. They were asked to maintain a comfortable bipedal stance with their arms hanging relaxed alongside their body and their feet pointing 30° outward. Visual stimuli were then presented 2 m in front of the participants using a video projector. Participants were instructed to watch the images presented without any additional movement and to imagine the pain that they would experience in the situations displayed. Pictures of painful and non-painful situations were presented in random order. For each picture, a trigger corresponding to each type of emotional stimulus was sent to the Biopac MP150. During a first recording session, 5 images were presented for 12 s. In order to avoid tiredness, participants were asked to stretch their legs or sit according to their preference. During a second session, 5 images were presented for the same duration. For each trial, stimulus presentation was preceded by a fixation cross for 0.5 s. The stimulus was then presented for 12 s with an inter-stimulus interval of 2 s.

Secondly, participants performed a pain judgment task of the painful and non-painful pictures (Jackson et al., 2005). At the beginning of the acquisition sequence, the participants were instructed to imagine the pain they would experience in the situations displayed. The trial sequence started with a fixation cross for 0.5 s. The stimulus was then presented until the participant's response. After responses, an inter-stimulus interval of 1 s was added. Immediately after onset of the stimulus, subjects were instructed to indicate their ratings by using their right hand to press 1 of 9 computer keys (with scores ranging from 0 = no pain to 9 = very severe pain).

DATA ANALYSIS

The mean postural response to both painful and non-painful situations was calculated for each experimental condition. The following indices were calculated for each trial: (1) the mean COP position in the anteroposterior direction (COP-AP), reflecting the extent to which a participant leaned toward the anterior or posterior direction during a 12-s trial; (2) the length of the sway path of the COP in the anteroposterior direction (Length [COP]-AP), reflecting the degree of body sway in the AP direction; (3) the area encompassed by displacements of the COP (COP-Area), corresponding to the surface of the confidence ellipse containing 90% of the sampled COP positions.

The level of muscle activation was quantified by calculating the root mean square (RMS) of raw data over 0.5 s with a sliding window. RMS-TA and RMS-SO indicated the level of activation of TA and SO muscles, respectively. Var-TA and Var-SO indicated the variation of TA and SO muscles (SD/mean), respectively. Heart rate (HR) was calculated from ECG data by AcqKnowledge software.

STATISTICAL ANALYSIS

Postural, physiological and pain rating data were submitted to a paired samples *t*-test to compare the response during painful and non-painful situations. Pearson's correlation coefficients between the subjects' rating in the pain judgment task, the posturographic parameters and the physiological responses were also calculated. A $p < 0.05$ value was considered statistically significant.

RESULTS

PAIN JUDGEMENT TASK

The *t*-test revealed a significant difference in mean pain ratings for painful stimuli ($M = 6.80 \pm 1.64$) compared to non-painful stimuli ($M = 0.33 \pm 0.60$) (**Figure 1A**).

POSTURAL RESPONSES TO VISUAL STIMULI

COP displacement during the 12-s presentation were demonstrated in response to painful as compared to non-painful stimuli (**Figure 1B**). The *t*-test revealed a significant effect for stimuli on AP path ($t = -2.34$; $p < 0.05$). AP path was shorter during presentation of painful visual stimuli ($M = 152.0 \pm 41.7$ mm) compared to non-painful visual stimuli (160.7 ± 43.2 mm).

PHYSIOLOGICAL RESPONSES TO VISUAL STIMULATION

Physiological responses were recorded during the 12-s presentation of painful or non-painful stimuli (**Figures 1C,D**; **Table 1**). The *t*-test revealed a higher RMS-TA ($t = 2.20$, $p < 0.05$) when subjects imagined themselves in a painful situation ($M = 3.38 \pm 1.95\%$ AU) compared to a non-painful situation ($M = 3.24 \pm 1.85\%$). No significant differences for var-TA were observed between painful ($M = 9.53 \pm 10.05\%$) and non-painful situations ($M = 9.64 \pm 12.43\%$). RMS-SO was also not significantly different between painful ($M = 8.31 \pm 6.92\%$) and non-painful situations ($M = 7.72 \pm 7.63\%$). *T*-test revealed a higher var-SO value during painful stimuli ($M = 12.83 \pm 14.96\%$) compared to non-painful stimuli ($M = 9.36 \pm 7.24\%$, $t = 2.62$, $p < 0.05$).

No significant differences for heart rate and electrodermal activity were observed between painful and non-painful stimuli (**Table 1**).

Correlations between postural, physiological data, and pain judgment were computed (**Table 2**). Pain rating was correlated with Length [COP]-AP ($r = -0.22$). Physiologic data were also correlated with posturographic parameters, heart rate was correlated with COP-Area ($r = 0.22$) and Length [COP]-AP ($r = 0.38$).

DISCUSSION

This study investigated postural changes and physiological correlates-induced by pictures depicting painful and non-painful situations of daily living. We hypothesized that simulation of

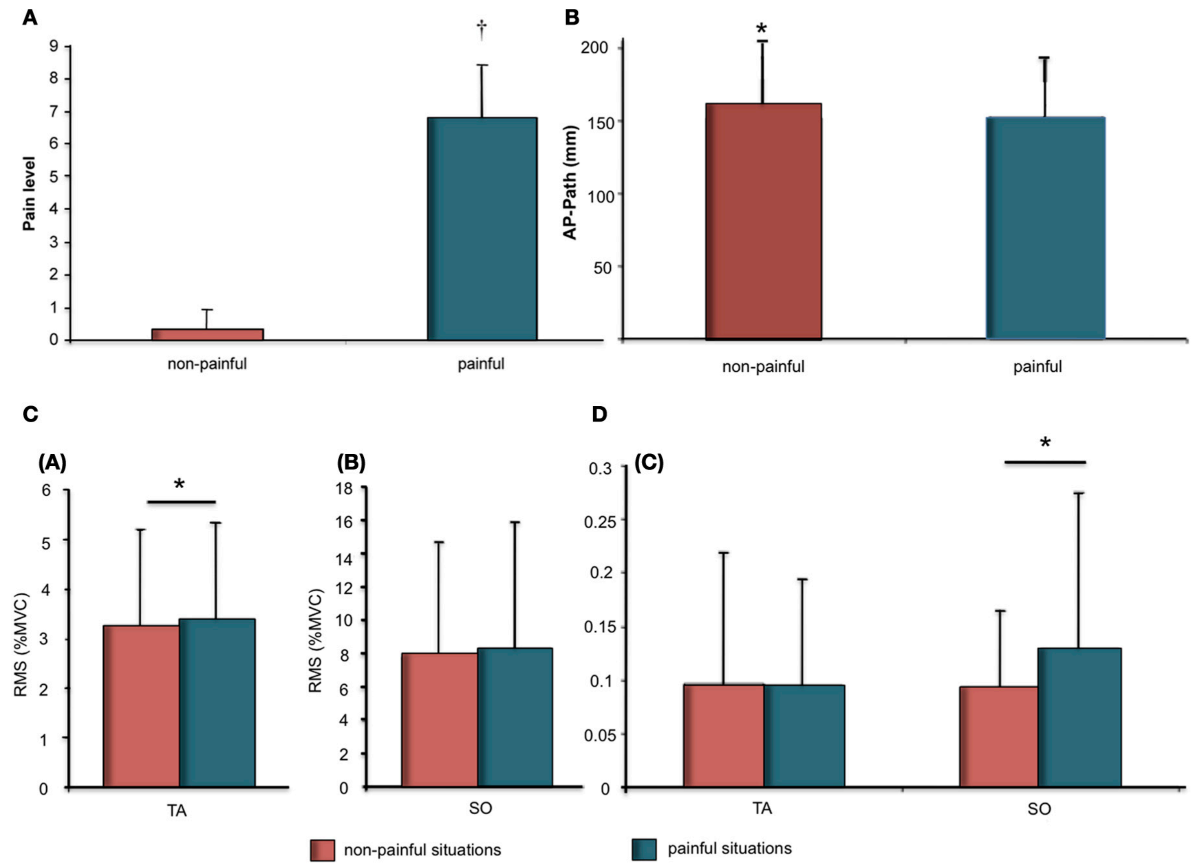

FIGURE 1 | (A) Pain ratings (Mean and SD) as a function of stimuli (Painful vs. Non-painful). Significant differences are indicated as: $^{\dagger}p < 0.001$; **(B)** Means and SDs of the anteroposterior length as a function of stimuli (painful vs. non-painful); **(C)** Means and SDs of electromyographic data for Soleus (SO) and Tibialis Anterior (TA) muscles. **(a)** RMS as % of MVC for TA as a function of stimuli (painful vs. non-painful). **(b)** RMS as % of MVC for SO as a function of stimuli (painful vs. non-painful); **(D) (c)** Variability of RMS as a function of stimuli (painful vs. non-painful). Significant differences are indicated as: $^{*}p < 0.05$.

Table 1 | COP displacement and physiological changes as a function of stimuli (painful vs. non-painful).

	Painful situation mean and (SD)	Non-painful situation mean and (SD)
COP-AP (mm)	0.69 (2.40)	0.01 (1.57)
COP-Area (mm²)	172.30 (242.98)	153.97 (170.00)
Length [COP]-AP (mm)	151.99 (42.42)	160.75 (43.97)*
RMS-TA (%)	3.38 (1.95)	3.24 (1.85)
Var-TA (%)	9.53 (10.05)	9.64 (12.43)
RMS-SO (%)	8.31 (6.92)	7.72 (7.63)
Var-SO (%)	12.83 (14.96)	9.36 (7.24)*
HR (bpm)	94.55 (14.93)	94.11 (14.60)
EDA (AU)	150.93 (90.42)	150.08 (90.62)

Significant differences are indicated as: $^{*}p < 0.05$.

Table 2 | Correlation between postural data, physiological data, and pain rating.

	HR	EDA	Pain rating
COP-AP	0.053	−0.084	0.001
COP-Area	0.218*	−0.136	−0.076
Length [COP]-AP	0.388**	−0.167	−0.220*
HR		0.063	0.058
EDA			−0.019

Significant differences are indicated as: $^{*}p < 0.05$; $^{**}p < 0.01$.

painful situations would induce a motor response characterized by changes in COP trajectory. This study confirmed that a 12 s presentation of emotionally charged stimuli-induced postural and physiological responses.

Presentation of emotional pictures has already been shown to affect equilibrium. However, to our knowledge, with the present study this is the first time that the experimental set up favors more representational and cognitively loaded emotions than instinctual responses to study whole body movement. Indeed, postural responses were obtained while subjects were instructed to imagine themselves in the painful and non-painful situations. The link between pain rating and body placement was found for the Length [COP]-AP. Firstly, postural changes were observed in the AP direction in response to the painful situation, confirming previous data recorded when subjects viewed pictures of mutilations (Azevedo et al., 2005; Facchinetti et al., 2006; Stins and Beek, 2007). Indeed, COP displacements were reduced during presentation of painful stimuli. We also described a negative correlation between length of COP-AP and pain rating, confirming the appearance of stiffening response to pain visual simulation. For visual stimuli rated the most painful, simulation induces a decrease of length of COP-AP. This point brings some evidence for a representational interpretation of the present study. Indeed, postural responses seem to be dependent of the perceived pain during simulation. Our results therefore confirmed that 12 s presentation of painful situations (Jackson et al., 2005) combined with instructions to imagine oneself in the situation displayed-induced postural modulations in the participants. According to previous studies, the reduction of COP excursion-induced by negative stimuli was explained by adoption of a freezing strategy (Hillman et al., 2004; Azevedo et al., 2005; Facchinetti et al., 2006; Stins and Beek, 2007). Many of these studies used aversive pictures from IAPS with high arousal, causing a feeling of disgust. The AP trajectory of the COP describes persistent adaptation of posture in response to a 12-s presentation of a painful situation, whereas backward motion of the COP might be identified with a shorter latency.

Secondly, the postural adjustments observed during the 12-s presentation of pain stimuli were also accompanied by physiological changes. We also described some links between length of COP-AP, COP-Area, and HR during picture presentation. Decrease in HR was associated with decrease in COP-Area and length of COP-AP. Changes in postural muscle activity in response to emotional stimuli were also described. The increase of RMS-TA, characterizing TA muscle tone, reflects adoption of a stiffening strategy. General stiffness has been reported in response to anxiety (Fridlund et al., 1986). A similar increase in RMS-TA has been previously associated with increased anxiety caused by a postural threat (Carpenter et al., 2001). Participants also exhibited an increased Var-SO in response to painful situation. Var-SO represents the coefficient of variation of muscle activity and may be related to increased postural adjustments or a motor response to the stimuli. To our knowledge, this is the first study to record postural responses simultaneously with changes in postural muscle activity. Up until now, EMG data recorded during presentation of emotional faces have been used to describe changes in facial muscle activity and mimicry (Sonnby-Borgstrom, 2002; Balconi et al., 2011). Several studies have demonstrated that EDA increases with the arousal-induced by visual stimuli (Lang et al., 1993; Horslen and Carpenter, 2011) and changes in heart rate have been previously described with freezing responses (Azevedo et al., 2005; Facchinetti et al., 2006; Stins and Beek, 2007). Our results are not consistent with these previous studies showing changes in physiological responses to aversive stimuli, probably because the painful pictures used in this study (Jackson et al., 2005) may have had a lower arousal level than the mutilation pictures used in previous studies. This difference should also be explain by the representational character of the present task whereas previous studies describe instinctual response to visual stimuli. However, changes in postural activity and muscle activation demonstrate the effect of simulation of painful situations. This response could also be explained by the involvement of a cognitive process in mental simulation. Mental simulation represents the cognitive process by which we can mentally represent perceptual information in the absence of appropriate sensory input (Munzert et al., 2009). This mental simulation is based on internal simulation of actions (Jeannerod, 2001; Grush, 2004). In order to simulate these scenes, the subject must be able to understand whether or not the scene describes a painful or non-painful situation. Moreover, evaluation of the valence of a stimulus occurs immediately and without attention leading to an automatic response (Bargh et al., 1996; Eerland et al., 2012). Moreover, a previous study reported that pictures representing attacks and pictures of human mutilation prompted the greatest evidence of defensive activation (Bradley et al., 2001). The contents of aversive stimuli are the most threatening from a survival perspective and responses to aversive stimuli are reflex responses that have evolved to facilitate survival of individuals and species (Rolls, 2000; Bradley et al., 2001; Lang and Bradley, 2010).

Further investigation should be conducted to identify the differences between responses to aversive stimuli (viewing aversive visual stimuli) and simulation of a painful situation. The present study demonstrate correlation between some variables (posturographic parameters, physiological parameters and pain rating). However, to confirm the correlation between pain rating and the other parameters, further works should use several categories of the perceived intensity of pain (not limited to low or high as in the present study).

CONCLUSION

This study highlights the relationship between simulation of painful situations and postural modulation and physiological responses (leg muscle activation). Changes in postural muscle activity and COP displacement during simulation of a painful situation were also consistent with adoption of a freezing strategy during the 12-s presentation of the stimuli.

Modulation of postural responses during painful simulation lays the basis for further studies concerning the role of perspective-taking in motivational dimension of motor control and social interaction. The present results using representational stimuli (imagining themselves experiencing pain) show similar results with previous study using instinctual stimuli (viewing negative stimuli). However, several studies are carried out to understand the mechanisms underlying motor responses during complex representational processes such as empathy. The effects of embodiment of painful situation should also be studied in further work by comparison of both conditions (viewing vs. imagining painful situation).

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Keep away from danger: dangerous objects in dynamic and static situations

Filomena Anelli[1,2]*, Roberto Nicoletti[1], Roberto Bolzani[3] and Anna M. Borghi[3,4]*

[1] Department of Philosophy and Communication, University of Bologna, Bologna, Italy
[2] Department of Education Sciences, University of Bologna, Bologna, Italy
[3] Department of Psychology, University of Bologna, Bologna, Italy
[4] Institute of Cognitive Sciences and Technologies, National Research Council, Roma, Italy

Edited by:
Diana M. E. Torta, University of Turin, Italy

Reviewed by:
Michael Schaefer, University Magdeburg, Germany
Susanne Becker, Central Institute of Mental Health, Germany

***Correspondence:**
Filomena Anelli, Department of Philosophy and Communication, University of Bologna, Via A. Gardino 23, 40122 Bologna, Italy
e-mail: filomena.anelli@unibo.it;
Anna M. Borghi, Department of Psychology, University of Bologna, Viale Berti Pichat 5, 40100 Bologna, Italy
e-mail: anna.borghi@gmail.com

Behavioral and neuroscience studies have shown that objects observation evokes specific affordances (i.e., action possibilities) and motor responses. Recent findings provide evidence that even dangerous objects can modulate the motor system evoking aversive affordances. This sounds intriguing since so far the majority of behavioral, brain imaging, and transcranial magnetic stimulation studies with painful and dangerous stimuli strictly concerned the domain of pain, with the exception of evidence suggesting sensitivity to objects' affordances when neutral objects are located in participants' peripersonal space. This study investigates whether the observation of a neutral or dangerous object in a static or dynamic situation differently influences motor responses, and the time-course of the dangerous objects' processing. In three experiments we manipulated: object dangerousness (neutral vs. dangerous); object category (artifact vs. natural); manual response typology (press vs. release a key); object presentation (Experiment 1: dynamic, Experiments 2 and 3: static); object movement direction (Experiment 1: away vs. toward the participant) or size (Experiments 2 and 3: big vs. normal vs. small). The task required participants to decide whether the object was an artifact or a natural object, by pressing or releasing one key. Results showed a facilitation for neutral over dangerous objects in the static situation, probably due to an affordance effect. Instead, in the dynamic condition responses were modulated by the object movement direction, with a dynamic affordance effect elicited by neutral objects and an escape-avoidance effect provoked by dangerous objects (neutral objects were processed faster when they moved toward-approached the participant, whereas dangerous objects were processed faster when they moved away from the participant). Moreover, static stimuli influenced the manual response typology. These data indicate the emergence of dynamic affordance and escaping-avoidance effects.

Keywords: dangerous objects, affordances, space, dynamic and static presentation, motor system, conceptual development, dynamic affordance effect, escaping/avoidance effect

INTRODUCTION

In our lives we constantly interact with different kinds of objects, characterized by different features, and we need to learn their properties. For example, so far literature investigated the importance of size (e.g., Tucker and Ellis, 2001), shape (e.g., Smith, 2005; Panis et al., 2008a,b), weight (e.g., Brouwer et al., 2006; Scorolli et al., 2009), and consistence (Anelli et al., 2010) for categorization. Among different properties of the objects, dangerousness can be considered of particular relevance for our survival. This implies that the study of the ability to discriminate between objects we can interact with and we can eventually use without any problem, and objects that can provoke pain represents an interesting and growing research field. We will call the first neutral objects, the second dangerous objects. Notice that, in keeping with the studies on dangerous objects we will briefly review, we will use a rather broad definition of object dangerousness. We define as dangerous those objects and entities that can provoke harm, independently of whether this harm is intentionally or accidentally provoked. Hence, we consider dangerous both a scorpio who approaches us and a cactus which can potentially hurt us when we approach it.

Since Gibson (1979) proposed a theory of affordances, defining them as properties in the environment that are relevant for an organism's goals, the notion that objects are represented in terms of potential actions (i.e., affordances) has gained growing interest. To clarify with an example, a cup provides affordances, i.e., it "invites" us to act, for example to reach and grasp its handle. More recent theorization on affordances conceived them as "brain assemblies" that represent objects, that is as the result in the brain of the connection between visual and motor responses that have developed during the adaptation to the physical and social environment (Ellis and Tucker, 2000). Over the past decade, a growing number of cognitive and neuroimaging studies has focused on affordances, and computational models have been proposed (for a recent review, see Thill et al., 2013). Data from neurophysiological and neuroimaging studies, both on monkeys and humans, revealed that specific parieto-frontal circuits are responsible for the encoding of the observed features in terms of action potentialities. In monkeys, the so-called "canonical neurons," that probably constitute the neural basis of affordances, were activated even when the monkey simply observed a graspable object and thus no overt response was required (e.g., Jeannerod et al., 1995; Murata et al., 1997; Raos et al., 2006; Umiltà et al., 2007).

As for humans, similar results have been obtained with brain activation studies (for a review, see Martin, 2007). For example, in a seminal PET study, Grafton et al. (1997) registered the automatic activation of the action observation network (i.e., the dorsal premotor cortex and the anterior intraparietal sulcus) during the mere observation of manipulable objects such as tools, even in the absence of overt motor response. Further fMRI studies demonstrated the activation of a fronto-parietal circuit (i.e., the left premotor cortex and the inferior parietal lobule) when graspable objects were observed (Chao and Martin, 2000) and during the execution of a specific hand grip posture, on the basis of the specific hand grip posture afforded by the object features (Grèzes et al., 2003).

In addition to these findings, several cognitive behavioral studies have demonstrated that overt reaching and grasping movements can be activated during objects observation (for reviews, see Borghi and Cimatti, 2010; Borghi et al., 2012).

One line of research particularly relevant to the issue addressed in our study concerns the relation between affordances and space. In a series of studies, Costantini and colleagues tried to clarify whether affordances differently emerged when objects, as for example bottles, were located within or outside the perceiver's peripersonal space, namely in the space that encompassed the objects within reach (Rizzolatti et al., 1997). In a first behavioral experiment, Costantini et al. (2010) employed a spatial alignment effect paradigm, requiring participants to replicate a grasping movement as soon as a go-signal became visible (i.e., a mug's handle, placed either within or outside the participants' reaching space). The study revealed that participants responded to affordances only when the object was in the observer's peripersonal space, and thus in her reachable space, and not when it was located in her extrapersonal space (see also Costantini et al., 2011a, for a replication of the same effects in a task in which not only images of objects but verbs were used as well; see Coello and Bonnotte, 2013, for an investigation of the link between the spatial content of determiners and the spatial representation of action possibilities). In a subsequent behavioral study, Costantini et al. (2011b) used the previous paradigm but introduced in half of the trials the presence of an avatar. They expanded previous results demonstrating the presence of an affordance effect even when the object was outside the observer's reachable space, provided that it was located within another individual's reaching space. For example, when a mug was located in the participant's far space but it was close to the avatar, the affordance effect was present. These findings were also supported by transcranial magnetic stimulation (TMS) studies (Cardellicchio et al., 2011, 2012).

Another line of research deserves to be introduced, namely studies aimed at investigating responses induced by the observation of others' pain. In a seminal study, Singer et al. (2004b) measured empathic brain activations *in vivo* with fMRI, by registering brain activity in the female partner of couples of participants. Painful stimulation was applied either to her own hand, thus measuring pain-related brain activation of the felt pain, or to her partner's hand, thus measuring pain-related brain activation of the empathy for pain. The results revealed the activation of bilateral anterior insula and anterior cingulate cortex, i.e., of parts of a complex neural network (the so-called "pain matrix"): the pain matrix was activated both when subjects experienced pain themselves and when they saw a signal indicating that the partner had experienced pain. Activation in this network was also registered when subjects watched videos showing body parts in potentially painful situations (Jackson et al., 2006), painful facial expressions (Lamm et al., 2007), or hands being pricked by needles (Morrison et al., 2004, 2007a). Further studies suggested that the magnitude of these empathic brain responses can be modulated by different factors, such as the perceived fairness of the other (Singer et al., 2004a, 2006) and the intensity of the inflicted pain (Avenanti et al., 2006; for a review, see de Vignemont and Singer, 2006).

In addition, in a series of TMS studies Avenanti et al. (2005, 2006) explored passive responses during pain observation. By measuring motor-evoked potentials (MEPs), results demonstrated a specific corticospinal inhibition when observers watched someone else suffer a painful stimulation (i.e., watching a needle inserted deep into a model hand). Indeed, the significant MEPs amplitude decrease was specific for the observed body part (i.e., for the hand and not for the foot) and for the involved muscle, while it was not present when the needle was inserted into a tomato (not body part) or when the hand was given to a tactile stimulation (innocuous cotton bud). Thus, pain observation led to a specific corticospinal inhibition, similar to directly experienced painful stimulation (e.g., Le Pera et al., 2001; Farina et al., 2003). This finding suggested an activation of pain representations in the observer's sensorimotor system due to motor resonance. This pointed out an important role of motor areas in the pain matrix, both during the first-person experience of pain and during empathy for others' pain.

Not only neural, but also behavioral evidence demonstrated a specific influence of pain observation on overt motor responses. A study of Morrison et al. (2007b) showed that observing a video of a painful stimulation (i.e., a needle penetrating a hand) speeded withdrawal movements (key-releases) and slowed approach movements (key-presses); this difference was not present when participants observed a neutral stimulation (i.e., a cotton bud touching a hand) or when both the painful and neutral stimulation concerned a non-biological (i.e., a sponge) rather than a biological stimulus (i.e., a hand).

On the whole, these findings reveal the emergence of resonance mechanisms when pain was passively induced by an object and participants could observe the direct interaction between a hand and a needle (see Haggard et al., 2013, for a review on the link between brain mechanisms of pain and its perceptual quality with the spatial structure of the body).

Thus, so far several works demonstrated that participants tend to respond to objects' affordances, and a variety of behavioral, brain imaging, and TMS studies with painful and dangerous stimuli were carried out in the domain of pain investigation. These two lines of research were merged in some recent behavioral studies on affordances and dangerous objects. Interestingly, recent evidence revealed that not only pleasant and neutral objects but also dangerous objects activate motor information during our interaction with them. In previous investigations (Anelli et al., 2012a,b), we studied resonance mechanisms activated during the observation of somebody in potential interaction with a dangerous object. We used a priming paradigm with both school-age children and adults, so that participants observed a hand or a control object followed by a neutral or dangerous object. Results revealed that, irrespective of age, motor responses were slower with neutral objects than with dangerous ones, indicating the emergence of a facilitation effect (affordance effect) with neutral objects and of an interference effect with dangerous objects, probably due to aversive affordances. In addition, in both children and adults, motor resonance mechanisms were activated during the observation of biological hands with respect to non-biological ones. To note, the higher the motor resonance induced by biological hands, the stronger the inhibition registered with dangerous objects. To sum up, these studies can be considered as a proof of the influence of objects dangerousness on the motor responses, when objects were preceded by a hand suggesting a potential interaction with them.

Along this line of research, in a subsequent study (Anelli et al., 2013) we adopted a cued bisection paradigm, in which the line to bisect was flanked by images of objects belonging to different categories (dangerous vs. neutral objects). This allowed us to investigate the influence of objects dangerousness on motor responses with a novel paradigm. We measured in both children and adults whether the performance was biased toward a specific object category, independently from the observation of others' actions, as happened in our previous studies (Anelli et al., 2012a,b). Results not only demonstrated that participants were sensitive to objects dangerousness, but also that this sensitivity was maintained across lifespan, since both in children and adults the line midpoint was shifted toward the neutral object or, in other words, on the side opposite to the dangerous object. This suggested the existence of two specific effects, namely an affordance effect occurring with neutral objects and an interference/inhibitory effect taking place with dangerous objects. This last effect seems to induce the tendency to "escape" from the dangerous object and to approach the neutral object, which is responsible of the motor response's bias.

To sum up, recent evidence suggests that even dangerous objects can modulate the motor system evoking aversive affordances, i.e., inducing the tendency to avoid dangerous objects. The research area about aversive affordances represents a new and intriguing research field, since so far the majority of studies with painful and dangerous stimuli strictly concerned the domain of pain investigation.

In the present work we focus on some unanswered questions on aversive affordances, by investigating object dangerousness without considering motor resonance mechanisms, and by exploring whether and how the observation of a neutral or dangerous object, in a static or dynamic situation, can differently modulate our motor responses.

First of all, previous studies investigated how motor responses were influenced by object dangerousness, but limited their focus to situations in which objects were preceded by hands in potential interaction with them, thus generating a motor resonance effect (e.g., Anelli et al., 2012a,b). Instead, in the present work we focused on neutral and dangerous objects processing when no agent was shown, investigating the perception of objects dangerousness independently from the observation of others' actions and thus from the emergence of motor resonance effects.

Second, in the literature static images are usually presented. Since objects/entities are typically threatening when they approach us, we chose to employ a more dynamic and ecologically rich experimental setting, by showing stimuli in dynamic scenes. This more natural embedding allows us to take into account the spatial relationship between stimuli and subject, and thus to consider dangerousness no longer as an objective property, but as a relational one.

Third, so far some aforementioned studies (e.g., Costantini et al., 2010, 2011a,b) investigated the relation between object features and space by manipulating 3D objects presentation in peripersonal vs. extrapersonal space. In the current study we consider the manipulation of the object size to give a cue indicating distance: when the object's size is larger this means it is closer to the participant's body, when it is smaller it means it is further away from the participant.

Fourth, it can be posited that different response modalities subtend different motor actions, and specifically key-releases can underlie withdrawal movements and key-presses can underlie approach movements. So far Morrison et al. (2007b) considered this kind of link between response modalities and motor actions in relation to empathy for pain. Conversely, we are interested in the link between response modalities and objects dangerousness aside from pain. In addition, we intend to explore the effects of different response modalities in a dynamic space, considering whether the tendency to press or to release a key is higher when objects come toward us or when they move away from us.

Finally, even if a couple of studies (Lloyd et al., 2006; Coello et al., 2012; see General Discussion) investigated the relationship between dangerous objects and bodily space, to our knowledge there is no evidence on how information on dangerousness emerges in time. The paradigm we chose allowed us to investigate the time-course of the emergence of the aversive affordance effect, evaluating the necessary time to process dangerousness and to respond to dangerous objects. Indeed, it is possible that we immediately respond to this kind of affordance, as soon as an object appears, or alternatively that we need time to process it and to prepare our motor response, for example to prepare ourselves to escape.

To explore these issues, we conducted three experiments requiring participants to perform a simple categorization task, i.e. to decide whether the stimulus shown was an artifact or a natural object. To respond they were required to either press or release one of two designed keys, observing objects in dynamic (Experiment 1) or static (Experiments 2 and 3) conditions. As in our previous works, we focused on how dangerous and neutral objects are perceived and processed at a motor level. We were not interested in the distinction between risk for pain and threat, but in the motor responses evoked by the observation of objects or entities that can potentially provoke pain, independently of their being active or passive.

The aims of the study and our predictions are the following. First, we aim to investigate the sensitivity to objects dangerousness and the emergence of related affordances without showing somebody in *interaction* or potential interaction with the object, and thus without considering motor resonance mechanisms. We hypothesize a facilitation effect of the motor responses with neutral objects, and an interference effect slowing down responses to dangerous objects, in line with our previous results (Anelli et al., 2012a,b).

Second, we focus on the impact of neutral and dangerous objects when they come toward us (dynamic presentation) or when they are close to us (static presentation) with respect to when they go away from us (dynamic presentation) or when they are distant from us (static presentation).

Third, and related to previous point, we intend to clarify how static and dynamic objects' presentations influence the response to neutral vs. dangerous objects, and whether there is a modulation due to the response modality (key press vs. release). We hypothesize that motor responses would be facilitated, and thus response times would be faster, with dynamic than with static presentations with dangerous objects and release response, due to the fact that humans might tend to escape from dangerous objects and entities as soon as possible, particularly when they have an aggressive behavior.

Fourth, we investigate the time-course of the process, and thus whether the processing of dangerous objects allows immediate responses or whether it requires to prepare responses, also considering the object's distance. Indeed, notice that distance and time are related: when we can see dangerous entities from far away, we have time to prepare our responses; this is not the case when these entities are very close to us. We do not advance a precise prediction on this point, but our aim is to examine the time-course of dangerous objects processing.

Finally, in light of our previous studies (Anelli et al., 2012a,b), that focused on the processing of objects typology and objects category both in children and in adults, we decided to explore age-related effects.

EXPERIMENT 1

The aim of the first experiment was to investigate whether participants were sensitive to differences in the direction of object movement. In particular, we intended to verify if observing a dangerous or a neutral object in a dynamic situation (i.e., a video of an object moving away or near to the participant) can differently influence the motor responses. In addition, we considered how motor responses can be modulated by the considered variables at different ages, by testing both children and adults.

To these aims, we ran an experiment in which participants were required to distinguish between an artifact and a natural object, so that the object dangerousness and movement direction were not relevant to the task.

METHOD

Participants

Fourteen undergraduate students from the University of Bologna (six males and eight females, mean age: 20.7 years, range: 19–27) and 14 children (seven males and seven females; mean age: 11.2 years, range: 10–12), took part in the experiment. All participants were right-handed and had normal or corrected-to-normal vision. All were naive as to the purpose of the experiment and they or their parents, as for children, gave informed consent. The present and the following experiments were approved by the Psychology Department's ethical committee of the University of Bologna.

Apparatus and stimuli

Participants sat in front of a 17″ color monitor (the eye-to-screen distance was approximately 50 cm). E-Prime 2.0 software was used for presenting stimuli and collecting responses.

The experimental stimuli consisted of 16 color pictures of common graspable objects (see **Table 1**). All objects were large and would normally be grasped with a power grip. There were four categories (dangerous-natural objects, dangerous-artifact objects, neutral-natural objects, neutral-artifact objects), with four objects for each class. The set of objects stimuli was the same used in other studies (Anelli et al., 2012a,b, 2013) in which we asked an independent group of 43 participants to rate on a five-points Likert scale the dangerousness of the target objects. The ANOVA with the factors *Object Typology* (neutral and dangerous) and *Object Category* (artifact and natural) manipulated within-items revealed that there was a significant difference between neutral and dangerous objects [main effect of *Object Typology*, $F\ (1, 12) = 95.3$, $\text{MSE} = 0.24$, $p < 0.001$].

Procedure

Participants were required to decide whether the stimulus was an artifact or a natural object, so that the *Object Dangerousness* (i.e., dangerous vs. neutral) was totally irrelevant to the task. As soon as the go-signal appeared (i.e., a green circle on the middle part of the object), participants had to respond by using one of two designed keys. Since we manipulated the *Manual Response Typology*, we divided the participants into two groups: the first group had to press the response-key, whereas the second had to release the response-key. Moreover, in both groups half of the participants were required to make a right-hand response if the target was an artifact object and a left-hand response if it was a natural one, whereas the opposite hand-to-category arrangement was applied to the other half.

The experiment consisted of one practice block of 16 trials and one experimental block of 128 trials. Each trial began with a fixation point (+) displayed for 500 ms in the center of the screen. Then, the video of a moving object was shown for 1000 ms and

Table 1 | The 16 experimental stimuli.

	Neutral objects	Dangerous objects
Natural objects	Cat	Porcupine
	Chick	Scorpio
	Plant	Cactus
	Tomato	Husk
Artifact objects	Bulb	Broken bulb
	Glass	Broken glass
	Lighted out match	Lighted match
	Spoon	Knife

followed by a static picture of the object (of the same size of the last video frame) containing the go-signal (a green circle) that remained on the center of the screen until a response had been made or 2000 ms had elapsed. Participants received feedback on reaction time (RT) after pressing the right or the wrong key (the RT value or "Error," respectively). The next trial began after the feedback disappeared.

Each object was presented eight times: during half of the presentation the object moved away from the participant, with a progressive zoom out of the object, while in the other half the object moved toward the participant, with a progressive zoom of the object.

Overall the experiment consisted of 144 trials and lasted about 20 min.

Data analysis

Reaction times for incorrect responses and RTs more than two standard deviations from each participant's overall mean were excluded from the analysis.

The correct RTs were entered into a repeated-measures ANOVA with *Object Movement Direction* (away and near), *Object Dangerousness* (dangerous and neutral), and *Object Category* (artifact and natural) as within-subjects factors, and *Manual Response Typology* (press and release) and *Age Group* (children and adults) as between-subjects factors. Fisher's LSD *post hoc* tests were also conducted on significant interactions.

RESULTS

The interaction between *Object Dangerousness* and *Object Movement Direction* [F (1, 24) = 8.14, MSE = 578, Cohen's f = 0.58, $p < 0.01$, power = 0.78] was significant. *Post hoc* test revealed that when the objects moved toward the participant neutral objects were processed faster than dangerous ones (255 and 265 ms, respectively, $p < 0.05$). In contrast, when the objects moved away from the participant responses to dangerous objects were faster than to neutral ones (264 and 273 ms, respectively, $p < 0.05$) (**Figure 1**).

Furthermore, the interaction between *Object Category* and *Object Movement Direction* [F (1, 24) = 4.79, MSE = 275, Cohen's f = 0.45, p = 0.04, power = 0.56] was significant. *Post hoc* test revealed that for artifact objects RTs were faster when objects moved toward than away from the participant (258 and 271 ms, respectively, $p < 0.001$) (**Figure 2**).

There were no other significant main effects or interactions ($ps > 0.05$).

DISCUSSION

Results showed that, in a dynamic condition, responses were specifically influenced by the object movement direction in a twofold way. First, the movement direction affected the processing of objects belonging to different typologies, since neutral objects were processed faster when moving toward-approaching the participant. This effect can be considered as a dynamic affordance effect. In contrast, we found that dangerous objects were processed faster when moving away from the participant. The longer RTs with dangerous objects when they approached participants are probably due to a blocking effect. We will discuss this issue more thoroughly in the Section "General Discussion."

Second, the object movement direction also modulated the processing of object category, since responses to artifact objects were faster when moving toward-approaching the participant. This finding adds to previous one as a further demonstration of a dynamic affordance effect, which emerges with a specific category, that of artifact objects. As shown in previous studies, this is likely due to artifact objects activation both of the tendency to manipulate them and to use them, differently from natural objects that convey only information related to manipulation (e.g., Borghi et al., 2007; Vainio et al., 2008; Anelli et al., 2010; Jax and Buxbaum, 2010).

To note, in this experiment we did not register any influence of manual response typology on motor responses. This could either indicate that the employed types of manual response are not effective or that the absence of effects can be rather attributed to the modality of stimuli presentation. We favored the latter interpretation that would imply that, in a dynamic condition, the movement

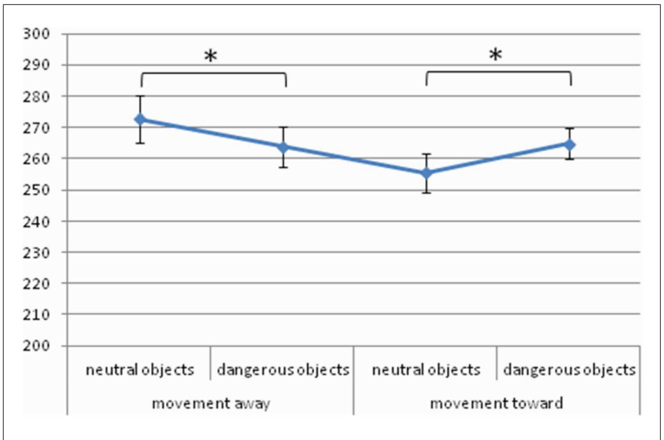

FIGURE 1 | Significant *Object Dangerousness* × *Object Movement Direction* interaction for RTs in Experiment 1, values are in milliseconds and bars are SEM.

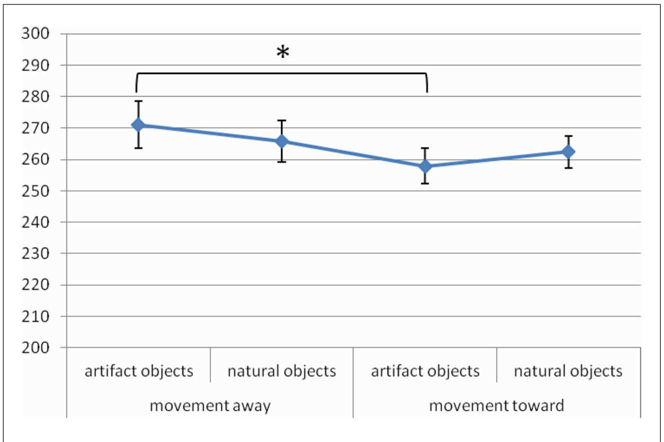

FIGURE 2 | Significant *Object Category* × *Object Movement Direction* interaction for RTs in Experiment 1, values are in milliseconds and bars are SEM.

direction of objects became more important than the different motor responses (i.e., press vs. release) at the disposal of participant. The next experiments will allow us to verify these two alternative hypotheses, since we presented objects in a static condition. If, in line with our second explanation, in Experiments 2 and/or 3 the effect of manual response typology will be present, this would mean that it effectively has a different role depending on the modality of objects presentation.

A final point deserved our consideration: the lack of influence of different age classes we considered, namely children and adults. These data allowed us to speculate that object dangerousness represents a salient object's property, probably because it is adaptive to learn to quickly distinguish between neutral and dangerous objects early on during development. This explanation fits well also with previous evidence on school-age children showing their early sensitivity to object dangerousness and the emergence later in life of more subtle differences, such as those related to object category (Anelli et al., 2012a). On the basis of the results of Experiment 1 and on previous evidence, we have good reasons to predict that the factor age will not influence the results. For this reason, even if it is not possible to completely exclude any effects of age, in the following experiments we will not take into account different age classes, but the sample will be constituted only by adults.

EXPERIMENT 2

Experiment 2 was aimed at understanding what happened when participants observed dangerous or neutral objects in a static situation, rather than in a dynamic one. The task was the same of the previous experiment, i.e. participants were required to distinguish between an artifact and a natural object. To note, in order to explore the time-course of dangerousness processing, participants had time to process objects and to prepare their motor responses: we presented a static picture of an object for 1 s before the appearance of another static picture of the same object containing the go-signal to respond. As explained above, here and in the next experiment we collected only data on adults.

METHOD

Participants

Sixteen undergraduate students from the University of Bologna (3 males and 13 females, mean age: 19.8 years, range: 19–25) took part in Experiment 2 for course credits. All participants were right-handed and had normal or corrected-to-normal vision. All were naive as to the purpose of the experiment and gave informed consent.

Apparatus, stimuli, and procedure

The stimuli and the task were the same of previous experiment. However, in the present experiment, participants observed the objects in a static situation, whereas during Experiment 1 the objects were presented in a dynamic situation.

The experiment consisted of one practice block of 12 trials and one experimental block of 192 trials. Each trial began with a fixation point (+) displayed for 500 ms in the center of the screen. Then, the static picture of an object was shown for 1000 ms and followed by another static picture of the same object containing the go-signal (a green circle) that remained on the center of the screen until a response had been made or 2000 ms had elapsed. Participants received feedback on RT after pressing the right or the wrong key (the RT value or "Error," respectively). The next trial began after the feedback disappeared.

Each object was presented 12 times: in one-third of the trials the object with the go-signal was larger than the first static picture (big size condition), in one-third it remained of the same size of the first static picture (normal size condition), and in the other-third it was smaller than the first static picture (small size condition). In the big size and in the small size conditions, the object with the go-signal had the same size of the last frame of the video clip shown in Experiment 1 (toward and away conditions, respectively).

Overall the experiment consisted of 204 trials and lasted about 25 min.

Data analysis

The data were treated according to the same criteria used for Experiment 1. RTs for incorrect responses and RTs more than two standard deviations from each participant's overall mean were excluded from the analysis.

The correct RTs were entered into a repeated-measures ANOVA with *Object Size* (big, normal, and small), *Object Dangerousness* (dangerous and neutral), and *Object Category* (artifact and natural) as within-subjects factors, and *Manual Response Typology* (press and release) as between-subjects factor. Fisher's LSD *post hoc* tests were also conducted on significant interactions.

RESULTS

The main effects of *Object Size* [$F(2, 28) = 8.05$, MSE = 781, Cohen's $f = 0.75$, $p < 0.01$, power = 0.93] and *Object Dangerousness* [$F(1, 14) = 5.70$, MSE = 412, Cohen's $f = 0.64$, $p = 0.03$, power = 0.60] were significant. RTs were faster when the object was big rather than normal and small (236 vs. 255 vs. 251 ms, respectively) (**Figure 3**). Moreover, participants were faster when the object was neutral rather than dangerous (244 vs. 251 ms, respectively) (**Figure 4**).

DISCUSSION

Results revealed that participants were sensitive to the objects' dangerousness, as response times were faster with neutral than

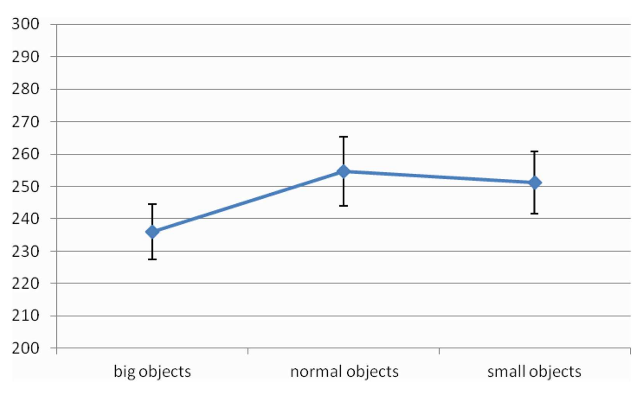

FIGURE 3 | Significant *Object Size* effect for RTs in Experiment 2, values are in milliseconds and bars are SEM.

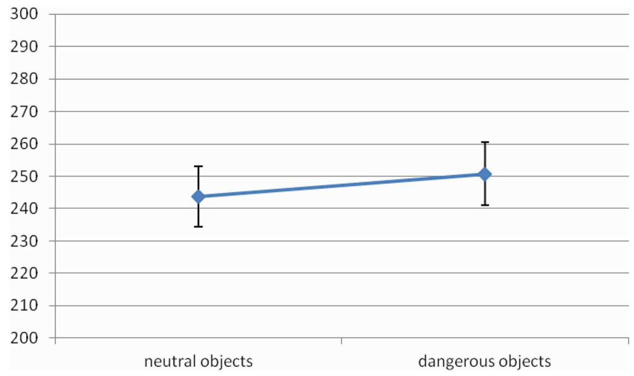

FIGURE 4 | Significant *Object Dangerousness* effect for RTs in Experiment 2, values are in milliseconds and bars are SEM.

with dangerous objects. In line with our hypothesis, this evidence pointed out the influence of a fine object property such as object dangerousness on motor responses. In line with our previous data (Anelli et al., 2012a,b), motor responses were facilitated when participants were faced with neutral objects, while they were slowed down with dangerous objects, probably due to an interference effect. It is worth to underline that here we replicated the emergence of an aversive affordance effect independently from the influence of hand's presentation and thus exclusively by means of the object presentation.

In addition, we registered an effect of the objects' size, as response times were faster with big than with normal and small objects. Two explanations were possible. The first referred simply to a perceptual effect, so that larger objects were processed faster than smaller ones. The second, and more interesting to us, explained this effect not only as visual but as motor as well. In this latter case, objects would evoke faster motor responses since grasping larger objects is less complex than grasping smaller ones (e.g., Bazzarin et al., 2007; Ranzini et al., 2011). One possible way to disentangle this point was to rely on time: one could hypothesize that this size effect may be affected by the time that a participant has to respond. In fact, in the current experiment participants had sufficient time (1 s) to process different objects' features and to prepare their motor responses. Conversely, in the next experiment participants will not have such a time interval, but they will have to respond immediately as soon as the object appears. If, in line with our second explanation, in Experiment 3 the effect of size will not be present, this would mean that the effect we found in Experiment 2 was only perceptual/visual. The absence of an interaction with the object dangerousness did not allow us to determine whether this supposed motor effect was linked to the object dangerousness. However, one could hypothesize that, in the case of dangerous objects, some time is needed to prepare ourselves to escape from them. If in Experiment 3 we will register an interaction between objects size and objects dangerousness, this would allow us to determine that a specific motor response for neutral and dangerous objects (i.e., grasping and escaping, respectively) emerges, hence demonstrating that the effect registered in Experiment 2 was not only perceptual but motor as well. This result would be also in line with data of Experiment 1 showing the emergence of a facilitation effect with neutral objects and of an escaping effect with dangerous ones.

One final aspect is worth noticing: we did not find any effect of the object category, in contrast with previous experiment and with the majority of the studies on this issue. Even if we cannot say much about a null result, we can speculate that this was due to the fact that the distinction between dangerous and neutral objects was much more salient, and washes out the distinction between an artifact and a natural object.

EXPERIMENT 3

Experiment 3 was a control experiment. The only difference from Experiment 2 was that participants were required to discriminate between an artifact and a natural object as soon as the object appeared on the screen, so that an immediate coding of the stimulus was required. Along with previous data, this manipulation allowed us to verify the time-course of sensitivity both to objects dangerousness and objects size, and to clarify the motor vs. perceptual features of the effect size emerged in previous experiment.

METHOD

Participants

Sixteen undergraduate students from the University of Bologna (5 males and 11 females, mean age: 20.3 years, range: 19–26) took part in Experiment 3 for course credits. As in previous experiments, all subjects were right-handed and had normal or corrected-to-normal vision. All were naive as to the purpose of the experiment and gave informed consent.

Apparatus, stimuli, and procedure

The apparatus and stimuli were the same used in Experiment 2. The only difference was that participants were instructed to respond as soon as the object appeared.

Each trial began with a fixation point (+) displayed for 500 ms in the center of the screen. Soon after, the static picture of an object containing the go-signal (a green circle) was shown until a response had been made or 2000 ms had elapsed. Participants received feedback on RT after pressing the right or the wrong key (the RT value or "Error," respectively). The next trial began after the feedback disappeared.

Each object was presented 12 times: in one-third of the trials the object with the go-signal was large (big size condition), in one-third it had a normal size (normal size condition), and in the other-third it was small (small size condition). In the big size and in the small conditions, the object with the go-signal had the same size of the last frame of the video clip showed in Experiment 1 (near and away conditions, respectively) and of the second object showed in Experiment 2.

Overall the experiment consisted of 204 trials and lasted about 25 min.

Data analysis

The data were treated according to the same criteria used for previous experiments. RTs for incorrect responses and RTs more than two standard deviations from each participant's overall mean were excluded from the analysis.

The correct RTs were entered into a repeated-measures ANOVA with *Object Size* (big, normal, and small), *Object Dangerousness* (dangerous and neutral), and *Object Category* (artifact and natural) as within-subjects factors, and *Manual Response Typology* (press and release) as between-subjects factor. Fisher's LSD *post hoc* tests were also conducted on significant interactions.

RESULTS

The main effect of *Object Dangerousness* [F (1, 14) = 10.08, MSE = 337, Cohen's f = 0.85, $p < 0.01$, power = 0.84] was significant. RTs were faster when object was neutral rather than dangerous (469 vs. 478 ms, respectively) (**Figure 5**).

The interaction between *Manual Response Typology*, *Object Size*, and *Object Dangerousness* [F (2, 28) = 3.64, MSE = 182, Cohen's f = 0.52, $p < 0.05$, power = 0.62] was significant. *Post hoc* test showed that when the task required to press the key, responses were faster when the object was neutral big, neutral normal, and neutral small than dangerous small (464 vs. 478 ms, $p < 0.01$; 464 vs. 478 ms, $p < 0.01$; 468 vs. 478 ms, $p < 0.05$, respectively) (**Figure 6A**). Moreover, when the task required to release the key, responses were faster in the following comparisons: (i) when the object was neutral big and neutral normal than dangerous big (474 vs. 487 ms, $p < 0.01$; 468 vs. 487 ms, $p < 0.001$, respectively); (ii) when the object was neutral big and neutral normal than dangerous normal (474 vs. 484 ms, $p < 0.05$; 468 vs. 484 ms, $p < 0.01$, respectively); (iii) when the object was dangerous small that dangerous big and dangerous normal (474 vs. 487 ms, $p = 0.01$; 474 vs. 484 ms, $p < 0.05$, respectively) (**Figure 6B**).

DISCUSSION

In keeping with what found in Experiment 2, participants responded faster to neutral objects than to dangerous ones.

Interestingly, participants were not sensitive to the objects' size, in contrast to what happened in Experiment 2. Most crucial for us was the significant interaction between *Manual Response Typology*, *Object Size*, and *Object Dangerousness*. With key press responses small dangerous objects were slower than neutral objects. This would suggest that the facilitation due to the tendency to grasp objects, as revealed by the key press responses associated to approach movements, was stronger with neutral objects, probably due to an affordance effect. In addition, with key release responses small dangerous objects were faster than other dangerous objects. This indicated that the interference due to the tendency to escape from dangerous objects, as revealed by the key release responses associated to withdrawal movements, was particularly marked when dangerous objects were large, thus closer to us. This can be due to the fact that, when the object is still far away from us, we can react moving away from it, while when the object is close to us a blocking effect is present. This blocking effect can be qualified in two different ways, both compatible with our results. First, dangerous stimuli could elicit freezing. The freezing behavior, i.e. the tendency to persist in an immobile state in front of aversive stimuli when there is no way to escape, has been documented in animals such as rats (e.g., Bolles and Collier, 1976). Alternatively, the presence of aversive stimuli could slow down dramatically motion speed inducing to perform more careful and cautious movements. Our data do not allow us to disentangle between these two different strategies, of which the first is probably more instinctive, the second more intentional. For these reasons we will refer more generically to a blocking effect.

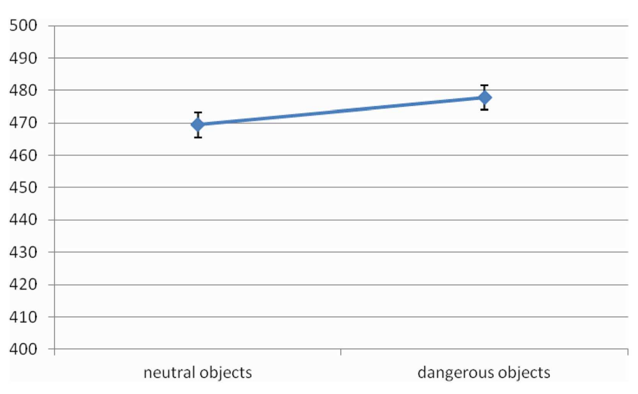

FIGURE 5 | Significant *Object Dangerousness* effect for RTs in Experiment 3, values are in milliseconds and bars are SEM.

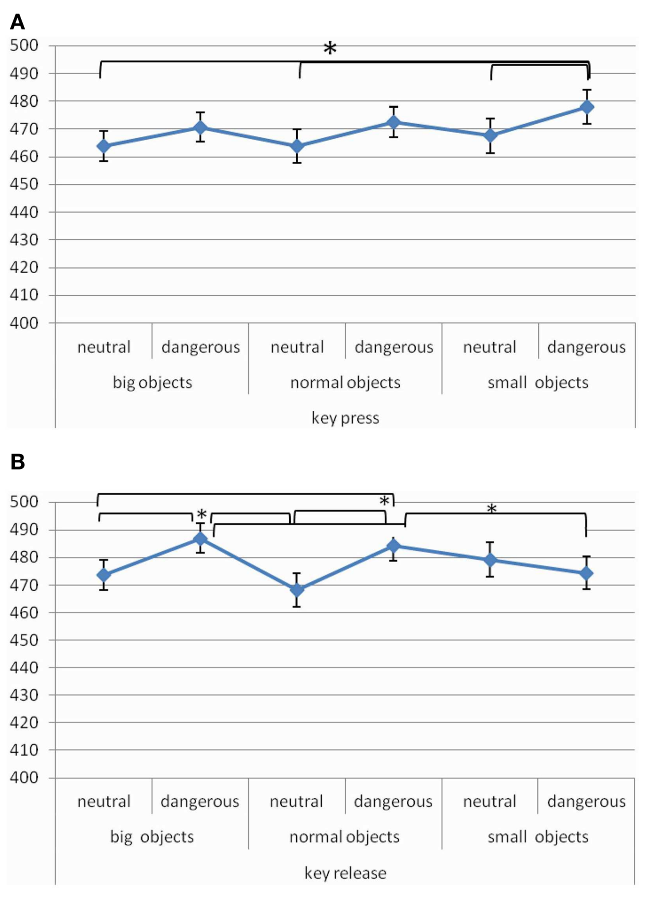

FIGURE 6 | Significant *Manual Response Typology* × *Object Size* × *Object Dangerousness* interaction for RTs in Experiment 3 [(A) key press manual response typology; (B) key manual release response typology], values are in milliseconds and bars are SEM.

Importantly, the current experiment clarified that this blocking effect with dangerous objects was not present only with key press but also with key release responses. In sum, the interaction revealed the presence both of an affordance effect and of an aversive affordance effect, and was therefore in line with results of Experiment 1. Importantly, these results also demonstrated that the type of stimuli presentation (dynamic vs. static) influenced the manual response typology. These points will be discussed in the next section.

In addition, this interaction helped to interpret the results of the previous experiment clarifying that the size effect was not simply a perceptual one, but was motor as well. Indeed, it seemed to imply the tendency to grasp neutral objects and to escape from dangerous objects.

Further, the difference between Experiments 2 and 3 allowed us to speculate that the size effect can be influenced by the time that participants had at their disposal to respond. In fact, when they had a brief delay (1 s) before responding, as in Experiment 2, and thus they can prepare a motor response, it is possible that they process information related to dangerousness and size in a separate fashion. On the contrary, when an immediate response was required, and thus participants cannot prepare a motor response, as in Experiment 3, they could process information on dangerousness in strict relation to information on size. This indicated that participants were able to integrate different kinds of information rather quickly when rapid responses were required.

GENERAL DISCUSSION

In the present study we investigate whether motor responses are influenced by the observation of object dangerousness in dynamic and static situations, without showing a direct or potential interaction between an object and an effector. In three experiments we focused on the conceptual distinction between neutral and dangerous objects, by asking participants to perform a simple categorization task (i.e., to decide whether the stimulus shown was an artifact or a natural object), by pressing or releasing one of two designed keys. The object size was manipulated in order to provide a cue indicating distance, namely smaller objects indicated objects more distant from the participant's body, whereas larger objects indicated objects closer to the participant. The object presentation could be dynamic (Experiment 1) or static (Experiments 2 and 3), as objects moved toward or away from participants (dynamic presentation) or objects were close or distant from participants (static presentation). Moreover, time-course has been considered, by investigating whether the processing of dangerousness differed depending on whether time to prepare motor responses was given (Experiments 1 and 2) or whether an immediate motor response was required (Experiment 3).

In Experiment 1 both children and adults were tested, while in Experiment 2 and 3 the sample was composed only by adults. Despite the complexity of our experimental design, our results are quite consistent across experiments. We will discuss them below.

First of all, results of all three experiments showed that participants were sensitive to the difference between dangerous and neutral objects, in line with our previous data (Anelli et al., 2012a,b). In particular, dangerous objects produced an interference effect, whereas neutral objects produced a facilitation effect, as we registered faster RTs with neutral and slower RTs with dangerous objects. Neither of the two effects was modulated by the manual response typology (key press vs. release). Interestingly, a recent study (Witt and Sugovic, 2013) demonstrated that threatening objects seemed to move faster than non-threatening ones, and that objects easier to block appeared to move slower than objects more difficult to block.

The present work allowed us to advance some speculations about the possible neural mechanisms involved in the processing of neutral and dangerous objects. To note, differently from previous behavioral and TMS studies (e.g., Avenanti et al., 2005; Morrison et al., 2007b; Anelli et al., 2012a,b), in the present study we did not present objects in real or possible interaction with a hand. Even if we cannot completely exclude that observing an object could induce the imagination of a hand interacting with it, we are certain that our stimuli did not directly induce resonance mechanisms, since no hand interacting with objects was presented. This allowed us to ascribe the interference and facilitation effects only to the objects' processing, whose underlying neural basis is represented by the canonical neuron system, and not to the emergence of resonance mechanisms due to the activation of the mirror neuron system. Indeed, researches on object observation (where only objects were shown), as the present one, highlighted the probable involvement of the canonical neuron system (i.e., neurons activated during both the execution of specific object-directed actions and the mere visual observation of the same objects; for a review, see Rizzolatti and Craighero, 2004). To date, it remains unclear whether the canonical system is not only responsible of the affordance effect, but also of the avoidance effect emerged with dangerous objects.

The second interesting result of our study concerns the influence of the spatial relationship between stimuli and subject on the objects' processing. Our data revealed that participants' responses were influenced by the kind of object movement direction in a dynamic condition (Experiment 1). In particular, neutral objects were processed faster when they moved toward-approached the participant than when they moved away from her. This result seemed to be in keeping with data showing the emergence of affordances only when objects were located within the perceiver's or observer's peripersonal space (Costantini et al., 2010, 2011a). Our finding revealed that a dynamic affordance effect may emerge when a neutral object moved toward/approached the participant. In fact, when an object is at our disposal we can easily simulate to interact with it, provided that it can be for example manipulated or used without any problem, exactly as in the case of neutral objects. In addition, in the dynamic condition we found that a different motor response emerged with dangerous objects, probably due to the activation of an escaping/avoidance mechanism when they move away from the participant.

On the whole, these findings demonstrated the emergence of selective motor effects related to different objects typologies, modulated by the object movement direction in the space and not by actions performed by an observed agent. It is worth noting that in this way dangerousness was considered as a relational property of objects, namely as a property which is neither of the object/environment nor of the acting organism, in keeping with the definition of affordances as intrinsically relational properties.

These results can be of particular interest since so far, to our knowledge, even if a number of studies investigated the relationship between object affordances and space (e.g., Costantini et al., 2010, 2011a,b), there was only sparse evidence on the relationship between dangerousness and space. In a recent study Coello et al. (2012) focused on the perception of reachable space and demonstrated that the size of such space was influenced by the specific level of objects' dangerousness: they found a significant reduction of the peripersonal space when the threatening part of dangerous objects was oriented toward the participants, with respect to when it was oriented away from them. The impact of the interaction between body and objects on the boundary of peripersonal space suggests an involvement of processes responsible for the simulation of the consequences that some kind of action upon objects can have for us. Notice that in the study by Coello et al. (2012) the stimuli presentation was not dynamical. As to the neural basis of the relationship between dangerous objects and space, a fMRI study of Lloyd et al. (2006) investigated how aversive objects were processed in peripersonal space. Data showed a significant increase in the activation of posterior parietal area when participants viewed a painful stimulation, with respect to an innocuous one, of a rubber hand in participants' peripersonal space. This suggested an involvement of this cortex in nocifensive responses to aversive stimuli.

A third result concerned the influence of manual response typology. When the object presentation was dynamic (Experiment 1) motor responses were not influenced at all by manual response typology, raising the possibility that the manipulation employed was not effective. Instead, data of Experiment 3, when the objects presentation was static, demonstrated that this was not the case, since two different effects have been registered. On one hand, a facilitation effect emerged when key press responses concerned neutral objects, probably linked to an affordance effect evoked by this kind of objects with a response modality associated to approach movements. On the other hand, key release responses led to a higher interference effect with large dangerous objects, probably due to a tendency to escape evoked by this kind of objects with a response modality associated to withdrawal movements. This finding was in line with the results of Morrison et al. (2007b) that revealed a specific influence of pain observation on overt motor responses. More specifically, when participants observed a painful stimulation, withdrawal movements were speeded whereas approach movements were slowed down. These results were interpreted as due to a facilitation of the kind of motor responses more suitable for avoiding or withdrawing from the object.

On the whole, findings on manual response typology point out the influence of the modality of objects presentation on the emergence of facilitation and interference effects. In fact, in the dynamic condition the movement direction of objects becomes more salient for the participants than their own actions. Conversely, in the static condition the manual response typology becomes relevant, as participants perceived the importance of their own specific actions in order to interact with objects or to avoid them.

As final point, the investigation of the time-course revealed that the processing of dangerousness was influenced by the amount of time that participants had at their disposal to respond. In this respect, the interaction between the three main factors found in Experiment 3, in which no time for action preparation was given, was particularly informative. Indeed, this interaction showed that, while with key press responses small dangerous objects were the slowest items to be processed, with key release responses the slowest items were large dangerous objects. This qualified the interference effect found in previous studies (Anelli et al., 2012a,b) anchoring it to a precise time-course. In fact, when there was no time for action preparation (Experiment 3), the interference effect with dangerous objects was particularly strong with large objects, i.e., when the objects were perceived as near. When the dangerous object was close to us and there was no time for action preparation, a sort of blocking effect occurred.

The situation was quite different when there was time for response preparation (1 s delay). Indeed, in Experiment 2, while the advantage of neutral over dangerous objects was present, there was no interaction and overall large objects were processed faster than small ones. One possibility was that the effect was due mostly to neutral objects; a qualitative analysis suggested this was the case, but the result was far from significance.

The results of Experiment 1 can help us to better comprehend the data. In fact, the advantage of the toward condition (in which the last video frame depicted large objects) was confined to neutral objects, probably due to an affordance effect, i.e. the tendency to grasp neutral objects, that was stronger when objects were approaching. Instead, the advantage of the away condition (in which the last video frame depicted small objects) concerned dangerous objects, probably due to an escaping/avoiding effect. Imagine the following situation: we see from far away a dangerous object/entity, for example a scorpio; given that it is far away, we have some time for action preparation. We immediately start escaping from it. When the scorpio is very close to us, instead, we are afraid, thus we stop and we avoid moving. Combining information on space and time, our results depict a situation similar to the one we have just described.

In the present study we simply presented dangerous and neutral objects, without introducing finer distinctions, for example between threatening and dangerous entities, even if the dynamic presentation suggested a potential threatening effect. Further research is needed to better understand how the motor responses to different kinds of dangerous entities occur in space and time.

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What color is my arm? Changes in skin color of an embodied virtual arm modulates pain threshold

Matteo Martini[1,2]*, D. Perez-Marcos[1,2] and M. V. Sanchez-Vives[1,2,3]

[1] Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain
[2] EVENT-Lab, Facultat de Psicologia, Universitat de Barcelona, Barcelona, Spain
[3] Institució Catalana de Recerca i Estudis Avançats (ICREA), Barcelona, Spain

Edited by:
Diana M. E. Torta, University of Turin, Italy

Reviewed by:
Shoko Kanaya, The University of Tokyo, Japan
G. Lorimer Moseley, University of South Australia, Australia

****Correspondence:***
Matteo Martini, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), C/Rosselló 149-153, 08036-Barcelona, Spain
e-mail: mmartini@clinic.ub.es

It has been demonstrated that visual inputs can modulate pain. However, the influence of skin color on pain perception is unknown. Red skin is associated to inflamed, hot and more sensitive skin, while blue is associated to cyanotic, cold skin. We aimed to test whether the color of the skin would alter the heat pain threshold. To this end, we used an immersive virtual environment where we induced embodiment of a virtual arm that was co-located with the real one and seen from a first-person perspective. Virtual reality allowed us to dynamically modify the color of the skin of the virtual arm. In order to test pain threshold, increasing ramps of heat stimulation applied on the participants' arm were delivered concomitantly with the gradual intensification of different colors on the embodied avatar's arm. We found that a reddened arm significantly decreased the pain threshold compared with normal and bluish skin. This effect was specific when red was seen on the arm, while seeing red in a spot outside the arm did not decrease pain threshold. These results demonstrate an influence of skin color on pain perception. This top-down modulation of pain through visual input suggests a potential use of embodied virtual bodies for pain therapy.

Keywords: virtual arm, virtual reality, body ownership, pain threshold, pain modulation, multisensory integration, multisensory stimulation

INTRODUCTION

Color is highly relevant in human visual perception. Colors can affect visual search and attention (Green and Anderson, 1956; Woodman, 2013) and, further, they can affect how a given stimulus is perceived. For example, colors have the power to endorse an implicit meaningful association in relation to temperature. Typically, red is linked to "hot" while blue to "cold" (Moseley and Arntz, 2007). Indeed, a controversial but intuitive hypothesis states that visual appearance of an object (mainly its color) should have some influence on thermal perception (Candas and Dufour, 2005). Durgin and coworkers observed that a blue light beam projected on the hands produces a thermal sensation that was cooler than the one elicited by a red light beam. Furthermore, the same illusory sensation holds true when these lights are pointed to embodied rubber hands (Durgin et al., 2007). Noteworthy is a recent study by Kanaya et al. (2012) who showed how thermal judgments about an object placed on one's hand are modified according to the thermal property of the object that touches an embodied rubber hand. Nevertheless, whether colors can act as visual modulators of pain perception is still poorly understood. Moseley and Arntz (2007) found that the pain is greater when a stimulus is associated to a red visual cue than when the same stimulus is associated to a blue visual cue. Subsequently, Landgrebe et al. (2008) found that somatosensory perception is altered by colored light exposure, and that diffuse red light decreases cold pain thresholds compared to white and green light, increasing the detection and pain thresholds for warm stimuli. A recent study investigating the effects of the perceived time lapsed during a painful stimulus did not find any influence of the color of the clock on the pain perceived (Peyron et al., 2012).

Different cognitive factors are known to modulate pain perception such as distraction, expectation, emotion, learning, and spatial attention (see Wiech et al., 2008; Legrain et al., 2009 for reviews on the topic). Yet, there is no study up to date on whether the manipulation of the skin color on a body felt as one's own affects pain perception.

Virtual reality (VR) technology represents a versatile mean for perception studies, as it allows the creation of sensory environments that can be replicated almost identically and that are under the full control of the experimenter (Sanchez-Vives and Slater, 2005). In the present experiment, we investigated whether the vision of different colors applied on an embodied virtual body affected the pain thresholds of healthy volunteers. We tested pain threshold by applying increasing ramps of heat stimuli to the wrist of the subjects while they were concomitantly seeing their virtual arm getting increasingly red, blue, or green. In order to create the illusion of embodiment of the virtual body we used visuo-proprioceptive correlations and first-person perspective with respect to the virtual body. Adequate sensorimotor correlations have been recently proven to be effective in fostering the embodiment of a virtual limb (Slater et al., 2009; Normand et al., 2011; Kilteni et al., 2012; Llobera et al., 2013), including as well as visuo-proprioceptive ones (Kalckert and Ehrsson, 2012). Since the colors blue and red are associated to cold and hot respectively, our hypothesis was that the heat pain threshold would be lower for red than for blue skin color. Further, in order to show that the association color-temperature is maximally effective only when it interests the body, we introduced a condition where the arm was left unaltered and a spot close to the avatar's arm, but off of it, got increasingly red.

MATERIALS AND METHODS

PARTICIPANTS

Thirty healthy participants (all females, mean ± SD age: 23.9 ± 5.7 years) were recruited for the experiment from the campus of Psychology Sciences of University of Barcelona. They had normal or normal-to-corrected vision, no history of neurological disorders and no other condition potentially interfering with pain sensitivity (e.g., drug intake). Upon arrival at the laboratory they were asked to read and sign a consent form. The experiment was approved by the Comité Ético de Investigación Clínica de la Corporación Sanitaria Hospital Clínic de Barcelona. All participants received a monetary reimbursement for their participation. Importantly, in a debriefing, all subjects could distinguish and correctly identify the colors presented.

VIRTUAL REALITY SYSTEM

The stereoscopic head-mounted display (HMD) was a NVIS SX111 with a resolution of 1280 × 1024 pixels per eye and a total field of view of 111° × 64°, displayed at 60 Hz. The head-tracking was realized with a 6-DOF InterSense IS-900 device (InterSense, Billerica, MA, USA). Finger tracking was permitted by attaching two markers on a plastic ring put on the participant's finger. These markers were constantly tracked by 12 infrared OptiTrack cameras, and their coordinates in the space computed with the Arena software (NaturalPoint, Corvallis, OR, USA). Hence, when the participant's finger was moved, the avatar's finger could move accordingly, mimicking exactly the same movements at the same time. The virtual environment was programed using the XVR system (Tecchia et al., 2010) and the virtual body using the HALCA library (Gillies and Spanlang, 2010). Noise isolation was ensured by the administration of pink noise through a surround audio system (Creative technology Ltd., Singapore), with a constant volume set at 65 dB SPL.

THERMAL STIMULATION

Thermal heat stimuli were delivered by means of a Thermotest machine (Somedic, Hörby, Sweden) with a 2.5 cm × 5.0 cm thermode tied with a Velcro strap on the palmar side of the right wrist. Pain thresholds were assessed with the method of limits (Yarnitsky et al., 1995). The probe temperature was increased from normal skin temperature (constant baseline temperature = 31°C) at 2°C/s. Participants were asked to press a button with their left hand as soon as they perceived the stimulation as being painful. Immediately after pushing the kill-switch button, the probe temperature rapidly decreased to the baseline temperature. For safety reasons, maximal temperature was set at 48°C.

PROCEDURE

Participants sat on a chair with both arms resting on a table covered with a black cloth (**Figures 1A,B**). Before donning the HMD, they were given two to three heat stimuli to familiarize with the heat ramps.

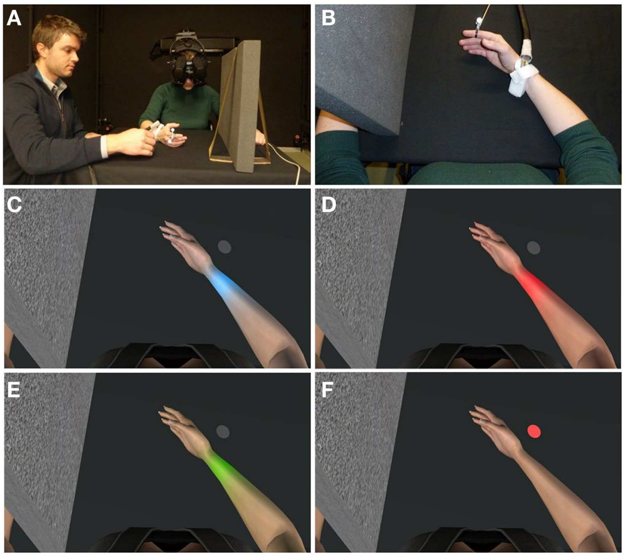

FIGURE 1 | The experimental set-up and the four experimental conditions: the participant saw the virtual environment through the HMD while an experimenter moved her right index finger to move the avatar's right index finger accordingly. When the heat stimulation provided on the right wrist was felt as painful by the participant, she stopped the stimulation by pressing the button held on her left hand **(A)**. Top view of the posture of participant's arm resting on the table, matching avatar's posture **(B)**. The visuo-proprioceptive congruent feedback given by the finger movements and the first-person perspective view of the avatar fostered the embodiment of the virtual limb while the skin color changed into blue **(C)**, red **(D)**, or green **(E)** as soon as the heat stimulation started increasing in temperature. In the fourth condition, the skin of the virtual arm did not change color but a gray spot on the table turned into red **(F)**.

As the subject donned the HMD the room's lights were turned off and the pink noise played. The HMD allowed participants to experience an immersive virtual environment around them and to see a virtual body, from a first-person perspective, in place of their own (Kilteni et al., 2012). Additionally, they were asked to move their right arm where they saw that the avatar's arm was, and keep it in the same position so that, when participants looked down at their own body, they could see the virtual body perfectly co-located with their own. They were also asked to place the hand and the arm mimicking as much as possible the position of the virtual ones. The left virtual arm was hidden behind a virtual foam shield, in order for the subject to see and concentrate only on the right arm. Importantly, both the virtual right hand and forearm were always kept in the field of view of the participants. Precisely, in all conditions, they were asked to focus their attention on the wrist only, while the finger movements clearly remained in their field of view. As the experiment started, an experimenter moved the participant's right index finger continuously in an outward-inward fashion. This passive movement was meant to provide the proprioceptive feedback without calling into play motor control and thus the role of agency (Kalckert and Ehrsson, 2012), and to ensure that all subjects constantly saw the finger moving throughout the whole experiment. Further, the correspondence between the visual and the proprioceptive inputs provided the experience of "embodying" the avatar's limb, a phenomenon already documented as "virtual hand illusion" (Slater et al., 2008, 2009). Four different visual conditions were presented to all participants (**Figure 1**), with the avatar's wrist becoming either blue (**Figure 1C**), red (**Figure 1D**), or green (**Figure 1E**). In a different condition, a gray spot placed on the virtual table, close to the participant's wrist, became red (**Figure 1F**). Each color transformation was presented four times for a total of 16 visual stimuli. In order to limit habituation to the same visual experience, stimuli were presented in an event-related fashion (intermixed). In each trial, the increase of the thermal stimulation was concomitant to the change of color (toward red, green, or blue) of the avatar's wrist and nearby skin area. In the "spot" condition, the increase of the stimulus temperature coincided with the round spot becoming red, while there was no change of the avatar's skin color. The color change started at the same time than the thermal stimulation and lasted for 3 s in both directions (color appearance and disappearance), independently of the condition. The color intensity increased/decreased linearly and reached its maximum when the temperature was 37°C, i.e., before reaching the pain threshold range (starting around 40°C). The color started disappearing once the participant had stopped the thermal stimulation. The order of the visual stimuli was pseudo-randomized across subjects, in order to avoid that one visual condition was affected more than others by habituation to the painful stimulation (Greffrath et al., 2007). The inter-stimulus interval was set at a random pace between 45 and 60 s. A pause of 2 min was introduced after the 8th stimulus to prevent from possible neck and head muscles fatigue (caused by the weight of the HMD and the inclination of the head).

SUBJECTIVE MEASURES

Subjective report about the level of embodiment was collected on a single trial basis immediately after each thermal stimulation. Subjects were instructed to spell out a number in order to reply to the question: "by the time you were seeing the color appearing on the wrist, did you feel as if the virtual right arm was your own right arm?". This item was referred as to the "embodiment level" and measured with a seven points Likert scale. A score of "1" meant "not at all" while "7" stood for "yes, completely."

DATA HANDLING

Pain thresholds (in °C) were averaged per each one of the visual conditions and subject. These were normally distributed according to the Kolmogorov–Smirnov test ($p > 0.05$). Five (out of 120) scores from two subjects were identified as outliers (higher than twice the standard deviation from the group's mean) and replaced with the mean scores of the group for the same visual condition (i.e., if the score was related to the "green arm" condition, it was replaced with the mean score obtained for the "green arm" condition). One-way repeated-measures ANOVA (one factor: "Condition" with four levels) was then conducted on mean pain thresholds. *Post hoc* analysis was conducted with Tukey HSD tests. The significance level was set at $p < 0.05$.

The scores reported for the "embodiment level" were averaged per each visual condition and participant, and then subjected to a Friedman ANOVA. *Post hoc* analysis with Wilcoxon Matched Pairs Tests was conducted, with a Bonferroni correction applied for the number of possible comparisons. This resulted in a significance level set at $p < 0.008$. Statistical comparisons between conditions were conducted with STATISTICA (StatSoft, Inc., Tulsa, OK, USA).

RESULTS

PAIN THRESHOLD

The one-way repeated-measures ANOVA showed an effect of the factor "Condition" ($F_{3,87} = 5.93$, $p < 0.001$), meaning that the vision of different colors influenced pain thresholds (**Figure 2**). Tukey *post hoc* tests revealed that the vision of the blue arm led to a higher pain threshold compared to the one reported in the red arm condition ($p = 0.020$).

A significantly higher pain threshold was also detected while participants were seeing the red spot on the table compared either to the red arm ($p = 0.001$) and the green arm ($p = 0.046$). No other comparison was found to be significant.

EMBODIMENT SCORES

The analysis with Friedman ANOVAs on the embodiment scores reported a significant *p*-level ($\chi^2_3 = 9.09$, $p = 0.028$). The embodiment level reported in the "red arm" condition was higher than that obtained in the "blue arm" ($p = 0.045$). However, *post hoc* comparisons did not confirm the statistical significance (Wilcoxon *post hoc* test, *p*-corrected level = 0.008). This means that there was no actual difference in terms of embodiment between conditions. No other comparison was found to be significant.

DISCUSSION

Mean ratings relative to embodiment level are displayed in **Table 1**. The present experiment tested for the first time whether the vision of different colors presented on the body affected heat pain perception. By means of immersive VR participants internalized a virtual body, thus permitting experimentally controlled visual changes of it. Our results evidence that the vision of different skin colors on the embodied virtual body affects pain threshold. Specifically, when subjects saw the virtual limb becoming blue there was a significant increase of pain threshold compared to when they saw it getting red. Moreover, we also show that pain threshold is affected

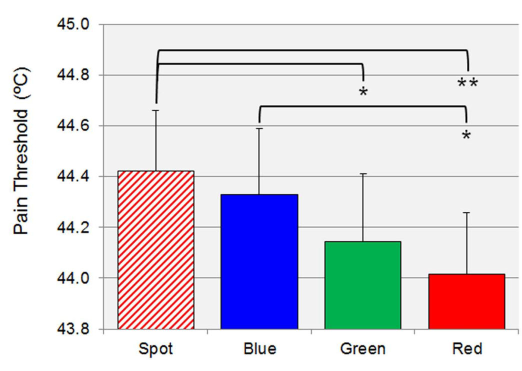

FIGURE 2 | Columns and vertical error bars respectively stand for group means and standard errors of the pain thresholds in each condition. Asterisks indicate significant comparisons (*$p < 0.05$; **$p < 0.01$).

Table 1 | Means (± SD) of the ratings relative to the embodiment question per each visual condition.

Condition	Embodiment ratings
Blue	5.47 ± 1.09
Red	5.75 ± 0.85
Green	5.48 ± 0.99
Red spot	5.67 ± 0.97

differently depending on whether color is presented on or off the body. An important finding is that the vision of the red color *per se* was not always associated to a decrease of the pain threshold. Rather, when a cue close to the avatar's arm, but off of it, got red, we registered the highest pain thresholds, significantly greater than the one recorded with the arm becoming either red or green.

Following the "hue-heat hypothesis," which states that colors toward the red end of the visual spectrum are perceived as "warm" and those toward the blue end as "cool," the idea that the vision of a particular color can be associated to a specific temperature is gaining experimental evidences (Landgrebe et al., 2008; Michael et al., 2010; Kanaya et al., 2012). Moseley and Arntz (2007) showed that when the noxious stimulus is associated with a red visual cue, it hurts more and it is actually perceived as hotter than when the same stimulus is associated with a blue visual cue signaling that the stimulus is "cold," although actually it is not. In a following investigation, fourteen healthy volunteers with normal color vision assessed temperature perception during exposure to different lights: colored lights exposure did alter somatosensory perception, with red light decreasing cold pain thresholds compared to white light, and green light increasing the detection and pain thresholds for warm stimuli (Landgrebe et al., 2008). One recent study, however, failed to find any specific regulatory effect on pain by the vision of a green or a red clock (Peyron et al., 2012). Our results uphold the idea that temperature-related colors, i.e., red and blue, may affect heat pain threshold and this effect changes according to whether they are seen on one's body or out of it. How can the vision of red and blue do that? Likely, the meaning attributed to the colored cue plays a major role in determining pain perception. For example, it could be that the vision of an intense reddened skin would bring the meaning that the arm is getting harmed by heat, conveying a threatening message and thus leading to an increase of the experience of pain (Arntz and Claassens, 2004). Seeing a blue arm instead would mean that a "cooling" of the skin is taking place, thus contrasting with the heating of the thermode and so yielding a higher pain threshold. In fact, when the body is exposed to different temperatures it reacts with thermoregulation through superficial vasodilation when it's hot, or vasoconstriction when it's cold; this in turn brings the tissues to be highly or poorly oxygenated by hemoglobin, which renders the skin red or blue (cyanotic), respectively (Hirschmann and Raugi, 2009; Everett et al., 2012).

Why the vision of a reddening cue out of the body led to the highest pain threshold? It is known that the experience of pain is modified by the direction of spatial attention, so that directing attention away from the pain location results in a reduction of pain. For instance, in a recent study participants perceived painful stimuli as significantly less painful when visual cues were presented at a different location from where the painful stimuli were applied, in comparison with the condition where visual cues were presented at the same location of the painful stimuli (Ryckeghem et al., 2011). Hence, in the present experiment, having a visual cue on the virtual table may have directed a shift of the spatial attention toward the cue as it started changing color (from gray to red), despite the instructions to focus only on the virtual wrist. Yet, the introduction of a technique allowing the measurement of the gaze direction of the participants (e.g., by means of eye tracking) would have provided an empirical support to this claim.

As expected, because the green color is usually not related to any temperature directly, it did not drive the pain threshold into a clear direction. Indeed, our data show that pain threshold during the vision of the arm getting green is between the bluish and the reddened arms (higher and lower, respectively). Most participants anecdotally reported a connection between a blue arm with a cold, and red arm with a warm sensation. However, only one reported a connection between the vision of green and a temperature-related ideation. This would rule out the possibility that the green color was generally associated to any temperature. So, given that the green color is temperature-unrelated (at least not related as red and blue are) and that the pain threshold value reported with the vision of the green arm stood just between the red and the blue arm, we could say that a bluish arm augments the heat pain threshold while a reddish one decreases it. Landgrebe et al. (2008) have shown that the vision of a green light would increase the heat pain threshold as compared to the vision of either a white or red light. Yet, we did not find any significant difference in pain threshold between the green and red conditions. This apparent incongruence could be due to several important differences between our study and Landgrebe's one. The following differential factors may explain these divergences: (i) the lights used in Landgrebe experiments were diffuse/environmental lights while, in our study, colors specifically implied a change of the embodied limb (except for the "spot" condition); (ii) the sample size of the present study ($n = 30$) doubled that from Landgrebe's study, which is relatively small ($n = 14$); and (iii) their sample was composed of male subjects only while ours was formed by female subjects only. As suggested by the authors, "gender might influence the cross-modal effects of colour" (Landgrebe et al., 2008).

Recently, it has been reported that the illusion of owning a rubber hand does not induce any significant change in the perception of pain (Mohan et al., 2012). Nevertheless, the focus of the present study was not to compare the effects of embodiment on pain threshold itself but, rather, to see whether the color of the skin of an embodied virtual arm could affect the pain threshold. Our results suggest a strong relationship between the vision of the skin color and the expected temperature, which may exert a top-down modulation of the pain threshold. This may reveal fundamental implications for the design of multimodal therapy approaches for the treatment of pain states that include visual feedback of the own body or of an embodied avatar.

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Pain and body awareness: evidence from brain-damaged patients with delusional body ownership

Lorenzo Pia[1,2]*†, Francesca Garbarini[1†], Carlotta Fossataro[1], Luca Fornia[3] and Anna Berti[1,2]

[1] Psychology Department, University of Turin, Turin, Italy
[2] Neuroscience Institute of Turin, University of Turin, Turin, Italy
[3] Section of Physiology, Department of Neuroscience, University of Parma, Parma, Italy

Edited by:
Camila Valenzuela Moguillansky, University Pierre et Marie Curie, France

Reviewed by:
Matthew R. Longo, Birkbeck University of London, UK
Aikaterini (Katerina) Fotopoulou, King's College London, UK

***Correspondence:**
Lorenzo Pia, Psychology Department, University of Turin, Via Po 14, 10123 Turin, Italy
e-mail: lorenzo.pia@unito.it

† Lorenzo Pia and Francesca Garbarini have contributed equally to this work.

A crucial aspect for the cognitive neuroscience of pain is the interplay between pain perception and body awareness. Here we report a novel neuropsychological condition in which right brain-damaged patients displayed a selective monothematic delusion of body ownership. Specifically, when both their own and the co-experimenter's left arms were present, these patients claimed that the latter belonged to them. We reasoned that this was an ideal condition to examine whether pain perception can be "referred" to an alien arm subjectively experienced as one's own. Seventeen patients (11 with, 6 without the delusion), and 10 healthy controls were administered a nociceptive stimulation protocol to assess pain perception. In the OWN condition, participants placed their arms on a table in front of them. In the ALIEN condition, the co-experimenter's left (or right) arm was placed alongside the participants' left (or right) arm, respectively. In the OWN condition, left (or right) participants' hand dorsum were stimulated. In the ALIEN condition, left (or right) co-experimenter's hand dorsum was stimulated. Participants had to rate the perceived pain on a 0–5 Likert scale (0 = no pain, 5 = maximal imaginable pain). Results showed that healthy controls and patients without delusion gave scores higher than zero only when their own hands were stimulated. On the contrary, patients with delusion gave scores higher than zero both when their own hands (left or right) were stimulated and when the co-experimenter's left hand was stimulated. Our results show that in pathological conditions, a body part of another person can become so deeply embedded in one's own somatosensory representation to effect the subjective feeling of pain. More in general, our findings are in line with a growing number of evidence emphasizing the role of the special and unique perceptual status of body ownership in giving rise to the phenomenological experience of pain.

Keywords: body ownership, disownership, pain, brain-damaged patients, body awareness

INTRODUCTION

Pain perception is at the root of animal life and is vital to survival. Being able to perceive pain protects us by triggering a reflexive withdrawal from potentially dangerous stimuli before we can suffer further injury, it tells us that an injury is about to occur, it lets us know when we need to seek medical help, and teaches us what behaviors to avoid in the future.

Given such a higher evolutionary significance of pain perception, one would be keen to consider it an all-or-none phenomenon or, at least, tightly regulated by the input features (e.g., stimulus modality, intensity, duration, etc.). However, the current evidence on pain perception tells us a different story. The neural encoding of internal or external events that injures, or threatens to injure, our body is known as nociception. Nociceptors (i.e., pain receptors) detect when thermal, chemical, and mechanical stimuli are above a threshold. Then, the information is sent through the spinal cord and the brainstem up to the cortex. Nociception automatically triggers a variety of autonomic responses (e.g., hypertension, tachycardia, and fainting). Nonetheless, it can also generate an emotional and unpleasant subjective experience related to the stimulation known as pain perception.

It is known that the relationship between noxious stimuli (input) and its pain perception (output) is usually non-linear. Along the route from nociception to pain, several psychological, and/or cognitive factors modulate the physiology of pain before it becomes part of our consciousness. It is known, for instance, that pain perception can be ameliorated by the context as demonstrated by the fact that soldiers suffering from compound fractures during battles can report only twinges of pain (Horstman and Flax, 1999). The same has been reported with respect to the focus of attention: noxious stimuli are perceived less intense when people are distracted by other potentially relevant stimuli (Terkelsen et al., 2004). In addition, expectations have a crucial role, as shown by the fact that healing expectations can enhance the placebo effect (Turner et al., 1994). In some cases, a person can even experience pain without nociception. Amputees, for instance, can experience phantom pain that is painful perception referred to the absent limb (Ramachandran and Hirstein, 1998).

Due to its complexity, pain perception does not rely on the activity of a single brain structure but, rather, on a large distributed cortical/subcortical network known as pain matrix (see, for instance, Iannetti and Mouraux, 2010). According to the projections sites from either the medial or the lateral thalamic structures to the cortex, this system can be broadly subdivided in two subcomponents a "medial pain system" that processes the emotional aspects (e.g., unpleasantness) and a "lateral pain system" that subserves intensity, location, and duration (Albe-Fessard et al., 1985). The first system includes amygdala, anterior cingulate cortex, hippocampus, hypothalamus, locus coeruleus, and periaqueductal gray matter, whereas the second involves primary and secondary somatosensory cortex, parietal operculum, and insula. However, the crucial problem is that the extent to which this activity represents, or even correlates, with pain perception is unclear since those brain responses can be generated in non-nociceptive conditions (e.g., Craig et al., 1996).

Another interesting point related to pain perception is its connection with body ownership, which is the conscious experience that bodily states are so clearly and inexorably "mine" (Gallagher, 2000). Experiencing the body as one's own is a prerequisite for almost every cognitive function, it is intimately related to human's self-consciousness, and it shapes individual psychological identity. Indeed, our body constantly receives flows of inputs (i.e., touch, vision, proprioception, and interception). Notwithstanding, in order to be considered as potentially noxious (i.e., relevant) stimuli, these inputs must be invariably perceived as parts of one's own body and as unique to oneself. Put in another way, human's experience of pain is strictly dependent from the way we represent the body itself and from the sense that it is *my* body that is undergoing a certain experience (i.e., body ownership).

A first hint with respect to the relationship between body ownership and pain is the feeling of "foreignness" toward the affected body part often observed in patients affected by regional pain syndrome (Bultitude and Rafal, 2010). Perhaps, the more compelling evidence of the tight link between body ownership and pain has been obtained in healthy participants by means of an experimental manipulation in which the physical constraints subserving body ownership are altered. Such a paradigm, known as the "rubber hand illusion" (Botvinick and Cohen, 1998), shows that synchronous touches onto a visible rubber hand and onto the hidden participants' hand produce the compelling feeling of ownership of that hand (e.g., Botvinick and Cohen, 1998; Farnè et al., 2000; Ehrsson et al., 2004; Tsakiris and Haggard, 2005; Costantini and Haggard, 2007; Longo et al., 2008). This is demonstrated both subjectively (i.e., by a self-report questionnaire) and behaviorally (i.e., the location of one's own hand is shifted toward the rubber hand).

Crucially, recent studies (Capelari et al., 2009; Mohan et al., 2012) showed that the rubber hand illusion arises also with synchronous tactile noxious stimuli (but, see also Valenzuela-Moguillansky et al., 2011) and the effects do not differ from those obtained with non-noxious tactile stimuli (Capelari et al., 2009). These experiments suggest that pain can be referred to the rubber hand as long as it is being perceived as part of one's own body (Capelari et al., 2009; Mohan et al., 2012). More in general, they indicate that the neurocognitive mechanisms involved in localizing touch during the illusion might be, at least in part, similar to those required to localize pain. This is an important point since it is often assumed that touch can be referred to external objects (e.g., tips of tools; Iriki et al., 1996), whereas pain cannot.

The effect observed during the rubber hand illusion implies that whenever we feel an external body part as part of our's own body, noxious, exactly as non-noxious, stimuli can be potentially referred to it. During the illusion, painful perception is reported to arise from the rubber hand while one's own hand is actually receiving the stimulation. In the present paper, we asked a further question that is whether an altered feeling of body ownership can affect painful perception to a degree that it is possible to experience the pain delivered to an alien hand without any simultaneous stimulation on one's own hand.

We aimed at answer this question within a neuropsychological approach. Indeed, patients' counterintuitive behavior can potentially unmask the inadequacies of theories on human brain functioning hidden from the view in the intact brain (see Churchland, 1986 for a discussion on this point). In the present context, studying the abnormalities of the integration among the different components of body ownership due to brain damages has a key role in addressing questions regarding the structure and functional signature of body consciousness. Here, we focused on a subgroup of right brain-damaged patients affected by a selective disturbance of body ownership, which is they misattribute another person's arm to themselves (Garbarini et al., 2013). Specifically, when both their own and the co-experimenter's left arms were visible, they tended to claim that the latter belonged to them. Moreover, these patients treated and cared the co-experimenter's left arm as their own's one even if provided with contrary evidence coming from different sensory modalities. Hence, we compared patients with such a delusion with participants who did not have this experience (i.e., right brain-damaged patients without the delusion and healthy subjects). The task required participants to rate the perceived pain evoked by nociceptive stimulators administered under different conditions (i.e., stimulation of both the participant and the co-experimenter's hands). If conscious experience of owning an alien arm is the result of a profound embodiment of the alien arm into the participant's sensory-motor circuits, it should produce a pain perception when stimuli are applied onto the co-experimenter's left hand only in patients affected by the delusion.

MATERIALS AND METHODS

BASELINE ASSESSMENT

Seventeen consecutive right-handed patients (five women; mean age 65.93 years, SD = 12.89 years; mean educational level 9.43 years, SD = 5.31 years) with right hemisphere lesion and 10 age and educational level-matched right-handed healthy subjects participated in the study after having given written informed consent according to the declaration of Helsinki. Patients' demographic, clinical, and neuropsychological data are reported in **Table 1**. Patients were admitted to a rehabilitation center for the treatment of their neurocognitive deficits and none of them had a history of substance abuse or previous neurological diseases. All suffered from a single right hemisphere lesion confirmed by CT or MRI scans. Lesions involved several cortical/subcortical structures, as well as white matter, within fronto-temporo-parietal

Table 1 | Demographic and clinical data of patients.

Id	G	S	A	S	E	D	NE			A		MMSE	Neglect			Som	Aso	Mis			
							V	M	S	M	S		EP		P			Arm		Arms	
													BIT-C	BIT-B	Fluff			Pt	Co-ex	Pt	Co-ex
1	E+	F	72	5	I	60	0–0	3–3	3–3	0–0	2–2	28	66	60	0	N	N	100	100	0	100
2	E+	F	50	18	I	40	0–0	3–3	3–3	0–0	2–2	29	139	79	0	N	N	100	100	50	50
3	E+	M	78	8	I	60	0–0	0–0	3–3	0–0	2–2	29	50	42	0	N	N	100	100	0	100
4	E+	M	82	8	I	45	0–0	3–3	2–2	0–0	2–2	27	89	46	0	N	N	100	100	0	100
5	E+	F	75	5	I	40	0–0	3–3	2–2	2–2	2–2	28	90	59	0	N	N	100	100	0	100
6	E+	M	68	5	I	70	1–1	3–3	3–3	0–0	2–2	25	14	1	3	N	N	100	100	0	100
7	E+	M	64	17	I	50	1–1	3–3	3–3	0–0	2–2	25	135	40	2	N	N	100	100	0	100
8	E+	F	77	17	H	35	0–0	3–3	3–3	0–0	0–0	28	140	73	0	N	N	100	100	0	100
9	E+	M	55	5	I	30	0–0	3–3	2–2	0–0	0–0	18	17	8	3	Y	N	100	100	0	100
10	E+	M	69	8	I	30	0–0	3–3	0–0	0–0	0–0	27	138	75	0	N	N	100	100	0	100
11	E+	M	64	17	I	50	1–1	3–3	0–0	0–0	0–0	25	140	70	0	N	N	100	100	0	100
12	E−	M	64	5	I	40	0–0	3–3	2–2	0–0	2–2	26	141	76	0	N	N	100	0	100	0
13	E−	M	65	8	I	50	0–0	3–3	3–3	0–0	2–2	28	100	56	0	N	N	100	0	100	0
14	E−	F	37	18	I	50	0–0	3–3	3–3	0–0	0–0	30	91	53	0	N	N	100	0	100	0
15	E−	M	68	8	I	30	0–0	3–3	0–0	0–0	0–0	30	131	79	1	N	N	100	0	100	0
16	E−	M	83	3	I	30	0–0	3–3	0–0	0–0	0–0	25	145	81	0	N	N	100	0	100	0
17	E−	M	48	13	I	101	0–0	3–3	0–0	0–0	0–0	30	144	82	0	N	N	100	0	100	0

Id, patient's code; G, group: presence (E+) or absence (E−) of embodiment of the co-experimenter's arm (see misattribution column); S, sex; M, male; F, female; A, age; S, schooling: years of formal education; E, etiology; H, hemorrhage; I, ischemia; D, duration of the disease: number of days (d) between the onset of the disease and the first assessment; NE, neurological examination: contralesional motor (M), somatosensory (noxious and non-noxious stimuli; S), and visual half-field (V) neurological deficits (the two values refer to the upper and lower limb/visual quadrants, respectively); scores ranged from normal (0) to severe defects (3). A, anosognosia: unawareness of the motor (M), somatosensory (S), neurological deficits (the two values refer to the upper and lower limbs respectively); for the motor deficits, scores ranged from normal (0) to severe defects (3), whereas for the somatosensory deficits, scores ranged from normal (0) to severe defects (2). MMSE, mini mental state examination: cut off 24. Neglect: EP, extrapersonal; BIT-C, Behavioral Inattention Test – Conventional subtest, cut off 129; BIT-B, Behavioral Inattention Test – Behavioral subtest, cut off 67); P, personal; FLUFF test, cut off 2). Som, somatoparaphrenia: Y, yes; No, no; Aso, verbal asomatognosia: Y, yes; N, no; Mis, misattribution: one (arm) or two (arms) are present; Pt, patient; Co-ex, co-experimenter; numbers represent the % of times in which patient reaches that arm (eight trials).

regions. Patients were initially screened with the mini mental state examination (Measso et al., 1993) to exclude the presence of severe cognitive impairments. Contralesional somatosensory, motor, visual field defects as well as unawareness for motor and somatosensory deficits were assessed according to the a standard neurological exam (see Pia et al., 2013 for details). It is worth noticing that somatosensory defects were assessed with both tactile and noxious (pinprick stimulators) stimuli. No dissociation was found between presence/absence of the defects, as well as unawareness of them. In other words, administering non-noxious or noxious stimuli did not make any difference. The presence of left extrapersonal neglect was assessed with the behavioral and conventional scales of the Behavioral Inattention Test (Wilson et al., 1987), and left personal neglect with the Fluff test (Cocchini et al., 2001). Patients were also evaluated for somatoparaphrenia (Fotopoulou et al., 2011) and verbal asomatognosia (Feinberg et al., 1990).

The misattribution of the co-experimenter arm was assessed in the following way: patients were requested to lie their arms on a table. A same-gender co-experimenter's left (**Figure 1C**) or right (**Figure 1B**) arm was positioned on the same table, aligned with the patients' trunk midline and internal with respect to the patients' left (**Figure 1C**) or right (**Figure 1B**) arm. In one condition (**Figure 1B**), patients were asked to reach (eight trials) with their right, intact hand their own left hand and to name the color (eight trials) of the object positioned in front of their own left hand (in fact, three objects of different colors were placed in front of the own left and right hand, and the co-experimenter's left hand). In another condition (**Figure 1C**), patients were asked to name the color (eight trials) of the object positioned in front of their own right hand. Respect to the right, all patients indicated (100%) the color of the object in front of their own hand. As regards the left, 11 patients consistently reached (90%) the co-experimenter's hand (and named the color of the objects in front of the co-experimenter's hand; hereinafter E+ group), whereas six reached (100%) their own hand (and named the color of the objects in front of their own hand; hereinafter E− group). It is worth noticing that patients correctly reached and (or) named their own hands when only their own arms were lying on the table (**Figure 1A**).

EXPERIMENTAL TASK

Each participant sat in front of a table desk and a same-gender co-experimenter sat behind her/him. In the OWN condition,

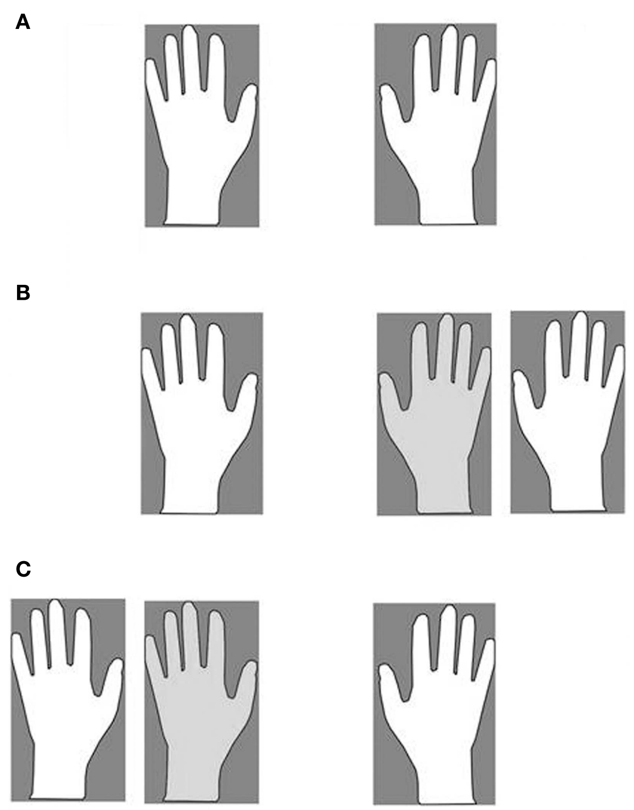

FIGURE 1 | The four experimental conditions. Own **(A)** and Alien **(B,C)**. Participant's hands (white), co-experimenter's hand (light gray).

participants simply laid down their arms on the table (**Figure 1A**). In ALIEN conditions, the co-experimenter placed his/her left (or right) arm, on the table (by passing under the patient's armpit), aligned with the participant trunk midline and positioned internally with respect to the participant's left (or right) arm, respectively (**Figures 1B,C**). Hence, in the ALIEN condition, the co-experimenter's hand was placed exactly where it was the participant's hand in the OWN condition. A white sheet was draped over patient's trunk, and arranged in order to prevent the direct vision of any body parts except hands. Noxious stimuli were administered by means of a homemade nociceptive stimulator with a cylindrical body in aluminum (length 20 cm, diameter 0.7 cm) and a retractable sharp tip in stainless steel able to apply fixed stimulus intensities (the exerted forces was about 500 mN). In the OWN condition, five stimuli for each participant's hand dorsum were administered while in the ALIEN condition, the five stimuli were administered to each co-experimenter's hand dorsum. The sequence was repeated twice (ABCD–DCBA order) and counterbalanced across participants. The total number of stimuli was forty. After each stimulation, participants were asked to rate the pain feelings evoked by the pinprick stimulators on a verbal rating scale (with 0 indicating "no pain," and 5 indicating "maximal imaginable pain"). In order to control the effects of sensitization or fatigue, successive stimuli were applied in different spot of skin (some millimeters away). The mean ratings were employed to perform statistical analysis between and within groups.

RESULTS

A repeated measures ANOVA on the mean score with OWNER (two levels: participant, co-experimenter) and HAND (left, right) as within-subjects factor, and GROUP (three levels: E+, E−, C) as between-subjects factor was performed (see **Figure 2**).

The main factor OWNER resulted to be significant [$F(1,24) = 236.34$, $p < 0.00001$)], namely participants gave a higher score when the stimulation was given on their own hands (mean = 3.579, SE = 0.201) respect to when it was administered to the co-experimenter's hands (mean = 0.47, SE = 0.103). Also the OWNER × GROUP interaction was significant [$F(2,24) = 15.26$, $p < 0.0001$)], with the score given by the E+ group when the co-experimenter's hands were stimulated (mean = 1.409, SE = 0.156) significantly (Duncan *post hoc* test $p < 0.0001$) higher respect to both E− (mean = 0, SE = 0) and C (mean = 0, SE = 0) groups. Crucially, the OWNER × GROUP × HAND interaction was significant.

As regards the right hand, each group gave a significant (Duncan *post hoc* test $p < 0.00001$) higher score when the stimulation was given on the own right hand (E+: mean = 3.64, SE = 0.306; E−: 4.416, SE = 0.414; C: 4.15, SE = 0.321) with respect to the co-experimenter's right hand (E+: mean = 0.182, SE = 0.117; E−: 0, SE = 0; C: 0, SE = 0). Indeed, no significant between-groups differences were found either for the own right hand or for the co-experimenter's right hand (Duncan *post hoc* test $p > 0.05$).

As regards the left hand, both E− and C groups gave a significant (Duncan *post hoc* test $p < 0.0005$) higher score when the stimulation was given on their own left hand (E−: mean = 2.583, SE = 0.623; C: mean = 4.05, SE = 0.483) than on the co-experimenter's left hand (E−: mean = 0, SE = 0; C: mean = 0, SE = 0). One the contrary, the E+ group gave similar rating (Duncan *post hoc* test $p > 0.05$) when the stimulation was on the own left hand or on the co-experimenter's left hand (own: mean = 2.636, SE = 0.46; alien: 2.636 = 0.305). Therefore for the left hand, significant between-groups differences were found (Duncan *post hoc* test $p < 0.05$). It is worth noting that in both E+ and E− groups the scores given to the own left hand was somehow lower than those given by the C group when their own left hand was stimulated (see above). This difference was mainly due to the presence in both groups of four patients who, being hemianesthesia, but not anosognosic, gave very low score to the capacity of the contralesional hand to perceive pain. Interestingly, the two E+ patients also gave low score to the co-experimenter's, embodied, left hand.

DISCUSSION

With the present investigation, we aimed at examining the relationship between humans' body ownership and the subjective experience of pain. We tested right brain-damaged patients who were convinced that the examiner's left hand belonged to them. We asked whether (or not) such a (pathological) feeling of owning someone else's hand can trigger pain perception each time the alien hand is stimulated with noxious stimuli. We predicted that if the alien hand is so deeply embodied in patients' body representation,

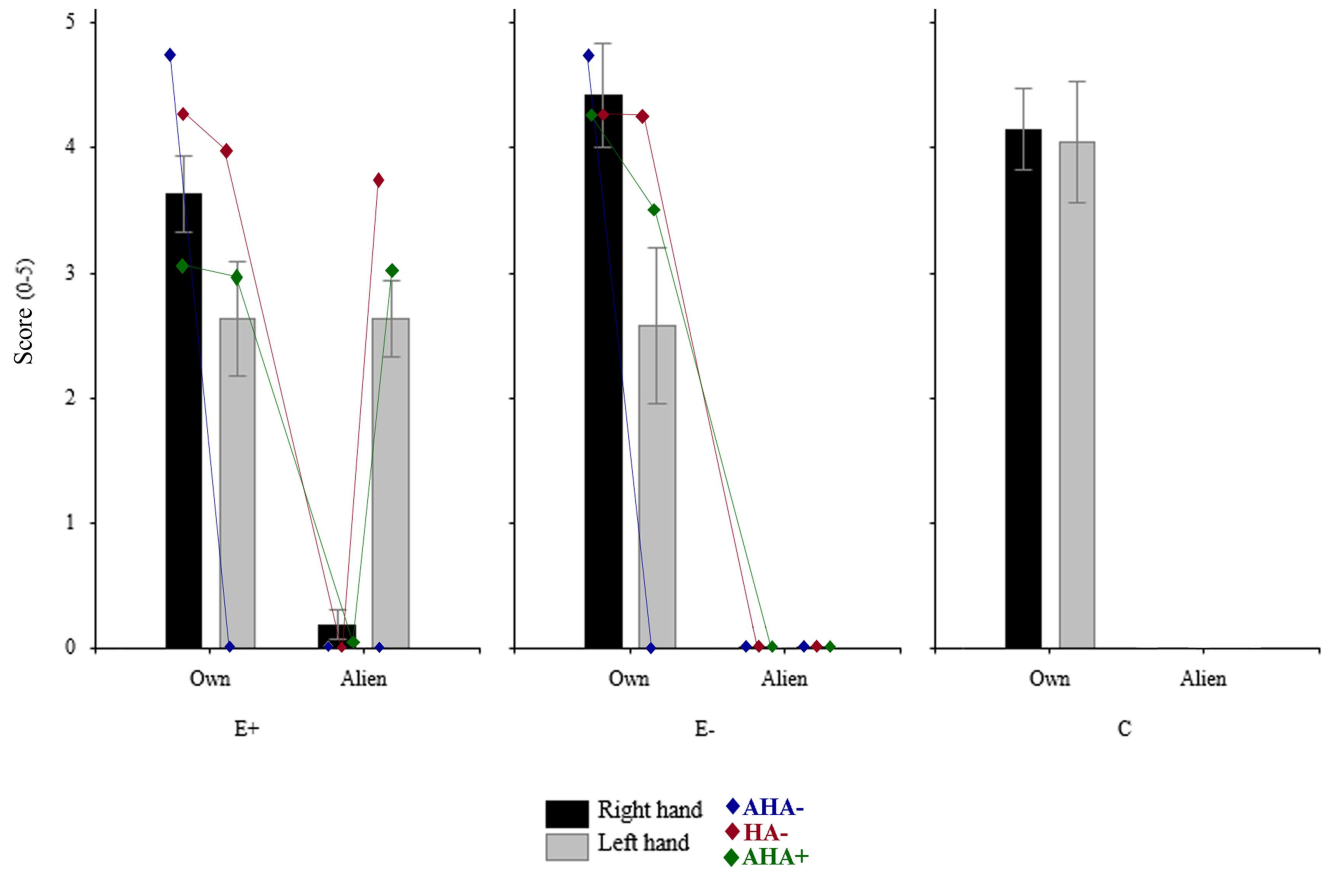

FIGURE 2 | Mean rating of the three groups (10 E+, 6 E–, and 10 C) in the four experimental conditions. Rating of each subgroups obtained taking into account sensory deficits, and awareness of them (i.e., AHA–, hemianesthesia without anosognosia; HA–, no loss; AHA+, anosognosia for hemianesthesia) are also plotted. *Significant ($p < 0.05$); n.s., not significant ($p > 0.05$).

noxious stimuli might be referred to the patients' body in absence of any concurrent stimulation of the own hand.

As expected, all participants correctly judged the delivering of noxious stimuli (i.e., gave scores significantly higher than zero) when their own right, but not the co-experimenter's right was stimulated (the score did not differ between groups). Similarly, healthy subjects and patients without delusion of ownership gave scores higher than zero only when the stimulation was administered to their own left hand. Most importantly, and according to our prediction, patients who misattributed the alien hand to their body gave scores higher than zero, not only when their own left hand was stimulated, but also when noxious stimuli were delivered to the co-experimenter's left hand. This result suggest that as long as an arm is subjectively perceived as part of one's own body, painful stimuli delivered to an alien hand are experienced as if given to the own hand. In order to understand this puzzling phenomenon, it is crucial to examine the possible mechanisms underlying the pathological embodiment of the alien hand. The embodiment *per se* cannot be ascribed to the presence of personal neglect (i.e., inattention to the left side of the body): beyond the fact that the neuropsychological baseline assessment revealed its presence in only three patients (#6, 7#, and #9), the assessment of misattribution of the co-experimenter's arm showed that E+ patients were perfectly able to reach their own left arm with their right (when the co-experimenter's left was not present). Therefore the presence of personal neglect does not seem necessary to cause the delusion. Much more interesting is the fact that the delusion emerged only under some specific constraints. Firstly, it appeared when the co-experimenter's left arm was placed parallel and internal, but not external, to the patient's left arm. It is worth noticing that when the delusion emerged, E+ patients "saw" both arms, their own and the co-experimenter's left, and often attributed their own to the co-experimenter (interestingly, these patients never displayed such a delusional beliefs about their own contralesional body part (Fotopoulou et al., 2011; Gandola et al., 2012), when only their own arms were lying on the table). Secondly, the delusion disappeared when the co-experimenter's left arm was 180° -oriented (independently from its horizontal position with respect to the patient's left arm). Finally, it disappeared also when the co-experimenter's left arm was replaced with a rubber glove (independently from its position or horizontal orientation with respect to the patient's left arm). We must emphasize that since we aimed at exclude a pure perceptual effect, the rubber glove was not realistic as in previous studies (Fotopoulou et al., 2008; Zeller et al., 2011) and participants clearly recognized it was non-human (see also below).

The interpretations of the rubber hand illusion effects on healthy participants may shed light on the above-mentioned constraints for the emergence of the delusion. There is a wide agreement in considering a bottom-up multisensory integration between vision and touch as a necessary condition for experiencing the illusion. However, for some authors (Armel and Ramachandran, 2003) this process is sufficient to generate the illusion. This, in turn, would predict the emergence of the illusion under a wide range of visual conditions as, for instance, when the rubber hand is in incongruent position with respect to the patient's body or even when it is replaced by a non-human object. On the contrary, other authors (Tsakiris and Haggard, 2005) suggested that multisensory integration is not sufficient for the illusion to emerge because the on-line sensation must be necessarily compared to pre-existing body representations. This, in turn, would predict that the emergence of the illusion is constrained by these pre-existing representations of the body as the congruence in terms of position and identity.

In the present study, the conditions for the emergence of the pathological delusion of ownership are in line with the latter above-mentioned hypothesis (constraints imposed by the internal body representations). It is interesting to note that, despite in E+ patients the brain-damage has altered the normal body ownership (i.e., pathological embodiment), spared pre-existing representations of the body imposed limits on the type representation and its configuration. Hence, the congruence of the alien hand in terms of position and identity is necessary in order to accept an external object as belonging to one's own body.

However, the fact that vision of someone else's hand was sufficient to immediately produce the delusion differs from the rubber hand illusion in which repeated simultaneous stimulation of the fake and real hand is necessary for the illusion to emerge. It is interesting to note that a delusion of ownership due to the interaction between internal representations of the body with bottom-up unimodal (visual) stimuli has been reported also in healthy subjects (Slater et al., 2010). The authors showed that a first person perspective of a life-sized virtual human body that appears to substitute the participant's own body was sufficient to generate a body transfer illusion. In other words, the authors demonstrated a delusion of ownership (i.e., a full body illusion) entirely due to visual capture mechanisms (i.e., without simultaneous synchronous tactile stimulations). Interestingly, first person perspective and level of skin realism were necessary in order the experience the illusion. This is in line with the fact that here the delusion disappeared when the co-experimenter's left arm was 180° -oriented or with the rubber glove.

The second point we should discuss is why E+ patients reported pain feelings when noxious stimuli were delivered to the embodied arm. Some interesting hints come from examining the presence or absence of noxious/non-noxious deficits and awareness of noxious/non-noxious deficits in our sample of patients. Although unawareness of sensory deficits (AHA+ in **Figure 2**) seems to be more frequent in E+ (7 out of 11) than in E− (2 out of 6) patients, AHA+ seems to be not sufficient to explain the misattribution of painful perception. Indeed, the two AHA+ patients of the E− group did not experience pain when the left alien hand was stimulated. This seems to suggest that the subjective feeling of pain might be somehow related to an *a priori* embodiment of the alien hand. More importantly, E+ patients who acknowledged the sensory deficit on their own hand (AHA− in **Figure 2**) did not experience noxious stimuli on the left alien hand, coherently with their normal sensory awareness. This means that the alien embodied hand is subject to the similar sensory properties as one's own hand. This is in line with the fact that when patients normally feel sensation on their left hand (HA− in **Figure 2**) or report to feel sensation on their left anesthetic hand due to the unawareness for the deficit (AHA+), the subjective feeling of pain delivered to the left alien hand is observed only in E+ patients.

Nonetheless, the crucial aspect related to the subjective feeling of pain when the co-experimenter's hand is stimulated is the fact that stimuli must be seen. This is not trivial but, rather, consistent with the everyday experience that visual awareness of body parts can highly affects incoming tactile information. For instance, when an insect crawls on our skin, we do not experience any sensation if the stimulation is beyond the mechanical threshold. However, if we shift our sight toward the insect a vivid tactile experience can arise due to the interaction between localization and tactile noise. Other less anecdotic findings supports this idea. For example, right brain damages patients with partial sensory loss can report improved tactile sensation when they see the affected hand being touched (Halligan et al., 1997; Rorden et al., 1999). Moreover, in phantom limb patients, phantom pain can be ameliorated by superimposing the unaffected limb on the amputated one in a mirror (Ramachandran and Rogers-Ramachandran, 1996; MacLachlan et al., 2003) or by controlling a limb in virtual reality (Murray et al., 2007; Cole et al., 2009; Sato et al., 2010). Similarly, during the rubber hand illusion, potentially harmful or noxious stimuli approaching the rubber hand elicits the same brain activity (Ehrsson et al., 2007) and skin conductance response (Armel and Ramachandran, 2003) as when the healthy participant's real hand is stimulated.

Tactile awareness, however, can be consciously reported even in situation in which the physical counterpart is absent (i.e., visual capture of touch). For instance, simply stroking a fake hand with a laser light can produce illusory thermal or tactile sensations in one's own arm (Durgin et al., 2007). Similarly, in synesthetic individuals (i.e., people who experience a sensation in one modality when the stimulation is delivered in another sensory modality), the observation of another person being touched can be experienced as tactile stimulation on the equivalent part of one's own body (Blakemore et al., 2005). Visual capture of touch has been interpreted in terms of a strong preference of the human's brain to operate, in normal circumstances, under the principle of multisensory integration. This means that if input has a high certainty in one sensory modality, it can induce perceptual consequences in a different modality (Driver and Spence, 2000).

On this basis, it is possible to suggest that when E+ patients "saw" noxious stimuli delivered to a body parts that they subjectively perceive as own, they report painful feelings (as if stimuli were delivered to their own body). Note that the misattribution is not aspecific so to make them to experience all sort of stimuli delivered to whatsoever body part in the environment. On the contrary, it is circumscribed to the embodied alien arm and, as such, strictly related to the altered body representation. It is interesting to note that in our patients such a visual capture of touch might be independent from the ability to potentially perceive stimuli. Indeed, the two E+ patients with no sensory loss (HA−), attributed pain perception to the co-experimenter's left hand despite they were able to feel tactile sensation on his/her left hand. In other words, being or not being able to feel does not affect the subjective feeling when the embodiment mechanism has induced the pathological body part attribution. Interestingly, the effect differed from the one reported during the rubber hand illusion (Capelari et al., 2009; Mohan et al., 2012) since here an altered feeling of body ownership can affect somatic sensation to a degree that it is possible to experience pain delivered to an alien hand in absence of any simultaneous stimulation of the own hand (in the rubber hand illusion the sensation is referred to the rubber hand while the own hand is receiving the stimulation). So far, only one study has reported similar findings (Aimola Davies and White, 2013). The authors administered a no-touch version of the rubber hand illusion (stimulation of the viewed prosthetic hand but no-touch of the participant's hidden hand) to individuals with vision-touch synesthesia and healthy controls. Only synesthetics experienced the rubber hand illusion: the tactile sensation on their hand was referred to the prosthetic hand and their own hand resulted shifted toward the prosthetic hand.

The third point we should address is the possible neural basis of the delusion and of the illusory painful perception. It is crucial to emphasize that at the time of testing not all the MRI or CT scans were available and, hence, we were not able to map and analyze in depth the lesional pattern in the whole sample of patients. Nonetheless, an inspection of the existing scans suggested that putamen, dorsolateral prefrontal cortex, external capsule, parietal periventricular white matter and part of the insula might be more critically associated to the damages of the E+, rather than E−, group. Among the above-mentioned structures, some authors suggested that insular cortex might subserve pain processing (Coghill et al., 1994, 1999) and the subjective experience of one's body (Karnath et al., 2005; Tsakiris et al., 2007). Nonetheless, damages to putamen and dorsolateral prefrontal cortex have been suggested to be crucial for the emergence of in such a delusion of ownership (Garbarini et al., 2013). Hence, these conclusions should be considered highly speculative and exhaustive anatomical analyses are needed.

The present data are in line with a study recently published by our group (Garbarini et al., 2013). In that paper, we demonstrated that the pathological embodiment of an alien hand can have objective consequences on the motor behavior of the intact hand. Indeed, in a bimanual task where subjects had to draw lines with the right hand and circles with the left, we found an ovalization of the lines when E+ patients observed an alien left hand drawing circles (the effect was similar to the one observed when healthy participants actually perform the task). It is interesting to note that, consistently with the above-mentioned constraints for the emergence of the delusion of ownership in E+ patients, coupling disappeared when the alien hand was arm was 180° -oriented. This effects indicate that the altered body ownership affects both motor awareness (despite usually aware of not being able to move, E+ patients, were convinced that their left hand was moving) and sense of agency (E+ patients ascribed the alien movements to themselves) by directly modulating action execution. These data suggested that the embodiment of someone else's arm body can affect also internal motor programs.

Summarizing, we showed that the pathological delusion of owning an alien arm triggers pain perception when the alien hand is stimulated. We suggest that brain damages might have led these patients to assign ownership and visual (noxious) stimuli to an alien hand. Pre-existing (spared) models of the body distinguished between objects that may (or may not) be part of one's own body on the basis of constraints (e.g., first person perspective, position with respect to the patient's trunk midline, skin realism). In these conditions, if a noxious stimulus touches what is felt as looks like their own arm, this will be painful.

We must acknowledge a limit of the present investigation: we do not have any direct electrophysiological or neuroimaging data showing the activation of patients' sensory processes. Hence, further studies are needed to answer this question. However, the phenomenon observed in E+ patients seems more likely to be explained in term of "perceiving" the stimulus rather than simply "reporting" what the patient see. Indeed, E+ patients aware that they could not feel any tactile stimulation on their own left hand (hemianesthesia without anosognosia), rated 0 noxious stimuli when both their own left and the co-experimenter's (embodied) left hand was stimulated, whereas rated significantly higher than 0 noxious stimuli delivered to their own right hand. This means, at least, that the phenomenon is linked to sensory functions.

To conclude, further studies are needed to clarify the anatomo-physiological mechanisms responsible for both pathological attribution of other's body part and the subjective experience of pain. Nonetheless, what clearly emerges from our data is that pain perception is not an all-or-none phenomenon, simply related to the direct bottom-up stimulation of nociceptors, but is intimately connected to the experience of body ownership that, in a top-down manner, may modulate self-consciousness and even personal identity (Merleau-Ponty, 1962; Edelman, 2004).

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Sensorimotor incongruence and body perception: an experimental investigation

Jens Foell [1,2] ****, Robin Bekrater-Bodmann*** [1]***, Candida S. McCabe*** [3,4] ***and Herta Flor*** [1] *******

[1] *Department of Cognitive and Clinical Neuroscience, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany*
[2] *Department of Psychology, Florida State University, Tallahassee, FL, USA*
[3] *University of the West of England, Bristol, UK*
[4] *Royal National Hospital for Rheumatic Diseases, Bath, UK*

Edited by:
Camila Valenzuela Moguillansky, University Pierre et Marie Curie, France

Reviewed by:
Alessandro Farne, INSERM, France
Matthew R. Longo, Birkbeck University of London, UK

****Correspondence:***
Jens Foell, Department of Psychology, Florida State University, 1107 West Call Street, Tallahassee, FL 32301, USA
e-mail: foell@psy.fsu.edu;
Herta Flor, Department of Cognitive and Clinical Neuroscience, Central Institute of Mental Health, Medical Faculty Mannheim, University of Heidelberg, Square J5, 68159 Mannheim, Germany
e-mail: herta.flor@zi-mannheim.de

Objectives: Several studies have shown that mirrored arm or leg movements can induce altered body sensations. This includes the alleviation of chronic pain using congruent mirror feedback and the induction of abnormal sensation in healthy participants using incongruent mirror feedback. Prior research has identified neuronal and conceptual mechanisms of these phenomena. With the rising application of behavior-based methods for pain relief, a structured investigation of these reported effects seems necessary.

Methods: We investigated a mirror setup that included congruent and incongruent hand and arm movements in 113 healthy participants and assessed the occurrence and intensity of unusual physical experiences such as pain, the sensation of missing or additional limbs, or changes in weight or temperature. A wooden surface instead of a mirror condition served as control.

Results: As reported earlier, mirrored movements led to a variety of subjective reactions in both the congruent and incongruent movement condition, with the sensation of possessing a third limb being significantly more intense and frequent in the incongruent mirror condition. Reports of illusory pain were not more frequent during mirrored than during non-mirrored movements.

Conclusion: These results suggest that, while all mirrored hand movements induce abnormal body perceptions, the experience of an extra limb is most pronounced in the incongruent mirror movement condition. The frequent sensation of having a third arm may be related to brain processes designed to integrate input from several senses in a meaningful manner. Painful sensations are not more frequent or intense when a mirror is present.

Keywords: pain, somatosensory system, sensory-motor incongruence, illusion, body representation, mirror

INTRODUCTION

In order to produce and control complex and precise body movements, the brain constantly processes and integrates input from several senses, such as the visual and sensorimotor domains. This is a rather complex task which can be disturbed by deliberately giving contradictory information to two or more senses. The reactions to such disturbances are diverse and might have important clinical implications. The critical interaction between motor movements and the central nervous system is based on von Holst and Mittelstaedt (1950), who postulated that every motor command (i.e., efference) is processed using a specific expectation of its effect (i.e., the efference copy). Incongruent feedback between the motor system and vision constitutes a mismatch between the expected and factual response of the motor action. On a neural level, such a conflict between the senses seems to be monitored by the dorsolateral and ventral prefrontal cortices (Fink et al., 1999), both of which have been shown to also modulate pain processing in humans (Ploghaus et al., 1999; Lorenz et al., 2003). Consequently, Harris (1999) proposed a model which states that such discordance between motor intent and its sensory feedback is able to elicit pain as a warning mechanism. If correct, this model may explain certain pain phenomena that occur in the absence of physical painful stimuli, such as phantom limb pain (PLP).

McCabe et al. (2005) examined the potential of mirrored movements and obscured visual feedback to cause unusual sensations, including pain. In their paradigm, one limb was hidden by either a non-reflective whiteboard or mirror. In the latter scenario, the reflection of the observed limb seemingly replaced the hidden limb. This setup enabled observation of the impact on an individual of a graded manipulation of conflict between proprioception, vision, and motor intention. The four intervention stages included two movement conditions without visual feedback (viewing a whiteboard with congruent and incongruent movements); accurate visual feedback of the moving limb but with minimal distortion/distancing via a mirror (congruent movements whilst viewing the mirror); and finally, incorrect visual feedback of the moving limb (incongruent movement whilst viewing the mirror).

Imaging studies using magnetoencephalography have shown that visual information plays a key role in activation of somatosensory areas during movement related tasks with increased activation of the secondary somatosensory cortex and parietal cortex when unexpected visual feedback is received (Wasaka and Kakigi, 2012). Subjects' "vulnerability" to a sensorimotor mismatch was determined by the sum of the number of conditions which generated novel sensory perceptions, that is the most "vulnerable" reported new sensations in all four intervention conditions. Using this paradigm, McCabe et al. (2005) reported that 66% of participants described a new sensory response at some stage in the protocol with the highest incidence of report in the incongruent mirror condition (59%). This pattern of response was also seen for pain reports with slight pain (<2/10 on a visual analog scale) described at each stage but the maximum incidence in the incongruent mirror condition [$n = 6$ (15%)].

They used this finding to establish a cortical model of pain, in which the predicted sensory feedback (i.e., the efference copy) is compared with the actual sensory feedback. If the comparison results in a discrepancy, the mechanism induces pain or other sensory anomalies as a sign of distress, similar to the induction of nausea during a discordance of the visual and the vestibular sensory systems (Della-Morte and Rundek, 2012). Due to its clinical importance, the study by McCabe et al. (2005) aroused strong interest in the field of experimental pain research. In their comment published shortly afterward, Moseley and Gandevia (2005) challenged the far-reaching conclusions by McCabe et al. (2005) with reference to sample selection and potential induction of a response bias, although these criticisms were defended by McCabe et al. (2006). In another study, conflicting proprioceptive input has been shown to evoke several alterations in bodily sensation, but not pain (Moseley et al., 2006). However, this study explicitly excluded the visual domain, so it is unclear how these results relate to those reported by McCabe et al. (2005). Clinically, Daenen et al. (2010, 2012) used sensorimotor incongruence to evaluate the alterations in sensory integration in whiplash-associated disorders and regional pain syndrome and found an exacerbation of symptoms. Also, McCabe et al. (2007) reported increasing baseline pain and induced new sensory perceptions in patients suffering from fibromyalgia through the induction of a visuoproprioceptive conflict.

The study presented here aimed at providing additional clarification to the important initial findings of sensory changes in general and pain in particular, induced by a conflict between motor intention and visual feedback. We assessed quantitative in addition to qualitative data in a large sample of healthy participants and controlled response biases. Furthermore, we implemented additional conditions reducing the exertion of performing arm movements in order to evaluate the evoked sensory alterations without their potential blurring by physical fatigue. As we describe later, we specifically focused on an underreported phenomenon induced by sensorimotor incongruence: the alteration of perceived body integrity.

MATERIALS AND METHODS

PARTICIPANTS

We investigated 113 subjects (74 female, 39 male, age range from 18 to 32, mean age 23.69, SD 2.92 years) with no current or past mental or physical illness and without any visible physical disfigurements, tattoos, or other markings on their hand and arms. All participants had normal or corrected-to-normal vision. The subject pool consisted mostly of University students from Mannheim, Heidelberg, and the surrounding region. All were informed about the movement tasks they would be expected to perform, but were held naïve with regard to the nature and purpose of the study and especially about the expected sensations during the mirrored movement task. All subjects were right-handed, as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). Self-reports about medical history, current medical conditions, and current medication or substance use, as well as any other conditions that might cause impaired visual, tactile, or proprioceptive processing (e.g., muscle fatigue from sports) were assessed using a standardized interview. Persons reporting any such conditions were excluded. Written informed consent was obtained prior to the study, which was approved by the Ethics Committee of the Medical Faculty Mannheim of the University of Heidelberg. The study conformed to the Code of Ethics of the World Medical Association (Declaration of Helsinki, sixth revision, 2008).

TASKS

Before the experiment, participants were asked to remove any jewelry, watches, or asymmetric articles of clothing which might have helped them to identify a specific arm or hand as their left or right one. We used a specialized mirror construction with a large mirror surface (48 × 59 cm) on one side and a white, non-reflecting wooden control surface on the other side (see **Figure 1**). Its frame was symmetrical and allowed for the whole device to be turned around easily. While there was no condition without mirror or whiteboard (i.e., a condition with an unobstructed view of the opposing limb), and while the introduction of a wooden wall may already have an influence on body perception, the whiteboard condition eliminates any form of visual feedback of the intended or performed movement and is therefore considered a control condition for the purposes of this study. The situations in the experimental condition and the control condition were, apart from the presence of the mirror surface, identical. The participants were seated in such a way that their arms, if stretched horizontally, were in the middle between the top and the bottom of the mirror surface. It was always the dominant right arm that was hidden from view by the mirror construction, the non-dominant arm was always in full view. The reverse condition was not employed. The movement tasks were demonstrated and explained to the participants. One condition was a hand movement task identical to the movements commonly used in the mirror training for PLP (Ramachandran and Rogers-Ramachandran, 1996; Diers et al., 2010): here, the participant was asked to bend his or her fingers in a way that mimics the opening and closing of a fist, yet without letting the fingers touch each other or the palm of the hand to avoid additional tactile sensations. While doing this, the participant's elbows were resting on the table and the hand was held in the middle between the top and bottom of the mirror surface. The movement was repeated for 20 s, at a frequency of 40 movements per minute, as guided by the sound of a metronome (13 movements). The other condition consisted of an arm movement similar to the one used by McCabe et al. (2005): the participants were asked to hold out their arms horizontally, palms downwards, and move them upwards and downwards, while taking care not

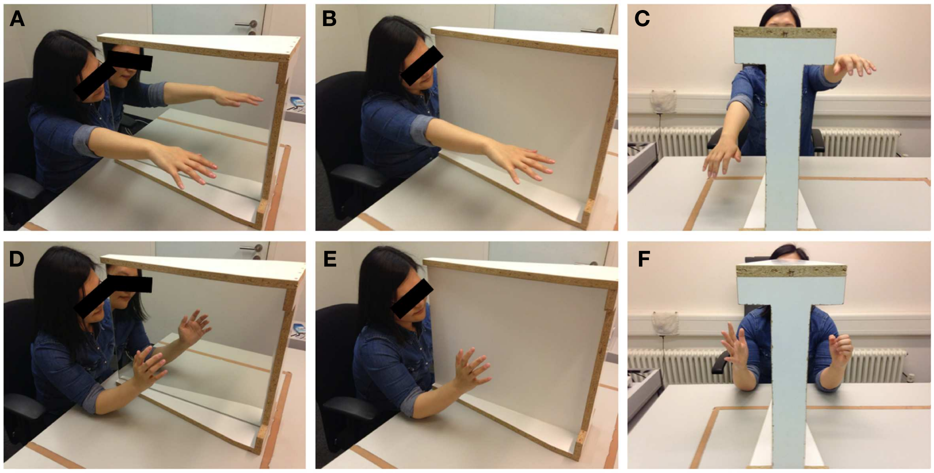

FIGURE 1 | Photographs of the experimental setup as used in the laboratory. The mirror/whiteboard instrument is placed between the arms of the participant. The photographs depict the mirror **(A,D)** and whiteboard **(B,E)** conditions as well as the range of incongruent movements **(C,F)** for the arm **(A–C)** and hand **(D–F)** conditions. Photographs taken by author Robin Bekrater-Bodmann.

to touch mirror or table. The duration and frequency of the movement were the same as in the hand condition. Regarding the initial arm position (elbow on the table for the hand condition, stretched arms for the arm condition), participants were allowed to adjust their arms in order to be as comfortable as possible, but were asked to keep in line with the standard positioning when the experimenters determined the adjustments to be too deviant.

After 20 s of movement, a verbal command was given to the participants: in the congruent condition, participants were asked to take a short break from the movement (approximately 1 s) and then continue the movement for 20 more seconds. In the arm condition, this break meant a return of the arms to a horizontal position before continuing the movement. In the hand condition, the break consisted of a relaxing of the fingers before continuing. This way, in the congruent condition, the participants performed congruent arm or hand movements for a total duration of 40 s.

The incongruent condition began the same way as the congruent condition, i.e., with 20 s of congruent movement. After this initial phase, participants were given a command to commence incongruent movements: in the arm condition, whenever one arm was held high, the other one was to be held low. In the hand condition, incongruence meant that one fist should be open while the other is closed. These motions, although they may be confusing at first, still needed to be performed fluidly. In order to ensure this, participants were informed about and demonstrated the required movements, and were told before each trial which command they had to expect. The sequence of these eight trials altogether (arms or hands, either in a congruent or incongruent manner, either in front of mirror or whiteboard) was randomized and all eight conditions were run once each for each participant. In all conditions and all phases, participants were instructed to direct their gaze to a horizontal black line that had been drawn across the middle of the surface (both on the mirror and on the whiteboard).

INTERVIEWS

As done earlier in McCabe et al. (2005), participants were asked two questions after each trial: "How did that feel?" and "Were you aware of any changes in either limb?", always in this sequence. In the study reported here, these questions were followed by 14 additional questions which were chosen according to the responses found by McCabe et al. (2005). These additional questions asked about sensory sensations such as pain, changes in temperature or weight, changes in the number of perceived limbs, etc., and were presented in randomized order. All questions are described in **Table 1**. The participants were asked to rate the intensity of those perceptions on a scale from 0 (not at all) to 10 (very strong). For each sensation, the participant had further to state in which body part he or she felt the sensation. According to McCabe et al. (2005) who found that the majority of induced sensations relate to the hidden limb, only somatosensory sensations attributed to the hidden right limb were included in further analyses.

STATISTICAL ANALYSIS

An omnibus χ^2 test of homogeneity for histograms was used to test for differences between the arm and hand conditions in the frequency of responses to the 14 items, regardless of intensity. The intensities of responses were compared across conditions for each item separately using Friedman's two-way analyses of variance; results are reported with a level of $p < 0.05$. Further *post hoc* analyses were only conducted for items which exhibited a significant difference between experimental and control conditions using Wilcoxon signed rank tests. When necessary, we applied Bonferroni correction for multiple comparisons and all given p-values have been adjusted accordingly.

RESULTS

FREQUENCY OF RESPONSES

Participants were asked to respond to each possible item. In the following section, the term "frequency" is used to indicate the

Table 1 | Interview questions.

Pain	Did you perceive any slight pain in either arm/hand during the experiment?
Itch	Did you perceive tickling or pins and needles in either arm/hand during the experiment?
Warmth	Did you feel your arm/hand getting warmer during the experiment?
Coldness	Did you feel your arm/hand getting colder during the experiment?
Lightness	Did you feel your arm/hand getting lighter during the experiment?
Heaviness	Did you feel your arm/hand getting heavier during the experiment?
Lost limb	Did you have the feeling of having less than two arms/hands during the experiment?
Extra limb	Did you have the feeling of having more than two arms/hands during the experiment?
Peculiarity	Did you perceive strange, not clearly identifiable sensations in either arm/hand during the experiment?
Pressure	Did you feel a change in pressure in either arm/hand during the experiment?
Shape	Did you perceive a change in length, circumference, or shape of either arm/hand during the experiment?
Numbness	Did you perceive numbness in either arm/hand during the experiment?
Nausea	Did you perceive nausea or dizziness during the experiment?
Other part	Did you perceive sensations in any other part of your body?

After each run, these questions were asked, in randomized order, with the reference to arm or hand changed according to the condition. Question names refer to the naming system used in the text and figure descriptions.

number of all responses other than "No," i.e., whenever the perception of the sensation was reported, regardless of its intensity. **Figure 2** shows the frequencies of the responses for all sensations compared between the experimental and control condition. In the experimental condition (mirror/incongruent), 2 participants (1.8%) reported pain in the arm condition and 1 (0.9%) in the hand condition. The feeling of additional limbs was reported by 38 (33.6%) participants in the experimental arm condition and 39 (34.5%) participants in the experimental hand condition.

The omnibus χ^2 tests did not reveal any significant differences between response frequencies in the arm and hand conditions (whiteboard incongruent: $\chi^2{}_{13} = 17.44$, $p = 0.72$; mirror incongruent: $\chi^2{}_{13} = 21.40$, $p = 0.28$; whiteboard congruent: $\chi^2{}_{13} = 20.86$, $p = 0.32$; mirror congruent: $\chi^2{}_{13} = 14.87$, $p = 1.00$). For this reason, we combined the arm and the hand conditions when looking for differences in sensation frequency between conditions.

A comparison of the conditions in this manner revealed a significant difference between the congruent and incongruent mirror condition (incongruent > congruent; $\chi^2{}_{13} = 34.38$, $p < 0.05$), but not between the congruent and incongruent whiteboard condition ($\chi^2{}_{13} = 4.40$, $p = 1.00$). Further comparisons revealed significant differences between the congruent mirror and congruent whiteboard condition (mirror > whiteboard; $\chi^2{}_{13} = 35.20$, $p < 0.05$) as well as the incongruent mirror and incongruent whiteboard condition (incongruent > congruent; $\chi^2{}_{13} = 75.40$, $p < 0.05$).

INTENSITY OF RESPONSES

Whenever a sensation was reported, participants were asked to determine its intensity, the values of which are analyzed in the following section. Due to the similarities of induced sensory alterations in the arm and hand conditions as indicated by the omnibus χ^2 tests mentioned above, we used the arithmetic mean of intensities derived from the combination of both conditions. The intensity of the reported sensations varied widely depending on the nature of the perception. **Figure 3** shows the reported intensities for all 14 sensations. By far the largest difference was visible for the feeling of supernumerary limbs: both in the arm and hand condition, this sensation showed the largest difference between the experimental and control conditions as well as the highest mean value of all responses in the experimental condition.

The comparison of the mean intensities of the 14 items across all conditions revealed a significant difference in only one of the items, which was the sensation of having an additional limb. For this item, the intensity was significantly higher in the experimental compared to all other conditions ($\chi^2{}_3 = 129.56$, $p < 0.001$; mirror incongruent: $M = 1.70$, SD = 2.39; mirror congruent: $M = 0.49$, SD = 1.30; whiteboard incongruent: $M = 0.02$, SD = 0.19; whiteboard congruent: $M = 0.00$, SD = 0.00).

DISCUSSION

The goal of this study was to investigate as rigorously as possible the subtle reactions to an incongruent mirror movement experience. This was done by using a threefold approach in terms of standardization and control: (a) the specific effects of incongruent visual feedback were set against congruent movement conditions with and without visual feedback, (b) all movements of the participants were highly standardized, including the direction of the participants' gaze, and (c) all responses were categorized to allow for statistical quantification. In addition, we used a large number of subjects in order to be able to document subtle or rare responses. This allowed us to gain several new insights into incongruent mirror feedback and body representation. The arm and hand conditions were not statistically different for response frequencies, suggesting that the magnitude of intentional body movements (hand movements are more subtle than arm movements) does not have an effect on the induction of illusory somatosensation. For the separate influences of the presence of a mirror or the presence of incongruence, we found that there was no significant difference in unusual somatosensory sensations across conditions, regardless of whether the condition only included incongruence or only included a reflected image. This suggests that sensorimotor conflict with a visual contribution does not induce more somatosensory perceptions than a non-conflicting

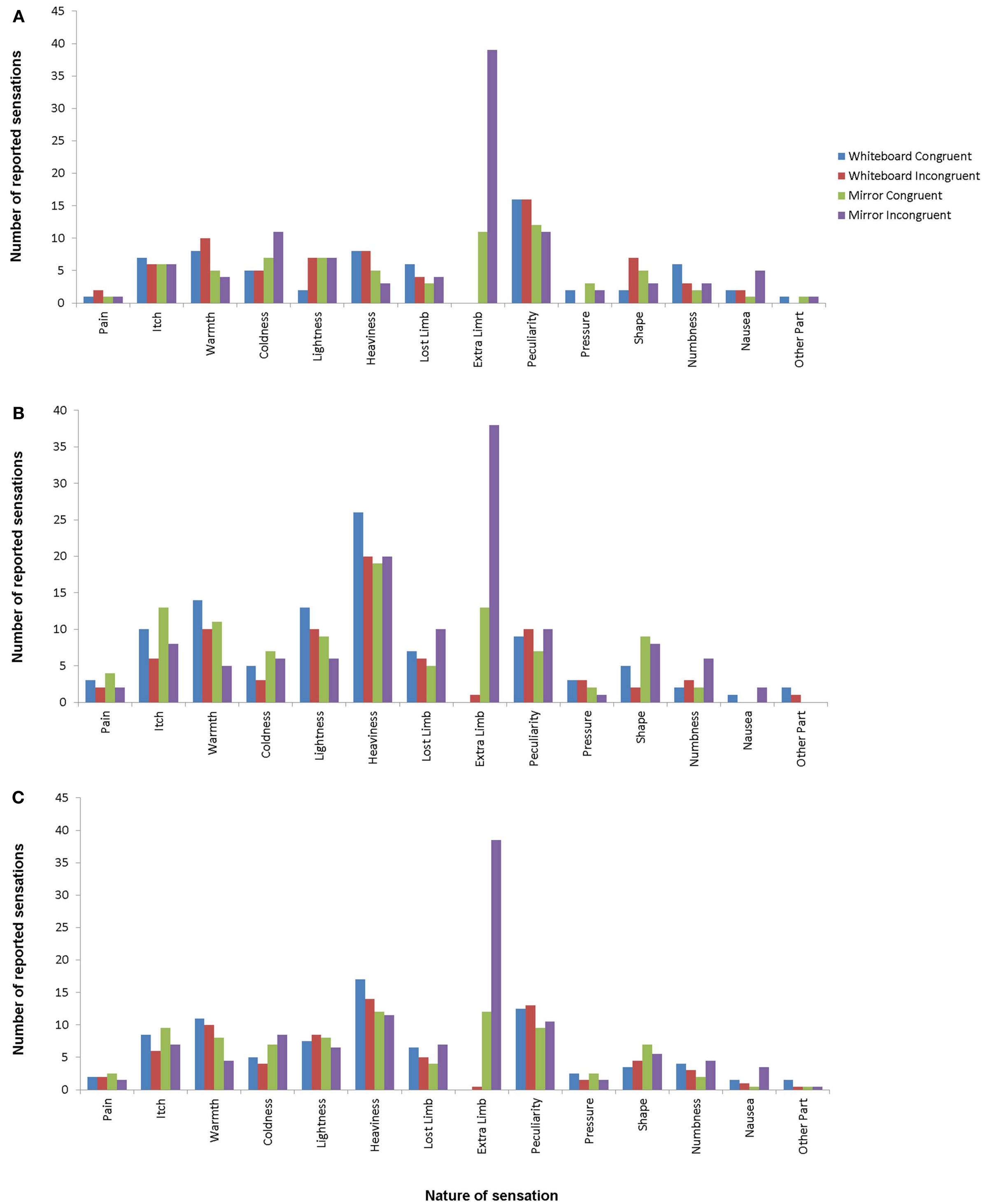

FIGURE 2 | Response frequencies for hand conditions (A), arm conditions (B), and average for all conditions (C). Different bars indicate different conditions, with mirror/incongruent being the experimental condition. Item definitions are given in **Table 1**.

condition, and that most of the reported experiences in this setup can be explained by an unfamiliar movement task, regardless of sensory feedback.

Pain was reported in less than 2% of participants, and was not more frequent during incongruent mirror feedback when compared to control conditions. The finding that pain was among

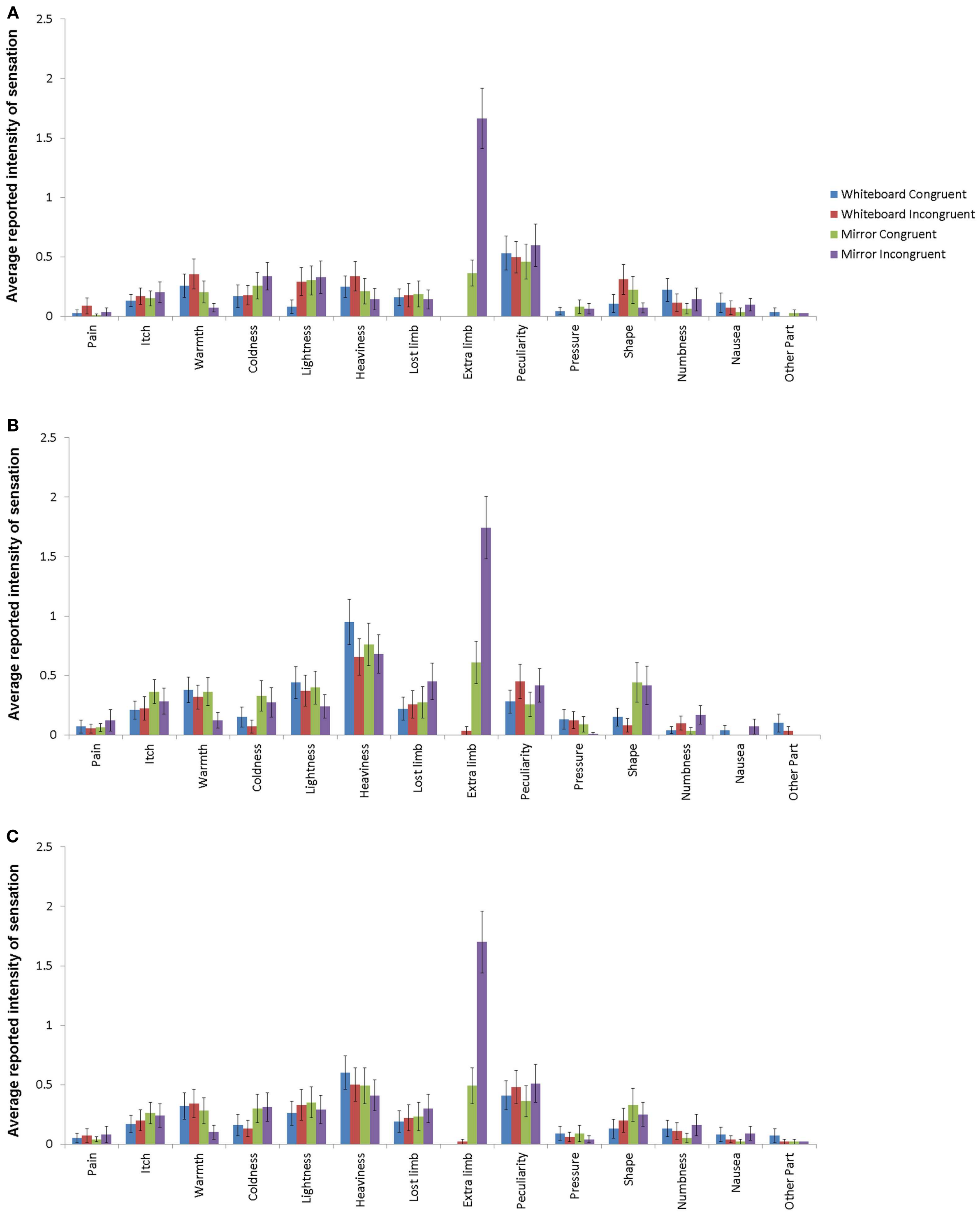

FIGURE 3 | Response intensities for hand conditions (A), arm conditions (B), and average for all conditions (C) with standard error depicted. Different bars indicate different conditions, with mirror/incongruent being the experimental condition. Item definitions are given in **Table 1**.

the rarest sensations that were found in the study described here may suggest that the reported painful sensations might not have been genuine perceptions of pain, but rather unusual, surprising sensations (such as tingling or pins and needles) bordering on painfulness, which were interpreted or categorized as painful only by a small percentage of participants. Those unusual sensations that are equally spread over control and experimental conditions might be explained by the high degree of attention on the limbs elicited by the study setup, combined with an unusual movement task which might cause pain in some cases by straining muscles which are not commonly used for comparable tasks or durations. However, even if these were genuine painful sensations, they were not more frequent in the incongruent mirror condition. It is important to mention that a study by McCabe et al. (2007) has reported unusual sensations during mirror and whiteboard conditions, but not when the other limb was observed (i.e., unobstructed visual feedback, without any alteration or impairment of the participant's visual field). From this perspective, both the mirror and the whiteboard conditions would be considered experimental, or interventional, conditions. However, our experimental setup demonstrates that the congruence or incongruence of the observed movements is not an influential factor on the frequency or intensity of reported pain. For some sensations, participants seem to have difficulties in determining whether the feeling is just uncomfortable or genuinely painful. Our questions to the participants were designed to provide the highest possible differentiation by including clear categorizations as well as assessing the intensity of the sensations. This mode of assessment and categorization of sensations that are odd and uncomfortable rather than painful, as well as the differences in establishing experimental and control conditions referenced above, may account for different findings in studies using comparable experimental setups (cf. McCabe et al., 2005; Moseley and Gandevia, 2005; Moseley et al., 2006).

The findings reported in the present study complement previous evidence of induced somatosensory perceptions elicited by sensory conflicts in so far as they suggest that a "pure" somatosensory incongruence (Moseley et al., 2006) as well as a cross-modal conflict with a visual contribution (the present study) does not appear to be sufficient to trigger substantial pain experiences in healthy volunteers. Nevertheless, this kind of incongruence might be able to affect the perceived integrity of one's body. McCabe et al. (2005) already found that inducing a motor-sensory conflict leads to the sensation of owning more or less than two limbs, and participants stated that they had additional limbs only in the mirror/incongruent condition. The feeling of supernumerary limbs, in both the arm and hand condition, was by far the most frequently reported unusual sensation in the present study. The unique position of this sensation among the other responses is supported by evidence from other studies researching the reaction to unusual sensory feedback: in the experimental paradigm known as the rubber hand illusion (Botvinick and Cohen, 1998), one of the participant's hands is hidden from view and replaced by a rubber hand. When this rubber hand is stimulated with a cotton swab while the hidden real hand receives tactile stimulation in a congruent manner, most participants report a feeling of ownership for the rubber hand. It is thought that, in this scenario, the incongruence between visual, tactile, and proprioceptive input is best resolved by the inclusion of the rubber hand into the body representation and that this external object basically replaces the actual hand in terms of body ownership (Longo et al., 2008). However, if the participant is allowed to observe his or her own stimulated hand *together* with the stimulated rubber hand, then participants no longer report the rubber hand as a replacement of their own hand, but instead perceive ownership for both the rubber hand and the actual hand (Guterstam et al., 2011). Another experimental study exploring sensorimotor incongruence using an adapted version of the rubber hand illusion (synchronous and asynchronous finger tapping of the rubber hand rather than stroking) demonstrated reduced ownership of the participant's limb when the participant viewed the illusion of asynchronous finger tapping. Furthermore, participants reported significantly higher levels of pain, discomfort, feelings of peculiarity, and the perception of having an extra limb when they viewed asynchronous movements versus synchronous ones (Derbyshire et al., 2010). Interestingly, this kind of illusion is accompanied by shifts in topography of the primary somatosensory cortex, indicating that the subjective illusory sensation is related to changes on a neuronal level (Schaefer et al., 2009) in an area that, among other things, is responsible for multisensory integration (Schaefer et al., 2006). Our results suggest that not only a visuotactile conflict might alter the representation of the body, but that a sensorimotor conflict is also able to affect perceived body integrity. In order to investigate the phenomenon of supernumerary illusory limbs further, Folegatti et al. (2012) induced the rubber hand illusions with two rubber hands at the same time and found that only the one nearest to the body will be integrated into the participant's body representation. It is interesting to note here that our mirror experiment is able to produce an illusory image (the mirrored hand) at the exact same location as the actual limb, which is something that the rubber hand illusion as described above is not able to do. This means that in the rubber hand illusion, there is a necessary contradiction between the location of the rubber hand and the participant's proprioception. The central role of proprioception for the integration of body signals has been described by Vallar and Ronchi (2009), who discuss the sense of position as the defining factor for the occurrence of somatoparaphrenia, or delusional beliefs about parts of the body.

A distinction between body representations relating to perception (body image) and action (body schema) has been proposed earlier (Kammers et al., 2006). By this definition, our experiment is distinct from the rubber hand procedures cited above in that it aims at manipulating the action aspect of a limb (movement) instead of the perception aspect (by tactile stimulation). This means that in our study, body schema, rather than body image, is influenced by the experiment. A study by Newport et al. (2010) has demonstrated that a moving fake hand (which is comparable to observing a hand moving in a mirror) can be incorporated into both body image and body schema.

As described above, all our mirror movement setups began with congruent movements. Applying the results from the rubber hand paradigm, we assume that the mirrored arm or hand image replaces the actual arm or hand in the body representation during congruent movements, much like it is shown in the rubber hand setup. Minor incongruence (e.g., caused by imperfect two-hand coordination or shifts in balance) may lead to occasional sensations of a third limb, but it would be expected that most participants accept the mirror image as a replacement of their actual limb, because the "virtual" limb reacts completely congruently. However, as soon as the incongruent condition begins, a replacement is no longer sufficient to explain the mismatch in regard to sensory input and the body representation has to adjust to this novel situation. The results of this study show that, at least in some participants, the adjustment consists of accepting the visual reflection as a third limb. This means that the illusion itself is not being eliminated by the switch from congruent to incongruent movements: in both conditions, the mirrored hand is included into the body representation. The mode of integration, however, is changed according to the condition, and can alternate between a replacement of the hidden hand and the addition of a third hand.

This idea assumes that the sensation of additional limbs is specific to the situation of sensorimotor incongruence, which is consistent with the results of this study: in all of the whiteboard conditions, only one of the participants reported this feeling, compared to numerous reports of this sensation in the mirror conditions. Also, the frequency of this sensation, both in the arm and the hand conditions, is lowest in the whiteboard conditions, followed by moderate numbers in the congruent mirror condition and finally being named frequently in the incongruent mirror condition, as would be expected based on the theoretical background described above.

The fact that certain participants react with adding a third limb to their body representation and others do not, might have interesting implications for phantom sensations and PLP as well as the use of prosthetic limbs: in both cases, there is a large inter-individual variability that has not yet been completely explained. In the mirror treatment for PLP (Ramachandran and Rogers-Ramachandran, 1996), congruent mirror feedback is used to alleviate phantom pain. This method has been shown to reduce pain after several weeks of application (Chan et al., 2007). However, this and similar treatments do not seem to improve every patient's condition (Weeks et al., 2010) and, if they work, the improvement is not always to the same degree (MacIver et al., 2008). A patient's individual susceptibility to be influenced by visual feedback appears to be important in determining the efficacy of mirror therapy, with those who have the strongest immersion in the illusion gaining the greater analgesic benefit (Mercier and Sirigu, 2009). It is also known that a majority of prostheses are not used regularly, because patients reject them for reasons that are not entirely clear (Biddiss and Chau, 2007). These two phenomena might be linked on a conceptual level to the findings described here, where discordance between visual and somatosensory feedback could be integrated by some, but not all, participants. Since the ability to integrate a foreign object into the body representation is critical both in mirror therapy and in prosthesis use, its inter-individual variation may support or obstruct therapeutic efforts and thus demands further investigation. The notion of such an inter-individual variation is supported by the recent finding that the reaction to the rubber hand paradigm is stable over time, both on a behavioral and on a neuronal level (Bekrater-Bodmann et al., 2012). In addition, the fact that incongruent feedback facilitates the interpretation of the mirror image as a third limb has direct consequences on the practical application of mirror therapy for chronic pain syndromes such as PLP. One possible mechanism of this kind of treatment is the integration of information from both the sensorimotor and the visual systems, which contributes to the perception of the phantom limb (Hunter et al., 2003) and activates the body representation in sensorimotor cortex (Diers et al., 2010). Dysfunctional alterations in this cortical area might be involved in PLP (Flor et al., 2006). Consequently, a visual image replacing the missing limb might be an important factor for the efficacy of mirror treatment (Foell et al., 2011). Our data suggest that an incongruence between a mirror image and the phantom limb should lead to a rejection of the image as a replacement for the lost limb and may thus diminish the effects of the treatment. It is known that the size and shape of a phantom limb can deviate from that of a healthy limb (Giummarra et al., 2010) or be shortened by a so-called telescopic distortion (Cronholm, 1951; Ramachandran and Hirstein, 1998). If these effects cause the visual or proprioceptive differences between mirrored hand and phantom hand to become too large, the discrepancy may lead to the re-interpretation of the mirror image as a third limb rather than a replacement. Consequently, treatment effectiveness may be impaired, probably due to different representations in the sensory and motor cortices (cf. Schaefer et al., 2009; Diers et al., 2010). It would be interesting to investigate whether patients with a distinctive distortion of their phantom limb report less pain alleviation after the application of mirror therapy.

In conclusion, we did not find incongruent mirror feedback to elicit pain, which casts doubt on some current models for the origin of PLP and other chronic pain states. The sensation of additional limbs, however, is sensitive to the illusion created by this setup, and could prove to be highly important in the application of mirror feedback as a treatment for chronic pain.

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Generalization gradients in cued and contextual pain-related fear: an experimental study in healthy participants

Ann Meulders[1]*†, Nele Vandebroek[1†], Bram Vervliet[1,2] and Johan W. S. Vlaeyen[1,2,3]

[1] *Department of Psychology, University of Leuven, Leuven, Belgium*
[2] *Center of Excellence Generalization Research in Ill Health and Psychopathology, University of Leuven, Leuven, Belgium*
[3] *Department of Clinical Psychological Science, Maastricht University, Maastricht, Netherlands*

Edited by:
Jörg Trojan, University of Koblenz-Landau, Germany

Reviewed by:
Susanne Becker, Central Institute of Mental Health, Germany
Robin Bekrater-Bodmann, Heidelberg University, Germany

****Correspondence:***
Ann Meulders, Department of Psychology, University of Leuven, Tiensestraat 102, Box 3726, 3000 Leuven, Belgium
e-mail: ann.meulders@ppw.kuleuven.be

†Ann Meulders and Nele Vandebroek have contributed equally to this work.

Increasing evidence supports the notion that pain-related fear plays a key role in the transition from acute to chronic pain. Recent experimental data show that associative learning processes are involved in the acquisition of pain-related fear. An intriguing yet underinvestigated question entails how spreading of pain-related fear in chronic pain occurs. In a voluntary movement paradigm in which one arm movement (CS+) was followed by a painful stimulus and another was not (CS−) in the predictable group and painful stimuli were delivered during the intertrial interval (context alone) in the unpredictable group, we tested generalization of fear to six novel generalization movements (GSs) with varying levels of similarity between the original CS+ movement and CS− movement. Healthy participants ($N = 58$) were randomly assigned to the predictable or unpredictable group. Fear was measured via verbal ratings and eyeblink startle responses. Results indicated that cued pain-related fear spreads selectively to novel movements that are proprioceptively more similar to the CS+ than to those similar to the CS− in the predictable group, but not in the unpredictable group. This is the first study to demonstrate a generalization gradient of cued pain-related fear. However, this effect was only present in the startle eyeblink responses, but not in the verbal ratings. Taken together, this paradigm represents a novel tool to scrutinize the largely understudied phenomenon of the spreading of fear and avoidance in patients with chronic musculoskeletal pain and mapping possible pathological differences in generalization gradients and the spreading of pain in patients as compared with healthy controls.

Keywords: fear conditioning, fear generalization, unpredictability, contextual pain-related fear, cued pain-related fear, generalization gradient

INTRODUCTION

It is commonly recognized that the relationship between nociceptive input and suffering in chronic pain is not straightforward (Fordyce, 1988). Evidence suggests that a great part of the patients' suffering is not due to the pain itself, but rather to the exaggerated emotional responses and the broad range of escape/avoidance behaviors accompanying it (Fordyce, 1988; Crombez et al., 1999). Consistent with this view, prevailing theoretical models consider chronic musculoskeletal pain disability in terms of the strength of fear of movement/(re)injury. Current fear-avoidance models indeed suggest that high *fear of movement-related pain* is an underlying deviant pathology that motivates patients to disrupt their daily activities instigating a vicious circle of pain, avoidance, hypervigilance, depression, and disuse. In comparison, patients with low fear of movement-related pain remain active after an acute pain episode, which in turn leads to functional recovery (Vlaeyen and Linton, 2000, 2012; Leeuw et al., 2007a).

According to fear-avoidance models fear of movement/(re)injury is acquired through associative learning processes, that is, initially neutral movements/activities (conditioned stimuli, CSs) that are associated with (increases in) pain (unconditioned stimulus, US) start to elicit defensive responses such as fear and avoidance (conditioned responses, CR). In chronic pain patients, fear and avoidance are often not restricted to movements/activities that were associated with pain during the initial pain episode (Leeuw et al., 2007b). Therefore, a fascinating yet empirically underinvestigated question entails how spreading of pain-related fear and avoidance occurs. Associative learning theory predicts that conditioned fear responses extend to a range of novel stimuli resembling the original fear-eliciting CS, that is, more similar generalization stimuli (GSs) activate more similar responses (i.e., *generalization gradient*). Stimulus generalization is a highly adaptive mechanism, because the ability to detect similarities between unique but related stimuli may contribute to avoiding harm in a dynamic environment (Kalish, 1969; Honig and Urcuioli, 1981; Pearce, 1987; Ghirlanda and Enquist, 2003; Lissek et al., 2008). Yet, together with reducing the risk of missing positive threat alarms, generalization bears an increased risk to respond to false threat alarms, which might be the case in persistent fear and avoidance behavior in chronic pain. In line with this reasoning, recent etiological accounts of anxiety disorders suggest that not fear intensity, but fear *(over)generalization* to novel, albeit similar settings is the central pathogenic marker in certain anxiety disorders (Lissek and Grillon, 2010; Lissek et al., 2010). A second mechanism that might contribute to the exacerbation and maintenance of chronic pain and disability is operant conditioning (Skinner, 1953). That is, successful escape or avoidance of situations, movements, and activities that induce fear and possibly pain can be instrumentally reinforced (Fordyce et al., 1973, 1982; Philips, 1987; McCracken and Samuel, 2007). In the same vein, situations and movements/activities that resemble the feared situations and movements/activities might be avoided as well, leading to the spreading of conditioned avoidance behavior.

Another interesting observation in the anxiety literature that is worth further scrutiny with regard to pain-related fear is that fear conditioning is not a steady state phenomenon but a dynamic process varying as a function of the contingencies between the CS and the US (Grillon, 2002, 2008; Grillon et al., 2006). In particular, *cued fear* is observed upon the presentation of a well-defined, short-lasting CS, and this response quickly subsides after the offset of the fear-eliciting CS. In the absence of a clear threat signal however, *contextual fear* gradually develops as static environmental cues act as continuous reminders of the US without signaling the exact time of its occurrence or non-occurrence (i.e., safety periods). Hence, contextual cues entail more unpredictability regarding the exact occurrence of the US *relative* to discrete cues. In the same vein, two types of pain-related fear can be distinguished depending on the temporal (un)predictability of the US: cued and contextual pain-related fear. Cued pain-related fear is experimentally induced by predictable pain (i.e., pairings of movement and pain), whereas contextual pain-related fear is induced by unpredictable pain (i.e., pain explicitly unpaired with movements) (Meulders et al., 2011; Meulders and Vlaeyen, 2012).

A recent study in our lab (Meulders and Vlaeyen, 2013a) investigated stimulus generalization using a voluntary movement conditioning paradigm in which, one arm movement (e.g., moving to the left, CS+) was followed by a painful stimulus and another was not (e.g., moving to the right, CS−) in the predictable condition, whereas pain stimuli were never delivered contingent upon the movements (i.e., moving up and down) but during the intertrial interval (ITI) in the unpredictable condition. In this particular set-up spreading of fearful responding to novel diagonal movements (e.g., left-top, right-top, left-bottom, right-bottom) was tested. These movements (GSs) had only one feature in common with the either the original CS+ or CS−, hence gradients could not be calculated. Therefore, the present study was designed to examine whether stimulus generalization of cued pain-related fear is characterized by a gradient. In order to do so, we used an adapted version of the voluntary movement paradigm using six generalization stimuli (GSs) with varying levels of similarity between the original CS+ and CS−. Healthy participants were randomly assigned to the predictable or unpredictable group. In the predictable group, one arm movement (CS+) was followed by the pain-US and another was not (CS−), but in the unpredictable group, painful stimuli were delivered during the ITI. Fear was measured via verbal ratings and eyeblink startle responses. We hypothesized that: (1) cued pain-related fear spreads selectively to new movements that are more similar to the CS+ than to those similar to the CS− (i.e., fear generalization gradient in the predictable group), (2) generalization gradients are flattened in the unpredictable group compared with the predictable group.

MATERIALS AND METHODS

PARTICIPANTS

Seventy healthy female undergraduate psychology students of the University of Leuven ($M_{age} = 20.19$ years; $SD_{age} = 1.66$, range = 19–29 years), volunteered to participate in this study as a partial fulfillment of course requirements or in exchange for a monetary compensation of €12. Participants were recruited using the departmental experiment management system (EMS; Sona Systems Ltd.), or by means of advertisements distributed at the University of Leuven. Participants completed a general health checklist to confirm they did not have one or more of the following conditions: cardiovascular disease, neurological disease, musculoskeletal disorder, or other pain-related conditions, psychiatric disorders, cardiac pacemaker, or the presence of any other electronic, medical devices, uncorrected vision/hearing problems, injury on hand/wrist, recent use of analgesic, anxiolytic, or anti-depressant medication, being pregnant, being under 18 years old, and being a non-native Dutch/Flemish speaker. All participants provided written informed consent and were told that they could decline their participation at any given moment during the experiment. Eight participants were excluded because they did not meet our inclusion criteria. Of the remaining 62 participants that actually participated in the study, 4 were excluded due to technical difficulties, leaving a total of 58 participants to be included in the statistical data-analysis. Participants were randomly assigned to the predictable pain group ($n = 29$) or the unpredictable pain group ($n = 29$). The study protocol was approved by the ethical committee of the Department of Psychology of Leuven University.

SOFTWARE

The experiment was run on a Windows XP computer (Dell OptiPlex 755) with 2 GB RAM and an Intel Core2 Duo processor. The visual stimuli were presented on a 19-inch computer screen. The presentation of the stimuli and the data acquisition was controlled with the free software package Affect (version 4.0) (Spruyt et al., 2010) and the data were stored using a National Instruments data acquisition card.

STIMULUS MATERIAL

The CSs and the generalization stimuli (GSs) were eight, equally spaced movement quadrants (**Figure 1**). These proprioceptive stimuli consisted of moving a (Logitech Attack 3) joystick with the dominant hand within one of the eight movement quadrants. Movements in quadrant 1 (CS_p+/CS_u1) and quadrant 8 (CS_p-/CS_u2) served as the CSs, and movements in quadrants 2–7 (GS_p1–$6/GS_u1$–6), served as the GSs in both groups. For half of the participants in the predictable group the movement in quadrant 1 (i.e., moving the joystick to the left) was followed by the pain (CS_p+) and the movement in quadrant 8 (i.e., moving the joystick to the right) was never followed by pain (CS_p-), whereas for the other half of the participants this combination was reversed. The pain-US was a 50 ms electrocutaneous stimulus, generated by commercial constant current stimulator (DS7

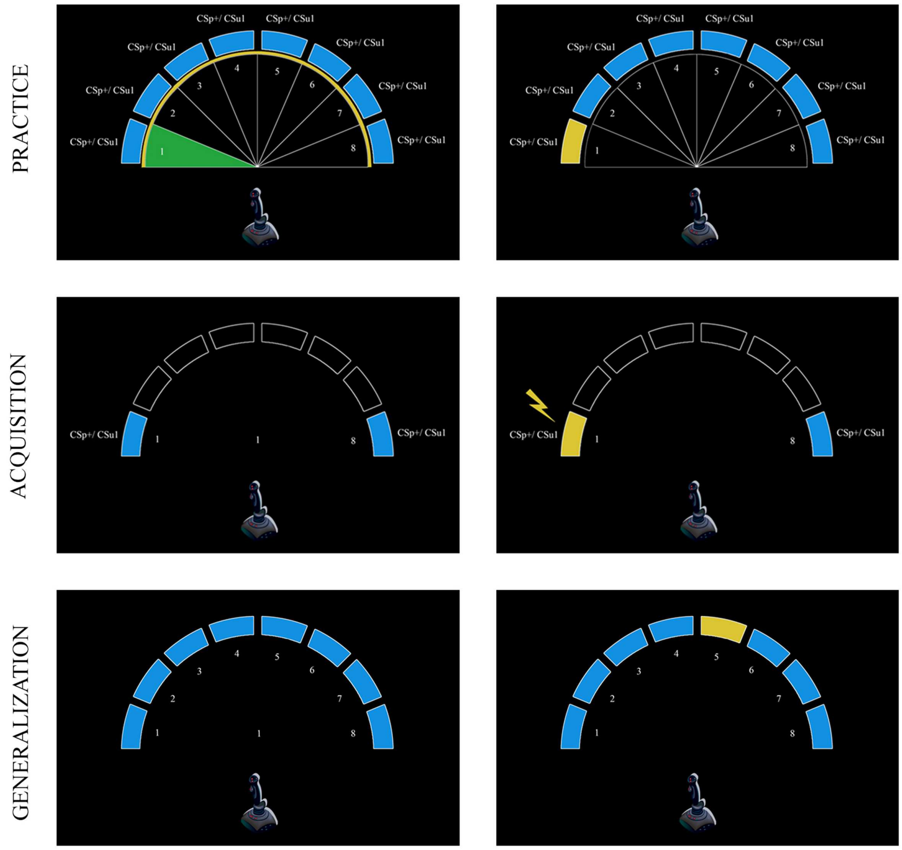

FIGURE 1 | Schematic overview of the experimental task during the practice, acquisition, and generalization phases. The eight equally spaced movement quadrants that served as CSs (1 and 8) and GSs (2–7) were delineated by white borders during the practice phase (upper panel). In the predictable group, the CSs and GSs are referred to as CS_p+, CS_p-, and GS_p1–GS_p6; these stimuli are referred to as CS_u1, CS_u2, GS_u1–GS_u6 in the unpredictable group. Participants had to move the joystick in the area that colored green and had to aim toward the yellow border. At the end of each of these movement areas a blue bar was positioned; the corresponding blue bar turned yellow when a movement was successfully performed. During the acquisition phase (middle panel), participants only carried out two movements (CSs). After "+" was presented in the middle of the screen, this was replaced by a number that indicated the movement direction (1 or 8). In the predictable group one of these movements was followed by a pain-US (CS_p+, i.e., left) indicated by a lightning bolt, whereas the other movement (CS_p-, i.e., right) was never followed by the pain-US. In the unpredictable group, movements (CS_u1/CS_u2) were never followed by the pain-US, but it was delivered during the ITI. Finally, during the generalization phase (lower panel) participants had to perform all movements (GSs and CSs) under extinction (i.e., none of the movements were followed by the pain-US).

Digitimer, Welwyn Garden City, UK). Pain stimuli were administered to the wrist of the dominant hand through two surface SensorMedics electrodes (8 mm diameter), spaced approximately 1 cm apart, and filled with K-Y gel. Prior to the experiment, the experimental pain-US was individually calibrated. Starting off with an intensity of 1 mA, the stimulus intensity was gradually increased in steps of 1–4 mA until participants rated the stimulus to be "*significantly painful and demanding some effort to tolerate*." Self-reported pain intensity was rated on an 11-point Likert scale ranging from 0 to 10, with "0" meaning no pain and "10" meaning the worst imaginable pain; a stimulus intensity of 8 on this scale was targeted. The mean self-reported stimulus intensity was 7.69 (SD = 1.16, range 5–10). The mean physical stimulus intensity was 23.78 mA (SD = 15.36, range 6–92 mA). We observed no differences between the predictable and the unpredictable groups with respect to the subjective intensity of the pain-US (predictable group: $M = 7.66$, SD = 1.11, unpredictable group: $M = 7.72$, SD = 0.22), $t(56) = -0.22$, $p = 0.82$, or the stimulus intensity in milliamperes (predictable group: $M = 24.28$ mA, SD = 15.45, unpredictable group: $M = 23.28$ mA, SD = 15.53), $t(56) = 0.25$, $p = 0.81$.

OUTCOME MEASURES

Eyeblink startle modulation

Orbicularis Oculi Electromyographic (EMG) activity was recorded with three re-usable Ag/AgCl SensorMedics electrodes (4 mm diameter) filled with electrolyte gel. Before attaching the electrodes on the left side of the face according to the site specifications proposed by Blumenthal et al. (2005), the skin was cleaned using an exfoliating peeling cream to reduce inter-electrode resistance. Startle eyeblink reflexes were elicited by a 100 dB burst white noise with instantaneous rise time presented binaurally for 50 ms through headphones (Hoher, stereo headphones, HF92). The raw EMG signal was amplified by a Coulbourn isolated bioamplifier, with band pass filter (LabLinc v75-04) with a cut-off frequency of 13 Hz (low pass filter) and 500 Hz (high pass filter). The signal was rectified online and smoothed by a Coulbourn multifunction integrator (LabLinc v76–23A) with a time constant of 20 ms. The EMG signal was sampled at 1000 Hz from 500 ms before the onset of the auditory startle probe until 1000 ms after probe onset. Eyeblink startle responses elicited by startle probes delivered during the CS/GS movements served as an index of cued pain-related fear and responses elicited by startle probes during the ITI served as an index of contextual pain-related fear.

Fear of movement-related pain ratings during the CSs and GSs

After each block during the acquisition and the generalization phase, participants rated the extent to which they were afraid of performing a certain movement on a computerized VAS with anchor points "*not fearful at all*" to "*the worst fear imaginable.*"

MANIPULATION CHECKS

Retrospective pain-US expectancy

As a manipulation check, pain-US expectancy was assessed at the end of the experiment. Participants indicated for both CSs to which extent they expected to receive a painful stimulus on a computerized VAS with anchors "not at all" and "very much." The VAS was coded from 0 to 100.

Retrospective affective valence of the CSs

After the experiment and as a manipulation check, a computerized version of the Self-Assessment Manikin (SAM) (Bradley and Lang, 1994) consisting of five pictographs, ranging from a smiling, happy figure to a frowning, unhappy figure, was used to measure the affective valence of the CS movements. Participants rated how they felt when performing the respective CSs movements. Scores ranged from 1 "very happy" to 5 "very unhappy."

EXPERIMENTAL SETTING

Participants were seated in a comfortable chair at eye level approximately 60 cm from the computer screen. The sound-attenuated experimental room was located adjacent to the experimenter's room. Communication with the experimenter was possible through an intercom system; participants and their physiological responses were monitored online by means of a closed-circuit TV installation. Central lightening was turned off but dimmed light was always available in the experimental room.

PROCEDURE

After obtaining written informed consent, the electrodes for the eyeblink startle measures and the electrocutaneous stimulation were attached. Next, participants went through the four experimental phases described below (see **Table 1** for a detailed study design overview), and completed the pain-US expectancy ratings and the SAM scales. After the experiment, participants were thoroughly debriefed.

Practice phase

Detailed oral and written instructions were provided to the participants before the onset of the experiment to make sure that the purpose of the joystick task was clear. Their main task was to move the joystick toward eight equally sized blue targets that were positioned at the borders of eight movement quadrants (see **Figure 1**). On each trial, the eight delineated, numbered (1–8) movement quadrants were made visible for the participants by white lines that separated each quadrant from the ones adjacent to it. In this way, participants could identify the valid "movement area"[1] covering each quadrant. The borders of the movement quadrants, which participants had to reach in order to hit the target regions were marked with a yellow circle as a means to learn them what constituted a "full" movement. After a 7 s pre-CS ITI, a fixation cross was presented in the middle of the computer screen for 2 s, which subsequently transformed into a randomly selected number ranging from 1 to 8. This number corresponded with one of the numbers depicted in the eight movement quadrants, and informed the participant within which movement quadrant they had to move the joystick during that given trial. The number was presented for 3 s. Participants had to perform the signaled movement as quickly and accurately as possible, and then a 7 s post-CS ITI was inserted before the next trial began. At the beginning of each trial the mouse cursor was positioned in the middle of the screen and the joystick was standing upright and centered, in the resting position. Whenever the mouse cursor representing the movement of the joystick correctly entered the signaled movement area, this area turned green (valid movement), but when

Table 1 | Experimental design.

Group	Practice phase	Startle habituation	Acquisition phase	Generalization phase
Predictable group	1 × CS_p+	Nine startle probes (9)	32 × CS_p+ (8)*	8 × CS_p+ (4)
	1 × GS_p1		32 × CS_p− (8)	8 × GS_p1 (4)
	1 × GS_p2		64 × ITI (8)	8 × GS_p2 (4)
	1 × GS_p3			8 × GS_p3 (4)
	1 × GS_p4			8 × GS_p4 (4)
	1 × GS_p5			8 × GS_p5 (4)
	1 × GS_p6			8 × GS_p6 (4)
	1 × CS_p−			8 × CS_p− (4)
				64 × ITI (4)
Unpredictable group	1 × CS_u1	Nine startle probes (9)	32 × CS_u1 (8)	8 × CS_u1 (4)
	1 × GS_u1		32 × CS_u2 (8)	8 × GS_u1 (4)
	1 × GS_u2		64 × ITI (8)	8 × GS_u2 (4)
	1 × GS_u3		32 × pain-US (during ITI)*	8 × GS_u3 (4)
	1 × GS_u4			8 × GS_u4 (4)
	1 × GS_u5			8 × GS_u5 (4)
	1 × GS_u6			8 × GS_u6 (4)
	1 × CS_u2			8 × CS_u2 (4)
				64 × ITI (4)

The number of startle probes given during each movement are placed between brackets. The asterisk indicates that the pain-US was administered. CS, conditioned stimulus; GS, generalization stimulus; ITI, intertrial interval.

[1] Note that the term movement area has a different meaning than target area in this context, the latter being defined as the region that participants had to reach in order to change the color of the blue bars, whereas the former refers to the area within which they move the joystick before reaching a given target region.

the mouse cursor wrongly entered another movement area than the signaled one, this area turned red (invalid movement) and an error message "*incorrect movement, please try again*" appeared in the middle of the screen for 3 s. Whenever the mouse cursor representing the movement of the joystick entered a valid target region, then the blue bar of the corresponding movement quadrant turned yellow, indicating that the movement was performed successfully. To ensure a steady baseline performance, blue bars did not change color in case of an invalid movement. When participants completed eight valid movements (one successful movement within each quadrant) the training phase was aborted and the next phase began. No startle probes or electrocutaneous stimulation was delivered during this phase of the experiment.

Startle habituation phase

Nine startle probes were delivered during the habituation phase (ITI = 18–25 s) to circumvent confounds in the data due to large startle responses to the first few probes. Startle habituation trials were excluded from the statistical analysis.

Acquisition phase

This phase was similar to the practice phase, except that: (1) the boundaries of the eight movement quadrants and the yellow circle marking the borders of these quadrants were no longer visible. (2) The range of movements in this phase was restricted to quadrants 1 (i.e., movement straight to the left) and 8 (i.e., movement straight to the right), indicated by a blue bar on either side. (3) The movement areas did not turn green or red anymore when the mouse cursor of the joystick reached a valid (green) or invalid (red) movement area. (4) The error message was no longer displayed on the screen when participants reached an invalid target region. (5) Startle probes and pain-USs were presented during this phase.

The acquisition phase consisted of two blocks of 16 trials. Each trial contained two randomly ordered movements, one CS_p+ movement, and one CS_p- movement in the predictable group, and one CS_u1 movement, and one CS_u2 movement in the unpredictable group. Although the duration of the CS movement itself was of variable length depending on the participants' response latency and movement speed, there was a fixed ITI consisting of a 7 s pre-CS interval and a 7 s post-CS interval. In the predictable group, a CS_p+ movement was paired with a painful US in 75% of the trials (12 pain-USs per block), whereas a CS_p- movement was never followed by the pain-US. In contrast, pain-USs were explicitly unpaired with both the CS_u1 and CS_u2 movements in the unpredictable group, and were delivered during the ITI, while keeping the number of pain-USs equal in both groups. In the predictable group, the pain-US was presented immediately after the CS_p+ movement. In the unpredictable group, the pain-US was delivered in a time window of 2–4 s after the onset of the pre-CS ITI or 4–6 s after onset of the post-CS ITI. A total of 12 startle probes were presented within each acquisition block; eight startle probes were presented during the CSs (four during CS_p+/CS_u1 and four during CS_p-/CS_u2), and four probes were administered during the ITI (two probes in the 2–4 s time window of the pre-CS ITI, and two probes in the 4–6 s time window of the post-CS ITI) (see **Figure 2** for the detailed trial timing). Due to concerns that

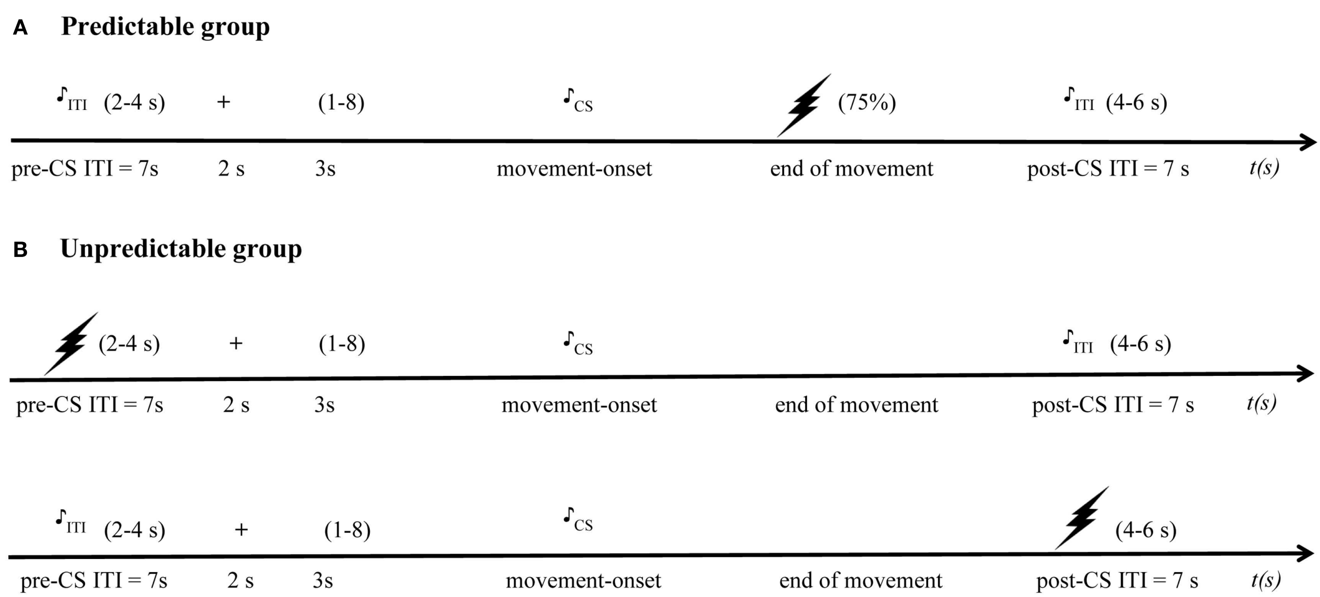

FIGURE 2 | Detailed trial timing schema. The drawing of a lightning bolt represents the pain-US, a drawing of a musical note represents the startle probe presentation, and the "+" represents the starting signal, "(1–8)" refers to the presentation of a number between 1 and 8 representing the quadrant in which the participants have to move. **(A)** In the predictable group, during the acquisition phase, pain-USs are delivered in 75% of the trials after the CS+ movements, but not after the CS- movements. On each trial only one startle probe was presented: in the predictable group, this could be during the CS movement or during the pre-CS ITI or post-CS ITI. **(B)** In the unpredictable group pain-USs are delivered at the same rate either during the pre- or post-CS intertrial interval (ITI) and startle probes also could be presented during the CS movement or during the ITI – when the pain-US was presented in the pre-CS ITI, probes were presented in the post-CS ITI, and if the pain-US was presented during the post-CS ITI, probes were delivered during the pre-CS ITI. In both groups, no pain-USs were delivered during the generalization phase.

the startle response during the ITI would be confounded by direct responses to the pain-US in the unpredictable group, startle probes were administered in the pre-CS interval when the pain-US was administered in the post-CS interval, and vice versa. Participants were never verbally informed about the CS-US contingency.

Generalization phase

To test the fear of movement-related pain generalization gradient, participants performed unreinforced movements in *each* of the eight quadrants (see **Figure 1**), while the rest of the joystick task remained the same as during acquisition. The generalization phase consisted of two blocks of four trials. Within one trial, participants had to perform eight movements in randomized order, one movement to each quadrant. The trial flow and timing was similar to that described in the acquisition phase. Startle probes were presented twice for each CS/GS within each block, and twice during the ITI (one probe in the 2–4 s time window of the pre-CS ITI and one in the 4–6 s time window of the post-CS ITI). No pain-USs were delivered during this phase.

RESPONSE DEFINITION

The startle data were treated offline with PSPHA, a modular script based program for analyzing psychophysiological data (de Clercq et al., 2006). Each startle waveform was visually inspected for technical abnormalities and artifacts, and considered invalid if the baseline period was contaminated with noise (e.g., movement artifact) or if a spontaneous or voluntary blink occurred during a 1–20 ms time window after probe onset. Based on this response qualification process, 2.10% of the startle responses were identified as being invalid. Afterward, for all valid trials, startle peak amplitude was defined as the maximal EMG value within a response onset window of 21–175 ms after probe onset. If multiple peaks occurred, the maximum value within this time window was still identified as the peak. Every peak response was scored by subtracting its baseline score (= average EMG signal between 1 and 20 ms after probe onset). Raw scores were transformed to T-scores to account for inter-individual differences in physiological reactivity and to optimize the visualization of the startle data (i.e., avoid negative values on the Y-axis).

OVERVIEW OF THE STATISTICAL DATA-ANALYSIS

Startle responses to every two intermediate GSs were averaged together to form the mean level of responding for that class of movement, thereby reducing the number of levels for the GSs from six to three (class 1: GS1–2; class 2: GS3–4; class 3: GS5–6). The decision to collapse every intermediaries took into account both the concerns that treating each of six GSs as a separate class would require a very long experiment (leading to excessive startle habituation, extinction, and subject fatigue) and that having only three gradients-of-movement would not allow a gradual enough continuum between the CS+ and the CS−. Therefore, we chose to have three classes of intermediaries with two types of movements in each class to evaluate the generalization gradient. That way, each intermediary required only half as many trials (Lissek et al., 2008). A similar procedure was applied to the fear of movement-related pain ratings. Both outcome measures (startle response and verbal fear ratings) were analyzed with separate repeated measures ANOVAs for the acquisition and the generalization phase with as between-subject (BS) factor group (predictable/unpredictable) and as within-subject (WS) factor stimulus type [2 (3)[2] levels in the acquisition phase, 5(6) levels in the generalization phase]. We hypothesized a group by quadrant interaction. More specifically, in the acquisition phase we expected the startle response and fear to be elevated in the CS+ than in the CS− quadrant in the predictable group, and we expected no difference between both CS movements in the unpredictable group. Furthermore, we expected the startle responses during the ITI to be higher in the unpredictable group than in the predictable group. In the generalization phase, we expected a group × linear quadrant interaction, that is, a decrease of startle response and verbal fear ratings with increasing distance from the CS+ quadrant in the predictable group, and no relation between quadrant and startle response or self-reported fear in the unpredictable group. Greenhouse–Geisser corrections are reported when applicable, that is, for effects involving a WSs factor with more than two levels. Generalization gradients were further evaluated using Fisher's LSD multiple comparisons. This test is known to have good power for detecting existing differences. Its vulnerability is generally a family-wise error rate that increases easily, unless the means are assumed to be simply ordered (Nashimoto and Wright, 2005). For all statistical tests, the α-level was set at 0.05.

RESULTS

EYEBLINK STARTLE MODULATION

Fear acquisition

Eyeblink startle responses during acquisition were analyzed using a 2 (Group: predictable vs. unpredictable) × 2 (Block: ACQ1 vs. ACQ2) × 3 (Stimulus type; CS+ vs. CS− vs. ITI) mixed (RM) ANOVA. This analysis yielded significant main effects for block, $F(1, 56) = 16.58$, $p < 0.001$, and stimulus type, $F(1, 56) = 16.69$, $p < 0.001$. Interestingly, the stimulus type × group interaction was significant, $F(1, 56) = 61.37$, $p < 0.001$, indicating that startle responses to the different movements differed between the predictable and unpredictable group. As expected, planned comparisons revealed higher startle responses to the CS+ than to the CS− in the predictable group by the end of acquisition (ACQ2), $F(1, 56) = 10.41$, $p < 0.01$, while there was no such difference in the unpredictable group, $F < 1$ (see **Figure 3**). Further, planned comparisons confirmed that ITI startle responses were significantly elevated in the unpredictable group compared with the predictable group by the end of acquisition (ACQ2), $F(1, 56) = 42.64$, $p < 0.001$.

Fear generalization

We used a 2 (Group: predictable vs. unpredictable) × 2 (Block: G1 vs. G2) × 5 (Stimulus type: CS+ vs. class1 vs. class2 vs. class 3

[2]The WS factor stimulus type had one extra level in the startle modulation analysis, i.e., the ITI representing the contextual fear measure. In particular, during acquisition this WS factor included two levels (CS+/CS−) for the verbal ratings and three levels (CS+/CS−/ITI) for the startle modulation. During generalization this WS factor included five levels (CS+/CLASS1/CLASS2/CLASS3/CS−) for the verbal ratings and six levels (CS+/CLASS1/CLASS2/CLASS3/CS−/ITI) for the startle modulation.

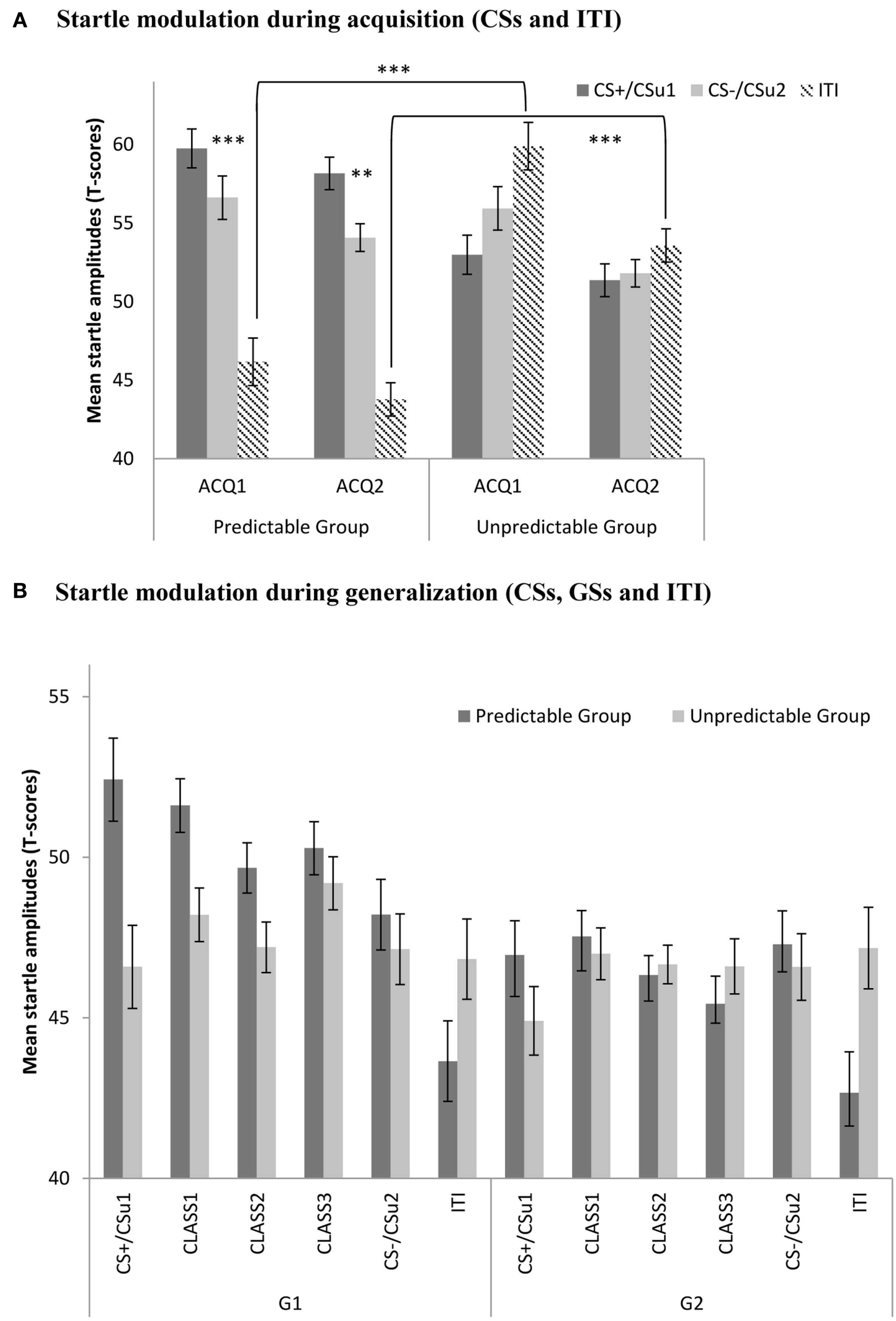

FIGURE 3 | (A) Mean eyeblink startle amplitudes (+SE's) during the CS movements and the ITI in the predictable (CS+/CS−) and the unpredictable group (CS_u1/CS_u2) during the two acquisition blocks (ACQ1-2), and **(B)** mean eyeblink startle amplitudes (+SE's) during the CS movements, the classes of GS movements (CLASS1-3) and the ITI in the predictable and the unpredictable group during the generalization blocks (G1–G2). **(A)** Startle modulation during acquisition (CSs and ITI). **(B)** Startle modulation during generalization (CSs, GSs, and ITI).

vs. CS−) mixed (RM)ANOVA. This analysis showed main effects for group, $F(1, 56) = 6.31$, $p < 0.05$, and block, $F(1, 56) = 26.18$, $p < 0.001$. Both the block × condition, $F(1, 56) = 6.00$, $p < 0.05$, the stimulus type × block, $F(4, 224) = 2.76$, $p < 0.05$, as well as the stimulus type × condition, $F(4, 224) = 2.61$, $p < 0.05$, interactions were significant. The three-way interaction, however did not reach statistical significance, $F < 1$. Planned comparisons were used to further test our *a priori* hypotheses. In line with our expectations, there was a significant linear decrease, $F(1, 56) = 7.18$, $p < 0.01$, in the startle responses with decreasing GS similarity to the CS+ in the predictable condition, but not in the unpredictable condition, ($F < 1$). This generalization gradient was present in the first generalization block, but not in the second generalization block (both $Fs < 1$). During the first generalization block, startle responses were still significantly higher for the CS+ than for the CS− in the predictable group, $F(1, 56) = 6.12$, $p < 0.05$, but not in the unpredictable group, ($F < 1$), and this difference was no longer significant in the second generalization block ($F < 1$). Contextual pain-related fear appeared to be attenuated during the first generalization block, ITI startle responses tended to be higher in the unpredictable group compared with the unpredictable group but this difference was no longer statistically significant, $F(1, 56) = 3.22$, $p = 0.08$. During generalization block 2, however, this difference did reach statistical significance, $F(1, 56) = 6.28$, $p < 0.05$. This effect was largely driven by the further decrease in startle responding during the ITI in the predictable group. The generalization gradient was further supported by multiple planned comparisons (see **Table 2**).

Table 2 | *p*-Values for the multiple comparisons using Fisher's LSD test for the verbal fear ratings and the startle modulation for the predictable group during the first block of the generalization phase.

	CLASS1 (*p*)	CLASS2 (*p*)	CLASS3 (*p*)	CS− (*p*)
STARTLE MODULATION				
CS+	0.443	0.009	0.043	<0.001
CLASS1		0.066	0.208	0.001
CLASS2			0.558	0.166
CLASS3				0.049
VERBAL FEAR RATINGS				
CS+	<0.001	<0.001	<0.001	<0.001
CLASS1		0.430	0.641	0.562
CLASS2			0.746	0.834
CLASS3				0.909

FEAR OF MOVEMENT-RELATED PAIN RATINGS

Fear acquisition

Data were analyzed with a 2 (Group: predictable vs. unpredictable) × 2 (Block: ACQ1 vs. ACQ2) × 2 (Stimulus type: CS+ vs. CS−)[3] mixed (RM)ANOVA. This analysis revealed significant main effects for stimulus type, $F(1, 56) = 21.27$, $p < 0.001$, and for group, $F(1, 56) = 6.58$, $p < 0.05$, the latter effect indicating that participants in the predictable group reported higher fear of movement-related pain compared to the unpredictable group. Of crucial importance, the stimulus type × group effect was significant, $F(1, 56) = 60.71$, $p < 0.001$. Planned comparisons at the end of acquisition (ACQ2) confirmed that participants in the predictable group reported significantly more fear of the CS+ compared to the CS−, $F(1, 56) = 74.91$, $p < 0.001$, while participants in the unpredictable group did not give differential fear ratings for both movements, $F(1, 56) = 10.06$, $p = 0.07$ (see **Figure 4**).

Fear generalization

We performed a 2 (Group: predictable vs. unpredictable) × 2 (Block: G1 vs. G2) × 5 (Stimulus type: CS+ vs. class1 vs. class2 vs. class 3 vs. CS−) mixed (RM)ANOVA. The main effect of stimulus type, $F(4, 224) = 3.10$, $p < 0.05$, was significant. There was also a significant main effect of block, $F(1, 56) = 4.13$, $p < 0.05$, indicating that the fear of movement-related pain ratings were declining across blocks. The stimulus type × block interaction effect, $F(4, 224) = 4.65$, $p < 0.01$, was significant, but the anticipated stimulus type × group interaction, $F(4, 224) = 1.18$, $p = 0.32$, and the three-way interaction did not reach statistical significance, $F(4, 224) = 1.98$, $p = 0.10$. Trend analysis further revealed a significant linear, $F(1, 56) = 8.07$, $p < 0.01$, and quadratic, $F(1, 56) = 8.40$, $p < 0.01$, in the predictable condition, but not in the unpredictable condition, [linear: $F < 1$, quadratic: $F(1, 56) = 1.39$, $p = 0.24$]. This trend was present in the first generalization block, but not in the second generalization block (both $Fs < 1$). During the first generalization block, fear of movement-related pain ratings were still significantly higher for the CS+ than for the CS− in the predictable group, $F(1, 56) = 8.20$, $p < 0.01$, but not in the unpredictable group, ($F < 1$), and this difference was no longer significant in the second generalization block ($F < 1$). These trends in the beginning of the generalization phase were further examined using multiple planned comparisons (see **Table 2**).

MANIPULATION CHECKS

Retrospective pain-US expectancy

We performed a 2 (Group: predicable vs. unpredictable) × 2 (Stimulus type: CS+ vs. CS−) mixed ANOVA on the retrospective pain-US expectancy ratings (see **Table 3**). This analysis showed a significant main effect for stimulus type, $F(1, 56) = 11.52$, $p < 0.01$, and a significant stimulus type × group interaction, $F(1, 56) = 62.90$, $p < 0.001$, indicating that US expectancy during the respective CS movements was different in both groups. In line with our expectations, participants in the predictable group expected the pain-US to occur more when they performed the CS+ movement than when performing the CS− movement, $F(1, 56) = 64.13$, $p < 0.001$. This difference also turned out to be significant in the unpredictable group, $F(1, 56) = 10.29$, $p < 0.01$, but to a much smaller extent.

Retrospective affective valence of the CSs

A 2 (Group: predictable vs. unpredictable) × 2 (Stimulus type: CS+ vs. CS) mixed ANOVA was run on the SAM happiness ratings (see **Table 3**). There was a significant main effect for stimulus type, $F(1, 56) = 6.55$, $p < 0.05$. More importantly, the stimulus type × group interaction, $F(1, 56) = 17.55$, $p < 0.001$, was significant. To break down this interaction, planned comparisons were calculated. As expected, participants were less happy when performing the CS+ movement compared to the CS− in the predictable group, $F(1, 56) = 22.77$, $p < 0.001$, while there was no such difference in the unpredictable group, $F(1, 56) = 1.33$, $p = 0.25$.

DISCUSSION

Recent experimental evidence suggests that generalization learning might be involved in the spreading of fear and avoidance

[3]Note that throughout this paper, the notations CS+ and CS− used in the descriptions of the statistical analyses and the figures, respectively refer to the CS_p+ and the CS_p- in the predictable group, and to the unreinforced CSs, (i.e., CS_u1 and CS_u2 in the unpredictable context).

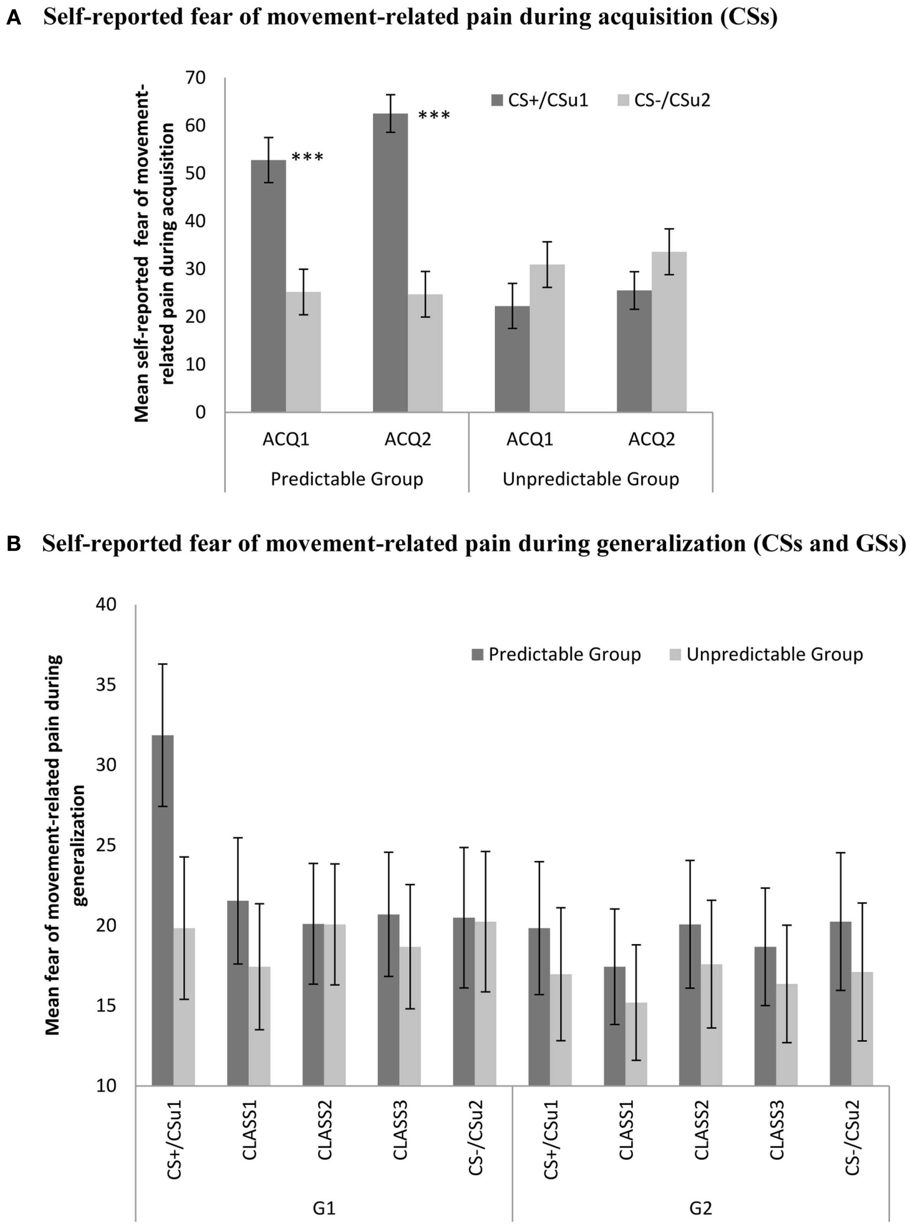

FIGURE 4 | (A) Mean self-reported fear of movement-related pain (+SE's) during the CS movements in the predictable (CS+/CS−) and the unpredictable group (CS_u1/CS_u2) during the two acquisition blocks (ACQ1-2), and **(B)** mean eyeblink startle amplitudes (+SE's) during the CS movements and the classes of GS movements (CLASS1–3) in the predictable and the unpredictable group during the generalization blocks (G1–G2). **(A)** Self-reported fear of movement-related pain during acquisition (CSs). **(B)** Self-reported fear of movement-related pain during generalization (CSs and GSs).

behavior that characterizes many musculoskeletal pain disorders (Meulders and Vlaeyen, 2013a). In addition, there is a growing interest for the study of fear generalization and in particular the possible psychological and neurological processes that could influence the process of fear generalization (Vervliet et al., 2010a,b; Lenaert et al., 2012). However, in the field of pain, research on this topic received little attention so far. Therefore, the present study, building on the previous work in our lab, aimed to investigate whether pain predictability by either, a discrete cue (predictable) or contextual cues (unpredictable) affects the degree of generalization learning to novel cues that were never paired with pain. We hypothesized that (1) cued pain-related fear spreads selectively to novel movements that are more similar to the CS+ than to those similar to the CS− (i.e., fear generalization gradient in the predictable group), (2) generalization gradients are flattened in the unpredictable group compared with the predictable group.

First, our findings corroborate previous research in establishing *cued pain-related fear* in response to a movement that was consistently paired (CS+) with a pain-US relative to a movement that was never paired (CS−) with pain (Meulders et al., 2011, 2012;

Table 3 | Manipulation check measures: mean SAM unhappiness ratings and retrospective pain-US expectancy ratings (and SD) for the CS_p+ and CS_p- in the predictable group and the CS_u1 and CS_u2 in the unpredictable group.

***N* = 58**	**Predictable group**		**Unpredictable group**	
	CS_p+	**CS_p-**	**CS_u1**	**CS_u2**
SAM unhappiness (Likert scale; 1–5)	3.17 (0.85)	2.17 (0.71)**	2.55 (0.91)	2.79 (0.77)
Retrospective pain-US expectancy (VAS; 0–100)	68.66 (20.63)	25.45 (21.09)**	36.17 (22.05)	53.48 (24.68)*

**p < 0.01; **p < 0.001; for the CS_p+/CS_p- differences and the CS_u1/CS_u2 differences in the predictable and the unpredictable group respectively.*

Meulders and Vlaeyen, 2012, 2013a,b). This was evident in the eyeblink startle data as well as in the verbal fear ratings in the predictable group. The unpredictable group on the other hand, did not demonstrate such differential conditioned responding for the unreinforced movements in either of the dependent measures. In line with previous research, the ITI startle amplitudes were significantly elevated in the unpredictable group compared with the predictable group, indicating that participants in the unpredictable group acquired *contextual pain-related fear*.

Second, we successfully demonstrated a fear generalization gradient in the predictable group, but not in the unpredictable group in both the verbal fear ratings as in the eyeblink startle measures. That is, there was a linear decrease in fear responses for the generalization movements (GSs) approaching the original CS− in both measures. However, this trend was more pronounced in the startle measures than in the verbal fear ratings. Moreover, there was an additional quadratic decrease in fear responses for the generalization movements approaching the original CS− in the startle measures. These data seem to suggest that the linear trend in the verbal ratings is rather driven by the CS+ and CS− differences than by the gradual decline in conditioned responding in response to the GS movement classes based on their similarity with the CSs. This interpretation is further supported by the presence of the quadratic trend in the verbal ratings (which was not present in the startle data). These linear trends were only present in the first generalization block but not in the second. There are several explanations for the absence of the gradient in the second generalization block and the absence of a true gradient in the verbal ratings. The generalization test was performed under extinction, hence CSs and GSs were unreinforced during this phase. Under condition of extinction there might be a steady decline in fearful responding that already starts within a few trials. The verbal ratings were assessed *retrospectively* after each block, that is, after not less than 32 trials, therefore partial extinction probably already took place at the test of the first block. These extinction effects combined with ongoing discrimination learning (differences between the CS+/CS− and the GS movement classes) during the generalization phase might explain the absence of a gradient in the fear ratings. Although the CS+ are still higher than for the CS− and the GS classes during generalization, compared with the end of the acquisition phase, the fear ratings have significantly decreased (mean fear ratings CS+ during ACQ2 = 62.48 vs. mean fear ratings CS+ during G1 = 31.86 vs. mean fear ratings CS+ during G2 = 19.83) which supports our *post hoc* interpretation of combined extinction and ongoing discrimination learning during the unreinforced generalization phase. This is not the case for the startle measures, because probes are delivered throughout the generalization test providing a more online representation of the fear responses. In line with our *post hoc* explanation, the difference in fear reported to the CS+ and the CS− declined significantly from the end of acquisition to the first generalization block, $F(1, 56) = 23.22$, $p < 0.001$, whereas this decline was not the significant in the startle measures $F(1, 56) = 1.33$, $p = 0.25$. Follow-up studies might consider using a partial reinforcement scheme during generalization testing.

Third, some procedural aspects deserve some more attention. For instance, another design feature that was different compared with the previous study by Meulders and Vlaeyen (2013a) is that the trial timing is more spread out as a BSs design was used instead of a WSs design [meaning that the relative (un)predictability of the US could not be derived from the experience with both conditions]. These features might have influenced the safety learning in the unpredictable group. That is, verbal fear ratings in response to the unreinforced movements in the unpredictable group are much lower than typically observed using this paradigm so far. Probably, because delayed trace conditioning is less likely to occur when inter intervals are longer and thus spilling-over of contextual fear to the technically safe movements is less obvious, suggesting that the unreinforced movements in the unpredictable group truly gained inhibitory properties.

Some limitations are worthy to discuss as well. *First*, the movements that the participants had to perform were not chosen voluntarily, like previous studies using a similar paradigm (Meulders et al., 2011, 2012; Meulders and Vlaeyen, 2012, 2013a), but instead were signaled by a number corresponding with the quadrant in which they had to move presented before each movement. This was mainly done for statistical purposes, as it assured an equal number of startle probes delivered during each of the movements. Nevertheless, one could argue that the number cue, and not the movement *per se* acted as a predictor for the pain-US because there was also a perfect contingency between the number cue and the occurrence of the pain-US. This is rather unlikely for at least two reasons: (1) because it is not just an inert cue, the movement is probably more salient which in turn leads to an advance in terms of cue competition (De Houwer and Beckers, 2002; Shanks, 2010), and (2), following the componential CS representation view (Vogel et al., 2003), late components of a CS typically gain excitatory properties by virtue of their temporal proximity with the US, whereas early components of a CS gain inhibitory properties. In the present study, the complex CS might comprise an early visual component (number cue) and a late proprioceptive component (movement). Hence, it would be predicted that participants would learn that the pain-US will not occur (i.e., inhibitory learning) before they actually performed the movement. *Second*, during the practice phase, the participants were already pre-exposed to the generalization stimuli which might have attenuated the generalization gradient. Generalization is the opposite of discrimination, which is the degree to which the cortical representation of one stimulus can be distinguished from that of other stimuli. In other words, the precision by which the representation of a stimulus is encoded is negatively related to the array of stimuli that it can activate (Flor et al., 2001). Therefore, if participants are familiarized with the GSs before the generalization test, it is possible that differences with the CSs are encoded in more detail leading to weakened generalization. *Third*, we only included female participants in our study so the results cannot be generalized to a male population. There are some indications that woman react with stronger pain sensitization to (un)predictable situations than men do (Meulders et al., 2012).

In conclusion, this study provided further evidence for the notion that associative learning is involved in the acquisition of cued and contextual pain-related fear. More importantly, this is the first study to demonstrate a generalization gradient of cued pain-related fear (predictable pain group), that is, more spreading of fear toward novel movements that are proprioceptively related to the original painful movement than to the ones resembling the non-painful movement. There was no such generalization gradient for contextual pain-related fear (unpredictable pain group). Taken together, this paradigm represents a novel tool to scrutinize the largely understudied phenomenon of fear generalization in patients with chronic musculoskeletal pain and mapping possible pathological differences in generalization gradients and the spreading of pain in patients as compared with healthy controls. Future research might focus on the conditions under which these generalization gradients can be broadened or reduced in order to develop new methods to limit the spreading of fear of movement in chronic pain patients. This line of research warrants further investigation, especially given the intriguing but untested idea that based on the close relationship between fear and pain, fear generalization might be associated with subsequent spreading of pain.

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Plasticity in the visual system is associated with prosthesis use in phantom limb pain

Sandra Preißler[1]*, Caroline Dietrich[1], Kathrin R. Blume[1], Gunther O. Hofmann[2,3], Wolfgang H. R. Miltner[1] and Thomas Weiss[1]

[1] *Department of Biological and Clinical Psychology, Institute of Psychology, Friedrich Schiller University, Jena, Germany*
[2] *Berufsgenossenschaftliche Kliniken Bergmannstrost Halle/Saale, Halle, Germany*
[3] *Department of Trauma, Hand and Reconstructive Surgery, University Hospital Jena, Jena, Germany*

Edited by:
Martin Diers, Central Institute of Mental Health, Germany

Reviewed by:
Martin Lotze, University of Greifswald, Germany
Florence B. Pomares, McGill University, Canada

****Correspondence:***
Sandra Preißler, Department of Biological and Clinical Psychology, Friedrich Schiller University, Am Steiger 3/1, D-07743 Jena, Germany
e-mail: s.preissler@uni-jena.de

The experience of strong phantom limb pain (PLP) in arm amputees was previously shown to be associated with structural neural plasticity in parts of the cortex that belong to dorsal and ventral visual streams. It has been speculated that this plasticity results from the extensive use of a functional prosthesis which is associated with increased visual feedback to control the artificial hand. To test this hypothesis, we reanalyzed data of cortical volumes of 21 upper limb amputees and tested the association between the amount of use of the hand prosthesis and cortical volume plasticity. On the behavioral level, we found no relation between PLP and the amount of prosthesis use for the whole patient group. However, by subdividing the patient group into patients with strong PLP and those with low to medium PLP, stronger pain was significantly associated with less prosthesis use whereas the group with low PLP did not show such an association. Most plasticity of cortical volume was identified within the dorsal stream. The more the patients that suffered from strong PLP used their prosthesis, the smaller was the volume of their posterior parietal cortex. Our data indicate a relationship between prosthesis use and cortical plasticity of the visual stream. This plasticity might present a brain adaptation process to new movement and coordination patterns needed to guide an artificial hand.

Keywords: phantom limb pain, magnetic resonance imaging, morphometry, use of myoelectric prostheses, visual stream

INTRODUCTION

After amputation and deafferentation of a limb, up to 98% of individuals report vivid sensations in the missing body part (Ramachandran and Hirstein, 1998). In turn, up to 80% of amputees describe these sensations as painful (Flor, 2002; Ephraim et al., 2005). Such painful sensations are referred to as phantom limb pain (PLP) (Jensen et al., 1985). PLP includes a variety of different qualities such as burning, stabbing, or cramping (Katz and Melzack, 1990; Sherman, 1997; Giummarra et al., 2007). PLP must be differentiated from stump pain, which is characterized by painful sensations solely located in the residual limb. Furthermore, PLP also needs to be differentiated from non-painful sensations (phantom limb sensations) and the feeling of the enduring presence of the missing body part (phantom limb awareness) (Flor et al., 2006).

Previous studies have described structural and functional plasticity in different parts of the neuraxis following amputation (Flor et al., 2006). Functional plasticity was described in animal studies (Merzenich et al., 1984; Pons et al., 1991) as well as in humans (Weiss et al., 1998, 2000; Lotze et al., 2001; Flor et al., 2006) especially in primary somatosensory cortex (SI). It was assumed that sensory areas that formerly represented the amputated structure of the body became overtaken by the neural representations of neighboring body structures in SI. Flor et al. (1995) reported that the amount of such functional cortical reorganization is highly correlated with PLP intensity.

Beside this well replicated observation of functional cortical plasticity, additional neural plasticity of cortical volume was identified following amputation by Draganski et al. (2006) using voxel-based morphometry as well as by our research group (Preissler et al., 2013) using freesurfer. Thereby, amputation in upper limb amputees is associated with anatomical alterations in parts of the cortex that belong to dorsal and ventral visual streams (Preissler et al., 2013). Such plasticity was hypothesized to reflect a use-dependent increase of visual control in operating a hand prosthesis due to the fact that somatosensory information is usually not provided by most functional prostheses. Therefore, most amputees have to compensate this loss of information by increasing visual control of the prosthesis. A former national survey of 1,575 amputees addressed the lack of sensory feedback and the increased requirement of visual control by requesting "better control mechanisms that require less visual attention" (Atkins et al., 1996). Given that the technology has not changed dramatically since then, it still represents an important issue for most amputees with prostheses (for review see: Biddiss and Chau, 2007).

Cortical plasticity in the visual system might be a significant consequence of intensive visuomotor training to improve hand-eye coordination, as it was recently shown by Draganski et al. (2004). These authors used voxel-based morphometry to compare a group of volunteers before and after extensive juggling training across a period of 3 months. Before training, there was no structural difference within the visual system between the training group and a control group that received no juggling training. However, after 3 months, the juggling group showed selective structural increase of cortical volume in areas of the visual system. Transferring these observations to the situation of an arm amputee and prosthesis user, the increased visual control of the prosthetic device might also result in an increase of gray matter volume in the visual pathways of such individuals.

In line with this assumption is that we recently observed a gain in volume in the visual stream of arm amputees (Preissler et al., 2013) that might be a consequence of prosthesis use. There is empirical evidence that functionality of a prosthesis and amount of prosthesis use are negatively associated with PLP (Lotze et al., 1999; Weiss et al., 1999; Raichle et al., 2008; Dietrich et al., 2012). Interestingly, amputees with strong PLP showed less volume gain in the areas belonging to the visual stream (Preissler et al., 2013).

Therefore, it can be hypothesized that the extent to which vision is needed to provide feedback about the artificial hand depends on the quality and the quantity of prosthesis use and might be result in (feedback-dependent) cortical plasticity in the visual system. The aim of the study was to investigate the relationship between prosthesis use, PLP, and anatomical alterations in the visual system. More precisely, we hypothesize, first, a negative association between PLP and prosthesis use, at least in a sample of patients with strong PLP, and second, a relationship between the amount of prosthesis use and cortical volume in the visual stream of patients after upper limb amputation.

MATERIALS AND METHODS

PARTICIPANTS

These data present a reanalysis of a published dataset (Preissler et al., 2013).

A sample of 21 patients amputated at their right upper limb participated in the study (age: mean: 44.5 years; min: 20 years, max: 62 years). Except for three female patients, all subjects were male. Exclusion criteria were plexus avulsion, amputations of further body parts, congenital malformation, and/or any neurological or psychiatric disorder (for sociodemographic and clinical data please refer to **Table 1**). Amputation was undertaken following trauma in 19 patients and due to sarcoma in two patients. The study was approved by the ethics committee of the Friedrich Schiller University. Informed consent was obtained from each subject prior to examination and participation in the study.

ASSESSMENT OF PHANTOM LIMB PAIN

The amputees were requested to rate the intensity of their PLP using a 10 cm Visual Analog Scale (VAS) with "no pain at all" represented by the left end point and "the strongest pain I can imagine" represented by the right end point of the scale (Scott and Huskisson, 1976).

Table 1 | Demographic and clinical details of all 21 amputated patients.

	Gender	Age in years	Side of amputation	Time since amputation in month	Stump length in cm	Cause of amputation	PLP rating (VAS)	BDI	Prosthetic use index	MPI_LI
1	M	32	r	19	ca. 45	Trauma	2.76	14	2	–
2	M	28	r	2	47	Trauma	0.50	2	16	1
3	M	43	r	180	63	Trauma	4.20	5	16	3
4	M	62	r	600	–	Sarcoma	1.40	8	8	3
5	M	24	r	29	37.5	Trauma	0.00	2	8	0
6	M	38	r	53	52.5	Trauma	2.45	30	16	2
7	F	56	r	133	–	Embolism	4.40	20	16	5
8	M	52	r	152	47	Trauma	5.20	8	1	5
9	M	27	r	14	42.5	Trauma	2.00	6	0	1
10	M	46	r	104	12	Trauma	9.00	12	12	5
11	M	20	r	1	11	Trauma	0.00	4	0	0
12	M	61	r	254	28	Trauma	0.00	1	6	2
13	M	53	r	230	14	Trauma	4.50	4	16	3
14	M	57	r	346	51	Trauma	0.00	6	16	1
15	M	59	r	59	26.5	Trauma	5.40	36	8	5
16	M	34	r	118	20	Trauma	0.00	5	16	2
17	M	59	r	11	46.5	Trauma	3.00	5	16	3
18	F	22	r	1	8	Trauma	6.05	40	0	–
19	M	57	r	60	71	Trauma	5.20	2	12	4
20	M	53	r	396	52	Trauma	7.50	17	16	6
21	F	51	r	105	40	Trauma	5.60	17	8	4

PLP, phantom limb pain; VAS, visual analog scale; BDI, Beck Depression Inventory-II; MPI_LI, life interference scale of the Multidimensional Pain Inventory.

ASSESSMENT OF PROSTHESIS USE

Participants were asked to rate their amount of prosthesis use on two scales. To describe their weekly amount of prosthesis use, the item "How often do you wear your prosthetic device within the week?" was utilized. For the rating a five point ordinal scale was used (0 = not at all, 1 = less than twice, 2 = every second day, 3 = nearly daily, 4 = every day). The second question focused on the daily amount of use ("How often do you wear your prosthetic device at each day?"). For this item, a five point categorical scale was used (0 = never, 1 = 1–2 h, 2 = several hours but not continuously, 3 = continuously the whole morning or afternoon, 4 = from morning to night). Since the prosthetic device might not be used every day, the overall amount of prosthesis use was expressed as the product of the subjects' score for the weekly rating multiplied by the score of the daily rating.

ASSESSMENT OF LIFE INTERFERENCE

In addition, subjects filled-in "The life interference scale" of the German version of the Multidimensional Pain Inventory (MPI; Kerns et al., 1985; Flor et al., 1990). The MPI is a questionnaire for multidimensional assessment of chronic pain. It consists of 52 items, which are subdivided into three sections (Kerns et al., 1985). The first section includes five scales that measure the patient's perception of pain severity, life interference caused by chronic pain, experienced life control, affective distress, as well as social support. The participants have to respond on a 7-point scale ranging from 0 to 6.

ASSESSMENT OF DEPRESSION SYMPTOMS

The subjects' depression symptoms were assessed with the Beck Depression Inventory-II (BDI-II; Beck et al., 1996). The BDI-II is a 21-item questionnaire that assesses somatic, affective, and cognitive symptoms due to depression. Participants answer questions based on a 4-point scale ranging from 0 (not at all) to 3 (extreme form of each symptom) for the last 2 weeks. Scores range from 0 to 63 whereby scores of 30 and higher point to a "severe depression."

GROUP ASSIGNMENT

The participants were subdivided into a group with low to medium PLP (age: mean: 38.3 years, min: 20 years, max: 62 years) and into a second group with strong PLP (age: mean: 50.1 years, min: 22 years, max: 59 years). Group assignment was based on the impact PLP has on the patients' daily life as measured by the life interference scale of the MPI according to a suggestion of Jensen et al. (2001).

Four ANOVAS with life interference as independent variable and mild versus severe pain as grouping variable were performed. The grouping variable was based on the VAS score (a) less than 2, (b) less than 3, (c) less than 4, (d) less than 5. Each model reached significance, with the second model with border VAS = 3 reaching the highest F-score [$F(19, 1) = 24.86$]. Based on these results, we divided our group into two subgroups, one with no to low PLP (VAS < 3) and the other with moderate to strong PLP (VAS ≥ 3).

Both groups do not significantly differ in the presented clinical and demographic variables besides as expected in PLP rating [low to medium PLP: $M = 0.9$; SD = 1.1; strong PLP: $M = 5.5$; SD = 1.6; $t(19) = 7.32$, $p < 0.000$] and experienced life interference [low to medium PLP: $M = 1.5$; SD = 1.1; strong PLP: $M = 4.3$; SD = 1.1; $t(19) = 5.84$, $p < 0.000$]. The groups do not differ in the amount of prosthetic use [low to medium PLP: $M = 8.8$; SD = 6.8; strong PLP: $M = 11.0$; SD = 6.1; $t(19) = 0.44$, $p = 0.78$].

MRI DATA ACQUISITION

For morphometric analyses, two T1-weighted sagittally oriented sequences were acquired for all subjects (192 slices; flip angle: 30° ; matrix: 256 × 256; voxel size: 1 × 1 × 1 mm). As the participants began to be studied in 2005, the first eight subjects were measured on a 1.5-T MRI scanner (Siemens Magnetom Vision Plus, Erlangen, Germany; TE: 5 ms; TR: 15 ms) using a single-channel circulary-polarized (CP) head coil. For the remaining 13 participants, a 3-T MRI scanner (Siemens Magnetom Trio, Erlangen, Germany; TE: 3.03 ms; TR: 2.3 ms) with a 12-channel head matrix coil was used. Head movement was minimized using a vacuum pad.

CORTICAL RECONSTRUCTION AND VOLUMETRIC SEGMENTATION

Cortical reconstruction and volumetric segmentation was performed with the Freesurfer image analysis suite, which is documented and freely available for download online (http://surfer.nmr.mgh.harvard.edu/). Briefly, the processing includes motion correction and averaging (Reuter et al., 2010) of the two volumetric T1-weighted images, removal of non-brain tissue using a hybrid watershed/surface deformation procedure (Segonne et al., 2004), automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures (Fischl et al., 2002, 2004), intensity normalization (Sled et al., 1998), tessellation of the gray matter-white matter boundary, automated topology correction (Fischl et al., 2001; Segonne et al., 2007), and surface deformation. The last procedure is accomplished by following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class (Dale and Sereno, 1993; Dale et al., 1999; Fischl and Dale, 2000). Once the cortical models are complete, a number of deformable procedures can be performed for further data processing and analyses including surface inflation (Fischl et al., 1999a), registration to a spherical atlas which utilizes individual cortical folding patterns to match cortical geometry across subjects (Fischl et al., 1999b), parcellation of the cerebral cortex into units based on gyral and sulcal structure (Fischl et al., 2004; Desikan et al., 2006), and creation of a variety of surface based data including maps of curvature and sulcal depth. This method uses both intensity and continuity information from the entire three-dimensional MR volume in segmentation and deformation procedures to generate representations of cortical thickness, calculated as the closest distance from the gray/white boundary to the gray/cerebrospinal fluid boundary at each vertex on the tessellated surface. Freesurfer morphometric procedures have been demonstrated to show good test-retest reliability across scanner manufacturers and across field strengths (Han et al., 2006). Volume measures may be mapped on the inflated surface of each participant's reconstructed brain. Maps are smoothed using a circularly symmetric Gaussian kernel across the surface with a standard deviation of 10 mm and averaged across participants using a non-rigid high-dimensional spherical averaging method to align cortical folding patterns. This procedure provides accurate matching of morphologically homologous cortical locations among participants, resulting in a mean measure of cortical thickness for each group at each point on the reconstructed surface. The entire cortex in each participant was visually inspected and any inaccuracies in segmentation were manually corrected by experts in brain anatomy who were blind to group membership.

Statistical comparisons of global data and surface maps were generated by computing a general linear model of the effects of amount of prosthesis use on volume at each vertex. Cortical volume clusters were first displayed using a threshold that shows all vertices with p-values below 0.005. Additionally, only clusters with a minimum size of 10 vertices were accepted (Lieberman and Cunningham, 2009).

STATISTICS

Apart from the Freesurfer analysis suite, statistical analyses were performed using IBM SPSS Statistics 20 (version 20.0, SPSS Inc., an IBM Company, Chicago, IL, USA). As the measure of prosthesis use is not a continuous variable, correlations were determined using a non-parametric measure of statistical dependence (Kendall's tau; τ).

RESULTS

BEHAVIORAL ANALYSIS

We found no relation between PLP and the amount of prosthesis use for the whole patient group ($\tau = -0.023$; $p = 0.448$). There was no relation between the aforementioned variables in the group with low PLP ($\tau = -0.111$; $p = 0.345$); however, in the group with strong PLP, PLP was significantly associated with less prosthesis use ($\tau = -0.415$; $p = 0.049$).

MORPHOMETRIC ANALYSES

All patients

We found correlations between the amount of prosthesis use and gray matter volume in different cortical areas, especially in parts of the left posterior parietal lobe, as well as a positive association between cortical volume of the right visual association cortex and the amount of prosthesis use (see **Table 2**; **Figure 1**).

Patients with low to medium phantom limb pain

Patients with low to medium PLP showed associations between cortical volume and amount of prosthesis use in two areas of the cortex. A region of the right posterior parietal lobe was negatively, and a part of the paracentral sulcus was positively associated with the amount of prosthesis use (see **Table 3**; **Figure 2A**).

Patients with strong phantom limb pain

Cortical volume of patients with strong PLP was negatively associated with the amount of prosthesis use in the left posterior parietal lobe, left middle temporal gyrus, and parts of the dorsolateral prefrontal cortex (DLPFC) on both hemispheres. The volume of a single cortex region showed a positive association with the amount of prosthesis use: the right intraparietal sulcus (see **Table 3**; **Figure 2B**).

Influence of covariates

To ensure that the results mentioned above are not caused by the different field power of the two different MRI scanners or age of the participants, we performed additional partial correlations with scanner type, or age as covariate, respectively. None of these covariates had a significant influence on the results.

DISCUSSION

The aim of this study was to investigate the relationship between prosthesis use, PLP, and cortical volume plasticity in the visual system. On the behavioral level, a significant correlation between PLP and prosthesis use was found in patients with strong PLP. Only in these patients stronger PLP was associated with less use of the prosthesis. This association was neither significant for the whole group of patients nor for the subgroup with low PLP.

Correlation analyses revealed significant associations between the amount of prosthesis use and the cortical volume of brain regions that are part of the visual streams for all patients as well as in the patient group with strong PLP.

BEHAVIORAL ANALYSIS

Previous studies have already shown that the amount of prosthesis use is associated with PLP reduction. Thus, Weiss et al. (1999) investigated nine patients using a Sauerbruch prosthesis and 12 persons wearing cosmetic prostheses. The authors demonstrated that the use of the "active" Sauerbruch prosthesis is accompanied

Table 2 | Areas with correlational relation between the reported amount of prosthesis use and cortical volume for all patients ($N = 21$).

Region		Subregion	Talairach coordinates			Cluster size	DCA	Z-score
			X	Y	Z			
Parietal lobe	LH	Intraparietal sulcus	−37.7	−46.1	34.5	35	−	3.24
		Superior parietal sulcus	−43.2	−58.2	27.5	29	−	3.40
Temporal lobe	RH	Middle temporal gyrus	42.4	−57.8	−9.6	86	−	4.20
Occipital lobe	LH	Cuneus, BA 18	−3.6	−79.6	21.2	20	−	3.24
	RH	Lingual gyrus, BA 18	10.5	−85.7	−12.7	21	+	3.22

LH, left hemisphere; RH, right hemisphere; BA, Brodmann area; DCA, direction of cortical association; −, negative correlation between cortical volume and amount of prosthesis use; +, positive association between cortical volume and amount of prosthesis use.

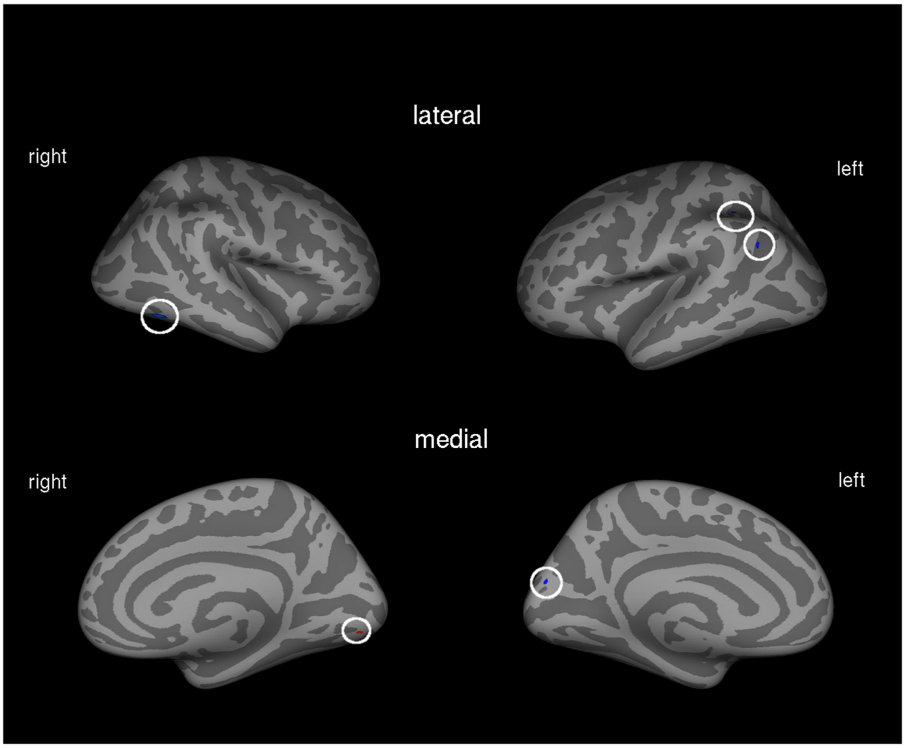

FIGURE 1 | Correlation between amount of prosthesis use and cortical volume in the total patient group ($N = 21$). Blue areas indicate negative associations, areas in red show positive associations.

Table 3 | Areas with correlational relation between the amount of prosthesis use and cortical volume for patients with low to medium phantom limb pain ($N = 10$) and for patients with strong phantom limb pain ($N = 11$).

Subregion			Talairach coordinates			Cluster size	DCA	*Z*-score
			X	Y	Z			
PATIENTS WITH LOW TO MEDIUM PHANTOM LIMB PAIN								
Parietal lobe	RH	Intraparietal sulcus	31.6	−55.2	40.3	20	−	3.47
Frontal lobe	RH	Paracentral	3.7	−29.0	66.9	34	−	3.93
PATIENTS WITH STRONG PHANTOM LIMB PAIN								
Parietal lobe	LH	Intraparietal sulcus (posterior)	−38.7	−49.2	34.3	26	−	3.19
	RH	Intraparietal sulcus	40.7	−40.8	35.5	15	+	3.59
Temporal lobe	LH	Middle temporal gyrus	−55.9	−3.4	−25.9	45	−	3.73
Frontal lobe	LH	Inferior frontal gyrus	−43.1	28.6	−14.2	113	−	3.59
		Inferior frontal gyrus	−52.3	29.3	6.0	57	−	3.57
	RH	Inferior frontal gyrus	30.7	23.4	−20.1	11	−	3.17
		Rostral middle frontal gyrus	36.6	28.7	31.8	29	−	3.43

LH, left hemisphere; RH, right hemisphere; DCA, direction of cortical association; −, negative correlation between cortical volume and amount of prosthesis use; +, positive association between cortical volume and amount of prosthesis use.

by a reduction of PLP, whereas the use of the cosmetic prosthesis had no impact on PLP; four of the 12 patients even reported stronger PLP. These results indicate that patients who use their residual limb with the prosthesis more often in daily life show less PLP. This finding confirms results of a recent study of our research group showing that "active" functional hand prostheses with additional somatosensory feedback lead to further decrease in PLP (Dietrich et al., 2012).

Our results are also in accordance with a study by Lotze et al. (1999). These authors showed that the relationship between PLP

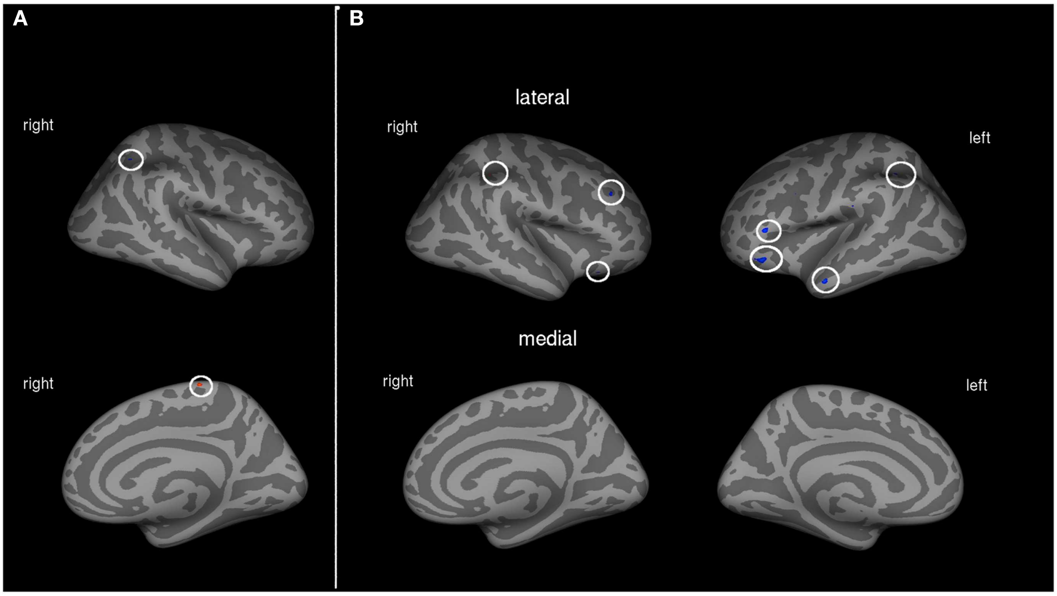

FIGURE 2 | (A) Correlation between amount of prosthesis use and cortical volume in patients with low to medium PLP ($N = 10$). Blue areas indicate negative associations, areas in red show positive associations. **(B)** Correlation between amount of prosthesis use and cortical volume in patients with strong PLP ($N = 11$). Blue areas indicate negative associations, areas in red show positive associations.

and functional cortical reorganization in SI was mediated by prosthesis use. Patients who were not provided with a functional myoelectric prosthesis showed stronger PLP and a significant larger extent of functional cortical reorganization than patients using a myoelectric prosthesis. Lotze et al. (1999) suggested that beside ongoing stimulation by the artificial device and muscular training, visual feedback from the artificial device might have a beneficial effect on functional cortical plasticity as well as on PLP. This goes in line with our former publication in which persons with strong PLP showed less cortical volume in areas belonging to the visual stream (Preissler et al., 2013).

Moreover, there is an effective therapy approach focusing on visual feedback, the mirror visual feedback therapy (Ramachandran et al., 1996; Ramachandran and Altschuler, 2009). In this therapy, a mirror is placed next to the patient's residual limb. Thereby, the mirror image creates an illusion of an intact limb (Ramachandran and Rogers-Ramachandran, 1996). The patients reported that they felt their amputated limb return. In most patients this vivid perception of their former limb seems to be followed by a reduction in PLP (Ramachandran and Rogers-Ramachandran, 1996; Ramachandran and Altschuler, 2009). An alternative approach which demonstrated that visual input is able to change somatic sensation is the rubber hand illusion (Botvinick and Cohen, 1998; Bekrater-Bodmann et al., 2012). Like mirror therapy it uses the visual but illusory replacement of the missing hand. To produce this illusion, a rubber hand is placed in front of the participant in a position that equals the perceived phantom hand of the amputee. A third therapeutic approach focusing partly on visual feedback is graded motor imagery (Moseley, 2004, 2006; Johnson et al., 2012). This training was developed for patients with complex regional pain syndrome. It aims at reducing pain by recognition, imaging and moving of the affected limb (Moseley, 2004). In the first stage, patients view photographs of a left or right hand in a variety of postures and are asked to decide whether a left or right hand is shown. These approaches demonstrate that the integration of visual feedback by means of photographs (Moseley, 2006), a mirror (Ramachandran and Altschuler, 2009; Diers et al., 2010), or a rubber hand (Ramakonar et al., 2011; Bekrater-Bodmann et al., 2012) can reduce chronic pain and PLP. This indicates that visual feedback modulates somatic, especially painful sensations. Therefore, our behavioral data suggest that the more the artificial arm is used, the more the visual system might be engaged, and the less PLP is developed. Surprisingly this only seems to hold for the group with strong PLP.

Only in amputees with strong PLP the amount of prosthesis use was negatively associated with PLP. However, as the paradigm of the present study was designed cross-sectionally, it cannot be differentiated whether the increased PLP is a consequence of the reduced prosthesis use or whether PLP affects the patients' behavior that, in turn, results in the reduced use of the artificial device. The relationship between PLP and the amount of prosthesis use might be non-linear.

MORPHOMETRIC ANALYSES

All patients

Based on the behavioral results, we suppose that structural cortical plasticity is associated with the use of the functional hand prosthesis. Such structural plasticity has been observed in many cortical areas and, according to previous observations of our research group, might also happen in the visual system when the use of the prosthesis requires increased visual control of its operation.

We found associations between cortical volumes and the amount of prosthesis use in several cortical areas. Negative associations were found in parts of the left posterior parietal cortex (intraparietal sulcus, and superior parietal sulcus), in the cuneus, and in the right middle temporal gyrus. Only the right lingual gyrus, as part of the visual association cortex, showed a positive association between volume and prosthesis use.

Visual areas in the ventral and dorsal pathways are critical areas for pattern recognition and the segmentation, classification, localization, and handling of the visual objects (Roelfsema, 2006; Kravitz et al., 2011). The dorsal stream includes occipital, posterior-temporal, and parietal regions and is mainly involved in the processing of spatial orientation of objects, the detection of movements, and eye-hand coordination. The ventral stream is located in occipital and temporal lobes; it is mainly involved in object perception (Roelfsema, 2006; Cavina-Pratesi et al., 2010; Kravitz et al., 2011; Monaco et al., 2011). The associations between the amount of prosthesis use and cortical volume are located in areas belonging to the dorsal stream.

One of the most striking results of the present investigation following upper limb amputation is the negative association between prosthesis use and cortical volume in posterior parts of the parietal lobe (intraparietal sulcus, superior parietal sulcus). We observed increasingly smaller volumes the more the amputees wore and used their prosthetic device. As part of the dorsal stream, these brain areas are important for hand orientation and eye-hand coordination in grasping (Castiello and Begliomini, 2008; Monaco et al., 2011). Since fine tuning of the prosthesis during grasping is lost due to the fact that the prosthetic devices used by the patients of our study did not include a flexible wrist, all patients lost the functional control of the wrist. This loss of wrist coordination might have been followed by a reduction of cortical volume in regions which formerly coordinated wrist movement.

The cortical volume of the intraparietal sulcus of the parietal lobe was negatively correlated to the amount of myoelectric prosthesis use. This area contains cells that organize convergence of vision and proprioception and enables subjects to perceive where objects are located in the peripersonal space (Hyvarinen and Shelepin, 1979; Hyvarinen, 1981). However, besides visual feedback, a myoelectric hand prosthesis does not provide somatosensory feedback. The more often the patients use their functional hand prosthesis, the more frequently they learn that proprioceptive and visual information do not converge during grasping which might be accompanied by a reduction of volume in the intraparietal sulcus.

The patients also showed a negative association between the amount of prosthesis use and the volume of the left cuneus. The cuneus is part of the visual association cortex. It is known to be involved in bottom-up, stimulus-driven control of visuo-spatial selective attention, e.g., it is engaged by stimulus-driven orienting (Hahn et al., 2006). However, prosthesis use is much more dominated by top-down control since patients need to plan ahead their movements intentionally (Atkins et al., 1996). It can be reasoned that with increasing prosthesis use, patients rely more often on top-down processes instead of bottom-up control. Amputees may be forced to focus their attention to their prosthetic device while using it, and therefore might pay less attention to their surroundings, and, as a result, show less cuneus activation. This may cause a diminished engagement of the cuneus. Therefore, the negative correlation between prosthesis use and the volume of the cuneus might represent a reduced functional use of this area accompanied by elevated use of the prosthetic device.

In addition to the described negative associations between cortical volume and prosthesis use, the right lingual gyrus showed a positive relationship with the amount of prosthesis use. For this part of the visual association cortex, Schiltz et al. (1999) showed an orientation-specific function of the lingual gyrus. They studied the effect of extensive training in a visual orientation discrimination task. Orientation-specific information is very important for individuals who need to use an artificial device during grasping. Unlike healthy people, they cannot change the position of the hand while grasping spontaneously. Therefore, persons with upper limb amputation need to plan the grip process further ahead. Thus, orientation-specific information of an object's position gains more importance. The amputee needs to focus on the object as well as on how to approach it before he/she starts grasping the object. More extensive use of the artificial device requires a more detailed processing of the object-specific orientation information. This can be followed by a use-dependent increase in cortical volume of areas that process such orientation-specific information. Hence, the patients show more volume of the right lingual gyrus, the more they actively used their artificial device.

Patients with strong phantom limb pain

Patients with strong PLP showed significant associations between prosthesis use and cortical volumes in a larger amount of areas than patients with low PLP. These associations indicate that PLP is accompanied by more cortical alterations than the amputation itself which is in line with previous data on anatomical alterations (Makin et al., 2013; Preissler et al., 2013). In patients with strong PLP, the amount of prosthesis use was negatively correlated with the cortical volume of different areas corresponding to the dorsal and ventral visual streams. Surprisingly, these alterations were negative, i.e., patients with strong PLP showed more cortical volume when prosthesis use was less frequent. Since we hypothesized that less frequent use of the prosthesis will result in lower necessity of visual control of the artificial hand, these findings seem to be contra-intuitive. However, it might well be that the brain is forced to adapt to the new requirements entailed by prosthesis use as explained in the previous paragraphs. Moreover, on the behavioral level we found that less prosthesis use was associated with stronger PLP within this group of strong PLP patients. As the PLP level in this group was constantly stronger, it might have an indirect influence on the cortical volume of the visual streams.

The most striking part of the visual stream which is negatively correlated to the frequency of prosthesis use is located in the left posterior parietal cortex, the intraparietal sulcus. This might reflect an adaptation to the use of an artificial device which substitutes a few functions of the former hand (e.g., wrist orientation, which is discussed extensively in the former section of discussion). The more often a prosthesis is worn, the more the brain adapts to the new movement patterns as it gains more experience with regard to functions of the former hand which are not necessary anymore to guide the artificial hand, and others which are still useful. Therefore, this might be an area showing a use-dependent specific adaptation. Interestingly, this association mirrors the result in the group of all patients, but was not existent in patients with low PLP.

Taken into account that higher prosthesis use is associated with lower PLP in patient group with strong PLP, this might indicate an adaptation process existing in patients with strong PLP but not in patients with low PLP.

Patients with low to medium phantom limb pain

In patients with low to medium PLP, only two of the analyzed brain areas showed associations with the amount of prosthesis use. One area that is part of the right intraparietal sulcus was negatively correlated with the amount of prosthesis use. The second region where associations between the amount of prosthesis use and cortical volume could be shown is the paracentral sulcus. The cortical volume in this area was positively associated with the amount of prosthesis use.

The negative association between the cortical volume in the right intraparietal sulcus as part of the posterior parietal cortex, and prosthesis use contrasts the result for the group with strong PLP. It supports the hypothesis that the prosthesis use differs qualitatively as a function of PLP and might indicate that patients with lower PLP need another amount of visual attention in their prosthesis use than patients with strong PLP. This is potentially reflected by the different associations between cortical volume and amount of prosthesis use in the right intraparietal sulcus.

There is a part of the paracentral sulcus where patients with low PLP showed more cortical volume when they used their prosthesis more frequently. This region is known as the supplementary eye field (Grosbras et al., 1999). It is located at the most rostral part of the supplementary motor area. This region is important for the control of eye movements. The association between the cortical volume and the prosthesis use was found right-sided. This goes in line with an assumption of Grosbras et al. (1999) that the right supplementary eye field is required for aspects of visual guidance. Using a prosthesis requires permanent visual guidance (Atkins et al., 1996; Biddiss and Chau, 2007). This correlation between cortical volume of the right paracentral sulcus and prosthesis use might reflect the greater demand of visual control in patients who need upper limb prostheses.

LIMITATIONS AND FUTURE DIRECTIONS

Our study has several limitations. The sample size is small. As we studied a rare patient group and due to technical development in the course of this research project the patients were measured on two different MRI scanners with different field strengths, this might, even if controlled for, induce a bias. However, none of the patients was scanned on two different scanners longitudinally, so that all changes are related to differences on the same scanner. Nevertheless, results should be interpreted with caution.

The quality of prosthesis use should be assessed in future studies as well as the quantity of prosthesis use to account for potential influences of both. Furthermore, we can only make limited conclusions regarding the dynamics of morphological brain changes over time. Further research with a longitudinal design might help to account more properly for changes over time on the behavioral level as well as for morphometric changes. Such studies would probably allow to access use-dependent cortical plasticity which may have vast clinical implications for the treatment of chronic pain.

CONCLUSION

Our behavioral data support the hypothesis that PLP might change as a function of increased prosthesis use. This association is strongly expressed in the group of patients suffering from strong PLP. Unfortunately, we cannot reason whether prosthesis use is followed by less PLP or strong PLP leads to a decrease of prosthesis use.

Based on the amputees' behavior, we differentiated structural cortical alterations connected to the amount of prosthesis use *per se* and those that reflect the intensity of PLP. Structures that showed volumetric plasticity are regions associated with both, the requirements of the use of a functional myoelectric hand prosthesis and visual control.

The relation between amount of prosthesis use and cortical volume in the left posterior parietal cortex as part of the dorsal stream seems to be specific for the group of patients with strong PLP. Given that we could give evidence that prosthesis use seems to be differently associated to changes in the visual streams in patients with low PLP compared to patients with strong PLP.

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Reduction of pain sensitivity after somatosensory therapy in adults with cerebral palsy

Inmaculada Riquelme[1,2], Anna Zamorano[1] and Pedro Montoya[1]*

[1] Research Institute on Health Sciences, University of the Balearic Islands, Palma de Mallorca, Spain
[2] Department of Nursing and Physiotherapy, University of the Balearic Islands, Palma de Mallorca, Spain

Edited by:
Diana M. E. Torta, University of Turin, Italy

Reviewed by:
Stefaan V. Damme, Ghent University, Belgium
Massimiliano Valeriani, Bambino Gesú Ospedale Pediatrico, Italy

***Correspondence:**
Pedro Montoya, Research Institute on Health Sciences, University of Balearic Islands, Carretera de Valldemossa km 7.5, 07122 Palma de Mallorca, Spain
e-mail: pedro.montoya@uib.es

Objective: Pain and deficits in somatosensory processing seem to play a relevant role in cerebral palsy (CP). Rehabilitation techniques based on neuroplasticity mechanisms may induce powerful changes in the organization of the primary somatosensory cortex and have been proved to reduce levels of pain and discomfort in neurological pathologies. However, little is known about the efficacy of such interventions for pain sensitivity in CP individuals.

Methods: Adults with CP participated in the study and were randomly assigned to the intervention ($n = 17$) or the control group ($n = 20$). The intervention group received a somatosensory therapy including four types of exercises (touch, proprioception, vibration, and stereognosis). All participants were asked to continue their standardized motor therapy during the study period. Several somatosensory (pain and touch thresholds, stereognosis, proprioception, texture recognition) and motor parameters (fine motor skills) were assessed before, immediately after and 3 months after the therapy (follow-up).

Results: Participants of the intervention group showed a significant reduction on pain sensitivity after treatment and at follow-up after 3 months, whereas participants in the control group displayed increasing pain sensitivity over time. No improvements were found on touch sensitivity, proprioception, texture recognition, or fine motor skills.

Conclusion: Data suggest the possibility that somatosensory therapy was effective in eliciting changes in central somatosensory processing. This hypothesis may have implications for future neuromodulatory treatment of pain complaints in children and adults with CP.

Keywords: somatosensory therapy, cerebral palsy, sensitivity, pain, somatosensory processing

INTRODUCTION

Cerebral palsy (CP) may lead not only to motor disability but also to somatosensory deficits. Recent neuroimaging studies have provided evidence of significant alterations in white matter fibers connecting to sensory cortex (radiata and internal capsule), indicating that CP injuries might be reflecting disruption of sensory as well as motor connections (Hoon et al., 2002, 2009; Thomas et al., 2005). Accordingly, previous studies have shown that CP individuals display poorer tactile discrimination, stereognosis, and proprioception (McLaughlin et al., 2005; Sanger and Kukke, 2007; Wingert et al., 2009), as well as enhanced pain than healthy controls (Vogtle, 2009; Doralp and Bartlett, 2010; Malone and Vogtle, 2010; Parkinson et al., 2010; Riquelme and Montoya, 2010; Riquelme et al., 2011). Moreover, studies from our lab have proven that reduced touch sensitivity are associated with increased pain sensitivity in children with early brain injury (Riquelme and Montoya, 2010), suggesting a potential link between abnormal somatosensory experiences in early life and long-term changes in pain processing (Schmelzle-Lubiecki et al., 2007). In this sense, animal studies have revealed that brain damage provoked by asphyxia may be worsened by aberrant sensorimotor experience during maturation and could be responsible for the disabling movement disorders observed in children with CP (Coq et al., 2008).

Rehabilitation techniques based on neuroplasticity mechanisms utilizes task specific training and massed practice to drive reorganization and improve sensorimotor function (Taub et al., 1999). It is known that intensive training of somatosensory stimulation, as it occurs in musicians, may induce powerful changes in the organization of the primary somatosensory cortex (Pantev et al., 2001; Schaefer et al., 2005). Somatosensory and sensoriomotor therapies including repetitive touch stimulation, two-point discrimination training, stretching exercises, and posture training have been also proved to reduce levels of pain and discomfort in neurological pathologies such as amputees, complex regional pain syndrome, and somatic tinnitus (Flor et al., 2001; Latifpour et al., 2009; Moseley and Wiech, 2009).

In the present work, we conducted a randomized controlled study to examine the influence of a 12 weeks somatosensory stimulation therapy on pain (pain pressure thresholds), touch sensitivity (tactile threshold, stereognosis, texture recognition), proprioception, and fine motor skills in adults with CP. According with previous studies, we hypothesized that intensive training of somatosensory processing (including repetitive touch stimulation, stereognostic exercises, touch discrimination, and proprioception) would result in reduced pain sensitivity in persons with CP.

MATERIALS AND METHODS

PARTICIPANTS

Subjects with CP were recruited from occupational centers established in Majorca and Albacete (Spain) between January 2010 and July of 2011. Potential subjects were initially identified by their own physicians and invited to participate using an informational letter explaining the details of the research study. Inclusion criteria were: (1) age between 18 and 40 years old, (2) absence of chronic pain (defined as persistent and generalized pain for more than 6 months), and (3) cognitive level that allows understanding and participating in the therapy activities. Augmentative communication devices and information from parents and caregivers were used as needed to facilitate data collection in subjects with communication difficulties.

Forty adults with CP met the inclusion criteria and decided to participate in the study. They were randomly assigned to one of two study groups: intervention ($n = 20$) (six females; mean age = 30.16, SD = 4.78) or control ($n = 20$; seven females; mean age = 31.15, SD = 4.86). Participants in the control group were in the waiting list for this intervention, and they were aware that there was another condition receiving a somatosensory training. At the moment of the study, all participants were receiving a standardized physical therapy with an emphasis on maintenance of motor skills (postural control, balance, range of motion, gait, etc.), and they were asked to continue with it during the study period. Three participants of the intervention group interrupted the study after the second session and five control participants did not attend to the follow-up assessment. Type of CP and cognitive level were obtained from health records. Level of gross motor impairment was determined using the Gross Motor Function Classification Scale (GMFCS) (Palisano et al., 1997) and level of fine motor impairment was determined using the Manual Ability Classification System (MACS) (Eliasson et al., 2006). **Table 1** displays clinical characteristics of both groups.

All participants granted written informed consent according with the Declaration of Helsinki. Parents or legal tutors signed informed consents and participants corroborated their decisions to participate in the study. The study was approved by the Ethics Committee of the Regional Government of the Balearic Islands.

Table 1 | Clinical characteristics of individuals with cerebral palsy.

ID	Group	Sex	Age	CP subgroup	GMFCS	MACS	Mental retardation
1	I	F	32	A	1	1	Mild
2	I	M	33	BS	5	4	Mild
3	I	M	40	A	2	1	Mild
4	I	M	27	D	4	4	None
5	I	F	29	BS	2	1	Mild
6	I	F	31	D	4	3	Mild
7	I	M	36	BS	4	3	Mild
8	I	M	31	BS	2	2	None
9	I	M	26	D	4	3	None
10	I	M	35	BS	5	5	None
11	I	M	25	BS	4	4	None
12	I	M	24	A	1	1	Mild
13	I	F	32	BS	2	5	None
14	I	F	25	A	1	1	Mild
15	I	F	24	BS	4	1	Moderate
16	I	M	34	BS	2	4	None
17	I	M	32	BS	2	4	None
18	C	M	31	BS	4	4	Mild
19	C	F	28	BS	4	5	None
20	C	M	30	D	2	2	None
21	C	M	30	A	1	1	Mild
22	C	M	28	A	1	1	None
23	C	M	32	BS	1	1	None
24	C	M	31	BS	4	2	None
25	C	M	22	BS	5	1	None
26	C	F	28	BS	4	1	None
27	C	F	33	BS	4	1	Mild
28	C	F	37	D	1	1	Moderate
29	C	F	22	BS	3	1	None
30	C	M	27	A	1	1	Mild
31	C	M	32	BS	5	3	Mild
32	C	F	24	A	1	1	Mild
33	C	F	31	BS	1	3	Mild
34	C	M	32	BS	2	2	Mild
35	C	M	29	BS	4	3	Mild
36	C	M	32	BS	4	2	None
37	C	M	30	BS	1	4	Moderate

C, control group; I, intervention group; M, male; F, female; BS, bilateral spastic; US, unilateral spastic; D, dyskinetic; A, ataxic.

SOMATOSENSORY ASSESSMENT

Several somatosensory and motor parameters were assessed before (pre-test), immediately after (post-test), and 3 months after the therapy (follow-up). Control participants were assessed at the same time as participants from the intervention group. Assessments were performed in the occupational centers by one member of the research team (IR), who was blind for the condition to which participants were allocated and different from physiotherapists providing the intervention. Following outcome measures were obtained.

Pressure pain

Pressure pain thresholds (expressed in kgf/cm^2) were measured with a digital dynamometer and using a flat rubber tip ($1\ cm^2$). Subjects were asked to say "pain" when the pressure became painful. Pressure was released when either the pain detection threshold had been reached or when the maximum pressure of the algometer was reached. Pressure stimuli were applied bilaterally in pseudo-randomized order at six body locations (lips, cheeks, thenar eminences, thumb fingers, index fingers, and both hand dorsum) until three measurements at each location were obtained. Two average pain threshold scores were computed considering measurements at the FACE (lips, cheeks) and HANDS (thenar eminences, thumb fingers, index fingers, and both hand dorsum). Subjects were familiarized with the assessment procedure by using non-painful ranges to relieve potential anxiety. The reliability of this procedure for assessing pain sensitivity has been demonstrated in previous studies (Cathcart and Pritchard, 2006).

Touch

Fine touch sensitivity by using von Frey monofilaments (Keizer et al., 2008) was measured bilaterally at the same six body locations described before. The test consisted of a set with plastic filaments of different diameter (0.14–1.01 mm). The assessment was performed by touching the skin in a perpendicular way, pressing it slowly down until it buckled, holding it steady during 1.5 s and removing it in the same way as it was applied. After several practice trials, subjects were instructed to notify if they felt any sensation of touch by saying "yes" or "not." The procedure started with a thick filament and depending on subjects' answers, thicker or thinner filaments were applied. The sensitivity score for each body location was calculated as the mean of the three thinnest filaments detected. Null stimuli were also used to find false positive responses and responses delayed more than 3 s were noted as abnormal. Body locations were stimulated in a pseudo-randomized order. Two average tactile threshold scores were computed considering body locations at the FACE (lips, cheeks) and HANDS (thenar eminences, thumb fingers, index fingers, and both hand dorsum).

Texture recognition

Participants were touched bilaterally on cheek, lip, and hand by using objects with different textures (soft, hard, smooth, and rough). Participants wore a sleeping mask and they were asked if the stimulus was soft or hard (smooth or rough) to facilitate the answer. The four texture sensations were tested, giving one point for each correct answer. Texture recognition has been used frequently as a way to test sensitivity (Carey and Matyas, 2005).

Stereognosis

Ten common objects were used (coin, bank note, scissors, pencil, pen, comb, towel, sponge, glass, and cup) to assess stereognosis of both hands. Participants wore a sleeping mask and they were instructed to touch the object with one hand and to identify it. For individuals with motor difficulties, the examiner moved the object in participants' hands. Stereognosis was scored from 0 to 2 for each object (2 = normal, the object was correctly identified; 1 = impaired, participant was able to describe some features of the object; 0 = absent, participant was unable to identify the object) and a sum score was computed. This procedure was adapted from the Nottingham Sensory Assessment test, whose reliability has been proven in previous studies (Gaubert and Mockett, 2000).

Proprioceptive tasks

Proprioception was assessed by asking participants to reproduce or to describe passive joint movements (wrist, elbow, metacarpophalangeal joints from the second to the fifth digit, and metacarpophalangeal joint of thumb) performed by the experimenter with participants wearing a sleeping mask. Proprioception was scored according to following criteria: 2 = Normal, able to achieve final joint position within 10° range of error; 1 = partially impaired, able to appreciate joint movement but fail to detect movement direction; 0 = impaired, no appreciation of joint movement. This procedure was adapted from the Nottingham Sensory Assessment test, whose reliability has been proven in previous studies (Gaubert and Mockett, 2000).

Fine motor skills

The Purdue Pegboard Test was used to assess fine motor skills of the hand. During the test, the subject was seated in front of a pegboard with two cups on the far-right and far-left corner each containing 25 pins. The task consisted in picking up one pin at a time from the cup (left or right, depending on which hand is used) by using the thumb and index finger only and placing it on the appropriate row (left or right). Subjects were instructed to place as many pins as possible in 30 s. Three trials were performed: one with the right, one with the left, and one with both hands. For the trial with both hands, subjects were instructed to pick up simultaneously one pin with the right hand and one pin with the left hand, and to place them on the corresponding row. The assembly part of the original test was excluded. This test has been previously used to assess fine hand performance in individuals with CP (Arnould et al., 2007).

SOMATOSENSORY THERAPY

The somatosensory therapy consisted of two 45-min weekly sessions for 12 weeks (24 sessions) and conducted by two trained physiotherapists. At the beginning of the study, all participants were already receiving one or two sessions per week of physiotherapy at their occupational centers. Participants were asked to continue with their scheduled sessions in agreement with their therapists.

The somatosensory therapy included four types of somatosensory tasks focused on face and hands: touch (e.g., touching different textures, tactile location), proprioception (e.g., pushing and weight exercises), vibration (e.g., massage at different frequencies), and stereognosis (e.g., recognition of geometric forms and common household objects). Task difficulty was increased from the first to the second weekly session. Physiotherapists were instructed to document all clinical observations within each session.

STATISTICAL ANALYSIS

Analyses of variance (ANOVAs) were computed on dependent variables by using GROUP (intervention vs. control) as between-subject factor, and TIME (pre-test vs. post-test vs. follow-up) and BODY LOCATION (face vs. hand) as within-subject factors. Significant interaction effects were further analyzed by using *post hoc* pairwise mean comparisons provided by the ANOVA procedure in SPSS.

RESULTS

Participants in the intervention and the control group were similar in age, gross motor performance, manual ability, touch sensitivity, pain thresholds, stereognosis, proprioception, texture recognition, and fine motor performance scores at the beginning of the study.

Figure 1 shows means and standard deviations of tactile and pain thresholds on face and hands for both groups during the three assessment intervals (pre-test, post-test, and follow-up). A significant GROUP × TIME × BODY interaction effect was found on pain sensitivity [$F(2,29) = 3.63$, $p < 0.05$], indicating that participants in the intervention group displayed higher pain thresholds (reduced sensitivity) on both body locations during post-test and follow-up assessments than

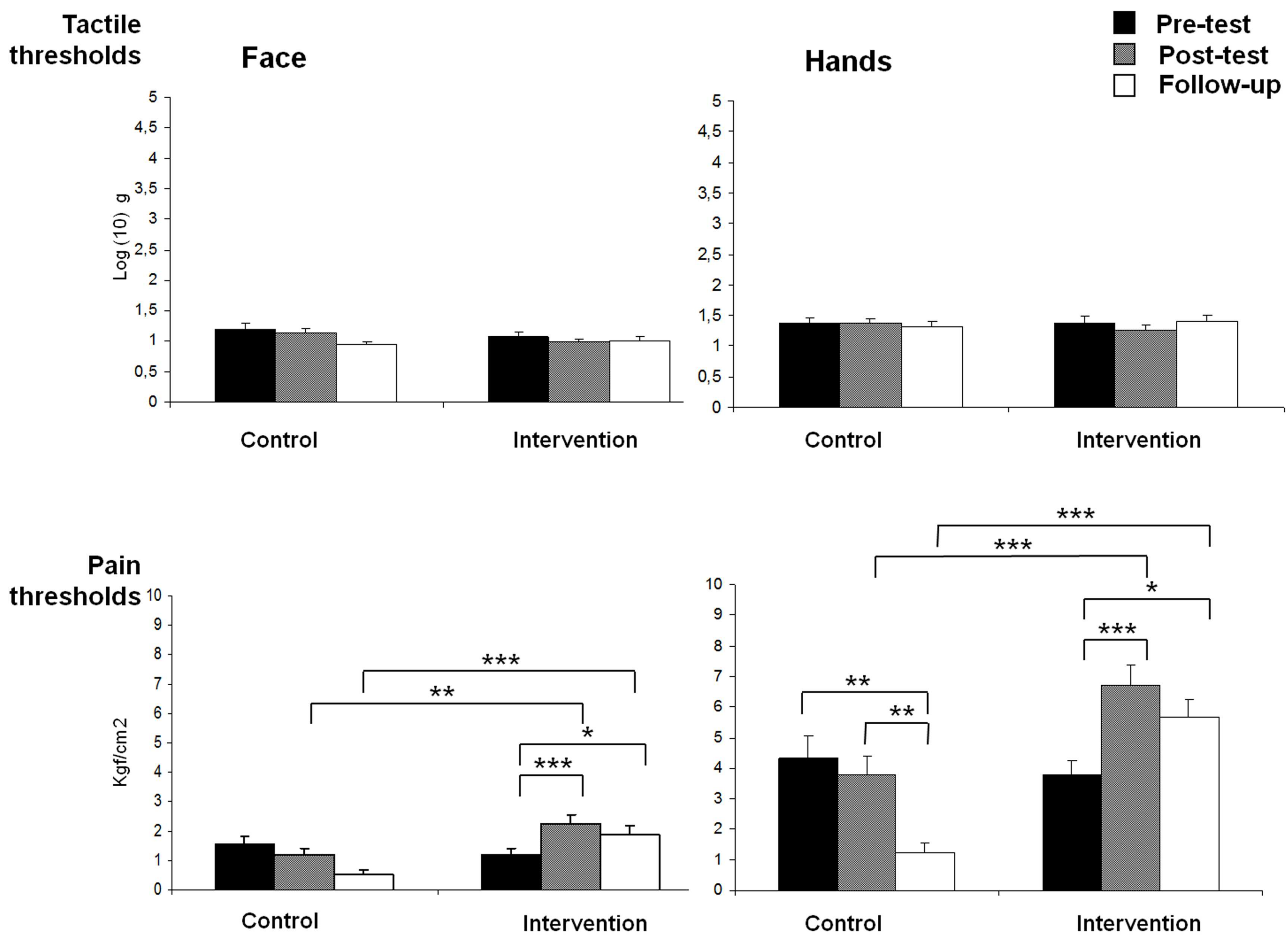

FIGURE 1 | Means of pain and tactile thresholds for each group (control and intervention), assessment time (pre-test, post-test, and follow-up) and body side (face and hands) (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$).

controls (all *post hoc* pairwise mean comparisons were significant at $p < 0.01$). Moreover, *post hoc* comparisons revealed that pain thresholds on both body locations were significantly increased from pre- to post-test (ps < 0.001) and from pre-test to follow-up (ps < 0.05) in the intervention group. By contrast, *post hoc* comparisons also indicated that pain thresholds on hand were significantly reduced (increased sensitivity) from pre-test to follow-up ($p < 0.01$), and from post-test to follow-up ($p < 0.01$) in the control group. In addition, significant effects due to GROUP [$F(1,30) = 22.18$, $p < 0.001$] (intervention group > control group), TIME [$F(2,60) = 7.29$, $p < 0.01$] (post-test > pre-test and post-test > follow-up), BODY LOCATION [$F(1,30) = 621.84$, $p < 0.001$] (hands > face), GROUP × TIME [$F(2,60) = 15.05$, $p < 0.001$], and GROUP × BODY LOCATION [$F(1,30) = 10.39$, $p < 0.01$] were observed.

For tactile thresholds, a significant GROUP × TIME effect was found [$F(2,29) = 3.72$, $p < 0.05$], showing a reduction of tactile thresholds from post-test to follow-up assessments in the control group ($p < 0.05$), but no significant effects in the intervention group. In addition, a significant effect due to BODY LOCATION was yielded [$F(1,30) = 48.05$, $p < 0.001$], indicating that tactile thresholds were higher on hands than on face.

Stereognosis and proprioception scores for both groups at the three assessment times (pre-test, post-test, and follow-up) are displayed in **Figure 2**. Significant effects due to GROUP [$F(1,27) = 4.89$, $p < 0.05$] and TIME [$F(2,26) = 5.46$, $p < 0.05$] were found on stereognosis, showing more reduced scores in the intervention group than in the control group, and an increased stereognosis from pre- to post-test assessment. No GROUP × TIME interaction effect was obtained.

For proprioception scores, a significant effect due to GROUP [$F(1,27) = 5.04$, $p < 0.05$] was also found, showing better proprioception in the intervention group than in the control group. No other significant effects were observed.

No significant effects were found on fine motor function and texture recognition scores (**Figure 2**).

DISCUSSION

The objective of this study was to evaluate the effects of a somatosensory therapy on pain and touch thresholds,

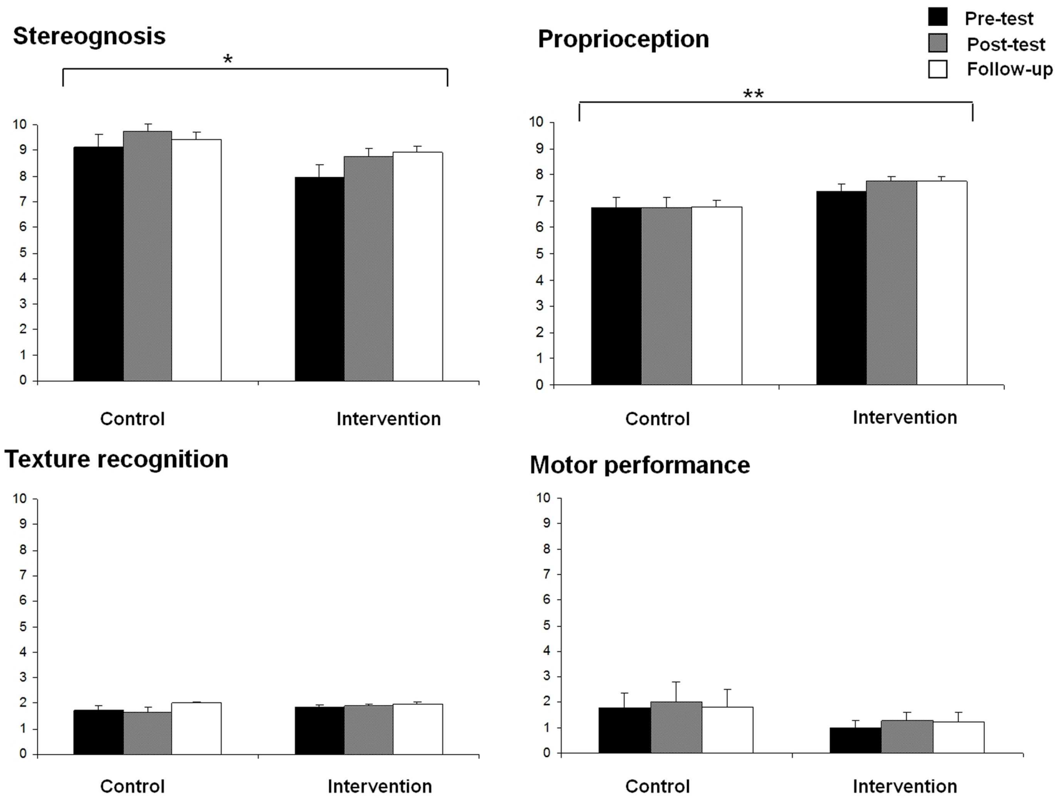

FIGURE 2 | Means of stereognosis, proprioception, texture recognition, and motor performance for each group (control and intervention) at all assessment times (pre-test, post-test, and follow-up) (*$p < 0.05$, **$p < 0.01$).

stereognosis, texture recognition, proprioception, and fine motor function in adults with CP. Our results revealed that participants in the intervention group showed a significant reduction of pain sensitivity after treatment, whereas participants in the control group displayed increasing pain sensitivity over time. These changes remained even at follow-up after 3 months. By contrast, no significant improvements in touch thresholds, texture recognition, proprioception, or fine motor skills were observed in any of the groups.

These results are relevant because pain is considered an important comorbidity factor in persons with CP (Vogtle, 2009; Doralp and Bartlett, 2010; Malone and Vogtle, 2010; Parkinson et al., 2010). In previous studies, we have found that individuals with CP reported more pain and lower touch sensitivity than healthy controls, and that clinical pain ratings in CP were associated with reduced touch sensitivity (Riquelme and Montoya, 2010). The present study further revealed that training of somatosensory processing may reduce pressure pain sensitivity in CP. All these findings are in accordance with growing evidence indicating that patients with enhanced pain sensitivity (such as chronic pain patients) are less able to identify the location and characteristics of a tactile stimulus when delivered to a painful body area (Moriwaki and Yuge, 1999; Maihofner et al., 2006). Furthermore, it has been observed that training in discriminating tactile stimuli (Moseley et al., 2008) and graded sensorimotor exercises (Pleger et al., 2005) can reduce pain perception. Although the neurobiological mechanism responsible for this link between sensory training and pain is still unknown, it has been suggested that changes in somatosensory processing could be mediated by changes in primary sensory cortices (cortical reorganization) in response to hyperstimulation (Jenkins et al., 1990; Kattenstroth et al., 2012). Thus, the finding that our somatosensory therapy led to significant reductions in pain sensitivity over time in CP individuals may suggest the possibility that these changes were due to relevant changes in central somatosensory processing. In this sense, previous data have shown that somatosensory therapies are able to reduce pain and discomfort, as well cortical reorganization in amputees, chronic pain, and somatic tinnitus (Flor et al., 2001; Latifpour et al., 2009; Moseley and Wiech, 2009; Moseley and Flor, 2012). Furthermore, it seems that those somatosensory interventions in which patients are required to discriminate actively between the type and location of tactile stimuli may be more effective than mere repetitive and passive body stimulation in reducing pain (Moseley et al., 2008). Thus, it seems plausible that the active components of our intervention might be responsible for the observed pain sensitivity effects in the present study.

Nevertheless, the finding that our somatosensory intervention was able to change pain, but not touch thresholds or somatosensory perception was puzzling. At a glance, this seems contrary to previous studies showing that tactile discrimination training and repetitive stimulation of the body can improve tactile function in healthy individuals (Godde et al., 1996) and patients with chronic pain (Pleger et al., 2005; Moseley et al., 2008). One possible explanation of these contradictory findings could be methodological differences between the present and the rest of studies. Thus, stimulation paradigms in previous studies mainly consisted of repetitive and intensive stimulation at specific sites of the body during minutes or hours, and changes of tactile acuity were often measured by using two-point discrimination thresholds, neither of which occurred here. In the present study, we used more ecological and functional, although less intensive exercises than the mere repetitive body stimulation used in previous studies. Moreover, it has been suggested that different cutaneous mechanoreceptive afferent systems are involved in distinct and separate central systems for processing of somatosensory information (form and texture perception, motion, vibration, stretching) (Johnson, 2001). Here, we used mechanical thresholds (von Frey monofilaments) to test the effects of the somatosensory intervention. Thus, it could be that our assessment tools were not appropriate for measuring the effects of our somatosensory intervention program on touch processing.

Our results also add new evidence about the benefits of somatosensory and sensoriomotor training in CP individuals. Several studies have reported that pressure splints improved the range of movement, balance, dynamic stability, motor control, postural and muscle readiness and walking function, and elicited an enhancement of SEP amplitudes (Hylton and Allen, 1997; Semenova, 1997; Kerem et al., 2001). Furthermore, it has been reported that sensorimotor exercises (e.g., vestibular system activities, balance and postural responses, coordination, motor planning, right-left discrimination training, visual spatial perception, sensory inputs, body awareness) produced an improvement of tactile perception, kinesthesia, graphesthesia, and daily living activities (Bumin and Kayihan, 2001). Again, these changes in sensoriomotor parameters could be attributed to brain mechanism of plasticity elicited by training and practice. In this sense, it is known that sensorimotor integration is based on feedforward and feedback contributions between different areas of somatosensory and motor cortices (Rizzolatti and Luppino, 2001). Thus, it may be argued that the joint activation of both cortical regions during these therapies could modulate the exchange of information between the somatosensory and motor systems, resulting in an improvement of somatosensory processing and motor abilities. In the present study, we found that somatosensory therapy was effective in eliciting long-lasting changes only on pain sensitivity, but not on fine motor skills. Although we have no clear-cut explanation for these results, the fact that individuals of both groups were simultaneously involved in a standardized motor therapy may explain the lack of differential effects on fine motor skills.

The present study has some limitations that should be taken into account for the interpretation of the results. Although individuals with CP seem to be representative of their community, a relative low sample of subject with heterogeneous etiologies was recruited. Moreover, an interference effect individuals' motor therapy with our intervention protocol could not be discarded. An active control condition, in which non-specific somatosensory stimulation were applied, could have added information to the specificity of our therapy.

All these findings highlight the importance of somatosensory experience in the enhanced sensibility to pain demonstrated in persons with CP (Riquelme and Montoya, 2010). The increase of somatosensory experiences provided by our somatosensory therapy may have effects on pain processing and may reduce pain perception in CP individuals. This hypothesis may have implications for future neuromodulatory treatment of pain complaints in children and adults with CP. Early interventions should be address to decrease sensitivity to pain throughout the adult years.

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Evaluation of a prototype tool for communicating body perception disturbances in complex regional pain syndrome

Ailie J. Turton[1]*, Mark Palmer[2], Sharon Grieve[3], Timothy P. Moss[1], Jenny Lewis[3] and Candida S. McCabe[1,3]

[1] Faculty of Health and Life Sciences, University of the West of England, Bristol, UK
[2] Faculty of Environment and Technology, University of the West of England, Bristol, UK
[3] Royal National Hospital for Rheumatic Diseases NHS Foundation Trust, Bath, UK

Edited by:
Jörg Trojan, University of Koblenz-Landau, Germany

Reviewed by:
Alessandro Farne, INSERM, France
Stephanie Cacioppo, The University of Chicago, USA

****Correspondence:***
Ailie J. Turton, Faculty of Health and Life Sciences, University of the West of England, Glenside Campus, Blackberry Hill, Bristol BS16 1DD, UK
e-mail: ailie.turton@uwe.ac.uk

Patients with Complex Regional Pain Syndrome (CRPS) experience distressing changes in body perception. However representing body perception is a challenge. A digital media tool for communicating body perception disturbances was developed. A proof of concept study evaluating the acceptability of the application for patients to communicate their body perception is reported in this methods paper. Thirteen CRPS participants admitted to a 2-week inpatient rehabilitation program used the application in a consultation with a research nurse. Audio recordings were made of the process and a structured questionnaire was administered to capture experiences of using the tool. Participants produced powerful images of disturbances in their body perception. All reported the tool acceptable for communicating their body perception. Participants described the positive impact of now seeing an image they had previously only imagined and could now convey to others. The application has provided a novel way for communicating perceptions that are otherwise difficult to convey.

Keywords: "body perception," "complex regional pain syndrome," assessment, body schema, communication

INTRODUCTION

Changes in body perception can occur following peripheral injuries, or central nervous system damage (Halligan et al., 1993; Fraser, 2002; Moseley, 2005, 2008; Lewis et al., 2007; Antoniello et al., 2010). However communicating altered body perception can be challenging for patients and assessing the changes over time is difficult for clinicians. The purpose of this project was to develop and evaluate a digital media application for communicating changes in body perception with a view to providing a useful tool for clinical practice. To achieve this aim, we required a model condition where body perception is significantly altered. Patients with Complex Regional Pain Syndrome (CRPS) provided the model for this proof of concept study. Altered body perception is commonly experienced in CRPS and has been well described (Galer and Jensen, 1999; Förderreuther et al., 2004; Moseley, 2005; Lewis et al., 2007).

Complex regional pain syndrome is a chronic pain condition of unknown etiology that usually affects a single limb. It is a syndrome that involves multiple systems with aberrant changes in vasomotor function, inflammatory mechanisms, and cortical processing (Marinus et al., 2011). These changes are probably triggered initially by a peripheral insult, but the condition quickly evolves into a centrally driven disorder for which there is currently no cure (Jänig and Baron, 2003; Marinus et al., 2011). Alongside severe pain, sufferers experience difficulty in moving the limb, disturbed proprioception, and somatosensory registration (Harden et al., 2010). Although their sensory discrimination is impaired there is often extreme hypersensitivity and painful reactions to everyday sensations such as the touch of clothing (McCabe and Blake, 2008). The limb is experienced as feeling hot or cold and other disturbances to their autonomic nervous system lead to visible changes: the limb may appear discolored with shiny skin; it may be sweaty or become more or less hairy than usual and there may be swelling. Although these changes have an impact on the appearance of the affected body part, people with CRPS often describe distressing changes in body perception which are different to the objective appearance and physical properties of their affected limb (Moseley, 2005; Lewis et al., 2007; Peltz et al., 2011). For example, a person with CRPS may describe dramatic enlargement of segments of their limb, or report perceiving sections of limb as missing. They may experience the affected limb as feeling very hot, when it is in fact cool to touch. These perceptions are usually accompanied by strong negative emotions toward the limb, which can include a desire for its amputation (Lewis et al., 2007). People with CRPS have reported they find it hard to talk about their altered body perceptions to clinicians as they do not match objective signs and they fear being disbelieved. They find it more difficult to articulate aspects of altered body perception than to describe their pain and fear being regarded as mad and having their experiences dismissed as psychosomatic (Lewis et al., 2007). Such difficulty in communicating altered body perceptions may further exacerbate their distressing emotional impact.

Currently CRPS patients are typically asked to give verbal descriptions of their body perception in clinical interviews or if using the Bath CRPS Body perception Disturbance Scale (Lewis and McCabe, 2010). These verbal descriptions may be used by the clinician to produce a drawing or patients may be asked to draw a self-portrait (Moseley, 2005; Lewis et al., 2007; Lewis

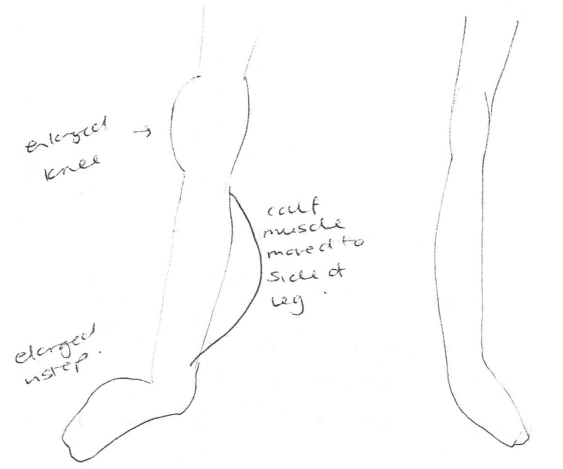

FIGURE 1 | Clinician's drawing from description provided by participant 2 as part of the Bath CRPS Body Perception Disturbance Scale. Notes on the drawing are: "enlarged knee," "enlarged instep," and "calf muscle moved to side of leg."

and McCabe, 2010). An example of a clinician's drawing from a patient's description is given in **Figure 1**. Although the use of drawings enable patients to describe the nature of the experiences these methods are limited by individuals' capacity to articulate and draw well enough to adequately represent the altered body perceptions. Digital media provides a more suitable method for rendering the sensations described by people with disturbed body perception. This was demonstrated by Alexa Wright's *After Image* project which dealt with the experience of people with amputations who experienced phantom limbs (http://www.alexawright.com/afteripg.html; Halligan, 1999). Wright manipulated photographic images of amputees to fit their described experience. In another example manipulation of digital photographs was used to represent perceived distortion of the size and shape of the face experienced by a patient with Wallenberg's syndrome after a brainstem stroke (Rode et al., 2012). In this case quantitative data to measure the distortion was extracted from the software. However photo software isn't quick and easy to use in the clinical setting. It is limited to one dimension and is prone to unwanted distortion of background which could influence perceptions of scale. The use of new media also offers the possibility of developing a 3D tool that would more readily enable patients to describe the nature of their altered body perception.

The aims of this project were to develop and evaluate an application that patients can use to create a 3D model of their perceived body image. This paper describes a usability and acceptability evaluation of the prototype 3D tool for communicating body perception in CRPS.

MATERIALS AND METHODS

SPECIFICATION OF THE BODY PERCEPTION APPLICATION

The specification for the digital media tool was determined using data from a previous exploratory study of body perception (Lewis et al., 2007), and consultation with a person with CRPS. The specification was that the tool should allow manipulation of the scaling, position, and surface texture of body segments and to display absence of parts on a model. This included the ability to lengthen and shorten limb segments, to make them thicker and thinner, and the ability to change limb position even to anatomically impossible positions. Colors and textures were to represent feelings of burning, cold, rough, smooth, and lack of substance. Finally it was also considered important to be able to view the model or "avatar" from different perspectives: front, back, left side, right side, through 360°.

The first prototype of the application satisfied all these criteria from a software perspective. It allowed modification of an avatar to depict alterations in size, shape, color, or visible surface texture of multiple body segments. Its use with consenting patients admitted to an inpatient CRPS rehabilitation program for the purposes of this research was approved by the Local NHS Research Ethics Committee.

RECRUITMENT OF PARTICIPANTS

Participants were recruited from a tertiary referral service for those with CRPS based in the South West of England. Inclusion criteria were: a clinical diagnosis of CRPS (Harden et al., 2010), admission to the inpatient multi-disciplinary CRPS rehabilitation program at the hospital and be able to understand and express themselves in English. Patients fitting the criteria were given the study information booklet by a member of the clinical team and were asked to contact the research nurse if they were interested. Before participation patients were required to give written informed consent to participate if willing to do so. Informed consent was obtained from all participants and is securely archived according to local NHS procedures.

PROCEDURE FOR USING THE APPLICATION

Ten participants used the first version of the application in a single consultation with the research nurse. The nurse showed the participant the application, its capacity for altering length, thickness and position of limb segments, and the color and texture choices available for applying to the avatar's body parts. She stressed that the illustrative meaning of colors and textures were for each individual participant to decide. Having demonstrated the scope of the software the nurse operated it in response to instructions from the participant to achieve a representation that was to their specification. For example in altering limb length she would ask the participant how long or short they wanted the limb segment to be; asking the participant to say when to stop the increase or decrease in length. Participants were asked to confirm they were satisfied with the accuracy of scaling after each manipulation.

Three further participants were included after modifications to the application were made. The avatar originally only allowed the manipulation of the hand as a whole; the ability to manipulate fingers and their parts was introduced, together with the facility to represent conflicting sensations such as "flames" and ice colored "shock" representing concurrent burning and freezing cold sensations. The starting screen for this second version of the application, and its menus for manipulating the avatar, is shown in **Figure 2**. The procedure for the 3 additional participants was the same as for the first 10.

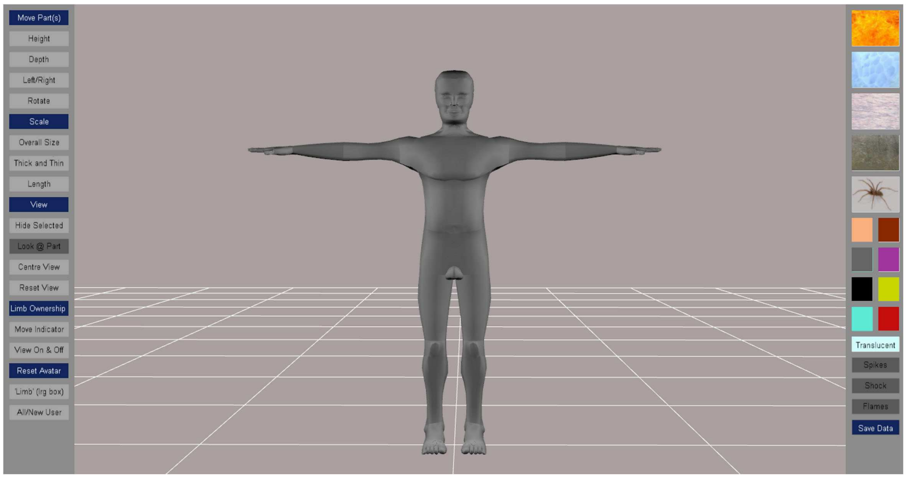

FIGURE 2 | Starting screen with options for manipulating the body perception avatar. Menus for moving body segments (height, depth, left/right, and rotate), scaling (overall size, thickness, length), for hiding segments and changing the view are on the left hand side of the screen. Menus for colors and textures that can be applied to selected body segments are on the right hand side of the screen.

COLLECTION OF EVALUATION DATA

Audio recordings were made of the participants using the application to allow interpretation of the images created. The recordings also allowed immediate reactions to the tool to be captured. Immediately after using it, participants were asked to complete a structured questionnaire which was administered face to face with the research nurse. The questionnaire had open questions to ascertain their views and experience of using the tool. The questionnaire was modified after the first 7 participants had completed the evaluation to include a rating out of 10 to determine how good a representation participants' thought the created image was and to explicitly ask whether using the tool caused increased pain and distress (see Appendix). This version of the questionnaire was used with six participants.

DATA ANALYSIS

Images were saved anonymously to protect the identity of participants. Questionnaire responses were all given an anonymized study identity code. The questionnaire responses were collated and the audio interviews were transcribed. They were analyzed for their content to determine acceptability and usability of the tool under the following headings: (i) the ability of the body perception tool to represent participant's experience, (ii) their reactions to using the tool, (iii) limitations and aspects for refinement.

RESULTS

PARTICIPANTS

Reflecting the CRPS population, participants were predominantly female (10 female). Ages ranged from 24 to 64 years (median 54), and CRPS duration ranged from 6 months to 7 years (median 14 months). Ten had an upper limb affected and three a lower limb (one participant had both upper and lower leg on one side affected). The characteristics of each participant are listed in **Table 1**.

Table 1 | Characteristics of participants.

Participant	Gender	Age	Duration CRPS (months)	Limb(s) affected
1	F	24	6	Right upper limb
2	F	57	72	Right lower limb
3	F	58	10	Left hand
4	F	56	14	Left hand
5	F	64	14	Right hand
6	F	55	10	Left upper limb
7	F	28	29	Right lower limb
8	F	54	61	Right upper & lower limb
9	F	60	12	Right wrist
10	M	27	21	Left lower limb
11	M	26	43	Right arm
12	F	44	13	Left arm
13	M	53	48	Right hand

THE ABILITY OF THE BODY PERCEPTION TOOL TO REPRESENT PARTICIPANT'S EXPERIENCE

The participants produced powerful images of the disturbances in body perception they experienced. Some examples supported with quotes of participants' verbal descriptions are given in **Figure 3**. Participant identification codes on the figures, and given in brackets after quotes used in the text, relate to the participant numbers in **Table 1**.

Alterations in scaling were common with participants feeling that limb parts were either larger or smaller than normal and these perceptions were illustrated on the computer model (examples are given in **Figure 3**). Participants liked the application's ability to scale and distort body parts. However, 5 of the 10 participants tested with the first prototype wanted more detailed representation of the hands.

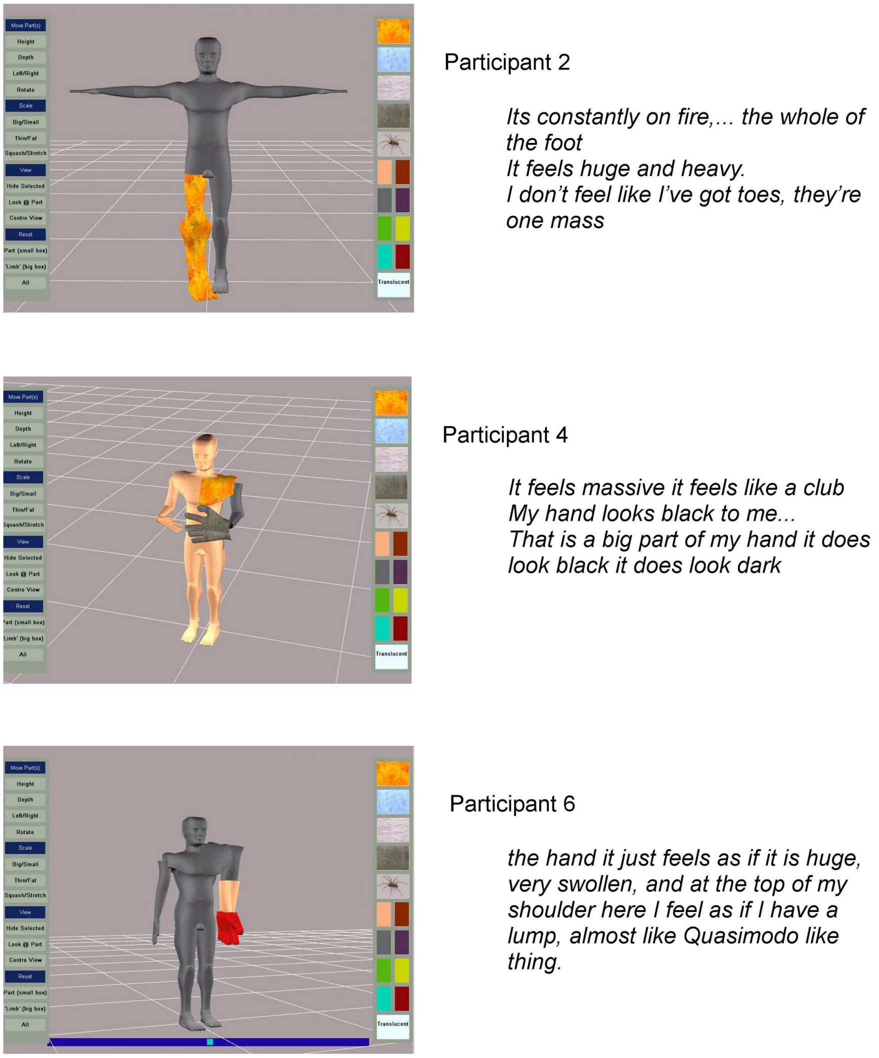

FIGURE 3 | Examples of images captured with participant's verbal descriptions.

Pain and altered somatosensation were illustrated by the application of a single color or texture in the prototype. Participants reported liking the colors, particularly the fire effect which they used to represent burning pain. Nevertheless it was not uncommon for participants to report dynamic sensations, pins, and needles or contradictory sensations, which could not be portrayed in the first version of the software. Participants frequently reported an extreme burning sensation but this was sometimes experienced with a contradictory cold sensation in the affected region.

> *The electric shocks that go up and down it are obviously not there, so I don't know how you could represent those sort of things.* [Participant 6]

> *My hand feels as if it's absolutely on fire and then if somebody touches it, it feels cold, and this pins and needles. I don't know how to represent that. It's like numb but I can feel it.* [Participant 5]

Regarding the avatar, participants liked the facility to view and manipulate it from different perspectives. Some participants, though not all, liked the fact the manikin was not portrayed as a human; preferring the impersonality of the schematic figure.

> *Interviewer: . . . at the moment it's kind of a grey figure I mean are you happy with that, do you think it would be an improvement to make it look more human*

> *No, because it's not, it if were more human it's going to be a more direct personal thing.* [Participant 3]

> *I think it's kind of better you don't feel as pushed as if maybe you saw like a human being.* [Participant 1]

> *It probably would be better if it was more of a human form because at the moment it's very robotic looking.* [Participant 6]

PARTICIPANTS' REACTIONS TO USING THE TOOL

In response to the question "Did you find using the body perception application an acceptable way to communicate how you view or feel about your limb or body parts?" All participants reported using the tool was a good method for communicating their body perception; both for themselves and for helping the clinician to understand patients' body perceptions. The last seven participants were asked to rate out of ten how satisfied they were with the images they created: three gave a rating of 7, one 8, one 9, and one 10. All participants were unanimous in the view that using the application was better than the standard interview about body perception experienced earlier in their admission. They appreciated the application was much more adaptable than a clinician's sketch. They found the application easy to use in consultation with the research nurse. One participant commented that they felt the process of the consultation with the nurse led to a more honest representation than might have resulted through independent use of the application.

> *I don't think for myself it would work if I were expected to use it, but I think getting somebody else to do it, you can explain more. I think that if I did it I'd perhaps not be quite as honest as telling you about it. I felt more honest being open with you and telling you exactly what, I sat there and I did it I might have made that little bit smaller but that's exactly how I see it.* [Participant 8]

Some participants expressed the idea that the image made them realize the extent of their altered body perception. Some participants expressed surprise at how they were able to depict their affected region using the system and at their own reaction to seeing the representations they created.

> *It was like quite bizarre seeing a picture of how exactly I felt as a person, cause I've never had that opportunity of looking at that like that . . . for me as I say to visualize that's how I feel. I felt a bit emotional, but the more I'm looking at it, it's only because I'm sitting here thinking that is exactly how in my mind's eye what I look like, so it was a bit of a shock I suppose.* [Participant 8]

> *This is much more true to life, I'm not saying I'm going to have a panic attack but this is making me think a lot more about my hand than any talking about it.* [Participant 4]

> *It makes you see how distorted your vision of your own body is, of your limb especially.* [Participant 6]

> *In your head I haven't said this word but I've felt this, you feel freakish, so you look at that and you think yeah that is how I feel.* [Participant 2]

Pain may be increased by dwelling on the affected body parts (Lewis and McCabe, 2010), so the last six participants were asked if using the tool increased their pain or distressed them. Two instances of increased pain were reported.

> Interviewer: *Did using the tool change your pain in any way?*

> Participant: *To be honest I know this is going to sound crazy probably but my hand is absolutely killing me; I don't know why.* [Participant 8]

The same participant reported that though she didn't like it, she was not distressed and there were benefits.

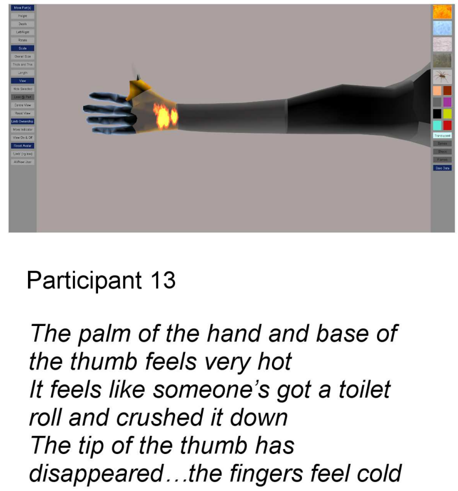

FIGURE 4 | Image produced after additional features were added to the application: particle texture effects and fractionation of digits.

> *No, I don't think I've got a bad feeling from doing this, it's not a bad feeling it's just to me looking at that puts it into perspective what I've got. It's just I don't know how to explain it. It looks in human form exactly how I feel and I've never had that. I've sat and said this hand feels longer and feels wider from there. I know how I can see it but this is the first time somebody else has.* [Participant 8]

LIMITATIONS AND ASPECTS FOR REFINEMENT

Main limitations of the prototype identified by the first 10 participants were the lack of detailed representation of the hands and the lack of ability to represent more than one sensation in a single body or limb segment. Program modifications allowing finer manipulation of individual fingers and additional surface options to portray conflicting temperatures and shooting sensations were made and version 2 was tested on the three last participants. All three used the refinements to fractionate the hand and the additional textures and found them to be acceptable features (for an example see **Figure 4**).

Other suggestions, not yet implemented, were to add in a representation of the sensation of compression of the limb segment and animation of perceived movement or tremor.

DISCUSSION

This is the first time CRPS evoked disturbances in body perception have been captured in such a graphical manner. The quality of the graphics enhanced the reality of the image thereby helping participants to fully convey to themselves and others how altered their bodies seem to them. Participants described the positive impact for them of now seeing an image of a limb that they had previously only imagined and could now convey to others. The experience of viewing the image resulting from their visualization elicited some interesting reactions. This was apparent in the surprise that was often expressed and in the pain experienced by some participants. These reactions to visualizing body perception are not confined to use of the body perception tool. It has been reported before when mental visualization was used to help patients to verbally describe their body perception (Lewis et al., 2007). Constructing an acceptable representation on the screen provided a more powerful and adaptable means to communicate body perception than the use of drawings and may also provide a method to help patients to accept the conflicting perceptions of the body they experience.

A limitation of the study was that consultations with the research nurse and the administration of the questionnaire were not completely independent of the application's developer. The software developer was present (with the consent of the participant and approval of the Research Ethics Committee) in many cases. This was because he wanted responses first hand and initially it was to help train the nurse in using the tool. This lack of independence in the evaluation could have led participants to be more positive about the application than they might otherwise have been. However both the nurse and the software developer stressed their desire for the participant's honest opinions in order to establish the acceptability of the body perception application to patients and for identifying aspects that needed to be changed.

Areas for improvement to the application were identified, for example animation of perceived involuntary movements and creating more sophisticated depictions of sensation. However future use of the application needs to be considered before adding greater levels of detail and complexity. With increasing use of telemedicine, future versions of the application could be made to enable the software to be used by patients independently of clinicians in their own homes over the internet. The participants tested seemed to like using the application with the nurse; perhaps because it was new to them and may have appeared complicated. One of the participants even expressed the view that she was likely to have been less honest if she had used it on her own. However with the increasing use of finger activated tablets development of the tool using touch screen operation that is intuitive and user-friendly is important for its future development. Manipulation using finger drags and taps to turn the avatar, enlarge and shrink parts, and drop on textures and color will need to be robust for use on these smaller screens. The operations will have to be easy to complete with the non-dominant hand, since in some individuals their condition will have affected dexterity in their preferred hand. Further careful evaluation of independent usability and comparison of results between methods of delivery will be needed to determine reliability.

There is also further work to do in exploring the best form of the avatar for patients to represent their disturbed body perception. Previous research using body image morphing techniques with fit healthy people and with obese people has indicated that body perception is influenced by the form of the image presented (Stewart et al., 2003; Johnstone et al., 2008). Our participants with CRPS expressed mixed views of the anonymous gray avatar with some participants preferring its impersonal nature. Preferences for the human-likeness or individual's likeness to an avatar may be influenced by age, culture, and emotional resilience (Walters et al., 2008). People with CRPS may experience increased pain or distress when using the tool if the avatar is created to look very like them.

Further development and evaluation is in progress to determine the use of the body perception application with people with stroke. A significant prevalence of phantom limb in the form of postural illusions of limb position has been found in people with stroke (Antoniello et al., 2010). Assessment of body perception is not routine in clinical practice but strong similarities in clinical presentation (i.e., motor and sensory and spatial cognition impairments), and in the findings from studies of cortical changes between CRPS and stroke suggest that some common disturbances in body perception may be found (Acerra et al., 2007).

Since there is potential to "repair" distressing body perception using rehabilitation interventions (Flor et al., 2001; Flor, 2002), it is conceivable that digital images of body perception could be used, not just for communicating body perception, but also as part of a treatment. Future versions of the application might allow virtual movements and sensory experiences and with the introduction of interfaces such as Microsoft's Kinect, it would be possible to represent movements of individuals in ways that might affect their body perception or reduce their pain (Huang et al., 2006; Slater et al., 2009).

Another potential function of the body perception application is to quantify changes in predominant features in response to treatment. Other investigators have taken measurements of scaling from photo software. Vector deviations of image manipulations of a patient's representation, relative to a reference photograph, were obtained to measure perceived size changes of one side of his face (Rode et al., 2012). The consistency of an individual's representation of size on an image or avatar manipulated on a screen, as well as sensitivity to change in the patient's body perception need to be tested. The reliability of scaling measurements extracted from the manipulated avatars is currently being investigated in a pilot study before testing in a larger sample. Pain and body perception are positively correlated (Lewis and Schweinhardt, 2012) and reliable measures of change in body perception might provide insight into mechanisms of interventions and the natural history of CRPS.

CONCLUSION

This proof of principle study has shown that the body perception tool provides a powerful vehicle for communicating and representing changes in body perception.

We envisage that this tool could extend beyond being a very useful communication device between patients and clinicians and also become a meaningful process measure and an interactive tool for intervention.

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APPENDIX 1

QUESTIONNAIRE

1 How did you find your experience of using the tool – did you find it an acceptable way to communicate how you view or feel about your limb or body parts?
2 Do you think the tool enabled you to describe your body perception better than you would in the usual interview with the occupational therapist?
3 What features of the computer program did you like?
4 Is there anything you didn't like about using the tool?
5 How could the tool be improved?

PATIENTS 8–13 WERE GIVEN A REVISED VERSION OF THE QUESTIONNAIRE WHICH ADDED THESE QUESTIONS

6 a) Did using the body perception tool change your pain in any way?
b) Was this experience any different, in terms of pain, to the one you had during your body perception interview with the occupational therapist?
7 a) Did using the body perception tool cause you any distress?
b) Was this any different, in terms of levels of distress, to your experience during your body perception interview with the occupational therapist?
8 Was the resulting image a good representation of how your limb (or body parts) look and feel to you? On the scale below put a mark to represent how happy you are with the image you made (0 = Not happy at all with image and 10 = image is exactly as I would like)

0	1	2	3	4	5	6	7	8	9	10

☹ ☺

9 Was the body perception application easy to use with the help of the research nurse?
10 Do you have any other comments about the application or your experience of using it?

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Dizzy people perform no worse at a motor imagery task requiring whole body mental rotation; a case-control comparison

Sarah B. Wallwork[1], David S. Butler[2] and G. Lorimer Moseley[1,3]*

[1] Sansom Institute for Health Research, University of South Australia, Adelaide, SA, Australia
[2] Neuro Orthopaedic Institute, Adelaide, SA, Australia
[3] Neuroscience Research Australia, Sydney, NSW, Australia

Edited by:
Diana M. E. Torta, University of Turin, Italy

Reviewed by:
Martin Diers, Central Institute of Mental Health, Germany
Benedict Martin Wand, The University of Notre Dame Australia, Australia

***Correspondence:**
G. Lorimer Moseley, Sansom Institute for Health Research, University of South Australia, PO Box 2471, Adelaide, SA 5001, Australia
e-mail: lorimer.moseley@gmail.com

We wanted to find out whether people who suffer from dizziness take longer than people who do not, to perform a motor imagery task that involves implicit whole body rotation. Our prediction was that people in the "dizzy" group would take longer at a left/right neck rotation judgment task but not a left/right hand judgment task, because actually performing the former, but not the latter, would exacerbate their dizziness. Secondly, we predicted that when dizzy participants responded to neck rotation images, responses would be greatest when images were in the upside down orientation; an orientation with greatest dizzy-provoking potential. To test this idea, we used a case-control comparison design. One hundred and eighteen participants who suffered from dizziness and 118 age, gender, arm pain, and neck pain-matched controls took part in the study. Participants undertook two motor imagery tasks; a left/right neck rotation judgment task and a left/right hand judgment task. The tasks were completed using the Recognise program; an online reaction time task program. Images of neck rotation were shown in four different orientations; 0°, 90°, 180°, and 270°. Participants were asked to respond to each "neck" image identifying it as either "right neck rotation" or a "left neck rotation," or for hands, a right or a left hand. Results showed that participants in the "dizzy" group were slower than controls at both tasks ($p = 0.015$), but this was not related to task ($p = 0.498$). Similarly, "dizzy" participants were not proportionally worse at images of different orientations ($p = 0.878$). Our findings suggest impaired performance in dizzy people, an impairment that may be confined to motor imagery or may extend more generally.

Keywords: motor imagery, dizziness, left/right judgments, vestibular, implicit movements

INTRODUCTION

Dizziness is common in people with neck pain – about 15% of people with Whiplash Associated Disorder (WAD) complain of dizziness within the first week after injury (Sterner and Gerdle, 2004). In addition to pain, several pathological processes can contribute to the perception of dizziness, the most common being vestibular disorders, followed by psychiatric disorders and presyncope (Kroenke et al., 1992). Dizziness often has multifactorial etiologies (Hoffman et al., 1999). One's perception of dizziness can be triggered by alterations of incoming sensory input, integration of these sensory inputs, or changes to the effector organs themselves (Luxon, 2004). Therefore, moving one's body into different orientations can be aggravating for the dizzy patient, as it triggers an influx of sensory information from the sensory organs.

It has been well established that a motor imagery task of making left/right judgments of body parts activates similar cortical areas to those activated for the actual or imagined movement (Parsons, 2001). Left/right body part judgment tasks require one to look at an image of a body part and identify it as either belonging to the left or right side of the body (i.e., hands or feet), or rotated or angled toward the left or right side of the body (i.e., neck or trunk rotation). It is thought that the process of choosing a side requires one to access cortical maps associated with the relevant body part and mentally maneuver that body part into the orientation seen in the image, thus revealing whether or not the initial judgment was correct. If the initial side of choice is wrong, the same process will be rerun but for the other side (Parsons, 2001).

Early investigations into the neurological processes involved in making left/right judgments of hands, found that responses were delayed if a high degree of mental rotation was required to match the orientation in the stimulus image (Parsons, 2001). That is, the time taken to perform a mental movement of rotating the hand from its current orientation during the task into the position of the stimulus hand is governed by the normal biomechanical constraints of moving one's actual hand into the position of the stimulus. In left/right judgments, this is usually undertaken as an implicit movement. That is, we do it without consciously thinking about it. Conversely, an explicit movement is an imagined movement that is consciously thought about. If then, a large and complex movement would be required to match the stimulus hand, a longer response time would be expected, whether or not the participant knew that they were mentally making such a movement. Similarly, in more recent studies looking at left/right neck rotation judgments (Wallwork et al., 2013) and left/right trunk rotation judgments (Bowering et al., 2012), response times were longer when the image was orientated upside down or tilted on the side, and shorter when images were not rotated at all. This finding, and the idiosyncratic pattern of reaction times (Bowering et al., 2012; Wallwork et al., 2013) suggests that left/right judgments of the neck and trunk also require implicit mental rotation of the whole body into a position that matches the image, before being able to make a left/right judgment response. For example, if an image shows a person with their neck rotated to their left, and the image itself is rotated 180° , one might expect that the participant would need to mentally rotate their entire body into the upside down position prior to identifying it as a left-sided neck rotation.

This established relationship between reaction time and "awkwardness" (Moseley, 2004) of the movement is dominated in people with arm pain, by a stronger relationship between reaction time and predicted pain on that movement (Moseley, 2004). That clearly shows that evaluative processes interfere with implicit motor imagery just as they do with executed movements. On the basis of these findings, one would predict that the dizzy patient would perform worse on motor imagery tasks requiring whole body mental rotation because moving the head often exacerbates dizziness in these people. Specifically, we would expect to see a delayed response because we would predict that people who suffer from dizziness would avoid those movements in much the same way that chronic pain patients show a delayed response to motor imagery of movements that would be painful (Moseley, 2004; Meulders et al., 2011).

We hypothesized that participants who reported dizziness would take longer to complete a left/right neck rotation judgment task than they would a left/right hand judgment task, when compared to healthy age, gender, and pain-matched controls. Our secondary hypothesis was that the delay in response time would be greatest for images of upside down orientation; that is, dizzy participants would take longer to respond to images that required implicitly turning oneself upside down.

MATERIALS AND METHODS

DESIGN

A case-control comparison design was used.

PARTICIPANTS

Data were obtained from a large cross-sectional study previously undertaken investigating left/right neck rotation judgments and left/right hand judgments (Wallwork et al., 2013). These data included 1737 participants from 40 countries, aged between 10 and 90 years, both males and females. Participants were recruited through social media strategies and by word of mouth, and were asked to complete the study online via a web connected computer. All participants volunteered their time and were able to withdraw at any point. Ethical approval was granted by the institutional ethics committee.

QUESTIONNAIRE

Prior to undertaking the left/right judgment tasks, participants were asked to complete a questionnaire regarding their demographic details, physical activity, presence of pain, and general health. Included in this questionnaire was a question relating to whether or not the participant suffers from dizziness; we asked, "Do you suffer from dizziness?" Participants were required to tick either a "yes" or a "no" box.

THE TASKS

In total there were three motor imagery tasks. Each task involved making responses to a different batch of 40 photographs. The first task required participants to respond to plain photographs of someone turning their head to one side, and respond to each as being either a left neck rotation or a right neck rotation. This task was repeated three times; the first run within this first task was considered a practice, the second run was used for analysis in the current study, and the third run was considered to be influenced by fatigue, and therefore not included in the analysis. The second task also required left/right neck rotation judgments, however the photographs were taken of people in contextually variable environments and was also not analyzed in the present study. The third task was a left/right hand judgment task. We did not include a practice run for this third task because previous data suggests that performance would be similar. This was confirmed when we compared the current results to previously published results (Wallwork et al., 2013). Responses were made using the "a" key for a left-sided response and "d" for a right-sided response. When a response was made, the next image would immediately appear. If no response was made, or if the participant did not respond within 5 s, the next image would appear and the time was recorded as 5 s for that image and a blank response would be displayed in place of a "left" or a "right" response. Response times were taken from all responses, not just correct responses, meaning that in the unlikely occasion that participants responded in exactly 5 s, we were not able to distinguish between them and people who were not able to respond within the allocated time frame.

THE PHOTOGRAPHS

Each task displayed a separate batch of 40 images (20 female). The first task displayed portrait images of a person wearing a black t-shirt with their head rotated to either their left or their right side, relative to their shoulders. There were equal numbers of left and right neck rotations, at 0° , 90° , 180° , and 270° of whole image rotation. The photographs were taken from either a front, back, or side view, and all participants viewed and responded to the same images. In the second task, photographs were taken of a range of people in different environments. This batch of images was not used for analysis in the current study. The third and final task displayed photographs of hands in varying postures with either a black, white, or green background. Only the hand, wrist, and distal arm were in view. We chose not to orientate the hand images as we did the neck images, on the basis that the hands have greater degrees of freedom than the neck, and rotating the image would not have the clear demarcation of rotation that we see for images of the neck.

DATA CLEANING

Prior to analysis, a total of 1792 data sets were "cleaned." This involved complete data sets being removed if the questionnaire had not been filled out or if all tasks were not finished; 55 data sets were removed for these two reasons, leaving 1737 complete data sets. Single responses were also removed if they were <500 ms, which we took to be too fast for a true judgment response (Kunde, 2001), or if they timed out for eight or more (≥20%) images in a row, which we took to be a distraction from the task or computer malfunction.

Participants who had reported in the questionnaire that they experience dizziness, were selected and allocated to the "dizzy" group. A control participant was randomly selected from the pool of participants who matched each dizzy participant for age, gender, neck pain, and arm pain. We did not ask participants about any other areas of pain, and therefore did not match for this. The participants identified in this process were allocated to the control group (see **Figure 1** for flow chart). Pain is known to affect performance in left/right judgment tasks (Moseley, 2004; Bray and Moseley, 2011; Bowering et al., 2012; Leake et al., unpublished data).

DATA ANALYSIS

Data were analyzed using SPSS 19.0. Descriptive statistics were first collated to get an idea of the sample population. Two repeated measures ANOVAs (response time and accuracy) were run to see whether people who reported suffering from dizziness performed differently to controls at the two left/right judgment tasks. For each ANOVA there were two factors; within-subjects (hand judgments or neck judgments) and between subjects (dizziness or no dizziness). To see whether there was an effect of image rotation during the left/right neck rotation task, another repeated measures ANOVA was conducted, again with two factors; within-subjects (image rotation – four levels) and between subjects (dizziness or no dizziness). Significance was set at $\alpha = 0.05$.

RESULTS

PARTICIPANTS

One hundred eighteen participants (104 females) reported symptoms of dizziness. Thirty four (28%) reported neck pain and 23

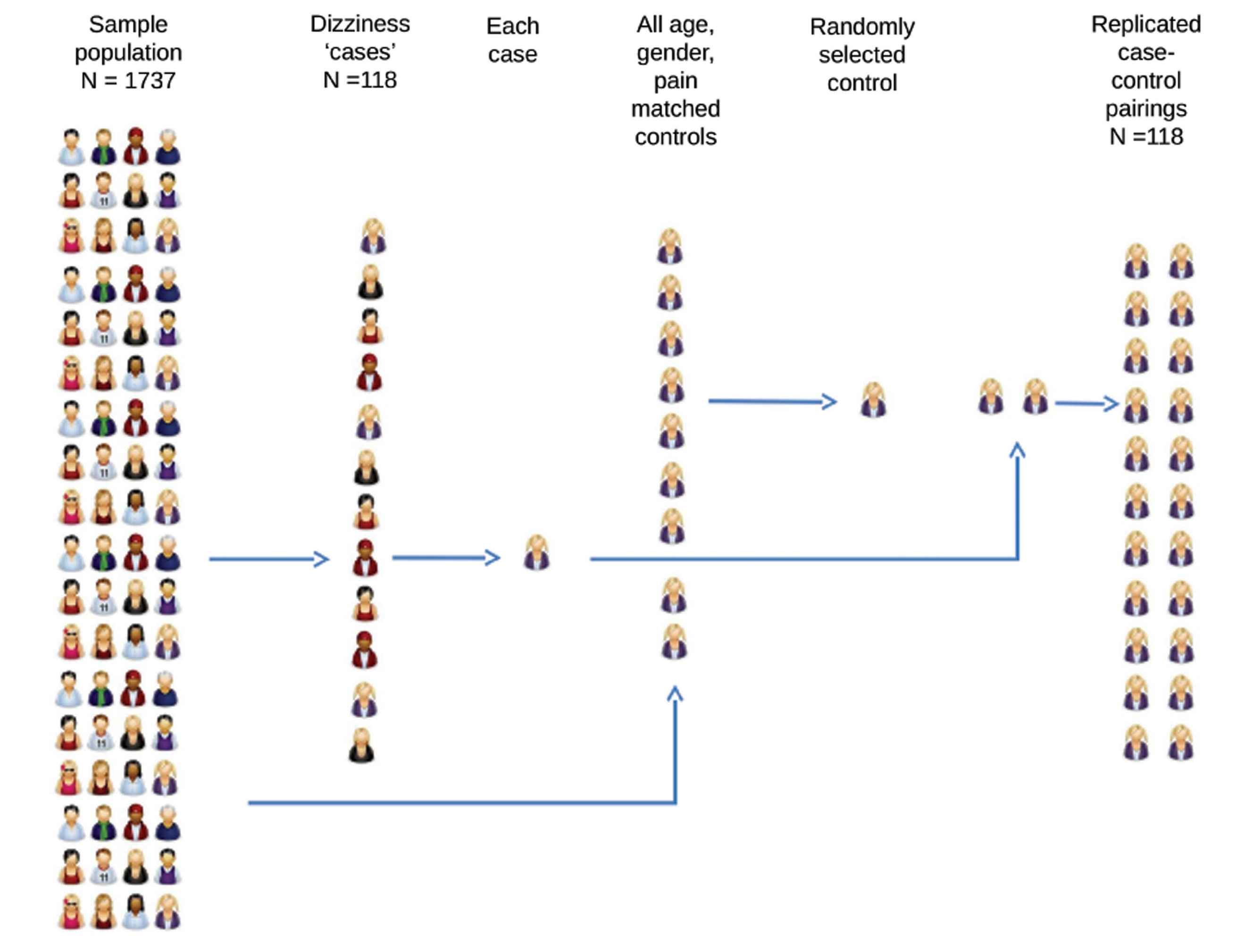

FIGURE 1 | Flow diagram detailing the case-control comparison design. Participants in the sample population who reported dizziness were identified and allocated to the "dizzy" group. Age, gender, and pain-matched controls were randomly selected from the remaining sample population.

Table 1 | Response time and accuracy for left/right neck rotation judgments and left/right hand judgments in people with and without dizziness symptoms.

	Neck judgments		Hand judgments	
	Response time (ms ± SD)	**Accuracy (% ± SD)**	**Response time (ms ± SD)**	**Accuracy (% ± SD)**
"Dizzy" group	1786.7 ± 516.3	88.0 ± 12.3	2096.9 ± 569.7	86.3 ± 11.0
Control group	1617.9 ± 455.7	88.5 ± 13.2	1974.1 ± 550.5	87.4 ± 10.9

(19.5%) reported arm pain. Mean age was 42 (SD 13) years. This group was matched for age, gender, neck pain, and arm pain to yield a cull cohort of 236 participants.

DIZZINESS VERSUS NO DIZZINESS

Response times and accuracies for the two groups are in **Table 1**.

RESPONSE TIME

There was a main effect of dizziness on response times. Participants in the "dizzy" group were slower at both tasks than controls [$F(1,234) = 6.032$, $p = 0.015$]. Mean difference and 95% confidence interval was 145.81 and 28.8–262.7 ms, respectively. Regardless of group, all participants were faster at left/right neck rotation judgments than they were at left/right hand judgments [$F(1,234) = 97.084$, $p < 0.001$], however there was no Dizzy × Task interaction ($p = 0.498$). That is, dizzy people were slower than the controls, but they were no more delayed in their responses for the neck judgment task than they were for the hand judgment task.

EFFECT OF IMAGE ORIENTATION ON THE LEFT/RIGHT NECK ROTATION TASK

Consistent with the above results, there was an effect of dizziness on response times [$F(1,234) = 7.115$, $p = 0.008$]. Mean differences and confidence intervals for the four image orientations are given in **Table 2**. There was an effect of image orientation [$F(3,702) = 203.65$, $p < 0.001$] (see **Figure 2**), but there was no Dizzy × Orientation interaction ($p = 0.878$). That is, dizzy people were no more delayed in their responses for the neck judgment task when the task required full body rotation than when it did not.

ACCURACY

There was no main effect of dizziness on accuracy scores. Participants in the "dizzy" group were no more or less accurate at either task [$F(1,234) = 0.364$, $p = 0.547$]. Regardless of group, participants were no more or less accurate at one task over another [$F(1,234) = 3.167$, $p = 0.076$], and again there was no Dizzy × Task interaction ($p = 0.673$).

DISCUSSION

The results of the current study did not support our hypothesis that in an online study, people who report dizziness, response time would be longer for a left/right neck rotation judgment task, but not a left/right hand judgment task, than it is for non-dizzy age, gender, and pain-matched controls. Nor did our results support our secondary hypothesis that the delay in response in dizzy people would be greatest for images that required full body rotation.

Table 2 | Mean differences and 95% confidence intervals for the four image orientations.

			
	−80.25 ms (mean) −131.54–−28.96 ms (95% CI)		
	−623.15 ms −711.60–−534.70 ms	−584.90 ms −628.53–−457.27 ms	
	−284.61 ms −349.10–−220.11 ms	−204.36 ms −263.20–−145.52 ms	338.54 ms 255.98–421.10 ms

Instead, we found that participants from the "dizzy" group were slower than controls at both tasks and the extent to which they were worse was not affected by image rotation.

Importantly, the majority of our participants were female (104 out of 118 participants). This stark imbalance was surprising. We have previously found that females take longer to respond to images in a left/right neck rotation judgment task than males (Wallwork et al., 2013), and that we controlled for gender in the current analysis helps us to account for this difference. Although we have no reason to suspect that females and males with and without dizziness would demonstrate differential results, it would seem imprudent to generalize the results to males before the finding is replicated with a greater representation of males.

Our results did show that participants took longer to respond to images with a high degree of rotation which would be expected based on previous studies of the hand (Parsons, 2001; Schwoebel et al., 2001; Moseley, 2004), neck (Wallwork et al., 2013), and trunk (Bowering et al., 2012), as the mental movement to match the stimulus would take longer when one is required to turn themselves upside down. However, we also expected that participants suffering from dizziness would take proportionally more time to respond to images rotated 180° , due to a dizzy-avoidance type behavior. That we did not find this suggests that people who suffer from dizziness either do not implicitly avoid dizziness-provoking movements, or may employ a different strategy by which to perform the task. Perhaps people with dizziness rotate the picture rather than their own body (Dey et al., 2012) to overcome this problem. Unfortunately the current study was not equipped to investigate potential mechanisms involved here.

That participants in the "dizzy" group were slower than controls at both left/right judgment tasks further reinforces that it probably is not the implicit whole body rotation that affected performance.

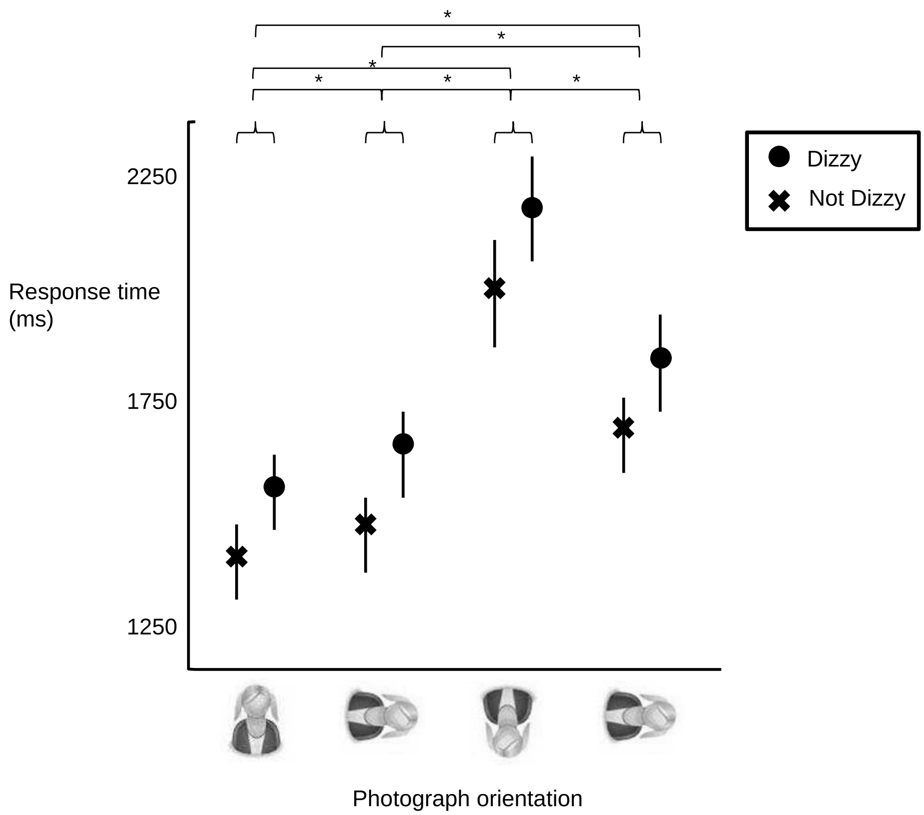

FIGURE 2 | Mean (circles and crosses) and 95% confidence intervals (lines) for response times for the "dizzy" group (circles) and control group (crosses) at the four image orientations. There was no Group × task interaction, but there was an effect of orientation. Asterisk (*) denotes significant at $p < 0.01$.

This raises the possibility that people who suffer from dizziness are worse at motor imagery, or indeed, worse at choice reaction tasks. Evidence suggests that people with vestibular dysfunction may have mild cognitive impairment (Smith et al., 2005); being both spatial and non-spatial in nature. The current study utilized only spatial tasks and to include a non-spatial task may have shed light on this possibility.

We cannot discount the potential for an order effect confounding the current findings. Although an important limitation, it seems unlikely that an order effect has contributed to the current findings, because if it did we should have seen a decline in accuracy scores, and response times slower than those obtained previously for identical tasks (Moseley, 2004; Hudson et al., 2006), neither of which we observed.

The role of the vestibular apparatus in spatial representation does appear to be important. It has been recognized that people with vestibular syndromes have poor spatial awareness (Borel et al., 2008). The vestibular system plays a key role in multisensory integration and information processing pathways, and allows one to stabilize their gaze, and orientate their head and body in space; hence the vestibular system is necessary in establishing internal representations of body position and body in space. It makes sense then, that people with vestibular disturbances would perform worse at a task requiring body and near-body spatial attention, such as in the left/right judgment tasks. That vestibular disturbances are the most common cause of dizziness (Kroenke et al., 1992) allows us to presume the same applied to our group, but importantly, we cannot be sure. However, people with vestibular dysfunction can include people with and without symptoms of dizziness, and people with dizziness can include people with and without vestibular disturbances (Kroenke et al., 1992), so at this stage we cannot verify this presumption. Further investigations in people with vestibular causes of dizziness would need to be conducted to test this idea.

A final and unsurprising finding of the current study was that participants in the "dizzy" group were no more or less accurate than those in the control group. Reduced accuracy is more likely to be due to imprecise cortical proprioceptive representation of the relevant body part (Bray and Moseley, 2011) and as such we would not predict a difference between dizzy and non-dizzy people. We do see reduced accuracy of left/right judgments in people with phantom limb pain (Nico et al., 2004), back pain (Bray and Moseley, 2011; Bowering et al., 2012), and neck pain (Leake et al., unpublished data), but in each case there is clear evidence of disruption of cortical proprioceptive representation (see Wand et al., 2011; Moseley et al., 2012 for reviews).

In summary, our results did not support the hypotheses that, in people who report dizziness, response time would be longer for a left/right neck rotation judgment task, but not a left/right hand judgment task, and that the delayed response in dizzy people would be greatest for images that required full body rotation. Participants in the "dizzy" group were not proportionally worse at responding to images thought to require implicit whole body rotation and that we expected would provoke dizziness if they were performed. Importantly, our participants are largely representative of females which needs to be acknowledged as it has the potential to create bias in the current results. Our results do suggest that dizziness might be associated with cognitive impairment, poor spatial processing, or poor motor imagery.

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The social modulation of pain: others as predictive signals of salience – a systematic review

Charlotte Krahé[1], Anne Springer[2], John A. Weinman[1] and Aikaterini Fotopoulou[3]*

[1] Department of Psychology, Institute of Psychiatry, King's College London, London, UK
[2] Department of Sport and Exercise Psychology, University of Potsdam, Potsdam, Germany
[3] Research Department of Clinical, Educational and Health Psychology, University College London, London, UK

Edited by:
Diana M. E. Torta, University of Turin, Italy

Reviewed by:
Stephanie D. Preston, University of Michigan, USA
Matthew R. Longo, Birkbeck University of London, UK

***Correspondence:**
Aikaterini Fotopoulou, Research Department of Clinical, Educational and Health Psychology, University College London, Gower Street, London WC1E 6BT, UK
e-mail: a.fotopoulou@ucl.ac.uk

Several studies in cognitive neuroscience have investigated the cognitive and affective modulation of pain. By contrast, fewer studies have focused on the social modulation of pain, despite a plethora of relevant clinical findings. Here we present the first review of experimental studies addressing how interpersonal factors, such as the presence, behavior, and spatial proximity of an observer, modulate pain. Based on a systematic literature search, we identified 26 studies on experimentally induced pain that manipulated different interpersonal variables and measured behavioral, physiological, and neural pain-related responses. We observed that the modulation of pain by interpersonal factors depended on (1) the degree to which the social partners were active or were perceived by the participants to possess possibility for action; (2) the degree to which participants could perceive the specific intentions of the social partners; (3) the type of pre-existing relationship between the social partner and the person in pain, and lastly, (4) individual differences in relating to others and coping styles. Based on these findings, we propose that the modulation of pain by social factors can be fruitfully understood in relation to a recent predictive coding model, the free energy framework, particularly as applied to interoception and social cognition. Specifically, we argue that interpersonal interactions during pain may function as social, predictive signals of contextual threat or safety and as such influence the salience of noxious stimuli. The perception of such interpersonal interactions may in turn depend on (a) prior beliefs about interpersonal relating and (b) the certainty or precision by which an interpersonal interaction may predict environmental threat or safety.

Keywords: pain, social modulation, social support, empathy, predictive coding, attachment, review

INTRODUCTION

Pain is a subjective psychological state which acts as an indicator of threat to the organism in association with actual or potential tissue damage (IASP, 1994). Pain is multidimensional, including unpleasant feelings (interoception; Craig, 2002) and sensations (nociception) about the state of the organism, as well as motivated behaviors, such as withdrawing from a noxious stimulus. Several studies in cognitive neuroscience have investigated the cognitive and affective modulation of pain (e.g., Tracey et al., 2002). For example, attention (e.g., Villemure and Bushnell, 2002), mood (e.g., Yoshino et al., 2010), and cognitive appraisals (e.g., Vlaeyen et al., 2009) have been found to modulate pain. By contrast, the modulation of pain by social factors has received far less experimental and neuroscientific attention to date. This is despite a plethora of clinical, correlational findings pointing to associations between pain and the social context in which it occurs (Leonard et al., 2006).

Close relationships are beneficial to both mental and physical health, including stress and pain. For example, a wealth of research has shown that support from others is linked to beneficial effects on physiological and psychological well-being (Uchino et al., 1996; Blasi et al., 2001; Kikusui et al., 2006), while social isolation and poor quality relationships are detrimental to health (House et al., 1988). However, support from others is not a panacea; rather, the effects of social support on health, such as stress and pain, depend on the facet of social support studied (e.g., Schaefer et al., 1981; Barrera, 1986) and on factors such as gender or relationship characteristics (Kirschbaum et al., 1995; Hennessy et al., 2009).

A similar picture emerges when studying social influences on pain. While there has been much research in clinical populations (e.g., Penner et al., 2008; Williams et al., 2011) and chronic pain populations more specifically (see below for a brief review), fewer studies have experimentally investigated the role of social context on pain in healthy individuals. Although clinical pain differs from experimentally induced pain (McGrath, 1983), studies in the latter tradition are indispensable for elucidating causal influencing factors because they allow controlled manipulation of the social variables of interest. Interestingly, such experimental manipulations reveal that multidimensional concepts such as social support may not be sufficient to characterize the social modulation of pain. Rather, particular facets of the social context seem to differentially influence whether and how interpersonal interactions can affect pain. Thus, this diversity and the specific causal mechanisms by which different social factors influence pain warrant systematic consideration. Unfortunately, to the best of our knowledge, there is no systematic review of these studies. Accordingly, the present paper aimed to provide a systematic review of studies that experimentally investigated the effects of interpersonal factors on pain with a focus on discovering the underlying causal mechanisms.

In addition, we aimed to use a framework from computational neuroscience, namely the free energy framework as applied to interoception (Seth et al., 2012) and social cognition (Brown and Brüne, 2012), as the theoretical basis for the integration and understanding of the findings presented in this review. Several perspectives exist which view pain (Sullivan et al., 2001; Craig, 2009a) and emotion more generally (Griffiths and Scarantino, 2009; Van Kleef, 2009; Coan, 2011) as embedded within a social context and posit mechanisms by which social partners affect an individual's experience (e.g., by providing support or contextual information). Adding to these, we believe a predictive coding scheme, such as the free energy framework (see below), to be particularly promising because it provides a unifying, neurobiologically plausible account of the integration of different hierarchical levels of processing, from nociception to social cognition. It can thus shed light on the mechanisms by which interpersonal factors affect pain-related perceptions and actions. Furthermore, this framework places emphasis on how pre-existing mental models shape current perception and action at different time scales. This focus is consistent with the pain literature under consideration, which has long stressed the pivotal role influence of anticipatory cognitions and emotions on pain (e.g., Wiech et al., 2010), as well as the corresponding social literature that has underlined the role of pre-learned social relating schemas in subsequent perceptions and reactions (Meredith et al., 2006).

Bayesian predictive coding models such as the free energy framework are powerful theoretical and neurobiological models of perception and action (Dayan and Hinton, 1996; Rao and Ballard, 1999; Schultz and Dickinson, 2000). The essence of these models is that neurobiological message-passing in the brain is achieved by coding potentially ambiguous (noisy) incoming information in light of prior expectations about the likely sensory causes of such information. Further, the related hypotheses ("generative models") of the hidden causes of sensory input are constantly updated on the basis of mismatches between expectation and experience ("prediction errors," also conceptualized as free energy), and optimized so as to minimize prediction error. While the above describes perceptual inference, the free energy framework includes a parallel process of active inference, which entails acting on the environment to change sensory input and also leads to the optimization of prediction errors (Friston et al., 2012). In general terms, prediction errors are assumed to be conveyed by feed-forward connections from lower to higher neural levels to improve representations in the latter, and higher-order predictions are transferred via feedback connections that can suppress prediction errors in lower levels. The reciprocal but asymmetric characteristics of this hierarchy (see also Mesulam, 2012) allow for an optimization that makes every level accountable to the others, delivering an internally consistent re-representation of sensory causes at multiple levels of the neurocognitive hierarchy.

Unfortunately, most psychological models based on the free energy framework concern exteroception (the perception of the environment or the self via, e.g., vision and hearing) and proprioception (the sense of the position of the body in space). Only very recently, a predictive coding model of interoceptive awareness has been proposed, describing subjective feeling states as arising from predictive inferences on the causes of interoceptive signals (Seth et al., 2012). With regard to pain, such a model is highly relevant because pain has recently been re-classified as an interoceptive modality (Craig, 2002, 2009b). Interoception in this renewed sense does not refer only to visceral sensation but to the central processing of all homeostatic afferent activity that can reflect the various components of the physiological condition of the body. In this view, pain and all feelings from the body are processed peripherally and centrally by a recently discovered lamina I spinothalamocortical pathway that projects to the posterior granular and mid-dysgranular regions of the insular cortex (serving as primary interoceptive cortex) via the brainstem parabrachial nucleus and posterior part of the ventromedial thalamic nuclei (Craig, 2003, 2009b). Primary interoceptive signals are thought to be represented in the mid/posterior insula, where they are also integrated with exteroceptive information coming from different brain areas. Further re-mappings within the anterior insula, the anterior cingulate cortex (ACC), and the orbitofrontal cortex are thought to consolidate body-state signals with social, motivational, and contextual information to ultimately give rise to the conscious experience of emotions, as well as to prepare the organism for the necessary action in the environment (Damasio et al., 2000; Craig, 2002, 2009b; Critchley, 2005).

A number of recent neuroimaging studies have included such areas and their observed functional connectivity in various hypothesized "salience networks" (Seeley et al., 2007; Medford and Critchley, 2010; Wiech et al., 2010; Legrain et al., 2011; Cauda et al., 2012). For instance, predictive signals from such a "salience network" process and integrate information about the significance of an impending noxious stimulus and determine whether or not such a stimulus will be consciously perceived as painful (Wiech et al., 2010), and indeed the insula cortex responds to interoceptive stimuli on the basis of expectations (Seth et al., 2012). Thus, the neural regions involved in interoception generate predictive signals of interoceptive salience. Pain can therefore constitute a process of perceptual inference about nociceptive signals on the basis of predictive, top-down signals about the homeostatic significance of such signals in the context of other synchronous biological, cognitive, and social conditions.

Furthermore, such re-mappings of interoceptive signals across the neurocognitive hierarchy suggest possible neurobiological mechanisms by which not only cognitive, but also social contextual factors can influence the awareness of interoceptive and other multimodal information about one's own body. In pain research, it is established that nociception ("the neural process of encoding noxious stimuli"; IASP, 1994) is not sufficient to explain the conscious experience of pain (e.g., Hofbauer et al., 2004; Baumgärtner et al., 2006; Nikolajsen and Jensen, 2006; Lee et al., 2009), and it has been repeatedly demonstrated that psychosocial factors can have important top-down effects on pain (e.g., the studies discussed in the present review). Thus, the application of the free energy framework to pain may be particularly fruitful to generate organized accounts of the dynamic relations between bottom-up (e.g., nociception) and top-down (e.g., psychosocial) influences on pain. In addition, pain engenders action, e.g., it motivates behaviors designed to ensure the organism is no longer under threat (Auvray et al., 2010; Wiech and Tracey, 2013). Hence, perceptual and motivational aspects of pain can be unified under the same optimization principle within a free energy framework. In particular, the motivational aspects of pain can be conceptualized as a process of active inference, where actions are performed to change nociceptive input and update predictions. In a social context, such actions may elicit help from others and change sensations via this social channel.

In the following, we explain the inclusion criteria and methods applied to our review (see Method), present the results (see Results and their Organization) and place these findings in the broader context of the free energy framework introduced above (see Discussion) to illustrate how interpersonal interactions may be integrated at different neural levels to influence the perception of pain and related behavioral responses. Before turning to these sections, we briefly consider two other research traditions, namely studies on the social modulation of clinical chronic pain, and pain in animals. While these traditions fall outside the remit of this review, we consider it important to briefly summarize their main findings as an introduction to the potential psychological and neurobiological mechanisms that may mediate the social modulation of pain in healthy human populations (see also, e.g., Payne and Norfleet, 1986; Newton-John, 2002; Cano, 2004; Panksepp, 2006; Cano et al., 2008; Mogil, 2009, respectively).

INSIGHTS FROM CLINICAL STUDIES

In clinical pain populations, a wealth of research has focused on the role of social support in chronic pain, and on the relationship between the pain patient and their partner (e.g., Block, 1981; Flor et al., 1987; Boothby et al., 2004; Cano et al., 2005). While some studies report correlations between perceived social support and lower pain intensity (López-Martínez et al., 2008), others have found a positive association between social support and pain behaviors (e.g., Gil et al., 1987), level of pain (Flor et al., 1987; Kerns et al., 1990), and disability (Romano et al., 1995). The majority of research has drawn on behavioral models to explain these associations, focusing strongly on operant conditioning (Cano and Williams, 2010). The operant conditioning perspective posits that repeated instances of social support serve to reward or punish pain behaviors, leading to positive or negative reinforcement of such behaviors. While this model has been broadly supported, also in an experimental study (Jolliffe and Nicholas, 2004), it does not include cognitive and affective factors and thus may not offer a complete picture of the complexity of social interactions (Newton-John, 2002). Cognitive-behavioral models focusing more on pain appraisals have emerged. One prominent example is the communal coping model of pain catastrophizing (e.g., Sullivan et al., 2001), which claims that individuals who tend to catastrophize – that is, exaggerate the threat value of pain and see themselves as unable to cope with pain themselves (Keefe et al., 2000) – might engage in more pain behaviors to attract support from others. Here, pain appraisals play a key role in the social context of pain. A further perspective integrating cognitive factors and placing them within a relationship context is the intimacy model (see Cano and Williams, 2010), in which communicating pain to a partner is viewed as an attempt to create and maintain an emotionally intimate relationship environment.

In sum, clinical pain studies, although correlational in nature, have led to the development of several models which have been adapted to experimental settings (e.g., Sullivan et al., 2004). Furthermore, clinical studies investigate long-term pain, in which pain appraisals may be more strongly established than in the transient context of experimental settings. As many chronic pain studies focus on the partner as supportive other, they also address the importance of the relationship between supportive other and pain patient. Thus, their findings are important in fostering our understanding of psychological mechanisms underlying the social modulation of pain in humans.

INSIGHTS FROM ANIMAL STUDIES AND IMPLICATIONS FOR HUMAN RESEARCH

Although direct comparisons between human and animal studies are not warranted, animal studies can provide tentative neurobiological insights into the social modulation of pain. Animals and particularly mammals are highly sociable, and many animals – including humans – rely on parental care for survival in early life. To regulate proximity to these critical caregivers, animals and humans possess an attachment system which manifests itself in the formation of close social bonds (Panksepp, 1998). Several studies have investigated whether such social bonds influence pain in animals, typically by studying the behavior of mouse dyads while pain is induced in one dyad member. Langford and colleagues found that female mice approaching a dyad member in pain led to less writhing from the mouse in pain. Crucially, these beneficial effects of social contact were seen only when the approaching mouse was a cagemate of the mouse in pain rather than a stranger (Langford et al., 2010). In this vein, D'Amato and Pavone (1993) discovered that interacting with siblings reduced pain sensitivity in mice, whilst interacting with stranger mice did not. In addition to establishing that close social relationships modulate pain in mice, these studies have also shed light on possible underlying neurobiological mechanisms. Specifically, endogenous opioids and oxytocin have been implicated, the former relating to reinforcement of social emotions (D'Amato and Pavone, 1993) and the latter playing an important role in social bonding (for a review, see Campbell, 2010). Regarding endogenous opioids, D'Amato and Pavone found that their socially induced analgesic effects were blocked when mice received naloxone, an opioid antagonist, pointing to a mediating role of endogenous opioids. Oxytocin has been linked to pain reduction *per se* (Yu et al., 2003) and interacts with opioid and also dopaminergic systems, with dopamine driving the motivation to affiliate and form social bonds (McCall and Singer, 2012). Furthermore, oxytocin exerts positive effects such as preventing the development of depressive-like behavior in socially isolated mice with nerve damage (Norman et al., 2010). Therefore, these proposed neurobiological mechanisms seem to relate both to social bonding and pain.

Indeed, similarities between pain and social loss have been observed in animals (Panksepp et al., 1997): both pain and social experiences include threat, unpleasantness, and loss (e.g., of a function or fellow animal) in phenomenological terms, and from a neurological viewpoint, opioid administration seems to alleviate both bodily pain and the pain of social isolation/absence of a caregiver. In light of these similarities, Panksepp and colleagues proposed that the drive to seek proximity and avoid separation is built upon the foundations of the older pain system (including, e.g., the opioid system); thus, social loss or separation hurts. Though caution is necessary when making comparisons between animals and humans, the neural links between pain and the distress of social loss have been investigated in humans.

In humans, higher baseline pain sensitivity has been linked to greater distress following social rejection, and heightened levels of social distress have been associated with more pain unpleasantness on thermal pain induction following social rejection (Eisenberger et al., 2006). Functional neuroimaging studies have suggested that similar neural regions to those implicated in bodily pain are activated during social pain (e.g., the dorsal ACC; Eisenberger et al., 2003; Eisenberger, 2012) though whether these regions are pain-specific is debated (e.g., Legrain et al., 2011; Mouraux et al., 2011). Taken together, these studies propose tentative neural mechanisms involved in the social modulation of pain and social connection in animals and as well as humans and underline the importance of close attachment bonds.

METHOD

SELECTION OF STUDIES

We conducted a systematic search of the on-line databases Web of Knowledge, PubMed, PsycInfo, and Google Scholar, using combinations of the following keywords: "pain," "interpersonal," "empathy," "attachment," "social context," "social interaction," "social support," "social presence," and "social modulation." Reference lists of relevant articles were also searched. The results were assessed for inclusion using the publication title and abstract. No restrictions regarding publication dates were applied.

Studies were included if they conformed to the following five *a priori* inclusion and exclusion criteria. Firstly, we excluded wider societal (intergroup) influences. Naturally, pain is generally experienced within the wider social world, and gender (e.g., Levine and De Simone, 1991), ethnicity (e.g., Weisse et al., 2005), and in-group/out-group influences (Buss and Portnoy, 1967), to name but a few, undoubtedly contribute to the social modulation of pain. However, we focused our review on experimental studies examining interpersonal influences rather than the larger social context of pain to advance our understanding of the causal interpersonal mechanisms that may shape an individual's pain experience. Specifically, we included those studies which manipulated an embodied or primed interpersonal exchange "between two or more individuals which is very largely determined by their individual characteristics and the nature of the personal relations between them" (the interpersonal extreme, Tajfel, 1982, p.13) and excluded "interactions which are largely determined by group memberships of the participants and very little – if at all – by their personal relations or individual characteristics" (the intergroup extreme, Tajfel, 1982, p.13). Hence, we excluded studies that varied, for example, experimenter gender or race, unless they also manipulated aspects of an interpersonal interaction. We also excluded social modeling studies in which *both* interaction partners received pain (or were made to believe the other received pain). Consistent with the tradition of studies addressing social support, our focus was on how the person in pain was affected by interpersonal interactions with pain-free individuals.

Secondly, studies were included if they experimentally induced pain (e.g., by means of a coldpressor task) and excluded if they used clinical procedures such as routine immunizations. We excluded clinical procedures because they differed from laboratory studies in the use of health-related procedures (which implicate additional variables such as illness perceptions, medical history etc.) and in the degree of experimental control (for a discussion, see Manimala et al., 2000). Thirdly, related to the previous point, studies were included if they examined the *causal* effects of interpersonal interactions on pain and were excluded if they merely correlated pain data with social variables. Fourthly, studies were included if they reported behavioral pain outcomes (e.g., pain intensity ratings, facial expressions) or pain-related physiological outcomes. To render studies comparable, neuroimaging studies were only included if they also yielded behavioral or physiological data. Finally, studies were included if they were published in English.

RESULTS AND THEIR ORGANIZATION

Twenty-six studies met the above five inclusion criteria. A summary of included studies is presented in **Table 1**. The terms "participant" and "person in pain" refer to the individual receiving pain, while "social partner" denotes the individual interacting with the person in pain, e.g., providing support. A variety of terms have been used in the literature in relation to the social modulation of pain, including "social support," "social interaction," "interpersonal interaction," "social presence," "social influence," and "social context." Each of these terms appears to place a slightly different emphasis on the social partner; for example, "social support" implies a directly caring attitude toward the person in pain compared to the broader term "social context." For the purposes of our analysis, we used the term "social context" when discussing the role of others generally and "interpersonal interaction" when discussing specific interactions between social partner and participant in pain as outlined above.

Due to the large variety in pain measures obtained across studies, we summarized and presented pain measures in five sub-categories in the table. (1) "Pain ratings" refers to participant-generated ratings, e.g., of pain intensity, unpleasantness, or pain threshold; (2) "pain behaviors" denotes pain-related behaviors such as pain tolerance or facial expressions; (3) "pain words" refers to pain-related verbalizations to the social partner; (4) "physiological measures" pertains to measures of heart rate, skin conductance levels, blood pressure, etc.; and (5) "neural activity" signifies magnetoencephalography (MEG), and blood-oxygen-level-dependent (BOLD) measures obtained from functional magnetic resonance imaging (fMRI). Further, only findings relating to the above pain outcome measures were included in the table and additional variables such as gender or catastrophizing were included only if they interacted with the social manipulation in affecting pain. We address methodological issues where relevant in the results section.

The studies meeting the inclusion criteria were based in different research and theoretical traditions (e.g., health sciences, social psychology, clinical psychology, and social cognitive neuroscience). To ensure valid comparisons between studies, the theoretical context of such concepts, their taxonomy, and precise operationalization in each study were addressed when appropriate in the following sections, and they were taken into account when reviewing and integrating the data.

Table 1 | Effects of interpersonal interactions on pain: a summary of experimental studies to date.

Reference	Social manipulation(s)	Sample	Social partner	Pain induction technique	Pain measures	Findings
Borsook and MacDonald (2010)	Between-subjects design: 1) Alone 2) Positive encounter 3) Negative encounter after baseline pain induction	Healthy students ($N = 45$)	Stranger	Pressure pain	Pain ratings	The negative encounter condition reduced pain intensity and unpleasantness relative to baseline. The other two conditions showed no change
Brown et al. (2003)	Between-subjects design: 1) Alone 2) Passive support (physical presence) 3) Active support 4) Interaction during pain	Healthy students ($N = 101$)	Friend or stranger	Coldpressor	Pain ratings	Participants in active and passive support conditions felt less pain than participants in alone or interaction conditions, regardless of type of interaction partner
Chambers et al. (2002)	Between-subjects design: 1) Pain-promoting (reassurance, empathy) 2) Pain-reducing (distraction) 3) Neutral interaction (interact as normal) during pain	Healthy children aged 8–12 ($N = 120$)	Mother	Coldpressor	Pain ratings; pain behaviors; physiological measures	For girls, pain intensity was highest in the pain-promoting condition, followed by neutral interaction and pain-reducing conditions. No differences in pain intensity between conditions were found for boys. Maternal interaction type did not affect other pain measures
Eisenberger et al. (2011)	Within-subjects design: Viewing pictures during pain	Healthy females in a relationship ($N = 17$)	Romantic partner, stranger, and object	Thermal pain	Pain ratings; neural activity	Pain ratings were lower when viewing partner pictures than when viewing stranger and object pictures. Participants showed less activity in the dACC and bilateral anterior insula when viewing partner pictures vs. other two conditions on high pain trials
Flor et al. (1995)	Within-subjects design: 1) Partner present 2) Partner absent during pain and 1) Neutral interaction 2) Conflict interaction after pain inductions 1 and 2, respectively	Chronic back pain patients ($n = 17$) and healthy controls ($n = 15$)	Romantic partner	Coldpressor	Pain ratings; pain behaviors; physiological measures; pain words	Patients with highly solicitous partners showed lower pain threshold and tolerance when the partner was present vs. absent. This was not found for patients with non-solicitous partners

(Continued)

Table 1 | Continued

Reference	Social manipulation(s)	Sample	Social partner	Pain induction technique	Pain measures	Findings
Hayes and Wolf (1984)	Between-subjects design: 1) Coping privately 2) Coping publicly 3) Attention-placebo control group between pain inductions	Students ($N = 84$)	Stranger (experimenter)	Coldpressor	Pain ratings; pain behaviors	Participants in the coping publicly condition showed greater tolerance than participants in the control group. The private coping condition did not differ from control group
Jackson et al. (2005)	Study 1: Between-subjects design: 1) No transaction (NT) 2) Transaction opportunity (TO) during pain	Young healthy adults ($N = 91$)	Stranger (empathic experimenter)	Coldpressor	Pain ratings; pain behaviors	No differences between conditions and no condition by gender interaction were found. Within the TO condition, speaking to the experimenter was related to lower pain tolerance, higher pain intensity, and more catastrophizing than not speaking to the experimenter
	Study 2: Between-subjects design: 1) No transaction (NT) 2) Transaction opportunity (TO) 3) Distraction (DT) 4) Reinterpretation (RT) 5) Encouragement (ET) during pain	Healthy participants ($N = 126$)				Women showed higher pain tolerance in DT, RT, and ET than in NT and TO conditions. Lowest tolerance was shown in the TO condition. No differences across conditions were found for men
Jackson (2007)	Between-subjects design: 1) No transaction (NT) 2) Distraction 3) Pain monitoring 4) Reinterpretation during pain	Healthy participants ($N = 118$)	Female stranger	Coldpressor	Pain ratings; pain behaviors	Women displayed lowest tolerance in the NT condition vs. all other conditions. Women showed highest tolerance in the reinterpretation group, followed by pain monitoring, distraction, and NT conditions. Women's reported pain intensity was highest in distraction condition, followed by NT, pain monitoring, and reinterpretation. No differences across conditions and measures were found for men
Jackson et al. (2009)	Between-subjects design: 1) Reassuring appraisal (participant and social partner read safety message) 2) Threat appraisal (both read threat message) 3) Mixed appraisal (participants read reassuring text, social partner read threatening text) before pain	Healthy participants ($N = 86$)	Person at least acquainted with (could include acquaintance, friend, partner)	Coldpressor	Pain ratings; pain behaviors; pain words used in dyad interactions during pain	Pain tolerance was reduced in the threat appraisal condition vs. reassuring and mixed appraisal conditions. Dyads in the threat appraisal condition used proportionally more pain words in conversation than reassured or mixed dyads. Mixed gender dyads used a higher proportion of pain words than same-sex dyads. Attention diversion by social partners increased pain tolerance

(Continued)

Table 1 | Continued

Reference	Social manipulation(s)	Sample	Social partner	Pain induction technique	Pain measures	Findings
	During pain, social partners were present and helped participants cope in any way they chose					
Jolliffe and Nicholas (2004)	Between-subjects design: 1) Reinforcement 2) Non-reinforcement during pain	Healthy participants ($N = 46$)	Stranger	Pressure pain	Pain ratings; physiological measures	Participants in the reinforcement condition reported more pain than participants who received no reinforcement
Kleck et al. (1976)	Study 1: Within-subjects design: 1) Presumed alone 2) Observer present (behind one-way window) during pain	Healthy male participants ($N = 20$)	Stranger (higher-status female)	Electric shock	Pain ratings; pain behaviors; physiological measures	Participants were less expressive and had lower skin conductance levels when observed than when alone, especially in high shock trials. The magnitude of both these effects increased as shock intensity increased. Pain intensity was lower across shock levels in observer condition than when alone
	Study 2: Within-subjects design: 1) Alone 2) Male observer present 3) Female observer present during pain	Healthy male participants ($N = 40$)	Stranger (age peer stranger)		Pain ratings; pain behaviors; physiological measures	Participants expressed less discomfort, had lower skin conductance levels and reported less pain when observed than when alone, regardless of observer gender
Master et al. (2009)	Within-subjects design: 1) Holding hand/object 2) Viewing photographs during pain	Healthy females in a long-term relationship ($N = 25$)	Romantic partner and stranger and object	Thermal pain	Pain ratings	For hand-holding, women reported less pain unpleasantness when holding partner's hand than when holding a stranger's hand or an object. The same pattern of effects was observed in the photograph conditions. Effects of condition were not confounded with distraction
McClelland and McCubbin (2008)	Between-subjects design: 1) Alone 2) Physical presence during pain	Healthy students ($N = 68$)	Same-sex friend	Coldpressor	Pain ratings; physiological measures	Men reported less pain and women reported more pain in the presence vs. alone condition. Women, but not men, reported greater VAS pain in the presence condition than when alone. Women reported more affective and sensory pain than men in the presence condition. Participants with low support reported more pain in the alone condition than the presence condition; the opposite was found for high support participants. Participants in the presence condition had greater blood pressure changes than in the alone condition

(Continued)

Table 1 | Continued

Reference	Social manipulation(s)	Sample	Social partner	Pain induction technique	Pain measures	Findings
Modic Stanke and Ivanec (2010)	Mixed design: Within-subjects factor: 1) Social presence 2) Absence during pain Between-subjects factor: 1) Small physical distance (0.5 m) 2) Large physical distance (1.5 m) during pain	Healthy females ($N = 48$)	Female stranger	Hot air	Pain ratings; pain behaviors	No significant effects of presence condition, distance condition, or their interaction
Montoya et al. (2004)	Between-subjects design: 1) Alone 2) Physical presence during pain	Fibromyalgia patients ($n = 18$) and migraine patients (control group; $n = 18$)	Romantic partner	Thermal pain (hot and cold)	Pain ratings; neural activity	Fibromyalgia patients reported less pain sensitivity, higher pain threshold, lower pain ratings and reduced brain activity when partner present than when alone for heat but not cold pain. These effects were not observed in migraine patients
Peeters and Vlaeyen (2011)	Between-subjects design: 1) Low social threat 2) Neutral 3) High social threat during pain	Healthy participants ($N = 82$)	Stranger	Electrical pain	Pain ratings; pain behaviors	Increased social threat increased pain intensity ratings for high – but not low – pain catastrophizers; higher social threat reduced facial expression across participants
Platow et al. (2007)	Between-subjects design: 1) Reassurance from in-group member 2) Reassurance from out-group member 3) No reassurance between pain inductions	Healthy students ($N = 54$)	Stranger (in-group: same university degree; out-group: different university degree)	Coldpressor	Pain behaviors; physiological measures	No significant results for pain tolerance. Galvanic skin response during the second coldpressor trial was significantly lower in the in-group condition than in either out-group or no reassurance conditions. Physiological arousal was lower in high vs. low identifiers in the in-group condition
Sambo et al. (2010)	Within-subjects design: 1) Alone 2) Presence of high empathy observer 3) Presence of low empathy observer during pain	Healthy participants ($N = 30$)	Stranger	Thermal pain	Pain ratings; physiological measures	Skin conductance and heart rate were lower in both observer present conditions vs. being alone. Higher attachment anxiety predicted lower pain rating when high-empathic vs. low-empathic observer was present. Higher scores on attachment avoidance predicted lower pain ratings in alone vs. presence conditions

(Continued)

Table 1 | Continued

Reference	Social manipulation(s)	Sample	Social partner	Pain induction technique	Pain measures	Findings
Sullivan et al. (2004)	Between-subjects design: 1) Alone 2) Observer present during pain	Healthy students ($N = 64$)	Stranger	Coldpressor	Pain ratings; pain behaviors	High catastrophizers showed communicative pain behaviors for a longer duration when observer present than when alone. This effect was not found for low catastrophizers. Within the presence condition, high catastrophizers reported more pain after the trial than low catastrophizers
Vervoort et al. (2008)	Between-subjects design: 1) Presence of parent observer 2) Presence of stranger observer during pain (children could not see observer)	Healthy children aged 9–15 years ($N = 84$)	Parent or stranger	Pressure pain	Pain ratings; pain behaviors	Low-catastrophizing children expressed less pain when stranger present vs. when parent present. High catastrophizing children expressed same amount of pain regardless of whether parent or stranger was observing. This pattern was not found for pain intensity or anxiety
Vervoort et al. (2011)	Within-subjects design: 1) Presumed alone (told no one observing but parent was observing from next room) 2) 3-min interaction with parent between CPT trials 3) Parent observing from next room during pain	Healthy children aged 10–18 years ($N = 38$)	Parent	Coldpressor	Pain ratings; pain behaviors	Low catastrophizers displayed more pain when observed than when presumed alone. High catastrophizing children showed same amount of pain when believed alone as when observed. Regardless of catastrophizing, pain intensity was lower when parent observed than when presumed alone. Higher levels of parental non-pain talk were related to increased facial expression and self-reports of pain only for high catastrophizing children. For low-catastrophizing children, both measures of pain were independent of parental pain talk
Vlaeyen et al. (2009)	Between-subjects design: 1) No threat/no observer 2) No threat/observer present 3) Threat/no observer present 4) Threat/observer present during pain	Healthy participants ($N = 149$)	Stranger	Coldpressor	Pain ratings; pain behaviors	Participants in the threat condition experiencing pain alone reported more pain than participants in the other three conditions. In the threatening context, the presence of a stranger inhibited pain facial expression during the pain induction. In the no threat conditions after the task, participants with an observer present displayed more pain expressions compared to participants who were alone
Wilson and Ruben (2011)	Within-subjects design: Interaction with partner before and during pain	Healthy couples – women took part in pain induction ($N = 65$)	Romantic partner	Muscle pain	Pain ratings; pain behaviors; physiological measures	Dismissively avoidant women showed lower pain tolerance and threshold when partner scored higher in attachment anxiety, and higher pain tolerance when partner scored lower in attachment anxiety (though pain intensity and physiological measures were not affected); secure women showed opposite pattern. Highest pain was reported when both couple members scored higher in attachment anxiety. Partner avoidance levels did not influence women's pain

(Continued)

Table 1 | Continued

Reference	Social manipulation(s)	Sample	Social partner	Pain induction technique	Pain measures	Findings
Younger et al. (2010)	Within-subjects design: 1) Viewing photographs 2) Distraction task (word-association task) during pain	Healthy students in early stages of romantic relationship ($N = 15$)	Romantic partner and acquaintance	Thermal pain	Pain ratings; neural activity	Partner task and distraction task both reduced pain, contrasted with viewing acquaintance photographs. No difference was found between partner task and distraction task. Pain relief in the partner condition was positively related to activation in the bilateral caudate head, bilateral nucleus accumbens, right dorsolateral prefrontal cortex, right superior temporal gyrus, bilateral lateral orbitofrontal cortex, left amygdala, and right thalamus (ventral anterior nucleus), and negatively related to activity in the right superior frontal gyrus, left dorsal anterior cingulate cortex, right brainstem, left anterior insula, right putamen, left supplementary motor area, and left parahippocampal area

Moreover, the studies manipulated a variety of interpersonal factors including verbal interactions (e.g., Chambers et al., 2002; Jackson et al., 2005), non-verbal interactions (e.g., hand-holding; Master et al., 2009), mere physical presence of the social partner (Brown et al., 2003; Vervoort et al., 2008), priming by photographs of partners (e.g., Eisenberger et al., 2011) and manipulations of participants' perception of the social partner (e.g., Sambo et al., 2010; Peeters and Vlaeyen, 2011). Also, studies differed in terms of the characteristics of their sample, for instance participant and partner gender, and personality traits (e.g., pain catastrophizing; Sullivan et al., 2004; or attachment style; Sambo et al., 2010; Wilson and Ruben, 2011). To review such heterogeneous data, and motivated by interactionist accounts of social cognition (e.g., Bartz et al., 2011), we drew a distinction between studies in which social partners were perceived by the participants to be active or to possess possibility for action (see The Social Partner's Possibility for Action), and studies in which social partners did not appear to have possibility for action (see No Perceived Possibility for Action). At the most apparent level, this involved distinguishing between on-line and off-line, or primed social contexts. While the former included interactions in which the social partner was physically present, the latter used social stimuli (e.g., photographs) rather than interactions with a live social partner; thus, the two contexts differed in possibility for action by the social partner.

Secondly, independent of this "possibility for action" subdivision, we distinguished between different types of relationships, according to whether the social partner was a stranger (e.g., Jackson et al., 2005), a parent (e.g., Vervoort et al., 2011), a friend (e.g., McClelland and McCubbin, 2008), or the romantic partner (e.g., Master et al., 2009) of the person in pain (see Relationship Between the Social Partner and the Person in Pain). We further particularly examined studies according to the interaction history, contrasting rich interaction histories (parent, partner, and friend) with one-off interactions with strangers. Previous experiences with the social partner were considered to be important not only from an attachment perspective (see below) but also in terms of predictability of the other's mental state, which we address in the discussion.

It is important to emphasize that while we organized the data around the categories of "possibility for action" and "type of relationship" separately, most aspects of interpersonal interactions are likely to interact in various dynamic ways to create the overall social context of pain. We point the reader to related sections as appropriate throughout the review and present an overall theoretical conceptualization (based on a free energy framework) of such dynamic patterns in the discussion.

THE SOCIAL PARTNER'S POSSIBILITY FOR ACTION

Twenty-two studies manipulated aspects of interpersonal interactions in which the social partner was physically present and was perceived to have the possibility to act toward the person in pain. In nine of these studies, the social manipulation involved the opportunity of engaging in verbal communication with a social partner, while the remaining 13 studies manipulated social presence without verbal communication.

Possibility for action and verbal interaction

In studies manipulating verbal interactions, the social partner was generally designed to act in a socially supportive role toward the person in pain. Social support is a complex construct, broadly conceptualized as "resources and interactions with others that help people cope with problems" (Masters et al., 2007, p. 11) and thus includes clear possibilities for action. Six studies (Chambers et al., 2002; Brown et al., 2003; Jackson et al., 2005, *studies 1 and 2*; Jackson et al., 2009; Wilson and Ruben, 2011) included conditions in which the content of the interaction was unstructured (i.e., not pre-determined by the experimenters). In Brown et al.'s (2003) study, this unstructured condition took the form of an "interaction" condition, in which the social partner was not instructed to behave in any particular way and the participant could shape the interaction. Three further conditions involved active support (explicitly supportive comments), passive support (presence without verbal interaction), and experiencing pain alone. Regardless of whether the social partner was a friend or a stranger, participants reported more pain in the unstructured interaction condition and when experiencing pain alone than they did in the active and passive support conditions (Brown et al., 2003). Though the authors did not record the verbal content of the unstructured interaction condition, they suggested that the interaction could have included negative comments, which may have counteracted any benefits of social support. Similarly, Jackson and colleagues found in a first study that participants who spoke to an empathic experimenter ("transaction opportunity" condition) showed reduced pain tolerance and increased pain intensity compared to participants who did not speak to the experimenter (Jackson et al., 2005, *study 1*). This was mirrored in their second study (Jackson et al., 2005, *study 2*), in which female participants displayed the lowest pain tolerance in the transaction opportunity condition, compared to structured conditions, such as distraction and encouragement conditions. Lastly, Chambers and colleagues trained mothers to respond to their children's pain in either pain-promoting ways (which included reassurance, empathy, mild criticism, and giving control to the child) or pain-reducing ways (which included distraction with an alternative task, humor, and "encouragement to use coping strategies"), or mother and child interacted as normal in an unstructured way. Girls reported highest pain intensity in the pain-promoting group, followed by the unstructured interaction, and then the pain-reducing condition (Chambers et al., 2002). These effects were not present in boys, in accordance with other findings (Jackson et al., 2005, *study 2*; Jackson, 2007). As the pain-promoting condition included different social attitudes (e.g., empathy and mild criticism were included in the same interaction condition), it may have been more mixed than other structured conditions, in accordance with Brown et al.'s explanation regarding their unstructured condition. It thus seems that unstructured or mixed valence verbal interactions with an observer can worsen the experience of pain.

In addition, Wilson and Ruben (2011) discovered that adult attachment style moderated the relationship between unstructured verbal interactions and pain. Attachment styles derive from attachment theory (Bowlby, 1977) and are individual differences in interpersonal relating formed in infancy over repeated interactions with a primary caregiver. These styles are relatively stable across the lifespan (Main et al., 1985; Waters et al., 2000). In adulthood, attachment styles are generally classified as secure or insecure; the latter commonly being subdivided into anxious and avoidant styles (though attachment styles are also viewed dimensionally, e.g., Fraley et al., 2000). In brief, securely attached adults are typically comfortable with closeness and depending on others, while anxious adults are preoccupied with the relationship and fear abandonment, and avoidant individuals are uncomfortable with closeness and lack trust in relationship partners (Hazan and Shaver, 1987). Wilson and Ruben found that in couples in which the woman received noxious stimuli, highest pain was reported when both members of the couple had higher levels of attachment anxiety. Further, avoidant women showed lower pain tolerance when the social partner was more anxiously attached, whereas securely attached women showed higher pain tolerance when the social partner was more anxiously attached (Wilson and Ruben, 2011).

In a related study examining the moderating role of attachment style, Sambo et al. (2010) manipulated the "perceived empathy" of a present social partner. While empathy predicts social support provision (Devoldre et al., 2010) and plays an important role in health care settings (Blasi et al., 2001; Tait, 2008), its effects on pain remain understudied in experimental contexts, though some studies have included empathy as one element of a multifaceted manipulation (e.g., Chambers et al., 2002; see above). "Perceived empathy" describes participants' knowledge of the social partner's level of understanding of their pain (Sambo et al., 2010). In a within-subject design, Sambo et al. informed participants prior to the administration of noxious stimuli that each of the experimenters present during each of two identical blocks of noxious stimulation had either expressed high or low empathy for them during initial thresholding (determining a participant's pain threshold). In a third condition, participants experienced pain alone. Although participant and social partner did not communicate during pain induction, the empathy manipulation was verbal, and is thus reviewed here. The perceived empathy manipulation interacted with the participants' adult attachment style to affect pain, in that higher attachment anxiety predicted less pain in the high empathy compared to the low empathy condition. However, it should be noted that the manipulated facet of empathy was thus quite "cognitive" in nature and it is unclear how it may compare to natural social contexts in which empathy is not only verbally but also behaviorally communicated.

Moreover, four experiments manipulated structured interpersonal interactions, that is, instances of interpersonal interactions with set verbal elements (e.g., certain sentences the interaction partner always used) or a clear theme (e.g., supportive comments). Conditions such as distraction, reinterpretation, and encouragement (Jackson et al., 2005) and active support (Brown et al., 2003) all led to increased pain tolerance relative to transaction opportunity conditions (see above). Although Chambers et al. (2002) included several verbal elements, the nature of their pain-reducing condition was supportive overall, and indeed it was found to reduce pain relative to other conditions in girls. While these interactions all exerted pain-reducing effects, it seems likely that the mediating mechanisms may have differed, since the interactions compared were quite varied, e.g., distraction vs. reinterpreting pain-related cognitions (Jackson et al., 2005) (see Discussion).

In summary, unstructured verbal interactions were found to increase pain and were influenced by adult attachment style. The effects of structured verbal interactions depended on the content and valence of the interaction. While interactions with a clear theme positive valence, e.g., encouragement, reinterpretation, and active emotional support, reduced certain pain measures, interactions with mixed verbal content, and valence were pain-promoting, even when they included one of the above "positive" factors such as reassurance. Notably, the effects of verbal interactions on pain were mainly found in women but not men.

Possibility for action and non-verbal social presence

Thirteen studies manipulated social presence during pain without verbal communication. Manipulations ranged from the mere presence of a supportive other (e.g., Flor et al., 1995) to varying the threat of the social partner (e.g., Peeters and Vlaeyen, 2011) and interpersonal distance (Modic Stanke and Ivanec, 2010), to conditions using hand-holding (Master et al., 2009). While some manipulations did not involve any actual interaction between person in pain and observer, possibility for action by the social partner was salient as the social partner was physically present. Further, though several studies placed the social partner in an adjacent observation room (Kleck et al., 1976, *studies 1 and 2*; Vervoort et al., 2008, 2011), we considered that participants perceived their partners as capable of action because participants were aware that their social partner was observing them *during* pain induction (as opposed to encounters prior to pain induction, see Social Partner without Perceived Possibility for Action during Pain). In addition, the results of these studies were comparable with the other studies in which the social partner was present in the same room, in that social manipulations influenced participants' facial expressions, which portray a communicative intent (e.g., Williams, 2002).

Kleck et al. (1976, *studies 1 and 2*) discovered that participants showed reduced facial expressions and reported less pain when they were observed than when they were alone; this was also found for physiological measures (Sambo et al., 2010), pain ratings in participants who received passive support from a friend or a stranger (Brown et al., 2003) or reported having low levels of social support in general (McClelland and McCubbin, 2008); for participants with high levels of self-reported everyday social support, pain ratings were higher in the presence of a friend than alone (McClelland and McCubbin, 2008). In addition, participants with a solicitous spouse showed a reduced pain threshold and tolerance in the presence of the spouse vs. alone (Flor et al., 1995). These latter findings fit within models of chronic pain positing that high social support may be positively reinforcing and ultimately lead to increased and prolonged pain (see Insights from Clinical Studies). Furthermore, in the aforementioned study on the role of perceived empathy on pain measures (Sambo et al., 2010), avoidant attachment was the only factor that moderated the relationship between social presence and pain report, such that higher attachment avoidance predicted more pain in the presence vs. alone condition, possibly because avoidant individuals prefer to cope on their own.

In addition to the above moderating factors, several studies which tested the communal coping model of pain catastrophizing (see Insights from Clinical Studies) reported that pain catastrophizing moderated the effects of presence on pain. Unfortunately, the direction of such effects varied between studies: only high pain catastrophizers (Sullivan et al., 2004) vs. only low pain catastrophizers (Vervoort et al., 2011) were found to exhibit facial expressions for a longer time period in the presence of a social partner than when alone. In addition, Vervoort et al. (2008) demonstrated that low-catastrophizing children displayed less pain when a stranger rather than their parent was present. It is possible that a stranger may be perceived as more threatening than a parent, leading to the inhibition of facial expressions. Indeed, three studies varied perceived threat during the social situation. They found that the presence of a stranger during a threatening situation (Jackson et al., 2009; Vlaeyen et al., 2009), as well as the threat appraisal of the strangers themselves (Peeters and Vlaeyen, 2011) led to attenuated facial expressions of pain (Vlaeyen et al., 2009; Peeters and Vlaeyen, 2011) and reduced pain tolerance (Jackson et al., 2009), i.e., increased pain sensations.

Lastly, we considered pain-modulatory effects of interpersonal distance between social partner/s and the person in pain. Interpersonal distance can modulate intimacy between people (Sussman and Rosenfeld, 1982), and violations of personal space can increase aversion of the social partner (Sussman and Rosenfeld, 1978). Conversely, a sense of safety and intimacy provided by a trusted other might be diminished if they are physically distant and unable to help. However, only one study directly investigated the effects of physical distance on pain (Modic Stanke and Ivanec, 2010). In this study, the social partner was positioned either 0.5 or 1.5 m from the person receiving pain. No effects of distance on pain were found. However, both social partner and participants in pain were female. Women have been found to maintain smaller interpersonal distances (i.e., choose to sit closer together) and do not see close distances as violations of space compared to men (Sussman and Rosenfeld, 1978, 1982; Holland et al., 2004). Therefore, at present, we cannot draw any conclusions on the effects of interpersonal distance on pain.

Overall, social presence differentially impacts pain according to individual differences of the person in pain or of the social partner. Participants reporting higher levels of everyday social support and higher attachment avoidance, as well as participants with a solicitous spouse, had worse pain outcomes when a social partner was present than when they were alone, while participants with low levels of everyday social support showed the opposite effects. Unfortunately, the direction of the moderating effect of pain catastrophizing remains unclear, while environmental threat seems to exacerbate pain.

Only one study coupled social presence with a direct action toward the participant (Master et al., 2009). In this study, hand-holding was employed as a form of social support. In different conditions in a within-subject design, female participants held the hand of their partner, or the hand of a stranger, or held an object. Reductions in pain unpleasantness were found when holding the hand of the romantic partner during pain compared to when holding a stranger's hand or holding an object (these differences were not due to distraction, as participants' reaction times to random computer-generated beeps did not differ across conditions). This finding is consistent with a study showing that unpleasantness ratings and neural responses to the threat of electric shocks were reduced when participants held their spouse's hand as opposed to a stranger's hand or no hand at all (Coan et al., 2006). Although the latter study assessed "threat of pain" and not pain *per se* (and hence was not included in **Table 1**), taken together both these studies suggest that holding the hand of the romantic partner can reduce pain-related unpleasantness. However, a few methodological issues deserve mention. Hand squeezing was not measured in either study and holding a stranger's hand may be a somewhat unusual and potential socially uncomfortable condition. Further, a condition without touch (i.e., holding no hand at all) arguably differs from the other two in terms of multisensory integration.

In conclusion, verbal and non-verbal interpersonal interactions with perceived possibility for action were found to be pain-reducing only when specific verbal behaviors with positive intention, such as supportive comments, reinterpretation, and distraction, or non-verbal interactions with a clear positive social meaning (e.g., holding one's partner's hand) were manipulated and participants had low levels of self-reported social support and attachment avoidance. By contrast, more unstructured, emotionally negative, varied, or vague social manipulations led to increases in pain, either directly (e.g., presence conditions with unstructured verbal content) or in interaction with variables linked to the perception of threat and anxiety, such as catastrophizing and threat manipulations.

NO PERCEIVED POSSIBILITY FOR ACTION

Studies with no possibility for action were defined by the absence of a social partner during pain induction. Here, social manipulations were classified according to two sub-categories. In a first set of three studies, interpersonal variables were manipulated by priming. Second, two studies involved a partner who was present *before* pain induction but not *during* pain induction.

Primed interpersonal contexts

Three studies presented participants with photographs of their partner and either a stranger and an object (Master et al., 2009; Eisenberger et al., 2011) or an acquaintance (Younger et al., 2010). All studies discovered that viewing pictures of the partner reduced pain relative to viewing stranger/acquaintance and object pictures. While such effects might be explained by distraction or familiarity of the partner, two studies assessed distraction (see Possibility for Action and Non-Verbal Social Presence for details on Master et al., 2009) and Younger et al. (2010) included a word-association task condition. They also controlled for familiarity by comparing viewing pictures of a partner with viewing pictures of an equally attractive and familiar acquaintance. However, the other two studies cannot rule out possible familiarity effects (Master et al., 2009; Eisenberger et al., 2011) and Eisenberger et al. (2011) cannot exclude possible distraction effects.

Two of the three studies (Younger et al., 2010; Eisenberger et al., 2011) also employed functional neuroimaging techniques and reported neural activations during the different social conditions. Most notably, pain attenuation in the partner picture condition was positively linked to activation in areas associated with safety-signaling (the ventromedial prefrontal cortex; Eisenberger et al., 2011), and reward processing (e.g., the caudate head and nucleus accumbens; Younger et al., 2010). Based on this finding, two neurocognitive mechanisms potentially mediating the beneficial effects of viewing partner pictures were put forward. First, ventromedial prefrontal cortex activation was not only found during partner picture viewing but was further negatively correlated with both pain ratings and pain-related neural activity. Hence, it was claimed that viewing pictures of an attachment figure (i.e., the partner) signaled safety in the face of threat (pain), which contributed to pain attenuation (Eisenberger et al., 2011). The second proposed mediating mechanism concerned reward-related neural activation, which has previously been positively associated with intense love (Aron et al., 2005). In Younger et al.'s (2010) study, viewing pictures of the partner and a distraction task both reduced pain, but only the partner condition was associated with activation in the bilateral caudate head, bilateral nucleus accumbens, amygdala, hypothalamus, pregenual ACC, and medial orbitofrontal cortex, which play a role in the processing of rewards (Aron et al., 2005). Reward processing has in turn been linked to pain attenuation (e.g., Wood, 2006) and placebo analgesia (e.g., Scott et al., 2007). Such mechanisms may explain why pain was not attenuated when viewing pictures of strangers or acquaintances, who are not involved in a pre-existing loving attachment relationship with the person in pain.

Taken together, showing participants photographs of their romantic partner may reduce pain by priming attachment or love themes and related brain networks. The role of distraction and familiarity in some of these studies remains to be established.

Social partner without perceived possibility for action during pain

Two studies employed a social partner who interacted with the participant before but was absent during pain induction (Platow et al., 2007; Borsook and MacDonald, 2010). The first investigated whether the effects of reassuring comments depended on in-group or out-group status of the social partner, while Borsook and MacDonald studied socially induced hypoalgesia (reduced pain in the face of a stimulus that is normally perceived as painful; IASP, 1994) by negative vs. positive interpersonal interactions. Contrary to studies with perceived possibility for action (see The Social Partner's Possibility for Action), both found that positive encounters *before* pain induction did not affect pain ratings or pain tolerance during pain induction, highlighting the importance of possibility for action. However, reassurance from an in-group member did selectively reduce physiological arousal (Platow et al., 2007). Furthermore, negative interpersonal interactions preceding pain induction were associated with reductions in pain ratings, attributed to social harm induced hypoalgesia (Borsook and MacDonald, 2010).

In sum, social manipulations characterized by the absence of a social partner during pain seemed to reduce pain only when they were interpersonally relevant, e.g., when there existed a close (attachment) bond between the social partner and the person in pain, or the social partner was an in-group member of the person in pain.

RELATIONSHIP BETWEEN THE SOCIAL PARTNER AND THE PERSON IN PAIN

The reviewed studies differed in terms of the relationship between participant and social partner. Most commonly, the social partner was a stranger (18 studies), the partner (six studies), a parent (three studies), or a friend/acquaintance (four studies) of the participant[1]. In one study, the nature of the social partner was not specifically defined (had to be at least an acquaintance but could also be the partner, Jackson et al., 2009; counted as acquaintance above), and thus it was not possible to evaluate relationship effects in this study.

Perhaps due to partner manipulation studies coming from similar research backgrounds and being designed to be positive (e.g., supportive), these studies generally found that the romantic partner reduced pain, although this effect was moderated by adult attachment style (Wilson and Ruben, 2011) and spouse solicitousness (Flor et al., 1995). Also, social manipulations were more homogeneous when the social partner was the romantic partner, presumably because they were constrained by the couple's relationship history. For example, a very empathic partner being assigned to a high social threat condition in which they supposedly chose to administer a high number of pain trials to their partner (as in Peeters and Vlaeyen, 2011) might not seem believable to the person in pain. Likewise, certain social manipulations such as hand-holding may be inherently more suitable for pre-existing relationships.

The effects of interacting with strangers were most diverse, possibly due to the range of social manipulations, social meanings, and varying degrees of knowledge of the stranger's mental state. For example, some studies gave participants no information about the stranger's mental state (e.g., Sullivan et al., 2004, stated that the stranger was present only to monitor the water temperature of the coldpressor), some presented personally irrelevant information about the stranger's mental state (e.g., Vervoort et al., 2008, informed participants that the stranger present was a student observing the experimental session to learn about the pain procedure) and others gave participants personally relevant information regarding the stranger's mental state, for example how much empathy the stranger had for the participant (Sambo et al., 2010). When interactions with different types of social partners were compared within the same experiment, with social manipulations remaining constant, partners were found to reduce pain more than strangers or acquaintances (Master et al., 2009; Younger et al., 2010; Eisenberger et al., 2011), but most of these studies did not control for familiarity effects. Parents did not differ from strangers in their impact on pain intensity but increased facial expressions of pain relative to strangers in low-catastrophizing children (Vervoort et al., 2008). Furthermore, interacting with a friend was found not to differ from interacting with a stranger in affecting pain (Brown et al., 2003).

Overall, it appears that the type of relationship between participant and social partner may moderate how interpersonal factors affect pain. In general, pain seems to be attenuated when the participant is receptive to support (e.g., anxiously attached) and knows the partner is positively oriented toward them (but not highly solicitous), either due to a pre-existing relationship (e.g., between romantic partners), or experimental manipulation (e.g., empathy levels of previously unknown confederates are communicated to the participant). Comparing different types of relationships within the same experimental set-up to tease apart the relative influence of social manipulation and interpersonal relationship on participants' pain remains an ongoing issue for future research.

[1]Note that the total number exceeds 26 because several studies included more than one type of social partner.

DISCUSSION

This paper aimed to provide a systematic review of experimental studies investigating how interpersonal factors influence pain perception and communication. We examined 26 studies with a focus on the type of social manipulations, individual difference characteristics, and the person in pain's relationship with the social partner. Overall, we found that unambiguously positive verbal and non-verbal interactions or positive interpersonally relevant primed interactions reduced pain, while negative, mixed valence, or ambiguous interactions led to increases in pain-related measures. These findings were moderated by individual differences of the person in pain and the social partner, such as adult attachment style.

We propose that the key findings from this review can be integrated into a free energy framework (see Introduction). Specifically, we argue that the perception of interpersonal interactions in the context of pain can affect perceptual and active inferential processes about pain by influencing the certainty or precision of an individual's predictions about an impending stimulus vs. the certainty or precision of related prediction errors. Top-down predictions are not just about the content of lower level representations but also predict their context, defined in mathematical terminology as the *precision* of a probability distribution (inverse variance or uncertainty; Friston, 2009). Thus, precision refers to confidence in predictions; for example, the allocation of attention toward appropriately salient events can optimize the confidence in prediction errors and influence the relative weighting or importance of prediction errors (Feldman and Friston, 2010). This kind of top-down prediction in sensory cortices is thought to be mediated by cholinergic neuromodulatory mechanisms that optimize the attentional gain of populations encoding prediction errors (Feldman and Friston, 2010), as well as by dopamine in frontostriatal circuits (Fiorillo et al., 2003). In interoception, precision may relate to attention to signals from the body or interoceptive sensitivity (Farb et al., 2013; Fotopoulou, 2013) and may be modulated by several contextual factors. Therefore, interpersonal interactions may affect pain by changing the precision of top-down predictions about pain. This notion of social modulation as precision modulation can be seen as similar to previous psychological accounts (e.g., Van Kleef, 2009) which put forward that social interactions inform inferential processing of the environment (e.g., in developmental research, a mother's facial expressions may influence processing regarding the safety vs. threat of a visual cliff environment). Integrating such notions within a predictive coding model places them in a wider and neurobiologically plausible framework.

INTERPERSONAL INTERACTIONS AS PRECISION MODULATION

Based on the reviewed studies, we put forward that interpersonal interactions may affect the precision of an individual's predictions and thus pain in at least two ways: (a) by signaling the safety or threat of noxious stimuli (interoceptive salience) or (b) by signaling the safety or threat of the environment in which stimuli occur (environmental salience).

Precision of predictions about an impending stimulus itself

The present review revealed that certain interpersonal interactions may directly signal information about the safety or threat of an impending stimulus. Supportive interactions focusing on the painful sensations themselves increased pain tolerance, while interactions in which the threat of noxious stimuli was emphasized reduced pain tolerance. Specifically, a social partner helping participants to re-interpret uncomfortable sensations as neutral or positive sensations increased pain tolerance scores (Jackson et al., 2005) and decreased pain intensity ratings (Jackson, 2007). The social partner signaling that the noxious stimulus was safe thus shaped participants' prediction that the stimulus was safe, which in turn may have reduced the salience of the stimulus and thus pain. In contrast, both social partner and participant reading threatening information about the noxious stimulus increased the number of pain words in their conversation during pain and decreased pain tolerance relative to other conditions (Jackson et al., 2009), possibly because the social partner amplified the threat and hence improved precision and salience.

Moreover, the present results showed that interpersonal interactions may influence the salience of noxious stimuli by modulating the participant's attention toward or away from the noxious stimulus. Verbal interactions directing the participant's attention away from the noxious stimulus (e.g., Chambers et al., 2002; Jackson, 2007), non-social distraction conditions (Younger et al., 2010), and conditions in which distraction could have been a factor (Eisenberger et al., 2011) generally found that diverting attention away from the noxious stimulus led to increased pain tolerance and reduced pain ratings. Therefore, distraction might attenuate pain by reducing the precision of top-down predictions, which in turn may have decreased the salience of the noxious stimulus and hence pain.

Precision of predictions about the environment

The reviewed studies highlighted that in addition to information about the impending stimulus itself, interpersonal interactions may signal safety or threat of the environment in which the stimulus will occur, and thus modulate pain. In particular, interactions with a clear content regarding the provision of safety or support, or the partner having the possibility to act to protect the person in pain might increase the perception of environmental safety and thus indirectly decrease the perceived threat of noxious stimuli. Indeed, explicitly supportive verbal (e.g., Brown et al., 2003) and embodied (hand-holding; Master et al., 2009) interactions reduced pain, while pain-promoting and threatening conditions increased pain (Chambers et al., 2002; Jackson et al., 2009). By contrast, interactions without a clearly supportive content or possibility of supportive action may not increase the safety value of the environment. Indeed, the present review revealed that unstructured or mixed verbal interactions led to more pain relative to structured verbal interactions with supportive content.

THE PERCEPTION OF INTERPERSONAL INTERACTIONS *PER SE*

In addition to the influence of interpersonal interactions on pain, the perception of interpersonal interactions themselves may depend on (a) an individual's prior beliefs about interpersonal relating and the meaning of related interactions, and (b) the certainty or precision with which an interpersonal interaction may predict environmental threat or safety.

Prior beliefs about interpersonal relating

When examining the effects of interpersonal interactions on pain, it is vital to take into account "historicity"; that is, the backdrop of individual social development against which current social exchanges are placed (Schilbach et al., in press). In a free energy framework, such consideration entails examining not only how predictions are updated "on-line," but also across the life span in slower time scales (Friston, 2009). In the reviewed studies (as well as in clinical studies on pain, see Insights from Clinical Studies), several individual characteristics were found to play a role in the perception of interpersonal interactions and how they influence pain. While the role of factors such as catastrophizing and gender remains unclear, the application of attachment theory in pain research has generated some convincing results. Attachment theory posits that from early in life, attachment figures can serve as a "secure base" from which the infant explores the world (Bowlby, 1977). If a secure attachment bond is formed over repeated instances of responsive caregiving, the "secure base" signals safety to the infant, while insecure bonds lead to more ambivalent or even threatening signals from others. These bonds lead to the formation of attachment styles, which remain relatively stable into adulthood (see also section Possibility for Action and Verbal Interaction). In the clinical pain literature, insecure attachment styles have been proposed as crucial vulnerability factors for developing chronic pain (Meredith et al., 2008).

In the reviewed experimental studies, differences in attachment style influenced the effects of interpersonal variables on pain. Sambo et al. (2010) found that participants characterized by higher attachment anxiety, i.e., a fear of abandonment and need for reassurance from others (Mikulincer et al., 2009), reported less pain when social partners showed high compared to low empathy. Hence, when a partner was ostensibly positively oriented toward the participant, and the participant's attachment style was characterized by seeking for signs of reassurance, the social partner signaled safety to the participant, which in turn may have led to the reduction in pain. In contrast, pain was increased when both members of a couple were highly anxious relative to other attachment style constellations (Wilson and Ruben, 2011), possibly because the partner was not able to signal the desired reassurance. Similarly, avoidant women showed lower tolerance when their partner was highly anxious and higher tolerance when their partner was low anxious, reflecting the detrimental effects of environmental anxiety cues on pain. More generally, avoidant individuals, who generally have low trust in others, reported more pain when with others than when alone (Sambo et al., 2010). Overall, the findings highlight the importance of attachment priors in affecting the perception of the social partner.

Precision of the salience of the social partner

In addition to prior beliefs about interpersonal relating, we found that the specificity or salience (precision, mathematically, see above) by which an interpersonal interaction may predict environmental threat or safety might influence how interpersonal interactions are perceived and ultimately how they affect pain. Relevant factors are (1) the transparency of the social partner's intentions and thoughts, (2) the social partner's possibility for action, and (3) the familiarity or the degree of social bonding with the social partner.

Firstly, knowledge of the social partner's mental state might determine the salience of a social interaction. Information provided in the experiment (e.g., the social partner's empathy toward the participant) and prior knowledge about the social partner's mental state and intentions may increase precision, while lack of knowledge of the social partner's mental state may have the opposite effects. Thus, "pure" presence conditions yielded mixed results (see Possibility for Action and Non-Verbal Social Presence), possibly due to lack of information about the intentions, and thoughts of the social partner. Interestingly, unstructured and mixed interactions (which mostly occurred with strangers) were found to increase pain (see Possibility for Action and Verbal Interaction), indicating that uncertain interpersonal interactions do not weaken the impact on pain but rather may even signal increased environmental threat.

Secondly, a social partner's possibility for action may influence the salience of interpersonal interactions. Specifically, the reviewed studies revealed that interpersonal interactions without possibility for action during pain did not affect pain as much as interactions with possibility for action (see Social Partner Without Perceived Possibility for Action During Pain). Exceptions included interactions that were also interpersonally relevant, in which case other mechanisms may have enhanced salience. From the free energy perspective, these findings can be understood as active inference "by proxy." Normally, action minimizes prediction error by changing sensory input (Friston, 2009). In the case of pain in the presence of others who possess possibility for action, social partners may represent an auxiliary action system; they are able to act to change the sensory input for the person in pain (e.g., by pulling a person's hand away from a noxious source). Within an experimental context, the social partner cannot usually change a participant's sensory input. However, they can possess the possibility to do so, e.g., by being present in the experimental setting. Therefore, the higher the perceived possibility for action, the higher the salience of the interaction in terms of influencing safety and threat. Unfortunately, to our knowledge, no study has specifically examined the effects of partners' actual actions on noxious stimuli and therefore this facet of the interpersonal modulation of pain requires further experimental exploration.

Thirdly, interacting with a familiar social partner might also enhance the salience of the social interaction. Close bonding and positive relationship histories (e.g., secure attachment relationships) with established trust may lead to precise predictions of environmental safety in interpersonal interactions with the romantic partner (e.g., Eisenberger et al., 2011). Indeed, our review brought out that positive interactions with romantic partners generally reduced pain measures, except when partners were overly solicitous or insecurely attached (Flor et al., 1995; Wilson and Ruben, 2011). These findings extended to paradigms where the partner was not physically present, but related cognitions and feelings were primed in the individual in pain (e.g., Younger et al., 2010). On the contrary, interactions with strangers yielded mixed results (Jackson et al., 2005; Vlaeyen et al., 2009). Moreover, one study observed that greater relationship quality and bonding between partners was associated with greater pain reduction when photographs of the partner were shown during pain (Eisenberger et al., 2011).

OVERVIEW OF EFFECTS AND THE OVERALL FRAMEWORK

In summary, we found that clear and structured experimental interactions may lead to reductions in pain measures when they signal safety of the noxious stimulus or the environment in which it occurs or they are designed to direct attention away from the noxious stimulus. These effects are particularly apparent when the interpersonal interaction itself is salient. However, in most cases, the beneficial effects of support will be moderated by characteristics of the person in pain, such as their attachment style and level of pain catastrophizing. Although more data is needed and some studies found contrary effects, the general trend thus far is that insecure attachment and catastrophizing coping strategies worsen the pain experience, particularly during interpersonal interactions that may be ambiguous.

We have put forward a free energy framework for integrating these findings in a unified, biologically plausible theoretical framework. Our key proposal is that the perception of salient interpersonal interactions may enhance *the precision* of predictive signals regarding the salience of a noxious stimulus in a given environment, thus ultimately affecting the perceptual and active inferential processes that lead to pain perception and related motivated actions. Specifically, interpersonal exchanges affect precision or salience by socially signaling the safety or threat of the impending stimulus itself or the environment in which the stimulus occurs. In turn, at higher levels of the neurocognitive hierarchy and at slower time scales, the perception and interpretation of such interpersonal variables themselves may depend on an individual's prior beliefs about interpersonal relating and the certainty by which an interpersonal interaction may predict environmental threat or safety. A schematic overview is presented in **Figure 1**.

The precise neurobiological mechanisms by which interpersonal interactions affect pain remain to be determined. Initial findings suggest that their precision-based modulatory role in pain may be related to dopamine-based motivational mechanisms that have been implicated in the rewarding and craving aspects of social bonding in both humans (Younger et al., 2010) and animals and/or their co-activation with opioid and oxytocin mechanisms (see Insights from Animal Studies and Implications for Human Research). Oxytocin is a neuropeptide that has been implicated in social bonding (e.g., Strathearn et al., 2009), attachment (Buchheim et al., 2009), the social modulation of stress (Heinrichs et al., 2003; Chen et al., 2011), and has been shown to increase the

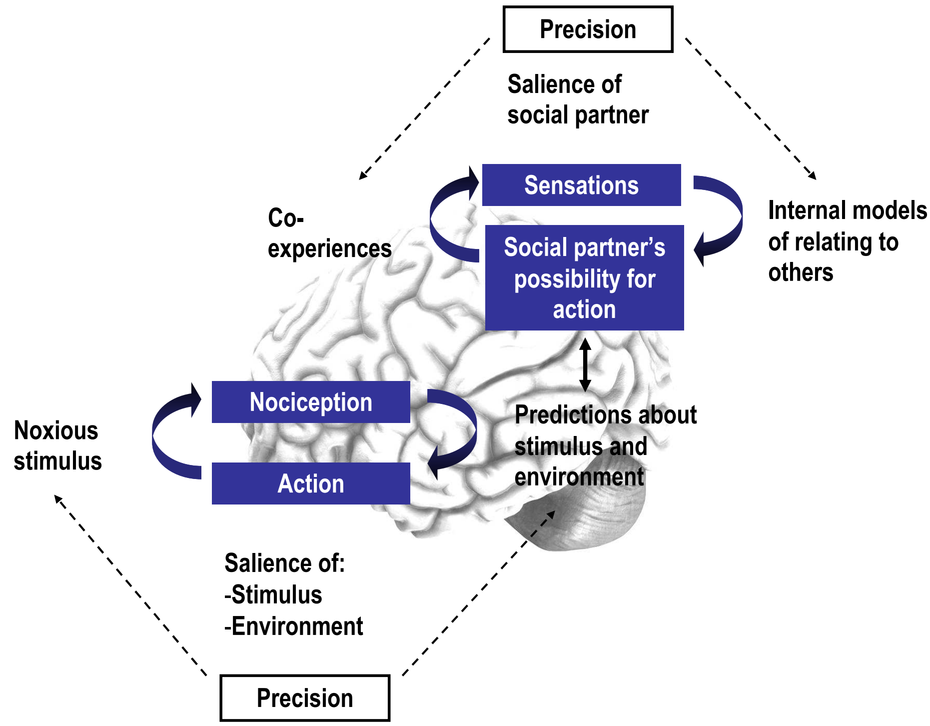

FIGURE 1 | A schematic representation of our free energy framework. The bottom panel depicts how interpersonal interactions may modulate the precision of interoceptive predictions, while the top panel shows the perception of interpersonal interactions *per se*, and how these influence interoceptive predictions in a top-down manner; the arrow is two-headed to show the interactive nature of the two hierarchical levels. Precision arrows are dashed to demonstrate the dynamic and modulatory, rather than permanent, influence of social context.

salience of social stimuli (see Bartz et al., 2011 for a review), perhaps to simultaneously reduce the salience of bodily threat during social experiences that may be valuable for survival (e.g., reproduction, birth etc.). Thus, future studies could explore the role of such neuromodulatory mechanisms and their interactions during pain in social contexts.

LIMITATIONS

While this paper represents the first systematic review of the social modulation of experimentally induced pain literature, a meta-analysis including direct, quantitative comparisons between studies was not possible due to the great methodological heterogeneity between studies. We were also not able to sufficiently address aspects of study quality, such as sample size, which differed across studies and may have explained some of the variation in findings. A further methodological difference of importance that we could not include was the diversity in study designs, such as sampling issues, ecological validity, pain induction methods, and type of pain measures obtained. For example, interpersonal interactions seem to have differential effects depending on the aspect of pain measured (e.g., pain catastrophizing studies in Possibility for Action and Non-Verbal Social Presence). As most studies included a subset of pain measures, it was not always possible to draw firm conclusions regarding the dependency of the findings on the specific pain measure used. It is further well-recognized that despite the potential of experimental studies to establish causality, the complexity of interpersonal interactions cannot be adequately operationalized in lab-based studies. Similarly, conclusions reached from studies on experimentally induced pain cannot be directly generalized to clinical pain due to the unique environmental and biological characteristics of the latter. Lastly, although we teased apart the different elements of the studies reviewed here to clarify their individual influences, many studies included composite elements within a single manipulation and further research is needed to determine the relative importance and weighting of these factors.

FUTURE PERSPECTIVES AND CHALLENGES

Although our review focused on interpersonal interactions between a (pain-free) social partner and a person receiving experimentally induced pain, the inclusion of other branches of research, such as social modeling studies and studies manipulating intergroup variables may provide a complementary picture to the present review.

Regarding the design of future studies, more specific manipulations focusing on certain aspects, for example safety or threat or particular facets of social support, could be employed and attempts made to replicate findings with previously used social manipulations. Furthermore, we suggest that varying perceived possibility for action, for example by using both live and primed interactions, and employing different kinds of social partners within the same experimental context (keeping the social manipulation constant) would be interesting avenues to explore. Individual differences, such as attachment style and pain catastrophizing, should also be taken into account in future studies.

Expanding on the proposed predictive coding framework, including several instances of interaction and measuring updating of safety vs. threat would be interesting, as well as investigating how lack of precision in interpersonal interactions impacts pain. Nevertheless, focusing on other mechanisms such as reward, attention/distraction by partner, and emotion regulation (e.g., the social baseline model; Coan, 2011) would also be important. Future neuroimaging studies focusing on safety- and threat-related neural activation during corresponding interpersonal interactions (e.g., Coan et al., 2006; see Vrticka and Vuilleumier, 2012, for a review related to attachment style) may add valuable insights into the neural mechanisms of the social modulation of pain. Finally, it could prove fruitful to study the central role of the neuropeptide oxytocin in parallel with manipulations of the interpersonal modulation of pain.

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