

Neural substrates underlying intentional empathy

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Abstract

Although empathic responses to stimuli with emotional contents may occur automatically, humans are capable to intentionally empathize with other individuals. Intentional empathy for others is even possible when they do not show emotional expressions. However, little is known about the neuronal mechanisms of this intentionally controlled empathic process. To investigate the neuronal substrates underlying intentional empathy, we scanned 20 healthy Chinese subjects, using fMRI, when they tried to feel inside the emotional states of neutral or angry faces of familiar (Asian) and unfamiliar (Caucasian) models. Skin color evaluation of the same stimuli served as a control task. Compared to a baseline condition, the empathy task revealed a network of established empathy regions, including the anterior cingulate cortex, bilateral inferior frontal cortex and bilateral anterior insula. The contrast of intentional empathy versus skin color evaluation, however, revealed three regions: the bilateral inferior frontal cortex, whose hemodynamic responses were independent of perceived emotion and familiarity, and the right middle temporal gyrus, whose activity was modulated by emotion but not by familiarity. These findings extend our understanding of the role of the inferior frontal cortex and the middle temporal gyrus in empathy by demonstrating their involvement in intentional empathy.

Abbreviations

BOLD: blood oxygenation level dependent, fMRI: functional magnetic resonance imaging, ROI: region of interest, SPM: statistical parametric mapping

Introduction

Empathy describes our ability to understand and share the emotional states of others (Batson, et al. 1987; Blair 2005; Decety and Jackson 2004). This ability is of striking importance for our survival and success in social environments (Blair 2003; Gallese, et al. 2004). Empathy consists of various

mechanisms, which can be dissociated psychologically and neuroscientifically (Blair 2005; Preston and de Waal 2002). At this, most empathic responses to emotional cues in perceived stimuli, such as facial expressions, occur automatically (Chartrand and Bargh 1999; Dimberg and Thunberg 1998; Dimberg, et al. 2000; Han, et al. 2008; Kramer, et al. 2010). Humans, however, are capable to voluntarily focus their empathy on others (Nummenmaa, et al. 2008). This intentionally controlled empathy may even occur when no salient emotional cues are available in the perceived stimuli and is dissociated from the automatic empathy processes in time course (Fan and Han 2008).

Most of the previous studies identified neural substrates underlying emotional empathy by comparing stimuli with different emotional intensities (Blair, et al. 1999; Breiter, et al. 1996; Morris, et al. 1996; Phillips, et al. 1997; Sprengelmeyer, et al. 1998), by comparing the perception of emotions and the observation of others experiencing the same emotions (Jabbi and Keysers 2008; Jabbi, et al. 2007; Wicker, et al. 2003), or by comparing the perception of emotions with the imitation of the same emotions (Carr, et al. 2003). While these studies found neural activity in brain areas such as the anterior cingulate (ACC), anterior insula, superior temporal cortex, amygdala, and inferior frontal cortex (Blair, et al. 1999; Breiter, et al. 1996; Carr, et al. 2003; Jabbi, et al. 2007; Morris, et al. 1996; Phillips, et al. 1997; Sprengelmeyer, et al. 1998; Wicker, et al. 2003), the designs employed in the previous work did not allow to isolate intentionally controlled processes from automatically generated processes of empathy. In addition, although a number of studies investigated the modulation of empathy for pain by cognitive mechanisms (Hein and Singer 2008; Lamm, et al. 2007a; Lamm, et al. 2007b) or experience to painful practices (Cheng, et al. 2007), the neuronal basis underlying the cognitive modulation of emotional empathy has, to our knowledge, not been investigated so far.

The first aim of our study was to uncover the neural mechanisms underlying intentionally controlled processes involved in emotional empathy. To differentiate between intentional empathy and automatic empathic responses, we applied a visual

fMRI paradigm that included two tasks. An intentional empathy task asked subjects to actively share the emotional state of perceived faces with angry and neutral expressions. Automatic emotional responses may particularly be triggered by the presence of emotional cues in the presented stimuli. It may hence be difficult to completely disentangle intentionally generated and automatic empathic processes in emotional stimuli. The application of facial stimuli showing neutral emotional expressions (Nomi, et al. 2008; Nummenmaa, et al. 2008) reduces the automatic empathic responses and thus may help to uncover the intentional empathy. A second task asked subjects to evaluate the skin color of the same face stimuli. The first task required understanding and sharing the emotion of faces and thus tackled the intentional process involved in empathy. The second task created a control condition in which subjects concentrated on the facial stimuli alike the first task and were able to generate an automatic emotional response, however without an intentional empathy component. In addition, the skin color evaluation task controlled for the processing of perceptual features of face stimuli and motor responses.

Which brain regions did we expect to be involved in intentional empathy? Considering the different empathy concepts, the paradigm used in the current study is similar to the tasks previously applied to investigate emotional mentalizing (Hooker, et al. 2008; Hooker, et al. 2010; Ochsner, et al. 2004). Hence, we expected to find the superior temporal sulcus, medial prefrontal cortex, the temporal poles, and the inferior frontal cortex to be activated during intentional empathy, since these areas were involved in emotional mentalizing (Hooker, et al. 2008; Hooker, et al. 2010; Ochsner, et al. 2004).

The second aim of our study was to investigate whether the brain regions involved in intentional empathy are modulated by emotion cues in the stimuli. Two alternative mechanisms are thinkable:

A brain region involved in intentional empathy may activate completely independently from the presence or absence of emotion in perceived facial stimuli. If this is the case, we should consider this region as responsible for genuine intentional em-

pathy. It may be, however, that neuronal activity of a brain region is modulated by the presence or absence of emotion. Then we would suggest that this brain region is not completely responsible of intentional empathy, but rather modulated by intentional empathy. In order to explore this effect, we applied emotional (angry) and neutral facial stimuli in the empathy task.

The third aim of our study was to investigate a potential effect of familiarity with target persons on intentional empathy. As recently shown by a number of studies, race-based familiarity is an effective modulator of empathy for pain (Avenanti, et al. 2010; Chiao and Mathur 2010; Mathur, et al. 2010; Xu, et al. 2009). The effects of race-based familiarity on intentional empathy have, however, not been investigated, so far. In order to test for a potential effect of race-based familiarity on intentional emotional empathy, we applied neutral stimuli of familiar (Asian) and unfamiliar (Caucasian) faces to Chinese subjects.

Materials and methods

Subjects

We investigated 20 healthy Chinese subjects (11 female, 9 male, mean age: 23, range: 21-26). After a detailed explanation of the study design and any potential risks, all subjects gave their written informed consent. All of the subjects were Chinese college students. The study was approved by a local ethics committee at the Department of Psychology, Peking University.

Paradigm

Experimental Design

The fMRI experiment was divided into 7 blocks of 312 s duration each. Prior to entering the scanner each subject read detailed information of the paradigm and completed a couple of trial runs in order to familiarize fully with the task. While lying in the scanner, the stimuli were displayed using the software package 'Presentation' (Neurobehavioral Systems, Albany, CA), and were projected onto a matt screen via an LCD projector, visible through a mirror mounted on the head coil. Every block started with 10 s pause to control for epistaturation effects. A total number of 24 trials (12 intentional empathy trials and 12 trials skin color

evaluation trials) were presented in a randomized order in each block. Figure 1 illustrates the intentional empathy task and the control task. After every 6 trials a baseline trial was included, which

consisted of the mere presentation of the fixation cross, lasting for 6 or 7 s.

Figure 1. Paradigm

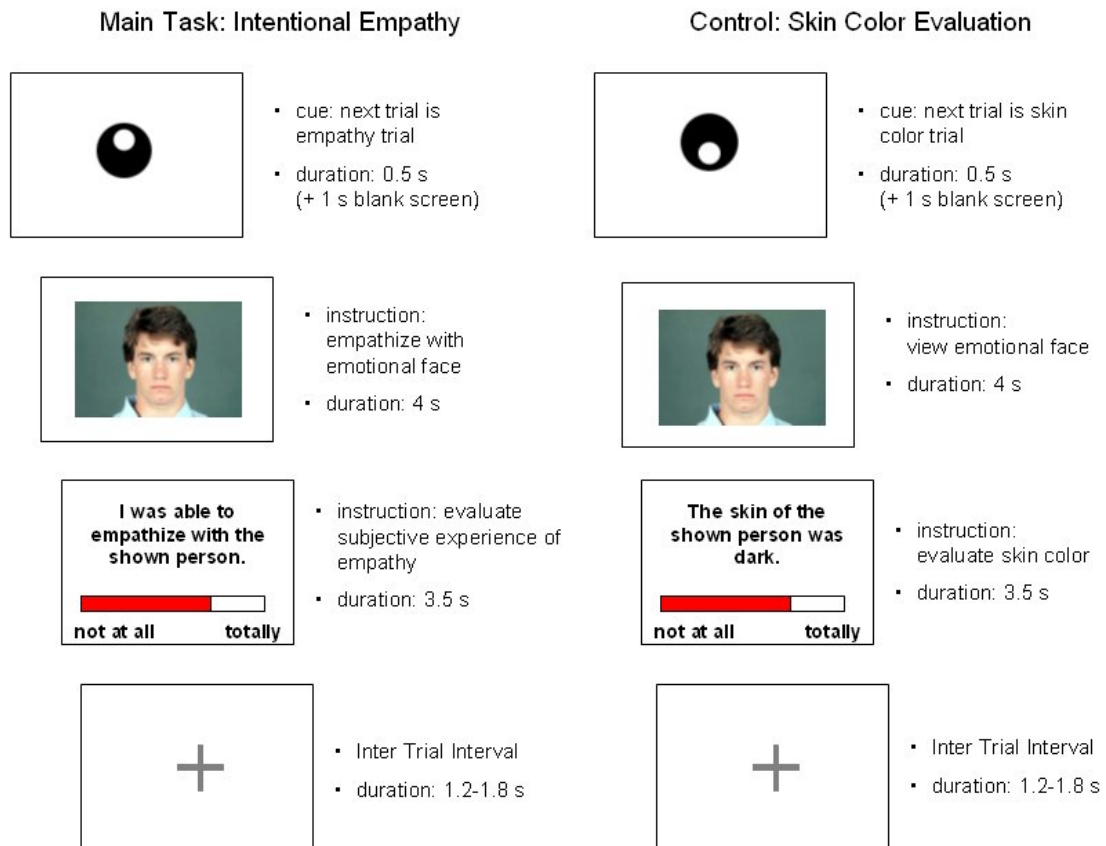


Figure 1: Paradigm

A black circle with a small white circle in the 'North'- or 'South'-position cued the task of the next trial. The white circle in the 'North'-position indexed an intentional empathy trial; the white circle in the 'South'-position cued a skin color evaluation trial. In intentional empathy trials subjects were instructed to empathize with perceived emotional or neutral faces. After a 4 s lasting viewing period, subjects were supposed to rate their subjective impression of empathy capability in the evaluation period, which lasted for 3.5 s. By virtually moving a red bar, they were instructed to make a statement on a visual analogue scale. In control trials subjects were instructed to concentrate on the skin color of the presented faces. Analogue to the intentional empathy task, a 4 s lasting viewing period was followed by a 3.5 s lasting evaluation period. After every trial a short inter trial interval of 1.2 to 1.8 s duration was presented. The face stimuli consisted of familiar (Chinese) neutral and angry faces as well as unfamiliar (Caucasian) neutral faces.

Stimuli

Our emotional face stimuli consisted of 12 different faces. Each of the three conditions, namely familiar angry, familiar neutral and unfamiliar neutral, contained four different faces (two female and two male). The four stimuli of the unfamiliar neutral condition were taken from the “Japanese and Caucasian Facial Expressions of Emotion (JACFEE) and Neutral Faces (JACNeuF)”-battery provided by Matsumoto and Ekman (Matsumoto and Ekman 1988). The eight stimuli of the familiar angry and familiar neutral condition were photographed and preprocessed for presentation by our own group. These pictures were taken in front of a comparable background and under comparable conditions to match them as close as possible to the four pictures taken from the JACNeuF battery. Every stimulus was presented twice during each block: once during intentional empathy, once during skin color evaluation.

Behavioral Tests

We applied the “Interpersonal Reactivity Index” (IRI, Davis 1983) to measure individual empathic characteristics of our subjects. The IRI is a commonly used self evaluation questionnaire (Kaplan and Iacoboni 2006), which is apt to state the subjective impression of different empathic skills. The IRI uses four subscales related to perspective taking, empathic fantasy, empathic concern and empathic personal distress.

Behavioral data analysis

The subjects’ performance and reaction times for intentional empathy and skin color evaluation trials were compared using paired t-tests.

fMRI data acquisition

The study was conducted using a General Electrics 3 Tesla Magnetic Resonance Imaging Scanner (24 slices parallel to the AC-PC plane, slice thickness 5mm, TR 2000 ms, TE 30 ms, flip angle $\alpha = 90^\circ$, 64 x 64 voxels per slice with 3.75 x 3.75 x 5 mm). Functional data were acquired in seven scanning sessions containing 156 volumes per session for each subject.

fMRI data analysis

The statistical analysis of the fMRI data was performed using the SPM2 software package (SPM2, <http://www.fil.ion.ucl.ac.uk>) and Matlab 6.5.1 (The Mathworks Inc., Natick, MA, USA). fMRI data were slice time corrected with regard to the first slice acquired and movement corrected by realignment to the first volume. Subjects’ T1-weighted anatomical images were coregistered to their first functional image. All functional images were normalized to a standard T1-weighted SPM template (Ashburner and Friston 1999). The normalization was generated by warping the subject’s coregistered anatomical image to the T1-weighted SPM template followed by the application of the same normalization parameters to the functional images. Smoothing was performed using a 8 x 8 x 8 mm full-width half-maximum Gaussian kernel. A statistical model for each subject was computed by applying a canonical response function (Friston, et al. 1998). All relevant periods (namely the viewing periods and evaluation periods for all emotions and both tasks, as well as viewing and evaluation periods for trials without confirmed responses, and the baseline event) were included in the SPM model. Regionally specific condition effects were tested by employing linear contrasts for each subject and different conditions. The resulting contrast images were submitted to a second level random-effects analysis. Here, one-sample t-tests were used on images obtained for each subject’s volume set and different conditions. To control for the multiple testing problem we performed a false discovery rate correction (Nichols and Hayasaka 2003). The anatomical localization of significant activations was assessed with reference to the standard stereotactic atlas and by superimposition of the SPM maps on a mean brain generated by averaging of each subject’s T1-weighted image. In a second step we analyzed the fMRI raw data using the Marseille Region of Interest Toolbox software package (Brett, et al. 2002, MarsBaR 1.86, <http://www.sourceforge.net/projects/marsbar>). Using a sphere-shaped “region of interest” (ROI, radius 5mm) we extracted the raw data from activations found in the second level analysis. fMRI raw data timecourses were processed using the software package PERL (<http://www.perl.org>). The timecourses were linearly interpolated and normalized with respect to a time window ranging from -6 s to

30 s before and after the onset of each event. fMRI signal changes of every event were calculated with regard to the fMRI signal value of 0 s. Mean normalized fMRI signal values from two following time steps (6s and 8s after onset of the viewing period) were included in the statistical analysis. We used paired t-tests to analyze the effect of the different emotion conditions on the fMRI raw data.

Results

Behavioral Results

Intra-scanner ratings We did not find any significant differences between intentional empathy trials and skin color evaluation trials with regard to performance (see Figure 2.a) and reaction times of the first response (see Figure 2.b). However, we detected significant faster confirmation responses during intentional empathy when compared to skin color evaluation trials (see Figure 2.b).

Figure 2. Behavioral results

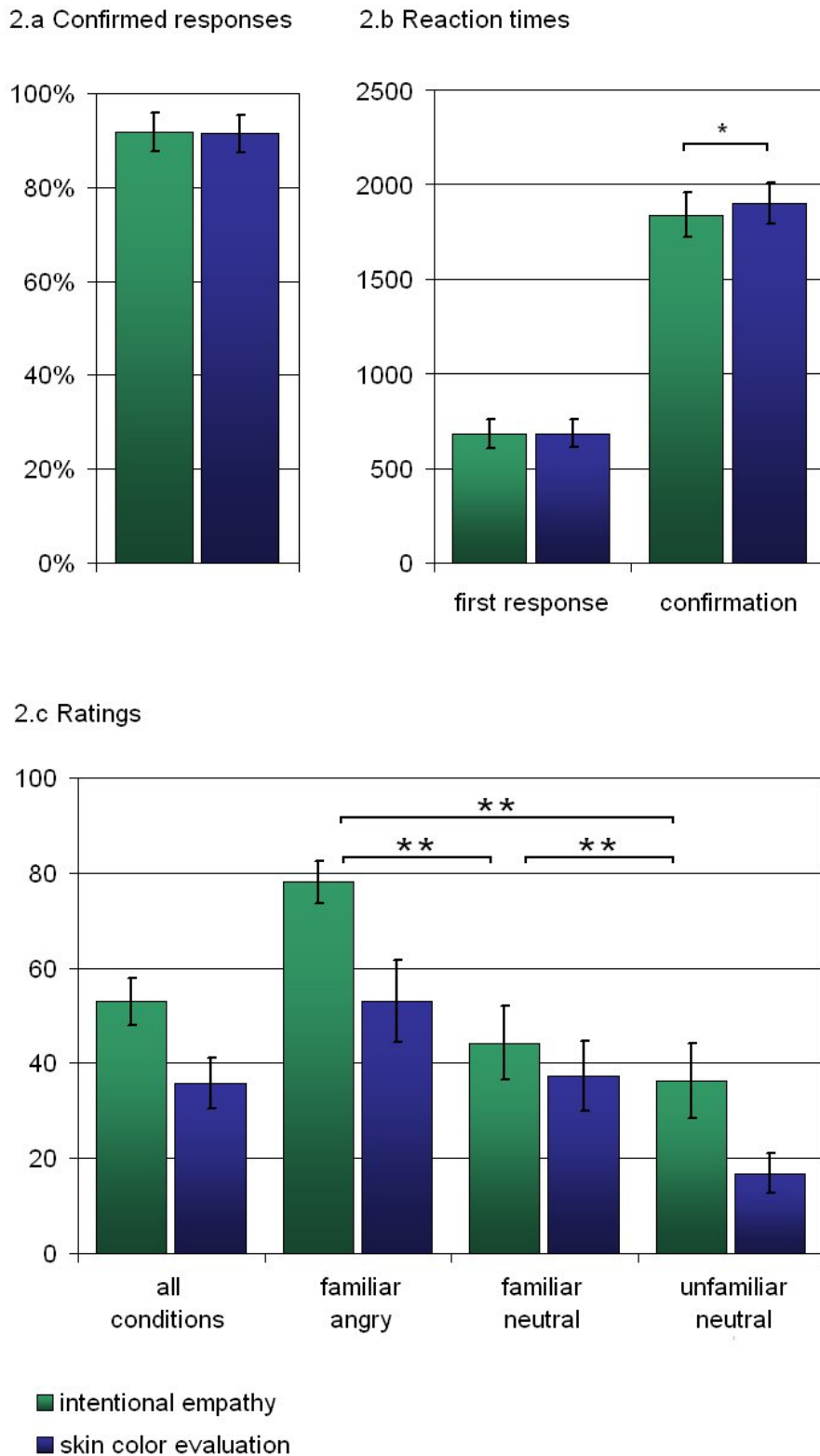


Figure 2: Behavioral Results

a. Confirmed responses. Confirmed responses required the press of the confirmation button after the right score on the visual analogue scale was chosen. The percentage of confirmed responses did not differ

significantly between intentional empathy and skin color evaluation trials ($t(19) = 0.326$; $p_{[\text{two-tailed}]} = 0.748$).

b. **Reaction times.** Reaction times for first responses (when the left or right button was pressed for the first time to move the bar of the visual analogue scale) and for confirmation responses (when the confirmation button was pressed to indicate the right position of the bar). There were no significant differences between the first responses of intentional empathy trials and skin color evaluation trials. However, comparing the confirmation responses showed significantly faster reaction times during intentional empathy trials compared to the skin color evaluation trials ($t(19) = -3.172$; $p_{[\text{two-tailed}]} = 0.005^{**}$).

c. **Ratings.** Intra-scanner empathy ratings for familiar neutral faces were significantly smaller relative to empathy ratings for familiar angry faces ($t(19) = 7.297$; $p_{[\text{two-tailed}]} < 0.001^{**}$). Ratings for familiar neutral faces were nevertheless larger compared to empathy rating for unfamiliar neutral faces ($t(19) = 4.914$; $p_{[\text{two-tailed}]} < 0.001^{**}$). Skin color ratings for familiar neutral faces were greater when compared to unfamiliar neutral faces ($t(19) = 5.183$; $p_{[\text{two-tailed}]} < 0.001^{**}$) and smaller when compared to skin color ratings of familiar angry faces ($t(19) = 9.713$; $p_{[\text{two-tailed}]} < 0.001^{**}$). In addition, skin color estimations of unfamiliar neutral faces were smaller than skin color scores of familiar angry faces ($t(19) = 7.926$; $p_{[\text{two-tailed}]} < 0.001^{**}$).

(Error bars indicate the 95% confidence interval. Not all significant differences are indexed in the diagram.)

Results of the Interpersonal Reactivity Index (IRI)

Mean scores of our subjects for the different IRI subcategories were: empathic fantasy: 18.0 (95%-CI: 15.6-20.4), empathic concern: 18.5 (95%-CI: 17.2-19.8), perspective taking: 18.5 (95%-CI: 17.2-19.8) and empathic distress 12.6 (95%-CI: 11.3-13.9).

fMRI Results

SPM contrast [intentional empathy] > [baseline]

This contrast revealed a number of brain regions commonly associated to the empathy network, including the inferior frontal cortex, anterior cingulate cortex, the supplementary motor area, the anterior insula, and others (see Table 1 for details).

region		x, y, z [mm]*			T	P[FDR]
left	inferior frontal cortex	-48	2	43	5.88	0.001
right	inferior frontal cortex	50	6	24	5.18	0.002
		48	6	32	5.11	0.002
		40	30	14	3.67	0.020
left	prefrontal cortex	-36	50	16	3.40	0.030
		-35	40	10	3.39	0.030
left	anterior cingulate cortex	-6	0	54	6.35	< 0.001
right	anterior cingulate cortex	10	8	48	6.50	< 0.001
left	supplementary motor area	-26	-10	54	7.04	< 0.001
right	supplementary motor area	26	-4	60	4.38	0.007
		38	-14	56	3.52	0.025
left	anterior insula	-30	22	4	4.90	0.003
right	anterior insula	32	22	6	4.08	0.010
left	putamen	-22	4	4	4.89	0.003
right	putamen	22	6	6	4.10	0.010
left	posterior parietal cortex	-10	-76	50	4.17	0.009
		-22	-72	40	3.16	0.042
		-32	-50	36	3.81	0.016
		-28	-66	52	3.14	0.044
left	occipital cortex	-14	-96	-8	10.47	< 0.001
		-40	-70	-28	9.17	< 0.001
		-34	-76	-28	8.44	< 0.001
right	occipital cortex	28	-88	-8	11.62	< 0.001
		24	-84	-15	11.08	< 0.001
		36	-62	-24	8.93	< 0.001

Table 1: Significant regions of the contrast [intentional empathy] > [baseline]

The contrast was calculated using a FDR correction for multiple comparisons. The table contains all clusters with $p_{[FDR]} < 0.05$ and a minimum cluster size of 10 voxels ($n = 20$).

* Coordinates refer to the MNI stereotactic space.

SPM contrast [intentional empathy] > [skin color evaluation]

This contrast revealed three regions associated with intentional empathy: the left and right in-

ferior frontal cortex and the right middle temporal gyrus (see Table 2 and Figure 3). The opposite contrast [skin color evaluation] > [intentional empathy] showed no regions activated above the threshold of $p_{[uncorrected]} \leq 0.001$.

region		x, y, z [mm]*			T	P _[uncorr]
left	inferior frontal cortex	-48	22	-2	4.66	< 0.001
right	inferior frontal cortex	48	28	4	4.66	< 0.001
right	middle temporal gyrus	62	-54	0	3.98	< 0.001

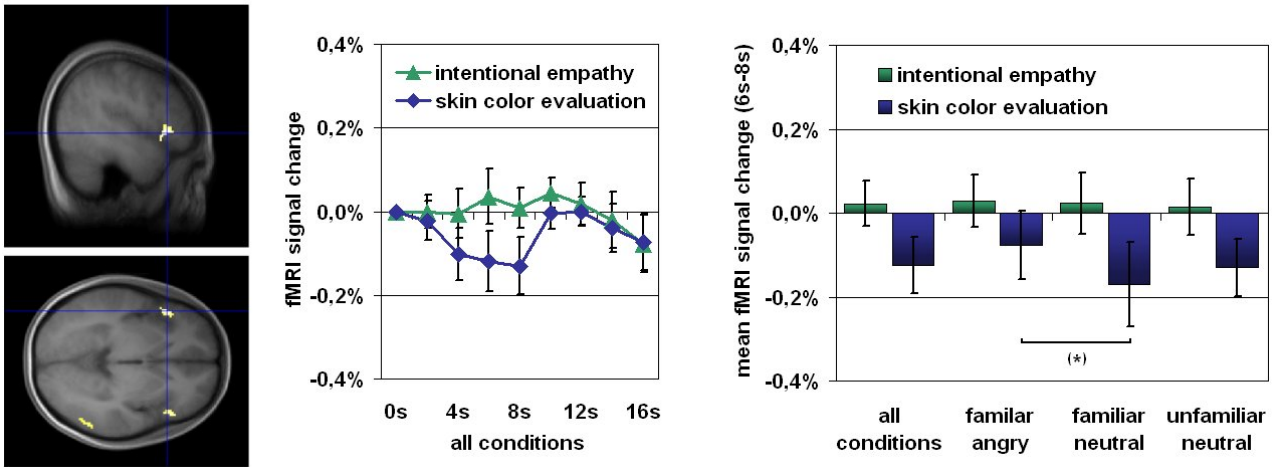
Table 2: Significant regions of the contrast [intentional empathy] > [skin color evaluation]

This contrast (n = 20, uncorrected threshold 0.001, minimum cluster size 10 voxels) revealed three regions with stronger hemodynamic responses during intentional empathy: The bilateral inferior frontal cortex and the right middle temporal gyrus. The opposite contrast [skin color evaluation] > [intentional empathy] did not reveal any significant regions under the same threshold conditions.

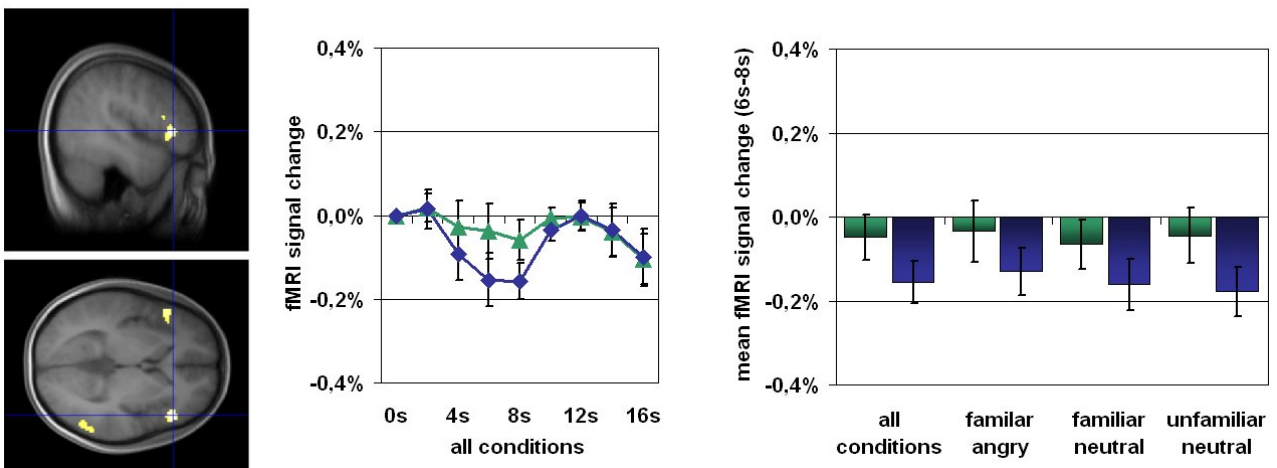
* Coordinates refer to the MNI stereotactic space.

3. Significant regions of the contrast [intentional empathy] > [skin color evaluation]

3.a Left inferior frontal cortex [-48, 22, -2]



3.b Right inferior frontal cortex [48, 28, 4]



3.c Right middle temporal gyrus [62, -54, 0]

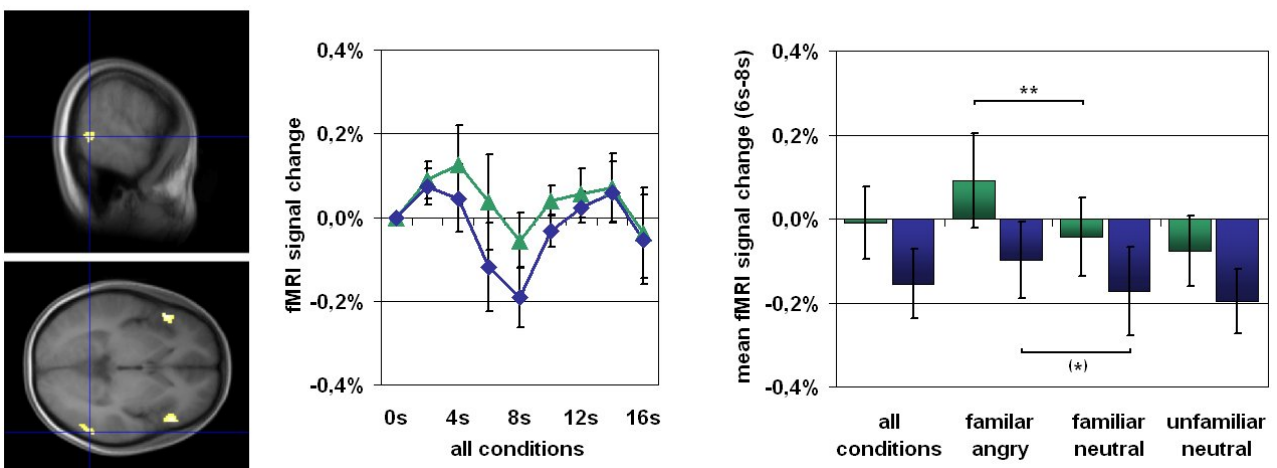


Figure 3: Significant regions of the contrast [intentional empathy] > [skin color evaluation]

Three regions showed stronger hemodynamic responses during the intentional empathy task when

compared to the skin color task: The left inferior frontal cortex (a), the right inferior frontal cortex (b), and the right middle temporal gyrus (c). SPM analysis was supplemented by an analysis of the raw fMRI signal data. The diagrams in the center of each line show the averaged time courses of the fMRI signal during intentional empathy and skin color evaluation for all conditions. The bar diagrams on the right depict the mean fMRI signal values (6s to 8s after onset) for the average of all conditions as well as for the single conditions separately. Looking for modulations by emotion, we only found the right middle temporal gyrus with significant stronger hemodynamic responses during the empathic perception of familiar angry faces compared to familiar neutral faces ($t(19) = 4.277$, $p_{[\text{two-tailed}]} = 0.001^{**}$, c). The left and right inferior frontal cortex did not show any modulation by emotion during intentional empathy (a, b). In addition, none of the regions showed a significant difference between the neutral familiar and neutral unfamiliar condition. Surprisingly, we found a statistical trend for a modulation of hemodynamic responses during skin color evaluation caused by emotion in two regions: the left inferior frontal cortex (a) and right middle temporal gyrus (c) showed the tendency to respond stronger during skin color evaluation of familiar angry faces compared to familiar neutral faces ($t(19) = 1.855$, $p_{[\text{two-tailed}]} = 0.079^{(*)}$ and $t(19) = 2.011$, $p_{[\text{two-tailed}]} = 0.059^{(*)}$). Interestingly, we found significant deactivations in all three regions during all skin color evaluation conditions (all $p_{[\text{two-tailed}]} \leq 0.061^{(*)}$).

(Error bars indicate the 95% confidence interval.)

Analyses of fMRI raw data

The results of the fMRI raw data analysis are presented in Figure 3.

SPM contrasts for the different emotion conditions

Using SPM one sample t-tests, we looked for regions with different hemodynamic responses during the intentional empathy subconditions (namely familiar angry, familiar neutral and unfamiliar neutral). Applying a threshold of $p_{[\text{uncorrected}]} < 0.001$ and a minimum cluster size of 10 voxels, we did not find regions with differences in hemodynamic responses during the presentation of familiar angry and familiar neutral faces. Using the same threshold, we did not find any areas with different hemodynamic responses during familiar neutral faces and unfamiliar neutral faces.

SPM contrast [familiar neutral] > [unfamiliar neutral]

In addition, we used an SPM one sample t-test, to look for regions with different hemodynamic responses during the perception (intentional empathy + skin color evaluation) of familiar neutral and unfamiliar neutral faces. Applying a threshold of $p_{[\text{uncorrected}]} < 0.001$ and a minimum cluster size of 10 voxels, we did not find any cluster for the contrast [familiar neutral] > [unfamiliar neutral].

In addition, we did not find any activations in the opposite contrast [unfamiliar neutral] > [familiar neutral] using the same threshold criteria.

SPM correlations using mean empathy ratings and Interpersonal Reactivity Index scores

We performed a supplementary SPM analysis, in which we introduced behavioral variables into simple SPM correlations using the images of the contrast [intentional empathy] > [skin color evaluation]. Looking for regions in which each subject's mean intra-scanner empathy rating predicted their contrast value of the contrast [intentional empathy] > [skin color evaluation], the SPM correlation revealed only one region, the left posterior fusiform gyrus (-34, -82, -20, $t(18) = 3.87$, $p_{[\text{uncorrected}]} < 0.001$, minimum cluster size 10 voxels, Figure 4). Correlating the same contrast images with each subjects mean IRI score for empathic fantasy, empathic concern, perspective taking and empathic distress, we found no significant voxels above the rational threshold of $p_{[\text{uncorrected}]} < 0.001$ and a minimum cluster size of 10 voxels.

4. Left posterior fusiform gyrus [-34, -80, -20]

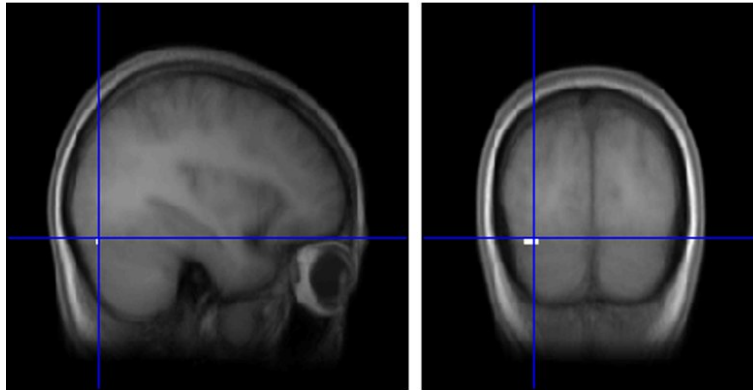


Figure 4: Correlation in the left posterior fusiform gyrus

The left posterior fusiform gyrus showed a significant correlation of hemodynamic responses for the contrast [intentional empathy] > [skin color evaluation] and mean empathy ratings (simple SPM correlation analysis, $p_{\text{uncorrected}} < 0.001$, minimum cluster size 10 voxels).

Discussion

Relative to the baseline condition, the intentional empathy task increased activity in a neural circuit consisting of the inferior frontal cortex, anterior cingulate cortex, the supplementary motor area, and the anterior insula. This is consistent with the observation of previous studies of empathy (Blair, et al. 1999; Breiter, et al. 1996; Carr, et al. 2003; Jabbi, et al. 2007; Morris, et al. 1996; Phillips, et al. 1997; Sprengelmeyer, et al. 1998; Wicker, et al. 2003). However, compared to the control condition that required skin color evaluation, the intentional empathy task induced significant stronger hemodynamic responses in the bilateral inferior frontal cortex and the right middle temporal gyrus, revealing brain regions specifically involved in intentional empathy. Looking for effects of emotion, we found only the right middle temporal gyrus with stronger hemodynamic responses during intentional empathy for familiar angry faces compared to familiar neutral faces. None of the regions showed evidence for modulations by the race-based familiarity between the observed and target person. Hemodynamic responses during skin color evaluation of the left inferior frontal cortex and the right middle temporal gyrus showed a tendency for an emotional effect, with stronger hemodynamic responses during familiar angry faces, compared to familiar neutral faces. Again, we did not find any modulation of hemodynamic responses caused by race-based familiarity. Differences in hemodynamic responses between intentional empathy and skin color evaluation of the left fusiform gyrus correlated with mean intra-scanner empathy ratings.

The inferior frontal cortex and middle temporal gyrus have been shown to be involved in emotional empathy (Blair, et al. 1999; Carr, et al. 2003; Chakrabarti, et al. 2006; Decety and Chaminade 2003; Jabbi, et al. 2007). Our fMRI results indicate that these brain areas engage in intentional empathy for other individuals even when no perceived emotional cues are available. In other words, the neuronal activity of left and right inferior frontal cortex during intentional empathy was independent of the emotional content of the stimuli. This finding demonstrates that neuronal activity in the bilateral inferior frontal cortex can be exclusively internally generated, without any modulation by the external emotional cues. Hemo-

dynamic responses of the right middle temporal gyrus, however were modulated by the emotional content of the presented pictures, indicating that neuronal activity of this region is not exclusively internally generated.

Our findings extend our understanding of the role of the inferior frontal cortex in empathy. The inferior frontal cortex is known to be part of the human mirror neuron system, a network of brain regions which are involved in the generation of actions as well as in the perception of actions performed by others (Carr, et al. 2003; Grezes, et al. 2003; Iacoboni 2005; Iacoboni and Dapretto 2006; Iacoboni, et al. 2005; Iacoboni, et al. 1999; Kaplan and Iacoboni 2006); at first, it was detected in the monkey (Buccino, et al. 2001; Ferrari, et al. 2003; Gallese, et al. 1996; Rizzolatti and Craighero 2004; Rizzolatti, et al. 1996; Rizzolatti, et al. 2001). A number of studies showed the involvement of the mirror neuron system and particularly the inferior frontal cortex in empathic processes such as emotional empathy (Kaplan and Iacoboni 2006), emotional imitation (Carr, et al. 2003; Lee, et al. 2006), passive emotion perception (Chakrabarti, et al. 2006), and emotion evaluation (Decety and Chaminade 2003). Since these studies used emotional stimuli, the observed inferior frontal activity may mainly subserve emotion regulation. In our work, however, the observed inferior frontal activity observed mainly reflects intentional control of emotional empathy, since it was detected in a task requiring empathy for neutral faces. This task reduced emotional responses to a minimum degree and thus did not require emotion regulation. Interestingly enough, two studies reported the inferior frontal cortex to be involved in intentional emotion imitation (Carr, et al. 2003; Lee, et al. 2006). Our study contributes to these findings in showing that the mere intentional emotional sharing of another's state is sufficient to activate the inferior frontal cortex - even without emotions expressed by the target.

In addition, the right middle temporal gyrus (as part of the posterior superior temporal sulcus region) showed stronger hemodynamic responses during intentional empathy when compared to the control task. These results complement previous findings which described the involvement of the superior temporal sulcus region in several emo-

tional tasks. Activation of the superior temporal sulcus region was often found together with co-activation of the inferior frontal cortex during the same contrasts (Carr, et al. 2003; Chakrabarti, et al. 2006; Grezes, et al. 2003; Hoekert, et al. 2008; Hooker, et al. 2008; Hooker, et al. 2010). Additional papers suggest nevertheless that the superior temporal sulcus region is comparatively more involved in social cognitive tasks, such as the passive perception of social scenes (Kramer, et al. 2010) or Theory of Mind (Vollm, et al. 2006). In their review paper, Allison and colleagues (Allison, et al. 2000) suggest that the superior temporal sulcus region is “sensitive to stimuli that signal the actions of another individual”. Interestingly, and in contrast to the inferior frontal cortex, the right middle temporal gyrus showed a significant modulation by emotion with stronger hemodynamic responses during familiar angry faces compared to familiar neutral faces. This finding can perhaps be explained by the assumption that angry facial expressions are comparatively more salient to neutral ones and imply greater social relevance (Blair 2005).

None of the three regions involved in intentional empathy observed in our study was affected by familiarity. Recently, a number of studies found race-based familiarity to be an effective modulator of brain activity related to empathy for pain. Regions modulated by race-based familiarity included the anterior cingulate cortex (Mathur, et al. 2010; Xu, et al. 2009), the insula (Mathur, et al. 2010), and the sensorimotor system (Avenanti, et al. 2010). In addition, differences in activity of the fusiform gyrus during the memorizing of facial stimuli of the same race (African-American) and another race (Caucasian) were reported (Golby, et al. 2001) as well as differences in the activity of the amygdala, the superior temporal cortex and other regions during very short presentations of other-race (African-American) and same-race (Caucasian) facial stimuli (Cunningham, et al. 2004). However, none of these studies reported differences of inferior frontal cortex activity related to race-based differences in familiarity. Moreover, none of these studies investigated intentional emotional empathy. Together these results suggest that the social relation between an observer and a target mainly modulates the automatic processes of empathy. The intentionally controlled process

of empathy mediated by the inferior frontal cortex, however, seems to function independently of the social relation between the observer and a target. These findings provide additional evidence for the dissociation between intentionally controlled processes from the automatically generated processes of empathy.

The voxel-based correlation analysis revealed a significant correlation of neuronal activity in the left posterior fusiform gyrus with subjective empathy ratings. This brain area is located posterior to the fusiform face area that is crucially involved in the processing of faces (Fusar-Poli, et al. 2009; Grill-Spector, et al. 2004; Iidaka, et al. 2006; Kanwisher, et al. 1997). The posterior fusiform region observed in our study seems nonetheless to overlap with regions observed in the processing of emotional faces (Etkin, et al. 2004; Geday, et al. 2003; Nomi, et al. 2008) and empathy with painful emotional faces (Lamm, et al. 2007a). The here observed correlation of hemodynamic modulation in the posterior fusiform gyrus and mean empathy ratings might hence be interpreted as increased processing of the facial stimuli in those subjects, which gave overall higher empathy ratings.

A few limitations of our study should be noted. First, during both tasks we were not able to control on which specific aspect of the facial stimuli our subjects focused. It might be that during the intentional empathy task subjects focused more on the eyes of the facial stimuli, while subjects possibly concentrated on the cheeks and the forehead during the skin color perception task. Second, as demonstrated in Figure 3, the contrast between the intentional empathy task and the skin color evaluation task was mainly shaped by the distinct negative signal changes during the skin color evaluation task, rather than by the positive hemodynamic responses during intentional empathy. We are puzzled by this finding and can only provide a rather speculative explanation that awaits further research. It may be the case that the pronounced negative fMRI signal changes during skin color evaluation reflect the intentionally controlled inhibition of empathy processes. In other words, neuronal activity of the bilateral inferior frontal cortex and superior temporal sulcus region may be not so much affected by the intentionally controlled generation of empathy,

but rather by its intentionally controlled inhibition. Third, the variety of emotions applied in our paradigm is rather low (only angry and neutral). Future studies may investigate intentional empathy with other emotions. In addition, it might be interesting for future studies to examine whether the influence of race-based familiarity on empathy is modulated by different emotions of perceived facial expressions.

Conclusions

Our results underline the important role of the bilateral inferior frontal cortex and the right superior temporal sulcus region in empathy. We were able to show that these regions play a pivotal role in intentional empathy. Hemodynamic responses of bilateral inferior frontal cortex during intentional empathy were only modulated by the task, whereas the right superior temporal sulcus region was affected by the emotional content of the facial stimuli. None of the three regions showed an effect of the race-based familiarity of perceived stimuli. Our findings suggest that the inferior frontal activity underlying intentionally controlled empathic responses is independent of both emotional contents in perceived stimuli and familiarity between the observer and target person.

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References

- Allison T, Puce A, McCarthy G. 2000. Social perception from visual cues: role of the STS region. *Trends Cogn Sci* 4(7): 267-278.
- Ashburner J, Friston KJ. 1999. Nonlinear spatial normalization using basis functions. *Hum Brain Mapp* 7(4): 254-66.
- Avenanti A, Sirigu A, Aglioti SM. 2010. Racial bias reduces empathic sensorimotor resonance with other-race pain. *Curr Biol* 20(11): 1018-22.
- Batson CD, Fultz J, Schoenrade PA. 1987. Distress and empathy: two qualitatively distinct vicarious emotions with different motivational consequences. *J Pers* 55(1): 19-39.
- Blair RJ. 2003. Facial expressions, their communicatory functions and neuro-cognitive substrates. *Philos Trans R Soc Lond B Biol Sci* 358(1431): 561-72.
- Blair RJ. 2005. Responding to the emotions of others: dissociating forms of empathy through the study of typical and psychiatric populations. *Conscious Cogn* 14(4): 698-718.
- Blair RJ, Morris JS, Frith CD, Perrett DI, Dolan RJ. 1999. Dissociable neural responses to facial expressions of sadness and anger. *Brain* 122 (Pt 5): 883-93.
- Breiter HC, Etcoff NL, Whalen PJ, Kennedy WA, Rauch SL, Buckner RL, Strauss MM, Hyman SE, Rosen BR. 1996. Response and habituation of the human amygdala during visual processing of facial expression. *Neuron* 17(5): 875-87.
- Brett M, Anton J-L, Valabregue R, Poline J-B. 2002. Region of interest analysis using an SPM toolbox [abstract]. . International Conference on Functional Mapping of the Human Brain. Sendai, Japan.
- Buccino G, Binkofski F, Fink GR, Fadiga L, Fogassi L, Gallese V, Seitz RJ, Zilles K, Rizzolatti G, Freund HJ. 2001. Action observation activa-

- tes premotor and parietal areas in a somatotopic manner: an fMRI study. *Eur J Neurosci* 13(2): 400-4.
- Carr L, Iacoboni M, Dubeau MC, Mazziotta JC, Lenzi GL. 2003. Neural mechanisms of empathy in humans: a relay from neural systems for imitation to limbic areas. *Proc Natl Acad Sci U S A* 100(9): 5497-502.
- Chakrabarti B, Bullmore E, Baron-Cohen S. 2006. Empathizing with basic emotions: common and discrete neural substrates. *Soc Neurosci* 1(3-4): 364-84.
- Chartrand TL, Bargh JA. 1999. The chameleon effect: the perception-behavior link and social interaction. *J Pers Soc Psychol* 76(6): 893-910.
- Cheng Y, Lin CP, Liu HL, Hsu YY, Lim KE, Hung D, Decety J. 2007. Expertise modulates the perception of pain in others. *Curr Biol* 17(19): 1708-13.
- Chiao JY, Mathur VA. 2010. Intergroup empathy: how does race affect empathic neural responses? *Curr Biol* 20(11): R478-80.
- Cunningham WA, Johnson MK, Raye CL, Chris Gatenby J, Gore JC, Banaji MR. 2004. Separable neural components in the processing of black and white faces. *Psychol Sci* 15(12): 806-13.
- Davis MH. 1983. Measuring individual differences in empathy: Evidence for a multidimensional approach. *Journal of Personality and Social Psychology* 44: 14.
- Decety J, Chaminade T. 2003. Neural correlates of feeling sympathy. *Neuropsychologia* 41(2): 127-38.
- Decety J, Jackson PL. 2004. The functional architecture of human empathy. *Behav Cogn Neurosci Rev* 3(2): 71-100.
- Dimberg U, Thunberg M. 1998. Rapid facial reactions to emotional facial expressions. *Scand J Psychol* 39(1): 39-45.
- Dimberg U, Thunberg M, Elmehed K. 2000. Unconscious facial reactions to emotional facial expressions. *Psychol Sci* 11(1): 86-9.
- Etkin A, Klemenhagen KC, Dudman JT, Rogan MT, Hen R, Kandel ER, Hirsch J. 2004. Individual differences in trait anxiety predict the response of the basolateral amygdala to unconsciously processed fearful faces. *Neuron* 44(6): 1043-55.
- Fan Y, Han S. 2008. Temporal dynamic of neural mechanisms involved in empathy for pain: an event-related brain potential study. *Neuropsychologia* 46(1): 160-73.
- Ferrari PF, Gallese V, Rizzolatti G, Fogassi L. 2003. Mirror neurons responding to the observation of ingestive and communicative mouth actions in the monkey ventral premotor cortex. *Eur J Neurosci* 17(8): 1703-14.
- Friston KJ, Fletcher P, Josephs O, Holmes A, Rugg MD, Turner R. 1998. Event-related fMRI: characterizing differential responses. *Neuroimage* 7(1): 30-40.
- Fusar-Poli P, Placentino A, Carletti F, Landi P, Allen P, Surguladze S, Benedetti F, Abbamonte M, Gasparotti R, Barale F and others. 2009. Functional atlas of emotional faces processing: a voxel-based meta-analysis of 105 functional magnetic resonance imaging studies. *J Psychiatry Neurosci* 34(6): 418-32.
- Gallese V, Fadiga L, Fogassi L, Rizzolatti G. 1996. Action recognition in the premotor cortex. *Brain* 119 (Pt 2): 593-609.
- Gallese V, Keysers C, Rizzolatti G. 2004. A unifying view of the basis of social cognition. *Trends Cogn Sci* 8(9): 396-403.
- Geday J, Gjedde A, Boldsen AS, Kupers R. 2003. Emotional valence modulates activity in the posterior fusiform gyrus and inferior medial prefrontal cortex in social perception. *Neuroimage* 18(3): 675-84.
- Golby AJ, Gabrieli JD, Chiao JY, Eberhardt JL. 2001. Differential responses in the fusiform region to same-race and other-race faces. *Nat Neurosci* 4(8): 845-50.

- Grezes J, Armony JL, Rowe J, Passingham RE. 2003. Activations related to mirror and canonical neurons in the human brain: an fMRI study. *Neuroimage* 18(4): 928-37.
- Grill-Spector K, Knouf N, Kanwisher N. 2004. The fusiform face area subserves face perception, not generic within-category identification. *Nat Neurosci* 7(5): 555-62.
- Han S, Fan Y, Mao L. 2008. Gender difference in empathy for pain: an electrophysiological investigation. *Brain Res* 1196: 85-93.
- Hein G, Singer T. 2008. I feel how you feel but not always: the empathic brain and its modulation. *Curr Opin Neurobiol* 18(2): 153-8.
- Hoekert M, Bais L, Kahn RS, Aleman A. 2008. Time course of the involvement of the right anterior superior temporal gyrus and the right frontoparietal operculum in emotional prosody perception. *PLoS One* 3(5): e2244.
- Hooker CI, Verosky SC, Germine LT, Knight RT, D'Esposito M. 2008. Mentalizing about emotion and its relationship to empathy. *Soc Cogn Affect Neurosci* 3(3): 204-17.
- Hooker CI, Verosky SC, Germine LT, Knight RT, D'Esposito M. 2010. Neural activity during social signal perception correlates with self-reported empathy. *Brain Res* 1308: 100-13.
- Iacoboni M. 2005. Neural mechanisms of imitation. *Curr Opin Neurobiol* 15(6): 632-7.
- Iacoboni M, Dapretto M. 2006. The mirror neuron system and the consequences of its dysfunction. *Nat Rev Neurosci* 7(12): 942-51.
- Iacoboni M, Molnar-Szakacs I, Gallese V, Buccino G, Mazziotta JC, Rizzolatti G. 2005. Grasping the intentions of others with one's own mirror neuron system. *PLoS Biol* 3(3): e79.
- Iacoboni M, Woods RP, Brass M, Bekkering H, Mazziotta JC, Rizzolatti G. 1999. Cortical mechanisms of human imitation. *Science* 286(5449): 2526-8.
- Iidaka T, Matsumoto A, Haneda K, Okada T, Sadato N. 2006. Hemodynamic and electrophysiological relationship involved in human face processing: evidence from a combined fMRI-ERP study. *Brain Cogn* 60(2): 176-86.
- Jabbi M, Keysers C. 2008. Inferior frontal gyrus activity triggers anterior insula response to emotional facial expressions. *Emotion* 8(6): 775-80.
- Jabbi M, Swart M, Keysers C. 2007. Empathy for positive and negative emotions in the gustatory cortex. *Neuroimage* 34(4): 1744-53.
- Kanwisher N, McDermott J, Chun MM. 1997. The fusiform face area: a module in human extrastriate cortex specialized for face perception. *J Neurosci* 17(11): 4302-11.
- Kaplan JT, Iacoboni M. 2006. Getting a grip on other minds: Mirror neurons, intention understanding, and cognitive empathy. *Soc Neurosci* 1(3-4): 9.
- Kramer UM, Mohammadi B, Donamayor N, Samii A, Munte TF. 2010. Emotional and cognitive aspects of empathy and their relation to social cognition—an fMRI-study. *Brain Res* 1311: 110-20.
- Lamm C, Batson CD, Decety J. 2007a. The neural substrate of human empathy: effects of perspective-taking and cognitive appraisal. *J Cogn Neurosci* 19(1): 42-58.
- Lamm C, Nusbaum HC, Meltzoff AN, 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* 2(12): e1292.
- Lee TW, Josephs O, Dolan RJ, Critchley HD. 2006. Imitating expressions: emotion-specific neural substrates in facial mimicry. *Soc Cogn Affect Neurosci* 1(2): 122-35.
- Mathur VA, Harada T, Lipke T, Chiao JY. 2010. Neural basis of extraordinary empathy and altruistic motivation. *Neuroimage* 51(4): 1468-75.

- Matsumoto D, Ekman P. 1988. Japanese and Caucasian Facial Expressions of Emotion (JACFEE) and Neutral Faces (JACNeuF). San Francisco: University of California, San Francisco.
- Morris JS, Frith CD, Perrett DI, Rowland D, Young AW, Calder AJ, Dolan RJ. 1996. A differential neural response in the human amygdala to fearful and happy facial expressions. *Nature* 383(6603): 812-5.
- Nichols T, Hayasaka S. 2003. Controlling the familywise error rate in functional neuroimaging: a comparative review. *Stat Methods Med Res* 12(5): 419-46.
- Nomi JS, Scherfeld D, Friederichs S, Schafer R, Franz M, Wittsack HJ, Azari NP, Missimer J, Seitz RJ. 2008. On the neural networks of empathy: A principal component analysis of an fMRI study. *Behav Brain Funct* 4: 41.
- Nummenmaa L, Hirvonen J, Parkkola R, Hietanen JK. 2008. Is emotional contagion special? An fMRI study on neural systems for affective and cognitive empathy. *Neuroimage* 43(3): 571-580.
- Ochsner KN, Knierim K, Ludlow DH, Hanelin J, Ramachandran T, Glover G, Mackey SC. 2004. Reflecting upon feelings: an fMRI study of neural systems supporting the attribution of emotion to self and other. *J Cogn Neurosci* 16(10): 1746-72.
- Phillips ML, Young AW, Senior C, Brammer M, Andrew C, Calder AJ, Bullmore ET, Perrett DI, Rowland D, Williams SC and others. 1997. A specific neural substrate for perceiving facial expressions of disgust. *Nature* 389(6650): 495-8.
- Preston SD, de Waal FB. 2002. Empathy: Its ultimate and proximate bases. *Behav Brain Sci* 25(1): 1-20; discussion 20-71.
- Rizzolatti G, Craighero L. 2004. The mirror-neuron system. *Annu Rev Neurosci* 27: 169-92.
- Rizzolatti G, Fadiga L, Gallese V, Fogassi L. 1996. Premotor cortex and the recognition of motor actions. *Brain Res Cogn Brain Res* 3(2): 131-41.
- Rizzolatti G, Fogassi L, Gallese V. 2001. Neurophysiological mechanisms underlying the understanding and imitation of action. *Nat Rev Neurosci* 2(9): 661-70.
- Sprengelmeyer R, Rausch M, Eysel UT, Przuntek H. 1998. Neural structures associated with recognition of facial expressions of basic emotions. *Proc Biol Sci* 265(1409): 1927-31.
- Vollm BA, Taylor AN, Richardson P, Corcoran R, Stirling J, McKie S, Deakin JF, Elliott R. 2006. Neuronal correlates of theory of mind and empathy: a functional magnetic resonance imaging study in a nonverbal task. *Neuroimage* 29(1): 90-8.
- Wicker B, Keysers C, Plailly J, Royet JP, Gallese V, Rizzolatti G. 2003. Both of us disgusted in My insula: the common neural basis of seeing and feeling disgust. *Neuron* 40(3): 655-64.
- Xu X, Zuo X, Wang X, Han S. 2009. Do you feel my pain? Racial group membership modulates empathic neural responses. *J Neurosci* 29(26): 8525-9.