Developmental Science

Developmental Science 13:6 (2010), pp 886–899 DOI: 10.1111/j.1467-7687.2009.00940.x

PAPER

Neurodevelopmental changes in the circuits underlying empathy and sympathy from childhood to adulthood

Jean Decety and Kalina J. Michalska

Center for Cognitive and Social Neuroscience, Department of Psychology and Psychiatry, University of Chicago, USA

Abstract

Empathy and sympathy play crucial roles in much of human social interaction and are necessary components for healthy coexistence. Sympathy is thought to be a proxy for motivating prosocial behavior and providing the affective and motivational base for moral development. The purpose of the present study was to use functional MRI to characterize developmental changes in brain activation in the neural circuits underpinning empathy and sympathy. Fifty-seven individuals, whose age ranged from 7 to 40 years old, were 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 to elicit empathic (feeling as the other) or sympathetic (feeling concern for the other) emotions, respectively. Results demonstrate monotonic age-related changes in the amygdala, supplementary motor area, and posterior insula when participants were exposed to painful situations that were accidentally caused. When participants observed painful situations intentionally inflicted by another individual, age-related changes were detected in the dorsolateral prefrontal and ventromedial prefrontal cortex, with a gradual shift in that latter region from its medial to its lateral portion. This pattern of activation reflects a change from a visceral emotional response critical for the analysis of the affective significance of stimuli to a more evaluative function. Further, these data provide evidence for partially distinct neural mechanisms subserving empathy and sympathy, and demonstrate the usefulness of a developmental neurobiological approach to the new emerging area of moral neuroscience.

Introduction

The ability to perceive, appreciate and respond to the affective states of another, and predict the subsequent events that will result, is an important and valuable interpersonal phenomenon (Decety & Batson, 2007). Among the psychological processes that are the basis for most of social perception and interaction, empathy and sympathy play key roles. Empathy is one of the higher-order emotions that typically emerge as the child comes to a greater awareness of the experience of others, during the second and third years of life, and that arises in the context of someone else's emotional experience (Robinson, 2008). Here, we distinguish between empathy (the ability to appreciate the emotions and feelings of others with a minimal distinction between self and other) and sympathy (feelings of concern about the welfare of others). While empathy and sympathy are often conflated, the two can be dissociated, and although sympathy may stem from the apprehension of another's emotional state, it does not have to be congruent with the affective state of the other.

Empathy and sympathy are thought to play a central role in moral development and prosocial behavior (Smetana & Killen, 2008). Individuals who experience another's emotion and feel concern for them are expected to be motivated to help and not hurt other people (Eisenberg & Eggum, 2009; Zahn-Waxler & Radke-Yarrow, 1990). Sympathy is viewed by developmental psychologists as contributing to the development and elicitation of higher levels of moral reasoning (Eisenberg, 1986; Grusec, Davidov & Lundell, 2004; Hoffman, 2000; Knafo, Zahn-Waxler, Van Hulle, Robinson & Rhee, 2008).

The complex construct of empathy can be decomposed in a model that includes bottom-up processing of affective sharing and top-down processing in which the perceiver's motivation, intentions, and self-regulation influence the extent of an empathic experience (Decety, 2007; Decety & Jackson, 2004; Decety & Meyer, 2008; Eisenberg & Eggum, 2009; Hodges & Wegner, 1997). Recent cognitive neuroscience empirical research with adult participants indicates that the affective, cognitive, and regulatory aspects of empathy involve interacting, yet partially non-overlapping neural circuits (Lamm, Batson & Decety, 2007a; Lamm, Nusbaum, Meltzoff & Decety, 2007b; Lamm, Meltzoff & Decety, 2009). There is, to our knowledge, no study that has explored the

Address for correspondence: Jean Decety, Center for Cognitive and Social Neuroscience, Department of Psychology and Psychiatry, University of Chicago, 5848 S. University Avenue, Chicago, IL 60637, USA; e-mail: decety@uchicago.edu

development of the neural underpinnings of empathy and sympathy, and their components across age. The focus of studying subcomponents of more complex behaviors can be particularly useful from a developmental perspective, when it is the case that only some components of or precursors to more complex behaviors are observable. In addition, developmental studies can provide unique opportunities to see how the components of the system interact in ways not possible in adults, where all the components are fully mature and operational (De Haan & Gunnar, 2009).

There is ample behavioral evidence demonstrating that the affective component of empathy develops earlier than the cognitive component. Affective responsiveness is known to be present at an early age, is involuntary, and relies on mimicry and somato-sensorimotor resonance between other and self. For instance, newborns and infants become vigorously distressed shortly after another infant begins to cry (Dondi, Simion & Caltran, 1999; Martin & Clark, 1987). Facial mimicry of basic emotional expressions also contributes to affective sharing, and this phenomenon starts very early in life, approximately by 10 weeks of age (e.g. Field, Woodson, Greenberg & Cohen, 1982; Haviland & Lewica, 1987). This primitive mimicry mechanism, which may be based on mirror neurons (i.e. sensorimotor neurons found in the premotor, motor and anterior intraparietal area), contributes to the development of empathy in the early preverbal period, and continues to operate past childhood (Lamm, Porges, Cacioppo & Decety, 2008; Sonnby-Borgstrom, Jonsson & Svensson, 2003). However, recent research has also documented that young children (18–25-month-olds) can sympathize with a victim even in the absence of overt emotion cues (Vaish, Carpenter & Tomasello, 2009), which suggests some early form of affective perspective taking that does not rely on emotion contagion or mimicry.

The cognitive aspects of empathy and sympathy are closely related to processes involved in theory of mind (ToM) and self-regulation. 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 mature empathic understanding and sympathetic concern. Such an understanding requires forming an explicit representation of the feelings of another person, an intentional agent, which necessitates additional computational mechanisms beyond the emotion sharing level, as well as self-regulation to modulate negative arousal in the observer (Decety & Moriguchi, 2007; Decety, Michalska & Akitsuki, 2008). 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 without confusion between self and other (a decoupling computational mechanism between first-person information and second-person information), for which the medial and ventromedial prefrontal cortex play a crucial role (Decety & Jackson, 2004; Frith & Frith, 2003).

The regulation of internal emotional states and processes is particularly relevant to the modulation of vicarious emotion and the experience of empathy and sympathy. Sympathy is strongly related to effortful control, with children high in effortful control showing greater empathic concern (Rothbart, Ahadi & Hershey, 1994). A number of developmental studies conducted by Eisenberg and her colleagues (Eisenberg, Fabes, Murphy, Karbon, Maszk, Smith, O'Boyle & Suh, 1994; Eisenberg, Fabes & Spinrad, 2006) found that individual differences in the tendency to experience sympathy versus personal distress vary as a function of dispositional differences in individuals' abilities to regulate their emotions. Well-regulated children who have control over their ability to focus and shift attention are hypothesized to be relatively prone to sympathy regardless of their emotional reactivity. This is because they can modulate their negative vicarious emotion to maintain an optimal level of emotional arousal. In contrast, children who are unable to regulate their emotions, especially if they are dispositionally prone to intense negative emotions, are found to be low in dispositional sympathy and prone to personal distress (Eisenberg *et al.*, 1994).

Both theory of mind and emotion regulation tap into executive function resources implemented in the prefrontal cortex (Zelazo, Carlson & Kesek, 2008; Stone & Gerrans, 2006), with different regions subserving distinct functions. The prefrontal cortex develops more slowly than other brain areas, reaching maturation only late in adolescence (Bunge, Dudukovic, Thomasson, Vaidya & Gabrieli, 2002). It is well documented that the prefrontal cortex and its functions follow an extremely protracted developmental course, and age-related changes continue well into adolescence (Casey, Tottenham, Liston & Durston, 2005; Toga, Thompson & Sowell, 2006). The maturation of the prefrontal cortex allows children to use verbalizations to achieve self-regulation of their feelings and exercise inhibitory control over their thoughts, attention, and action (Diamond, 2002). Specifically, frontal lobe maturation is associated with an increase in a child's ability to activate areas involved in executive and emotional control. For example, Killgore and colleagues (Killgore, Oki & Yurgelun-Todd, 2001; Killgore & Yurgelun-Todd, 2007) provided evidence that as a child matures into adolescence there is a shift in response to emotional events from using more limbic-related anatomic structures, such as the amygdala, to using more frontal lobe regions to control emotional responses.

Pain serves evolved protective functions not only by warning the suffering person, but also by impelling expressive behaviors that attract the attention of others (Craig, 2004). The perception of pain in others has recently been used as a window to investigate the neurophysiological mechanisms that underpin the experience of empathy (Decety, 2007; Decety & Lamm, 2009; Goubert, Craig & Buysse, 2009). In that context, a growing number of functional magnetic resonance imaging (fMRI) studies have demonstrated that perceiving or imagining another

individual in pain is associated with specific activation in the neural regions that belong to the pain matrix (Price, 2000), particularly areas coding for the motivational-affective dimension of pain (e.g. Botvinick, Jha, Bylsma, Fabian, Solomon & Prkachin, 2005; Cheng, Lin, Liu, Hsu, Lim, Hung & Decety, 2007; Gu & Han, 2007; Jackson, Meltzoff & Decety, 2005; Jackson, Brunet, Meltzoff & Decety, 2006b; Lamm *et al*., 2007a, 2007b, Moriguchi, Decety, Ohnishi, Maeda, Mori, Nemoto, Matsuda & Komaki, 2007a; Morrison, Lloyd, di Pellegrino & Roberts, 2004; Saarela, Hlushchuk, Williams, Schürmann, Kalso & Hari, 2007; Singer, Seymour, O'Doherty, Kaube, Dolan & Frith, 2004; Zaki, Ochsner, Hanelin, Wager & Mackey, 2007). This neural network includes the supplementary motor area (SMA), dorsal anterior cingulate cortex (ACC), the anterior midcingulate cortex (aMCC), anterior insula (AI), and the periaqueductal gray (PAG). Some studies have also reported activation of the somatosensory cortex (e.g. Benuzzi, Lui, Duzzi, Nichelli & Porro, 2008; Cheng *et al*., 2007, 2008; Lamm & Decety, 2008; Lamm *et al*., 2009; Moriguchi *et al*., 2007a), a region coding the sensory-discriminative dimension of pain. It is worth mentioning that the activation of these regions (i.e. ACC, AI, PAG, SMA) is not specific to the processing of noxious stimuli. The same neural network, which includes the amygdala, responds to any unpleasant salient stimuli, and its involvement in empathy for pain may thus reflect a general aversive response to a threat (Akitsuki & Decety, 2009; Benuzzi *et al*., 2008; Ogino, Nemoto, Inui, Saito, Kakigi & Goto, 2007; Yamada & Decety, 2009).

Previous work in our laboratory has successfully used dynamic visual stimuli depicting painful situations either occurring accidentally or painful situations purposefully caused by another individual to chart the neural response associated with empathy in the sense of sharing what the other feels (to the former category of stimuli), and sympathy in the sense of feeling concern for the other (to the latter category of stimuli) in three independent functional MRI studies with young children (Decety *et al*., 2008), adolescents (Decety, Michalska, Akitsuki & Lahey, 2009), and adults (Akitsuki & Decety, 2009). Results from these studies show that attending to painful situations caused by accident is associated with activation of the pain matrix, including the aMCC, SMA, insula, PAG, and somatosensory cortex. Interestingly, when participants watch another person intentionally inflicting pain onto another, regions that are consistently engaged in representing social interaction, affective evaluation, and moral reasoning (i.e. temporo-parietal junction, amygdala, medial and orbital frontal cortices) were additionally recruited, and increased their functional connectivity with the frontoparietal attention network. These results indicate that situations depicting an individual intentionally hurting another person is a way to apprehend the neural response associated not only with empathy but also with sympathy and perhaps moral sensitivity. This is quite important since sympathy acts as a proximate mechanism in motivating altruistic prosocial behavior. This has been demonstrated in numerous studies in social and developmental psychology (e.g. Batson, 1991; Zahn-Waxler & Radke-Yarrow, 1990).

One limitation of these three separate studies, however, is that they cannot capture any continuous functional changes across age. This is unfortunate because among areas of the brain undergoing considerable remodeling from childhood to adolescence is the prefrontal cortex, both dorsal and ventromedial (Gogtay, Giedd, Lusk, Hayashi, Greenstein, Vaituzis, Nugent, Herman, Clasen, Toga, Rapoport & Thompson, 2004). Lesion and functional MRI studies documented the critical role of these regions in recognizing emotions in others and experiencing social emotions such as guilt or embarrassment (Beer, Heeray, Keltner, Scabani & Knight, 2003; Berthoz, Armory, Blair & Dolan, 2002; Bramham, Norris, Hornak, Bullock & Polkey, 2009; Kringelbach & Rolls, 2004; Shamay-Tsoory, Tibi-Elhanany & Aharon-Peretz, 2006). Further, both the insula and the amygdala may differentially contribute to the experience of interpersonal sensitivity during development. For instance, while significant signal change was detected in the right insula in all three studies from our laboratory (three separate age groups) when participants were exposed to visual stimuli depicting painful situations, there were differences in the anatomical location of the activated clusters (see Figure 1 for an illustration). Such differences may be meaningful with regard to the functions that have been attributed to the posterior and the anterior sectors of insula in relation to interoception, and subjective awareness of feelings respectively (Craig, 2003). While human neuroimaging studies using pain empathy paradigms all report activations in the insula, no

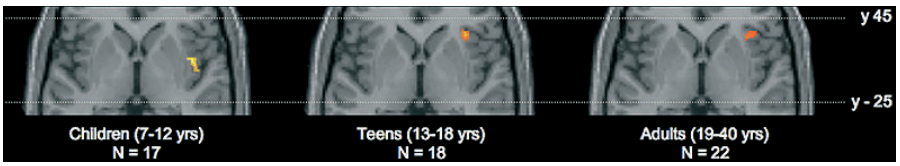

Figure 1 *Activated cluster in the right insula in the 57 participants watching painful situations accidentally caused by self versus non-painful situations (p < .05, FDR corrected). Note that the peak of the clusters lies in the anterior portion of the insular cortex in adults [x 40, y 24, z 0] and in the middle/posterior portion of the insula in children [x 42, y 02, z 0].*

systematic attention has been paid to the anatomical subdivisions of the insula, particularly with regard to their respective functional contribution across age.

Therefore, the goal of the current investigation was to relate age change to functional differences associated with empathy and sympathy by reanalyzing all of the functional and behavioral data from the three previous studies in a single data set. Further, to ensure that all ages were equally represented, we also scanned 10 adolescent participants and incorporated their data into this new analysis.

Until recently, relatively limited research has existed on the neurobiological changes that accompany the affective and cognitive changes that occur during normal development, from early childhood to adulthood. Nevertheless, advances in neuroimaging techniques over the past decade have allowed us to begin tracking changes in the structural and functional brain organization (Casey *et al*., 2005; Yurgelun-Todd, 2007). On the basis of this knowledge, a differential neurodevelopmental pattern of response to empathy- and sympathy-eliciting stimuli may be anticipated. It is hypothesized that the affective response to the perception of others in painful situations will be maximal in childhood, potentially to motivate attention to important social cues during the most formative period of socialization, in contrast to adults who can enlist mature social perceptual skills to determine the emotional significance of the stimuli. In that case we anticipate amygdala response to be greater in children than in older participants. Adolescent participants are postulated to fall in the middle of this range. It is predicted that age-related reductions in the affective response elicited by painful situations will be associated with attenuation of limbic and visual cortical activity. In other words, the expected pattern of reduced limbic and visual cortical activity in contrasts of young children and adults should also be shown in the period from adolescence to adulthood. This is best examined in a continuous manner rather than by comparing age groups separately as any categorical division between these groups is arbitrary. Given what we know about the critical role of the ventromedial prefrontal cortex, and particularly the orbitofrontal cortex, in emotional behavior, empathy, sympathy and moral reasoning (e.g. Blair, 2005; Hornak, Bramham, Rolls, Morris, O'Doherty, Bullock & Polkey, 2003; Rankin, Gomo-Tempini, Allison, Stanley, Glenn, Weiner & Miller, 2006; Moll, de Oliviera-Souza, Garrido, Bramati, Caparelli-Daquer, Paiva, Zahn & Grafman, 2007; Shamay-Tsoory, Tomer, Berger & Aharon-Peretz, 2003), we expect that region to be preferentially recruited when participants are exposed to situations in which an individual is intentionally hurt by another. Finally, greater signal change with increasing age should be associated with prefrontal regions that are responsible for cognitive control and response inhibition, such as the dorsolateral prefrontal cortex and the inferior frontal gyrus (Kawashima, Sato, Itoh, Ono, Furumoto, Gotoh, Koyama, Yoshioka, Takahashi & Takahashi, 1996; Konishi, Nakajima, Uchida, Kikyo, Kameyama & Miyashita, 1999; Swick, Ashley & Turken, 2008).

We believe that this is the first study that explores neurodevelopmental changes to empathy- and sympathy-inducing stimuli in a large group of participants ranging from 7 to 40 years of age. Such investigations are valuable in shedding light on the neurobiological mechanisms underpinning the basic building blocks of morality and their age-related functional changes.

Methods

Subjects

Fifty-seven individuals (29 males) were recruited from the local community of the University of Chicago campus. Age ranged from 7 to 40. Participants' written consent was obtained. For subjects under age 18, parents' written informed consent was obtained as well as children assent. All participants 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.

Stimuli preparation and validation

A series of dynamic visual stimuli was created and validated prior to the functional MRI study. These animated stimuli contained scenes of various types of painful and non-painful everyday situations (see Figure 1 in Akitsuki & Decety, 2009, for an illustration). Each animation displayed one or two persons (different ages and gender) whose right hands or right feet were visible but not their faces. When presented, the two individuals were easily distinguished from one another in clothing or shoe type. Seventy-two stimuli belonged to three 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 her hand (PCS, pain caused by self).
2. Only one person is involved in a non-painful situation, e.g. opening a door (NPS, no pain situation).
3. One person is in a painful situation caused by another, e.g. stepping purposely on someone's toe (PCO, pain caused by other).

Each dynamic stimulus consisted of three digital color pictures, which were edited to the same size (600×480 pixels) and presented in a successive manner to imply motion. The durations of the first, second and third pictures in each animation were 1000 ms, 200 ms and 1000 ms, respectively.

Validation of the material was conducted with a group of 222 healthy participants (110 females, age range 10–38 yrs; middle school to college educated) who were shown these dynamic stimuli on computer desktops, and asked to estimate on visual analog scales (VAS) how

painful these situations were, whether they believed that the pain was caused intentionally or not, and how much empathic concern (sympathy) these situations elicited (Estabrook, 2007). Further, the stimuli were rated for perceived intentionality and empathic concern by an additional group of 32 participants whose age ranged between 18 and 23 years. Eye tracking and pupillary dilatation data were simultaneously recorded with a Tobii T120 system (Hempel, 2009). Results showed that subjective ratings of empathic concern were higher when participants were watching the stimuli depicting people being hurt intentionally than when watching people whose pain was accidentally caused ($p < .001$). An effect of perceived agency was found in relation to pupillary dilation and eye gaze patterns indicating that the pupil size was significantly larger during the sympathy-eliciting conditions than during the empathy-eliciting conditions ($p < .0001$). This finding supports the notion that the autonomic nervous system is sensitive to highly arousing emotions. Subjects looked more frequently at the person who was intentionally hurt than at the person who was hurt by accident ($p < .05$).

Training in a mock-up scanner

Prior to MRI scanning, participants were acclimated to the procedures in a mock-up scanner. They were asked to lie in the mock scanner while a documentary movie was played. When participants felt comfortable, they were presented with 24 stimuli (six per condition) depicting situations similar to, but not the same as, those they would watch in the actual scanning sessions. MRI noise was simulated through a recording played during the mock session.

Magnetic resonance imaging measurements

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 seven baseline blocks (duration 17.6 s each) during which a fixation cross was presented and six active blocks (duration 19.8 s each) during which stimuli from one of the three categories were presented. The presentation order was counterbalanced across runs and across subjects. Each block consisted of six stimuli (2200 ms each) with five inter-stimulus intervals (1100 ms each) during which a black fixation cross was presented against a gray background.

Participants were shown the stimuli in two short sessions (6 min each) to maintain their attention. To avoid confounding motor-related activation in the ACC and pre-SMA/SMA, no overt response was required. Instead, participants were instructed to watch the stimuli carefully.

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 & Lai, 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 × 3.75 mm. An axial T1-weighted 3D magnetization-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).

Behavioral measures

After the scanning session, participants were presented with the same stimuli (in a randomized order) that they saw in the scanner on a computer desktop, and asked to rate how painful each situation was using a computer-based visual analogue scale (VAS) ranging from 'no pain' (i.e. score = 0) to 'extreme pain' (i.e. score = 100).

Data 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. Structural T1 images were first coregistered to the mean EPI image for each participant. The coregistered T1 images were then spatially normalized and an average of these normalized T1 images of all the participants was calculated. Results are shown on mean normalized averaged T1 images. All 57 subjects had less than 0.5 voxels of in-plane motion throughout the entire experiment. 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. Condition effects at the subject level were modeled by box-car regressors representing the occurrence of each of the four block types.

The resulting first-level contrast images were then entered into a second-level random effects analysis. Pain-related activation was identified using the contrast between stimuli depicting 'pain caused by self' vs. 'no pain stimulus' (PCS–NPS). Perception of agency-related activation was identified using the contrast between 'pain caused by other' vs. 'pain caused by self' (PCO–PCS). The significant voxels and clusters were given a threshold at $p = .005$ and a spatial extent threshold of k = 10,

corrected for multiple comparisons across the whole volume using the false discovery rate approach (Genovese, Lazar & Nichols, 2002). The choice of this threshold was determined based on previous studies on empathy for pain and on power considerations for the current paradigm (Jackson *et al.*, 2005; Lamm & Decety 2008; Lamm *et al.*, 2007a). These included regions associated with theory of mind (TPJ, medial prefrontal cortex), and emotion regulation (OFC, dACC). 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.

In order to assess the relationship between age and hemodynamic response to the stimuli, random effects correlation analyses were performed with participants' age in weeks. Only clusters that survived false discovery rate (FDR) at $p = .05$ were considered.

Results

Participants' subjective ratings for both painful situations caused by self (PCS) and painful situations caused intentionally by another (PCO) conditions were submitted to a correlational analysis with age (in weeks). Results indicate that there is a gradual decrease in the subjective evaluation of pain intensity for both painful conditions across age, with younger participants rating them significantly more painful than older participants (for PCS, $r = -0.327$, $p < .01$; for PCO, $r = -0.267$, $p < .05$). Further, while on average participants rated the pain caused intentionally (PCO) conditions as significantly more painful than when pain was caused accidentally by the self (PCS) ($t(56) = 2.581$, $p < .01$), this effect was not, however, driven by age (see Figure 2). Gender had no effect on the subjective measures.

To investigate if females and males differed in their pain intensity ratings over the two conditions, we computed repeated-measures, two-way ANOVAs with pain intensity as dependent variable and condition (repeated measure) and gender as independent variables. There was no main effect of gender ($p = .32$) and no significant interactions between gender and condition, indicating that males and females did not differ in their subjective pain ratings dependent on condition.

Whole group analysis

Direct comparison in the 57 participants between conditions of pain caused by self versus no pain shows a significant hemodynamic signal increase in the neural regions that belong to the pain matrix, including the insula, ACC, PAG, SMA, left premotor cortex, and left somatosensory cortex (Figure 3, and Table 1).

The contrast between painful situations intentionally inflicted by another versus pain caused by self demonstrates a significant hemodynamic increase in the right

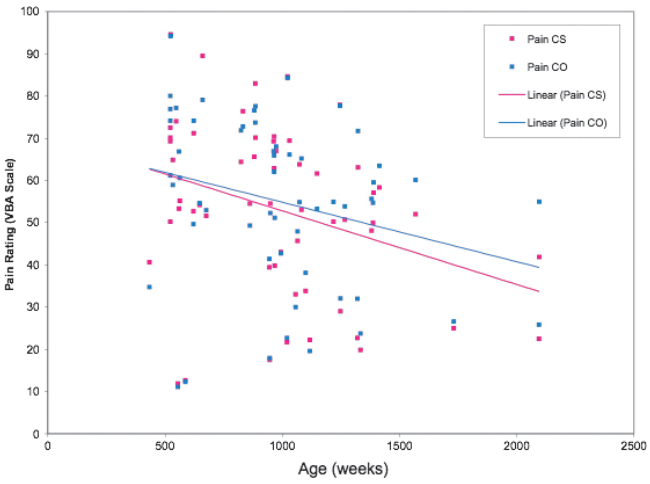

Figure 2 *Subjective ratings to dynamic visual stimuli depicting painful situations accidentally caused by self (PCS) and painful situations intentionally caused by another individual (PCO) across age (in weeks). There is a gradual decrease in the subjective evaluation of pain intensity for both painful conditions across age, with younger participants rating them significantly more painful than older participants (for PCS $r = -0.327$, $p < .01$, for PCO $r = -0.267$, $p < .05$). Further, while on average participants rated the pain caused intentionally (PCO) conditions as significantly more painful than when pain was accidentally caused by self (PCS) ($t(56) = 2.581$, $p < .01$), this effect was not driven by age.*

TPJ, the amygdala, the left dorsal prefrontal gyrus, and the medial and ventromedial prefrontal cortex.

Age-related brain activity associated with empathy-eliciting stimuli

The younger the participants, the stronger the hemodynamic activity found in the amygdala (x 22, y −6, z −16; $r = -0.33$, $p < .01$, see Figure 4), supplementary motor area (x 6, y 0, z 68; $r = -32$, $p < .01$) and posterior insula (x 46, y 6, z 24; $r = -30$, $p < .01$) when they watched painful situations caused accidentally by the self. The older the participants, the higher the activity detected bilaterally in the left inferior (x −46, y 44, z −8; $r = 0.46$, $p < .005$) and right superior frontal gyri (x 26, y 20, z 50; $r = 0.30$, $p < .05$).

Age-related brain activity associated with sympathy-eliciting stimuli

The younger the participants, the stronger the activity detected in the medial orbitofrontal cortex (x 10, y 50, z −2; $r = -0.43$, $p < .001$), and bilaterally in the fusiform gyrus ($r = -0.34$, $p < .001$) when they observed painful situations intentionally caused by another individual. The older the participants, the stronger the activity detected in the lateral orbitofrontal cortex (x 38, y 48, z −8; $r = 0.34$, $p < .01$) and in the right anterior insula (x 40, y 24, z 1; $r = 0.30$, $p < .01$). Figure 5 illustrates the shift in activation in the ventral OFC across age.

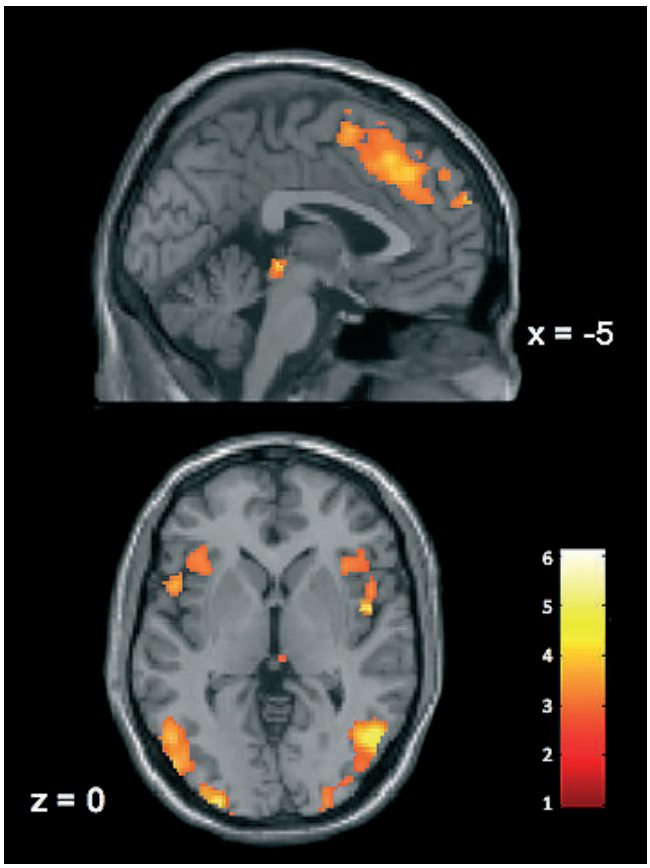

Figure 3 *Activation map of regions associated with pain empathy-eliciting stimuli in the whole group. The images depict t-statistic values rendered onto a normalized template MRI, with sagittal (top) and horizontal (bottom) slices. Significant signal change was identified in the medial prefrontal cortex, including the SMA and ACC, PAG, insula, somatosensory cortex (not shown), STS and fusiform gyrus.*

Correlation between pain ratings and brain activity

Higher pain ratings were correlated with increased hemodynamic activity in the left somatosensory cortex (x −28, y −28, z 70; $r = 0.33$, $p < .01$), and bilaterally with the amygdala (x 30, y 8, z −20; $r = 0.32$, $p < .01$; x −30, y 8, z −24; $r = 0.27$, $p < .05$), whereas the lower the ratings the higher the activation in the medial prefrontal cortex (x 8, y 42, z 28; $r = 0.39$, $p < .01$). When age was used as a control variable in the computation of correlation between the subjective ratings of pain and the brain response, the correlation with the amygdala reached greater significance ($p < .01$) and the somatosensory activation remains significant ($p < .05$). In addition, the correlation with the medial prefrontal remains the same.

Table 1 *Brain regions showing significant activation ($p < .05$, FDR corrected for multiple comparison, $k > 10$ voxels) in the 57 participants when they watched dynamic visual stimuli depicting painful situations accidentally caused by oneself and painful situations intentionally caused by another individual*

	MNI coordinates			
Regions of Interest	x	y	z	*t*-value
Pain Caused by Self vs. No Pain Situation				
R: insula	38	22	0	4.54
L: insula	36	22	2	4.80
L: anterior cingulate cortex	−4	34	40	4.72
L: supplementary motor area	−6	8	58	3.61
R: supplementary motor area	6	22	54	4.66
L: supplementary motor area	7	22	38	2.98
L: somatosensory cortex	−44	−41	54	5.62
L: premotor cortex	−50	11	18	4.71
R: periaqueductal gray	4	−28	−8	4.01
L: periaqueductal gray	−6	−28	−8	4.10
Pain Caused by Other vs. Pain Caused by Self				
L: medial orbitofrontal cortex	−5	56	−10	3.52
R: medial orbitofrontal cortex	2	43	−14	3.92
L: Septal nuclei	−4	10	−08	3.63
R: temporoparietal junction	52	−43	18	4.76
R: amygdala	18	0	−14	3.12
R: superior frontal gyrus	47	18	24	3.74
R: medial prefrontal cortex	8	51	10	4.15

Discussion

This study examined age-related differences in brain activation when participants were exposed to empathy- and sympathy-eliciting dynamic stimuli. It is important to note that no task was required during stimuli presentation in the scanner, thus any difference in hemo-

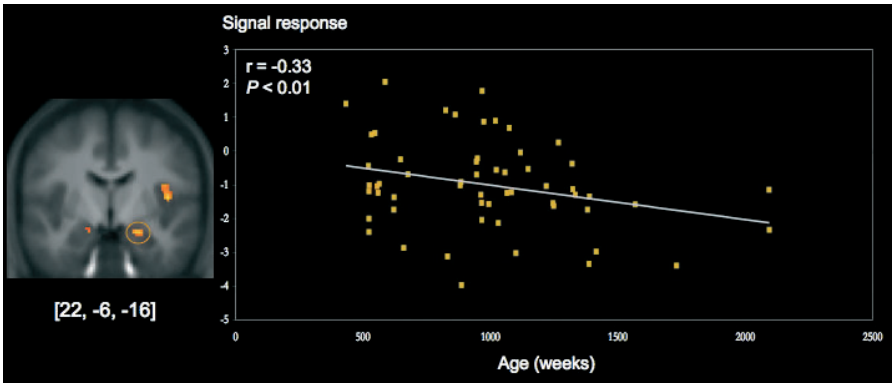

Figure 4 *Results of correlation analysis for the right amygdala [x 22, y −6, z −16]. A significant negative correlation between age and degree of activation was detected in the amygdala.*

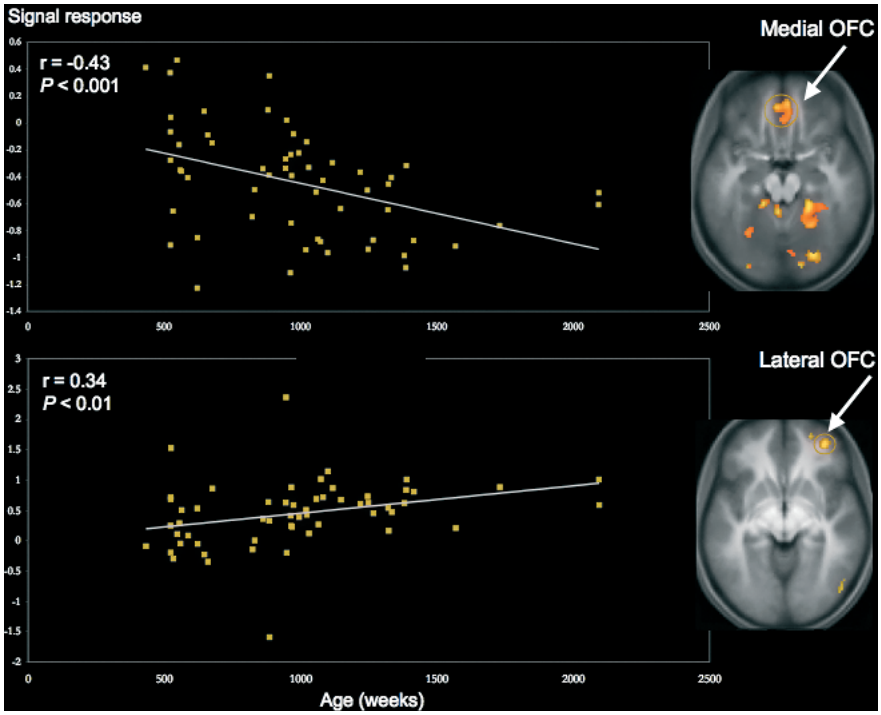

Figure 5 *Results of correlation analysis for the ventromedial prefrontal cortex. A significant negative correlation (r = −43, p < .001) between age and degree of activation was detected in the medial portion of the orbitofrontal (x 10, y 50, z −2) cortex, while a significant positive correlation (r = 0.34, p < .01) was noted in the lateral portion of the orbitofrontal cortex (x 38, y 48, z −8).*

dynamic signal change cannot be attributable to accuracy of performance. Furthermore, pain ratings obtained after the scanning session demonstrate that all participants, regardless of their age, evaluated the painful situations similarly; specifically, they rated situations that involved pain intentionally caused by another individual as more painful than painful situations accidentally caused by the self. Although a significant gradual decrease in pain evaluation was found across age, the difference in the ratings of the two conditions did not interact significantly with age.

Whereas decreases in pain evaluation were significantly correlated with hemodynamic response in the medial prefrontal cortex, increases in pain ratings were correlated with bilateral amygdala activation.

These behavioral results are important for interpreting region-specific differences in activation with age as reflecting functional maturation and not simply (and unlikely in our case) differences in performance. The use of simple stimuli that convey painful information in conjunction with agency attribution (i.e. who is the cause of the pain) constitutes an ecologically valid means to explore the brain response and potential age-related differences in relation to interpersonal sensitivity. Indeed, not only does pain have clear adaptive value in signaling danger and in distinguishing harmful from harmless situations, but its expression provides a crucial signal which can motivate helping behavior in others. Pain is ubiquitous across individuals and cultures, and all individuals have some experience with both physical and social pain at an age much younger than that of our youngest participants (7 years). Similarly, there is agreement in the developmental literature that children understand intentional agency and have mature theory of mind (TOM) well before 7 years of age (Baird & Baldwin, 2001; Sommerville, 2007). Importantly, post-scan debriefing further indicated that participants considered the situations in which an individual was hurt intentionally by another as morally wrong and socially inappropriate given that no context was provided.

While all participants activated the network subserving pain processing when exposed to empathy-eliciting stimuli, and regions of the prefrontal cortex when perceiving the sympathy-eliciting stimuli (Table 1), several regions that were predicted in our a priori hypotheses, including the amygdala, insula and orbitofrontal regions, exhibited interesting patterns of change with age.

The younger the participants, the more strongly the amygdala, posterior insula, and SMA were recruited when they watched painful situations caused accidentally. In addition, a similar effect was detected in the medial portion of the orbitofrontal cortex, and the septal nuclei when they watched painful situations intentionally inflicted by another individual, such that these areas were significantly more activated the younger the participants. Young participants also evaluated the situations as more painful than older participants, and these ratings correlated significantly with activity in the amygdala and somatosensory cortex. The co-activation of the amygdala, posterior insula and medial orbitofrontal cortex

can be interpreted as reflecting negative arousal and more broadly a visceral response to a potential threat. The fact that the amygdala was highly responsive in children when they were exposed to empathy-eliciting stimuli fits well with its role in affective development. Indeed, the amygdala activity in children is consistent with countless studies that have documented that this region plays a critical role in fear-related behaviors, such as the evaluation of actual or potential threats (LeDoux, 2000). Interestingly, the signal in the amygdala was stronger in young participants when they watched pain intentionally inflicted by another individual than when observing pain accidentally caused by the self (Decety *et al*., 2008). The former situation is certainly more arousing and this is coherent with a general role of the amygdala in processing relevant and salient stimuli (Norris, Chen, Zhu, Small & Cacioppo, 2004). There is also evidence from neuropsychology suggesting that the amygdala plays an important role in the neural systems supporting the normal development of ToM reasoning. For instance, Shaw and colleagues (Shaw, Lawrence, Radbourne, Bramham, Polkey & David, 2004) examined the effects of lesions of the amygdala which occurred at different stages of development on this key aspect of social cognition. Subjects with early damage to the amygdala were impaired relative to all other groups on more advanced tests of theory of mind reasoning. In contrast, subjects who acquired damage to the amygdala in adulthood (usually as part of an anterior temporal lobectomy) were not impaired in ToM reasoning relative to both clinical and healthy controls, supporting the position that the amygdala is not part of the neural circuitry mediating the 'online' performance of ToM reasoning.

Regarding activity in the insula, an interesting pattern of activation along a posterior–anterior gradient was observed across age. A significant negative correlation between age and degree of activation was found in the posterior insula. In contrast, a positive correlation was found in the anterior portion of the insula. The insular cortex has regions of variable cell structure or cytoarchitecture, changing from granular in the posterior portion to agranular in the anterior portion. The insula also receives differential cortical and thalamic input along its length (Dupont, Bouilleret, Hasboun, Semah & Baulac, 2003). A posterior-to-anterior progression of increasingly complex re-representations in the human insula is thought to provide a foundation for the sequential integration of the individual homeostatic condition with sensory environment and motivational condition (Craig, 2004). The posterior insula receives inputs from the ventromedial nucleus (posterior part) of the thalamus that are highly specialized to convey emotional/homeostatic information such as pain, temperature, hunger, thirst, itch, and cardiorespiratory activity. It serves as a primary sensory cortex for each of these distinct interoceptive feelings from the body. The posterior part has been shown to be associated with interoception, due to its intimate connections with amygdala, hypothalamus, and cingulate and orbitofrontal cortices (Jackson, Rainville & Decety, 2006a). Whereas painful sensations are evoked by direct electrical stimulation in the dorsal and posterior part (but not anterior) of the insula in epileptic patients (Ostrowsky, Magnin, Ryvlin, Isnard, Guenot & Mauguiere, 2002), and lesion of the posterior insula critically reduces pain sensation (Greenspan, Lee & Lenz, 1999), lesions of right anterior insula can reportedly produce conditions regarded clinically as anosognosia, i.e. the lack of emotional awareness of oneself (Karnath, Baier & Nagele, 2005). It has been proposed that the right insula serves to compute a higher-order metarepresentation of the primary interoceptive activity, which is related to the feeling of pain and its emotional awareness (Craig, 2003). The results of a meta-analysis on neuroimaging studies of emotion (Wager, Luan Phan, Liberzon & Taylor, 2003) also showed an above-chance density of withdrawal-related activation foci in the mid-insula. In light of these neurophysiological considerations, we posit that the anatomical progression (from sensory to emotional awareness) parallels the neurodevelopmental response to seeing people in pain or distress. In other words, a visceral response to painful stimuli associated with danger and negative affect is less likely to occur with increasing age and such a response may be replaced by a more detached appraisal of the stimulus. Indeed, the older the participants the greater the activity in the dorsolateral prefrontal cortex and inferior frontal gyrus, which are implicated in cognitive control and response inhibition (Swick *et al*., 2008). This is in line with evidence that regulatory mechanisms continue to develop into late adolescence and early adulthood. Increased activity in the prefrontal cortex has been associated with significant down-modulation of amygdala responses to affective stimuli, particularly with regard to fearful faces (Hariri, Bookheimer & Mazziotta, 2000). Overall, this pattern of response in the amygdala and insula can be interpreted in terms of the frontalization of inhibitory capacity, hypothesized to provide a greater top-down modulation of activity within more primitive emotion-processing regions (Yurgelun-Todd, 2007). This finding provides neurophysiological support for developmental studies showing that emotion regulation is an important aspect of empathy and sympathy especially in relation to prosocial behavior. Sympathy has been associated with high levels of children's regulation whereas low levels of regulation have been associated with personal distress (Eisenberg & Fabes, 1995; Decety & Lamm, 2009). Well-regulated children can modulate their vicarious negative arousal, and consequently focus their attention on others' affective states and needs rather than on their own aversive emotion.

Brain response to sympathy-eliciting stimuli exhibited a striking age-related change in the orbitofrontal cortex, characterized by a shift from the medial portion in young participants to the lateral portion in older participants

(see Figure 5). The ventromedial prefrontal cortex plays a critical role in empathy and sympathy, and more generally in social cognition. Prefrontal damage tends to disrupt the contingent rather than constitutive aspects of emotion and motivation. For instance, patients with frontal lobe damage have no major change in appetite but may become less discriminating in their food preferences; prefrontal lobotomy does not alter the threshold for withdrawing from painful stimuli but blunts the concern for the pain (Mesulam, 2002). Lesions of the orbitofrontal cortex are associated with poor judgment, socially inappropriate behavior and impulsivity (Damasio, 1994). Impaired empathic response has been described in patients with ventromedial lesions, particularly on the right side (Rankin *et al*., 2006; Shamay-Tsoory *et al*., 2003). Especially interesting for developmental science, early dysfunction of the ventromedial prefrontal cortex causes abnormal development of social and moral behavior (e.g. Anderson, Bechara, Damasio, Tranel & Damasio, 1999).

The ventromedial prefrontal cortex has intrinsic networks that are defined on the basis of their cortico-cortical connections and also connections with other parts of the cerebral cortex and subcortical structures, including the mediodorsal nucleus of the thalamus, sensory areas, virtually all limbic structures and brainstem, subserving distinct functions (Ongur & Price, 2000). To this extent, these networks are expected to contribute differently to emotional processing. The medial network is characterized by outputs to visceral control structures in the hypothalamus and brainstem. It is interconnected with the amygdala, hippocampus and STS and has been involved in mood and emotion behavior. The orbital lateral network is characterized by its sensory inputs from almost all of the sensory modalities. Anatomical connectivity of the lateral OFC gives it the potential to integrate sensory information, to modulate sensory and cognitive processing via feedback connections, and to influence motor and autonomic responses. Neuropsychological evidence indicates that lateral orbitofrontal cortex also participates in the executive control of information processing and behavioral expression by inhibiting neural activity associated with irrelevant, unwarranted, or uncomfortable (e.g. painful) information, sensation, or actions (Hooker & Knight, 2006; Shimamura, 2000). Interestingly, a shift from the ventral to the dorsal part of the medial prefrontal cortex has been reported during late childhood and adolescence for a theory of mind task, but no age-related change in the amygdala (Moriguchi, Ohnishi, Mori, Nemoto, Matsuda & Komaki, 2007b). The differences between that study and our findings are twofold. First, the ToM task used relied on the visual presentation of geometrical abstract shapes that, by their motion, elicit perception of goals, intentions and emotions, whereas our study employed animations depicting real people in ecologically valid scenarios. Second, the group in that study was more restricted both in age (9–16 years) and number of participants ($N = 16$), while our present study included 57 individuals spanning a wider age range (7–40 years). Therefore, we believe our stimuli are more emotionally salient and thus elicit an amygdala response with a monotonic decrease across age.

We propose that the pattern of developmental change in the orbitofrontal cortex reflects a gradual shift between the monitoring of somatovisceral responses in young children, mediated by the medial aspect of the OFC, and the executive control of emotion processing implemented by its lateral portion in older participants. This interpretation is also in line with the suggestion that the ventromedial prefrontal cortex contains two feedback-processing systems, consistent with hypotheses derived from anatomical studies (Hurliman, Nagode & Pardo, 2005). One subsystem, situated laterally in the orbitofrontal cortex, preferentially processes information from the external environment; the other subsystem, situated medially, preferentially processes interoceptive information such as visceromotor output critical for the analysis of the affective significance of stimuli.

One limitation of this study is noteworthy. The design used in this re-analysis does not include a condition of social interaction between two individuals with no pain, or a condition depicting accidental pain with another person. Therefore one cannot unequivocally disentangle the possibility that some hemodynamic changes during the sympathy-eliciting situations can be associated with both the perception of a malevolent interaction and the mere presence of another individual. However, findings from previous studies that employed additional conditions with either two persons in the stimuli or one individual alleviating the pain of another clearly indicate that the sympathy-associated activations are driven by the outcome of the interaction (Decety *et al*., 2008; Akitsuki & Decety, 2009).

Conclusion

Overall, our findings indicate that although children and adults have similar patterns of brain response to perceiving other people in pain (in the ACC, somatosensory cortex, PAG and insula), there are important changes in the functional organization in the neural structures implicated in empathy and sympathy that occur over an extended period from childhood, and likely infancy, through adulthood. Importantly, some structures such as the amygdala and posterior insula come online much earlier in ontogeny than other structures such as the dorsal and lateral ventromedial prefrontal cortex, which become progressively specialized for the evaluation of social stimuli, and are slower to mature. Different regions of the prefrontal cortex mature at different rates. In particular, gray matter volume reaches adult levels earliest in the orbitofrontal cortex, followed by ventrolateral and then dorsolateral prefrontal cortex (Giedd, Blumenthal, Jeffries, Castellanos, Hong & Zijdenbos, 1999). This pattern of functional changes supports the general notion

that the development of affective processing from childhood to adulthood is accompanied by reduced activity within limbic affect processing systems, and increased involvement of other prefrontal systems (Killgore & Yurgelun-Todd, 2007). Watching someone in pain elicits a negative arousal response in the observers, to a stronger degree in children than in young adults. These findings provide strong developmental support for the integrated emotion systems developed by Blair (2004), which proposes an emotional learning system mediated by the amygdala and a system for decision-making on the basis of reinforcement expectations mediated by the medial orbital frontal cortex. Our data also document partially distinct neural mechanisms subserving empathy and sympathy, here based on perceived intentionality, and age-related functional changes in the orbitofrontal cortex. This is important because many recent functional neuroimaging studies confuse empathy and emotion contagion (also called resonance or mimicry) based on the putative mirror neuron system (Decety, in press). There is a problem with equating empathy with motor resonance because the latter does not convey insight into another's internal state and does not account for any other-oriented motivational state that characterizes sympathy (Decety, 2009). In addition there no evidence from neurological studies that lesion of the regions involved in the mirror neuron system (ventral premotor, motor cortex and anterior IPS) leads to any dysfunction in empathy, sympathy or moral reasoning, whereas, as discussed above, lesions of the ventromedial prefrontal cortex are associated with such socio-cognitive disturbances (e.g. Hornak *et al.*, 2003). Finally, our study demonstrates the usefulness of a developmental neurobiological approach in the new emerging area of moral neuroscience, and the relevance to understanding and developing interventions for individuals with atypical development.

Acknowledgement

The study was supported by an NSF grant to Jean Decety (BCS-0718480).

References

Akitsuki, Y., & Decety, J. (2009). Social context and perceived agency affects empathy for pain: an event-related fMRI investigation. *NeuroImage*, **47**, 722–734.

Anderson, S.W., Bechara, A., Damasio, H., Tranel, D., & Damasio, A.R. (1999). Impairment of social and moral behavior related to early damage in human prefrontal cortex. *Nature Neuroscience*, **2**, 1032–1037.

Baird, J.A., & Baldwin, D.A. (2001). Making sense of human behavior: action parsing and intentional inference. In B.F. Malle, L.J. Moses, & D.A. Baldwin (Eds.), *Intentions and intentionality* (pp. 193–206). Cambridge, MA: MIT Press.

Batson, C.D. (1991). *The altruism question: Toward a social-psychological answer*. Hove: Lawrence Erlbaum Associates.

Beer, J.S., Heeray, E.A., Keltner, D., Scabani, R.T., & Knight, R.T. (2003). The regulatory function of self-conscious emotion: insights from patients with orbitofrontal damage. *Journal of Personality and Social Psychology*, **85**, 594–604.

Benuzzi, F., Lui, F., Duzzi, D., Nichelli, P.F., & Porro, C.A. (2008). Does it look painful or disgusting? Ask your parietal and cingulated cortex. *Journal of Neuroscience*, **28**, 923–931.

Berthoz, S., Armory, J., Blair, R.J.R., & Dolan, R. (2002). Neural correlates of violation of social norms and embarrassment. *Brain*, **125**, 1696–1708.

Blair, R.J.R. (2004). The roles of orbital frontal cortex in the modulation of antisocial behavior. *Brain and Cognition*, **55**, 198–208.

Blair, R.J.R. (2005). Responding to the emotions of others: dissociating forms of empathy through the study of typical and psychiatric populations. *Consciousness and Cognition*, **14**, 698–718.

Botvinick, M., Jha, A.P., Bylsma, L.M., Fabian, S.A., Solomon, P.E., & Prkachin, K.M. (2005). Viewing facial expression of pain engages cortical areas involved in the direct experience of pain. *NeuroImage*, **25**, 312–319.

Bramham, J., Norris, R.G., Hornak, J., Bullock, P., & Polkey, C.E. (2009). Social and emotional functioning following bilateral and unilateral neurosurgical prefrontal cortex lesions. *Journal of Neuropsychology*, **3**, 125–143.

Bunge, S.A., Dudukovic, N.M., Thomasson, M.E., Vaidya, C.J., & Gabrieli, J.D.E. (2002). Immature frontal lobe contributions to cognitive control in children: evidence from fMRI. *Neuron*, **33**, 301–311.

Casey, B.J., Tottenham, N., Liston, C., & Durston, S. (2005). Imaging the developing brain: what have we learned about cognitive development? *Trends in Cognitive Sciences*, **9**, 104–110.

Cheng, Y., Lin, C., Liu, H.L., Hsu, Y., Lim, K., Hung, D., & Decety, J. (2007). Expertise modulates the perception of pain in others. *Current Biology*, **17**, 1708–1713.

Cheng, Y., Yang, C.Y., Ching-Po, L., Lee, P.L., & Decety, J. (2008). The perception of pain in others suppresses somatosensory oscillations: a magnetoencephalography study. *NeuroImage*, **40**, 1833–1840.

Craig, A.D. (2003). Interoception: the sense of the physiological condition of the body. *Current Opinion in Neurobiology*, **13**, 500–505.

Craig, A.D. (2004). Human feelings: why are some more aware than others? *Trends in Cognitive Sciences*, **8**, 239–241.

Craig, K.D. (2004). Social communication of pain enhances protective functions. *Pain*, **107**, 5–6.

Damasio, A.R. (1994). *Descartes' error: Emotion, reason and the human brain*. New York: G.P. Putnam.

Decety, J. (2007). A social cognitive neuroscience model of human empathy. In E. Harmon-Jones & P. Winkielman (Eds.), *Social neuroscience: Integrating biological and psychological explanations of social behavior* (pp. 246–270). New York: Guilford Press.

Decety, J. (2009). Empathy, sympathy and the perception of pain. *Pain*, **145**, 365–366.

Decety, J. (in press). To what extent is the experience of empathy mediated by shared neural circuits? *Emotion Review*.

Decety, J., & Batson, C.D. (2007). Social neuroscience approaches to interpersonal sensitivity. *Social Neuroscience*, **2** (3–4), 151–157.

Decety, J., & Jackson, P.L. (2004). The functional architecture of human empathy. *Behavioral and Cognitive Neuroscience Reviews*, **3**, 71–100.

Decety, J., & Lamm, C. (2009). Empathy versus personal distress – recent evidence from social neuroscience. In J. Decety & W. Ickes (Eds.), *The social neuroscience of empathy* (pp. 199–213). Cambridge, MA: MIT Press.

Decety, J., & Meyer, M. (2008). From emotion resonance to empathic understanding: a social developmental neuroscience account. *Development and Psychopathology*, **20**, 1053–1080.

Decety, J., Michalska, K.J., & Akitsuki, Y. (2008). Who caused the pain? A functional MRI investigation of empathy and intentionality in children. *Neuropsychologia*, **46**, 2607–2614.

Decety, J., Michalska, K.J., Akitsuki, Y., & Lahey, B.B. (2009). Atypical empathic responses in adolescents with aggressive conduct disorder: a functional MRI investigation. *Biological Psychology*, **80**, 203–211.

Decety, J., & Moriguchi, Y. (2007). The empathic brain and its dysfunction in psychiatric populations: implications for intervention across different clinical conditions. *BioPsychoSocial Medicine*, **1**, 22–65.

De Haan, M., & Gunnar, M.R. (2009). The brain in a social environment. Why study development? In M. De Haan & M. R. Gunnar (Eds.), *Handbook of developmental social neuroscience* (pp. 3–10). New York: Guilford Press.

Diamond, A. (2002). Normal development of prefrontal cortex from birth to young adulthood: cognitive functions, anatomy, and biochemistry. In D.T. Stuss & R.T. Knight (Eds.), *Principles of frontal lobe function* (pp. 446–503). New York: Oxford University Press.

Dondi, M., Simion, F., & Caltran, G. (1999). Can newborns discriminate between their own cry and the cry of another newborn infant? *Developmental Psychology*, **35**, 418–426.

Dupont, S., Bouilleret, V., Hasboun, D., Semah, F., & Baulac, M. (2003). Functional anatomy of the insula: new insights from imaging. *Surgery and Radiologic Anatomy*, **25**, 113–119.

Eisenberg, N. (1986). *Altruistic emotion, cognition and behavior*. Hillsdale, NJ: Lawrence Erlbaum Associates.

Eisenberg, N., & Eggum, N.D. (2009). Empathic responding: sympathy and personal distress. In J. Decety & W. Ickes (Eds.), *The social neuroscience of empathy* (pp. 71–83). Cambridge, MA: MIT Press.

Eisenberg, N., & Fabes, R.A. (1995). The relation of young children's vicarious emotional responding to social competence, regulation, and emotionality. *Cognition and Emotion*, **9**, 203–228.

Eisenberg, N., Fabes, R.A., Murphy, B., Karbon, M., Maszk, P., Smith, M., O'Boyle, C., & Suh, K. (1994). The relations of emotionality and regulation to dispositional and situational empathy-related responding. *Journal of Personality and Social Psychology*, **66**, 776–797.

Eisenberg, N., Fabes, R.A., & Spinrad, T.L. (2006). Prosocial behavior. In N. Eisenberg (Vol. ed.), W. Damon & R. M. Lerner (Series eds.), *Handbook of child psychology: Vol. 3. Social, emotional, and personality development* (pp. 646–718). New York: Wiley.

Estabrook, S. (2007). Does context modulate empathy for pain? Master of Art Thesis under direction of Dr Jean Decety at the University of Chicago.

Field, T.M., Woodson, R., Greenberg, R., & Cohen, D. (1982). Discrimination and imitation of facial expression by neonates. *Science*, **219**, 179–181.

Frith, U., & Frith, C.D. (2003). Development and neurophysiology of mentalizing. *Philosophical Transactions of the Royal Society, London B*, **358**, 459–473.

Genovese, C.R., Lazar, N.A., & Nichols, T. (2002). Thresholding of statistical maps in functional neuroimaging using the false discovery rate. *NeuroImage*, **15**, 870–878.

Giedd, J.N., Blumenthal, N.O., Jeffries, F.X., Castellanos, L., Hong, A., & Zijdenbos, J. (1999). Brain development during childhood and adolescence: a longitudinal MRI study. *Nature Neuroscience*, **2**, 861–863.

Glover, G.H., & Law, G.S. (2001). Spiral-in/out bold fMRI for increased SNR and reduced susceptibility artifacts. *Magnetic Research Medicine*, **46**, 515–522.

Gogtay, N., Giedd, J.N., Lusk, L., Hayashi, K.M., Greenstein, D., Vaituzis, A.C., Nugent, T.M., Herman, D.H., Clasen, L.S., Toga, A.W., Rapoport, J.L., & Thompson, P.M. (2004). Dynamic mapping of human cortical development during childhood through early adulthood. *Proceedings of the National Academy of Sciences of the USA*, **101**, 8174–8179.

Goubert, L., Craig, K.D., & Buysse, A. (2009). Perceiving others in pain: experimental and clinical evidence on the role of empathy. In J. Decety & W. Ickes (Eds.), *The social neuroscience of empathy* (pp. 153–166). Cambridge, MA: MIT Press.

Greenspan, J.D., Lee, R.R., & Lenz, F.A. (1999). Pain sensitivity alterations as a function of lesion location in the parasylvian cortex. *Pain*, **81**, 273–282.

Grusec, J.E., Davidov, M., & Lundell, L. (2004). Prosocial and helping behavior. In P.K. Smith & C.H. Hart (Eds.), *Blackwell handbook of childhood social development* (pp. 457–474). Oxford: Blackwell Publishing.

Gu, X., & Han, S. (2007). Attention and reality constraints on the neural processes of empathy for pain. *NeuroImage*, **36**, 256–267.

Hariri, A.R., Bookheimer, S.Y., & Mazziotta, J.C. (2000). Modulating emotional responses: effects of a neocortical network on the limbic system. *NeuroReport*, **11**, 43–48.

Haviland, J.M., & Lewica, M. (1987). The induced affect response: 10-week-old infants' responses to three emotion expressions. *Developmental Psychology*, **23**, 97–104.

Hempel, J. (2009). Eye-tracking as a method to investigate empathy and sympathy. Honors Thesis under the direction of Dr J. Decety, University of Chicago.

Hodges, S.D., & Wegner, D.M. (1997). The mental control of empathic accuracy. In W. Ickes (Ed.), *Empathic accuracy* (pp. 311–339). New York: Guilford.

Hoffman, M.L. (2000). *Empathy and moral development: Implications for caring and justice*. Cambridge: Cambridge University Press.

Hooker, C.I., & Knight, R.T. (2006). The role of the lateral orbitofrontal cortex in the inhibitory control of emotion. In D.H. Zald & S.L. Rauch (Eds.), *The orbitofrontal cortex* (pp. 307–324). New York: Oxford University Press.

Hornak, J., Bramham, J., Rolls, E.T., Morris, R.J., O'Doherty, J.O., Bullock, P.R., & Polkey, C.E. (2003). Changes in emotion after circumscribed surgical lesions of the orbitofrontal and cingulated cortices. *Brain*, **126**, 1691–1712.

Hurliman, E., Nagode, J.C., & Pardo, J.V. (2005). Double dissociation of exteroceptive and interoceptive feedback systems in the orbital and ventromedial prefrontal cortex of humans. *Journal of Neuroscience*, **25**, 4641–4648.

Jackson, P.L., Brunet, E., Meltzoff, A.N., & Decety, J. (2006b). Empathy examined through the neural mechanisms involved in imagining how I feel versus how you feel pain: an event-related fMRI study. *Neuropsychologia*, **44**, 752–761.

Jackson, P.L., Meltzoff, A.N., & Decety, J. (2005). How do we perceive the pain of others? A window into the neural processes involved in empathy. *NeuroImage*, **24**, 771–779.

Jackson, P.L., Rainville, P., & Decety, J. (2006a). To what extent do we share the pain of others? Insight from the neural bases of pain empathy. *Pain*, **125**, 5–9.

Karnath, H.O., Baier, B., & Nagele, T. (2005). Awareness of the functioning of one's own limbs mediated by the insular cortex? *Journal of Neuroscience*, **25**, 7134–7138.

Kawashima, R., Sato, K., Itoh, H., Ono, S., Furumoto, S., Gotoh, R., Koyama, M., Yoshioka, S., Takahashi, T., & Takahashi, K. (1996). Functional anatomy of go/no-go discrimination and response selection – a PET study in man. *Brain Research*, **728**, 79–89.

Killgore, W.D.S., Oki, M., & Yurgelun-Todd, D.A. (2001). Sex-specific developmental changes in amygdala responses to affective faces. *NeuroReport*, **12**, 427–433.

Killgore, W.D.S., & Yurgelun-Todd, D.A. (2007). Unconscious processing of facial affect in children and adolescents. *Social Neuroscience*, **2**, 28–47.

Knafo, A., Zahn-Waxler, C., Van Hulle, C., Robinson, J.L., & Rhee, S. H. (2008). The developmental origins of a disposition toward empathy: genetic and environmental contributions. *Emotion*, **8**, 737–752.

Konishi, S., Nakajima, K., Uchida, I., Kikyo, H., Kameyama, M., & Miyashita, Y. (1999). Common inhibitory mechanism in human inferior prefrontal cortex revealed by event-related functional MRI. *Brain*, **122**, 981–991.

Kringelbach, M.L., & Rolls, E.T. (2004). The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neuropsychology. *Progress in Neurobiology*, **72**, 341–372.

Lamm, C., Batson, C.D., & Decety, J. (2007a). The neural substrate of human empathy: effects of perspective-taking and cognitive appraisal. *Journal of Cognitive Neuroscience*, **19**, 42–58.

Lamm, C., & Decety, J. (2008). Is the extrastriate body area (EBA) sensitive to the perception of pain in others? *Cerebral Cortex*, **18**, 2369–2373.

Lamm, C., Meltzoff, A.N., & Decety, J. (2009). How do we empathize with someone who is not like us? *Journal of Cognitive Neuroscience*, Epub ahead of print.

Lamm, C., Nusbaum, H., Meltzoff, A.N., & Decety, J. (2007b). What are you feeling? Using functional magnetic resonance imaging to assess the modulation of sensory and affective responses during empathy for pain. *PLoS ONE*, **12**, e1292.

Lamm, C., Porges, E.C., Cacioppo, J.T., & Decety, J. (2008). Perspective taking is associated with specific facial responses during empathy for pain. *Brain Research*, **1227**, 153–161.

LeDoux, J.E. (2000). Emotion circuits in the brain. *Annual Review of Neuroscience*, **23**, 155–184.

Martin, G.B., & Clark, R.D. (1987). Distress crying in neonates: species and peer specificity. *Developmental Psychology*, **18**, 3–9.

Mesulam, M.W. (2002). The human frontal lobes: transcending the default mode through contingent encoding. In D.T. Stuss & R.T. Knight (Eds.), *Principles of frontal lobe function* (pp. 8–30). New York: Oxford University Press.

Moll, J., de Oliviera-Souza, R., Garrido, G.J., Bramati, I.E., Caparelli-Daquer, E.M.A., Paiva, M.L., Zahn, R., & Grafman, J. (2007). The self as a moral agent: linking the neural bases of social agency and moral sensitivity. *Social Neuroscience*, **2** (3–4), 336–352.

Moriguchi, Y., Decety, J., Ohnishi, T., Maeda, M., Mori, T., Nemoto, K., Matsuda, H., & Komaki, G. (2007a). Empathy and judging other's pain: an fMRI study of alexithymia. *Cerebral Cortex*, **17**, 2223–2234.

Moriguchi, Y., Ohnishi, T., Mori, T., Nemoto, K., Matsuda, H., & Komaki, G. (2007b). Changes of brain activity in the neural substrates for theory of mind during childhood and adolescence. *Psychiatry and Clinical Neurosciences*, **61**, 355–363.

Morrison, I., Lloyd, D., di Pellegrino, G., & Roberts, N. (2004). Vicarious response to pain in anterior cingulate cortex: is empathy a multisensory issue? *Cognitive, Affective & Behavioral Neuroscience*, **4**, 270–278.

Norris, C.J., Chen, E.E., Zhu, D.C., Small, S., & Cacioppo, J.T. (2004). The interaction of social and emotional processes in the brain. *Journal of Cognitive Neuroscience*, **10**, 1818–1829.

Ogino, Y., Nemoto, H., Inui, K., Saito, S., Kakigi, R., & Goto, F. (2007). Inner experience of pain: imagination of pain while viewing images showing painful events forms subjective pain representation in human brain. *Cerebral Cortex*, **17**, 1139–1146.

Ongur, D., & Price, J.L. (2000). The organization of networks within the orbital and medial prefrontal cortex of rats, monkeys and humans. *Cerebral Cortex*, **10**, 206–219.

Ostrowsky, K., Magnin, M., Ryvlin, P., Isnard, J., Guenot, M., & Mauguiere, F. (2002). Representation of pain and somatic sensation in the human insula: a study of responses to direct electrical cortical stimulation. *Cerebral Cortex*, **12**, 376–385.

Price, D.D. (2000). Psychological and neural mechanisms of the affective dimension of pain. *Science*, **288**, 1769–1772.

Rankin, K.P., Gorno-Tempini, L.G., Allison, S., Stanley, C.M., Glenn, S., Weiner, M.W., & Miller, B. (2006). Structural anatomy of empathy in neurodegenerative disease. *Brain*, **129**, 2945–2956.

Robinson, J. (2008). Empathy and prosocial behavior. *Encyclopedia of Infant and Early Childhood Development*, **1**, 441–450.

Rothbart, M.K., Ahadi, S.A., & Hershey, K.L. (1994). Temperament and social behavior in childhood. *Merrill-Palmer Quarterly*, **40**, 21–39.

Saarela, M.V., Hlushchuk, Y., Williams, A.C. de C., Schürmann, M., Kalso, E., & Hari, R. (2007). The compassionate brain: humans detect intensity of pain from another's face. *Cerebral Cortex*, **17**, 230–237.

Shamay-Tsoory, S.G., Tibi-Elhanany, Y., & Aharon-Peretz, J. (2006). The ventromedial prefrontal cortex is involved in understanding affective but not cognitive theory of mind stories. *Social Neuroscience*, **1** (3–4), 149–166.

Shamay-Tsoory, S.G., Tomer, R., Berger, B.D., & Aharon-Peretz, J. (2003). Characterization of empathy deficits following prefrontal brain damage: the role of the right ventromedial prefrontal cortex. *Journal of Cognitive Neuroscience*, **15**, 324–337.

Shaw, P., Lawrence, E.J., Radbourne, C., Bramham, J., Polkey, C.E., & David, A.S. (2004). The impact of early and late damage to the human amygdala on theory of mind reasoning. *Brain*, **127**, 1535–1548.

Shimamura, A.P. (2000). The role of prefrontal cortex in dynamic filtering. *Psychobiology*, **28**, 207–218.

Singer, T., Seymour, B., O'Doherty, J., Kaube, H., Dolan, R.J., & Frith, C.D. (2004). Empathy for pain involves the affective but not sensory components of pain. *Science*, **303**, 1157–1162.

Smetana, J.G., & Killen, M. (2008). Moral cognition, emotions, and neuroscience: an integrative developmental view. *European Journal of Developmental Science*, **2**, 324–339.

Sommerville, J.A. (2007). Detecting causal structure: the role of interventions in infants' understanding of psychological and physical causal relations. In A. Gopnik & L.E. Schulz (Eds.), *Causal learning: Psychology, philosophy and computation* (pp. 48–57). New York: Oxford University Press.

Sonnby-Borgstrom, M., Jonsson, P., & Svensson, O. (2003). Emotional empathy as related to mimicry reactions at different levels of information processing. *Journal of Nonverbal Behavior*, **27**, 3–23.

Stone, V.E., & Gerrans, P. (2006). What's domain-specific about theory of mind? *Social Neuroscience*, **1** (3–4), 309–319.

Swick, D., Ashley, V., & Turken, A.U. (2008). Left inferior frontal gyrus is critical for response inhibition. *BMC Neuroscience*, **9**, 102e.

Toga, A.W., Thompson, P.M., & Sowell, E.R. (2006). Mapping brain maturation. *Trends in Neuroscience*, **29**, 148–159.

Vaish, A., Carpenter, M., & Tomasello, M. (2009). Sympathy through affective perspective-taking, and its relation to prosocial behavior in toddlers. *Developmental Psychology*, **45**, 534–543.

Wager, T.D., Luan Phan, K., Liberzon, I., & Taylor, S.F. (2003). Valence, gender, and lateralization of functional brain anatomy in emotion: a meta-analysis of findings from neuroimaging. *NeuroImage*, **19**, 513–531.

Yamada, M., & Decety, J. (2009). Unconscious affective processing and empathy: an investigation of subliminal priming on the detection of painful facial expressions. *Pain*, **143**, 71–75.

Yurgelun-Todd, D. (2007). Emotional and cognitive changes during adolescence. *Current Opinion in Neurobiology*, **17**, 251–257.

Zahn-Waxler, C., & Radke-Yarrow, M. (1990). The origins of empathic concern. *Motivation and Emotion*, **14**, 107–130.

Zaki, J., Ochsner, K.N., Hanelin, J., Wager, T.D., & Mackey, S.C. (2007). Different circuits for different pain: patterns of functional connectivity reveal distinct networks for processing pain in self and others. *Social Neuroscience*, **2**, 276–291.

Zelazo, P., Carlson, S., & Kesek, A. (2008). The development of executive function in childhood. In C.A. Nelson & M. Luciana (Eds.), *Handbook of developmental cognitive neuroscience* (pp. 553–574). Cambridge, MA: MIT Press.

Received: 8 May 2009
Accepted: 26 September 2009