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Love hurts: An fMRI study

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ABSTRACT

Being in a close relationship is essential to human existence. Such closeness can be described as including other in the self and be underpinned on social attachment system, which evolved from a redirection of nociceptive mechanisms. To what extent does imagining a loved-one differs from imagining an unfamiliar individual being in painful situations? In this functional MRI study, participants were exposed to animated stimuli depicting hands or feet in painful and non-painful situations, and instructed to imagine these scenarios from three different perspectives: self, loved-one and stranger after being primed with their respective photographs. In line with previous studies, the three perspectives were associated with activation of the neural network involved in pain processing. Specifically, adopting the perspective of a loved-one increased activity in the anterior cingulate cortex and insula, whereas imagining a stranger induced a signal increase in the right temporo-parietal junction (TPJ) and superior frontal gyrus. The closer the participants' relationships were with their partner, the greater the deactivation in the right TPJ. A negative effective connectivity between the right TPJ and the insula, and a positive one with the superior frontal gyrus were found when participants imagined the perspective of a stranger. These results demonstrate that intimacy affects the bottom-up information processing involved in empathy, as indicated by greater overlap between neural representations of the self and the other.

Introduction

Being in a close relationship is essential to well being and health. The cognitive mechanism of intimacy can be described as including the other in the self with aspects of resource allocation strategy, actor/observer perspective, and vicariously sharing other's characteristics (Aron et al., 1991). However, how intimacy modulates the neural underpinnings of the experience of empathy remains to be determined. Drawing from the social attachment and social pain literatures which suggest that both are built up from more primitive regulation systems such as those involved in thermoregulation and physical pain (MacDonald and Leary, 2005; Panksepp, 1998), one may anticipate differences in the extent of neural representation in response to the distress experienced by target individuals depending on their relationship to the observer.

A large number of functional magnetic resonance imaging (fMRI) studies have demonstrated that the perception or imagination of another individual in pain is reliably associated with the activation of neural regions that belong to the pain matrix (Price, 2000), particularly areas coding the motivational-affective dimension of pain (Botvinick et al., 2005; Cheng et al., 2007; Gu and Han, 2007; Jackson et al., 2006a,b, 2005; Lamm et al., 2007a,b, 2009; Moriguchi et al., 2007; Morrison et al., 2004; Saarela et al., 2007; Singer et al., 2004; Zaki et al., 2007). This neural network includes the supplementary motor area (SMA), dorsal anterior cingulate cortex (dACC), anterior midcingulate cortex (aMCC), anterior insula, and periaqueductal gray (PAG). Some fMRI studies have also reported activation of the somatosensory cortex (Akitsuki and Decety, 2009; Benuzzi et al., 2008; Cheng et al., 2008; Lamm and Decety, 2008; Moriguchi et al., 2007), a region encoding the sensory discriminative dimension of pain. It is worth mentioning, however, that activation of these regions reflects a general aversive response not specific to nociception. Indeed, this network of regions underpins a physiological mechanism that mobilizes the organism to react – with heightened arousal and attention – to threatening physical and social situations: the dACC plays a key role in conflict monitoring; the aMCC is involved in autonomic regulation associated with processing of fear and anxiety; the anterior insula processes visceral bodily sensations; the PAG integrates physiological changes in response to stress, and in the context of danger the SMA as a result of feedback from the limbic system, represents one anatomical substrate for activating motor responses associated with danger and threats (Decety, in press).

Work in social psychology has documented that interpersonal relationships influence empathic responses and associated phenomena

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such as sympathy, for instance, similarity between an observer and a target (Batson et al., 1997a,b,c), how likable the target is (Kozak et al., 2006), and how well the target belongs in a group (Stürmer et al., 2006; Yabar et al., 2006). In addition, based on the fact that couples are more likely to respond to each other, one fMRI study enrolled only female participants who received a painful stimuli on the hand, or watched a signal indicating that their partners were receiving a similar stimuli, and demonstrated common activation in the dACC and anterior insula for the two conditions (Singer et al., 2004). However, it is not clear from that study whether the perception of a loved-one in pain is really different from that of another individual.

Imaging someone in pain is valuable window onto the processes that are involved in human empathy because it allows the researchers to vary various interpersonal factors that may modulate the responses toward the target person (Decety, 2005). For example, one fMRI study used pictures of hands and feet in painful or non-painful situations and required participants to imagine and rate the level of pain perceived either from a self or another perspective (Jackson et al., 2006a,b). Both the self- and other-perspectives were associated with activation in the dACC, and anterior insula. However, the former condition yielded higher subjective pain ratings and involved the pain matrix more extensively in the aMCC, insula, and somatosensory cortex while the latter condition was associated with specific signal increase in the posterior cingulate cortex and the right temporo-parietal junction (TPJ). That is, despite of similarities, there are also differences between the self- and other-pain neural representations during pain empathy. Moreover, another fMRI study observed graded hemodynamic responses related to perspective-taking instructions in the insula, aMCC, medial and lateral premotor areas while participants were exposed to videos depicting facial expressions of pain (Lamm et al., 2007a). Of note, the other-perspective in these studies was limited to unfamiliar persons, not significant others.

Considering that intimate relationships may change the actor/observer perspective by allowing more overlap between other and self, we hypothesized that imagining oneself, a loved-one, and a stranger in pain will result in different degrees of activation in the pain matrix, especially in the dACC and anterior insula. Furthermore, the degree of activation in the pain matrix elicited when imagining a loved-one in pain may be related to the participants' subjective reports of closeness with their partner.

Materials and methods

Participants

Thirty-six (18 males) right-handed, ethnic Chinese healthy participants were enrolled from the university campuses in Taipei (mean age 23; SD 3 years) after providing written informed consent. The study was approved by the local Ethics Committee and conducted in accordance with the Declaration of Helsinki. None of the participants had any history of neurological or psychiatric disorders and all were free of medication at the time of the testing. All of them had normal or corrected-normal visual acuity. Participants received monetary compensation for their participation. Prescreening interviews were conducted to verify whether they are heterosexual, and to assess their personal relationships. All participants reported to be in a close relationship for an average of 31 months (range: 3 to 81 months). Beside, while considering potentially dyadic non-independence (Kenny, 1996), members of the same couple did not participate in this study.

General procedures

Before the fMRI scanning, participants were required to fill in the inclusion of other in the self (IOS) scale (Aron et al., 1992), which is scored from 1 (no overlap) to 7 (almost complete overlap) to assess closeness in their relationships.

After fMRI scanning, participants were asked to evaluate the pain intensity supposedly felt by the target (Self, Loved-one, Stranger) and the unpleasantness felt by themselves when observing painful stimuli with these different perspectives. This evaluation was measured with a 6-point visual analog scale, using “from no pain to extreme pain” and “from no effect to extreme unpleasantness” as target words, on the Facial Pain Scale-Revised (FPS-R), which depicts six photocopied faces showing neutral to extremely painful expressions (Bieri et al., 1990).

Visual stimuli

The stimuli consisted of the successive presentation of animated images displaying hands and feet in blocks depicting painful (Pain) and non-painful (Neutral) situations. A series of 48 animated visual stimuli were previously validated and used in three fMRI studies (Akitsuki and Decety, 2009; Decety et al., 2008, 2009b). All situations depicted familiar events that can happen in everyday life to people (e.g., pinching one's finger in a door, or catching one's toe under a heavy object). Various types of pain (mechanical, thermal, and pressure) inflicted to right limbs were depicted. Neutral pictures displayed limbs in visually similar situations without the painful component (e.g., a hand on the handle of a drawer as opposed to being caught in the same drawer). Each animation is composed of three digital pictures, which were edited to the same size (600 × 480 pixels). The duration of the first, second, and third pictures were 1000 ms, 200 ms, and 1000 ms respectively.

Functional MRI scanning

The scanning followed a block design (13.2 s ON/17.6 s OFF). Each run was preceded by a priming photo cue, which indicated to the participants which perspective they were supposed to adopt: a photo of the participant (Self), his/her partner (Loved-one) or another unfamiliar person (Stranger). The Stranger was of the same sex and age as the Loved-one. All of their photos were edited with similar visual quality by an experimenter. Each run consisted of 8 ON intermixed with 8 OFF blocks. Each ON block consisted of four trials with the same type of stimuli (Pain or Neutral) (2200 ms each) and four inter-stimulus intervals (1100 ms each) with a fixation cross presented against a gray background (see Fig. S1). The order of the stimulus condition (Pain vs. Neutral) was randomized within each run. The order of the runs was counterbalanced across participants.

Functional and structural images were acquired using a 3 T MRI scanner (Siemens Magnetom Tim Trio, Erlangen, German) equipped with a high-resolution 12-channel head array coil. Changes in blood oxygenation level-dependent (BOLD) T2* weighted MR signal were measured using a gradient echo-planar imaging (EPI) sequence (repetition time TR = 2200 ms, echo time TE = 30 ms, FoV = 220 mm, flip angle = 90°, matrix size = 64 × 64, 36 transversal slices, voxel size = 3.4 mm × 3.4 mm × 3.0 mm, no gap). For each run, a total of 112 EPI volume images were acquired along the AC–PC plane. High-resolution structural MR images were acquired with 3D magnetization-prepared rapid gradient echo sequence (3D-MPRAGE; TR = 2530 ms, TE = 3.5 ms, FoV = 256 mm, flip angle = 7°, TI = 1100 ms, matrix size = 256 × 256, 176 sagittal slices, voxel size = 1.0 mm × 1.0 mm × 1.0 mm, no gap).

Functional data sets were pre-processed and analyzed with SPM2 (Wellcome Department of Imaging Neuroscience, London, UK) and implemented in MATLAB 6.5 (Mathworks Inc., Sherborn, MA). Images were slice-timing corrected, realigned and normalized into the standard stereotaxic space of the Montreal Neurological Institute (MNI) template. Subsequently, the normalized images were smoothed with an isotropic 8 mm full-width at half-maximum (FWHM) Gaussian kernel. The first fixed-level of analysis was computed subject-wise using the general linear model with hemodynamic response function for each of the conditions. Contrast images of each condition (Pain vs. Neutral) were calculated for the different perspectives (Self vs. Loved-one vs. Stranger) in all participants. First-level contrasts were introduced in second-level random-effect analysis to allow for population inferences. One-sample *t*-tests including all subjects for each contrast of interest were computed, yielding a statistical parametric map of the *t*-statistic (SPM *t*). A voxel-level threshold of $P<0.05$ (FDR corrected for multiple comparisons, $t=3.15$) and an extent threshold of $k>20$ voxels were used to identify significant activity changes for pain across perspective taking conditions.

Random-effects correlation analyses

Random-effects correlation analyses were performed for whole-brain correlations to determine the brain regions where hemodynamic response elicited by the imagination of a loved-one in pain was correlated to the intimacy degree of close relationships. Each individual's IOS ratings were subjected to regression with parameter estimates of the contrast “Loved-one pain minus Loved-one neutral” while statistically treating the Self as a regressor. In addition, to test a potential effect of familiarity, the log of each participant's dating length was correlated with this contrast. A significance threshold of $P<0.05$ and $k>25$ voxels was selected for analysis. To avoid abundant false positives associated analyses, significant correlations were interpreted only if they were located in previously defined regions of the pain matrix (Derbyshire, 2000).

Psychophysiological interaction (PPI) analyses

Psychophysiological interaction (PPI) analyses (Friston et al., 1997) were conducted: 1) to identify areas in the brain that exhibit significant co-variation with the right TPJ during pain empathy across the three perspectives; and 2) to elucidate the role of these regions in perspective taking and empathy. The selection of the right TPJ was based on the *a priori* hypotheses that this region is engaged in bottom-up computational processes associated with the sense of agency, reorientation of attention to salient stimuli, as well as metacognitive processes such as theory of mind (Decety and Lamm, 2007). Individual volumes of interest (VOIs) in each participant were defined as a 4 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. Pain>Neutral). The significance threshold for VOI extraction was set to $P=0.001$ (uncorrected), $k=5$. PPI analyses were performed as follows: (1) extraction of the time-series data for 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.

Region of interest (ROI) analyses

Region of interest (ROI) analyses were computed to examine whether significant interaction of perspective taking conditions and neural response in the pain matrix reflected relative increases in pain-related activity for one main effect, relative decreases in pain-related activity for the comparison main effect, or both. At the group level, activated voxels in the Pain vs. Neutral stimuli were used to extract the parameter estimates. The ROIs of the right TPJ, dACC, and anterior insula were defined separately for each participant from the pain-related activation. Further, coordinates of the right TPJ region had to be anatomically congruent with two recent meta-analysis studies on pain empathy, theory of mind, perspective taking, and attention (Jackson et al., 2006b; Lamm et al., 2007a).

Results

Behavioral measures

Mean values of the IOS were 4.8 ± 1.2, ranging from 1 to 7 (on scale 1–7). Analysis of the FPS-R ratings of pain intensity revealed a main effect of perspective taking (Self vs. Loved-one vs. Stranger) ($F_{2,\ 31}=14.831$, $P<0.001$) as well as for pain unpleasantness felt by themselves ($F_{2,\ 31}=13.46$, $P<0.001$). *Post-hoc* comparison showed that the effect of perspective taking was mainly driven by higher ratings of pain intensity and unpleasantness elicited by imagination of the Self and the Loved-one, than the Stranger ($P<0.05$). This result indicates that participants rated the scenarios to be more painful and unpleasant when imagining from their loved- one's perspective as opposed to that of a stranger.

However, the IOS score was not correlated with the ratings of pain intensity (Self: $r=0.091$, $P=0.605$; Loved-one: $r=-0.039$, $P=0.825$; Stranger: $r=-0.030$, $P=0.864$) and unpleasantness (Self: $r=0.035$, $P=0.841$; Loved-one: $r=-0.042$, $P=0.810$; Stranger: $r=0.04$, $P=0.817$) to each perspective. Also, the IOS was not correlated with the pain rating differences across targets [pain intensity: Self vs. Loved-one ($r=0.239$, $P=0.167$); Self vs. Stranger ($r=0.136$, $P=0.435$); Loved-one vs. Stranger ($r=-0.012$, $P=0.947$)] [unpleasantness: Self vs. Loved-one ($r=0.143$, $P=0.411$); Self vs. Stranger ($r=-0.002$, $P=0.990$); Loved-one vs. Stranger ($r=-0.103$, $P=0.554$)].

Functional MRI data

Pain matrix response irrespective of perspective taking

The hemodynamic response elicited by the painful content of the visual stimuli, irrespective of the perspective adopted by the participants, was found in a set of regions similar to that observed in previous studied of pain empathy including the dACC, SMA, PAG, postcentral gyrus, and anterior insula (Table 1).

To further examine whether hemodynamic activity in the pain matrix is differentially modulated by perspective taking instructions, an analysis contrasting Pain vs. Neutral stimuli was conducted separately with Self, Loved-one, and Stranger perspectives (Table S1). Activation in the anterior insula showed a gradient decline from the Self, the Loved-one, to the Stranger perspectives (Fig. 1). Moreover, the perspectives of Self and the Loved-one were associated with similar activation in dACC (BA 24), whereas the Stranger was restricted to paracingulate/SMA region (BA32). These findings are consistent with a previous fMRI study that used a similar design with self vs. other' perspectives (Jackson et al., 2006a).

Direct comparison between perspectives

Direct and reverse comparisons between the Self and Stranger perspectives revealed the involvement of a neural network similar to that observed in previous fMRI studies with similar designs in pain empathy (Jackson et al., 2006a). Activations associated with the Self vs. Stranger were detected in the dACC (BA 24), anterior insula, and bilaterally in the thalamus. The reverse comparison (i.e., Stranger vs. Self in painful situations) resulted in increased activity in the superior frontal gyrus (SFG), medial prefrontal cortex (MPFC), and right TPJ. Interestingly, direct and reverse comparisons between the Loved-one vs. Stranger perspectives in painful situations also revealed such double dissociation (Table S2). The dACC was more activated in the

Table 1
Brain regions showing a significant effect of pain.

Pain-related regions	MNI coordinates			*t* value
	x	*y*	*z*	
L dACC	−2	20	40	8.85
L SMA	−2	12	46	8.94
R SMA	1	4	62	7.98
R MPFC	14	6	−14	3.18
L thalamus	−8	6	0	3.95
R thalamus	8	10	−2	3.60
L SFG	−36	50	26	4.91
L anterior insula	−40	12	−6	7.24
R anterior insula	42	10	−8	6.74
L inferior frontal gyrus	−52	10	2	6.58
R inferior frontal gyrus	34	20	20	3.94
L parietal operculum	−66	−26	24	3.18
R postcental gyrus	64	−24	26	3.93
L periaqueductal gray	−2	−22	−24	3.53

Stereotactic coordinates and *t* values are provided for local voxel maxima in the regions showing a significant main effect of pain ($P<0.05$, FDR corrected). Coordinates are defined in Montreal Neurologic Institute (MNI) stereotactic space in millimeters: $x>0$ is right of the mid-sagittal plane, $y>0$ is anterior to the anterior commissure and $z>0$ is superior to anterior–posterior commissure plane.
L, left hemisphere; R, right hemisphere; dACC, dorsal anterior cingulate cortex; SMA, supplementary motor area; MPFC, medial prefrontal cortex; SFG, superior frontal gyrus.

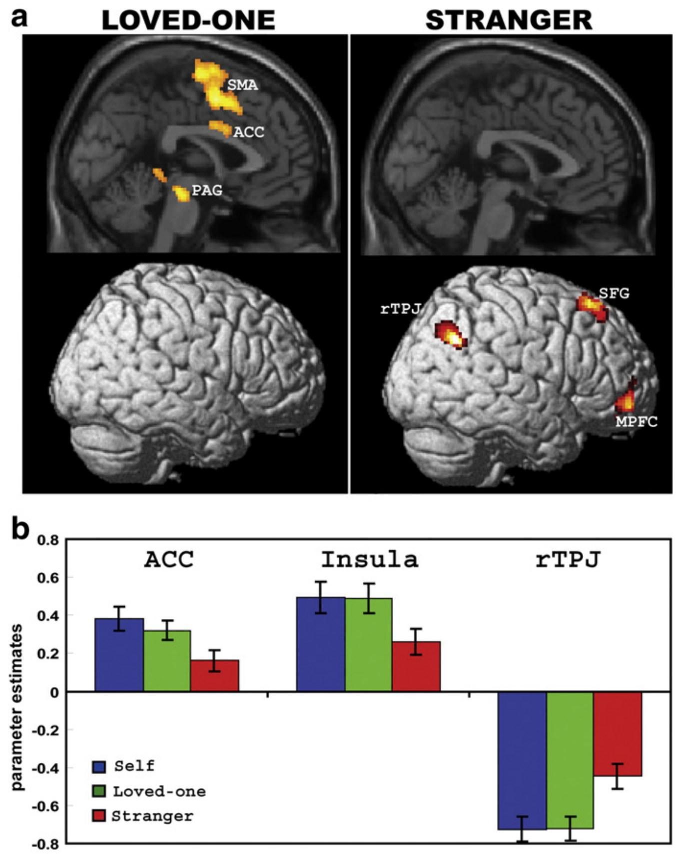

Fig. 2. Pain empathy responses associated with imagining a loved-one and a stranger in pain. (a) Double dissociation of pain empathy-related hemodynamic activity in the anterior cingulate cortex (ACC) and right temporo-parietal junction (rTPJ). Imagining a loved-one vs. stranger in painful situations was associated with increased activation in the ACC but not in the right TPJ, while imagining a stranger vs. loved-one showed the opposite pattern. (b) Parameter estimates in the ACC, insula and rTPJ in each condition. Hemodynamic response in the ACC (*x* 2, *y* 2, *z* 50), anterior insula (*x* −34, *y* 18, *z* 10) and rTPJ (*x* 58, *y* −58, *z* 30) are shown respectively for imagining the self, loved-one, and stranger in painful situations.

Loved-one, whereas the right TPJ was selectively activated in the Stranger (Fig. 2a).

Correlations with IOS and dating length

To examine whether the neural activation detected when participants imagined a loved-one in painful situations was affected by the reported quality of their relationship, whole-brain correlation analysis was computed between the contrast image (Loved-one pain vs. Loved-one neutral) and the IOS (Table S3). A significant cluster of activation, detected in the right TPJ (*x* 58, *y* −58, *z* 30), showed a significant negative correlation with the IOS ratings ($t=-2.124$, $P=0.043$) (Fig. 3). In addition, correlation analysis between the contrast (Loved-one pain vs. Self pain) and the IOS also found that the right TPJ activity was negatively related to the closeness score (Table S4). That is, the closer the relationship coupled with the greater the right TPJ deactivation and the less the self/other overlap. Interestingly, the correlation analysis between the contrast (Loved-one pain vs. Loved-one neutral) and the log of dating length showed that weaker activity of right TPJ and superior frontal gyrus was coupled with longer time of participants' relationship (Table S5). The hemodynamic response elicited by the imagination of their loved-one in pain may result from intimacy and familiarity.

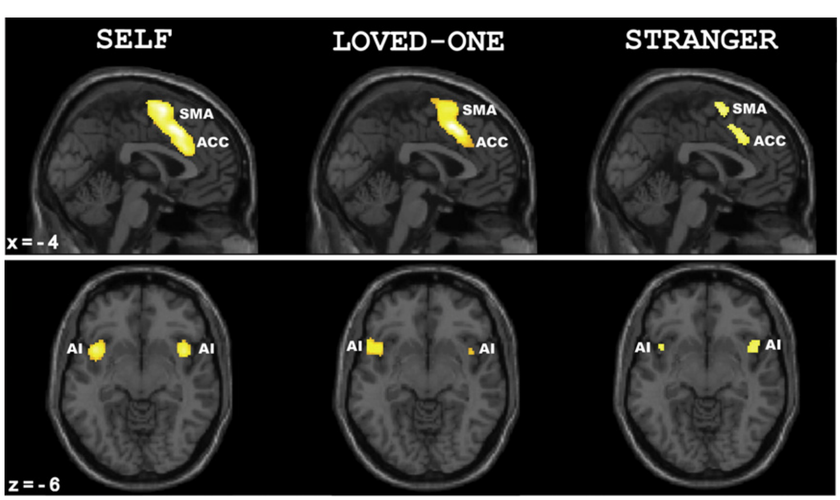

Fig. 1. Neural response to pain empathy during each perspective taking condition (Self vs. Loved-one vs. Stranger). SMA, supplementary motor area (0, 4, 62); dACC, dorsal anterior cingulate cortex (−4, 20, 28); AI, anterior insula (−34, 18, −6; 34, 22, −4).

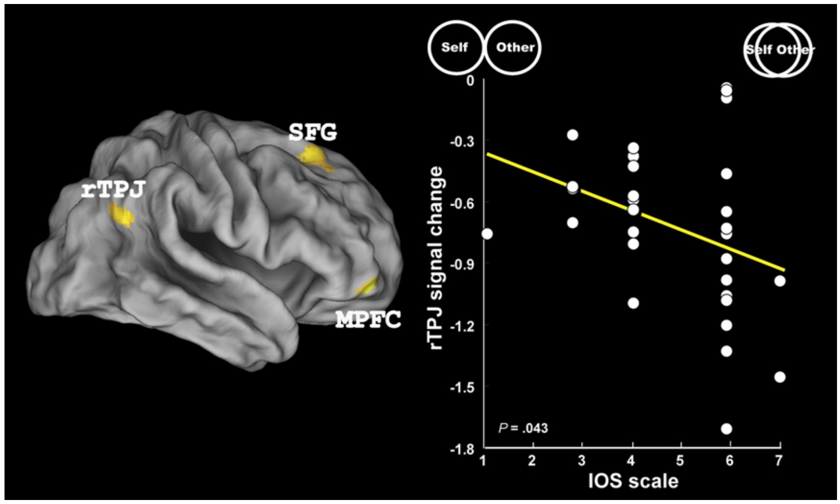

Fig. 3. Correlation between the activity in the right temporo-parietal junction (rTPJ) while participants imagine their loved-one in painful situations and the Inclusion of Other in the Self (IOS) scale. Lower activity in the rTPJ was associated with higher IOS scores.

Functional connectivity

PPI analyses indicated an effect of perspective taking with the right TPJ, insula, and SFG. The right TPJ exhibited enhanced effective connectivity (i.e., correlations in the time courses of the BOLD response) with the right SFG (x 30, y 52, z 34) ($Z=3.26$, $k=16$) in the Stranger, but not during the Loved-one and Self. The right TPJ showed a significant negative connectivity with the right insula (x 34, y −14, z 18) ($Z=3.92$, $k=85$) in the Stranger condition (Fig. 4).

ROI analysis

The parameter estimates of dACC, insula, and right TPJ were computed respectively for the Self, Loved-one, and Stranger's perspectives (Fig. 2b). One-way repeated measure ANOVA confirmed a major effect of the perspective taking (dACC: $F_{2,\ 68}=4.856$, $P=0.035$; anterior insula: $F_{2,\ 68}=6.558$, $P=0.015$; right TPJ: $F_{2,\ 68}=8.546$, $P=0.001$). *Post-hoc* Bonferroni correction for multiple comparisons demonstrated that the effect in the dACC was mostly driven by the contrast between Self vs. Stranger perspectives ($P=0.028$). The insula effect came from the Self vs. Stranger ($P=0.009$) and the Loved-one vs. Stranger ($P=0.005$) perspectives. Similarly, the right TPJ effect mainly resulted from the Self vs. Stranger ($P=0.003$) and the Loved-one vs. Stranger perspectives ($P=0.002$). A significant decrease was detected in the right TPJ when participants imagined a stranger in pain, whereas significant increase was observed in the insula when they imagined a loved-one in pain.

Discussion

The current study clearly demonstrates how intimacy modulates the neural response of empathy for pain, as indicated by the effect of perspective taking on the neural response in regions that belong to the pain matrix. In line with previous neuroimaging studies of empathy (Jackson et al., 2006b; Lamm et al., 2007a), the Self-perspective yielded higher pain ratings and involved the pain matrix more extensively in the dACC and the insula, whereas the Stranger perspective was associated with selective increased activation in the SFG and the right TPJ. Interestingly, adopting the perspective of a Loved-one elicited greater activation in regions that belong to the pain matrix than adopting the perspective of a Stranger. Parameter estimates of the signal change in the dACC, anterior insula, and right TPJ demonstrated graded responses related to perspective taking. Notably, the Stranger, not the Loved-one, exhibited a positive effective connectivity of the right TPJ with SFG, and a negative connectivity with the anterior insula. Together, these results

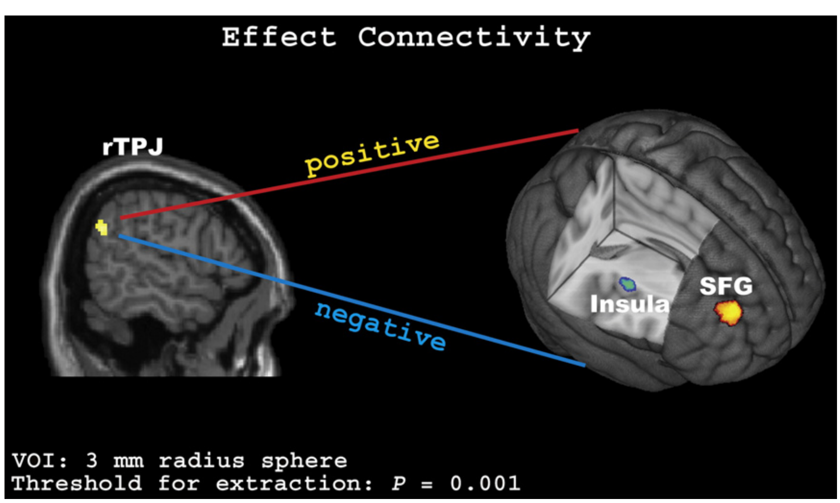

Fig. 4. Functional connectivity related to perspective taking and empathy. There was a negative functional connectivity between the right temporo-parietal junction (rTPJ) and the anterior insula, and a positive connectivity between the rTPJ and the superior frontal gyrus (SFG) when participants adopted the perspective of a stranger.

provide support to the hypothesis that social attachment and empathic concern are elaborated from elemental controls on bodily integrity, mediated through the perception of pain (Tucker et al., 2005).

In addition to intimacy, differential ingroup/outgroup relation, affective link, social attitudes, and familiarity may contribute to the differential brain activation across the three perspectives used in our study. First, the Self and Loved-one can be categorized as ingroup members whereas the Stranger as a outgroup member. Recent fMRI studies showed evidence that such ingroup/outgroup relation can modulate the hemodynamic activity in the dACC during empathy for pain (Krill and Platek, 2009; Xu et al., 2009). Second, as the affective link between the Self and the Loved-one is usually stronger than that between the Self and the Stranger, this may also contribute to the differential empathic responses to the Loved-one and Stranger, as shown in one fMRI study that documented that affective relationship modulated the activity in the anterior insula (Singer et al., 2006). Third, social attitudes towards a loved-one are usually more positive than to a stranger, which may also influence empathic responses (Batson et al., 1997b; Decety et al., 2009a). Finally, when imaging self and their loved-one, the evoked mental images are much clearer than when imaging a stranger. The difficulty in imagination possibly due to the difference of familiarity may also influence the process to take others' perspective, and in turn, modulate empathic responses (Cialdini et al., 1997). Here, weaker activity of the right TPJ coupled with more closeness and longer time in the relationship provides additional evidence that intimacy and familiarity play a role in the hemodynamic response elicited by imaging the loved-one in pain.

More importantly, the results of our study demonstrate that intimacy modulates the bottom-up processing of pain empathy. Cognitively, being in a close relationship can be described as including the other in the self with regards to resources, perspectives, and characteristics (Aron et al., 1991). Examples of such a process abound. For instance, affective interaction in chronic pain couples promotes the expressions of negative affect (Johansen and Cano, 2007). Empathic communication appears distinct from solicitous spouse response (Cano et al., 2008). Here, our fMRI study shows that imagining a loved-one in painful situations produces greater activation in the pain matrix and less activation in regions important for self/other distinction. In addition, more closeness in participants' relationships was associated with more overlap between the self and other, as indicated by reduced activation in right TPJ and increased activation in the anterior insula. These results lend support to the cognitive implications posited by Aron et al. (1991, 1992) regarding close relationships.

Furthermore, manipulation of the three different perspectives (Self vs. Loved-one vs. Stranger) clearly demonstrates the implication of specific computational mechanisms reflected by the differential activation of the right TPJ, SFG, and MPFC. Accumulating evidence from neuroimaging studies (Blakemore and Frith, 2003; Blanke and Arzy, 2005; Chaminade and Decety, 2002; Decety et al., 2002; Farrer et al., 2003; Farrer and Frith, 2002; Jackson and Decety, 2004; Leube et al., 2003; Ruby and Decety, 2001, 2003; Uddin et al., 2006) indicates that the right TPJ plays a critical role in the experience of agency and self–other discrimination. The TPJ is a heteromodal association cortex that integrates input from the lateral and posterior thalamus, as well as visual, auditory, somaesthetic, and limbic areas. It has reciprocal connections to the prefrontal cortex and temporal lobes. Due to these anatomical characteristics, this region is a pivotal neural locus for the self-processing involved in multisensory body-related information processing and the processing of phenomenological and cognitive aspects of the self (Blanke and Arzy, 2005). In addition, fMRI data suggest that the right TPJ is involved in empathy (Decety and Lamm, 2007). This region is specifically activated when participants imagine how another person would feel in painful experiences or daily situations that elicit social emotion, but not when they imagine themselves in these situations (Jackson et al., 2006b; Lamm et al., 2007a; Ruby and Decety, 2004). The right TPJ activity was negatively associated with the degree of overlap between self and other during the social perception judgment task (Lawrence et al., 2006). In this study, the activity of right TPJ was negatively correlated to the degree of closeness of the couples. It exhibited a positive functional connectivity with the SFG and a negative one with the insula in the Stranger, not in the Loved-one.

The SFG, MPFC, and right TPJ were significantly involved when imagining a stranger in pain, whereas the dACC and anterior insula were more activated when imagining a loved-one in pain. Two fMRI studies indicate that third-person perspective versus first-person perspective is associated with hemodynamic increase in the SFG and MPFC (Jackson et al., 2005, 2006b). The SFG is engaged in spatially oriented processing (du Boisgueheneuc et al., 2006) and task switching (Crone et al., 2006; Cutini et al., 2008). The MPFC is known to be involved in executive control (Miller and Cohen, 2001) and theory of mind (Gallagher et al., 2000; Vollm et al., 2006). It is more likely for the Stranger's perspective than the Loved-one's perspective to recruit more executive processing, which is associated with selective activation of the SFG and MPG and less activity in the pain matrix. Furthermore, the PPI analysis revealed that the Stranger's perspective led to, significant functional connectivity between the SFG and right TPJ but a negative functional connectivity between the insula and right TPJ. One fMRI study that compared physicians versus matched control participants watching body parts being pricked by needles reported a negative co-variation of activity in the MPFC with the insula in conjunction with involvement of the dorsolateral prefrontal cortex in the physicians (Cheng et al., 2007). This pattern of activity was interpreted as reflecting cognitive inhibitory control. We therefore argue from present study that less intimacy to the stranger than the loved-one may result in stronger cognitive inhibition of the affective processing in the pain matrix.

Overall, our study indicates that intimacy modulates the bottom-up processing of pain empathy. Imagining a Loved-one in pain was associated with stronger hemodynamic response in the dACC and anterior insula, and then more deactivation in the right TPJ, MPFC, and SFG. Overall, these fMRI findings are consistent with the cognitive and affective implications of intimacy posited by Aron et al. (1991, 1992) as well as the mechanisms on which social attachment and empathic concern is built upon (Tucker et al., 2005).

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2010.02.047.

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