

Who caused the pain? An fMRI investigation of empathy and intentionality in children

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ABSTRACT

When we attend to other people in pain, the neural circuits underpinning the processing of first-hand experience of pain are activated in the observer. This basic somatic sensorimotor resonance plays a critical role in the primitive building block of empathy and moral reasoning that relies on the sharing of others' distress. However, the full-blown capacity of human empathy is more sophisticated than the mere simulation of the target's affective state. Indeed, empathy is about both sharing *and* understanding the emotional state of others in relation to oneself. In this functional magnetic resonance imaging (fMRI) study, 17 typically developing children (range 7–12 yr) were scanned while presented with short animated visual stimuli depicting painful and non-painful situations. These situations involved either a person whose pain was accidentally caused or a person whose pain was intentionally inflicted by another individual. After scanning, children rated how painful these situations appeared. Consistent with previous fMRI studies of pain empathy with adults, the perception of other people in pain in children was associated with increased hemodynamic activity in the neural circuits involved in the processing of first-hand experience of pain, including the insula, somatosensory cortex, anterior midcingulate cortex, periaqueductal gray, and supplementary motor area. Interestingly, when watching another person inflicting pain onto another, regions that are consistently engaged in representing social interaction and moral behavior (the temporo-parietal junction, the paracingulate, orbital medial frontal cortices, amygdala) were additionally recruited, and increased their connectivity with the fronto-parietal attention network. These results are important to set the standard for future studies with children who exhibit social cognitive disorders (e.g., antisocial personality disorder, conduct disorder) and are often deficient in experiencing empathy or guilt.

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1. Introduction

Our understanding of the neural mechanisms underpinning the experience of empathy has increased significantly during the past decade. This is mainly due to the application of cognitive neuroscience and neuroimaging tools that have expanded to study interpersonal sensitivity, i.e., the ability to perceive and respond with care to the internal states (e.g., cognitive, affective, motivational) of another, understand the antecedents of those states, and predict the subsequent events that will result (Decety & Batson, 2007).

Notably, a growing number of functional neuroimaging studies have demonstrated striking similarities (as well as differences) in

the neural circuits involved in the processing of both the first-hand experience of pain and the second-hand experience of observing other individuals in pain (Jackson, Rainville, & Decety, 2006 for a review). These studies have consistently shown that the perception of pain in others elicits activation of the neural circuit subserving the processing of the affective and motivational dimension of pain (Gu & Han, 2007; Jackson, Meltzoff, & Decety, 2005; Jackson, Brunet, Meltzoff, & Decety, 2006; Lamm, Batson, & Decety, 2007; Moriguchi et al., 2007; Morrison, Lloyd, di Pellegrino, & Roberts, 2004; Morrison, Peelen, & Downing, 2006; Ogino et al., 2007; Saarela et al., 2007; Singer et al., 2004; Zaki, Ochsner, Hanelin, Wager, & Mackey, 2007). This neural circuit includes the dorsal anterior cingulate cortex (ACC), the anterior midcingulate cortex (amCC) and anterior insula (Derbyshire, 2000; Price, 2000). In addition, transcranial magnetic stimulation (Avenanti, Bueti, Galati, & Aglioti, 2005), somatosensory-evoked potentials (Bufalari, Aprile, Avenanti, Di Russo, & Aglioti, 2007), magnetoencephalography (Cheng, Yang, Lin, Lee, & Decety, 2008), and functional magnetic resonance imaging (fMRI) studies (Benuzzi, Lui, Duzzi, Nichelli, &

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Porro, 2008; Lamm, Nusbaum, Meltzoff, & Decety, 2007; Moriguchi et al., 2007) have also demonstrated that areas processing the sensory dimension of pain (somatosensory cortices/posterior insula) may also be elicited by the mere visual perception of pain in others.

Altogether, there is strong evidence to suggest that perceiving the pain of others triggers an automatic somatic sensorimotor-mirroring mechanism between other and self, which activates almost the entire neural pain matrix including the periaqueductal gray (PAG), a major site in pain transmission and for processing of fear and anxiety, the supplementary motor area (SMA) that programs defensive movements in the context of nociceptive information, and thalamus. Such a resonance mechanism provides a functional bridge between first-person information and third-person information, grounded in self–other equivalence, which allows for analogical reasoning, and offers a possible, yet partial, route to understanding others (Decety & Sommerville, 2003; Decety & Grèzes, 2006; Gallese, 2001). In the case of pain, individuals are predisposed to find distress of others aversive and learn to avoid actions associated with this distress. This is even the case in many mammalian species including rodents. For instance, rats that had learned to press a lever to obtain food would stop doing so if their response was paired with the delivery of an electric shock to a visible neighboring rat (Church, 1959). This example illustrates the functional connection between the first-hand experience of pain, its perception in others, and empathic concern, which draws on the encephalization of pain evaluation (Tucker, Luu, & Derryberry, 2005).

However, the full-blown capacity of human empathy is more sophisticated than the mere automatic resonance of the target's affective state. Indeed, empathy is both about sharing the emotional state of others and understanding it in relation to oneself (Decety & Moriguchi, 2007; Eisenberg, Spinrad, & Sadovsky, 2006). The capacity for two people to resonate with each other emotionally, prior to any cognitive understanding, is the basis for developing shared emotional meanings, but is not enough for empathic understanding. Such an understanding goes beyond this reflex-like response. Indeed, although affective resonance contributes to empathy, it is not sufficient for grasping another's distinct emotional perspective. This requires forming an explicit representation of the feelings of another person, an intentional agent, which necessitates additional computational mechanisms beyond the shared representation level, as well as self-regulation to modulate negative arousal in the observer (Decety & Jackson, 2004). In order to understand the emotions and feelings of others in relation to oneself, second-order representations of the other need to be available to awareness (a decoupling computational mechanism between first-person information and second-person information: theory of mind), for which the medial prefrontal cortex, especially the paracingulate cortex (PCC) and the temporo-parietal junction (TPJ) play a special role (Decety & Jackson, 2004; Frith & Frith, 2003; Saxe & Kanwisher, 2003). The importance of the medial prefrontal cortex in self-awareness and self-conscious emotions is also supported by studies with neurological patients suffering from fronto-temporal lobar degeneration. For instance, Sturm, Rosen, Allison, Miller, and Levenson (2006) found preserved peripheral physiological response and negative emotional reactivity, but diminished self-conscious emotional behavior such as empathic concern.

To our knowledge there is no functional MRI study that has investigated the neural underpinnings in empathy for pain and theory of mind in school-aged children. We believe that such investigations are critical to set the standard for future studies with children who exhibit social cognitive disorders (e.g., antisocial personality disorder, conduct disorder) and are often deficient in experiencing empathy or guilt. Given the age of the children included in our experiment, we posited that the different com-

ponents of empathy (i.e., emotion sharing, self–other distinction, self-regulation) are already in place. This reasoning is based on behavioral and physiological studies by developmental psychologists (e.g., Eisenberg & Eggum, *in press*; Eisenberg & Miller, 1987; Zahn-Waxler & Radke-Yarrow, 1990) that have documented that by the age of 4–5 yr, typically developing children exhibit mature empathic ability and prosocial behaviors (see Decety & Jackson, 2004; Decety & Meyer, 2008 for reviews). By the same age, children are equipped with cognitive mechanisms that subserve theory of mind capabilities (Baron-Cohen, Tager-Flusberg, & Cohen, 2000). In support of this view, one functional MRI study with children of a similar age (mean age 10 yr, range 7–13) as our participants, found the same neural network activated by a theory of mind task as in adult participants, including the medial prefrontal cortex and right TPJ (Ohnishi et al., 2004).

The goals of our study were twofold: (1) to map the brain response in typically developing children associated with the perception of pain in others; (2) to examine the respective contribution of mechanisms that contribute to theory of mind and implicit moral reasoning in the context of pain perception. In this experiment, children in middle childhood were shown dynamic visual animations depicting body parts in painful situations. These situations involved one person whose pain was either ostensibly caused by accident or inflicted by another individual. It was predicted that when children watched the painful situations involving one person, the neural circuits engaged in pain processing (e.g., the aMCC, insula, SMA, somatosensory cortex, PAG) would be activated. When the situations involved another individual inflicting pain on another, we hypothesized that, in addition to areas that belong to the pain matrix, significant signal increase would be detected in the neural regions associated with mentalizing and self-regulation such as the PCC, the TPJ and the orbital medial frontal cortex (oMFC). The PCC and oMFC have been implicated in social behavior, such as making inferences about others' thoughts and the monitoring of outcomes that relate to punishments and rewards (Amodio & Frith, 2006; Anderson, Bechara, Damasio, Tranel, & Damasio, 1999), which are critical processes in moral reasoning. Individuals with damage to the orbital medial prefrontal cortex show little control over their emotions as well as limited awareness of the moral implications of their actions (Damasio, 1994; Grafman et al., 1996). Further, it is possible that perceiving another individual intentionally inflicting pain upon another person recruits the amygdala, which plays a critical role in fear-related behaviors, such as the evaluation of actual or potential threats (e.g., LeDoux, 2000; Phelps et al., 2001). It is generally acknowledged that the amygdala is necessary for normal processing of negative emotional stimuli, and its damage most often leads to impairments in recognizing threat and/or arousal-related information from visual stimuli (Adolphs, 2002). Of particular interest, individuals who lack empathy, such as in psychopathy, exhibit dysfunction in a circuit that includes the amygdala and oMFC (Blair, 1995; Kiehl, 2006). This anomaly precludes learning the basics of care-based morality, that is, learning that some actions harm others and because of this are to be avoided (Blair, 2007). The amygdala and oMFC are both anatomically and functionally connected (Amaral & Price, 1984) and their effective interactions are critical for decoding emotionally salient information and guiding social behavior (Saddoris, Gallagher, & Schoenbaum, 2005).

2. Methods and materials

2.1. Subjects

Seventeen right-handed typically developing children (9 females, mean = 9 yr, range 7–12 yr) participated in this study. Children were recruited from the local community of the University of Chicago campus. Parents written informed consent

was obtained as well as children assent. Children were paid for their participation. The study was approved by the University of Chicago Institutional Review Board and conducted in accordance with the Declaration of Helsinki.

2.2. Stimuli preparation and validation

The task consisted of the successive presentation of animated images of hands and feet in blocks depicting painful and non-painful situations. A series of 96 animated visual stimuli were created and validated for this study. Validation of the material was conducted with a group of 222 participants who were exposed to these dynamic stimuli and asked to estimate how painful these situations were and whether they believed that the pain was caused intentionally (Estabrook, 2007). Each animation consisted of three digital color pictures, which were edited to the same size (600 × 480 pixels). The durations of the first, second and third pictures were 1000 ms, 200 ms and 1000 ms respectively. These animated stimuli contained scenes of various types of painful and non-painful everyday situations.

Each animation displayed one or two persons whose right hands or right feet are visible but not their faces. When presented, the two people are distinguished from one another in clothing or shoe type. These 96 stimuli belong to four categories (24 each) of pain and involved person types, including:

1. Only one person is in a painful situation caused by accident, e.g., a person dropping a heavy bowl on their hand (pain caused by self, PCS).
2. Only one person is involved in a non-painful situation, e.g., a box is dropped next to but not on a foot (no pain self, NPS).
3. One person is in a painful situation caused by another, e.g., stepping purposely on someone's toe (pain caused by other, PCO).
4. One person is in a painful situation at first but this pain is alleviated by the other, e.g., helping another get his or her hand out of a door (alleviated pain by other, APO).

2.3. Training in the mock scanner

Prior to MRI scanning, children were acclimated to the scanning environment and procedures in a mock scanner. The children were asked to lie in the mock scanner while a documentary movie was played (Jacques Cousteau's *Pacific Explorations*). When children felt comfortable, then they were presented with 24 stimuli (6 per condition) depicting situations similar (but not the same) to those they would watch in the actual scanning sessions. The MRI noise was simulated through a recording and played during the practice session. The training session lasted approximately 10–15 min and parents remained in the room with their children.

2.4. Behavioral paradigm

Stimuli were presented with E-prime software (Psychology Software Tools, Inc. Pittsburgh, PA, USA) and a back-projection system. A block-design paradigm was used with 9 baseline blocks (duration 17.6 s each) during which a fixation cross was presented and 8 active blocks (duration 19.8 s each) during which stimuli from one of the four categories were presented. The presentation order was counterbalanced across runs and across subjects. Each block consisted of 6 stimuli (2200 ms each) with 5 inter-stimulus intervals (1100 ms each) during which a black fixation cross was presented against a gray background. Children were shown two sessions, which were kept relatively short (6 min each) to maintain their attention. No overt response was required. Instead, children were instructed to watch the stimuli carefully.

2.5. Functional MRI procedure

Magnetic resonance Imaging was performed on a GE 3T magnet (Horizon LX). Functional images were obtained using T2*-weighted gradient echo spiral in/out pulse sequence (Glover & Law, 2001). Thirty-six coronal slices of 5-mm slice thickness without spatial gap were obtained for 160 repetitions (including 16 discarded acquisitions at the onset of each of two runs) using the following parameters: TR = 2200 ms, TE = 26 ms, flip angle = 81°, FOV = 24 cm, matrix = 64 × 64, and in-plane resolution = 3.75 mm × 3.75 mm. The spiral-in/-out sequence was shown to be effective in recovering blood oxygenation level-dependent (BOLD) signal in frontal regions important to this study (Preston, Thomason, Ochsner, Cooper, & Glover, 2004). An axial T1-weighted 3D magnetisation-prepared rapid acquisition gradient echo (MP-RAGE) anatomical scan was also acquired for 3D localization (TR = 8 ms, TE = 3.2 ms, flip angle = 6°, FOV = 24 cm, matrix = 256 × 192, slice thickness = 1.5 mm, 124 slices).

2.6. Image processing and analysis

Image processing was carried out with SPM5 (Wellcome Department of Imaging Neuroscience, London, UK), implemented in MATLAB 7.0 (Mathworks Inc., Sherborn, MA). Preprocessing included slice-timing correction, correction for head motion, normalization to the EPI template provided in SPM5, and smoothing using a 6-mm full-width half-maximum isotropic Gaussian kernel. Images were realigned and normalized using standard SPM procedures. No participant was excluded from the data

analysis because of excessive head motion. A two-level approach for block-design fMRI data was adopted using SPM5. A voxel-by-voxel multiple regression analysis of expected signal changes for each of the four block categories, which were constructed using the hemodynamic response function provided by SPM5, was applied to the preprocessed images for each subject.

Individual subject data were analyzed using a fixed-effects model. Group data were analyzed using a random-effects model using one-sample *t* tests. Condition effects at the subject level were modeled by box-car regressors representing the occurrence of each of the 4 block types. Except where noted, a voxel-level threshold of $P < 0.05$ for group contrasts, uncorrected for multiple comparisons (with an extent threshold of 8 contiguous voxels) was used to identify significant activity changes in pain-related regions and other regions of a priori interest, based on the literature and previous work in the Lab. These also included regions associated with theory of mind (TPJ, PCC), and emotion regulation (oMFC, dACC). For other regions, a threshold of $P < 0.005$ corrected for multiple comparisons was used. Activations were overlaid on a representative high-resolution structural T1-weighted image from a single subject from the SPM5 canonical image set, co-registered to Montreal Neurological Institute (MNI) space.

Pain-related activation was identified using the contrast "Pain Caused by Self vs. No Pain Self" (PCS–NPS). Agent-related activation was identified using the contrast "Pain Caused by Other vs. Pain Caused by Self" (PCO–PCS). The effect of agency was calculated by using the contrast (PCO–APO)–(PCS–NPS) and the reverse contrast.

Specific regions of interest (ROI) were computed with the MarsBaR toolbox in SPM5. ROIs in the insula, ACC, and TPJ were defined as a 6-mm spherical region centered on the following MNI coordinates: left Insula $x = -48, y = 0, z = -48$; right Insula $x = 42, y = 2, z = 0$; ACC $x = -12, y = 38, z = 32$; TPJ $x = 50, y = -42, z = 20$. These coordinates were determined on the basis of neuroanatomical atlases as well as two recent meta-analysis on 20 fMRI studies of pain empathy (Jackson, Rainville, et al., 2006) and 70 fMRI studies of theory of mind, perspective-taking, empathy and attention for the right TPJ region (Decety & Lamm, 2007).

2.7. Effective connectivity analyses

Psychophysiological interaction (PPI) analyses (Friston et al., 1997) were performed to identify the brain regions that showed stronger covariation with PPC and oMFC in the context of pain intentionally caused by another agent compared with pain that occurred accidentally. These two regions were selected upon *a priori* hypotheses: the former has consistently been associated with the representation of mental states (e.g., Gobbini, Koralek, Bryan, Montgomery, & Haxby, 2007; Walter, Adenzato, Ciaramidaro, Enrici, & Bara, 2004), and the latter with awareness of moral implications of one's and others' actions (e.g., Damasio, 1994; Moll et al., 2007).

Individual volumes of interest (VOIs) were defined as a 3-mm radius sphere. The center of this sphere was the local maximum nearest to the respective cluster maximum determined by the main effect of the segregation analysis (i.e., PCS > baseline). The significance threshold for VOI extraction was set to $P = 0.005, k = 5$. PPI analyses were performed in the following way: (1) extraction of the time-series data of the first eigenvariate of the seed VOI (low-pass filtered and mean corrected, BOLD-deconvolved) to get an estimate of the actual neural response; (2) generating a vector contrasting the time-series of the estimated neural response for the targeted conditions (representing the interaction between the psychological and physiological factors, i.e., the PPI regressor), a second vector representing the main effect of the selected contrast (the psychological variable, i.e. the *P* regressor), and a third vector representing the VOI time course (the physiological variable, *Y* regressor); and (3) forward-convolving these regressors with the canonical hemodynamic response function in order to estimate the effects of the PPI regressor. The resulting statistical parametric maps (SPMs) showed clusters for which connectivity differed in the chosen conditions.

2.8. Post-scan pain ratings

After the fMRI sessions, the same stimuli that had been shown during MRI scanning were presented to the children on a computer screen, and they were asked to rate how painful each situation was using a computer-based visual analogue scale (VAS) ranging from "no pain" to "extreme pain." Children were also asked to report what they felt when watching the stimuli in the scanner.

2.9. Correlation analysis

Parametric analyses were performed to determine the regions whose activity varied with the pain ratings. To assess the relationship between pain intensity ratings and hemodynamic responses, random-effects correlation analyses were performed. Each individual's average scores for "Pain caused by Self" on the VAS ratings was correlated with parameter estimates of the contrast "Pain caused by Self" > Baseline. A significance threshold of $P < 0.005$ (uncorrected) and $k > 5$ was selected for these analyses. To avoid an abundance of false positives associated with the multitude of analyses, significant correlations were only interpreted if they were located in a priori defined regions of the pain matrix (Derbyshire, 2000).

3. Results

3.1. Behavioral data

Repeated-measure ANOVA on the pain ratings indicated that children rated the painful situations significantly ($F_{1,16} = 65.8$, $P < 0.001$) higher (PCS: 58 ± 22 , and PCO: 60 ± 23) than the neutral ones (APO: 36 ± 23 , and NPS: 1 ± 2). Although watching hands and feet in unpleasant situations resulted in the highest pain ratings for PCO than all the other three conditions, there was no statistical difference between this condition and the PCS condition ($P > 0.26$). There was no gender difference in pain ratings ($P > 0.5$).

3.2. Functional MRI results

The main effect for the observation of body parts in pain (PCS) relative to body parts not in pain (NPS) resulted in hemodynamic signal increase in a network of brain regions that process the visual aspects (i.e., medial and lateral occipital cortex), action understanding (inferior frontal gyrus), and that belong to the pain matrix (Table 1). This network includes the middle insula, the dorsal ACC and aMCC, the ventral lateral thalamus, the somatosensory cortex (stronger in the left hemisphere), the left premotor cortex, the PAG, and SMA.

Regions significantly more active when perceiving painful situations caused by another (PCO) relative to the situations of pain caused by self (PCS) included the right orbitofrontal cortex, the right PCC, the right TPJ, as well as the right amygdala (Fig. 1). This finding of greater activation in the oMFC, PCC and TPJ resulting from the observation of pain caused by another agent (PCO) was further confirmed by the contrast assessing the effects of the presence of social interaction between two agents relative to one individual ((PCO–APO)–(PCS–NPS)). No significant signal change was found for the reverse contrast ((PCS–NPS)–(PCO–APO)).

Hemodynamic signal change in each of these areas across all conditions was further investigated with an anatomically defined region of interest (ROI) analysis, contrasting mean parameter esti-

mates across each trial type ($P < 0.01$). Results were consistent with the group analyses and revealed a higher signal change in the right TPJ across subjects when they were watching pain inflicted by another agent, than when they were watching images of pain inflicted accidentally by oneself (Fig. 2). There was also a higher signal change in the right oMFC (mean = 0.27, S.D. = 0.3) in the PCO condition relative to PCS condition (mean = 0.01, S.D. = 0.3) and in the right PCC (mean = 0.16, S.D. = 0.2). In comparison, when contrasting the APO vs. NPS conditions the only active cluster found was in the right temporo-parietal junction. No other activation was observed.

3.3. Functional integration: PPI analyses

The results from the PPI analyses indicated the involvement of a 'cognitive-attentional' network with both the oMFC and PCC. These two areas predominantly showed increased connectivity with clusters bilaterally located in the anterior intraparietal sulcus [x 30, y 53, z 55], precentral sulcus [x 39, y 11, z 29], and the right TPJ [x 55, y 44, z 20]. The oMFC additionally showed increased connectivity with the aMCC.

3.4. Correlation between brain activity and pain ratings

To examine whether the neural activation detected from the contrast between painful and non-painful situations was related to each individual's assessment of pain ratings, a regression analysis was computed between this contrast and pain ratings. A significant cluster of activation was detected in the right aMCC (x 6, y 6, z 46). The plot between the signal change at these coordinates and the subjective rating shows a significant linear correlation ($r = 0.58$, $P < 0.01$).

4. Discussion

From the design of our study it was predicted that stimuli depicting painful situations caused by accident to the self would be associated, in the observer, with specific activation in the pain matrix including the dorsal ACC and aMCC, insula, somatosensory cortex, and PAG. This is in line with previous work on pain empathy in adults that showed that a large part of the neural circuits that subserve the processing of nociceptive information is recruited by the sight of other people in pain (Jackson, Rainville, et al., 2006). Further, such situations are sufficiently transparent so that the perceiver resonates to the content of the dynamic stimuli without any mental state inferences. Such a pattern of activation in children should not be surprising given the behavioral and physiological data that document that affective sharing and vicarious emotional arousal, especially in response to others distress, is hardwired and functional very early in life (e.g., Decety & Jackson, 2004; Decety & Meyer, 2008; Eisenberg & Eggum, in press; Hoffman, 2000). This rudimentary capacity for resonating with the pain of others may trigger empathic distress in the observer, and provides the affective and motivational base for moral development (Hoffman, 1982).

However, additional neural/computational mechanisms are at play when the situations involved a social interaction between two people. As predicted, specific activation of the anterior PCC, oMFC and right TPJ was found when the children observed social interactive contexts, in which the pain was caused or alleviated by another individual. Neuroimaging studies have supported the existence of a distributed neural network underlying the ability to understand other people and oneself as intentional and emotional agents (theory of mind mechanism), which includes the superior temporal sulcus, the TPJ, the temporal poles and the medial prefrontal/anterior paracingulate cortex (e.g., Ciaramidaro

Table 1

Regions that demonstrate significant hemodynamic signal change during the conditions of interest ($P < 0.005$, $k > 8$)

Brain regions	MNI coordinates			t value
	x	y	z	
Effect of pain				
R: middle insula	42	2	0	3.84
L: middle insula	-48	0	-4	2.45
L: anterior midcingulate cortex	-6	6	46	5.65
L: dorsal anterior cingulate cortex	-10	36	31	2.72
L: premotor cortex	-52	4	40	5.70
R: inferior frontal gyrus	56	6	2	2.92
L: somatosensory cortex (SII)	-54	-30	46	4.57
R: somatosensory cortex (SII)	59	-29	38	2.39
R: supplementary motor area	10	0	68	4.45
L: supplementary motor area	-2	0	62	3.02
R: periaqueductal gray	6	-28	-11	3.58
Effect of agent				
R: anterior paracingulate cortex	2	64	10	6.56
L: orbitofrontal cortex	-6	48	-18	6.81
R: temporo-parietal junction	50	-46	20	3.76
R: amygdala	14	0	-10	3.44
Effect of pain caused by agent				
R: anterior paracingulate cortex	8	58	2	3.83
L: orbitofrontal cortex	-2	34	-24	3.13
R: anterior insula	31	29	-1	3.26
R: inferior temporal gyrus	48	-52	-10	4.14

MNI, Montreal Neurological Institute; L, left hemisphere; R, right hemisphere.

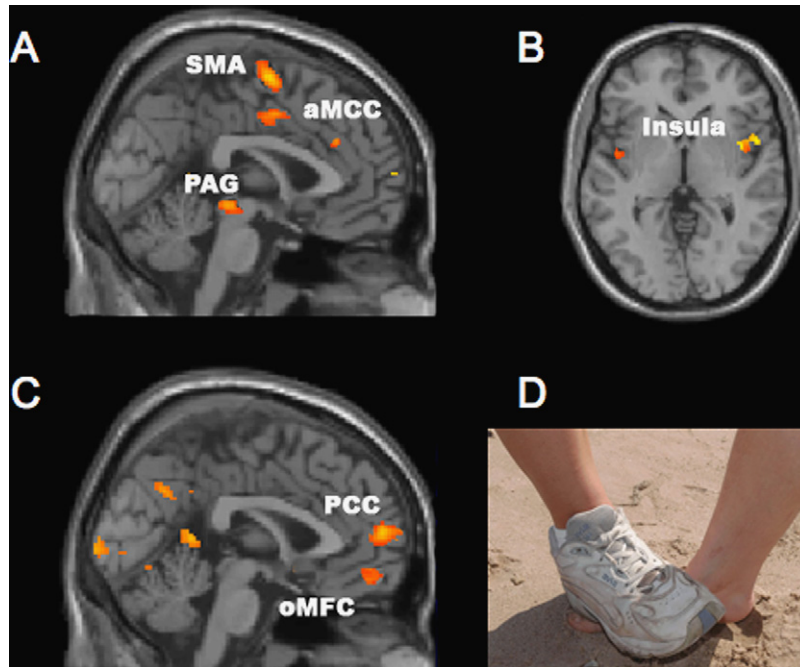


Fig. 1. When children observed other people accidentally in pain, hemodynamic signal increases neural regions that belong to the pain matrix, including the aMCC, dorsal ACC, SMA, PAG (A) and middle insula (B). The somatosensory cortex was also bilaterally activated (stronger on the left hemisphere) (result not shown). When the participants observed an agent intentionally harming another individual (D), regions involved in representation of intention and social interaction (anterior PCC, posterior cingulate (C) and right TPJ are additionally recruited).

et al., 2007). Specifically, neuroscience research indicates that the anterior PCC is implicated in understanding the mental states of an agent involved in social interaction, regardless of whether this interaction is observed, taking place online or even imagined (e.g., Walter et al., 2004). Importantly, significant activation from the interaction of pain and agent was detected in the PCC and oMFC. This finding can be associated with the intention of the agent (i.e., hurting the other) and not by the mere presence of a second individual in the situations, nor the pain aspect alone.

The contribution of the medial prefrontal cortex and the ACC to affective processing is well acknowledged. It is important however to consider that the ACC is structurally complex and contains a number of anatomically and functionally distinct regions. The pattern of activation across the different conditions in the ACC fits neatly with the broad division into dorsal and ventral areas (Koski & Paus, 2000). The dorsal aspect of the ACC is strongly associated with specific motor, attention and cognitive functions, whereas the ventral aspects (rostral, subcallosal and subgenual regions) are involved with emotions, mood and autonomic control (Devinsky,

Morrell, & Vogt, 1995). Perceiving painful situations without an interacting agent was associated with increased activity in the dorsal ACC (attention-related) and aMCC (component of the pain network), also activated during anxiety related to aversive stimuli and pain anticipation (Vogt, Berger, & Derbyshire, 2003).

Interestingly, hemodynamic activity in the right TPJ was significantly greater for the two situations that involved the presence of an agent interacting with another, and regardless of the outcome of the interaction (Fig. 2). This finding is consistent with previous functional MRI studies that demonstrated that this region is sensitive to intentionality and theory of mind (e.g., Materna, Dicke, & Their, 2007; Pelphrey, Morris, & McCarthy, 2004; Saxe & Kanwisher, 2003; Saxe & Powell, 2006). However, the fact that the TPJ is necessary for the perception of intentionality does not mean that this region is specific to that function (Stone & Gerrans, 2006). Recently, Decety and Lamm conducted a meta-analysis of 70 functional neuroimaging studies that reported right TPJ activation in various cognitive tasks, including theory of mind, empathy, perception of agency and attention-reorienting. Based on the results of this meta-analysis, and the overlap in activation, the authors

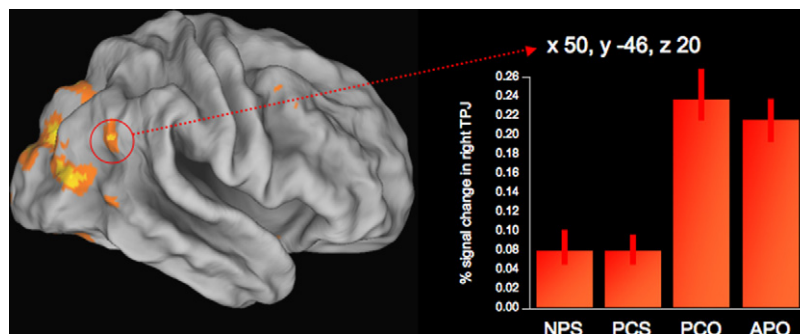


Fig. 2. Specific neuro-hemodynamic signal increase in the right TPJ associated with the perception of situations involving an interaction between two individuals (PCO and APO).

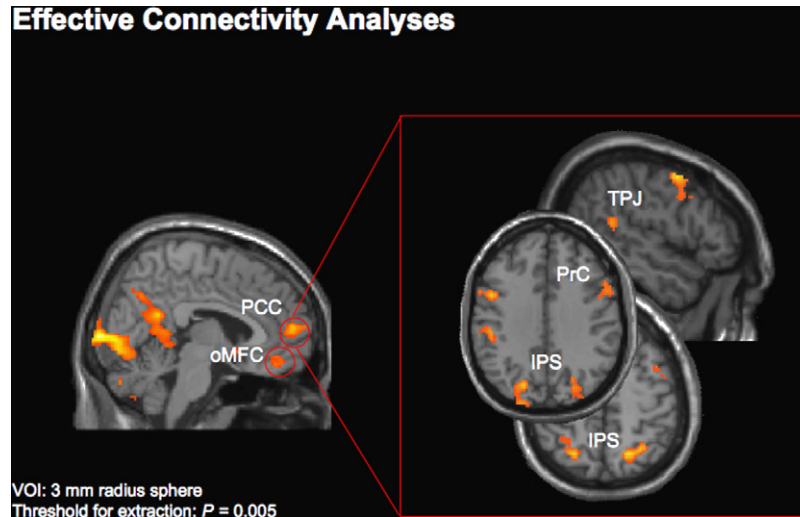


Fig. 3. PPI analyses demonstrated, in the context of pain intentionally inflicted by another individual, increased effective connectivity between the regions of the medial prefrontal cortex (PCC and oMFC) underpinning social reasoning and cortical areas that belong to the fronto-parietal attention network including the precentral sulcus (PrC), intraparietal sulcus (IPS), and the right temporo-parietal junction (TPJ) critical to the reorienting of attention toward salient stimuli.

proposed that the contribution of the right TPJ to social cognition – as seen in theory of mind or empathy tasks – relies on a low-level computational mechanism involved in generating, testing, and correcting internal predictions about external sensory events (Decety & Lamm, 2007). This mechanism is necessary for the perception of agency, and precedes meta-cognitive abilities such as reading intentions. The results of the current study endorse this functional hypothesis. Situations that involved a second agent require greater attentional demands and predictions about their behavior. As illustrated in Fig. 3, the PPI analyses demonstrate increased effective connectivity between regions of the medial prefrontal cortex (PCC and oMFC) and the fronto-parietal supramodal attention network (Corbetta, Kincade, & Shulman, 2002). The right TPJ was also strongly connected with the PCC and oMFC. Based on evidence from electrophysiological recordings in monkey as well as psychophysics and functional neuroimaging studies in humans, Corbetta and Shulman (2002) proposed that the right TPJ plays a critical function to direct attention to behaviorally relevant sensory stimuli. Additional support for the function of the TPJ was recently provided by an fMRI study that demonstrated that theory of mind and attention-reorienting tasks are associated with similar activation sites in the TPJ (Mitchell, 2008).

Although our study did not explicitly tap into moral judgment and moral emotion, perceiving an individual intentionally harming another person is likely to elicit the awareness of moral wrongdoing in the observer. Already by the age of 39 months, healthy individuals distinguish, in their judgments, moral transgression and conventional transgressions (Smetana, 1981). In support of the link between the perception of agency and wrongdoing, participants' post-scan debriefing indicates that a number of children ($N=13$) thought that the situations in which pain was caused by another person were unfair, and they were asking about the reason that could explain this behavior. The new field of moral neuroscience suggests a critical role of a cortico-limbic network subserving moral judgment. This network includes the oMFC, the TPJ (sometimes labeled posterior STS), the amygdala, and anterior PCC (Moll, de Oliveira-Souza, & Eslinger, 2003; Moll et al., 2007). Furthermore, the monitoring of outcomes that relate to punishments and rewards is linked to activity in the oMFC (Amodio & Frith, 2006; Kringelbach & Rolls, 2004). It is thus worth emphasizing that the regions selectively associated with the perception of an agent harming the other

belong to the neural systems underlying moral thinking. Developmentally, while the prefrontal cortex continues to mature until adolescence (Fuster, 1997) and self-regulation improves throughout childhood (e.g., Brocki & Bohlin, 2004), all of the components that underpin the experience of empathy and moral reasoning are in place in school-aged children (Eisenberg, 2000). Of particular relevance, the different aspects of the orbital medial frontal cortex are already in place by 44 weeks (Chi, Dooling, & Gilles, 1977).

We believe our results are important and of general interest for future research in the domain of affective developmental neuroscience and psychopathology. Many developmental theorists have argued that children who experience empathy and can regulate their emotions will be more motivated to show prosocial behaviors or to stop aggressive behavior toward another individual (Zahn-Waxler & Radke-Yarrow, 1990). The current study is the first to examine both the neural response to the pain of others and the impact of agency (who caused the pain) in young children. We demonstrate that the sight of others in pain is associated with an aversive response in the observer, underpinned by the neural circuits involved in somatosensory mirroring and processing nociceptive information. However, intentionality also plays a role in how painful situations and experiences are perceived, which in turn fuels empathic concern and moral judgments. The medial prefrontal cortex and amygdala critically contribute to this process. Altogether, these results provide an empirical framework for future investigations of social behavior disorders in children. Abnormal social cognitive behavior may result from an impairment of an inhibitory mechanism, in emotion regulation or from a lack of emotional empathy (Decety & Moriguchi, 2007; Raine, 1997). Ongoing research in our laboratory investigates antisocial children, adolescents and adults, using a similar paradigm with functional MRI and structural anatomical measures.

Our study did not address the neuro-developmental changes in relation to empathy-eliciting situations. Rather, it focused on a homogenous typically developing group of children. Future research should examine the neural response associated with empathy, sympathy, personal distress and their functional links to moral reasoning across different age groups, especially with younger children in order to determine changes in social cognitive abilities that can be associated with maturation of subregions of the prefrontal cortex and social cognitive functions.

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