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Atypical electrophysiological activity during pain observation in amputees who experience synaesthetic pain

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There are increasing reports of people experiencing pain when observing pain in another. This describes the phenomenon of synaesthetic pain which, until recently, had been primarily reported in amputees with phantom pain. In the current study, we used electroencephalography (EEG) to investigate how amputees who experience synaesthetic pain process pain observed in another. Participants were grouped according to amputees who experience phantom and synaesthetic pain ($n = 8$), amputees who experience phantom pain but not synaesthetic pain ($n = 10$) and healthy controls ($n = 10$). Participants underwent EEG as they observed still images of hands and feet in potentially painful and non-painful situations. We found that pain synaesthetes showed some reduced event-related potential (ERP) components at certain electrode sites, and reduced theta- and alpha band power amplitude at a central electrode. The finding of reduced ERP amplitude and theta band power may reflect inhibition of the processing of observed pain (e.g. avoidance/guarding as a protective strategy), and reduced alpha band power may indicate a disinhibition in control processes that may result in synaesthetic pain. These results provide the first documentation of atypical neurophysiological activity in amputees who experience synaesthetic pain when processing pain in another.

Keywords: synaesthesia for pain; empathy for pain; phantom pain; electroencephalography

INTRODUCTION

Synaesthesia describes the phenomenon whereby an unusual perceptual experience occurs in one modality, in response to sensory stimulation typically in another (e.g. Rich and Mattingley, 2002). Of late, reports have emerged suggesting that it is possible to experience actual pain when seeing another person experience pain: 'synaesthesia for pain' (Giummarra and Bradshaw, 2008; Fitzgibbon *et al.*, 2010). We describe this phenomenon as a type of mirror-sensory synaesthesia where synaesthetic pain is induced in response to the observation or imagination of pain in another person (for a review, see Fitzgibbon *et al.*, 2010). Until recently, synaesthesia for pain had only been reported following trauma (acquired), and most commonly in people who have lost a limb and experience phantom limb pain (PLP) (Giummarra and Bradshaw, 2008). In fact, in the first report of the incidence of synaesthetic pain in a group of amputees, our group documented the surprisingly high rate of 16.2% (Fitzgibbon *et al.*, in press). Osborn and Derbyshire (2010) have, however, reported a similar experience in a healthy population, suggesting that while phenomenologically the same as previously reported synaesthetic pain experiences, synaesthesia for pain may result from factors other than physical trauma e.g. epigenetic factors (for a discussion, see Zhang and Meaney, 2010) that predispose one to have heightened sensitivity to stress/pain/threat, and potentially even from birth (developmental).

Similar to synaesthesia for pain is the experience of synaesthetic touch, also known as mirror-touch synaesthesia, where phenomenological touch is induced by observing a tactile sensation in another person (Banissy *et al.*, 2009). Reports of synaesthetic touch have been primarily documented in healthy populations (Banissy and Ward, 2007; Blakemore *et al.*, 2005), but synaesthesia for touch may also be brought about in an amputee population (see Ramachandran and Brang, 2009). It is argued that both synaesthetic pain and touch fit under the domain of synaesthesia as they involve the elicitation of an unusual experience that: (i) occurs outside of a psychiatric or neurological context; (ii) is not common to the general population; (iii) appears to happen involuntarily; and (iv) is similar to another perceptual experience (for synaesthesia criteria, see Ward and Mattingley, 2006). It is also argued that in the case of amputees, synaesthetic pain is more than just normal PLP as it is specifically triggered by observed or imagined pain in

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another instead of, as is typically seen in PLP, occurring spontaneously or in response to non-sensory triggers (Giummarra *et al*., 2006). Finally, these induced mirror-sensory synaesthetic experiences are more than standard empathic responses, as not only does the observer understand the other person's sensory stimulation, but also actually experiences a sensation of touch or pain themselves as well as associated motor responses such as avoidance, contraction and withdrawal (see Giummarra *et al*., 2010). As such, these experiences are potentially maladaptive to the individual, as is the case in patients with imitation behaviour, a disorder where an individual automatically imitates actions and/or gestures they observe in another person (De Renzi *et al*., 1996).

The reality that these mirror-sensory synaesthetic sensations can occur is supported by the finding that observing or imagining pain or touch in another activates overlapping areas of the cortex, as if the individual is actually experiencing pain or being touched (e.g. Bufalari *et al*., 2007). These shared neural circuits are referred to as 'mirror systems'. In the case of pain perception, therefore, 'empathy for pain', the automatic and unconscious perception of pain in another, activates overlapping areas of the brain involved in processing pain to the self (Jackson *et al*., 2006). For example, studies have identified activation in areas primarily involved in the affective (e.g. Morrison *et al*., 2004; Singer *et al*., 2004; Botvinick *et al*., 2005; Jackson *et al*., 2005; Godinho *et al*., 2006) and sensory (e.g. Avenanti *et al*., 2005, 2006; Avenanti and Aglioti, 2006; Bufalari *et al*., 2007; Cheng *et al*., 2008; Yang *et al*., 2009) brain regions involved in pain perception. Inconsistencies in the activation of these areas of the pain matrix may result from methodological issues between studies, such as stimuli including observed bodily pain *vs* observed facial expression of pain, or differences between picture-based stimuli *vs* the person experiencing pain being present next to the participants (see Fitzgibbon *et al*., 2010; Lamm *et al*., 2011). Regardless, activation of overlapping areas is not as widespread or increased as if experiencing pain. This is thought to reflect inhibitory processes involved in the mirror system that prevents one from experiencing or carrying out the observed sensation/emotion or action (e.g. Kraskow *et al*., 2009). Thus, when we observe pain in another person, we appear to understand their experience through some of the same neural circuitry as if we were in actual pain ourselves, yet we do not typically experience pain.

Electroencephalography (EEG) has been used to investigate empathy for pain in normal populations. One such study found that observing pain in another elicits early event-related potential (ERP) positive shifts around 140 ms over the frontal lobe (thought to reflect emotional sharing, bottom-up processing), and late ERP response positive shifts 380 ms after stimulus presentation over parietal regions (thought to reflect cognitive evaluation, top-down processing) (Fan and Han, 2008). Of these components, Li and Han (2010) have demonstrated that taking the perspective of oneself *vs* another influences the late controlled component but not the early automatic component of empathy for pain. Findings by Decety and colleagues (2010) suggest that physicians do not demonstrate an early or late component, which the authors suggest may reflect regulation of emotion required in order to carry out their job. Other studies investigating empathy for pain using EEG have investigated band power, which involves an examination of continuous neural activation. Band power analysis has found that painful stimuli compared to non-painful stimuli elicit theta event-related synchronization (ERS) at 200–500 ms, and alpha event-related desynchronization (ERD) at 200–400 ms after stimulus presentation (Mu *et al*., 2008). Mu rhythm suppression (i.e. alpha ERD over sensorimotor cortices) has also been observed to be significantly stronger when observing painful compared to non-painful images (Cheng *et al*., 2008), and Betti and colleagues (2009) found that γ-band coherence values were significantly higher in response to painful compared to non-painful images, and that these values correlated with pain ratings. Taken collectively, these findings suggest that specific electrophysiological components are associated with processing pain in another person.

To the authors' knowledge, only one imaging study has been conducted to investigate synaesthetic pain. In this fMRI study, Osborn and Derbyshire (2010) compared undergraduates who report experiencing pain in response to images depicting pain (pain responders) to those who do not (non-pain responders). The authors measured neural activation while participants observed images with pain content, and contrasted the elicited brain activity to that generated from images with an emotional content but no pain-related content. The authors found that the pain-responder group demonstrated greater and more widespread activation in pain-related neural circuits when observing painful images compared to emotional images than the non-responders.

The current study aimed to provide the first EEG investigation into the neural mechanisms underlying synaesthetic pain in amputees. ERPs and band power responses were examined as participants observed still images of hands and feet in potentially painful and non-painful situations. As discussed, previous research has already indicated that such procedures are effective in detecting empathy for pain differences in ERPs (Fan and Han, 2008; Decety *et al*., 2010; Li and Han, 2010) and band power (Cheng *et al*., 2008; Mu *et al*., 2008; Betti *et al*., 2009) in normal populations. In accordance with the only fMRI study of synaesthetic pain (Osborn and Derbyshire, 2010), and with studies of mirror-touch synaesthesia that demonstrate atypical activation compared to controls (e.g. Blakemore *et al*., 2005), we hypothesized that amputees who report synaesthetic pain when seeing or imagining others in pain would demonstrate different neural activation compared to controls. In particular,

that there would be increased neural activation when observing potentially painful images that may reflect a failure to inhibit mirror system activation. This idea of altered function in otherwise normal connections is consistent with current theories on other types of synaesthesia (e.g. Grossenbacher and Lovelace, 2001). Finally, we also investigated whether pain synaesthetes had higher scores on questionnaires investigating such personal dispositions as empathy or pain catastrophization, both known to affect pain perception (e.g. Sullivan *et al.*, 2006).

METHODS

Subjects

Twenty-eight participants were involved in the study. There were three groups: (i) lower limb amputees who experience phantom and synaesthetic pain (pain synaesthetes: PS, $n = 8$); (ii) lower limb amputees who experienced phantom pain, but not pain synaesthesia (phantom pain: PP, $n = 10$); and (iii) healthy controls (HCs, $n = 10$) who have no amputations or significant pain history. HCs were excluded if they had a diagnosis of mental illness or neurological condition as verified by self-report, however, due to the difficulty in recruiting amputee groups, amputee participants were only excluded if they had a neurological condition. A one-way analysis of variance (ANOVA) revealed no significant difference between the ages of each group. Chi-square tests for independence revealed no significant difference between sex for each group or cause of amputation between the pain synaesthete and phantom pain group (Table 1). All subjects were right handed, had normal or corrected-to-normal vision, and were not colour blind. Informed consent was obtained by all participants prior to commencement of the study. The study was approved by Monash University Ethics Committee and the Alfred Hospital Ethics Committee.

Stimuli

Visual stimuli consisted of 160 still images, each presented twice ($n = 320$), depicting right hands and right feet (80 each: 40 painful, 40 non-painful) in everyday painful and non-painful situations from first person perspective (see Figure 1 for examples). This image set was developed by J. Decety and P. Jackson and was successfully used in an fMRI study by Jackson and colleagues (2005). Our group created 32 stylistically similar additional images to allow an increased number of trials with little repetition. All images were edited to the same size (600×450 pixels).

Procedure

The experiment was divided into two phases. In the first phase, participants underwent EEG with stimuli being presented using Stim^2 software (Neuroscan; Compumedics, Charlotte, NC, USA). Each participant observed the stimuli in four blocks, differing by attentional task demands, presented pseudo-randomly (Figure 2a). Blocks differed by task demand as attention is known to modulate pain processing (Tracey and Mantyh, 2007). In two blocks, participants were asked to verbally state if a hand or a foot was in the image (called the 'extremities' task where participants attended away from pain content), and in the other two blocks participants were asked to rate verbally the intensity of the pain they thought each image would cause if it was real (called the 'pain intensity' task where participants directly attended to pain content). Participants made this assessment on a likert scale ranging from 'no pain' (1) to 'worst possible pain' (5). Each block began with the presentation of an instruction slide for 11 s, which detailed the task for the block. There were 80 trials in each block, each presented for 3 s, followed by a blank screen for 1.5 s (Figure 2b).

In the second phase, participants were asked to complete five questionnaires assessing empathy, anxiety, depression and pain catastrophization. Empathy was assessed using the Empathy Quotient (EQ) (Baron-Cohen and Wheelwright, 2004) and the Interpersonal Reactivity Index (IRI) (Davis, 1980). Anxiety was assessed by the State and Trait Anxiety Inventory (STAI) (Spielberger *et al.*, 1970), depression by the Beck Depression Inventory (BDI-II) (Beck *et al.*, 1961), and pain catatstrophization by the Pain Catastrophizing Scale (PCS) (Sullivan *et al.*, 1995).

Data aquisition and analysis

EEG recordings were acquired using a Synamps^2 EEG system (Compumedics Neuroscan, TX USA) with 62 single Ag/AgCl surface electrodes, placed according to the international 10–20 system (Jasper, 1958), plus two mastoid electrodes. EEG was recorded in DC at a sampling rate of 1000 Hz. Impedance was kept below 5 kΩ. Each participant experienced 80 sweeps in each task (pain intensity *vs* extremities) × image-type (painful *vs* non-painful images) combination

Table 1. Participant demographics

	PS ($n = 8$)	PP ($n = 10$)	HC ($n = 10$)	*P*-value
Age (*M*: s.d.)	54.63 (7.43)	49.3 (12.07)	48.8 (9.08)	$F(2, 25) = 0.92$, $P = 0.41$
Sex (male: female)	5:3	9:1	6:4	x^2 (2, $n = 28$) = 0.31, $P = 0.27$, phi = 0.31
Cause of amputation				
Trauma/accident	4	7	n/a	x^2 (1, $n = 18$) = 0.20, $P = 0.39$, phi = 0.20
Disease/surgical removal	4	3		

Fig. 1 This figure presents two sets of examples of stimuli used. The left side shows non-painful images, the right side shows the matched potentially painful images.

(i.e. number of images in each group of stimuli) while EEG was recorded. EEG recordings were processed offline. Data were re-referenced to the global reference. Data were low pass (zero phase shift) filtered at 30 Hz 12 dB/oct, and artefact rejection was applied to data ± 50 μV. This was undertaken to ensure the exclusion of trials contaminated by excessive ocularmotor activity. Data were then epoched from −200 to 1200 ms (i.e. 200 ms prior to stimulus presentation, and 1200 ms after stimulus presentation), baseline corrected from −200 to −1 ms before stimulus presentation and then averaged across all accepted trials for each task × image-type combination.

ERPs were analysed at anterior electrode sites F3, F4, C3 and C4, and posterior electrode sites P7, P8, PO7 and PO8. As all electrodes showed similar trends, these sites were selected as representatives based on the prior research, where regions of interest were selected (see Fan and Han, 2008). Mean amplitude and latency of ERP response were extracted at N110, P180, N240, N340 and P3 in frontal central electrodes, and the P1, N170, P320 and N3 over posterior-parietal electrodes, consistent with the study by Fan and Han (2008), and the proposal that the presentation of a sensory stimulus elicits early negative components (between 100 and 300 ms after stimulus presentation), perhaps reflecting selective attention and feature analysis, and the P3 (after 300 ms) thought to be involved in stimulus evaluation (Fabiani *et al.*, 2000).

To assess band power (theta, alpha, beta, delta), we quantified power for active period (1200 ms post-stimulus) of each task and condition at electrodes C3, CZ and C4. Although no source analysis was carried out, these electrodes were selected as they are thought to be located over the area of the sensorimotor cortex, an area likely involved in empathy for pain and associated mirror system activity for observed pain (for a discussion, see Yang *et al.*, 2009).

EEG data were analysed using non-parametric statistics as the data violated the normality assumption for ANOVA. Instead, to assess whether between-group differences (categorical independent variable with three groups) were present for ERP components or band power (continuous dependent variable), we used tests of Kruskal–Wallis. For all significant effects ($P < 0.05$) or those indicating a trend ($P < 0.06$) of group, follow-up tests of Mann–Whitney U-test were performed between pairs of groups. To avoid type 1 error, a simple Bonferroni adjustment was applied ($P < 0.017$) by dividing the alpha level of 0.05 by the number of tests we used [three paired comparisons: (i) pain synaesthete *vs* HC groups; (ii) pain synaesthete *vs* phantom pain group; and (iii) HC *vs* phantom pain group]. Effect size was determined by dividing the *z*-value by the square root of *N*.

Personal dispositional data were screened to determine that no assumptions of ANOVA or *t*-tests were violated. One-way between-groups ANOVAs were then conducted to determine if there were differences between the groups in scores on the five questionnaires. A paired samples *t*-test was used to evaluate the impact of stimuli (pain *vs* no pain) on pain intensity ratings across the groups. The η^2 statistic

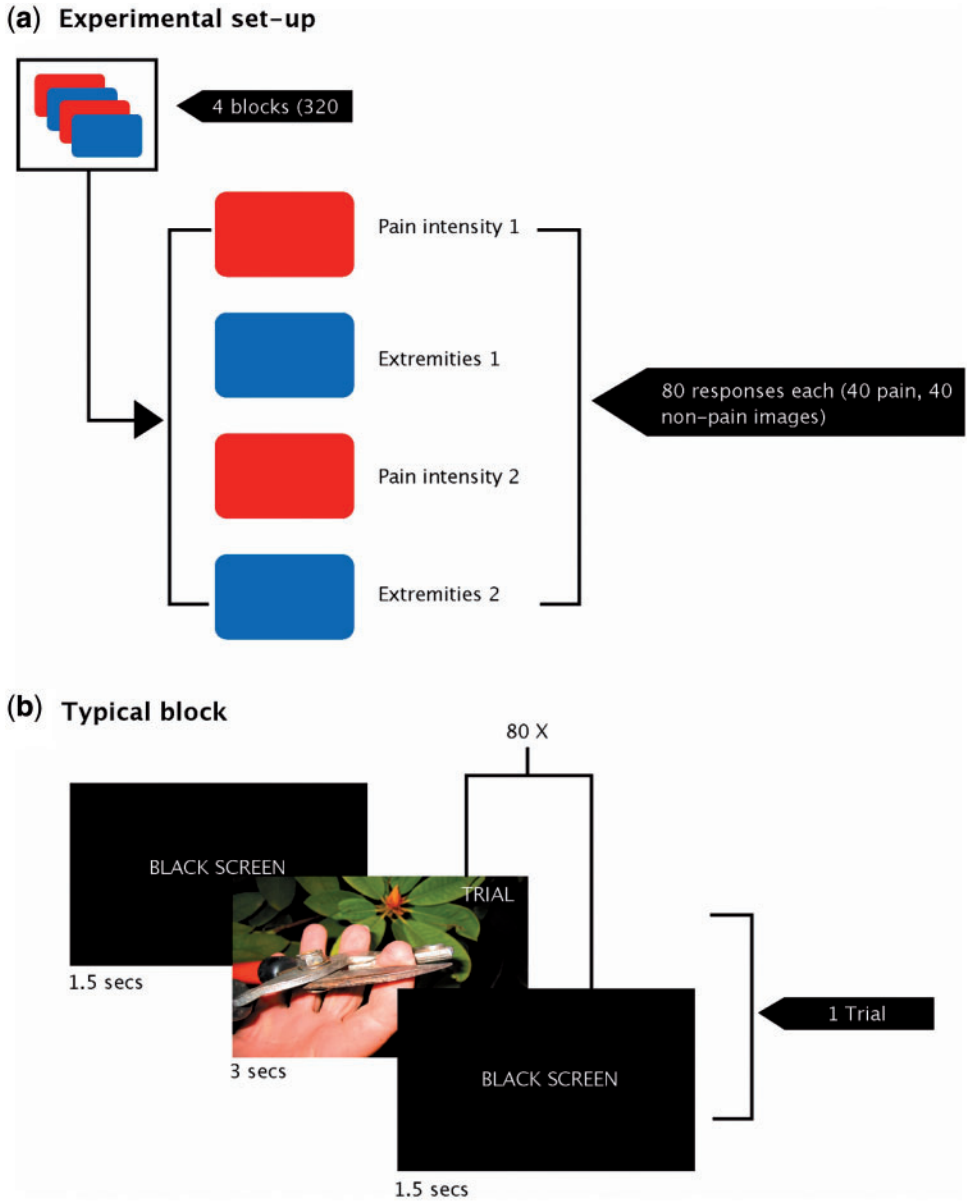

Fig. 2 Schematic diagram of (**a**) the experimental setup, and (**b**) the presentation of a typical trial.

was used to determine effect size. A repeated measures ANOVA was carried out to investigate if stimulus type impacted differently on pain intensity ratings across the three groups.

RESULTS

ERPs

For amplitude of ERP response, an effect of group was observed at electrode F3 at component P180 during the extremities condition with non-painful images, x^2 (2, $n = 28$) $= 7.12$, $P = 0.028$. Further analysis revealed a significant difference between the pain synaesthete [median (Md) $= 1.10$, $n = 8$] and HC (Md $= 2.98$, $n = 10$) groups, $U = 11.00$, $z = -2.58$, $P = 0.01$, $r = -0.61$ (Figure 3; non-significant results are not reported throughout this section for brevity). A difference between groups in amplitude response was observed at electrode PO7 at component N170 during the pain intensity condition with non-painful images, x^2 (2, $n = 28$) $= 6.19$, $P < 0.05$. Subsequent analysis revealed a significant difference between the pain synaesthetes (Md $= -0.54$, $n = 8$) and HC (Md $= -3.03$, $n = 10$) groups, $U = 12.00$, $z = -2.49$, $P = 0.013$, $r = -0.59$ (Figure 3). An effect of group was also seen for amplitude response at electrode P7 at component N3 during the extremities condition with non-painful images, x^2 (2, $n = 28$) $= 6.89$, $P = 0.03$. Further analysis revealed a significant difference between the pain synaesthete (Md $= -0.56$, $n = 8$) and phantom pain (Md $= -1.15$, $n = 10$) groups, $U = 13.00$, $z = -2.40$,

$P = 0.02$, $r = -0.57$ (Figure 3). Finally, there was a trend towards significance for group at the posterior electrode of P7 at component N3 during the pain intensity condition with painful images, x^2 (2, $n = 28$) = 5.93, $P = 0.05$. Further analysis revealed a significant difference between the pain synaesthete (Md = −0.46, $n = 8$) and the HC (Md = −1.27, $n = 10$) groups, $U = 13.00$, $z = -2.40$, $P = 0.02$, $r = -0.57$ (Figure 3). For means and standard deviations (s.d.) of significant results, see Table 2.

Band power

In the theta band wave, a group effect was observed in electrode C3 during the active period of the pain intensity condition with non-painful images, x^2 (2, $n = 28$) = 6.38, $P = 0.04$. Further analysis revealed a significant difference between the pain synaesthete (Md = 0.52, $n = 8$) and HC (Md = 1.09, $n = 10$) groups, $U = 12.00$, $z = -2.49$, $P = 0.013$, $r = -0.59$. Also in the theta band wave, there was trend towards significance during the active period of the extremities condition with painful images across three different groups, x^2 (2, $n = 28$) = 5.93, $P = 0.05$. Subsequent analysis revealed a trend towards significance between the pain synaesthete (Md: 0.51, $n = 8$) and HC (Md: 1.00, $n = 10$) groups, $U = 14.00$, $z = -2.31$, $P = 0.021$, $r = -0.55$.

In the alpha band wave, an effect of group was observed in electrode C3 during the active period of the pain intensity condition with non-painful images, x^2 (2, $n = 28$) = 6.73, $P = 0.04$. Further analysis revealed a significant difference between the pain synaesthete (Md: 0.31, $n = 8$) and the HC (Md: 1.07, $n = 10$) groups, $U = 12.00$, $z = -2.49$, $P = 0.013$, $r = -0.59$. Also in the alpha band wave, an effect of group was observed in electrode C3 during the active period of the pain intensity condition with painful images, x^2 (2, $n = 28$) = 6.31, $P = 0.04$. Subsequent analysis revealed a significant difference between the pain synaesthete (Md: 0.32, $n = 8$) and the HC (Md: 1.03, $n = 10$) groups,

Table 2. Means and s.d. of amplitude values of significant ERP results in each group

Electrode	Component	Task	Pain	PS mean (s.d.)	PP mean (s.d.)	HC mean (s.d.)
F3	P180	Ext	NP	1.00 (0.71)	2.38 (1.68)	2.96 (1.76)
PO7	N170	PI	NP	−0.74 (0.90)	−2.66 (2.86)	−4.66 (3.88)
P7	N3	Ext	NP	−0.57 (.36)	−1.31 (0.88)	−1.07 (.46)
P7	N3	PI	P	−0.13 (1.13)	−0.99 (1.60)	−1.20 (1.11)

Ext, extremities condition; PI, pain intensity condition; NP, non-painful stimuli; P, painful stimuli.

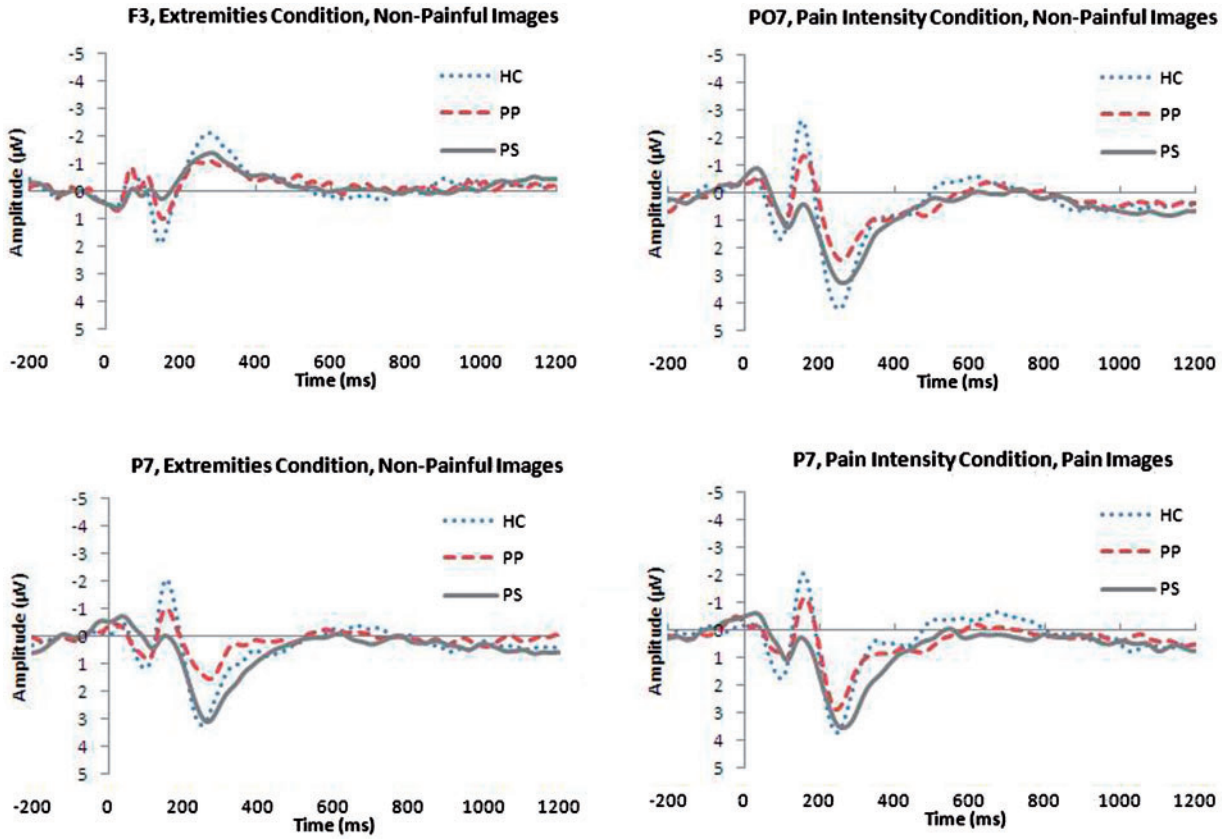

Fig. 3 ERPs where significant differences were found between groups are illustrated.

$U = 13.00$, $z = -2.40$, $P = 0.016$, $r = -0.57$. For means and s.d.'s of significant results, see Table 3.

Personal dispositional data

A statistically significant effect of group was found on scores on the STAI: state: $F(2,25) = 5.44$, $P = 0.01$, trait: $F(2,24) = 6.60$, $P = 0.01$. *Post hoc* comparison indicated that the HC group had significantly lower state and trait scores than the phantom pain group ($P = 0.01$ and $P < 0.01$, respectively; Table 4) indicating lower levels of anxiety in HCs. A significant effect of group was also found on scores of the BDI-II: $F(2,25) = 4.92$, $P = 0.02$. *Post hoc* comparison indicated that HCs scored significantly lower than the phantom pain group ($P < 0.05$; see Table 4), and the pain synaesthete group ($P = 0.03$; Table 4), indicating lower levels of depression in HCs. No other significant differences were found between groups on any of the remaining three questionnaires ($P > 0.05$; Table 4).

Pain intensity ratings

Across the three groups, there was a significant decrease in ratings of pain intensity for non-painful images (*M*: 1.25, s.d.: 0.51) compared to painful images (*M*: 3.6, s.d.: 0.81), $t(27) = 14.61$, $P < 0.001$ (two-tailed). The mean decrease in ratings of pain intensity was 2.36 with a 95% confidence interval ranging from 2.03 to 2.70. The η^2 statistic (0.89) indicated a large effect size. No main effect was found for group, $F(2,25) = 0.96$, $P = 0.40$, suggesting that there was no difference between groups in pain intensity scores (see Table 5 for group means and s.d.'s).

Table 3. Means and s.d. of band power values of significant results in each group

Electrode	Band	Task	Pain	PS mean (s.d.)	PP mean (s.d.)	HC mean (s.d.)
C3	Theta	PI	NP	0.75 (0.95)	1.67 (2.16)	1.20 (0.65)
C3	Theta	E	P	0.64 (0.61)	1.65 (2.08)	1.13 (0.62)
C3	Alpha	PI	NP	0.82 (1.46)	2.12 (3.73)	1.35 (0.89)
C3	Alpha	PI	P	0.68 (1.11)	2.01 (3.48)	1.34 (0.90)

Ext, extremities condition; PI, pain intensity condition; NP, non-painful stimuli; P, painful stimuli.

Table 4. Mean and s.d. of questionnaire scores for each group

	HC ($n = 10$)	PP ($n = 10$)	PS ($n = 8$)
Beck depression inventory II	2.40 (2.63)	11.90 (10.77)	13.25 (9.10)
State trait anxiety inventory			
State	27.60 (5.02)	45.50 (17.51)	33.50 (10.82)
Trait	30.70 (5.58)	45.70 (11.26)	40.57 (10.64)
Pain catastrophizing scale	11.70 (7.89)	15.00 (9.37)	15.29 (9.27)
Empathy quotient	43.7 (9.70)	37.00 (11.18)	35.75 (8.0)
Interpersonal reactivity index			
Overall score	61.50 (7.74)	58.00 (9.44)	59.63 (10.42)
Perspective taking scale	18.40 (2.55)	16.33 (3.97)	18.00 (3.70)
Fantasy scale	13.20 (3.46)	11.44 (5.88)	12.13 (5.36)
Empathic concern scale	19.10 (3.41)	19.00 (5.00)	21.00 (3.70)
Personal distress scale	10.8 (3.71)	10.11 (5.37)	8.50 (2.0)

DISCUSSION

We investigated whether amputees who experience synaesthetic pain differed to control groups in electrophysiological response to observed pain in another. Differences were observed in the amplitude of some ERP components, and in theta and alpha band power at specific sites between groups. It was also found that while the pain synaesthete group scored higher than the HC group on the BDI-II, the pain synaesthete group did not have significantly different scores on measures of empathy or pain catastrophization compared to the control groups. This study, therefore, provides some evidence for atypical EEG response in pain synaesthetes in response to the implication of potential pain. Further, the experience of pain synaesthesia does not appear to be mediated by interpersonal differences.

Differences in ERP amplitude

Amplitude of ERP response at an early component at a frontal site (F3 P180) and at an early and late component at parietal sites (N170 PO7 and N3 P7, respectively) was significantly decreased in the pain synaesthete group compared to HCs. In addition, the amplitude of ERP response at a late component at a parietal site (N3 P7) was significantly reduced in the pain synaesthete group compared to the phantom pain group. These results indicate a decrease during either task or condition in the ERP amplitude in the pain synaesthete group though only at some electrodes and only at some components. It is important to note, however, that although the current electrode sites and components are justified based on previous research in the area (see Fan and Han, 2008), this is not to say that alternate sites and/or components will not be identified in future studies.

Based on past research demonstrating large amplitudes in response to pleasant and/or unpleasant (i.e. painful) images, we expected pain synaesthetes to have had significantly larger amplitudes than the control groups. The reduced ERP amplitude in the pain synaesthete group compared to controls may reflect inhibition of response as a possible protective strategy. That is, pain synaesthetes attempt to guard themselves from experiencing unpleasant synaesthetic pain

Table 5. Mean and s.d. of pain intensity ratings for non-pain and pain images for each group

Group	Non-pain images	Pain Images
HC ($n = 10$)	1.05 (0.05)	3.7 (0.83)
PP ($n = 10$)	1.53 (0.70)	3.7 (0.57)
PS ($n = 8$)	1.14 (0.42)	3.4 (1.07)

by applying fewer cognitive resources during the task. This is perhaps similar to the emotional regulation suggested to be responsible for the atypical neural activation observed in physicians (see Decety *et al*., 2010). As these effects are seen in both conditions and tasks, we further suggest that pain synaesthetes are susceptible to the implication of possible pain in images (i.e. although in non-pain images there was no direct contact between an object and a limb, there was still the contextual suggestion that the object could induce pain). Finally, as these amplitude effects were observed in both early and late EEG components, our findings of atypical pain processing in another may affect both the emotional sharing and evaluation stages of processing.

Differences in band power

Our significant findings for band power were only observed in theta or alpha (not in delta or beta) in response to pain intensity evaluations, at a central electrode in the left hemisphere and between the pain synaesthete and HC groups. As reductions in the theta and alpha band power of the pain synaesthete group are only observed in the pain intensity condition, where participants are required to pay attention to the pain by rating its intensity, we suggest that differences in the band power of pain synaesthetes result from top-down processing of pain in another.

In terms of interpreting the functional meaning of reduced theta and alpha, we speculate the following: typically, an increase in theta is observed in response to an increase in cognitive tasks involving attention (e.g. Basar-Eroglu and Demiralp, 2001), memory (for a review, see Klimesch, 1999) or emotion (e.g. Krause *et al*., 2000; Aftanas *et al*., 2001) related to cortico-hippocampal–limbic interaction (for a review, see Basar *et al*., 2001). Consequently, we suggest that the decrease in theta band power observed in pain synaesthetes may be indicative of reduced cognitive and emotional functioning, again, perhaps as an attempt to avoid the inducement of synaesthetic pain.

Compared to theta, an increase in alpha band power is associated with an increase in inhibition and therefore reduced information processing, whereas a decrease in alpha oscillations is associated with task performance and therefore active cognitive processing (Klimesch *et al*., 2007a). The reduced alpha band power observed in pain synaesthetes may reflect a disinhibition of response. Such reduced inhibitory (top–down processing) control may reflect cognitive engagement of avoidance/inhibition strategies relating to observed real or potential pain. Further, as Mu rhythm activity is a type of alpha seen over the sensorimotor cortex that is typically influenced by observed movement or actions, our findings of reduced inhibitory control at an electrode placed over the sensorimotor cortex provides support for a motor component to be involved in pain synaesthesia in addition to a sensory (Giummarra *et al*., 2010). In addition, the reduction in amplitude of alpha band power over the sensorimotor cortex suggests the potential involvement of mirror systems, as it is suggested that Mu rhythms may be involved in understanding the actions of others (Pineda, 2005). However, cortical reorganization, a process potentially integral to the production of synaesthetic pain, is known to occur within the sensorimotor cortex following amputation (e.g. Merzenich *et al*., 1983; Flor *et al*., 1995). Therefore although unjustified in the current study, this does not mean that targeting other sites may not be valuable in future research.

Differences in personal dispositional measures

The phantom pain group scored higher than the HC group on both the state and trait scales of the STAI. The pain synaesthete and the phantom pain group had higher scores on the BDI-II than the HC group. This is not surprising as co-morbidity of depression and anxiety within pain populations is common (Nicolson *et al*., 2009). Indeed, this dissociation is difficult to untangle due to the complex relationship between pain, anxiety and depression; i.e. pain may worsen anxiety, and depression and anxiety may worsen pain. The inclusion of a control group of participants with depression and/or anxiety may be valuable in future research.

There were no group differences in the questionnaires assessing empathy or pain catastrophization. As yet, it is unknown what factors may be involved in bringing about synaesthetic pain in an individual who, until the occurrence of pain-related trauma (i.e. amputation), had not previously experienced the phenomenon. Nor is it known what may make some people susceptible to experience synaesthetic pain from birth. It may, for example, involve physical or psychological aspects, or both, or be related to a personal trait such as empathy (M.J. Giummarra *et al*., unpublished data). People who experience synaesthetic touch, for example, report higher scores of empathy than people who do not (Banissy and Ward, 2007). It would therefore have been reasonable to expect that the pain synaesthete group would have scored higher on these empathy measures than the control groups. However, the small sample sizes of the current study may have prevented any detectable differences, should they exist.

The measures used in the current study may not be reliable for identifying interpersonal empathic differences. In fact, in studies of normal populations, while some have shown a relationship between empathy scores and cerebral response in HCs (Singer *et al*., 2004; Cheng *et al*., 2008; Loggia *et al*., 2008; Avenanti *et al*., 2009), other have not (Avenanti *et al*., 2005; Jackson *et al*., 2005; Lamm *et al*., 2007). This inconsistency, in addition to recent claims that impossibly high correlations are being reporting in fMRI studies and, for example, empathy (Vul *et al*., 2009) suggests that empathy questionnaires may not be reliable measures of empathy responses in the general population, and therefore, may be unable to detect any potential differences in empathy in pain synaesthetes.

Differences in pain intensity ratings

Participants rated painful images higher than non-painful images. However, no difference was observed between the groups. Indeed, this may seem unlikely as one may expect the pain synaesthete to rate the painful images higher than those who do not experience pain upon viewing it in others. However, participants were asked only to rate the intensity of the pain they thought each image would cause if it was real. As such, we have only ascertained that each group can adequately tell the difference between painful and non-painful images. Should we have asked about level of pain experienced by the participants in response to the images, then it would be more likely to expect differences between groups.

General discussion

Our findings support the only other study to investigate synaesthestic pain (see Osborn and Derbyshire, 2010), both of which report atypical neural processing in people who experience synaesthetic pain when observing injury in another. However, while the study by Osborn and Derbyshire reported an increase in activation compared to controls, our study has found that pain synaethetes generate a consistent decrease in neural activity in response to painful images, particularly compared to HCs. However, these results are not necessarily opposing as increased haemodynamic activity may reflect active inhibitory processes (for a discussion, see Arthurs and Boniface, 2002).

Our ERP *vs* band power results may appear inconsistent and contradictory. However, these two measures of EEG assess different aspects of neural activity and have long been considered independent. ERPs, for example, are specifically time-locked to an event (stimulus) and thought to reflect the brain's response to such an event (Pfurtscheller and Lopes da Silva, 1999a; Fabiani *et al.*, 2000). In contrast, band power refers to the ongoing EEG wave in different frequency bands thought to reflect activity of large populations of neurons. Therefore, while ERPs rely on the synchronous activity of only a small area of the brain, band power requires the synchronous activity of larger areas of the cortex (Pfurtscheller and Lopes da Silva, 1999b). Nonetheless, band power may in fact influence the generation of ERPs (Sauseng *et al.*, 2007; Klimesch *et al.*, 2007b).

During mental effort, theta power increases and alpha power decreases (Klimesch, 1999). This typical pattern, while there have been exceptions (e.g. Schack and Klimesch, 2002), has led to claims that an increase in theta and a decrease in alpha provides a common EEG profile for increases in cognitive load (Meltzer *et al.*, 2007). The results here, however, demonstrate a significant decrease in theta and alpha band power in the pain synaesthete group compared to HCs in one electrode. We postulate that these unlikely simultaneous reductions in theta and alpha reflect a decrease in cognitive processing and a failure to prevent inhibitory mechanisms, and therefore active processing, respectively. While it is surprising to find a decrease in theta when alpha is also decreased, it could be due to variability of inter-individual EEG characteristics. That is, when comparing individuals, there may be theta/alpha band overlap, and therefore defining band widths may not be appropriate (Klimesch, 1999). Future research may seek to individualize band widths.

Band power amplitude did not significantly differ between the pain synaesthete and phantom pain group. In the case of ERP amplitude, only one of the four significant findings was between the pain synaesthete and phantom group. In fact, in all but one comparison where significant findings were observed, the pain synaesthete group had significantly decreased ERP and band power amplitude compared to the HC group. However, the phantom pain group demonstrated a pattern of similarly reduced activity to HCs. Although non-significant, this may suggest that following pain-related trauma (in this case, amputation) how another's pain is processed may be modified. Future research should examine this possibility.

Significant ERP amplitude differences were seen in both tasks, even though the pain intensity task required more attention than the extremities task. Indeed, previous studies in empathy for pain have shown an effect of task demand. For example, using fMRI, Gu and Han (2007) found increased activation in pain-related brain areas when participants rated pain intensity *vs* counting limbs. Further, in an EEG study by Fan and colleagues (2008), while the early empathic response was found to be independent of task demands, the late component was modulated by task demands. Our study did not directly investigate the effect of top–down control, but rather possible differences between groups when task demands were manipulated. We can thereby only conclude that group differences exist regardless of task demands, suggesting that the experience of pain synaesthesia may be automatic and not necessarily under the influence of top-down processes.

Group effects were also observed in response to both images with and without pain content, even though our pain intensity rating data indicate that participants rated levels of pain intensity higher for images with pain content *vs* those without. We expected group differences only in response to images depicting pain, as it is this feature that is thought to trigger synaesthetic pain. However, these findings are consistent with a recent meta-analysis that suggests fMRI activation within the empathy for pain core network, somatosensory areas specifically, is also present in response to non-painful stimuli. This may indicate that some activation in response to both pain and non-pain images may not be active in response to pain but rather to body parts being touched (Lamm *et al.*, 2011). Alternatively, we suggest that pain synaesthetes may be susceptible to the suggestion of possible pain as is seen in the no-pain image set, where a limb and a potential for pain was presented side-by-side. This suggestion is supported by anecdotal accounts from pain synaesthete participants, who, for example, indicated the sight

of tools such as a knife could trigger pain in the phantom. Moreover, synaesthetic pain in amputees may not be a consistent phenomenon. That is, seeing another person in pain may not always cause synaesthetic pain, and indeed in the case of the stimuli used here, still images depicting potentially painful situations did not induce synaesthetic pain consistently, or necessarily at all, in the pain synaesthete group. This is in accord with the study by Osborn and Derbyshire (2010) where actual pain was not induced in the observer in response to all images. Future research will wish to record subjective experience from participants in response to stimuli.

Limitations

As the current study was the first EEG study of synaesthesia for pain, the phenomenon was difficult to identify, leading to low recruitment levels of pain synaesthetes. As such, it is possible that the study did not have enough power to detect possible differences between groups. Low sample size also meant factors that could possibly affect EEG response, such as gender in empathy processing (Han *et al.*, 2008; Yang *et al.*, 2009), medication (e.g. Fink, 1969; Blume, 2006) or co-morbidity with other disorders such as depression and anxiety (e.g. Davidson *et al.*, 1987), were unable to be controlled for. While gender effects will require further investigation in synaesthetic pain, we suggest that it is unlikely that medication or co-morbidity with other disorders had a contaminating effect. We argue that if any artefact was present, then the same results would be found in both amputee groups where participants used medication (Table 6) and had higher scores on measures of anxiety and depression compared to HCs.

Table 6. Table listing medication taken by each participant in both amputee groups

Group	Medication
Pain synaesethete ($n = 8$)	
1	Analgesics; blood pressure/heart medication
2	Anticonvulsant
3	Other
4	None
5	Analgesics; blood pressure/heart medication; antidepressants; diabetes medication
6	Analgesics; blood pressure/heart medication; antidepressants; diabetes medication
7	Blood pressure/heart medication; corticosteriod
8	Blood pressure/heart medication; diabetes medication
Phantom pain ($n = 10$)	
1	Analgesics; antidepressants; blood pressure/heart medication
2	Diabetes medication
3	Analgesics
4	None
5	Analgesics; antidepressants; blood pressure/heart medication; sleeping medication
6	Blood pressure/heart medication
7	Analgesics
8	Antidepressants
9	Analgesics; blood pressure/heart medication; antidepressant; anticonvulsant
10	None

CONCLUSIONS

The present findings suggest that amputees who experience synaesthesia for pain process pain observed in another person differently. Specifically, participants with synaesthesia for pain showed significantly decreased ERP amplitude in some anterior and posterior electrodes in both hemispheres, and alpha and theta band reduction in a central electrode located over the left hemisphere. These results may reflect both inhibition of processing observed pain (e.g. avoidance/guarding as a protective strategy) as well as a disinhibition in inhibitory control processes that may result in the experience of synaesthesia for pain. Future research will need to directly test the hypothesis of neural disinhibition as the mediating factor involved in producing synaesthetic pain, perhaps through the use of novel techniques such as transcranial magnetic stimulation.

Conflict of Interest

None declared.

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