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Interoception as a social alarm amplification system. What multimethod (EEG-fNIRS) integrated measures can tell us about interoception and empathy for pain?

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Abstract

We examined whether the modulation of Interoceptive Attentiveness (IA) influences the cortical correlates of observation of pain in others. Healthy participants observed painful/non-painful stimuli while brain response [oxygenated and deoxygenated hemoglobin (O2Hb; HHb), and electroencephalographic cortical oscillations] was measured. Participants were divided into experimental (EXP) and control group: EXP group was required to focus on its interoceptive correlates during the task. Interpersonal Reactivity Index (IRI) scale was administered to test empathic traits. Focusing on prefrontal cortex activity, theta band and O2Hb in the right frontal hemisphere while observing painful stimuli positively correlates in the EXP. Delta band and O2Hb in left frontal hemisphere for non-painful stimuli positively correlates in controls. IRI (Perspective Taking and Empathic Concern subscales) and right frontal activity for painful stimuli negatively correlates in the EXP. Findings were discussed in light of the modulating role of IA in enhancing the negative experience of observing pain in others.

Keywords: interoceptive attentiveness; EEG; fNIRS; pain; empathy

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1. Introduction

The construct of interoception, conceived as the multidimensional perception of internal states of bodily arousal, is central to several theoretical accounts of emotion, from James Lange to Damasio's theory (Damasio, 1999; Lange, 1922). These models argue that an emotional stimulus automatically initiates visceral, vascular, or somatic reactions, and it is the perception of these bodily reactions that crucially constitutes the emotional component of the experience. Recent research showed that interoception (namely, interoceptive sensitivity (IS) that is the individual difference in perceiving the changes in internal body states) is positively associated with the self-regulation of behavior in situations that are accompanied by somatic and/or physiological changes (Dunn et al., 2010; Herbert et al., 2007; Pace-Schott et al., 2019; Pollatos et al., 2012; Werner et al., 2009). Interestingly, these studies highlight a possible link between self-regulation and interoceptive processes beyond the field of emotions, for instance, physical workload, decision-making, and pain.

About pain, one of these studies demonstrated that IS was positively correlated with measures of pain threshold, pain tolerance, and pain experience (Pollatos et al., 2012). Indeed, Pollatos and colleagues (2012) suggested that high IS might facilitate the detection of bodily changes accompanying pain experience. Pain is modulated on a cognitive level depending on attention, anticipation, emotion, and memory of previous pain experiences (Stoeter et al., 2007). Numerous empirical studies demonstrate that measures of pain perception are associated with changes of internal bodily reactions, such as heart rate (Breimhorst et al., 2011; Loggia et al., 2011), highlighting that bodily states and their representations also shape the experience of pain, even only when observed in others.

By linking interoception to the observation of pain experienced by another individual, it has been demonstrated that, when painful visual stimuli were observed, a higher interoceptive aware response can be related to a greater estimated degree of pain (outcome interpreted as representative of cognitive empathy), as well as a higher state of arousal and feelings of compassion, evidence indicating the activation of the affective component of empathy (Grynberg & Pollatos, 2015).

Indeed, when observing pain in others, individuals reproduce their bodily representations of pain thanks to the shared activation of pain matrix and empathic brain circuits and this leads to more intense empathic responses (Ernst et al., 2013; Singer & Lamm, 2009). In line with this assumption, enhanced attention to interoceptive states is a key aspect of anxiety disorder (Mumford et al., 1991), thus suggesting a possible association between the interoceptive experience and the negative valence of the emotional response for instance to unpleasant conditions or painful stimuli. Bowling and colleagues (Bowling et al., 2019), suggested that the focus of attention directed towards the internal physiological variations could enhance conscious vicarious pain perception in adults.

Between the interoceptive dimensions, the focused attention to a particular interoceptive signal for a given time interval has been previously defined as Interoceptive Attentiveness (IA) (Schulz, 2016; Tsakiris & De Preester, 2018). IA is a higher-level dimension that can be modulated and can be trained (Farb et al., 2013). Therefore, this leads to suppose IA could amplify the typical mirroring effect evoked by empathy for pain processes in at least two directions: i) the representation for the negative valence of the situation, and ii) the activation of increased empathic response. However, the relationship between pain perception, interoception, and empathic response remains still unanswered.

Secondly, considering the neural network of empathy for pain, previous fMRI studies showed that observing pain in others triggers the mirror neural systems (MNS), which makes possible to understand a painful condition, as such perception stimulates identical neural pathways as if we felt the sensations and emotions of the pain ourselves (Fitzgibbon et al., 2010). Empathizing with others' pain appears to recruit the entire pain matrix, including a collection of frontal regions that are especially involved in the affective and motivational pain assessment and the cognitive attentional dimension of pain (Apkarian et al., 2005; Hauck et al., 2008; Tracey & Mantyh, 2007). Among these areas, the Dorsolateral Prefrontal Cortex (DLPFC) was found to respond to the observation of pain in others, and to be specialized for emotional regulation towards salient emotional stimuli (e.g., angry-pain face with negative valence; Enzi et al., 2016), it was associated to high subjective empathy and could, therefore, reflect a protective mechanism from emotional hyper-arousal (de Greck et al., 2012). Regarding hemispheric frontal lateralization, previous studies suggested both left and right DLPFC activation have been related to the downregulation of self-pain perception (Boggio et al., 2008; Lorenz et al., 2003; Rêgo et al., 2015) and this modulation seems to be associated with its main function on general emotional regulation processes, such as cognitive reappraisal and attention modulation of affective responses (Ochsner et al., 2012). Therefore, there is a link between the pain observed in others, the valence of this emotional experience, and the emotional regulation processes going on at the neural level.

Indeed, according to Ochsner, Silver, and Buhle (2012), different emotional regulation strategies are associated with a lateralized DLPFC activity: while the left side is often involved with the meaning reinterpretation of the affective response, the right side seems to play a role on psychological distancing from the emotional stimulus. Alternative interpretative models related the hemispheric lateralization response to stimuli emotional valence. According to the Right Hemisphere Hypothesis (RHH), the right hemisphere is specifically deputy to the elaboration of emotional content (Borod et al., 1998; Schwartz et al., 1975); instead, the Valence-Specific Hypothesis (VSH) argued that both hemispheres process emotion, and that each hemisphere is specialized for valence-specific emotion: with left hemisphere more dominant for positive, and right hemisphere for negative emotions (Ahern & Schwartz, 1979; Balconi & Lucchiari, 2006; Balconi & Mazza, 2010; Balconi & Pozzoli, 2009; Davidson, 1992, 1993).

So, what is the relationship between the hemispheric activation, emotional value of pain, and emotional regulation? Secondly, which is the role of interoception? Does it work as a sort of amplifier of the emotional response to pain?

From a methodological perspective, however, nor the classical imaging (with functional Magnetic Resonance Imaging, fMRI) nor the electrophysiological measure alone seem to completely describe in depth the nature of empathy for pain experience and its interoceptive correlates. Although studies have provided functional images of activated areas of the brain associated with emotional tasks, they have seldom addressed the temporal course of the activation. Due to its fast temporal evolution and its representation and integration among complex, widespread neural networks, the emotion perception should preferably be examined employing imaging methods that offer good resolution in both temporal and spatial domains. Moreover, classic neuroimaging techniques, such as fMRI and magnetoencephalography have some limitations, such as the level of invasiveness, they are highly expensive and subject to movement artifacts.

Therefore, thirdly, a more suitable approach could combine EEG/fNIRS measurements that allow for the complementary examination of neural as well as hemodynamic aspects of brain activation with a good temporal and spatial resolution (Biallas et al., 2012). Indeed, fNIRS is particularly well-suited for evaluating the prefrontal cortex (PFC) activity in terms of hemodynamic variations related to emotional processing (Balconi et al., 2015), and empathy for pain (Balconi et al., 2020; Xie et al., 2018). Despite the low time resolution if compared to an electroencephalogram (EEG), the fNIRS system has a good spatial resolution, a low sensitivity to body movements, it is portable, easy to use, non-invasive, and makes possible for participants to view stimuli in a more naturalistic way. It is a relatively low-cost tool, suitable for exploratory neuroscientific studies that aim to identify cortical regions involved in perceptual, cognitive, and emotional processes. In addition, previous research showed that fNIRS is successful at discriminating cortical response to painful stimuli in healthy individuals (Yücel et al., 2015).

Regarding the main advantages of EEG application, in a previous study, specifically increased theta band oscillations were found for the observation of painful stimuli (Mu et al., 2008). Specifically, the theta band positively correlated with subjective ratings of perceived pain and self-unpleasantness, suggesting that theta oscillations are involved in emotional sharing during empathy for pain (Mu et al., 2008). Theta rhythm modulation was also associated with affective valence discrimination of visual displays (Aftanas et al., 2001, 2003; Balconi et al., 2015; Balconi & Lucchiari, 2006; Balconi & Pozzoli, 2005, 2007, 2009), activation of memory and emotion regulation systems (Knyazev, 2007). In contrast, exiguous data concern the modulation of the delta and beta bands when considering the emotional significance of a stimulus (Karakaş et al., 2000). In some previous studies, it was shown that delta could be a marker of the novelty of the emotional cues and that it can respond to the exigency of stimulus updating in memory (Fernandez et al., 1995).

Thus, to explore IA impact on the cortical correlates of observation of pain in others, a fNIRS and EEG paradigm was performed to assess participants' hemodynamic and electrophysiological frontal activity while viewing painful and non-painful stimuli, in two different conditions: direct and indirect IA focus, respectively requested to the experimental (EXP) and control (CTR) group. In this research, EEG frequency bands were recorded simultaneously with fNIRS measurements as potential biological markers of interoceptive correlates of empathy for pain.

Finally, these multiple measures were then related to a self-report empathy measure. Indeed, an important factor that may contribute to explain the way individuals modulate IA and empathy for pain may depend on intrinsic personality factors such as empathic abilities. Subjects were required to complete the Interpersonal Reactivity Index (IRI) scale (Davis, 1983), to assess their empathic concern and interpret their responsiveness to the affective induction. Regarding the link with interoception, a recent study reported no association between Interoceptive Awareness (IAw) and IRI questionnaire as a measure of general empathy (Ainley et al., 2015); in contrast, other research reported correlations between IAw and the IRI Perspective Taking (PT) subscale (Tajadura-Jiménez & Tsakiris, 2014) and found that participants with good IAw, who viewed pictures of people in painful situations, rated the pain as greater and felt more compassion for the sufferer, although they reported no greater PD than controls (Grynberg & Pollatos, 2015). This result was interpreted as greater emotional arousal and affect sharing reported by the participants with high IAw (Grynberg & Pollatos, 2015). Nonetheless, to our knowledge, available current literature mainly focuses on IAw and interoceptive sensitivity, but not on IA. Conversely, we aim to test the presence of significant relations between empathic traits and prefrontal cortical responsiveness in subjects modulating IA.

Specifically, this study aims to show how the modulation of IA may impact the cortical correlates of observation of pain in others.

Given these premises, in the present study, we expect an amplification of the negative effect of pain observation for the EXP group compared to the CTR group, since the explicit attention on interoceptive correlates could direct the focus on negative emotional experiences (Mumford et al., 1991; Weiss et al., 2014).

Secondly, we expect the EXP group would display a higher activation of frontal areas, that, based on valence and lateralization effects of emotions (Balconi & Mazza, 2010; Ochsner et al., 2012; Russell, 2003), could be significant for the right hemisphere sensitive to the negative emotional valence of the observation of painful stimuli, compared to the CTR group.

Thirdly, we hypothesize a parallel modulation of the EEG/fNIRS response, with a positive correlation between EEG low-frequency bands and right frontal activity during the observation of painful stimuli for the EXP group. On the contrary, for the CTR group, we expect a positive correlation between low-frequency bands and left frontal activity for non-painful stimuli, signaling a possible positive experience related to non-painful stimuli together with the reinterpretation processing of the affective response (Ochsner et al., 2012).

Fourthly, we suppose a relationship between individual differences such as the empathic traits measured with IRI and frontal activity during the observation of pain in others, for which higher empathic abilities could down-modulate the negative effect of pain experience at the neural level.

2. Methods

2.1 Sample

Twenty healthy participants (1 male, M_{age} = 22.87; SD_{age} = 2.31) took part in the research. Exclusion criteria were physiological condition of chronic or acute pain, major medical and chronic illnesses, seizures, traumatic brain injury, pregnancy, and any psychiatric or neurologic disorder. Included participants had a normal-to-corrected vision and were right-handed. They were randomly assigned to experimental (EXP) and control (CTR) group condition and balanced for age (M_{EXP} = 23.78; SD_{EXP} = 2.88; M_{CTR} = 22.66; SD_{CTR} = 1.55). Written informed consent was provided by all participants before the experiment. They received no compensation for taking part in the research. This research was approved by the Department of Psychology of the Catholic University of the Sacred Heart of Milan, Italy, and conducted in accordance with the Declaration of Helsinki.

2.2 Heartbeat Detection Task (HBD)

To control IS, all participants underwent the measure of their heartbeat perception ability by performing the Mental Tracking Method (Schandry, 1981), which has been proven to have good test-retest reliability (Ricciardi et al., 2016). Participants were seated in a sound-attenuated room and their heart rate was measured by applying a physiological recording tool. Signal was sampled at 500 Hz and analysed by a computer-based data acquisition system (Biofeedback Xpert 2000, version 7.01, Schufried GmbH, Mödling, Austria).

Participants were instructed to start silently counting their heartbeat when a visual start cue would appear on a pc screen (grey desktop) until they received a visual stop cue. After a brief 15 s test session, the HBD task experimental phase began. The experimental phase of this task consisted of four different time intervals of 25 s, 35 s, 45 s, 100 s, presented randomly across participants. They were requested to type in the number of heartbeats counted at the end of each interval. During the task, participants were not allowed to take their pulse, and no feedback on the counting phases length on their performance quality was provided.

ISI was derived from the HBD task by calculating the mean of the four heartbeat perception intervals according to the formula of Schandry (1981):

$$\frac{1}{4}\sum(1-(|\text{recorded heartbeats}-\text{counted heartbeats}|)/\text{recorded heartbeats})$$

According to this formula, the ISI can vary between 0 and 1 with higher scores indicating small differences between counted and recorded heartbeats.

2.3 Stimuli

Thirty-two pictures showing a person (male or female, opportunely randomized) receiving a painful (needle penetration) or non-painful (Q-tip touch) stimulation composed the set of stimuli (Figure 1). Each picture, subtending a visual angle of 21° × 17° (width × height) at a viewing distance of 80 cm, lasted 5 s and depicted individuals with facial neutral expressions. The stimuli were checked for the following perceptual characteristics: position, size, brightness, and content. A pool of independent judges, controlled for gender and age, evaluated the emotional neutrality of the stimuli by using an easier adapted 5-point version of the Self-Assessment Manikin scale (SAM) (Bradley & Lang, 1994). Selected stimuli were validated for emotional features and were rated with average values for emotional valence (*M* = 2.50; *SD* = 0.52) and arousal (*M* = 2.60, *SD* = 0.36).

2.4 Procedure

Subjects were seated in a dimly lit room, in front of a computer monitor that was placed about 70 cm from the subject. The stimuli were presented using E-Prime 2.0 software (Psychology Software Tools Inc., Sharpsburg, PA, USA) running on a personal computer with a 15-inc screen, with a visual horizontal angle of 4° and a vertical angle of 6°. A standardized set of instructions were used to explain the procedure to each participant.

Participants were required to observe each stimulus during cortical EEG oscillations recording. The sample, previously differentiated into the experimental (EXP) and control (CTR) group, was required to observe each stimulus and then was asked to evaluate stimuli observed by pressing on the computer keyboard the letter "K" for pain stimuli and "L" for no-pain stimuli. After each stimulus, participants were instructed to provide the behavioral response by pressing keyboard buttons using the right index or middle finger. The EXP group was also explicitly required to focus on its interoceptive changes while observing the stimuli and received the following instruction "*During this task, we ask you to focus your attention on your bodily sensations (such as the breath). Try to observe how you feel and if there are any variations in your body as you look at the pictures*.". While the CTR group received the general instruction to observe the stimuli and evaluate them for pain and no-pain, therefore controls were not explicitly required to focus their attention on their interoceptive correlates.

Pictures were presented in a random order in the centre of a computer monitor for 5 s, with an inter-stimulus interval of 10 s during which participants fixed at a central cross. The order of stimulus presentation was counterbalanced to prevent potential biases due to sequence effects. The total of 160 stimuli was divided into four blocks counting 40 stimuli each. Following the disappearance of the stimulus from the monitor, during the interval, participants could provide the behavioral response for painful/non-painful stimulus features.

Potential differences in Interoceptive Sensitivity were assessed by applying the Heartbeat Detection task (Schandry, 1981) to all participants. This task was proposed after the previous task in order to avoid effects at the interoceptive level on the two groups of participants. Finally, subjects were asked to complete the IRI questionnaire and the manipulation checks.

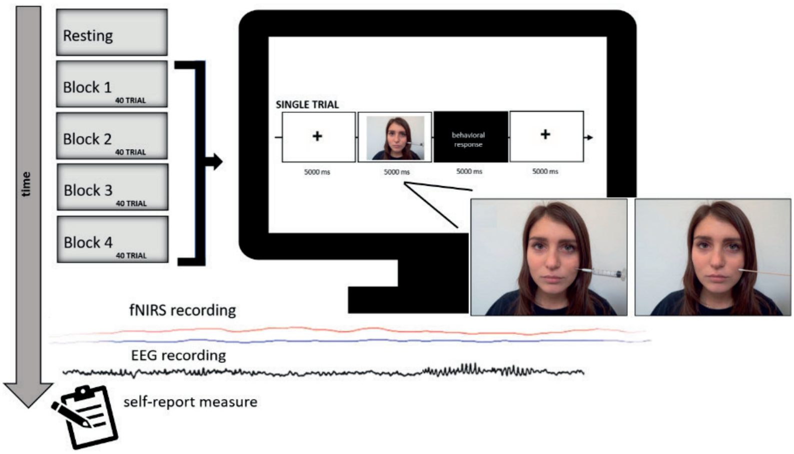

Figure 1. Experimental procedure. Experimental setting with EEG and fNIRS recording during observation of pain in others' task performance and self-report measure (IRI) administration at the end of the procedure. In the figure, samples of stimuli used in the study for painful (left) and non-painful (right) stimulation were shown

2.5 Interpersonal Reactivity Index measure

The Italian version of the interpersonal reactivity index (IRI) was used (Albiero et al., 2006; Davis, 1980) to measure both cognitive and emotional components of empathy and consists of 28-item answered on a 5-point Likert scale. The measure has 4 subscales, each made up of 7 items. The fantasy scale (FS) measures the tendency to transpose oneself into fictional situations; the empathic concern scale (EC) assesses the tendency to experience compassion for unfortunate others; the perspective-taking scale (PT) measures the tendency to adopt the psychological point of view of others; the personal distress scale (PD) taps the tendency to experience discomfort in response to extreme distress in others. (EXP group. FS: 15.27; *SD* = 3.46. EC: 13.73; *SD* = 1.90. PT: 16.36; *SD* = 2.87. PD: 13.27; *SD* = 3.16. CTR group. FS: 13.89; *SD* = 2.36. EC: 13.44, *SD* = 2.12. PT: 14.78; *SD* = 3.52. PD: 13.00; *SD* = 3.24).

2.6 EEG recording and reduction

EEG activity was recorded via an EEG wireless System (Live-Amp) and processed via Analyzer2 software (Brain Products GmbH, Gilching, Germany). The montage included 15 active electrodes (Fp1, Fp2, AFF3h, Fz, AFF4h, T7, C3, Cz, C4, T8, P3, Pz, P4, O1, O2; placement according to the 10-20 International System (Jasper, 1958). Electrodes impedance was monitored for each subject prior to data collection and kept under 5 kΩ. Data were acquired using a sampling rate of 250 Hz and then filtered offline with a 0.5 - 45 Hz IIR bandpass filter (slope: 48db/octave). Data were then segmented and visually inspected for ocular, muscle, and movement artifacts. Fast Fourier Transform (Hamming window, resolution: 0.5 Hz) was applied to artifact-free segments to compute the average power spectra. Finally, the average power for the main EEG frequency bands (Delta - 0.5-3.5 Hz, Theta - 4-7.5Hz, Alpha – 8-12.5 Hz, Beta - 13-30 Hz) was extracted. 120 seconds resting baseline was registered at the beginning of the experiment before the picture series.

To explore the frontal contribution of interoception for pain representation, in the statistical analysis of the data, frontal electrodes were divided for left (Fp1, AFF3h) and right hemisphere (Fp2, AFF4h).

2.7 fNIRS acquisition and analysis

A NIRScout System (NIRx Medical Technologies, LLC. Los Angeles, California) with a 14-channel optodes matrix was used to record hemodynamic responses consisting of a variation of oxygenated hemoglobin (O2Hb) and deoxygenated hemoglobin (HHb) concentrations. Through the adoption of a fNIRS Cap, 8 light sources/emitters and 8 detectors were positioned over the scalp according to the international 10/5 system (Oostenveld & Praamstra, 2001). The eight emitters were placed on the following positions: AF3-AF4, F5-F6. While detectors were placed on AFF1h-AFF2h, F3-F4. Emitter-detector distance was kept at 30mm for contiguous optodes and near-infrared light of two wavelengths (760 and 850 nm) was used. In this way, the following channels were acquired: Ch1 (AF3-F3), Ch2 (AF3-AFF1h), Ch3 (F5-F3), Ch4 (AF4-F4), Ch5 (AF4-AFF2h), Ch6 (F6-F4) correspond to the left and right DLPFC (Brodmann Area 9, BA9) (Figure 2). To associate our locations to Brodmann coordinates, we considered sources and detectors' positions, as well as the area between them, which includes the channel. Then, we looked for the best underlying functional region and the more fitting Brodmann Area. To do so, we combined several references and online atlases (see for example Giacometti et al., 2014; Koessler et al., 2009).

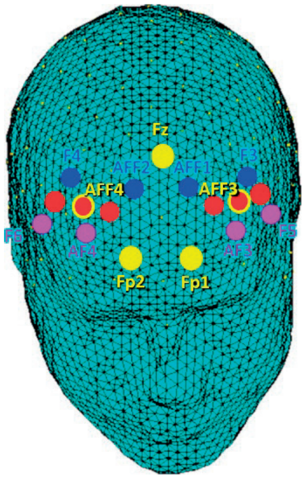

Figure 2. Locations of measurement channels. fNIRS: Location of the sources (violet) and detectors (blue) of fNIRS montage. Sources were located in the following positions: AF3-AF4, F5-F6. Detectors were placed on: AFF1h-AFF2h, F3-F4. The following 6 channels (red) were acquired: Ch1 (AF3-F3), Ch2 (AF3-AFF1h), Ch3 (F5-F3), Ch4 (AF4-F4), Ch5 (AF4-AFF2h), Ch6 (F6-F4).
EEG: EEG activity was recorded from channels on the following positions: AFF3, AFF4, Fz, AFp1, AFp2, C3, C4, Cz, P3, P4, Pz, T7, T8, O1, O2 (yellow dots). fNIRS optodes and EEG channels were attached to the subject's head using a NIRS-EEG compatible cup, with respect to the international 10/5 system

With NIRStar Acquisition Software, changes in the concentration of oxygenated (O2Hb) and deoxygenated hemoglobin (HHb) were recorded continuously throughout the task, starting from a 120 s resting baseline. Signals obtained from the 14 NIRS channels were acquired with a sampling rate of 6.25 Hz and analyzed and transformed with nirsLAB software (v2014.05; NIRx Medical Technologies LLC, 15Cherry Lane, Glen Head, NY, USA), according to their wavelength and location, resulting in values for the changes in the concentration of oxy and deoxygenated hemoglobin for each channel, scaled in mmol*mm. The raw O2Hb and HHb data from each channel were digitally band-pass filtered at 0.01–0.09 Hz (Pinti et al., 2019). Then, the mean concentration of each channel was calculated by averaging data across the trials, an average value for each condition was calculated starting from the stimulus onset presentation for the following 5 s. According to the mean concentrations in the time series, the effect size in every condition was calculated for each channel and subject. The effect sizes (Cohen's d) were calculated as the difference of the means of the baseline and trial divided by the standard deviation (sd) of the baseline: D= (m1-m2)/s, with m1 and m2 being the mean concentration values during baseline and trial, respectively, and s the SD of the baseline. Then, the effect sizes obtained from the 6 channels were averaged to increase the signal-to-noise ratio. Although fNIRS raw data were originally relative values and could not be directly averaged across subjects or channels, effect sizes normalized data could be averaged regardless of the unit since the effect size is not affected by differential pathlength factor (DPF).

In the statistical analysis of the data, factors such as the two Regions of Interest (ROI) grouping the Frontal (F) left/right homologous channels and the lateralization (left/right hemisphere) were considered. Specifically, for Frontal ROI the values obtained from Ch1-Ch2-Ch3 and Ch4-Ch5-Ch6 were averaged as representative of the activity of the left and right, respectively, DLPFC areas.

3. Results

3.1 Interoceptive Sensitivity Index (ISI)

An independent-samples *t*-test was applied to control ISI homogeneity between groups. The threshold for statistical significance was set to $\alpha = 0.05$. Equality of variances between groups was checked by Levene's test was computed to test homogeneity of variances between the two groups and to adapt the computation of subsequent inferential tests accordingly. No significant differences were found in the ISI measure between the two groups (M_{EXP} = 0.50; SD_{EXP} = 0.24; M_{CTR} = 0.50; SD_{CTR} = 0.17) (all $p > 0.05$).

3.2 Self-report measure (IRI)

An independent-samples *t*-test was applied to IRI scores to control individual differences in empathy traits between groups. No significant differences were found between the two groups (all $p > 0.05$).

3.3 Behavioral results

Response accuracies were calculated as the percentage of correct responses on the total responses for pain/non-pain stimuli and were high for both groups.

During the pain judgment, the accuracy for painful stimuli was 99% for EXP and 96% for the CTR group, while concerning non-painful stimuli was 99% for the EXP and 100% for the CTR group. A two-factor mixed ANOVA (IBM SPSS 25) with Pain (2: Pain, No Pain) as within factor, and as between factor the Group (2: EXP, CTR) was performed. No significant results were found between the two groups (all $p > 0.05$).

3.4 Correlation analyses

Pearson's correlation analysis was applied to O2Hb and EEG bands values, in every condition, for frontal ROI, with respect to IRI scores.

3.4.1 EEG and O_2Hb

Firstly, a significant positive correlation between theta band and O2Hb in the right frontal side for painful in the EXP group was found ($r = .561$; $p = .002$) (Figure 3a). Secondly, a significant correlation between delta band and O2Hb in the left frontal hemisphere for non-painful stimuli was detected in CTR group ($r = .601$; $p = .001$). No other significant correlations were found (Figure 3b).

3.4.2 IRI and O_2Hb

For the EXP group, a first significant negative correlation was found ($r = -.818$; $p = 0.002$) between IRI Empathic Concern and right frontal area for painful stimuli (Figure 3c). In this group, also IRI Perspective Taking subscale negatively correlates with the right frontal region for painful stimuli ($r = -.662$; $p = 0.026$) (Figure 3d). No other significant correlations were found.

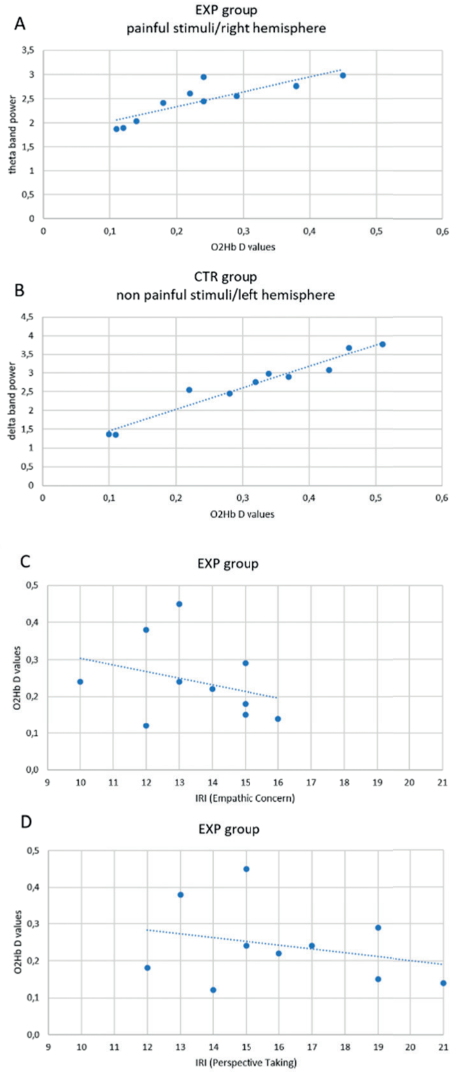

Figure 3a-d. Scatter plots of correlational analyses (a-b) between hemodynamic and EEG measures, and (c-d) between hemodynamic right frontal activity for painful stimuli and IRI subscales in the EXP group. Each dot corresponds to a single participant

4. Discussion

The present study provided new insights on the way interoception may affect the representations of observing others in painful conditions and its effect at the cortical level, by using EEG-fNIRS co-registration and self-report measures. The modulation of IA was previously supposed to influence neural correlates of observation of pain in others and empathy for pain. However, to the best of our knowledge, this aspect was not tested with neurophysiological protocols so far.

In this research, the following main results were obtained: firstly, a significant positive correlation was found between theta band and O2Hb in the right frontal side during the observation of painful stimuli in the EXP group. Secondly, a significant positive correlation between delta band and O2Hb in the left frontal hemisphere for non-painful stimuli was detected in the CTR group. Thirdly, correlational analyses between questionnaires and hemodynamic activity revealed a negative correlation between IRI (PT and EC) and right frontal activity in the EXP group.

Firstly, a significant correlation was found between the theta band and O2Hb in the right frontal side during the observation of painful stimuli in the EXP group.

Theta band underlies mechanisms for cognitive control over the situation (Cavanagh & Frank, 2014), alertness, attention, and readiness to process the presence of emotional information (Aftanas et al., 2001, 2003; Balconi et al., 2015; Balconi & Lucchiari, 2006; Balconi & Pozzoli, 2007, 2009), activation of memory and emotion regulation systems (Knyazev, 2007). Also, theta duration was interpreted as a correlate of increased attention and arousal due to the emotional content of the stimulus (Balconi & Lucchiari, 2006). Frontal theta band modulation has been previously shown to be related to cognitive control over salient emotional stimuli (Balconi et al., 2015) and to the affective and motivational evaluation of pain in others (Apkarian et al., 2005; Hauck et al., 2008; Tracey & Mantyh, 2007).

Regarding the right-side hemodynamic activation, a previous study demonstrated the increased activity of anterior cortex and insula in the right hemisphere in association with negative images during fast breathing, in contrast, increased insular and cingulate activation was found in the left hemisphere in association with positive images during slow breathing (Strigo & Craig, 2016). Moreover, right DLPFC has been related to the downregulation of self-pain perception (Boggio et al., 2008; Lorenz et al., 2003; Rêgo et al., 2015) and this modulation seems to be associated with its main function on general emotional regulation processes, such as cognitive reappraisal, attention modulation of affective responses and psychological distancing from the emotional stimulus (Ochsner et al., 2012).

Our finding could be interpreted as the distinctive effect of IA modulation that leads the EXP group focused attention mainly on painful unpleasant stimuli. In this group, the right hemisphere prevalent hemodynamic response together with theta band increase suggested empathy for pain as a negative experience.

As a second result, a significant positive correlation between delta and O2Hb in the left frontal hemisphere for non-painful stimuli was detected in the CTR group.

So far, there is little evidence on the modulation of the delta band when considering the emotional significance of a stimulus (Karakaş et al., 2000). However, in some previous studies, it was shown that delta could be a marker of the novelty of the emotional cues and that it can respond to the exigency of stimulus updating in memory (Fernandez et al., 1995). Knyazev and colleagues (2009) showed theta and delta synchronization as a marker of emotion processing. Regarding the left hemisphere activation, previous neuroanatomical models of emotional brain activity (functional and EEG) asymmetry concluded that positive/negative valence, approach/withdrawal behavior, and/or affiliative/personal relevance are associated with left/right hemispheric forebrain activity, respectively (Allen & Kline, 2004; Davidson, 2004; Murphy et al., 2003; Wager et al., 2003). Recently Craig has extended this model to the homeostatic activity and proposed that the left/right forebrain is associated predominantly with parasympathetic/sympathetic activity, and the previously mentioned positive/negative emotions components (Craig, 2008).

Since in the CTR group, the attention was directed towards the non-painful condition, and a left-lateralized hemispheric activation was found, it can be suggested this result could represent a positive emotional response mainly towards non-painful stimuli. Therefore, it could be plausible IA renders negative experiences (painful ones) more salient, while a normal condition (control) emphasizes positive aspects of the experience (no pain). Interception can be conceived as a system that allows us to share the negative experiences of others, not only as our alarm system related to our experience of pain. But it can be conceived as a "social" sharing system of pain, therefore a social alarm system that interoception is able to modulate.

Thirdly, correlational analyses between questionnaires and hemodynamic activity revealed a negative correlation between IRI (specifically Perspective Taking and Empathic Concern subscales) and right frontal responsiveness in the EXP group.

This evidence seems to confirm the trend described above: participants with low IRI PT that are focusing on their interoceptive correlates can experience an increase of the negative echo of painful stimuli. Perhaps it means that individuals amplify the negative perception of pain as an automatic (not controllable) mechanism: without assuming the perspective of the other's suffering. Does it mean this is not a genuine empathic processing?

The same effect was found for the empathic concern dimension: participants belonging to the EXP group with low IRI empathic concern scores displayed a higher right frontal activation. If the empathic concern for others covers a marginal role, then the right frontal activation becomes a pure reaction to the pain that is amplified by IA. It is possible that this is not a real empathic mechanism?

A possible explanation could be that this could be a defense mechanism: when individuals do not empathize with the situation, an alarm mechanism is triggered, that warns the person facing the nearly extraneous condition. By not taking the other perspective, they could not have the resources to control this automatic response, that is an automatic mirroring, a primordial negative response to the painful condition. Less cognitive empathy abilities may lead to mirroring automation of the situation *(*e.g., you cry, and I cry).

Additionally, the focused attention on the bodily responses leads an individual to feel more the negative echo of pain observation in others, as suggested by previous studies on anxiety disorder (Mumford et al., 1991), thus suggesting a possible association between the interoceptive experience and the negative valence of the emotional response for instance to unpleasant conditions or painful stimuli.

However, when the focus is on the self, individuals could be less responsive to the external world and others. Thus, the alarm is triggered for us, not because we are feeling the pain ourselves, but because we predict that we could feel the same as the person we are observing. We just see ourselves in the other, without the experience of social empathy. In this study, this effect emerged in the EXP group: it is a useful mechanism for our survival, but it is not a genuine social empathic response.

Another possible explanation is that if individuals focusing on the interoceptive correlates (EXP) have high scores of IRI empathic concern and IRI perspective-taking then they could be able to reduce the negative experience of pain (decreases of O2Hb in the right frontal activation). Conversely, subjects with lower empathic traits scores display an increase in the perception of pain as a negative experience. Therefore, IA could be seen also as an amplifier of the good (or bad) ability to self-regulate the empathic response to others pain, which in the context of the observation of pain in others promote the downregulation (with a decrease of O2Hb in the right frontal hemisphere) or, on the contrary, the increase (higher O2Hb right frontal activation) of the negative experience of pain.

In line with this, Weiss and colleagues (2014) showed that in healthy participants better detection of internal signals and evoked bodily changes seems to facilitate pain perception arguing IS facilitates successful self-regulation by providing a fine-tuned feedback of the actual emotional state across a variety of bodily variables. This assumption is in accordance with further data showing that IS is associated with better emotion regulation in response to negative affect (Füstös et al., 2012). Interoceptive processes might therefore modulate the relationship between bodily responses, affective and cognitive variables which are in accordance with the pivotal role in introduced concepts of embodied cognition.

5. Conclusion

To summarize, the present study highlighted that in participants focusing on their interoceptive correlates there is a relation between the emotional representation of painful stimuli, highlighting their negative and unpleasant features, as reflected by the concomitant presence of theta band and prefrontal right hemisphere activation. On the other hand, controls showed a positive association between delta band and left hemisphere responsiveness when observing non-painful stimuli, plausibly signalling the emotional response to positive cues.

Moreover, in the EXP group, an association between empathic abilities (perspective-taking and empathic concern) and right DLPFC activation for painful stimuli was found, suggesting subjects with lower empathic traits scores display an increase in the perception of pain as a negative experience. An alternative explanation is that when focusing the interoceptive correlates (EXP) individuals with high scores of IRI empathic concern and IRI perspective taking could be able to reduce the negative experience of pain (decreases of O2Hb in the right frontal activation). Future research is needed to clarify this relationship.

Besides, such multimethod protocol could be further expanded, and future studies could explore both the IA effect induced by the central system on the peripheral autonomic system, by measuring and monitoring the temporal dynamics of this relationship.

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