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The good, the bad, and the suffering. Transient emotional episodes modulate the neural circuits of pain and empathy

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ABSTRACT

People's sensitivity to first-hand pain is affected by their ongoing emotions, with positive states (joy, amusement) exerting analgesic-like effects, and negative states (sadness, fear) often enhancing the subjective experience. It is however less clear how empathetic responses to others' pain are affected by one's own emotional state. Following embodied accounts that posit a shared representational code between self and others' states, it is plausible that pain empathy might be influenced by emotions in the same way as first-hand pain. Alternatively, other theories in psychology suggest that social resources (including empathetic reactions) might be enhanced by positive states, but inhibited by negative states, as only in the former case, one's mindset is sufficiently broad to take into consideration others' needs. To disambiguate between these opposing predictions, we conducted two experiments in which volunteers observed positive, neutral, or negative video clips, and subsequently either received painful thermal stimuli on their own body (first-hand pain), or observed images of wounded hands (others' pain). We measured subjective pain ratings as well as physiological responses and brain activity using fMRI. We found that, contrary to the case of first-hand pain, others' pain produced weaker galvanic responses and lower neural activity in anterior insula and middle cingulate cortex following negative (relative to neutral and positive) videos. Such inhibition was partially counteracted by personal empathy traits, as individuals with higher scores retained greater sensitivity to others' pain after negative emotion induction, in both behavioral and neural responses in medial prefrontal cortex. Furthermore, multivoxel pattern analysis confirmed similar neural representation for first-hand and others' pain in anterior insula, with representation similarity increasing the more the video preceding the observation of others' suffering was positive. These findings speak against the idea that emotion induction affects first-hand and others' pain in an isomorphic way, but rather supports the idea that contrary to negative emotions, positive emotions favors a broader access to social resources.

1. Introduction

In the last decade, psychology and neuroscience research made considerable efforts to elucidate brain processes underlying our ability to empathize with others, as well as the factors that might influence such ability. One aspect of great relevance for empathetic responding is the observer's emotional state, as being happy or scared might change one's sensitivity for others' fate. Unfortunately, despite wealthy research in this field, the role of emotion in empathy is still unclear.

Indeed, several theoretical and empirical studies suggest that individual social proficiencies (including empathic responses) are enhanced by positive emotions, but inhibited by negative states. On the one hand, depression and depressive states have been repeatedly associated with impaired empathic abilities (see (Thoma et al., 2013) as a review). On the other hand, laboratory-induced positive emotions have been shown to improve individuals' social proficiency, with consistent increases in social engagement (Isen, 1970), social inclusiveness (Dovidio et al., 1995), self-disclosure (Cunningham, 1988), interpersonal trust (Dunn and Schweitzer, 2003), dyadic motor coordination (Kuhbandner et al., 2010), facial mimicry (Likowski et al., 2011), as well as perspective-taking and compassion (Nelson, 2009). Furthermore, positive emotions eliminate racial biases in visual processing of other faces (Johnson and Fredrickson, 2005). On theoretical grounds, it is often posited that, contrary to negative emotions, positive states can

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broaden one's mindset, by boosting creativity, associative processing and one's thought–action repertoire (Fredrickson, 2004). Such broadened mindset may lead individuals to build new resources, of physical, intellectual, and also social nature (*broaden–and–build theory*, (Fredrickson, 2004).

In neuroscience, empathy has often been investigated through the model of pain processing. In particular, empathizing with others' pain is held to trigger brain responses that are isomorphic with those elicited by first-hand pain, suggesting that the recognition of others' states is embodied (or grounded) in the representation of the same states when they occur in oneself (Bernhardt and Singer, 2012; Lamm et al., 2011). This has been robustly documented by neuroimaging studies that unveiled shared activity patterns in response to first-hand and to others' pain in regions such the anterior insula (AI) and middle cingulate cortex (MCC) (Braboszcz et al., 2017; Corradi-Dell'Acqua et al., 2011, 2016), but see (Krishnan et al., 2016). Furthermore, both first-hand and others' pain can be similarly affected by administration of analgesia, for instance through acetaminophen, placebo, or hypnotic manipulations (Braboszcz et al., 2017; Mischkowski et al., 2016; Rütgen et al., 2015b, 2015a).

In light of this embodied account of pain empathy, it is reasonable to argue that the effect of emotions on our sensitivity to others' suffering should be isomorphic to their effect on first-hand pain. Several studies reported that first-hand pain experience is enhanced after exposure to negative emotional information (through videos, pictures, texts, music or odors), but reduced after exposure to positive/elative information (Berna et al., 2010; Boettger et al., 2011; de Wied and Verbaten, 2001; Loggia et al., 2008; Meagher et al., 2001; Roy et al., 2008; Tang et al., 2008; Villemure et al., 2003; Weisenberg et al., 1998; Whipple and Glynn, 1992; Zelman et al., 1991), accompanied with concomitant modulation of neural activity in insular and cingulate cortex (Berna et al., 2010; Roy et al., 2009; Villemure and Bushnell, 2009). In this perspective, negative emotional information should enhance also our empathic reactions to others' pain, whereas positive emotion should reduce them. However, previous studies report mixed results: unfairness-induced anger made individuals less sensitive to others' pain (Singer et al., 2006), whereas exposure to negative words enhanced individuals' sensitivity (Yamada and Decety, 2009), and exposure to negative facial expressions led to no effect (impacting only neural activity of the dorsolateral prefrontal cortex – (Enzi et al., 2016). However, these studies are extremely heterogeneous in their methods, both when compared to one another and also in relation to the paradigms of emotion induction for first-hand pain.

Here we set out to directly test the two opposing hypotheses emerging from previous literature concerning the role of emotion induction on pain empathy. According to the *broaden-and-build* theory (Fredrickson, 2004), empathy should be strengthened by positive emotion induction, as a result of a broadened mindset and enhanced resources for other-oriented processing. Conversely, embodied accounts are consistent with the idea that empathy for a given state should be influenced by emotion induction in an isomorphic way than first-hand experience of the same state. Therefore, pain empathy should be enhanced by negative states and reduced by positive states.

To this aim, the present study combined two well-established paradigms from our laboratory to ascertain the role played by emotion induction in the experience of first-hand and others' pain. We induced positive (amusement) and negative (fear) emotions, as well as neutral states, using brief video-clips, which have been shown to produce long-lasting effects on large-scale brain networks centered on insula-cingulate areas (Eryilmaz et al., 2011; Richiardi et al., 2011). Under such emotionally-induced state, participants underwent painful or painless thermal stimuli on their own body (first-hand pain task) and, in a separate session, observed pictures of hands in painful or painless situations (Braboszcz et al., 2017; Corradi-Dell'Acqua et al., 2011). This paradigm proved successful in showing how the representation of others' pain in AI and MCC is partly similar to that evoked by first-hand experience, despite the many differences between the two conditions in terms of stimulus modality and duration, task, etc. (Braboszcz et al., 2017; Corradi-Dell'Acqua et al., 2011). Here, the experiment was conducted a first time by recording only behavioral and physiological responses (Experiment 1), and a second time inside the MRI scanner to measure brain activity (Experiment 2). Following the literature reviewed above, we expected both first-hand and others' pain to produce distinctive effects on behavioral and physiological responses, as well as shared activity patterns in pain-sensitive regions such AI and MCC. Furthermore, we expected the responses associated with first-hand pain to be enhanced by negative states and diminished by positive states. The key question concerned responses evoked by others' pain, and whether they are affected by emotion induction in an isomorphic or dissociated way with respect to first-hand pain.

2. Materials and methods

2.1. Participants

41 neurotypical volunteers took part in the present study. 17 participated to Experiment 1 (11 females, mean age: 33, std: 9, range: 24–56), whereas 24 healthy volunteers participated to Experiment 2 (13 females, mean age: 27.6, std: 6, range: 18–42). Participants had no history of psychiatric or neurological disease. Written informed consent was obtained from all subjects. This study was approved by the local ethics committee and conducted according to the declaration of Helsinki.

2.2. Stimuli

2.2.1. Video-clips

Emotion-induction was achieved through the presentation of video-clips with negative (e.g., extract from "The Shining" movie), positive ("When Harry met Sally") or neutral (science documentary) content. These videos were taken from previous studies implementing an emotion-induction paradigm similar to ours, which elicited reliable changes in behavioral (Qiao-Tasserit et al., 2017) and neural response (Eryilmaz et al., 2011; Pichon et al., 2014; Richiardi et al., 2011) in the first two minutes following the video. A set of 18 video-clips was used (6 for each emotion context), each lasting approximately one minute. Full description and validation (e.g., emotional ratings) of these videos is provided by (Eryilmaz et al., 2011).

2.2.2. Image stimuli

Following (Corradi-Dell'Acqua et al., 2011), we presented our participants with 192 color images of hands depicted in either painful, aversive but painless, or neutral control situations. Among these, 159 images were taken from (Corradi-Dell'Acqua et al., 2011), whereas 33 were selected ad hoc for the present study. The images were organized as follows: 1) 48 pictures showed hands in *Painful* situations (e.g., a scalpel/syringe piercing the skin). 2) 48 pictures were matched *Painless* controls for the previous category, with which they shared the same hand laterality (right/left), orientation (angular distance from the viewer's own hand position at rest), and global visual features (presence of a scalpel or syringe), but were purged from any painful features. 3) 48 pictures showed hands in an *Arousing* (but not painful) context (e.g. a hand with a knife held in a threatening fashion). 4) Finally, 48 pictures were matched *Non-Arousing* controls for the previous category. All images were equated in luminance. Full description and validation of these images is provided by Corradi-Dell'Acqua et al. (2011).

2.2.3. Thermal stimuli

We used a computer-controlled thermal stimulator with a 25 × 50 mm fluid-cooled Peltier probe (MSA Thermal Stimulator–Somedic AB, Sweden) to deliver mildly painful or painless control temperatures. The probe was attached to the participants' right calf to minimize potential influences of the magnetic field on the MSA function. The painful temperature was individually calibrated for each participant based on a double random staircase (DRS) thresholding session (Corradi-Dell'Acqua et al., 2016; Gracely et al., 1988; Sharvit et al., 2015) and converged on average around 49.4 ± 1.6 °C (for Experiment 1) and 49.8 ± 2.5 °C (for the Experiment 2). The painless control temperature was fixed to 38 °C.

Our DRS procedure selected a given temperature on each successive trial according to the previous response of the participant to the question "*To which extent is this thermal stimulation painful?*" To enter their response, participants used a horizontal Likert scale, displayed as 9 points with colors ranging from pink on the left of the screen (with the word "None" written above) to red on the right (with the word "Maximal"). The slider was initially positioned at the middle (5 out of 9) when the response screen was displayed. Participants had to move the slider even if they eventually wanted to come back to the initial middle position to confirm their answer. Trials rated as more unpleasant than the given cut-off (8 out of 9) led to a subsequent lowered temperature in the next trial; whereas trials rated as less unpleasant than the given cut-off led to a subsequent higher temperature. This resulted in a sequence of temperatures that rapidly ascended towards, and subsequently converged around, a subjective pain intensity threshold, which was in turn calculated as the average value of the first 4 temperatures leading to a direction change in the sequence. In order to prevent participants to anticipate a systematic relationship between their rating and the subsequent temperature, two independent staircases were presented randomly. Initial thermal stimulations for the two staircases were 40 °C and 42 °C. Within each staircase, stimulus temperatures increased or decreased with steps of 2 °C, while smaller changes (1 °C) occurred following direction flips in the sequence. None of our subjects was stimulated at temperature larger than 52 °C.

2.3. Experimental set-up

For both experiments, participants underwent three sessions of about 15 min each, separated by a small break. In one session, participants watched six video clips (two for each emotional context), each of which was followed by a thermal stimulation on their right leg (First-Hand Pain – see Fig. 1A). In the two other sessions, video-clips were followed by images of hands in either painful, arousing, or neutral control contexts (Others' pain – see Fig. 1B). Among the 18 video-clips available for emotion induction, six (two for each emotional context) were randomly assigned to "First-Hand Pain" session, whereas the remaining 12 were used in the two "Others' Pain" sessions. Such assignment changed on participant-to-participant basis. In half of the participants the "First-Hand Pain" session preceded the two "Others' Pain" sessions; the order was reversed in the remaining participants.

2.3.1. First-Hand Pain session

The session was organized in 6 blocks, one for each video-clip. In each of these blocks participants were first instructed to watch the clip (Pichon et al., 2014; Qiao-Tasserit et al., 2017). Subsequently, participants received a pseudo-randomized series of six thermal stimulations (3 painful and 3 painless). The randomization was constrained in such way that the same temperature could never be delivered more than twice in a row. Each thermal stimulus comprehended: (*a*) a fixation cross (1 s) (*b*) a ramp-up phase (3 s) during which the text string "The temperature is changing…" was presented on the screen, and the Peltier probe warmed from the baseline (35 °C) to the target temperature; (*c*) a plateau phase (2 s), in which the target temperature was delivered; (*d*) a descending phase, in which the temperature returned to baseline and subject evaluated the intensity of the pain just felt. Pain intensity was rated through the same 9-point Likert scale as used for the thresholding phase. Participants had 3.5 s to provide a response. Each thermal stimulus was followed by an inter-trial interval (ITI) of average 3.3 s (ranging from 2.6 to 4.2 s, to accommodate standard requirements in MRI research). This jitter was followed by a delay corresponding to the time for the thermode to return to the baseline temperature (average 2.1 s). Overall, the sequence of thermal stimuli following each clip lasted about 14.9 s.

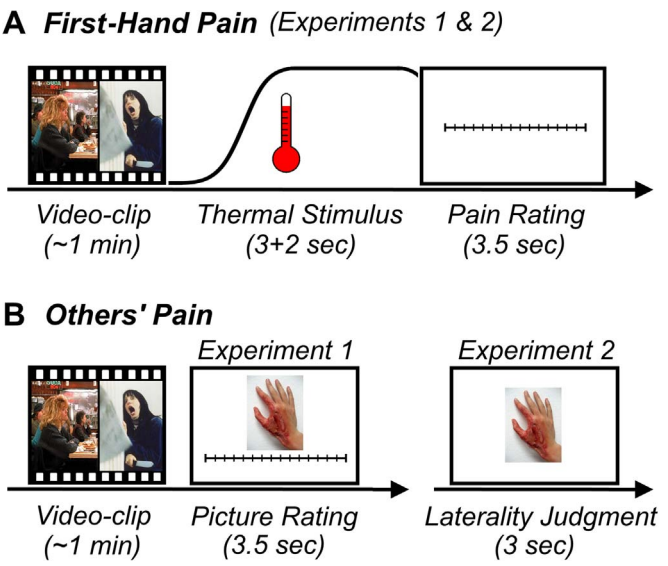

Fig. 1. Experimental Set-up. (**A**) First-Hand Pain task. Participants saw brief video-clips of positive, neutral or negative content, which were followed by a sequence of thermal stimulations. Each thermal stimulation comprehended a rump-up phase (of approximately 3 s) and a plateau phase (of approximately 2 s). After the plateau phase, participants were asked to rate the pain associated with the thermal stimulus on a visual analogic scale. (**B**) Others' Pain task. Video clips were followed by a sequence of pictures depicting hands in painful/painless situations. In Experiment 1, participants had to rate the unpleasantness associated with each picture on a visual analogic scale. In Experiment 2, participants had to evaluate the handedness of the hand stimulus.

The 6 blocks associated with the First-Hand Pain session were presented in a pseudo-randomized order. In particular, to potentiate emotion induction, movies from the same valence were grouped in successive blocks. The order of the blocks (e.g., first two negative movies, followed by two neutral and then two positive movies) changed across sessions and subjects.

2.3.2. Others' Pain sessions

As for the case of First-Hand Pain, each of the two "Others' Pain" sessions was organized in 6 blocks, one for each video-clip. After every video clip, participants were presented with 16 pictures (from the overall 192 hand stimuli), four for each condition (*Painful*, *Painless*, *Arousing*, *Non-Arousing*), in a pseudo-randomized order. Randomization was constrained in such way that the same condition could never be delivered more than twice in a row. In Experiment 1, participants were asked to evaluate the emotional arousal elicited by the image by answering to the question "*Which intensity is the emotion elicited by this image?*" (using a simultaneously-presented 9-point Likert scale which lasted for about 3.5 s). Each trial was followed by an ITI of average 2.4 s (ranging from 1.6 to 3.5 s).

In Experiment 2, pictures were presented for 3.5 s with displayed

below the words *"Left"* and *"Right"*. Participants were asked to perform a handedness task: if the stimulus depicted a right hand they had to press the key corresponding to the right hand, whereas if the stimulus was a left hand they had to press the key corresponding to the left hand. This task is known to be accomplished by mentally imagining to move one's own hand until it is aligned with the viewed hand (Corradi-Dell'Acqua et al., 2009; Parsons, 1987), without any explicit demand to process the painful/aversive cues in pictures (see (Corradi-Dell'Acqua et al., 2011; Gu et al., 2010). Each trial was followed by an ITI of average 2.4 s (ranging from 1.7 to 3.3 s). Overall, the sequence of images stimuli following each clip lasted about 5.9 s. Please note that such rapid design allows good estimate of differential neural response across different conditions (see also Braboszcz et al., 2017; Corradi-Dell'Acqua et al., 2011), but is inadequate for measuring changes in BOLD signal associated with the implicit baseline activity level. In this perspective, parameters describing increase of neural responses associated with one condition should be interpreted only in relation to other conditions, but not in absolute terms.

The 6 blocks associated with each of the two Others' Pain sessions were presented in a pseudo-randomized order, with movies from the same valence grouped in successive blocks. The order of the blocks changed across sessions and subjects.

2.3.3. Procedure and apparatus

We presented the stimuli with Matlab and Psychophysics Toolbox extensions (http://psychtoolbox.org/). For Experiment 1, we projected the stimuli on Dell PC screen (1024 × 768 resolution) outside of the scanner. Key-presses were recorded on Dell keyboard. For Experiment 2, we projected the stimuli on a LCD projector (CP-SX1350; Hitachi –1024 × 768 resolution). Participants saw the stimuli through a mirror fixed on the head coil and answered with key presses on an MRI-compatible bimanual response button box (HH- 2 × 4-C; Current Designs).

Each subject underwent the three main experimental sessions for about 45 min in total. These were followed by a post-experimental debrief session in which participants watched the beginning of every video clip and recalled their subjective experiences associated with each clip during the experiment. In particular, for each clip, they were asked to rate, on a visual analog scale, the emotional arousal, valence (because negative videos are often associated with fear, and positive videos with amusement, the scale had two side anchors labelled as "afraid" and "amused"), pain, and also how much they felt absorbed while watching the video (Eryilmaz et al., 2011; Pichon et al., 2014; Qiao-Tasserit et al., 2017).

Finally, participants compiled the following questionnaires: the Interpersonal Reactivity Index (Davis, 1980), Pain Catastrophizing Scale (Sullivan et al., 1995) and Positive and Negative Affective Schedule (Crawford and Henry, 2004).

2.4. Data processing

2.4.1. Behavioral data

For each task, for each subject and for each condition, we calculated the median rating value (from rating tasks), the average accuracy and median response time of correct responses (from the handedness task). These measures were then modeled as follows. For the First-Hand Pain task, we fed the median pain ratings to 2 (*Pain*: painful, painless) by 3 (*Emotional Context*: positive, neutral and negative) Repeated Measure ANOVA. The same model was used to analyze the data from the Others' Pain sessions (emotional arousal rating for Experiment 1, response times and accuracy for the Experiment 2) involving *Painful* and control *Painless* pictures. Paired *t*-tests were used for the *post-hoc* analyses. Statistical analyses were carried out with R 3.0.2 (https://www.R-project.org) freeware software.

2.4.2. Electrodermal activity

In Experiment 1, we recorded the skin conductance with an MP36R system and SS57L sensors coupled with pre-gelled EL507 electrodes (Biopac Inc, Santa Barbara, CA). Electrodes were pasted on participants' second and third fingers of the non-dominant hand, on the middle phalanges, palmar side. We sampled the data at 1000 Hz with AcqKnowledge software. Data were then filtered (low-pass cut-off 5 Hz; high-pass cut-off 0.01 Hz), downsampled to 10 Hz, *z*-transformed, and fed to a general linear model (GLM) as implemented in PsPM 3.0.2 (http://pspm.sourceforge.net) (Bach and Friston, 2013). We run a hybrid design in which video clips epochs were modeled with a boxcar functions, whereas thermal and picture events were modeled using finite impulse response as basis function, which poses no *a priori* assumption on the properties of the event-related response. The thermal stimuli were modeled with 16 bins of 1 s each, whereas picture events were modeled with 8 bins. This led, for each GLM, to an overall of 195 parameters (plus intercept), corresponding to 96 parameters associated with thermal stimuli (16 for painful and painless, and for each emotional context), 96 parameter associated with picture events (8 for painful, painless, arousing and non-arousing), and 3 for clip epochs (negative, neutral, positive). At the group level, the parameter estimates associated with thermal events were then fed in a 2 (*Pain*: painful, painless) by 3 (*Emotional Context*: positive, neutral and negative) by 16 (*Time-Bins*) Repeated Measure ANOVA. The parameter associated with Painful and Painless images were instead analyzed with a 2 (*Pain*) by 3 (*Emotional Context*) by 8 (*Time-Bins*) Repetitive Measure ANOVA.

2.4.3. Imaging data

In Experiment 2, participants performed the task while undergoing MRI scanning of brain activity. We acquired gradient-echo T2*-weighted transverse echo-planar images (EPIs) with blood oxygenation level-dependent (BOLD) contrast and a high-resolution T1-weighted anatomical image with a 3T Magnetom TIM Trio scanner (Siemens, Erlangen, Germany). Each functional volume contained 36 slices (3.2 mm thickness, 0.6 mm gap). We used a repetition time of 2100 ms, echo time of 30 ms, descending acquisition mode, flip angle of 80°, and in-plane resolution of 64 × 64 voxels (isometric voxel size of 3.2 mm).

We analyzed MRI images with SPM12 (Wellcome Department of Cognitive Neurology, London, UK). For each participant, we realigned functional images to the first volume of each session. We then co-registered the images with the T1 anatomical image, which was in turn used to estimate the deformation field necessary for the normalization to the standard Montreal Neurological Institute (MNI) through the unified segmentation approach (Ashburner and Friston, 2005). The deformation field was then applied to the functional images, which were then resampled them to an isotropic voxel size of 2 mm, and spatially smoothed with an isotropic full-width at half-maximum Gaussian kernel of 8 mm.

Preprocessed data were fed into a first-level analysis using the GLM framework as implemented in SPM. Movie epochs were modeled (separately for each emotional context) through a boxcar function describing blocks with duration of the corresponding videos. Thermal stimuli were modeled (separately for each emotional context and pain level) as events with 2 s duration, occurring at the time when the temperature reached plateau. This led to 9 parameters of interest (3 movie epochs, 6 thermal stimuli epochs) which were then convolved with the canonical hemodynamic response function (HRF) and associated with regressors describing their first order temporal derivative. We also included six movement parameters as covariates of no interest (x, y, z translations, pitch, roll and yaw rotations). We filtered the low-

frequency signal drifts with a cutoff period of 128 s and applied global scaling (transforming the fMRI signal value of each scan to a percentage of the average whole-brain signal). The 6 parameter estimates associated with thermal events were then fed into a second-level flexible factorial design with "conditions" as a within-subjects factor, and "subjects" as random factor, using a random effects analysis. In modelling the variance components, we allowed the "condition" factor to have unequal variance between its levels, whereas equal variance was assumed for the "subject" factor.

Data from both "Others' Pain" sessions were fed to a first-level GLM similar to the one used for the analysis of First-hand Pain data. However, instead of thermal stimuli, picture events were modeled as events with 0 s duration (Corradi-Dell'Acqua et al., 2011), separately for each condition and emotional context. Furthermore, to account to potential idiosyncratic image-differences in trial difficulty, we also modeled participants' response time during the task through four parametric modulators, one for each picture condition (Corradi-Dell'Acqua et al., 2011), but independently of the emotional context. This led to 19 regressors (3 movie epochs, 12 pictures epochs, 4 parametric modulators) which were then convolved with standard hemodynamic response function, associated with regressors describing their first-order time derivative and with six movement parameters. As for the case of First-Hand Pain, also the 6 parameters associated with *Painful* and *Painless* images were fed to a second level flexible factorial with "conditions" and "subjects" as factors.

In all analyses voxels were identified as significant only if they passed an extent threshold corresponding to $p < 0.05$ corrected for multiple comparison (Friston et al., 1993), with an underlying height threshold of $p < 0.001$ (uncorrected). Furthermore, we also applied small volume correction for predicted regions of interest (ROIs) in insula and middle cingulate cortex, known as key structures mediating the processing of both one's and others' pain. The volume of interest was defined through the Brainnetome Atlas that provides connectivity-based parcellation of human brain into 246 subregions (Fan et al., 2016). For others' pain, we focused on the "core" pain empathy network as described by Lamm et al. (2011) which involves bilateral AI and MCC (see also Rütgen et al., 2015a). We therefore created an AI-MCC mask, defined as bilateral cingulate regions 2 and 5 (corresponding approximately to Broadmann area 24) and insular regions 2 and 3 (corresponding approximately to the anterior agranular insular cortex). For first-hand pain, following previous investigations identifying emotion-induction effects in the most posterior portions of the insula (e.g., Berna et al., 2010), we created a wider Insula-MCC mask, defined as bilateral cingulate regions 2 and 5 and the whole insular cortex. We report activations within each volume when their peak reached $p < 0.05$ FWE-corrected at the voxel level.

2.4.4. Multivoxel pattern analysis

Similar to previous investigations (Corradi-Dell'Acqua et al., 2011, 2016), we ran a classification-based *multivoxel pattern analysis* (MVPA) to assess the similarity between the neural representations of pain cues in different experimental conditions. This analysis was conducted on the parameter estimates (*βs*) from first-level GLMs which, at variance with the standard univariate approach, were based on unnormalized and unsmoothed preprocessed data. Furthermore, for each participant and each task, the onsets of each trial were modeled independently, yielding trial-wise parameter estimates of each of the conditions-of-interest (Corradi-Dell'Acqua et al., 2011, 2016).

Following previous studies, we performed a searchlight-decoding approach that does not rely on a priori assumptions about informative brain regions, but searches for predictive information throughout the whole brain (Corradi-Dell'Acqua et al., 2011, 2014, 2016; Kriegeskorte et al., 2006). For each coordinate of the individual native brain image, a spherical volume-of-interest surrounding the coordinate was defined (5 voxels diameter, 81 voxels total). Hence, for each individual subject, and for each condition, the *βs* of all voxels in the sphere were extracted and then submitted to the following processing steps. First, the response patterns associated to each condition were mean centered through *z*-transformation to ensure that the MVPA analysis would not be biased by differences in the average sphere activity across conditions (Misaki et al., 2010). Data were then fed into a linear kernel support vector machine (SVM) classifier, which operates by finding an optimal linear decision boundary (hyperplane) that separates experimental classes with maximum margin (using a fixed regularization parameter, C = 1). New data (not used to define the decision boundary) are classified according to which side of the hyperplane they fall onto (Boser et al., 1992). Signal detection methods were used to compute *d′* (Green and Swets, 1966) as a measure of the sensitivity of the hyperplane to detect, in new data, the occurrence of one painful condition. Classification analysis was performed using the LIBSVM 3.18 software (Chang and Lin, 2011).

In particular, we assessed whether a classifier trained to detect First-hand pain (vs. tailored painless temperature) in one specific emotional context (Positive, Neutral & Negative) could discriminate Others' pain (vs. painless pictures) from another context, and vice versa. The analysis was conducted through 2 independent folds: for instance, we first trained a SVM on the trials associated with pain vs. no-pain in first-hand pain following positive videos ($\text{First-Hand}_{\text{POS}}$), then tested the ability of the estimated hyperplane to classify the pain vs. no-pain in others' pain following negative videos ($\text{Other}_{\text{NEG}}$). In the second fold, we trained a SVM on the trials associated with pain vs. no-pain in $\text{Other}_{\text{NEG}}$, and then tested the estimated hyperplane on the trials associated with pain vs. no-pain in $\text{First-Hand}_{\text{POS}}$. *d′* values were then estimated from the classified trials from both folds. Reliable cross-target classifications (in this example $\text{First-Hand}_{\text{POS}} \leftrightarrow \text{Other}_{\text{NEG}}$) can be interpreted as showing that pain-related signals evoke at least partly similar response pattern across different targets and emotional contexts. This approach was implemented to test for cross-modal activity patterns across all 3 emotional contexts (modulated in each of the two targets separately) thus leading to 9 *d′* values. Each of these *d′* values were assigned to the center voxel of the sphere and the procedure was repeated for the next voxel. For each participant, this led to 9 independent *d′*-maps which were then spatially normalized to the MNI single-subject template (using the deformation field obtained during the normalization of the T1-weighted anatomical image) and smoothed using a 8 mm FWHM Gaussian kernel.

We subsequently fed the 9 cross-target *d′* maps in a group-level linear regression probing for regions where the 9 cross-target *d′*s changed consistently with the prediction of our two main models of interest. Specifically, following accounts suggesting that empathy may increase during positive emotions, but be weakened during negative emotions (e.g., *broaden–and–build theory*, (Fredrickson, 2004), we assumed that *d′* increased linearly the more participants observed others' pain while being in a positive state. Hence, we fit participants *d′*-maps with a predictor set to 1 during $\text{Other}_{\text{POS}}$, 0 during $\text{Other}_{\text{NEU}}$, and -1 during $\text{Other}_{\text{NEG}}$ (Model 1: Positive state). On the other hand, embodied accounts are consistent with the idea that activity patterns associated with pain should be affected in similar way by emotional context in both First-Hand and Others' sessions. Hence, we fit participants *d′*-maps with a predictor set to 1 whenever the two targets experienced pain in matching states ($\text{First-Hand}_{\text{POS}} \leftrightarrow \text{Other}_{\text{POS}}$, $\text{First-Hand}_{\text{NEU}} \leftrightarrow \text{Other}_{\text{NEU}}$, $\text{First-Hand}_{\text{NEG}} \leftrightarrow \text{Other}_{\text{NEG}}$), 0 whenever the two tasks were given in partially mismatching states ($\text{First-Hand}_{\text{POS}} \leftrightarrow \text{Other}_{\text{NEU}}$, $\text{First-Hand}_{\text{NEU}} \leftrightarrow \text{Other}_{\text{POS}}$, $\text{First-Hand}_{\text{NEG}} \leftrightarrow \text{Other}_{\text{NEU}}$, $\text{First-Hand}_{\text{NEU}} \leftrightarrow \text{Other}_{\text{NEG}}$), and -1 whenever the two tasks were in totally distinct/mismatching states ($\text{First-Hand}_{\text{POS}} \leftrightarrow \text{Other}_{\text{NEG}}$, $\text{First-Hand}_{\text{NEG}} \leftrightarrow \text{Other}_{\text{POS}}$ – Model 2:

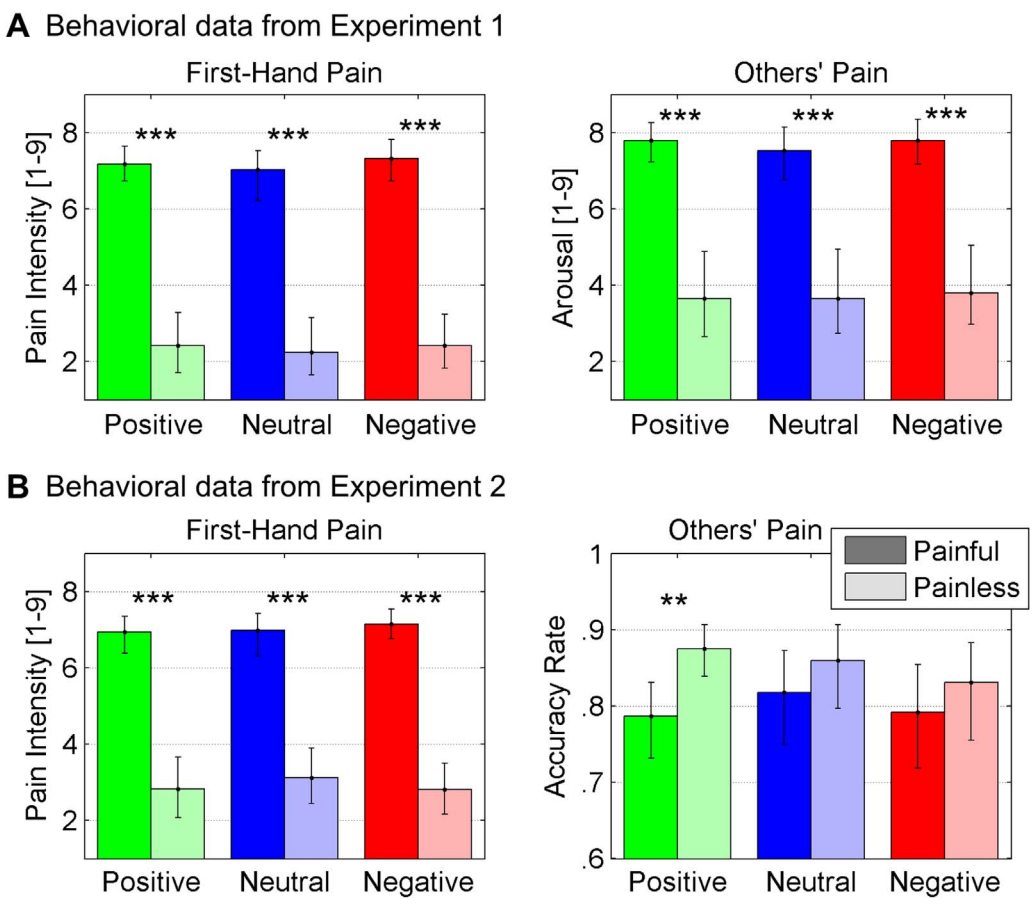

Fig. 2. Behavioral Results from First-Hand Pain and Others' Pain in Experiments 1 (**A**) and Experiment 2 (**B**). Bar plots display average rating values (Experiment 1 and First-Hand Pain task in Experiment 2) and average accuracy values (Others' Pain task in Experiment 2) associated with bootstrap-based confidence intervals. Green, Blue and Red bars refer to responses provided following the exposure to Positive, Neutral and Negative video-clips respectively. Dark colors refer to painful temperatures/images, whereas light colors refer to painless temperatures/images. (**C**) Participants' Response Times during the Others' Pain Task in Experiment 2 plotted against Empathic Concern scores from the IRI questionnaire. Each plot, corresponding to data from different emotional contexts, is associated with a linear regression line, together with a shaded area describing the 95% confidence interval. "***" one-sample *t*-test revealing differential performance between painful and painless condition at $p < 0.001$; "***"$p < 0.01$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Isomorphic effect).

This led to a group-level analysis testing the two main predictors of interests (from model 1 and model 2) and participants' identity as random factor. Regions were identified as significantly associated with one model if they exceeded an extent threshold corresponding to $p < 0.05$ corrected for multiple comparison, with an underlying height threshold of at least $t_{(190)} = 3.13$, corresponding to $p < 0.001$ (uncorrected). We used as extent threshold the 95th percentile of the distribution of the largest cluster obtained through 1000 replications with the same analysis on permuted data sets. Second-level *t*-tests were performed using the SnPM toolbox of SPM (http://warwick.ac.uk/snpm).

3. Results

3.1. Video Epochs

Appendix A reports all the data associated with the processing of video clips. For both experiments, when debriefed, participants rated positive and negative clips as more arousing and absorbing than neutral clips. As expected, positive videos elicited significantly more positively-valenced feelings than neutral clips, whereas negative videos elicited more negative-valenced feelings. At the neural level, emotionally-valenced videos engaged a widespread network including occipito-temporal cortex, precuneus, and inferior frontal gyrus (Eryilmaz et al.,

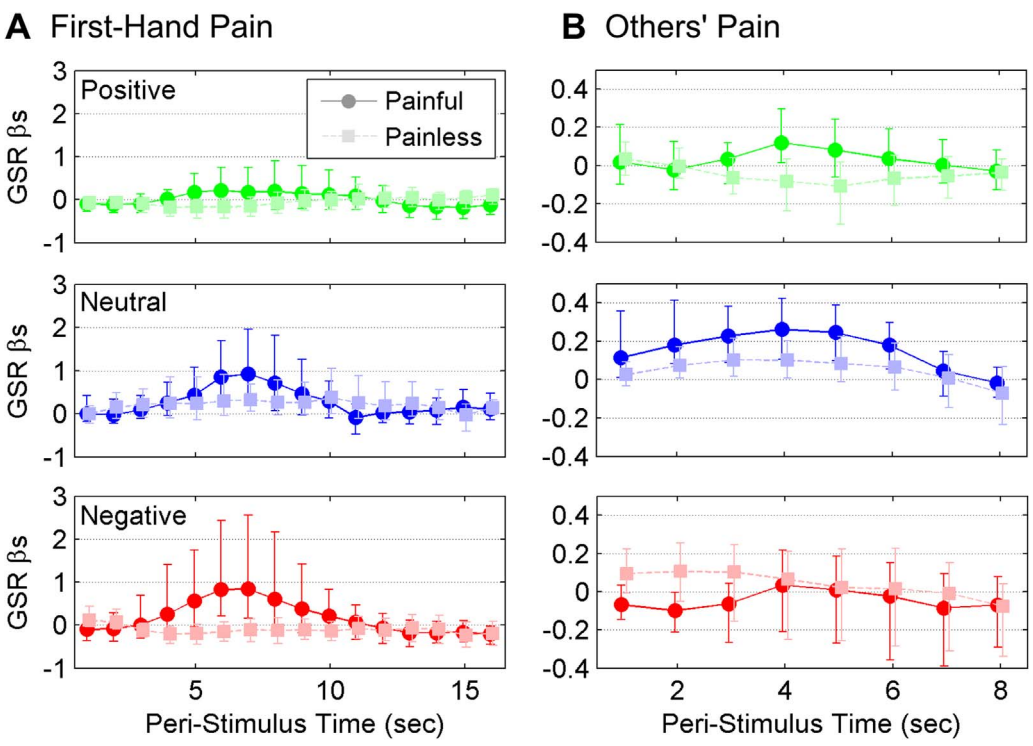

Fig. 3. Peri-stimulus time plots of Galvanic Skin Response (GSR) from Experiment 1. For both First-Hand Pain (**A**) and Others' Pain (**B**) task, and for each emotional context, evoked GSR is displayed for a time window of 16 s (**A**) or 8 s (**B**). Error-bars refer to with bootstrap-based confidence intervals. Green, Blue and Red lines refer to responses provided following the exposure to Positive, Neutral and Negative video-clips respectively. Dark colors refer to painful temperatures/images, whereas light colors refer to painless temperatures/images. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

2011), relative to the neutral videos. They also elicited decreased activity in medial prefrontal regions extending to the middle cingulate cortex, and in left posterior insula (PI). No significant effects were found for the amygdala in this contrast (contrary to (Eryilmaz et al., 2011; Pichon et al., 2014) who used the same films), although this region was activated together with the right anterior insula specifically for positive videos.

3.2. Behavioral responses

3.2.1. First-Hand Pain

To examine the subjective emotional effects of thermal stimuli, the participants' median pain intensity ratings (ranging from 1 to 9) were submitted to a 2 (*Pain*: painful, painless) × 3 (*Emotional Context*: positive, neutral, negative) Repeated Measure ANOVA. As expected, in both experiments, a main effect of *Pain* was found, confirming that painful temperatures were associated with significantly higher ratings (Experiment 1: $F_{(1,16)} = 140.03$, $p < 0.001$; Experiment 2: $F_{(1,23)} = 112.43$, $p < 0.001$), relative to the painless control temperatures (see Fig. 2). However, no main effect of *Emotional Context* or *Pain*Emotional Context* interaction was found ($F \leq 1.06$, *n.s.*).

3.2.2. Others' Pain

We then analyzed behavioral responses associated with the processing of pictures showing hands in pain, as well as painless control images, using a similar 2 (*Pain)* × 3 (*Emotional Context)* ANOVA, as used for temperatures. In Experiment 1, where participants reported their subjective arousal elicited by the images (ranging from 1 to 9), we found a main effect of *Pain*, reflecting higher ratings for painful than painless control images ($F_{(1,16)} = 51.81$, $p < 0.001$ – see Fig. 2A). In Experiment 2, in which participants were engaged in a handedness task, a main effect of *Pain* was also observed for both accuracy ($F_{(1,23)} = 20.56$, $p < 0.001$) and response time on correct trials ($F_{(1,23)} = 8.57$, $p < 0.01$). This is in line with our previous study showing that judging the laterality of painful/wounded hands is slower than judging control/unwounded hands (Corradi-Dell'Acqua et al., 2011). In neither analysis, we found a significant main effect of *Emotional Context* or *Pain*Emotional Context* interaction ($F \leq 1.15$, *n.s.*).

3.3. Electrodermal activity

Electrodemal responses were recorded in Experiment 1 only. For self-experienced thermal stimuli, these data were analyzed with a 2 (*Pain)* × 3 (*Emotional Context)* × 16 (*Time*: from 1 to 16 s after stimulus onset) Repeated Measure ANOVA. This analysis revealed a significant main effect of *Time* ($F_{(15,210)} = 2.68$, $p < 0.001$) and a *Pain*Time* interaction ($F_{(15,210)} = 3.21$, $p < 0.001$), indicating robust pain-related modulation around 5–7 s after stimulus delivery (see Fig. 3A). No other effects were found. Hence, autonomic responses to self-experienced pain were not modified significantly by the preceding emotional movie type.

Similarly, electrodemal responses to pictures of others' hands were submitted to a 2 (*Pain)* × 3 (*Emotional Context)* × 8 (*Time*: from 1 to 8 s) Repeated Measures ANOVA. This analysis revealed a significant main effect of *Time* ($F_{(7,98)} = 3.00$, $p = 0.006$) and a marginal *Pain*Time* interaction ($F_{(7,98)} = 1.99$, $p = 0.064$), again pointing to pain-related modulation around 5 s after picture onset. More importantly, a significant *Pain*Emotional Context* interaction was found ($F_{(2,28)} = 3.91$, $p = 0.03$), reflecting stronger electrodermal activity to painful (*vs.* painless) images following positive and neutral, but not negative, video clips (see Fig. 3B). All other effects in the ANOVA were not significant ($Fs \leq 1.38$, *n.s.*). Thus, prior exposure to negative emotional information in movies abolished subsequent autonomic arousal responses evoked by observing pain in others.

3.4. Neural responses

Neural activations (from Experiment 2) were reported if exceeding a

Table 1
Neural Activations associated with Painful – Painless thermal stimuli. Regions displaying differential activity between painful and painless stimuli. All clusters survive correction for multiple comparisons at the cluster level (with an underlying height threshold corresponding to $p < 0.001$, uncorrected), or small volume correction of the insular cortex and MCC. L and R refer to the left and right hemisphere, respectively. M refers to medial activations.

	SIDE	Coordinates			T	Cluster size
		x	y	z		
Positive Emotions: *Painful – Painless temperatures*						
Anterior insula (AI)	R	38	16	0	3.60	378** *
Superior temporal gyrus	R	48	16	− 8	5.30	
Anterior insula (AI)	L	− 42	6	− 6	5.40	485**
Central operculum	L	− 54	2	2	4.80	
Cerebellum	L	− 32	− 56	− 32	5.20	464**
Supplementary Motor Area	M	− 4	12	44	5.60	791**
Middle Cingulate Cortex (MCC)	M	2	12	42	4.60	
Neutral Emotions: *Painful – Painless temperatures*						
Anterior insula (AI)	R	46	12	− 6	5.60	1222***
Frontal operculum	R	54	12	− 2	5.40	
Putamen	R	12	6	4	5.60	511**
Anterior insula	L	− 40	4	− 6	5.20	988***
Middle cingulate Cortex (MCC)	M	6	12	38	5.30	897***
Negative Emotions: *Painful – Painless temperatures*						
Anterior insula (AI)	R	44	14	− 6	4.30	610***
Central operculum	R	36	8	10	4.90	
Anterior insula (AI)	L	− 40	6	− 6	6.00	1966***
Posterior insula	L	− 36	− 20	16	5.90	
Central operculum	L	− 58	− 10	10	5.90	
Precentral gyrus	L	− 32	−6	60	4.30	371**
Superior frontal gyrus	L	− 24	−4	66	4.50	
Middle frontal gyrus	L	− 26	4	54	4.20	
Supplementary motor area	M	− 4	10	46	5.20	1200***
Middle cingulate gyrus (MCC)	M	2	14	40	4.90	
Conjoint Effects: *Positive ∩ Neutral ∩ Negative*						
Anterior insula (AI)	R	44	14	− 6	4.30	228*
Anterior insula (AI)	L	− 40	6	− 6	5.00	365**
Middle cingulate Cortex (MCC)	M	2	12	42	4.60	460**
Interaction effects: *$(Painful_{(Neg+Neu)/2} - Painless_{(Neg+Neu)/2}) > (Painful_{Pos} - Painless_{Pos})$*						
Posterior insula	R	34	− 10	10	4.10†	50
Posterior insula	L	− 38	− 10	8	4.30†	66

* $p < 0.05$ family-wise corrected for multiple comparisons at the cluster level.
** $p < 0.01$ family-wise corrected for multiple comparisons at the cluster level.
*** $p < 0.001$ family-wise corrected for multiple comparisons at the cluster level.
† $p < 0.05$ small volume corrected for an anatomical mask of the insular cortex and MCC.

cluster-level threshold corresponding to $p < 0.05$, family-wise (FWE) corrected for multiple comparisons for the whole brain. Furthermore, we also reported regions surviving small volume correction for insular-MCC masks of interest (see methods).

3.4.1. First-Hand Pain

Table 1 and Fig. 4A display, separately for each *Emotional Context*, the neural responses elicited by painful, relative to painless, temperatures. Conjoint effects across the three emotional contexts (Fig. 4A, white blobs), were observed in the bilateral anterior insula (AI) and the middle cingulate cortex (MCC). Interestingly, pain-related responses following positive video clips appear restricted to the most anterior portion of the insula, whereas responses following neutral and negative movies extend also to middle/posterior portions. No suprathreshold effect was observed in the postcentral gyrus contralateral to the stimulation site, corresponding to primary somatosensory areas (see Derbyshire et al., 1991; Disbrow et al., 1998; Jones et al., 1991, for failing to find postcentral activity under stationary thermal stimulations setting similar to ours).

We then formally tested for the *Pain*Emotional Context* interaction to assess for emotion-induced changes in the neural response to self-experienced pain. When testing for *positive-specific* effects [i.e., $(Painful_{(Neg+Neu)/2} - Painless_{(Neg+Neu)/2}) \neq (Painful_{Pos} - Painless_{Pos})$, we found that thermal pain (vs painless stimuli) produced no differential increase in the bilateral posterior insula (PI) following positive movies, unlike negative and neutral movies (see Fig. 4B and Table 1). Simple post-hoc *t*-tests run on the average parameters extracted from both regions showed that this interaction in insula reflected increased response to thermal painless stimuli following positive relative to negative/neutral videos ($ts_{(23)} \geq 3.57$, $ps < 0.001$). No significant difference was observed for the painful temperatures ($|t|s_{(23)} \leq 1.29$, *n.s.*). No region exhibited significant increase of pain-related response after positive video-clips. Furthermore, when testing for *negative*-specific effects [i.e., $(Painful_{(Pos+Neu)/2} - Painless_{(Pos+Neu)/2}) \neq (Painful_{Neg} - Painless_{Neg})$, we found no suprathreshold activation.

3.4.2. Others' Pain

Table 2 and Fig. 5A display, separately for each *Emotional Context*, the neural responses elicited by images of wounded hands, relative to their control stimuli. Conjoint effects across the three emotional contexts (Fig. 5A, white blobs) were observed only in the right supramarginal gyrus extending to postcentral gyrus (Corradi-Dell'Acqua et al., 2011; Lamm et al., 2011). However, in the neutral condition, increased activation to pain-related pictures was observed in the right AI (Fig. 5A, blue blobs), consistent with previous studies using the same pain empathy task without any emotion-induction (Corradi-Dell'Acqua et al., 2011; Jackson et al. (2006a, 2006b, 2005); Lamm et al., 2011).

We then formally tested for the *Pain*Emotional Context* interaction to assess for emotion-induced changes in brain responses to pain images. When testing for *positive-specific* effects [i.e., $(Painful_{(Neg+Neu)/2} - Painless_{(Neg+Neu)/2}) \neq (Painful_{Pos} - Painless_{Pos})$, we found no suprathreshold activity. However, when testing for *negative*-specific effects [i.e., $(Painful_{(Pos+Neu)/2} - Painless_{(Pos+Neu)/2}) \neq (Painful_{Neg} - Painless_{Neg})$, we found decreased pain-related activity in the left AI and MCC, as well as the periaqueductal gray. Simple *t*-tests run on average parameters extracted from each of these three regions showed that the interaction reflected stronger response to painful pictures following positive/neutral, relative to negative videos ($ts_{(23)} \geq 2.27$, $ps < 0.033$). No difference between emotion conditions was observed for the control pictures ($|t|s_{(23)} \leq 0.90$, *n.s.*) except for the case of PAG ($t_{(23)} = -2.16$, $p = 0.042$ – see Appendix C). Thus, in all regions, exposure to negative movies led to attenuated pain responses relative to positive and neutral, video clips (see Fig. 5B). No region exhibited significant increase of pain-related neural response following negative video-clips.

3.4.3. Multivoxel pattern analysis

Our results insofar highlight a differential impact of Emotional Context on First-Hand and Others' pain, without however comparing directly the effects from the two sessions. In this perspective, previous studies used MVPA to estimate the degree of similarity between pain representation in First-Hand and Others conditions at the voxel-by-voxel level (cross-target similarity). This technique was used to assess whether the appraisal of other people's sufferance is grounded on the same neural representation as engaged by one's own pain (Braboszcz et al., 2017; Corradi-Dell'Acqua et al., 2011, 2016; Krishnan et al., 2016). Here, we extended this approach by assessing whether cross-

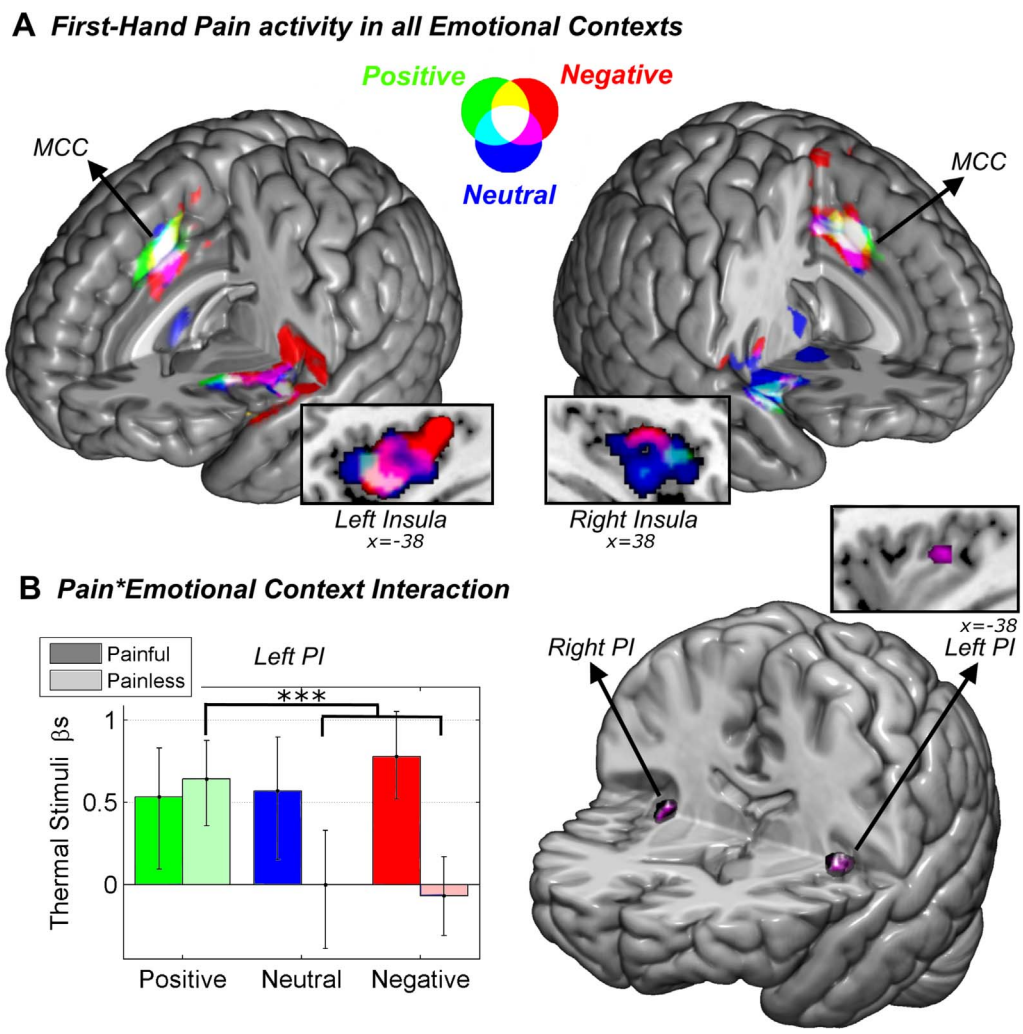

Fig. 4. Neural response to First-Hand Pain from Experiment 2. (**A**) Whole-brain map highlighting the differential activity evoked by painful (relative to painless) temperatures for each emotional context separately. Green, Blue and Red blobs refer to neural responses following the exposure to Positive, Neutral and Negative video-clips respectively. White blobs refer to neural responses observed in all three emotional contexts. (**B**) Whole-brain map highlighting the regions in which pain-related activity changed as function of the emotional context (*Pain*Emotional Context* Interaction). Parameters extracted from the left posterior insula are also displayed with bootstrap-based confidence intervals. Green, Blue and Red bars refer to responses provided following the exposure to Positive, Neutral and Negative video-clips respectively. Dark colors refer to painful temperatures, whereas light colors refer to painless temperatures. *MCC*: Middle Cingulate Cortex. *PI*: Posterior Insula. "***" one-sample *t*-test on parameters extracted revealing differential activity for painless temperatures in positive context compared to neutral and negative contexts averaged together at $p < 0.001$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

target similarity was changed as function of different Emotional Contexts.

In particular, given that the Emotional Context to First-Hand pain was manipulated independently from the Emotional Context to Others' pain, 9 independent measures of cross-target similarity were drawn from our dataset, and then tested according to two main models of interests (see Fig. 6A). Model 1 (*Positive State* model – derived from the *broaden–and–build theory*, see introduction) posits increased empathic responses when individuals are in positive states, and lesser empathic responses when individuals are in negative states. It is therefore possible that, when observing others' under positive states, individuals have facilitated access to the same pain-representation that underlie First-Hand Pain, whereas when they are under negative states this access in impeded. We therefore tested whether the cross-target similarity increased in the positive emotional state, relative to other states. In contrast, Model 2 (*isomorphic effect* model) suggests that different emotional states alter the representation of pain shared between First-Hand and Others' sessions. In this perspective, cross-target similarity should be the strongest when First-Hand and Others' pain are experienced under the same emotion induction condition.

We therefore tested for regions significantly associated with either model, by implementing a full-searchlight analysis, using permutation-based correction for multiple comparisons across the whole brain (see methods). Results revealed that a portion of the left anterior insula (MNI coordinates: − 34, 8, − 4, t = 4.54, 547 consecutive voxels [cut-off 329]), extending to the inferior frontal gyrus (− 36, − 26, 16, t = 4.23), was selectively implicated in model 1 (see Fig. 6B). Average parameters extracted from this cluster (Fig. 6C) revealed larger cross-target similarity whenever participants observed others' pain in a positive state. Smaller cross-modal similarity was observed when participants were in a negative state. No region was found to be implicated in model 2, neither when testing the whole brain, nor when applying a less stringent threshold on the insula and MCC anatomical masks.

3.5. Empathy scores

Finally, we tested whether the emotional modulation of pain processing (in self or other conditions) varied according to individual traits. For the First-Hand task, we examined how responses were influenced by personal scores related to catastrophizing (PCS) and positive/negative affect (PANAS). Given that this task was identical in Experiment 1 and 2, the ratings of all 41 participants from both experiments were combined together and then fed in analyses of covariance (ANCOVAs) in which each individual score was modeled as covariate. None of these scores was significantly associated with pain ratings, neither as a main effect nor as interaction with the factors of

Table 2
Neural Activations associated with Painful – Painless Images. Regions displaying differential activity between painful and painless stimuli. All clusters survive correction for multiple comparisons at the cluster level (with an underlying height threshold corresponding to $p < 0.001$, uncorrected), or small volume correction of AI and MCC. L and R refer to the left and right hemisphere, respectively. M refers to medial activations.

	SIDE	Coordinates			T	Cluster size
		x	y	z		
Positive Emotions: *Painful – Painless Images*						
Supramarginal/ Postcentral Gyrus	R	56	− 22	42	6.90	670***
Precentral Gyrus	R	48	6	28	5.30	233*
Inferior occipital Cortex	R	22	− 94	− 6	7.50	3310***
Fusiform Gyrus	L	− 16	− 88	− 12	7.60	2393***
Neutral Emotions: *Painful – Painless Images*						
Ant. Insula (AI)/Inf. Frontal Gyrus	R	42	36	8	5.20	256*
Supramarginal/ Postcentral Gyrus	R	54	− 24	36	5.00	252*
Precentral Gyrus	R	48	6	30	4.70	367**
Fusiform Gyrus	R	18	− 94	− 6	9.40	4976***
Anterior insula (AI)	L	− 32	14	− 12	4.00	333**
Calcarine cortex	L	− 12	−92	− 6	7.70	3409***
Negative Emotions: *Painful – Painless Images*						
Supramarginal/ Postcentral Gyrus	R	60	− 22	40	5.10	312**
Calcarine cortex	R	14	− 92	2	6.70	2047**
Calcarine cortex	L	− 8	− 94	− 6	7.40	1541***
Conjoint Effects: *Positive ∩ Neutral ∩ Negative*						
Supramarginal/ Postcentral Gyrus	R	54	−24	34	4.80	205*
Calcarine cortex	R	14	−92	2	6.70	1944***
Calcarine cortex	L	− 14	−86	−12	7.3	1395***
Interaction effects: $(Painful_{(Pos+Neu)/2} - Painless_{(Pos+Neu)/2}) > (Painful_{Neg} - Painless_{Neg})$						
Anterior insula (AI)	L	− 36	16	− 10	3.80†	45
Middle cingulate gyrus	L	− 10	14	34	3.90†	11
Periacqueducal Gray	M	− 8	− 28	− 14	5.80	661**

* $p < 0.05$ family-wise corrected for multiple comparisons at the cluster level.
** $p < 0.01$ family-wise corrected for multiple comparisons at the cluster level.
*** $p < 0.001$ family-wise corrected for multiple comparisons at the cluster level.
† $p < 0.05$ small volume corrected for an anatomical mask of the anterior insular cortex and MCC.

interest ($F \leq 2.35$, *n.s.*). No effects were found when focusing on the ratings from Experiment 2 alone ($F \leq 2.81$, *n.s.*). In addition, these personal scores did not affect brain responses evoked by First-Hand pain when running a whole-brain voxelwise parametric analysis.

For the Others' Pain task, in addition to measures of positive/negative affect, we included individual scores in empathy (derived from the IRI questionnaire). Repeated measures ANCOVAs on behavioral performance in Experiment 2 revealed that participants' response times were significantly modulated by inter-individual difference in empathic concern – i.e., other-oriented feelings of sympathy and concern for unfortunate others (Davis, 1980) – resulting in an *Emotional Context* Empathic Concern* interaction ($F_{(2,30)} = 3.32$, $p = 0.045$). As visible in Fig. 2C, individuals with higher scores in empathic concern generally took longer to assess the laterality of the hands (possibly reflecting greater interference caused by the painful content of stimuli), and this effect was weaker following positive video-clips. No other effects were found for any of the scores ($F \leq 3.19$, *n.s.*).

We also tested for the effect of these personal scores on brain responses to pictures of others' pain. We found that individuals with higher scores of perspective taking – i.e., the tendency to spontaneously adopt the psychological point of view of others (Davis, 1980) – exhibited higher activity in the medial prefrontal cortex when observing others' pain (*vs*. control painless condition) after exposure to negative clips (see Fig. 7, x = − 2, y = 44, z = 16, T = 4.21, 291 consecutive voxels, $p < 0.05$ corrected). Such modulation of neural pain responses by perspective taking was significantly stronger following exposure to negative clips, relative to positive and neutral clips, as revealed by a direct interaction contrast (x = − 2, y = 44, z = 16, T = 4.31, 248 consecutive voxels, $p < 0.05$ corrected). No other suprathreshold effects in the neural response to others' pain were associated with IRI empathy scores Fig. 7.

4. Discussion

Our study examines whether (and how) emotion episodes that produce lingering changes in brain (Eryilmaz et al., 2011; Pichon et al., 2014; Qiao-Tasserit et al., 2017; Richiardi et al., 2011), could subsequently modulate the perception of noxious stimuli directed to oneself (thermal stimulations) and pain scenes observed in other people (Corradi-Dell'Acqua et al., 2011). Across two separate experiments, we found that galvanic response and brain activity in AI and MCC were reduced when viewing painful scenes in others following exposure to negative emotions, as compared with positive and neutral emotion conditions. This is in sharp contrast with the effects found for first-hand pain (noxious stimuli directed to the participant themselves), which modulated activity in more posterior insular portions and selectively occurred following positive emotion induction. Furthermore, our multivoxel pattern analyses confirmed that first-hand and others' pain elicit similar activity patterns in left AI (as in Braboszcz et al., 2017; Corradi-Dell'Acqua et al., 2011; but see Krishnan et al., 2016), while they challenged the idea that these neural responses are affected by emotion induction in an isomorphic way. Instead, voxelwise similarity of insula activity between first-hand and others' pain was the strongest when participants witnessed others' pain following positive video-clips, relative to the neutral or negative videos. Overall, our results favor seminal proposals (e.g., *broaden–and–build theory*, (Fredrickson, 2004) according to which positive emotions strengthen one's social abilities (including empathic responses and their neural signatures), whereas negative emotions may attenuate them.

4.1. Positive emotions effects on first-hand pain

Previous studies have repeatedly shown that transient emotion induction (by using movies similar to ours) can profoundly affect brain functioning, not only during the observation of the video themselves, but also during subsequent rest (Eryilmaz et al., 2011; Richiardi et al., 2011) or perceptual tasks (Pichon et al., 2014; Qiao-Tasserit et al., 2017). Notably, positive and negative emotion episodes lead to sustained decreases in activity of the insula and anterior cingulate cortex over a few minutes following the inducing movie scenes (Eryilmaz et al., 2011). Furthermore, these lingering effects of emotion are accompanied by changes in the functional connectivity between insula and cingulate cortex, as well as their interaction with other parietal, precuneus, and thalamic regions (Eryilmaz et al., 2011; Richiardi et al., 2011).

Such network affected by transient emotions overlaps with circuits engaged by first-hand pain, often referred to as the *pain matrix* (Farrell et al., 2005; Salimi-Khorshidi et al., 2009) – see also Fig. 4A). This might account for why pain experience is reported to vary according to different emotional states, as induced by videos, but also pictures, text, music, odors, etc. Indeed, subjective pain intensity is enhanced after exposure to sadness (Berna et al., 2010; Boettger et al., 2011; Tang et al., 2008; Zelman et al., 1991) and during other negative states (de Wied and Verbaten, 2001; Loggia et al., 2008; Meagher et al., 2001; Roy et al., 2009; Zillmann et al., 1996), whereas it is reduced after exposure to positive/elative situations (de Wied and Verbaten, 2001;

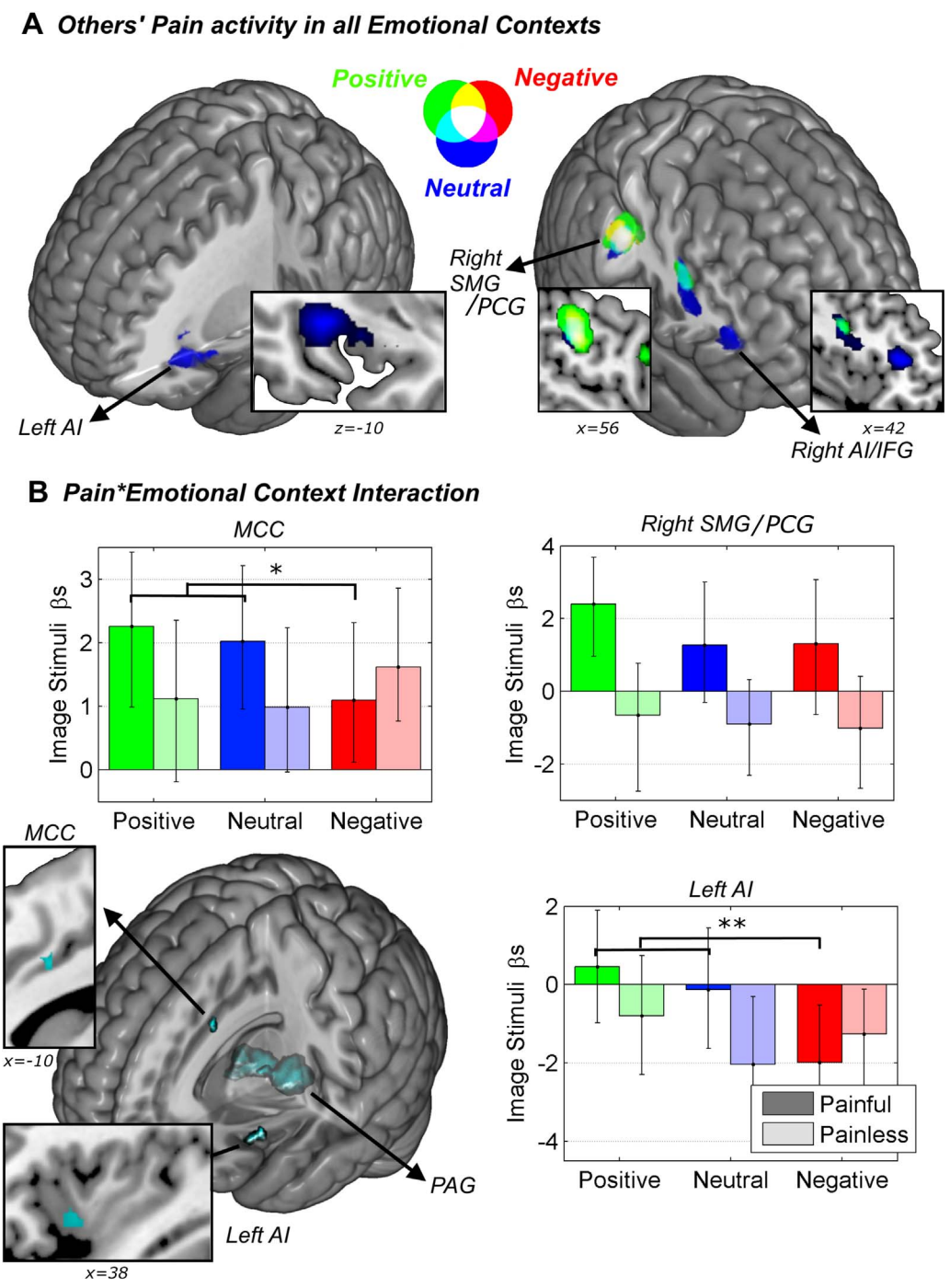

Fig. 5. Neural response to Others' Pain from Experiment 2. (**A**) Whole-brain map highlighting the differential activity evoked by painful (relative to painless) Images for each emotional context separately. Green, Blue and Red blobs refer to neural responses following the exposure to Positive, Neutral and Negative video-clips respectively. White blobs refer to neural responses observed in all three emotional contexts. (**B**) Whole-brain map highlighting the regions in which pain-related activity changed as function of the emotional context (*Pain*Emotional Context* Interaction). Parameters extracted from predefined regions of interest are also displayed with bootstrap-based confidence intervals. Green, Blue and Red bars refer to responses provided following the exposure to Positive, Neutral and Negative video-clips respectively. Dark colors refer to painful temperatures, whereas light colors refer to painless temperatures. *AI*: Posterior Insula. *IFG*: Inferior Frontal Gyrus. *SMG*: Supramarginal Gyrus. *PCG*: Postcentral Gyrus. *MCC*: Middle Cingulate Cortex. *PAG*: Periaqueductal Gray. "**" one-sample *t*-test on parameters extracted revealing differential activity for painful images in negative context compared to neutral and positive contexts averaged together at $p < 0.01$; "*"$p < 0.05$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Meagher et al., 2001; Roy et al., 2008; Tang et al., 2008; Villemure and Bushnell, 2009; Villemure et al., 2003; Weisenberg et al., 1998; Whipple and Glynn, 1992; Zillmann et al., 1996). Furthermore, pain-evoked activity in insula (especially its posterior portion) and cingulate cortex is enhanced by depressed mood (Berna et al., 2010) or exposure to unpleasant pictures (Roy et al., 2009), but reduced by exposure to pleasant odors (Villemure and Bushnell, 2009). Our data converge with previous finding, by showing that the sensitivity of PI to noxious temperatures (compared with painless control thermal stimuli) decreased following positive (relative to neutral and negative) videos.

Within the *pain matrix,* PI is held to receive direct nociceptive inputs from thalamic nuclei (Craig et al., 1994, 2000), and might contribute to a first analysis of the sensory properties of the painful experience (Craig et al., 2000; Segerdahl et al., 2015). In this perspective, it is plausible that positive emotion state might perturb the functional processing of this early pain detection stage, by preventing this region from discriminating noxious from non-noxious stimuli, without affecting other portions of the *pain matrix* that could still receive incoming nociceptive information by the thalamic-cingulate nociceptive pathway (Craig, 2003; Craig et al., 1994). In-depth analysis of activity parameters extracted from PI (as displayed in Fig. 4B) suggests that positive emotions operate by making this region hypersensitive to painless control

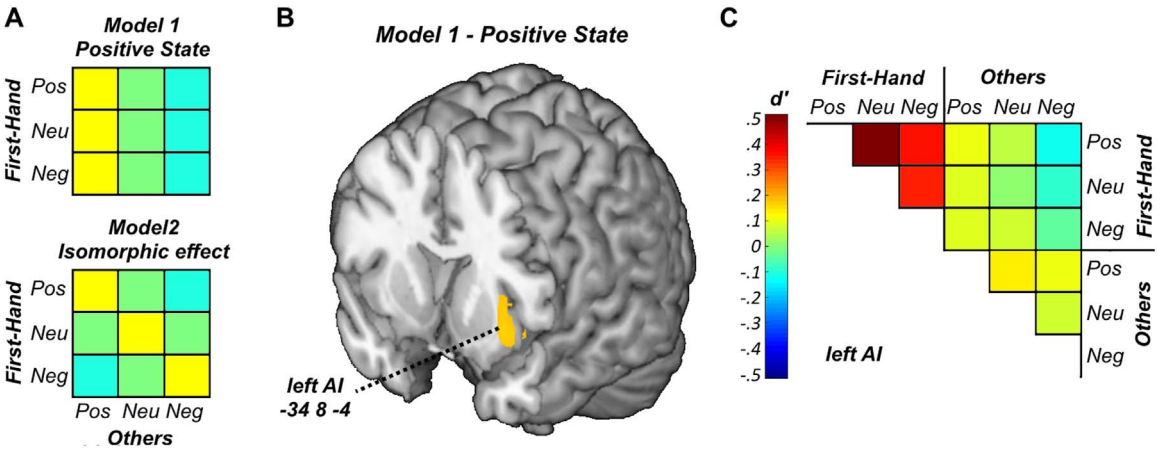

Fig. 6. Multivoxel Pattern Analysis. (**A**) Two models of interest inspecting the change of cross-target similarity in pain representation across different levels of Emotional Context. Each model is described as a 3 × 3 grid reflecting three levels of Emotional Context in First-Hand pain (Vertical Axis) plotted against three levels of Emotional Context in Others' pain (Horizontal Axis). Yellow squares refer to conditions associated with the highest cross-target similarity (according to each model's prediction), whereas light blue squares refer to conditions associated with the lowest cross-modal similarity. (**B-C**) Whole-brain map highlighting the regions significantly associated with Model 1. Average *d'* parameters extracted from this region are also displayed in matrix form. The magnitude of *d'* is identified by corresponding color-coding as highlighted by the associated bar. The portion of the matrix associated to cross-target similarity (the one comparing activity patterns from First-Hand and Others' pain) is remarkably similar to that predicted in Model 1. *AI*: Anterior Insula.

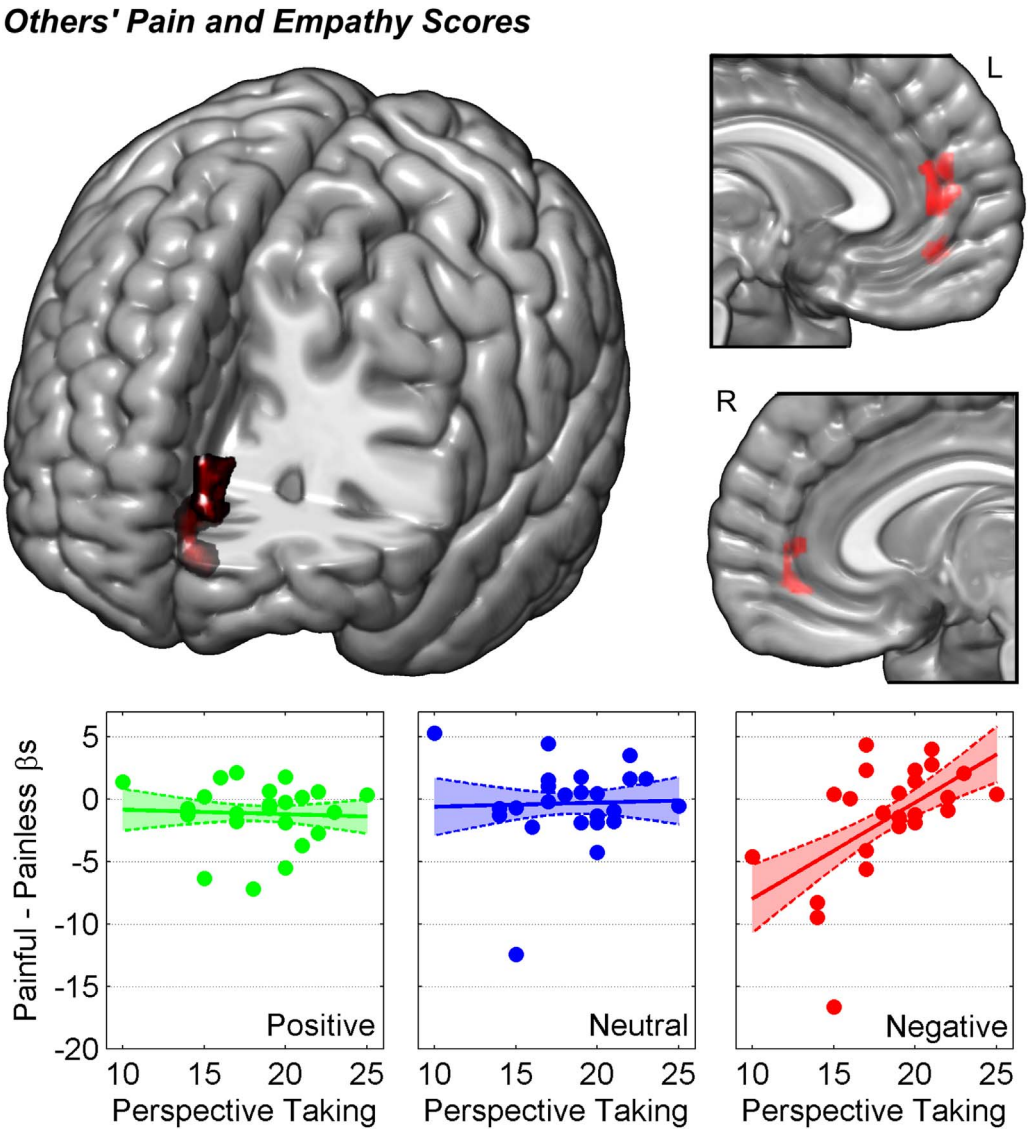

Fig. 7. Neural response to Others' Pain correlates with Perspective Tasking scores. Whole-brain map highlighting part of the medial prefrontal cortex in which pain-evoked neural response in a Negative emotional context is modulated by individual Perspective Taking as measured in the IRI questionnaire. The parameter extracted from the region are also plotted against individual scores, together with a regression line and a shaded area describing the 95% confidence interval. Green, Blue and Red data refer to neural responses following the exposure to Positive, Neutral and Negative video-clips respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

temperatures, rather than by reducing its' responsiveness to noxious events. Alternatively, changes in baseline level activity in the insula between emotion states might alter the magnitude of the event-related response to pain but cannot be readily detected by the BOLD fMRI signal, eventually leading to the observed lack of differential responses to painful vs painless stimuli in the positive context. Hence, although the direction of the interaction effect in PI accord to the literature and our hypothesis, caution should be used in interpreting this effect as due to some inhibition of pain processing. Moreover, higher BOLD responses in PI might not necessarily correspond to higher intensity of subjective pain, but reflect more general dimensions of salience or arousal (Menon and Uddin, 2010; Uddin, 2014). Future studies are needed to further dissect the nature of emotional modulation of pain-related activity in PI.

4.2. Negative emotions effects on others' pain

The effect of emotion induction on first-hand pain contrasts sharply with the effect that the same manipulation has on viewing others' pain. When analyzing both galvanic skin signal (from Experiment 1) and neural activity in AI and MCC (from Experiment 2), we found reduced responses to pictures showing wounded hands (*vs.* painless controls) after negative emotions, but no change in the positive compared to neutral condition. Furthermore, in Experiment 2, we found that others' pain evoked activity patterns in AI which were similar to those associated with first-hand pain. Such similarity in pain response patterns is often interpreted as a correlate of empathy (Bernhardt and Singer, 2012; Corradi-Dell'Acqua et al., 2011), and appeared to be enhanced by prior exposure to positive event but diminished by negative video-clips.

Previous studies provided conflicting results concerning how responses to others' pain are influenced by emotion state (e.g., (Enzi et al., 2016; Singer et al., 2006; Yamada and Decety, 2009). It should be stressed, however, that emotion induction approaches used by these previous studies were extremely different, not only from one another but also compared to studies on first-hand pain. To our knowledge, ours is the first research that used a well-established emotion induction paradigm to directly compare the impact of different affective states on both first-hand and others' pain. Moreover, task discrepancies (as well as other divergences related sensory and temporal properties of the stimuli) become less problematic in our MVPA, which probed for representation similarity between first-hand and others' pain over and around idiosyncratic differences in the experimental set-up.

It could be argued that the emotion-induction effect on the neural response to others' pain (Fig. 5B) may reflect a conflict between the valence of one's current state (neutral and positive) in relation to the valence of the state observed in others (pain is always negative). This interpretation would accord with recent work (Silani et al., 2013) where individuals were exposed to pleasant/unpleasant tactile stimulations whilst showing others undergoing a consistent or inconsistent experience. Authors found that the right supramarginal gyrus was more active during inconsistent (as opposed to consistent) events, presumably suggesting a role for this region in maintaining the self-other distinction, and thus preventing inappropriate use of self as proxy for interpreting others' states (Silani et al., 2013). We feel however that this interpretation is not sufficient to explain our results. First, Silani et al. (2013) implicated the right supramarginal gyrus, whereas we found modulations in AI and MCC. The only contrast implicating the right supramarginal gyrus (extending to postcentral gyrus) in our dataset was the conjunction analysis revealing regions sensitive to others' pain across all emotional contexts (see Fig. 5). Second, and most critically, our MVPA analysis suggested that positive emotions strengthen the degree of similarity between a representation of self and other in AI, which is consistent with the idea of enhanced reenactment of others' pain on oneself, rather than the engagement of a mechanism serving to maintain distinction.

In our study, the emotional state induced by video-clips (amusement, fear) was qualitatively different from those observed in others' (i.e., pain), presumably recruiting distinct affective representations (even if negative videos shared a similar valence with painful pictures). It is therefore not surprising that the effects found here diverge from cases where induced and observed states tap into a shared representation. For instance, it has been documented that first-hand exposure to painful stimuli enhances (and conversely is enhanced by) the processing of painful facial expressions (Godinho et al., 2012; Reicherts et al., 2013). Similarly, the same negative (fearful) video-clips used here biased individual classification of ambiguous facial expressions towards fear, whereas positive (amusing) absorbing video-clips biased the classification of the same expression towards amusement (Qiao-Tasserit et al., 2017).

In light of these considerations, emotion induction might lead to two distinct kinds of effects. If the induced and felt state recruit a shared representation, one's own state might affect directly the content of the representation used for understanding others (Godinho et al., 2012; Qiao-Tasserit et al., 2017; Reicherts et al., 2013; Silani et al., 2013), and thereby require parallel or compensatory processes for maintaining self-other distinction (Silani et al., 2013). If however the induced and felt state tap into distinct representations or share only core affective dimensions (as in our case), one's own state may not alter the representation of others per se, but rather modulate its access. This is in line with models such as the *broaden–and–build theory*, suggesting that positive emotional states broaden one's mindset and strengthen access to social resources, whereas negative emotional states exert an opposite limiting effect (Fredrickson, 2004).

4.3. Others' pain and empathy scores

Negative emotions inhibited responses to others' state especially in individuals with low empathy scores, as measured by the well-established Interpersonal Reactivity Index (IRI) questionnaire (Davis, 1980). In the handedness task (Experiment 2), response times (RTs) were generally delayed when the hand stimulus was in pain (see also (Corradi-Dell'Acqua et al., 2011), suggesting an interference by the negative content of images (Ito et al., 1998). Interestingly, following negative videos, this slowing was modulated by individual scores in the Empathic Concern subscale of IRI, which is held to reflect other-oriented feelings of sympathy and concern for unfortunate others (Davis, 1980). Thus, under negative emotions, individuals with low scores of empathic concern were more proficient at ignoring the arousing pain content of images, whereas individuals with high scores were still influenced by others' states. The relationship between RTs and empathic scores was significantly weaker or even absent following positive and neutral videos (see Fig. 2C and interaction analysis).

Individual scores of empathic concern did not correlate with neural responses. On the other hand, however, activity of the medial prefrontal cortex, over and around the anterior cingulate cortex, was increased in individual with higher scores in perspective taking, which reflects the tendency to spontaneously adopt the psychological point of view of others (Davis, 1980). Such modulation was also emotional-specific, with stronger effect during negative, than during neutral and positive, states. The medial prefrontal cortex has already been associated with the ability to take the point of view of others, and more generally with cognitive appraisal of others' mental and affective states (e.g., (Corradi-Dell'Acqua et al., 2014, 2015; Mar, 2011; Peelen et al., 2010; Saxe and Kanwisher, 2003; Skerry and Saxe, 2014). Moreover, some models of empathy suggest that, whereas insular regions mediate an affective response to others' states, medial prefrontal regions might instead

underlie a more cognitive facet of empathy (Shamay-Tsoory, 2011). Accordingly, previous studies showed that individual scores in perspective taking (but not empathic concern) correlated with the volume of the medial prefrontal cortex (Banissy et al., 2012), and were significantly reduced following its damage (Shamay-Tsoory et al., 2009). In this perspective, it seems that information about others' pain in our task is not processed only in AI and MCC, but also in the medial prefrontal cortex following a more "cognitive" pathway. This result support the idea that highly empathetic individuals use higher-order processes to down-regulate negative emotion and reduce self-other assimilation, in order to be able to help others (Mailhot et al., 2012; Vachon-presseau et al., 2011).

Altogether, our data reveal the interplay between negative emotion and individual empathy towards others' pain. Negative emotions tend to reduce sensitivity to others' pain in proportion to individual empathy traits, but this individual-specific effect was no longer observed after participants saw amusing videos. This might reflect a "normalizing" role and "broadening" influence of positive emotions that abolish inter-individual differences and boost one's empathic responses.

4.4. Limitations of the study and overall conclusions

Although extensively validated in studies measuring neural activity under rest (Eryilmaz et al., 2011; Richiardi et al., 2011) and in emotion processing tasks (Pichon et al., 2014; Qiao-Tasserit et al., 2017), our emotion induction paradigm is not immune from critiques. For instance, post-scanning ratings associated with our videos suggests that positive and negative clips were not fully matched for arousal (see Table A1) – unlike previous findings with the same movie dataset, see Eryilmaz et al., 2011. Nevertheless, it is unlikely that our results are confounded by arousal differences, because otherwise both positive and negative conditions would differ from the neutral and be similar to each other overall, unlike what we observed. Furthermore, our negative video-clips contained more frequent pain-related situations than neutral and positive clips (extracts from thrillers and horror movies may be suggestive of injuries or death – Table A1), which leaves open the possibility that negative-specific effects might be at least partly related to the painful content of videos, rather than to their emotional valence per se. Future studies implementing different kinds of emotion induction paradigms (e.g., music) will need to extend and disentangle these effects.

Another issue to consider is that, in our study, the task exposing participants to others' pain changed across experiments, from an explicit rating (Experiment 1) to a handedness task aimed at engaging implicit pain processing (Experiment 2). This was different from the first-hand pain session, which involved explicit ratings in both experiments. The design of Experiment 2 allows good comparison with previous studies using the same settings (Braboszcz et al., 2017; Corradi-Dell'Acqua et al., 2011). Furthermore, previous investigations failed to find differences in AI response to others' pain between explicit ratings and the handedness task (although some differences were found in the cingulate cortex – see Gu et al., 2010). Nevertheless, it is possible (at least in principle) that neuroimaging differences between first-hand and others' pain sessions might partly reflect the nature of the task, rather than just the target of the pain. However, we note a high consistency between the physiological effects to others' pain in Experiment 1 (Fig. 3B) and the neural modulations of AI and MCC in Experiment 2 (Fig. 5B) which makes this conjecture unlikely.

In any case, these limitations do not undermine the main findings of our study that responses to first-hand and others' pain are differentially affected by prior exposure to the same emotionally-valenced videos. In particular, contrary to the case of one's own pain, sensitivity to others' suffering (as measured by galvanic skin response and neural signal in AI and MCC) increases progressively as the preceding emotional episode (clip) was more positive. Furthermore, individual empathy might help counteract the social deficit caused by negative emotions, but has no effect when individuals are already in a positive state. Overall, our data highlight the positive nature of pain empathy, which may entail the ability to be broad-minded and allocate sufficient processing resources in order to recognize and understand others' well-being, an ability that may become limited when individuals are in negative emotional states.

Acknowledgments

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Appendix A. Video Epochs

The post-experimental ratings associated with the video clips used for mood induction are reported in Table A1. For both experiments, for each question of interest, the post-experimental ratings were analyzed with a repeated measures ANOVA testing the effect of *Emotional Context*. In both experiments, and all questions of interests, a main effect of *Emotional Context* was found (Experiment 1: $F_{(2,\ 32)} \geq 23.79$, $p < 0.001$; Experiment 2: $F_{(2,\ 46)} \geq 11.18$, $p < 0.001$). Post-hoc contrasts revealed that positive clips were rated as more positively-valenced, more arousing and more absorbing than neutral clips (Experiment 1: $t_{(16)} \geq 5.18$, $p < 0.001$; Experiment 2: $t_{(23)} \geq 2.46$, $p \leq 0.022$). Instead, negative clips were rated as more negatively-valenced (Experiment 1: $t_{(16)} = -5.54$, $p < 0.001$; Experiment 2: $t_{(23)} = -4.14$, $p < 0.001$), more arousing, more absorbing and more associated with pain than neutral clips (Experiment 1: $t_{(16)} \geq 5.63$, $p < 0.001$; Experiment 2: $t_{(23)} \geq 4.96$, $p < 0.001$). These data are in line with those from previous studies using the same video database (Eryilmaz et al., 2011; Pichon et al., 2014; Qiao-Tasserit et al., 2017; Richiardi et al., 2011). We run also the same ANOVA on the parameters estimates of GSR associated with the video-clips epochs (from Experiment 1), but found no significant effect of *Emotional Context* ($F_{(2,\ 28)} = 1.19$, *n.s.*).

The neuroimaging data (from Experiment 2) were analyzed by feeding the average parameters associated with the video epochs in with a second-level flexible factorial second-level design, with *Emotional Context* and "subjects" as random factor, using a random effects analysis. This analysis revealed that emotionally-valenced videos elicited increased activity in the middle-occipital cortex, the fusiform gyrus, precental gyrus, inferior frontal gyrus (bordering the anterior insula), and precuneus (Eryilmaz et al., 2011), see Fig. A1. No effects were found in the amygdala (contrary, (Eryilmaz et al., 2011; Pichon et al., 2014), which however was implicated in the processing of positive (relative to neutral/negative) videos together with the right anterior insula. Finally, neutral videos (relative to emotionally-valenced clips) displayed enhanced activity in the middle/anterior cingulate cortex, extending to ventral portions of the medial prefrontal cortex. A similar effect (although at an uncorrected threshold) was observed in the left posterior insula. Full results from this analyses are displayed in Table A2.

Table A1
Average post-experimental ratings associated with Positive, Neutral and Negative video-clips. All values are from an 11-points Likert scale ranging from 1 to 11 (except for Valence for which the scale ranged from − 5 to + 5).

	Experiment 1			Experiment 2		
	Positive	*Neutral*	*Negative*	*Positive*	*Neutral*	*Negative*
Valence	3.18	0.18	− 3.15	2.98	− 0.08	− 2.21
Arousal	7.50	4.15	8.24	6.50	4.35	7.60
Absorption	8.09	5.32	8.79	7.12	5.44	8.12
Pain	2.00	2.06	8.15	1.79	1.73	7.67

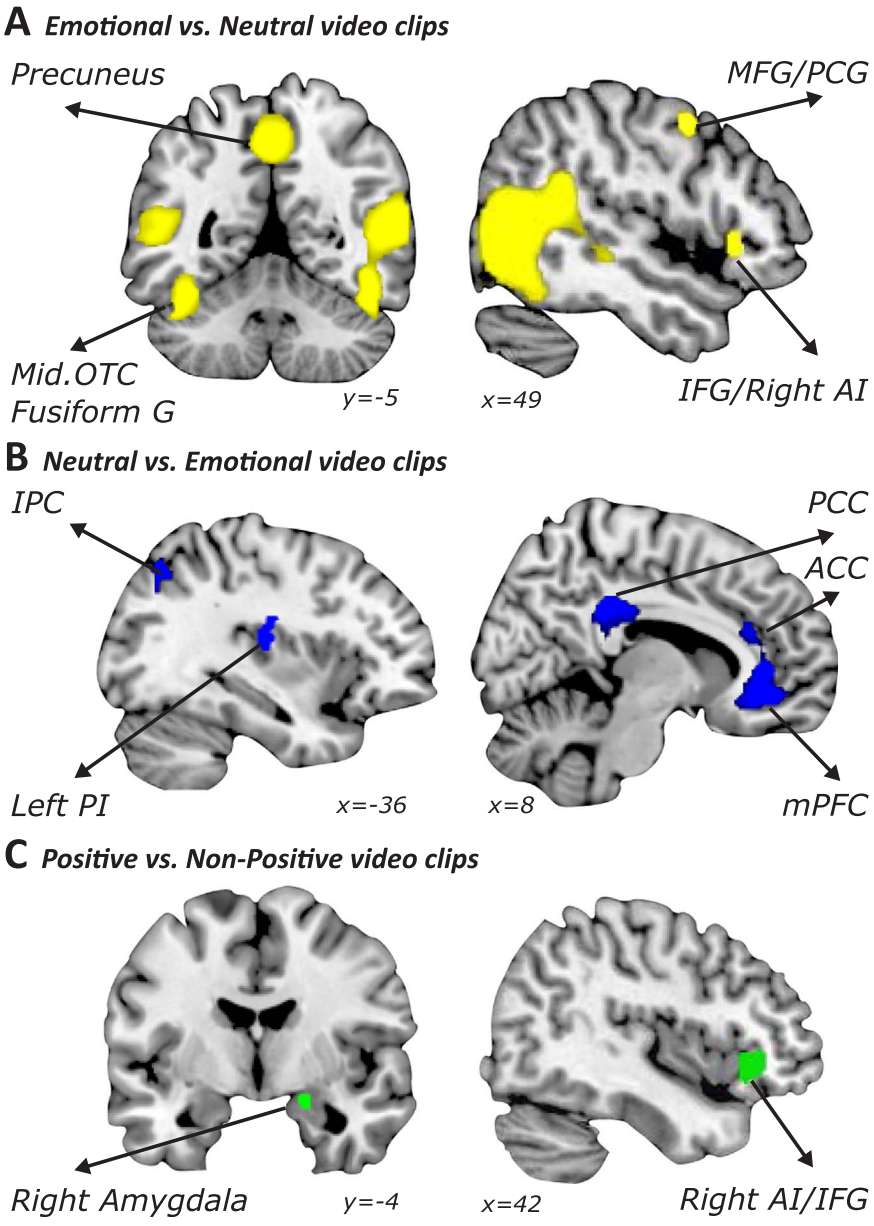

Fig. A1. Neural response to video clips from Experiment 2, illustrating Appendix A and Table A2. Whole-brain maps highlighting the differential activity elicited by (**A**) Emotional vs. Neutral video clips ((Positive –Neutral) ∩ (Negative –Neutral)) (**B**) Neutral vs. Emotional video clips ((Neutral–Positive) ∩ (Neutral–Negative)) (**C**) Positive vs. Non-Positive video clips ((Positive –Neutral) ∩ (Positive–Negative)). *Mid.OTC*: Middle Occipito-Temporal Cortex. *Fusiform G*: Fusiform Gyrus. *MFG*: Middle Frontal Gyrus. *PCG*: Precentral Gyrus. *IFG*: Inferior Frontal Gyrus. *AI*: Anterior Insula. *IPC*: Inferior Parietal Cortex. *PI*: Posterior Insula. *PCC*: Posterior Cingulate Cortex. *ACC*: Anterior Cingulate Cortex. *mPFC*: Medial Prefrontal Cortex. See Table A2 for details.

Table A2
Neural Activations associated with the processing of Video-clips. Regions displaying differential activity between different kinds of videos. Clusters surviving correction for multiple comparisons at the cluster level (with an underlying height threshold corresponding to $p < 0.001$, uncorrected) are highlighted. L and R refer to the left and right hemisphere, respectively. M refers to medial activations.

	SIDE	*Coordinates*			*T*	*Cluster size*
		x	*y*	*z*		
Emotional vs. Neutral video clips *(Positive – Neutral) ∩ (Negative – Neutral)*						
Middle Occipo-Temporal Cortex	R	50	− 62	10	9.67	4258***
Fusiform Gyrus	R	44	− 50	− 20	7.33	
Mid. Front. Gyrus/Precen. Gyrus	R	38	− 2	58	6.89	385*
Inf. Front. Gyrus/Anterior Insula	R	52	22	0	5.06	113
Middle Occipo-Temporal Cortex	L	− 50	− 70	4	9.61	3284***
Fusiform Gyrus	L	− 40	− 50	−20	7.31	
Cerebellum	L	− 20	− 78	−34	6.82	
Precuneus	M	− 2	− 52	50	6.96	655**
Neutral vs. Emotional video clips *(Neutral – Positive) ∩ (Neutral – Negative)*						
Posterior Insula	L	− 36	− 18	12	4.13	56
Inferior Parietal Cortex	L	− 48	− 50	46	4.94	340*
Middle/Anterior Cingulate Cortex	M	10	30	24	4.04	1793***
Ventromedial Pref. Cortex	M	8	42	−8	5.29	
Posterior Cingulate Cortex	M	0	− 36	30	6.44	1096***
Positive vs. Non-Positive video clips *(Positive – Neutral) ∩ (Positive – Negative)*						
Anterior Insula/ Inf. Frontal Gyrus	R	44	28	− 4	4.91	137
Amygdala	R	20	− 4	− 16	3.96	14

* $p < 0.05$ family-wise corrected for multiple comparisons at the cluster level.
** $p < 0.01$ family-wise corrected for multiple comparisons at the cluster level.
*** $p < 0.001$ family-wise corrected for multiple comparisons at the cluster level.

Appendix B. Effects of Arousing Images

We analyzed the behavioral responses associated with the processing of pictures describing hands in arousing (but painless) situations, together with corresponding painless controls. In Experiment 1, we fed the individuals' ratings associated with these images into a 2 (*Arousal)* by 3 (*Emotional Context)* ANOVA used for the case of temperatures, and found a main effect of *Arousal* ($F_{(1,16)} = 31.95, p < 0.001$), related to higher rated values for arousing (vs. non-arousing control) images. We also found a main effect of *Emotional Context* ($F_{(2,\ 32)} = 5.41$, $p < 0.001$), suggesting larger rating values following emotionally-valenced videos, relative to controls. The interaction was not found to be significant ($F_{(2,\ 32)} = 0.60$, *n.s.*). In Experiment 2, in which participants were engaged in a handedness task, a main effect of *Arousal* was observed in the analysis of the accuracy values ($F_{(1,23)} = 10.53$, $p < 0.01$) and response time of correct trials ($F_{(1,23)} = 7.01$, $p < 0.05$). Neither the *Emotional Context* main effect nor the *Pain*Emotional Context* interaction were found to be significant ($F \leq 2.34$, *n.s.*).

The electrodermal activity associated with these images (from Experiment 1) was analyzed with 2 (*Arousal)* by 3 (*Emotional Context)* by 8 (*Time*: from 1 to 8 s) Repeated Measures ANOVA. This analysis revealed only a main effect of *Time* ($F_{(7,98)} = 3.44$, $p = 0.002$), suggesting picture-evoked modulation of electrodermal response across the 8 s following the presentation of the stimulus. No other main effect or interaction was found to be significant ($F \leq 3.27$). Finally, we analyzed the neural responses associated with these pictures (from Experiment 2) following the same procedure used for the other conditions (see main text). This analysis did not reveal any suprathreshold activation.

Appendix C. Periaqueductal Gray

As shown in Fig. 5B, the left anterior insula and middle cingulate gyrus were implicated in the *Pain*Emotional Context* interaction, showing how the activity associated with painful (relative to painless) images was stronger following positive and neutral video-clips, as opposed to negative ones. Also the periaqueductal gray was associated with the same contrast. Fig. A2 displays the parameters extracted from the periaqueductal gray: as for the case of MCC and AI, this region showed stronger activity for painful (*vs.* painless) images under positive and neutral emotional context. However, differently from MCC and AI, the effect reversed under negative emotional context, with painless images eliciting higher activity than painful images.

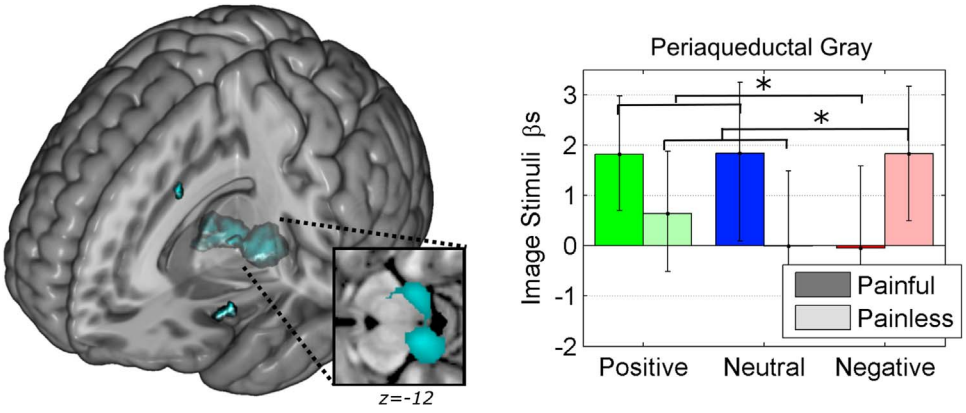

Fig. A2. Neural response to Others' Pain from Experiment 2. Whole-brain map displaying regions in which pain-related activity changed as function of the emotional context (*Pain*Emotional Context* Interaction). The midbrain section of the brain is highlighted, revealing an involvement of the Periaqueductal Gray (*PAG*). Parameters extracted from *PAG* are also displayed with bootstrap-based confidence intervals. Green, Blue and Red bars refer to responses provided following the exposure to Positive, Neutral and Negative video-clips respectively. Dark colors refer to painful temperatures, whereas light colors refer to painless temperatures. "*" one-sample *t*-test on parameters extracted revealing differential activity between painful and painless images at $p < 0.05$.

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