Research Report

Visual similarity and psychological closeness are neurally dissociable in the brain response to vicarious pain

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ABSTRACT

Personal and vicarious experience of pain activate partially overlapping brain networks. This brain activity is further modulated by low- and high-order factors, e.g., the perceived intensity of the model's pain and the model's similarity with the onlooker, respectively. We investigated which specific aspect of similarity modulates such empathic reactivity, focusing on the potential differentiation between visual similarity and psychological closeness between the onlooker and different types of models. To this aim, we recorded fMRI data in neurotypical participants who observed painful and tactile stimuli delivered to an adult human hand, a baby human hand, a puppy dog paw, and an anthropomorphic robotic hand. The interaction between type of vicarious experience (pain, touch) and nature of model (adult, baby, dog, robot) showed that the right supramarginal gyrus (rSMG) was selectively active for visual similarity (more active during vicarious pain for the adult and baby models), while the anterior cingulate cortex (ACC) was more sensitive to psychological closeness (specifically linked to vicarious pain for the baby model). These findings indicate that visual similarity and psychological closeness between onlooker and model differentially affect the activity of brain regions specifically implied in encoding interindividual sharing of sensorimotor and affective aspects of vicarious pain, respectively.

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1.   Introduction

Observing others in pain triggers in the onlooker an internal simulation of the observed state which induces feelings similar to those occurring when experiencing pain in first-person (Betti & Aglioti, 2016; Keysers & Gazzola, 2009; Preston & de Waal, 2002). This form of vicarious pain lays the foundations of a psychological construct broadly referred to as empathy: a complex set of affective, motivational, and cognitive processes that play a key role in social interaction (Davidov, Zahn-Waxler, Roth-Hanania, & Knafo, 2013; Feldman, 2017; Kim, Strathearn, & Swain, 2016). Empathic responses seem independent from the sensory modality exploited by the onlooker, as both acoustically- and visually-driven vicarious pain activate neurophysiologic circuitries partially overlapping with those involved in processing first-person experiences of pain (Hipwell, Guo, Phillips, Swain, & Moses-Kolko, 2015; Jean Decety, 2015; Liu et al., 2019). The overlapping brain activity within specific nodes of the so-called "pain matrix" (including mainly the sensory, insular, and cingulate cortices; Iannetti & Mouraux, 2010) during physical and vicarious pain (Jackson, Meltzoff, & Decety, 2005; Lamm, Batson, & Decety, 2007; Xu, Zuo, Wang, & Han, 2009) has been proposed as the neural counterpart of the ability to "perceive" others' pain and "feel" their emotional reaction (J. Decety, 2011). Originally, empathy for pain has been attributed to the activation of the affective nodes of the pain matrix like the insular and cingulate cortices (Lamm, Decety, & Singer, 2011; Morrison, Lloyd, di Pellegrino, & Roberts, 2004; T.; Singer et al., 2004; T.; Singer et al., 2006). However, it is now held that empathic response can also activate the brain regions encoding the somatosensory-discriminative features of pain, including somatosensory, motor, and sensorimotor regions (Akitsuki & Decety, 2009; Avenanti, Bueti, Galati, & Aglioti, 2005; Avenanti, Minio-Paluello, Bufalari, & Aglioti, 2009; Avenanti, Minio-Paluello, Sforza, & Aglioti, 2009; Aziz-Zadeh, Sheng, Liew, & Damasio, 2012; Bufalari, Aprile, Avenanti, Di Russo, & Aglioti, 2007; Bufalari & Ionta, 2013; Novembre, Zanon, & Silani, 2015; Saarela et al., 2007; Voisin, Marcoux, Canizales, Mercier, & Jackson, 2011).

Far from being a discrete phenomenon, the reactivity to others' pain is sensitive to a number of personal factors. Contextually to the experimental settings, the onlooker's empathic reactivity can be modulated by her/his perception of the models' fairness (T. Singer et al., 2006), reputation (Zheng et al., 2016), attractiveness (Jankowiak-Siuda, Rymarczyk, Zurawski, Jednorog, & Marchewka, 2015), as well as by how much intense s/he evaluate the model's experience of pain (Avenanti, Minio-Paluello, Bufalari, & Aglioti, 2006; Lamm, Nusbaum, Meltzoff, & Decety, 2007). In addition, empathic reactivity is influenced also by the onlooker's pre-existent personality traits (Avenanti, Minio-Paluello, Bufalari, & Aglioti, 2009; Jabbi, Swart, & Keysers, 2007; Lawrence et al., 2006; Minio-Paluello, Baron-Cohen, Avenanti, Walsh, & Aglioti, 2009) and previous experience with the feelings contextually attributed to the model in pain (Cheng et al., 2007). Importantly, also the similarity between the onlooker and the model in pain is of fundamental importance for shaping empathic reactivity. For instance, belonging or not to the same social group on the basis of ethnicity (Avenanti, Sirigu, & Aglioti, 2010; R. T.; Azevedo et al., 2013; Mathur, Harada, Lipke, & Chiao, 2010), body weight (Ruben Teixeira Azevedo, Macaluso, Viola, Sani, & Aglioti, 2014), or mental states (Majdandzic, Amashaufer, Hummer, Windischberger, & Lamm, 2016), modulates the behavioral and the neural reactivity to the observation of others in pain. The influence of the onlooker/model similarity has been repeatedly confirmed with a variety of neuro-investigation techniques, including electroencephalography (Contreras-Huerta, Hielscher, Sherwell, Rens, & Cunnington, 2014; Perry, Bentin, Bartal, Lamm, & Decety, 2010; Sheng & Han, 2012), functional magnetic resonance (fMRI) (R. T. Azevedo et al., 2013; Lamm, Meltzoff, & Decety, 2010; Lamm, Nusbaum, et al., 2007), and transcranial magnetic stimulation (Avenanti et al., 2010).

Nevertheless, much less is known about how this onlooker/model link is influenced by the different instances of similarity, which can vary from inherently physical properties (e.g., the shape of the body - *visual similarity*) to higher-order psychological dimensions (e.g., attribution of a mind to the model, his/her supposed sufferance, his/her humanness or closeness to the onlooker - *psychological closeness*).

The main aim of the present study was to investigate the influence of visual similarity and psychological closeness on the modulation of the neuro-behavioral empathic response to the observation of others in pain. To this aim, we recorded fMRI data while healthy human participants (adults) observed tactile and painful stimulation delivered to four different models: the hand of an adult; the hand of a human baby; the paw of a dog puppy; an anthropomorphic robotic hand. We hypothesized that psychological closeness would take into account the humanity-related properties of the model and, therefore, may bring about a different pattern of neural reactivity where adult and baby are coded together (despite visually different) and separately from the dog puppy and robotic hand.

2.   Methods

No part of the study procedures and analyses were pre-registered prior to the research being conducted. We report how we determined our sample size, all data exclusions, all inclusion/exclusion criteria, whether inclusion/exclusion criteria were established prior to data analysis, all manipulations, and all measures in the study. In order to guarantee confidentiality, queries by readers seeking access to the data should be submitted to and will be evaluated by the corresponding author(s), access to data may be granted to named individuals in accordance with the study's procedures governing the reuse of sensitive data, and any potential reuse should be subject to completion of a formal data sharing agreement/contract.

2.1.   *Participants*

Taking into consideration the risks of evaluating statistical power based only on the sample size, as well as the related dangers associated with both too large (K. Friston, 2012) and too small samples (Button et al., 2013), we included fourteen

healthy right-handed volunteers in the study (8 females; 23.6 ± 2.5 y.o.) and we computed the effect size (Cohen's d) for each significant effect. According to the inclusion criteria, all participants were adult, had normal vision, and were naive as to the purposes of the experiment. Exclusion criteria included previous history of neuropathology, drug abuse, contraindications to the experimental procedures. No participant met the exclusion criteria. All included participants signed the informed consent prior to the experiment. The study was approved by the local Ethics Committee and was conducted in accordance with the 1964 Declaration of Helsinki and its following amendments.

2.2. Stimuli and procedure

During fMRI recording, participants observed sets of different videos according to the following conditions. During the "Pain" condition, the dorsal view of a limb was deeply penetrated by a hypodermic syringe. During the "Touch" condition, the same limb was touched by the back of the syringe. During the "Control" condition, participants observed a static limb, without moving syringe. Four models of limb were used: human adult hand, human baby hand, anterior leg of a dog puppy, anthropomorphic robotic hand. The syringe was not held by anyone (Fig. 1). Each video lasted 4s with a 0.5s period of white screen between two subsequent videos. Videos were
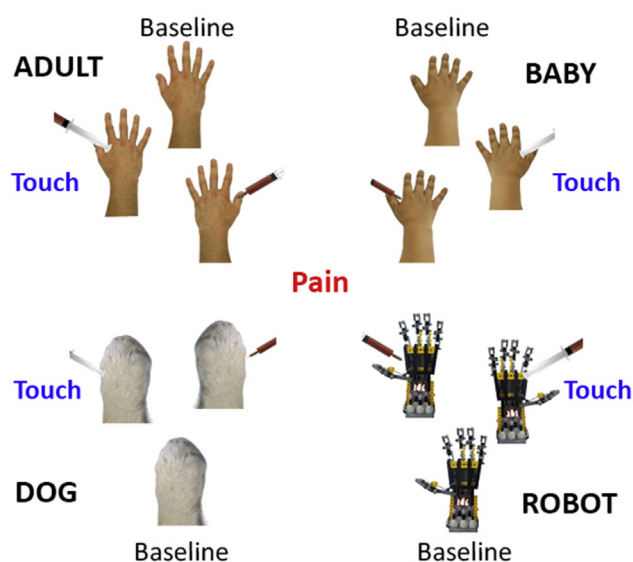

Fig. 1 — Stimuli. Snapshots of the videos for each combination of two Stimuli [Pain (center of figure) and Touch (left and right sides of the figure)] and four Models [Adult (top left), Baby (top right), Dog (bottom left), and Robot (bottom right)]. For one model at a time, during fMRI data recording participants observed videos of the model's limb either being pinpricked by a syringe (pain) or being touched by the back of the syringe (touch). The resulting brain activity was controlled for the neural response elicited by mere observation of non-stimulated limbs (Baseline; top and bottom sides of the figure). The syringe varied in terms of size and color, but for illustrational purposes the figure shows only the big red syringe.

organized in blocks lasting 13.5s, each comprising three videos belonging to the same condition (Pain, Touch, or Control). To minimize habituation effects, the videos showed two syringes differing in terms of size and color. Blocks of Pain and Touch videos were presented in a fixed pseudo-randomized sequence and counterbalanced across participants. A block of Control was presented after each Pain or Touch block. Each participant underwent four consecutive fMRI data acquisition runs, each comprising 32 blocks (8 Pain, 8 Touch, and 16 Control blocks). Participants were instructed to carefully watch the videos without any explicit request to empathize with the model. To avoid distraction, they were informed that they would be asked questions about the content of the videos at the end of the experiment.

2.3. State-empathy

After the fMRI session we administered four measures of self- and other-oriented state-empathy, concerning the "sensory" and "affective" properties of the observed videos (Pain and Touch), plus two control measures. In particular, each participant was shown a picture of each model (adult, baby, dog puppy, robot) in each condition (Pain, Touch) and was asked to provide ratings concerning to six questions (Qs) - along a ten-point Likert scale (0–9) where 0 represented the minimum and 9 the maximum (Table 1). One-sample t-tests were used to directly compare the scores obtained in Pain versus Touch, sensory pain versus affective unpleasantness, self-oriented versus other-oriented ratings, all four models, as well as the two control questions ($p < .05$, Bonferroni-corrected).

2.4. Trait-empathy

In order to evaluate the participants' general empathic reactivity, at the end of the experimental session all participants completed the Italian version (Bonino, Coco, & Tani, 1998) of the Interpersonal Reactivity Index (IRI; Davis, 1996), a 28-item self-report survey that consists of four subscales: Empathic Concern (EC) to assess the tendency to experience feelings of sympathy and compassion for others in need; Personal Distress (PD) to assess the extent to which an individual feels distress as a result of witnessing another's emotional distress; Perspective Taking (PT), to assess the dispositional tendency of an individual to adopt the perspective of others; Fantasy Scale (FS), to assess the propensity to become imaginatively involved with fictional characters and situations. EC and PD refer to affective components of empathy (FeldmanHall, Dalgleish, Evans, & Mobbs, 2015), PT and FS refer to cognitive components of empathy (Shamay-Tsoory, Aharon-Peretz, & Perry, 2009). Legal copyright restrictions prevent public archiving of the Interpersonal Reactivity Index. This material may be obtained from the copyright holders in the cited references.

2.5. MR data recording

Functional and anatomical brain images were collected using a 1.5T Siemens Magnetom Vision scanner with a standard head coil. All videos were projected onto a back-projection

Table 1 − **State-empathy self-reports. Participants indicated whether and how much they experienced sensory/affective, self/other-oriented reactions to the observation of painful and tactile stimulations delivered to each model.**

Type	Focus	Question
Sensory Pain	Self	Q1: How much physical pain did you feel?
	Other	Q2: How much physical pain did the model feel?
Affective Unpleasantness	Self	Q3: How much unpleasantness did you feel?
	Other	Q4: How much unpleasantness did the model feel?
Control	Baseline	Q5: Was the static limb unpleasant in general?
	Neutral	Q6: How much attention did you pay attention to the video?

screen situated behind the participant's head and were visible through a mirror covering the whole visual field. T1-weighted anatomical images were collected using a 3D MPRAGE sequence (1mm3 isotropic voxels, 160 sagittal slices, flip angle 12°; TR = 9.7 msec, TE = 4 msec). Brain activity was recorded by means of functional images collected with a gradient echo EPI sequence. Each experimental session included 158 consecutive volumes comprising 26 transaxial slices oriented parallel to the anterior-posterior commissure axis and covering the whole brain (TR = 2.9s, TE = 60 msec, flip angle 90°, 64 × 64 image matrix, 4 mm × 4 mm in-plane resolution, slice thickness 5mm).

2.6. fMRI data analysis

fMRI data were analyzed using SPM12 (Wellcome Department of Cognitive Neurology, Institute of Neurology, London). First, for each participant, functional images were corrected for head movements using a least-squares approach and six-parameter rigid body spatial transformations (K. J. Friston et al., 1995). Then, the anatomical image and the functional images relative to each participant were stereotaxically normalized to the Montreal Neurological Institute (MNI) brain template used in SPM (Mazziotta, Toga, Evans, Fox, & Lancaster, 1995). Functional images were re-sampled with a voxel size of 3 × 3 × 3 mm and spatially smoothed with a three-dimensional isotropic Gaussian filter of 6mm full width at half maximum to increase signal-to-noise ratio and accommodate anatomical variations between participants (K. J. Friston et al., 1995). These images were subsequently analyzed using a random effect approach.

The time series of functional images obtained for each participant were analyzed separately. The effects of the experimental paradigm were estimated on a voxel-by-voxel basis using the principles of the general linear model (Worsley & Friston, 1995). Each experimental block was modeled using a boxcar, convolved with a canonical hemodynamic response function chosen to represent the relationship between neuronal activation and blood flow changes. These single-subject models were used to compute eight contrast images per participant, each representing the estimated amplitude of the hemodynamic response in the Pain and Touch conditions for each of the four models (adult, baby, dog puppy, robot) relative to the respective Control conditions. These contrast images from all participants were entered into an analysis of variance with non-sphericity correction, as implemented in SPM (Worsley & Friston, 1995), in order to identify the regions where the effect of any of these contrasts was

significant, i.e., regions discriminating any of the eight conditions from Control ($p < .05$ corrected for multiple comparisons at the voxel level using the False Discovery Rate) (Costantini, Galati, Romani, & Aglioti, 2008; Dubis, Siegel, Neta, Visscher, & Petersen, 2016; Ionta et al., 2011). These regions were identified by assessing both the hemodynamic response function and its temporal derivative of the conditions-related BOLD changes to show the regions where the mean of the parameter estimates for the hemodynamic response function, or its temporal derivative, for all experimental conditions were different from zero and removing all confounds, including motion. This procedure lead to the individuation of 11 regions (ROIs). Then, in order to understand the directionality of the significant effects, for each identified ROI we extracted the BOLD percent signal change in each condition (with respect to the relative Control) for each participant, and entered these average regional response estimates into region-specific two-way repeated measures ANOVA with Stimulus (pain, touch) and Model (adult, baby, dog puppy, robot) as main factors (Costantini et al., 2008; Dubis et al., 2016; Ionta et al., 2011). Post-hoc comparisons were carried out by means of the Newman−Keuls test ($p < .05$) and the effect size of the significant effects was evaluated with the Cohen's d test (d).

Localization, visualization, and anatomical labeling of the activated clusters were achieved by using an in-house software (BrainShow; Galati et al., 2008), implemented in Matlab (MathWorks Inc., Natick, MA, USA). To visualize the location of the active clusters, we projected the group activations onto a folded cortical surface of the PALS atlas (Van Essen, 2005) and automatically assigned anatomical labels to the clusters at the level of cortical gyri of the MNI brain (Tzourio-Mazoyer et al., 2002).

3. Results

3.1. State-empathy

All subjective ratings are reported in Fig. 2. Considering only Pain, the comparison of the scores for the four models indicated that self-oriented sensory pain (Q1) and self-oriented affective unpleasantness (Q3) were not statistically different for adult and baby models (all $p_s > .2$), and both were significantly higher than the related scores for the dog puppy and robot models (all $p_s < .008$), which were not significantly different between them.

Further analysis of ratings of the sensory sensations (Q1+Q2) experienced during Pain and Touch for each model,
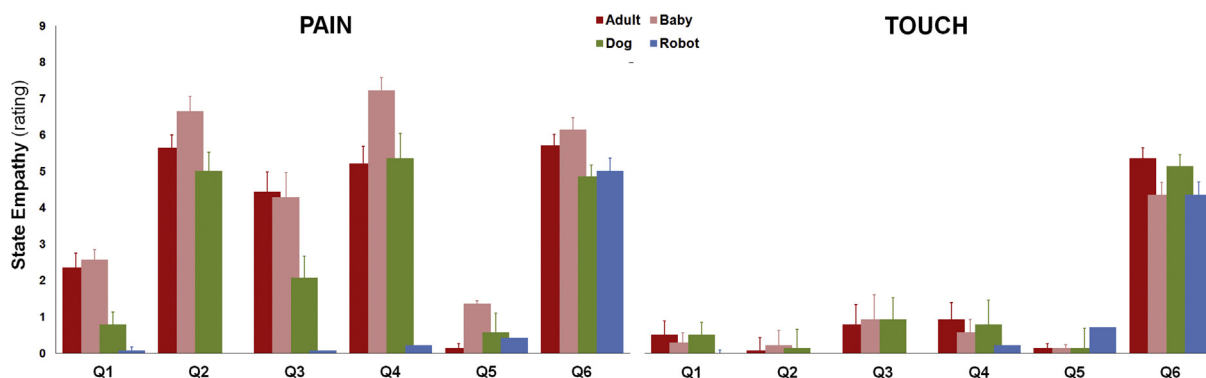
Fig. 2 – State-Empathy. Responses to sensory and affective questions (Q1 to Q4) indicated that participants reacted mores strongly to the observation of videos showing models undergoing a painful stimulation (syringe) with respect to a tactile one (brush). No different reactions were indicated by the participants for the control questions (Q5 and Q6) between the two type of videos.

showed that participants rated the Pain videos as significantly more painful than the Touch videos for the adult (mean $\pm$ SD; pain $= 4 \pm .9$; touch $= .3 \pm .4$), and baby model (pain $= 4.6 \pm .9$; touch $= .3 \pm .4$), with respect to the dog puppy (pain $= 2.9 \pm 1.1$; touch $= .3 \pm .4$) and robot model (pain $= 0 \pm .2$; touch $= 0 \pm 0$) (all $p_s < .01$). For the robot model, the Pain and Touch videos were not significantly different and were both evaluated as non-painful. The sensory ratings given to the adult ($4 \pm .9$) and baby model ($4.6 \pm .9$) in Pain were significantly higher than the sensory ratings for the dog puppy (2.9 ± 1.1) and robot models in Pain ($0 \pm .2$) (all $p_s < .001$), but were not significantly different from each other. The sensory ratings for the dog puppy model in Pain were significantly higher than those for the robot model in Pain ($p < .001$). The sensory ratings among all models during Touch were not significantly different from each other (adult $= .3 \pm .4$, baby $= .3 \pm .4$, dog puppy $= .3 \pm .4$, robot (0 ± 0) (Fig. 3A).

With regards to the affective (Q3+Q4) versus sensory components (Q1+Q2) of state-empathy only in Pain, participants rated their feelings as more unpleasant than sensory intense for the adult (affective $= 4.8 \pm 1.5$; sensory $= 4 \pm .9$), baby (affective $= 5.8 \pm 1.3$; sensory $= 4.6 \pm .9$) and dog puppy models (affective $= 3.7 \pm 2.0$; sensory $= 2.9 \pm 1.1$) (all $p_s < .01$). Affective and sensory ratings for the robot model were not statistically different and personal feelings were rated as affectively not

unpleasant ($.1 \pm 0$) and sensorially not intense ($0 \pm .2$). In particular, the affective ratings given to the adult (4.8 ± 1.5) and baby models (5.8 ± 1.3) were not significantly different from each other, but were significantly higher than those for the dog puppy (3.7 ± 2) and robot models ($.1 \pm 0$) (all $p_s < .001$). Similarly, also the sensory ratings given to adult ($4.0 \pm .9$) and baby models ($4.6 \pm .9$) were not significantly different from each other, but were significantly higher than those for the dog puppy (2.9 ± 1.1) and robot ($0 \pm .2$) (all $p_s < .001$) (Fig. 3B).

Taking into account the self-oriented (Q1+Q3) versus other-oriented (Q2+Q4) ratings, only in Pain, participants rated the other-oriented sensations as more painful than the self-oriented ones for the adult (other $= 5.4 \pm 1$; self $= 3.4 \pm 1.2$), baby (other $= 6.9 \pm 1$; self $= 3.4 \pm 1.6$), and dog puppy models (other $= 5.2 \pm 2$; self $= 1.4 \pm 1.4$) (all $p_s < .001$). There was no significant difference between the self- and other-oriented ratings for the robot model (other $= .1 \pm 0$; self $= .1 \pm .2$). In particular, the self-oriented ratings given to the adult (3.4 ± 1.2) and baby models (3.4 ± 1.6) were not significantly different from each other, but they were significantly higher than the ratings for the dog puppy (1.4 ± 1.4) and robot models ($.1 \pm .2$) (all $p_s < .001$). Conversely, the other-oriented ratings given to the baby model (6.9 ± 1) were significantly higher than those for the adult (5.4 ± 1) and dog puppy models (5.2 ± 2), which were not significantly different from each other. Both the self- and other-
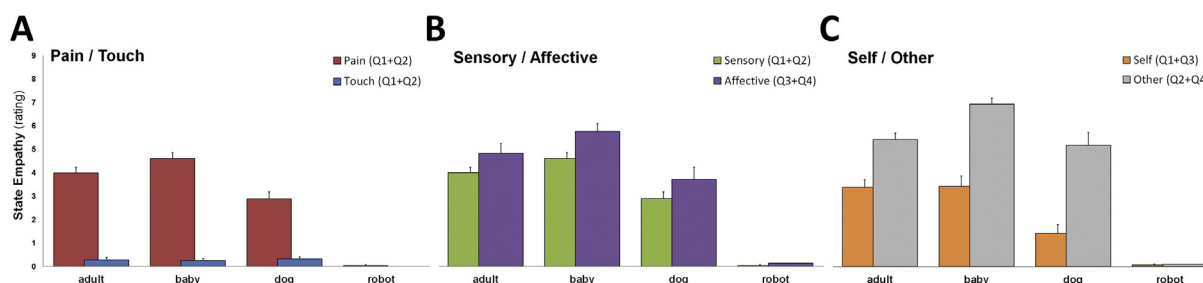

Fig. 3 – Pain-related Empathic States. Self-reports indicated that for adult, baby, and dog model the pain videos were perceived as more sensory painful than touch videos (Q1 + Q2), more affectively unpleasant than sensory painful (Q1+Q2 vs. Q3+Q4), more painful in other-oriented than self-oriented perspective (Q1+Q3 vs. Q2+Q4). The two control questions indicated that participants were not disturbed by and paid the same attention to the four models (Q5 and Q6). Error bars represent standard error.

oriented ratings for the robot were significantly the lowest with respect to all the other models (all $p_s < .001$) (Fig. 3C).

3.2. Trait-empathy

Participants' IRI scores [mean(SD)] in Fantasy Scale [16.9(5.7)], Empathic Concern [18.6(5.7)], Perspective Taking [20.1(5.3)], and Personal Distress [10.1(5.7)] were comprised within the range reported in previous work (Costantini et al., 2008; Lamm, Nusbaum, et al., 2007).

3.3. Brain activation

From the group-level whole-brain analysis, we identified eleven cortical regions where the BOLD signal was significantly different during at least one of the eight experimental conditions with respect to the related control condition (Table 2 and Fig. 4). These regions encompassed bilaterally the precentral gyrus (Prec), superior parietal lobule (SPL), supramarginal gyrus (SMG), insula (Ins), and occipito-temporal cortex (OT). In addition, the anterior cingulate cortex (ACC) was also activated including both the left and right medial wall of the cingulate gyrus. Hereafter, clusters positioned in the left or right hemisphere will be labeled as "l" or "r".

The activated clusters in the left hemisphere comprised: lPrec [97% of the voxels within Brodmann Area (BA) 6]; lSMG (35% in BA2; 23% in BA48; 14% in BA3; 8% in BA40); lIns (90% in BA48); lSPL (70% in BA7; 14% in BA40; 12% in adjacent regions); lOT (44% in BA19; 29% in BA37; 13% in BA18). The activated clusters in the right hemisphere comprised: rPrec (88% of the voxels within BA44); rSMG (38% in BA43; 32% in BA48); rIns (97% in BA48); rSPL (75% in BA7; 20% in BA20); rOT (40% in BA37, 39% in BA19, 6% in BA18). The ACC cluster comprised the medial aspect of the left anterior cingulum, the left medial superior frontal gyrus, and the right superior frontal gyrus (59% in BA10; 20% in BA10; 10% in BA32). Stereotaxic and statistical values of these clusters are reported in Table 2.

3.3.1. Brain activity contingent upon observation of different stimuli on different models
As shown in Fig. 5, the analysis of BOLD signal changes indicated that the interaction between Stimulus and Model was significant in rSMG [$F(3,39) = 3.1$; $p = .037$] and ACC [$F(3,39) = 3.2$; $p = .032$].

In rSMG, the post-hoc comparisons showed that the Pain videos with the adult model [mean(SD); .49%(.23)] were associated with stronger BOLD responses with respect to the dog puppy [.28%(.23); $d = .92$] and robot models [.28%(.2); $d = .99$] (all $p_s < .05$). Similarly, the observation of Pain videos with the baby model [.43%(.32)] elicited higher BOLD signals with respect to the dog puppy ($d = .53$) and robot models ($d = .56$) (all $p_s < .05$) (Fig. 5 - left panel). The difference between the brain activity associated with Pain versus Touch videos was significant for all the models (all $p_s < .002$; all $d_s > .91$).

In ACC, the post-hoc comparisons of the interaction showed that during Pain videos the percent of BOLD signal was smaller for the baby model [-.22%(.19)] with respect to the adult [.08%(015); $d = -1.72$], dog puppy [.01%(.2); $d = -.99$], and robot models [-.04%(.24); $d = -.79$] (all $p_s < .05$) (Fig. 5 - right panel). The difference between BOLD changes during Pain and Touch was significant only for the baby model (pain $= -22\%$; touch $= .05\%$; $p = .002$; $d = -1.18$), but not in the other models (adult: pain $= .08\%$, touch $= .13\%$, $p = .49$; dog puppy: pain $= .01\%$, touch $= -.03\%$, $p = .64$; robot: pain $= -.04\%$, touch $= -.02\%$, $p = .83$).

3.3.2. Main effect of stimulus (pain, touch)
In the left hemisphere, the main effect of Stimulus was significant in: lPrec [$F(1,13) = 16.8$; $p < .01$; $d = .59$], lSMG [$F(1,13) = 33.9$; $p < .01$; $d = 1.25$], lIns [$F(1,13) = 60.3$; $p < .01$; $d = 1.17$], lSPL [$F(1,13) = 15.2$; $p < .01$; $d = .61$], lOT [$F(1,13) = 60.6$; $p < .01$; $d = .72$], with stronger activity during the observation of pain videos (lPrec $= .56\%$; lSMG $= .82\%$; lIns $= .30\%$; lSPL $= .79\%$; lOT $= 1.2\%$) with respect to touch videos (lPrec $= .37\%$; lSMG $= .37\%$; lIns $= .04\%$; lSPL $= .56\%$; lOT $= .92\%$) (all $p_s < .05$) (Fig. S1, left panel).

In the right hemisphere, we found the significant main effect of Stimulus in: rPrec [$F(1,13) = 40.6$; $p < .01$; $d = .81$], rSMG [$F(1,13) = 58.5$; $p < .01$; $d = 1.26$], rIns [$F(1,13) = 82.2$; $p < .01$; $d = 1.23$], rSPL [$F(1,13) = 13.6$; $p < .01$; $d = .56$], rOT [$F(1,13) = 92.9$; $p < .01$; $d = .91$], with stronger activation during the observation of pain [rPrec $= .53\%(.13)$; rSMG $= .37\%(.11)$; rIns $= .17\%(.04)$; rSPL $= .67\%(012)$; rOT $= 1.1\%(012)$] than touch

Table 2 – Stereotaxic details of the regions activated during at least one of the experimental conditions with respect to the control condition (still hand). Asterisks indicate the regions where the interaction between Model and Stimulus was significant.

| Label	Anatomical Region	Hemisphere	F score	Cluster Size (voxels)	MNI coordinates		
					X	Y	Z
lPrec	Precentral gyrus	Left	10.34	28	−54	3	39
rPrec	Precental gyrus	Right	7.90	11	51	9	33
lSMG	Supramarginal gyrus	Left	17.52	588	−63	−24	42
*rSMG	Supramarginal gyrus	Right	8.88	15	63	−18	30
lIns	Insula	Left	5.35	112	−42	−3	−6
rIns	Insula	Right	4.81	73	42	3	9
lSPL	Superior Parietal lobe	Left	17.64	588	−24	−63	63
rSPL	Superior Parietal lobe	Right	6.39	160	27	−60	60
lOT	Occipito-Temporal cortex	Left	33.04	1275	−45	−69	0
rOT	Occipito-Temporal cortex	Right	25.37	1293	48	−63	−3
*ACC	Anterior Cingulate cortex	Left + Right	3.47	45	12	54	3
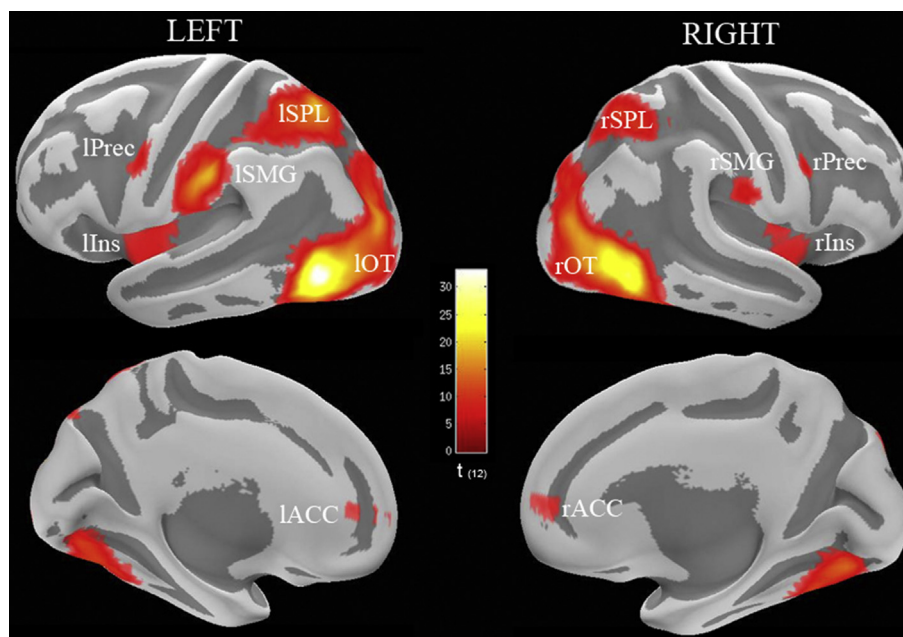
Fig. 4 — Brain Activation. Stronger activation during the experimental conditions (with respect to the relative control) was found in a widespread bilateral network including the supramarginal gyrus (SMG) precentral (Prec), as well as the insula (Ins), superior parietal lobule (SPL), anterior cingulate cortex (ACC), and an occipito-temporal complex (OT). Group activations are rendered and projected on the cortical inflated surface of the PALS atlas.
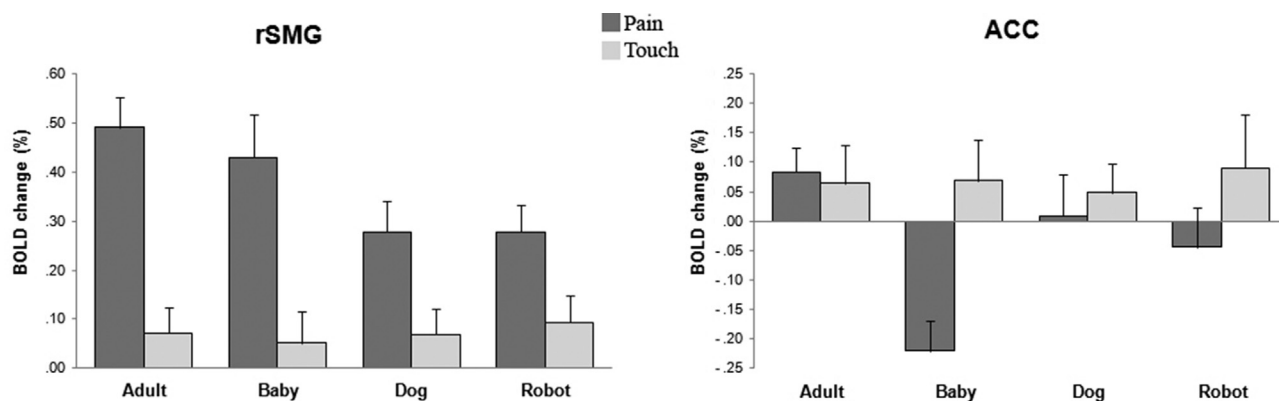

Fig. 5 — BOLD signal change. Modulation of the neural response associated with the observation of pain and touch videos in the four models. The interaction between Model (adult, baby, dog, robot) and Stimulus (pain, touch) was significant in the right supramarginal gyrus (left panel) and anterior cingulate cortex (right panel). Error bars represent standard error.

videos [rPrec: .26%(.07); rSMG: .07%(.02); rIns: −.03%(.06); rSPL: .48%(.11); rOT = .79%(.13)] (all p_s < .01) (Fig. S1, right panel).

3.3.3. Main effect of model (adult, baby, dog puppy, robot)

In the left hemisphere the main effect of Model was significant in lSMG [F(3,39) = 3.2; p < .05] and lSPL [F(3,39) = 4.0; p < .01]. In lSMG there was a stronger activation during the observation of the adult [.72%(.44)] than dog puppy model [.47%(.42); p < .05; d = .18]. In lSPL, a stronger activation was present during observation of the adult [.86%(.15)] with respect to all the other models [baby: .65% (.16), d = .61; dog puppy: .54% (.24), d = .76; robot: .65% (.09); all p_s < .05].

In the right hemisphere the main effect of Model was significant in rPrec [F(3,39) = 3.0; p < .05], rSPL [F(3,39) = 5.2; p < .01],

rOT [F(3,39) = 5.0; p < .01]. The activation during the observation of the adult model was significantly stronger with respect to the observation of the robot model in rPrec [adult: .50%(.32); robot = .26%(.31); d = .23], of all the other models in rSPL [adult: .73%(.26); baby: .58%(.34), d = .49; dog puppy: .50%(.34), d = .77; robot: .49%(.4), d = .72] (all p_s < .05), and of the non-human models in rOT [adult: 1.09%(.25); dog puppy: .85%(.32), d = .83; robot: .81(.39), d = .85; all p_s < .05].

4. Discussion

Combining subjective reports and fMRI data, we explored the specific effects of visual similarity and psychological

closeness on the behavioral and neural responses to the experience of visually-mediated vicarious pain. To induce vicarious pain, we asked participants to observe videos of four different models (adult, baby, dog puppy, and robot) receiving painful and tactile stimulations. One of the main results of the present study is the differential activity induced by the observation of conspecifics in pain (with respect to other species) in brain regions belonging to both the sensorimotor and the affective nodes of the cortical pain matrix.

4.1. Behavioral reactivity to different models in pain

State-empathy subjective ratings confirmed that the stimuli were effective in eliciting congruent vicarious sensations, with higher scores for in Pain than Touch for all the models except the robot. Previous work showed that vicarious pain for human models is associated with higher state-empathy ratings than vicarious touch (Avenanti, Minio-Paluello, Bufalari, & Aglioti, 2009), that the difference between the ratings for painful and non-painful conditions is larger for a human than robotic hand model (Suzuki, Galli, Ikeda, Itakura, & Kitazaki, 2015), and that the attribution of minimal humanity cues can increase the empathic responses for unanimated entities (Vaes, Meconi, Sessa, & Olechowski, 2016). The present study fits and extends this previous work by showing that the difference between state-empathy ratings for vicarious pain and touch was significant only for the living beings (no matter the species), but not for the robot. Considering also that psychological closeness can affect the interactions between humans and also other species (e.g., dogs), especially with respect to empathy ratings (Kujala, Somppi, Jokela, Vainio, & Parkkonen, 2017), we interpret the present finding as evidence that the behavioral empathic resonance mechanisms are modulated by the psychological closeness between the onlooker and the model, with a particular differentiation between psychologically close living beings (like dogs) and unanimated objects. This interpretation is in line with evidence that the observation of others' in pain is influenced by the onlooker's psychological states and traits (Fusaro, Tieri, & Aglioti, 2019; Valentini, Koch, & Aglioti, 2014). For instance, prior history of pain decreases the difference between the neural response to the observation of painful and non-painful situations (Cheng et al., 2007; Eidelman-Rothman et al., 2016), low mood increases distress reactions to the pain of others (Yuan Cao, Dingle, Chan, & Cunnington, 2017), hypnotic analgesia reduces the neural activity in brain areas involved in empathic reactivity (Braboszcz, Brandao-Farinelli, & Vuilleumier, 2017), and specific personality traits influence the way our motor system reacts to seeing people experiencing pain (Avenanti, Minio-Paluello, Bufalari, & Aglioti, 2009).

With respect to the sensory versus affective aspects of empathy-states, higher ratings for both sensory and affective aspects of vicarious experience were given to Pain than Touch videos. Interestingly, there was a clear effect of the model, with minimal ratings of intensity and unpleasantness for the robot versus living beings. In particular, the ratings for the sensory pain experienced by the adult and baby models were higher than those for the dog puppy model, indicating a specific sensitivity for conspecifics experiencing pain. Such

sensitivity seemed to remain at a general level for human beings, as the difference between pain ratings for the adult and baby model in Pain was not significant. This finding is consistent with and adds novel insights to previous evidence that empathy-related neural activity increases when the observed people in pain are from the same ethnicity of the onlooker (Y. Cao, Contreras-Huerta, McFadyen, & Cunnington, 2015; Hein, Silani, Preuschoff, Batson, & Singer, 2010; Mathur et al., 2010; Xu et al., 2009), are liked by the onlooker (Fox, Sobhani, & Aziz-Zadeh, 2013), are supporters of the onlooker's team (Cikara, Botvinick, & Fiske, 2011), and are considered by the onlooker as close friends with respect to strangers (Wang et al., 2016), fair with respect to unfair (T. Singer et al., 2006), moral with respect to immoral (F. Cui, Abdelgabar, Keysers, & Gazzola, 2015; Fang Cui, Ma, & Luo, 2016), endowed with high than low reputation (Zheng et al., 2016). Conversely, the onlooker's empathic reactivity is weaker for outgroup individuals in terms of different ethnicity (Avenanti et al., 2010; R. T.; Azevedo et al., 2013; Mathur et al., 2010; Xu et al., 2009), physical features (Ruben Teixeira Azevedo et al., 2014), or soccer fanship (Hein et al., 2010). Altogether, showing the modulatory effect of psychological closeness on empathy-state responses to vicarious pain, the present findings support that not only personal features affect the response to vicarious pain, but also the social variables concerning the psychological closeness between the onlooker and the model in pain (Betti & Aglioti, 2016; Nicolardi, Panasiti, D'Ippolito, Pecimo, & Aglioti, 2020).

With regards to perspective taking, for all animated models the other-oriented ratings were significantly higher than self-oriented ones. In addition, the self- and other-oriented ratings for the robot model were identical and very low. The former finding indicates that onlookers are able to dissociate the self-versus other-perspectives. The latter finding suggests that such differentiation was specific for living beings. The preference for conspecifics was further supported by the self-oriented ratings, in that ratings for the adult and baby models were significantly higher than those for the dob puppy model, indicating a higher personal reactivity to conspecifics. This observation is line with evidence showing the role of perspective taking in the cognitive resonance mechanisms associated with vicarious pain. In particular, it has been shown that the ability to imagine oneself in painful situations experienced by others is associated with a specific physiological responses (Fusaro, Tieri, & Aglioti, 2016) and brain activation patterns within the temporo-parietal junction, including the SMG (Vistoli, Achim, Lavoie, & Jackson, 2016), the same region found in the present study where Stimulus and Model significantly influenced the neural reactivity to vicarious pain.

4.2. Neural modulation for empathic reactivity to others' pain

The neural activity in rSMG and ACC was significantly affected by the joint effect (interaction) of Stimulus (pain, touch) and Model (adult, baby, dog puppy, robot). These two regions are part of the pain matrix and contribute to the processing of the somatosensory (rSMG) and affective aspects (ACC) of the vicarious experience of pain (Bzdok et al., 2012; Lamm et al., 2011; Tholen, Trautwein, Bockler, Singer, & Kanske, 2020).

4.2.1. Supramarginal gyrus

In rSMG the vicarious experience of painful stimulation delivered to the adult model elicited the strongest neural response, followed by the neural response to the baby model in Pain, which was significantly higher than the response for the dog puppy and robot models in Pain. The difference of neural response in rSMG for the dog puppy and robot models in Pain was not significant. As control, the Touch vicarious experience for the all four models did not elicit significantly different neural responses in rSMG. We interpret these findings as evidence that activity in rSMG is species-specific and further modulated by visual similarity: rSMG is more active specifically for human beings in pain and, within human models, it is more active for the (adult) model which is visually more similar to the onlooker (adult).

The rSMG has been linked to the ability to experience sensory aspects of vicarious pain in neurotypical (Benuzzi et al., 2018; Costantini et al., 2008; Riva, Triscoli, Lamm, Carnaghi, & Silani, 2016; Silani, Lamm, Ruff, & Singer, 2013; van der Heiden, Scherpiet, Konicar, Birbaumer, & Veit, 2013) and neurpathic conditions (Flasbeck, Enzi, & Brune, 2019; Hoffmann, Koehne, Steinbeis, Dziobek, & Singer, 2016). In line with this evidence, our findings fit the idea that SMG is implied in empathy-related processing (Costantini et al., 2008; Hoffmann et al., 2016; Lawrence et al., 2006) and its activity patterns are associated with the ability to differentiate the self from the other (Tholen et al., 2020). Indeed, beyond the classic somatosensory and proprioceptive processing (Gazzaniga, Ivry, & Mangun, 2006), supramarginal activity especially in the right hemisphere is involved in empathic reactivity to vicarious pain both in neurotypical (Benuzzi et al., 2018; Silani et al., 2013; Steinbeis, Bernhardt, & Singer, 2015) and neuropathic populations (Flasbeck et al., 2019; Hoffmann et al., 2016). In addition, neural activity in rSMG is correlated with the ability to emotionally distinguish the self from the other (Steinbeis et al., 2015), the regulation of emotional egocentricity (Silani et al., 2013), and is further modulated by dispositional empathic understanding (Ruff et al., 2019) and intake of hormones affecting empathic reactivity (Spies et al., 2016). Finally, SMG is generally involved in the differentiation between empathy-related processing related to oneself versus somebody else, both in neurotypical (Beckes, Coan, & Hasselmo, 2013; Lawrence et al., 2006) and emotionally impaired clinical populations (Hoffmann et al., 2016). In this framework we propose that the higher the visual similarity between the onlooker and the model, the stronger the activity in rSMG. In particular, as the inhibition of rSMG reduces the ability to empathize with others in pain (Silani et al., 2013), we propose that a stronger activity in rSMG reflects a better ability to empathize with close conspecifics in pain than other models. This finding extends previous work by showing that the neural reactivity of rSMG is not an all-or-none response to the experience of vicarious pain, but rather is it finely modulated by the visual similarity between the onlooker and the model in pain.

4.2.2. Anterior cingulate cortex

We found that activity in ACC was also modulated by the interaction between the type of vicarious experience and the nature of the models. In particular, the neural response of ACC was significantly the weakest during the observation of the baby model in Pain with respect to all the other conditions (vicarious pain and touch in all models), which did not significantly differ between them. These findings support the idea that the neural reactivity of ACC in response to vicarious pain is dependent on the nature of the model in pain, with a specific sensitivity to particularly vulnerable conspecifics as babies (psychological closeness). ACC is a core region of the pain matrix, encoding the affective aspects of the vicarious experiences (Keum & Shin, 2019), including the pain of others (Tania Singer & Lamm, 2009). Typically, stronger activity in ACC is associated with better empathizing with others' pain-related unpleasantness (e.g., Gu et al., 2012). However, stronger activity in ACC has been reported also in altruistic (O'Connell et al., 2019) and low-empathy people (J. Decety, Michalska, Akitsuki, & Lahey, 2009). Thus, the former finding is evidence that reactivity of ACC is influenced by one's own sensitivity to others, and the latter study suggests that a weaker activation of ACC might reflect specific empathic abilities. In this framework, and considering that in the present study the baby model was the most vulnerable among the human models, we propose that the suppression of activity in ACC reflected a specific empathizing for the unpleasantness experienced by the psychologically closest model during the painful stimulation.

It might be argued that the same interaction effect (Stimulus by Model) results in different activity patterns between ACC and rSMG. Such a peculiarity can be explained by taking into consideration the different role played by each of these regions in the context of the empathic response to vicarious stimulation. While SMG encodes the sensorimotor aspects of empathy, ACC encodes the affective aspects of empathy. It is therefore not surprising that the fMRI data are differently distributed among the experimental conditions. The different effect of the Stimulus by Model interaction can be seen as a sign that experimental manipulations determined a model-dependent quasi-gradient modulation (from adult to robot) of the brain responsiveness for the sensorimotor aspects of vicarious empathy for visually more similar models (rSMG). Conversely, there was a tendency towards an all-or-none modulation (mainly for the baby model) for the brain responsiveness to the affective aspects of vicarious empathy for psychologically closer models (ACC).

Another argumentation could be that ACC has been reported as equally active during the observation of people, animals, and natural entities in pain (Mathur, Cheon, Harada, Scimeca, & Chiao, 2016). Excluding any Model-related modulatory effect in the activity of ACC, this finding might seem in contrast with the present study. However, such inconsistency might derive from methodological differences in experimental procedures and protocols. In particular, we note that the participants of the study by Mathur et al. were presented with images showing the aftereffects of an eventual "painful" situation happened in the past (pain inference), e.g., a crying person, a dead animal, a polluted natural environment. Conversely, the participants of the present study were presented with exactly the same vicarious painful stimulation (syringe penetrating the hand) while the owner (model) of the hand in pain varied. In this way our participants were exposed to vicarious experience of someone being in pain in real-time.

Addressing different aspects of vicarious pain (inference versus real-time), such difference might have affected the modulation (or not) of neural response in ACC.

4.3.   Other activations

The BOLD modulation in bilateral SPL showed the single main effects of Stimulus and Model. In regards to the main effect of Stimulus, SPL is involved in processing the sensorimotor resonance of empathy for pain (Jauniaux, Khatibi, Rainville, & Jackson, 2019) and is specifically active when the vicarious experience of pain is the result of the observation of noxious stimuli delivered on a model (as in our experiment) (Timmers et al., 2018). In the present study the stronger activation of SPL in Pain, can be seen as a sign that the observation of painful stimuli activated the sensorimotor aspects of empathic response and elicited a stronger action expectancy of the models' motor reaction, which has been associated with activity in SPL (Rizzolatti & Sinigaglia, 2016). The main effect of Model showed that activity in SPL was stronger during the observation of the adult model with respect to the other models. We interpret such effect as a sign that, not only SPL is more active during self-related painful experience (Benuzzi et al., 2018), but also its activity is modulated by the visual similarity between the onlooker and the model, with stronger reactivity for models more similar to the onlooker. Such a sensitivity of SPL to similarity is further supported by recent evidence showing that socializing with a visually dissimilar model (e.g., a robot) can invert the reactivity of SPL in response to the observation of noxious stimulation delivered to a similar versus a dissimilar model (Cross et al., 2019).

The BOLD modulation in bilateral OT showed the main effect of Stimulus, with stronger activity during the observation of pain videos with respect to touch ones. As both types of videos showed objects in movement and were contrasted with the related static limb, it is unlikely that the activation of OT was associated to merely visual features. Extending previous evidence of a direct relationship between empathic competences and reactivity in occipital regions during evaluation of vicarious pain (Yang et al., 2017), our finding highlights that empathy-related mechanisms may influence the responsiveness of regions whose activity was classically limited to early visual processing. This interpretation complements the idea that occipital activity can reflect the interaction between biological meaningfulness and emotional valence during vicarious experience of pain (Proverbio, Adorni, Zani, & Trestianu, 2009).

4.4.   Potential limitations

It might be argued that the inclusion of a possibly small sample size in the present study (N = 14) might have resulted in a low statistical power (Button et al., 2013). While we acknowledge that this may be a potential limitation, we note that the statistical power is commonly evaluated in terms of effect size, and not of sample size only (K. Friston, 2012). This implies that large effect sizes represent good statistical power, even in relatively small samples, avoiding the risks associated with potentially inflated effects due to testing large samples (K. Friston, 2012). On this basis, in the present study we reported the effect size

(Cohen's ds) for each significant effect, showing that: 13.8% of the effects had a Cohen's d within the "Very Large" effect size range (1.2 < d < 2); 37.9% had a "Large" Cohen's d (.8 < d < 1.2); 37.9% had a "Medium" Cohen's d (.5 < d < .8; the most commonly accepted effect size); only 10.3% had a "Small" Cohen's d (.2 < d < .5). In this context, despite a relatively small sample size, the large effect sizes of the present study can provide a solid base for the obtained results. It is likely that this or similar reasonings constituted the basis on which recently published fMRI studies included samples sizes (of neurotypical participants as ours) as small as 14 (Barbieri, Mack, Chiappetta, Europa, & Thompson, 2019), 12 (DeWind, Park, Woldorff, & Brannon, 2019), 14 (Freud & Behrmann, 2020), 16 (Borghesani et al., 2019), and 17 (Filik, Turcan, Ralph-Nearman, & Pitiot, 2019).

A second critical issue might derive from running a high number of (uncorrected) multiple comparisons in parallel on 11 ROIs and the related post hoc tests. Trying to avoid such a risk, first we FDR-corrected for multiple comparisons the contrast used to identify the ROIs. Then, separately for each ROI (without including the putative factor "ROI" and its 11 levels in the analysis), the variations of BOLD signal were analyzed as a function of the factors Stimulus (pain, touch) and Model (adult, baby, dog, robot). This procedure resulted in limiting the post hoc tests to only the significant effects for each specific ROI. By correcting for multiple comparisons, separating the analysis of the BOLD variations for each ROI, and limiting the number of post hoc tests, we felt that such procedure should guarantee a safe strategy to control for possibly spurious effects.

5.   Conclusions

The present study investigated the influence of visual similarity and psychological closeness on the neuro-behavioral responsiveness to vicarious experience of pain. fMRI data showed that the neural activity in brain regions encoding the somatosensory (supramarginal gyrus) and affective aspects (anterior cingulate cortex) of vicarious pain was modulated by visual similarity and psychological closeness between the observer and the model in pain, respectively. Behavioral data showed a specific sensitivity for conspecifics, in that participants' vicarious experience of pain was stronger for psychologically closer models in pain (adult and baby) with respect to psychologically more distant models (dog and robot). These findings show the importance of the onlooker-model visual similarity and psychological closeness in the brain responsiveness for interindividual sharing of sensorimotor and affective aspects of vicarious pain.

Declaration of competing interest

All authors declare no conflicts of interest and take full responsibility for the data recording, analyses, and interpretation. This manuscript is not under consideration by any other journal and will not be submitted for publication elsewhere until a decision is made regarding its acceptability for publication in CORTEX.

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Supplementary data

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