



Inter-individual differences in successful perspective taking during pain perception mediates emotional responsiveness in self and others: An fMRI study

Linda van der Heiden^{a,b,1}, Sigrid Scherpiet^{a,c,1}, Lilian Konicar^{a,d}, Niels Birbaumer^{a,e}, Ralf Veit^{a,*}

^a Institute of Medical Psychology and Behavioral Neurobiology, University of Tübingen, Tübingen, Germany

^b Department of Cognitive Psychology, University of Finance and Management, Warsaw, Poland

^c Graduate School of Neural & Behavioural Sciences, International Max Planck Research School, University of Tübingen, Tübingen, Germany

^d International Centre for Ethics in the Sciences and Humanities, Research Training Group Bioethics, University of Tübingen, Tübingen, Germany

^e IRCCS Ospedale San Camillo, Venezia-Lido, Italy

ARTICLE INFO

Article history:

Accepted 4 October 2012

Available online 12 October 2012

Keywords:

Perspective taking

Empathy

fMRI

Emotion regulation

ABSTRACT

Human empathy is an important component of social cognition that involves complex processes of emotional perspective taking and the issue of self/other distinction. Empathic perception enables us to experience negative emotions when someone else undergoes painful events. We investigated the influence of an extended time interval (10 s) and subjective performance evaluation (following each trial) of perspective taking on the cortical and subcortical correlates of pain empathy in eighteen healthy subjects using functional magnetic resonance imaging (fMRI). Subjects were presented pictures of hands and feet in painful and non-painful situations. They were instructed to simply view the picture (*View*) or adopt either their own perspective (*Self*) or the perspective of a third-person (*Other*). Prolonged time intervals of stimulus presentation enabled the analysis of different perspective taking processes (*Self* versus *Other*). Enhanced activation in the left supramarginal gyrus was detected for adopting the *Self* compared to the *Other* perspective. Time course analysis showed an early peak in the trials, suggesting that taking the first-person perspective is an intuitive more automatic process. The comparison between the *Other* and *Self* condition evoked stronger activity in dorso- and ventrolateral prefrontal areas and the superior temporal sulcus (STS). For these areas, a peak in the later phase of the trials was found, suggesting that taking the third-person perspective requires more effort and is an ongoing process. This was also supported by the fact that the participants were subjectively more successful in adopting the *Self* perspective compared to the *Other*. Our findings support that especially during the *Other* condition, prolonged time periods seem to facilitate empathic responses.

Individual ratings of performance enabled the comparison between subjects that were successful and unsuccessful at taking the *Self* or *Other* perspective. For *Self*, differential activations were found in the left insula and postcentral gyrus. For *Other*, differential activations were mainly observed in the left pallidum, bilateral VLPFC, the right middle orbitofrontal cortex OFC and the middle cingulate cortex (MCC). These results suggest that trial-specific success ratings allow us to disentangle differences between effort-related and successful engagement in perspective taking.

These two adjustments to the well-known paradigm showed new insight into the aspects of perspective taking during pain perception.

© 2012 Elsevier Inc. All rights reserved.

Introduction

A central aspect of social cognition is our ability to mentalize. Humans are able to understand another person's mental states, including their beliefs, desires, and intentions, as well as being able to anticipate other people's behaviors. This capacity is known as the 'theory of mind' describing the cognitive ability to take the perspective of another individual (Frith and Frith, 1999; Gallagher and Frith, 2003). Perspective

taking and empathy are often referred to as overlapping concepts; however researchers agree that empathy is a more complex form of psychological inference by which observation, memory, knowledge, and reasoning are combined to provide insight into the thoughts and feelings of others. It covers not only some perceptual function to comprehend other's emotional state, but it also involves sharing the affective experience of that actual state of mind (Decety and Jackson, 2004). Perspective taking constitutes a crucial component of empathy, which involves the cognitive capacity of regulatory mechanisms, such as 'theory of mind' (Batson, 2009; Hodges and Klein, 2001; Lamm et al., 2007). This study investigated long time intervals after perspective taking tasks to get more insight into the regulatory mechanisms needed for this cognitive component of empathy.

* Corresponding author at: Institute of Medical Psychology and Behavioral Neurobiology, Gartenstr. 29, 72076 Tübingen, Germany. Fax: +49 7071 295706.

E-mail address: ralf.veit@uni-tuebingen.de (R. Veit).

¹ These authors contributed equally to this work.

In recent years, multiple studies investigated the neural mechanisms that mediate empathy. The majority of these studies have focused on pain perception to explore empathic processes (Jackson et al., 2005, 2006; Ochsner et al., 2008; Singer et al., 2004; Zaki et al., 2007). One vital question in studying these processes has been to which degree “shared representation” (Lawrence et al., 2006) of pain in oneself (*Self*) and in another individual (*Other*) make it possible to appreciate the physical and affective states of a counterpart. To what extent do we need the capability of adopting another individual’s perspective by means of imagination, in order to understand and feel the pain of that person? These inferences about mental states may affect a perceiver’s empathic reaction to the pain of another person (Decety and Lamm, 2006; Jackson et al., 2006). The present study investigated the difference between subjects that were successful in taking the *Self* perspective compared to subjects unsuccessful at taking the *Self* perspective. The same comparison has been done for the *Other* perspective.

Several functional magnetic resonance imaging (fMRI) studies have shown that the observation of pain in others is “automatically” mediated by various brain regions that are implicated in processing the affective aspects of pain. (“Automatic refers to a process that does not require conscious and effortful processing, but can nevertheless be inhibited or controlled” (Singer et al., 2004)). It has been demonstrated that observing and receiving painful stimuli to the right hand resulted in brain activity in the anterior cingulate cortex (ACC), the anterior insula (AI), and the cerebellum (Singer et al., 2004). Although brain activity for the actual experience of pain and the perception of pain in others was found in similar brain regions, different activation patterns were observed when adopting the *Self* or *Other* perspective. First-hand experience of pain resulted in additional activity in the primary somatosensory cortex, while the prefrontal cortex (PFC) was activated during the *Other* condition (Singer et al., 2004). Similar results were found by Jackson et al. (2005). They investigated whether perceiving or assessing pain of another individual would lead to changes in activations in the network involved in affective pain processing. After presenting subjects with pictures of hands or feet in situations that were likely to cause pain versus matched pictures without any painful events, the authors observed brain activity predominantly in the ACC, AI, and cerebellum. As expected, no increased activation was found in the somatosensory cortex (Jackson et al., 2005) because no “real” pain was presented. However, when subjects were asked to imagine themselves in the situation or to adopt the other persons’ perspective (Jackson et al., 2006), additional neural networks were involved producing different activation patterns between both perspectives. The *Self* perspective revealed activity more extensively in the affective pain matrix and in the secondary somatosensory cortex, while adopting the *Other* perspective showed increased activation in the temporo-parietal junction (TPJ). Imagining oneself or another person in a particular situation requires perspective taking that modulates brain activity accordingly. These processes go along with different affective responses triggering either personal distress or empathic concern (Jackson et al., 2006; Lamm et al., 2007).

However, none of the above mentioned studies measured subjective ratings of performance in perspective taking. To date, this has only been done in emotion regulation studies, indicating that even trained individuals show some variability in their regulation ability and thus influence the brain activation differentially. Eippert et al. (2007), for example, reported a strong positive correlation between self-reported regulation success and amygdala activation during emotional regulation of threat related stimuli. Leiberger et al. (2012) found a linear relationship between the activity in several prefrontal areas and successful engagement or disengagement toward victims of violence, an emotional response closely related to empathy. Both studies highlight the importance of subjective ratings and show new insight in specific regulatory mechanisms. The individual ratings of success enable comparisons between successful and unsuccessful trials and subjects, giving new insight into the key-areas important for adopting both perspectives successfully.

Moreover, most empathy related studies have used short time intervals up to 5 s picture presentation on average, mainly focusing on stimulus perception, e.g. pain, rather than the regulatory processes like perspective taking. Yet, a close functional relationship between social cognition and the ability to successfully regulate emotions is central to the experience of empathy (Decety and Jackson, 2004; Eisenberg et al., 1994). To be able to capture all bottom-up and top-down processes related to empathy, this study used a time interval of around 10 s, to investigate early intuitive and more automatic responses and late regulatory responses in brain regions showing differences between the different perspectives. Prolonged time intervals are frequently applied in emotion regulation studies (Kalisch, 2009) and much longer than the previously mentioned empathy studies (Jackson et al., 2005, 2006; Lamm et al., 2007).

The goal of the present study was to probe the neural correlates involved in successful compared to unsuccessful perspective taking and evaluate the contribution of empathizing with the pain of others by using pictures of hands or feet in painful and non-painful situations, as previously used in the study by Jackson et al. (2005). We aimed to investigate to which extent brain activity correlates with the self-reported success of the adopted perspective. We hypothesized that prolonging the time interval will show activations in the lateral PFC, contributing to successful perspective taking. Different emotion regulation tasks, so far, have reported that lateral prefrontal brain areas are often activated in emotion regulation tasks with longer time intervals (Davidson et al., 2003; Ochsner et al., 2004a; Olsson and Ochsner, 2008) leading to the assumption that more active regulatory processing might be needed for trials in which we instructed the subjects to adopt the *Other* perspective.

Methods

Subjects

Eighteen right-handed (as assessed by the Edinburgh handedness inventory (Oldfield, 1971), healthy individuals (9 males, 9 females) aged between 21 and 31 years (mean age = 25.3, SD = 2.54) were recruited from the University of Tübingen and the surrounding community. None of the subjects had a history of psychiatric, medical or neurological illness. All subjects gave written informed consent prior to participation in the fMRI experiment. The study was approved by the Ethics Committee of the Medical Faculty of the University of Tübingen.

Self-report measures

The different facets of empathy were investigated using the German version of the Interpersonal Reactivity Index (IRI; (Davis, 1980; Paulus, 2009)). The questionnaire is divided into two primary components of empathy, mainly affective and cognitive empathy. While the affective aspects of empathy are measured by the subscales empathic concern (measures the tendency to experience feelings of sympathy and compassion for unfortunate others) and personal distress (taps the tendency to experience distress and discomfort in response to extreme distress in others), cognitive empathy subscales include the perspective-taking scale (measures the reported tendency to spontaneously adopt the psychological point of view of others in everyday life) and the fantasy scale (measures the tendency to imaginatively transpose oneself into fictional situations). Each subscale had 7 items measured on a 5-point Likert scale ranging from “does not describe me at all” to “describes me very well”.

Stimuli

Pictures serving as visual stimuli in this study were selected from a larger sample (Jackson et al., 2005). A series of 48 digital color pictures showing right hands and right feet of people, shot from angles that promoted first-person perspective, in painful or non-painful situations were

chosen. All situations depicted familiar events that can happen in everyday life. Various types of pain (mechanical, thermal, and pressure) were presented and the target persons in the picture varied in gender. Pictures were presented once per experiment in a pseudo-randomized order, using E-Prime 1.1.4 (Psychology Software Tools, Pittsburgh, PA, USA).

Experimental paradigm

Subjects were asked to adopt different perspectives when cued according to single word instructions – *Self*, *Other*, and *View* according to the study of Eippert et al. (2007) (Fig. 1). Following the instruction *Self*, subjects were explicitly asked to adopt their own perspective imagining that it is them suffering as seen on the picture. If the word *Other* appeared on the screen, subjects should try to put themselves into the perspective of an observer. They were asked to imagine watching someone else, an unfamiliar individual, who is experiencing the event presented in the picture. Following the instruction *View*, subjects should perceive the stimuli simply as a picture itself, not representing any real life situation. Following each scenario, a 9-point scale varying from 1 (“perspective taking was successful”, indicated by a thumbs up, see Fig. 1) to 9 (“perspective taking was not successful”, indicated by thumbs down, see Fig. 1) was presented. Subjects were instructed to subjectively evaluate how successful they were in adopting the given perspective. Note that after the *View* trials, subjects were asked to press the button twice in order to hold motor responses comparable across trial types. To familiarize the subjects with the task and to ensure that they fully understood the perspective taking task, a practice session was performed outside the scanner prior to the fMRI experiment, showing pictures that were not used in the experiment itself.

Subjects underwent three fMRI runs, each consisting of 16 trials. Every run included four conditions namely, *View-No-Pain*, *View-Pain*, *Self-Pain*, and *Other-Pain*, referring to the different instructions and whether the picture showed a painful of neutral situation. Block order was pseudo-randomized among subjects.

Pictures (visual angle $\sim 25^\circ \times 20^\circ$) were projected onto a translucent screen in front of the scanner that subjects could see through a tilted mirror mounted on the head coil. The instruction panel (*Self*, *Other*, *View*) appeared for 2 s in the center of the screen signaling the following task at the beginning of the trial. Followed by a fixation cross, presented for 500 ms, the picture appeared for 10 s then a fixation cross was again displayed for 500 ms. Subsequently, a rating scale was presented for 3 s, with which subjects indicated their success in emotional perspective taking by button press. Subjects used a two-button response box with their dominant hand in order to move a cursor horizontally on the scale. The inter-trial interval varied from 4 to 10 s.

fMRI data acquisition

The experiment was performed using a 1.5 T scanner (Magnetom Sonata, Siemens, Erlangen, Germany) equipped with an eight channel head

coil. Functional T2*-weighted images were acquired in transversal orientation (TR = 2 s, TE = 40 ms, flip angle = 90° , FOV = 192×192 mm, matrix 64×64 , slice thickness 3 mm, 24 slices, 0.75 mm gap) covering the whole brain. Furthermore, a high-resolution T1-weighted anatomical image (MPRage) was obtained (TR = 1940 ms, TE = 3.93 ms, TI = 1100 ms, FOV = 256×256 mm, voxel size $1 \times 1 \times 1$ mm³, 176 slices, bandwidth = 130 Hz/px). To correct for static geometric distortions in EPI images caused by magnetic field inhomogeneities, a gradient echo fieldmap including a magnitude and a phase map was acquired.

Self-report analysis

Correlation between the individual scores in the subscales of the IRI questionnaire and the subjective ratings in perspective taking were calculated by using the Statistical Package for the Social Sciences (SPSS). A *p*-value of $p < 0.05$ was considered as significant.

fMRI data analysis

Data were analyzed using Statistical Parametric Mapping (SPM8, Wellcome Department of Imaging Neuroscience, London, UK) run on Matlab R2008b (Mathworks, Inc., Sherborn, MA, USA). Images of each subject were realigned and unwrapped to correct for head movements during the measurements. The Fieldmap toolbox for SPM8 was used to create a voxel displacement map. This pre-calculated phase map was included during preprocessing to unwarp the geometrically distorted functional images in the phase encoding direction. Following this step, each anatomical image was coregistered to the mean unwrapped functional EPI image using linear rigid body transformation with 6 degrees of freedom. The segmentation procedure was used to estimate the normalization parameters. The calculated nonlinear transformation parameters were applied to all functional images for spatial normalization in MNI space. Functional images were resampled at a resolution of $3 \times 3 \times 3$ mm³ and the anatomical image at a resolution of $1 \times 1 \times 1$ mm³. Finally, the functional images were spatially smoothed using an 8 mm full-width half-maximum (FWHM) isotropic Gaussian kernel. Prior to statistical analysis data were high-pass (128 s) and low pass filtered (AR (1)).

For each subject a design matrix was created with the conditions: *Self*, *Other*, *View-Pain*, *View-No-Pain*, Instruction and Rating. A separate regressor was defined for each condition and each regressor was modeled with a canonical hemodynamic response function combined with time derivatives as informed basis set. The six movement regressors were included as confounds in the design matrix to capture residual movement-related variance. On a first level analysis specific contrasts were created for *Self*, *Other*, *View-Pain* and *View-No-Pain*.

To allow for population inferences, each subject's contrast images were entered into a second level group analysis. Based on previous neuroimaging studies (Jackson et al., 2005, 2006), a paired *t*-test, including the individual contrast images for *View-Pain* and *View-No-Pain*, was computed in order to detect significant activity changes in brain regions

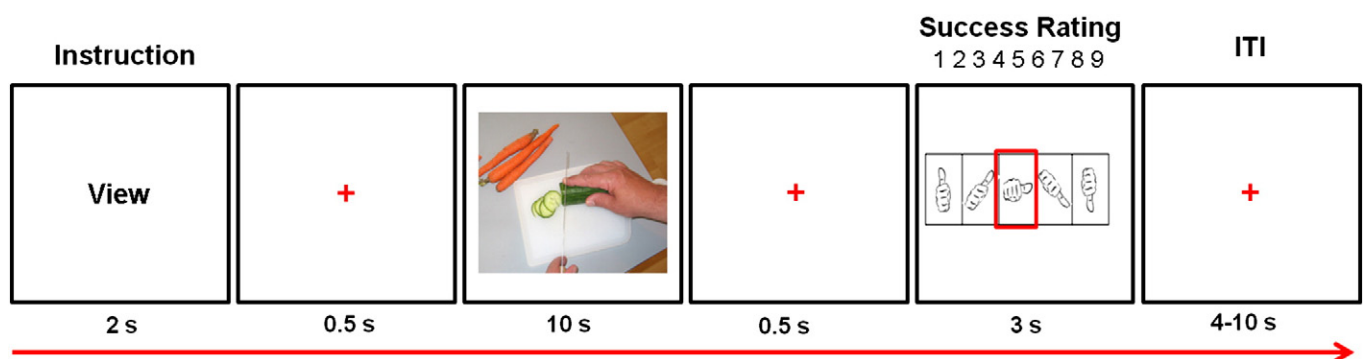


Fig. 1. Experimental paradigm showing the timeline and different panels presented to the subjects per trial. The success rating was done on a 9-point scale, allowing the subjects to rate ‘in between’ two images.

related to the affective pain matrix. Likewise, a paired-*t*-test with the individual contrast images for *Self* and *Other* was computed to evaluate the effect of perspective taking. To investigate the effect of (subjectively rated) successfulness in relation to less successful perspective taking in a particular task, the group was divided into good and bad performers according to their mean success ratings, using the median as cut off. A two-sample *t*-test between good and bad performers was carried out, separately for *Self* and *Others*. In addition to the categorical allocation of good and bad performers, a voxel-wise regression analysis was applied using the individual mean success ratings as continuous covariate and the parametric maps during the perspective taking tasks as dependent variable.

For all group statistics a cluster-level threshold of $p < 0.05$ corrected for the Family Wise Error rate (FWER) of the whole brain was used. For the good versus bad performer and the *View-Pain* versus *View-No-Pain* contrast a small volume correction of $p < 0.05$ (FWE corrected) was applied in predefined regions based on the significant clusters during empathy for pain in the coordinate based meta-analysis of Lamm et al. (2011). A spherical ROI of 10 mm centered around the reported coordinates for the anterior/middle cingulate cortex, the bilateral fronto-insular cortex, the bilateral supramarginal gyrus, the globus pallidus, the postcentral gyrus and the mid-insular cortex was created. Followed by the sequential Bonferroni–Holm correction (Holm, 1979) starting with the most significant *p*-value divided by the number of significant ($p < 0.05$) areas.

To additionally identify regions that showed common activity in perspective taking, a conjunction analysis of the Contrasts *Self* and *Other* using the “Conjunction Null Hypothesis” was performed. By applying this option, a minimum *T* map is computed and *p*-values are calculated. (Nichols et al., 2005). For this analysis a FWER of $p < 0.05$ on the peak level was used to precisely identify significant activations.

Significant activations were assigned to anatomical regions using the “Automated Anatomical Labeling” software (AAL, (Tzourio-Mazoyer et al., 2002)) implemented in the WFU PickAtlas software tool (Wake Forest University, Winston-Salem, NC, USA; <http://www.ansir.wfubmc.edu>). In addition to the anatomical labels in the tables, more exact functional definitions for comparability with other studies were included in the discussion.

Event-related BOLD responses in brain regions of interest in the critical conditions (*Self*, *Other*, *SelfGood performer*, *SelfBad performer*, *OtherGood performer* and *OtherBad performer*) were computed using the *rfxplot* toolbox for SPM8 (Glascher, 2009). The time courses were extracted from suprathreshold voxels in the selected regions within a sphere of 6 mm using a condition-specific Finite Impulse Response (FIR) and standard SPM filter settings. Temporal bins were created starting 1 s before the onsets of all trials belonging to a particular condition and discontinued 10 s after the actual condition duration in order to observe any post stimulus effects (e.g. during rating) of the BOLD signal in the specified areas (extracted time course in total 21 s). The time courses were resampled to 1 s time bins. Statistical analysis of the time courses was performed using repeated measures ANOVA. Significant condition or interaction effects were further analyzed using paired *t*-tests between corresponding time bins.

Results

Self-report data

The subjects reported an average of 14.56 (SD = 2.87) on perspective taking, 15.89 (SD = 2.22) on empathic concern, 9.67 (SD = 2.85) on personal distress and 13.78 (SD = 5.01) on fantasy.

Behavioral data results

A comparison of the mean success ratings of all trials and all subjects between *Self* and *Other* revealed a significant difference (two-sided, $z = -2.68$; $p = 0.007$) with higher performance ratings for the *Self*

(mean = 2.87, SD = 0.75) compared to the *Other* (mean = 3.67, SD = 1.06) condition, supporting our idea that the *Self* perspective is easier to achieve. In general, the ratings were skewed towards more successful trials. For *Self* trials, 25.5% of all trials were rated with “1”, 21.8% with “2”, 31.5% with “3” and only 15.3% with “4”, “5”, “6”, “7”, “8” or “9”. During the *Other* condition, 10.6% of the trials were rated with “1”, 10.6% with “2”, 39.8% with “3” and 38.9% were rated with “4”, “5”, “6”, “7”, “8” or “9”).

Correlation analysis between mean performance ratings in perspective taking during the *Other* condition and self-report measurements revealed a significant negative correlation (two-sided, $r = -0.656$, $p = 0.003$) between the rating for *Other* and high scores on the IRI-factor Cognitive Empathy (scores of Perspective taking and Fantasy combined) (Fig. 2).

fMRI data results

Main effects of perspective taking

Differential activation in the left supramarginal gyrus was detected in the *Self* versus *Other* contrast (Table 1). The direct comparison between imagining *Other* versus *Self* in painful situations showed enhanced activation in several brain regions in the visual and temporal cortices. More interesting, the left rostrolateral prefrontal cortex (RLPFC, middle frontal gyrus), the right dorsolateral prefrontal cortex (DLPFC, middle frontal gyrus), the left anterior superior temporal sulcus (STS, middle temporal gyrus), right lingual gyrus, left supplementary motor area (SMA), left inferior frontal operculum and left inferior frontal triangularis (Table 1) were differentially activated during the *Other* condition.

A time course (Fig. 3) analysis using a FIR basis set for extracting the time series revealed a significant condition effect between *Self* and *Other* in the supramarginal gyrus ($F(1,18) = 4.38$, $p < 0.05$). Post-hoc tests showed a significant increased BOLD response during *Self* compared to *Other* in the early phases (at 4, 5, 6 and 7 s) of the task.

The comparison of the time courses between *Other* and *Self* showed a significant condition effect in the left ($F(1,17) = 5.63$, $p < 0.05$) and right DLPFC ($F(1,18) = 5.98$, $p < 0.05$). Significant differences between particular time points were found between seconds 5 and 14 in the left DLPFC and between seconds 8 and 13 in the right DLPFC. A significant condition by time interaction was found in the right VLPFC ($F(18,31) = 1.74$, $p < 0.05$) and a marginally significant interaction in the left VLPFC ($F(18,31) = 1.59$, $p = 0.060$). Interestingly, significant differences between corresponding time points were only found in the late phase of the task (left VLPFC at 10, 11 and 12 s; right VLPFC at 8, 9, 10 and 11 s).

Specific effects of successful perspective taking

Brain regions selectively activated by *OtherGood* compared to *OtherBad* include the bilateral VLPFC (inferior frontal triangularis),

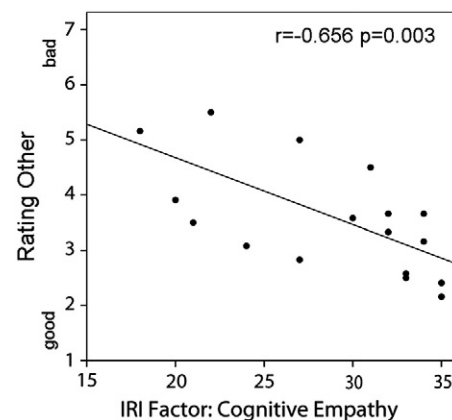


Fig. 2. Successful perspective taking during the *Other* condition (1 = successful perspective taking) correlated significantly with the factor cognitive empathy subscale of the IRI empathy questionnaire.

Table 1
Main effects of perspective taking.

Contrast	Region (Brodmann's area)	Lat	t-value	MNI coordinate		
				x	y	z
<i>Self</i> > <i>Other</i>	Supramarginal gyrus	L	5.35	−54	−28	40
<i>Other</i> > <i>Self</i>	Middle temporal gyrus (BA 22)	L	7.24	−60	−37	4
	Lingual gyrus	R	6.34	15	−85	1
	Middle frontal gyrus	R	6.15	39	32	37
	Middle frontal gyrus	L	5.75	−36	53	13
	Inferior frontal operculum (BA 9)	L	5.56	−48	14	31
	Supplementary motor area (BA32)	L	5.36	−3	14	46
	Inferior frontal triangularis	L	5.35	−51	32	−2

FWE corrected on cluster-level $p < 0.05$.

right middle orbitofrontal cortex (OFC), left pallidum (globus pallidus) and the medial cingulate cortex (MCC) (Table 2). The contrast between good versus bad performers during *Self* revealed differential activation in the left insula and left postcentral gyrus (Table 2).

A time course (Fig. 4) analysis revealed a significant condition effect in the left VLPFC ($F(1,8) = 6.78$; $p < 0.05$) and in the right middle OFC ($F(1,8) = 10.77$; $p < 0.05$) during *OtherGood* in comparison to *OtherBad* performers. A significant condition*time interaction was found in the MCC ($F(1,18) = 1.93$; $p < 0.05$). Comparing the time courses (Supplement Fig. 1) between *SelfGood* versus *SelfBad* showed a significant condition effect in the left postcentral gyrus ($F(1,18) = 6.39$; $P < 0.05$).

During the *Other* condition, activity in the left and right inferior frontal triangularis cortex was linearly modulated by the subjective success ratings (Supplement Fig. 2).

Regions showing common activation for *Self* and *Other*

The conjunction analysis for the perspective taking trials (contrast *Self* and *Other*) revealed that the right DLPFC (middle frontal gyrus), left VLPFC (inferior frontal triangularis gyrus and inferior orbitofrontal gyrus), left OFC (middle orbitofrontal gyrus), and bilateral inferior frontal operculum were conjointly activated in both perspective conditions (Table 3).

Discussion

The present study investigated the effects of successfully adopting the first- and third-person perspectives on the neural correlates of pain perception using daily life situations. In comparison to previous studies, we applied an extended time period in order to evaluate different perspective taking processes. The *Other* as opposed to the *Self* perspective revealed enhanced brain activity in the prefrontal areas and in the left anterior superior temporal sulcus (STS). Analyses of the BOLD time courses showed significant differences in the late phases of the task, with a condition effect for DLPFC and VLPFC. Significant differences in the BOLD response related to perspective taking during the *Self* versus *Other* condition was detected primarily in the left supramarginal gyrus with a significant condition effect during the early phases of the task. The fact that the differences showed up in different time periods, with the *Self* condition in the early phase and the *Other* condition in the later phase, suggests that taking the first-person perspective is a more intuitive and automatic process while the third-person perspective requires more effort and is an ongoing process. The second main finding of this study is the observation of the regions relating to successful perspective taking during the *OtherGood* versus *OtherBad* and *SelfGood* versus *SelfBad* conditions, which include the left pallidum, the bilateral VLPFC and right middle OFC, as well as the MCC for the third-person perspective and left insula and postcentral gyrus for the first-person perspective. As expected, successful perspective taking eliciting empathy for another person recruited networks, mainly involving the MCC, pallidum and the bilateral VLPFC. Besides these study specific results,

we replicated the finding that viewing painful events elicited activations in parts of the affective pain matrix. Watching other individuals in pain-inducing situations triggers part of the pain network, particularly the insular cortex and the ACC, which processes the affective experience of pain (Jackson et al., 2005, 2006; Singer et al., 2004). In the present

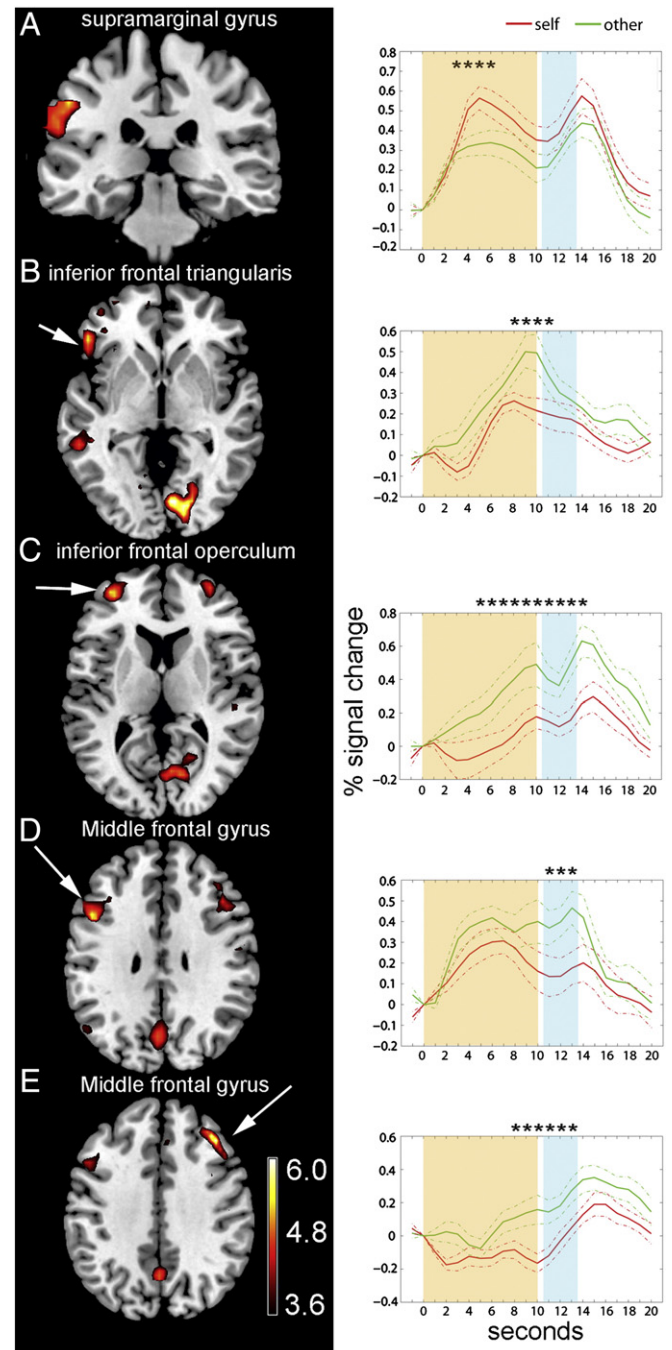


Fig. 3. Differential activations for *Self* versus *Other* (A) and *Other* versus *Self* (B–E) conditions and the time-courses of these areas are shown at the right side of the figure: left supramarginal gyrus (A: $x = -54$, $y = -28$, $z = 40$), left inferior frontal triangularis (B: $x = -51$, $y = 32$, $z = -2$), the left inferior frontal operculum (C: $x = -48$, $y = 14$, $z = 31$), the left middle frontal gyrus (D: $x = -60$, $y = -37$, $z = 4$) and right middle frontal gyrus (E: $x = 39$, $y = 32$, $z = 37$). The t-values of the activations are given in the adjacent color bar. The red time-courses are for the *Self* and the green for the *Other* perspective. The dotted lines indicate the standard error of the mean. The light apricot background depicts the time range (10 s) in which the picture was presented, whereas the blue background stands for the rating phase (3 s). Significant differences between corresponding time-points in *Self* and *Other* are indicated with black stars.

Table 2
Successful perspective taking.

Contrast	Region (Brodmann's area)	Lat	t-value	MNI coordinate		
				x	y	z
<i>OtherGood > OtherBad performer</i>	Globus pallidus*	L	5.62	−12	5	1
	Medial cingulate cortex*	R	4.19	3	26	40
	Inferior frontal triangularis (BA 45)*	L	5.06	−51	44	−2
	Middle orbitofrontal cortex (BA 10)**	R	4.15	42	56	−5
	Inferior frontal triangularis (BA 47)*	R	3.64	48	35	−2
<i>OtherBad > OtherGood performer</i>	No differential activation					
<i>SelfGood > SelfBad performer</i>	Insula*	L	5.33	−36	−16	7
<i>SelfBad > SelfGood performer</i>	Postcentral gyrus*	L	4.75	−54	−19	34
	No differential activations					

*FWE corrected $p < 0.05$ for predefined region-of-interest ** $p < 0.001$ uncorrected.

study, mainly the right and left insula extending into the secondary somatosensory cortex were activated.

Perspective taking

Self versus Other and Other versus Self

An increased BOLD signal in the left supramarginal gyrus was found comparing the *Self* with *Other* condition. This area has been attributed to the integration of multisensory information, which detects distinctions between self-generated and allothetic signals. It has been shown that the observation of body parts in painful situations activates this area, in the depicted pictures. For this area and condition, different time courses of the BOLD signal have been found in the early phases of the trials, showing significant condition effects, which suggests that *Self* perspective taking is possibly an intuitive automatic response, especially when the pictures are presented in the first-person perspective.

In comparison to the *Self* condition, an increased BOLD activation in distinct prefrontal regions, including the left RLPFC and right DLPFC, was detected during the *Other* condition. Those areas of the PFC have been shown to process external information coding of cognitive aspects of higher order mental states (Ochsner et al., 2004a; Olsson and Ochsner, 2008). Brain activity in the anterior PFC has often been linked to perspective taking (Gilbert et al., 2006; Hynes et al., 2006; Olsson and Ochsner, 2008), as well as to socio-emotional judgments (Karim et al., 2010). The RLPFC is related to reasoning processes, such as multitask coordination, as was proposed by Gilbert et al. (2006). The DLPFC has been specifically associated with performance monitoring and reflective processes allowing an individual to recognize and judge one's own personal versus another's emotional states (Olsson and Ochsner, 2008). In particular, its role in mediating evaluative processes of perceptual stimuli has been reported (Moriguchi et al., 2007). In addition, activation in the left anterior STS was found during the *Other* condition. Evidence from previous studies suggests that the STS is a key-area for social perception (Gallagher and Frith, 2003; Moll et al., 2005). In agreement with Ruby and Decety (2004), the STS appears to be an important brain area underlying perspective taking and is associated with theory of mind abilities (Allison et al., 2000; Ruby and Decety, 2004). The interplay of rostralateral and dorsolateral prefrontal areas and the STS shows that taking the third-person perspective requires the conscious realization of the "other" and emotional processing, which was more complex and difficult compared to the first-person perspective.

A significant condition effect was found in the time courses during the late phases of the trials in the DLPFC and VLPFC for the *Other* versus *Self* condition. This is also true for the comparison between good and bad performers for the *Other* condition, in which a significant condition effect was found in the VLPFC, middle OFC, pallidum and MCC. This supports the assumption that adoption of the *Other* perspective using pictures of hand and feet in painful situations is an active process, first overwriting the early intuitive response, requiring more effort in order

to recruit distinct neural networks for the empathic response. Based on the currently described data, perspective taking seems to depend on complex strategies involving both emotional and cognitive components. Thereby, our findings point out that in order to be successful in adopting a perspective, evaluative processes and attentive monitoring mechanisms are required.

Results from the individual evaluations on perspective taking indicate that it is easier for subjects to image *Self* as opposed to *Other*. This is an additional indication that taking the egocentric perspective (first-person) underlies more intuitive processes and self-reference, while adopting the perspective of an observer depends on more ongoing complex cognitive processes, such as mentalizing and cognitive control of emotions. More support for this idea is also found by the correlation between the IRI factor, *Cognitive empathy*, and the *Other* ratings, showing that taking the perspective of a third-person is highly associated with the ability to imagine. Subjects scoring high on the successfulness of the *Other* trial, scored also high on cognitive empathy (the fantasy and perspective taking scale). The fantasy scale, in fact, has been considered to examine the tendency to put oneself in the place of a character in movies or books (Davis and Franzoi, 1991; Paulus, 2009).

Successful versus non successful

Enhanced neural activity between successful versus unsuccessful third-person perspective taking was predominantly found in the VLPFC. Activation in this region is consistent with other studies proposing the VLPFC as an important contributor to affective reappraisal processes within perceptual situations (Ochsner et al., 2004a,b; Wager et al., 2008). The activity in the VLPFC is also linearly modulated by the subjective success ratings, suggesting that this area is important for the successfulness of taking the *Other* perspective. For the same contrast, left pallidum and the MCC are also activated. Pallidum is part of the ventral striatum and found to be activated when subjects had to imagine to alleviate the pain of others versus harming another individual (Decety and Porges, 2011) and when subjects watched video clips depicting faces of others listening to a painful sound (Lamm et al., 2007). MCC has been identified as a shared pattern of neural activity between pain felt on oneself and seen in others (Corradi-Dell'Acqua et al., 2011), as well as part of the core network for pain empathy (Lamm et al., 2011). The neural response when empathizing with the pain of others and being part of the shared representations account for understanding others, which proposes that neural circuits involved in the personal experience of an emotion underpin the understanding and sharing of the same emotion perceived in others (Lamm et al., 2011). Our results show that these areas make the difference between successful and unsuccessful perspective taking, indicating a key-role for the VLPFC, pallidum and MCC in empathizing with the pain in others.

Furthermore, the good compared to the bad performer during *Self* revealed enhanced brain responses in the left posterior insula and left postcentral gyrus (primary somatosensory cortex). They are part of

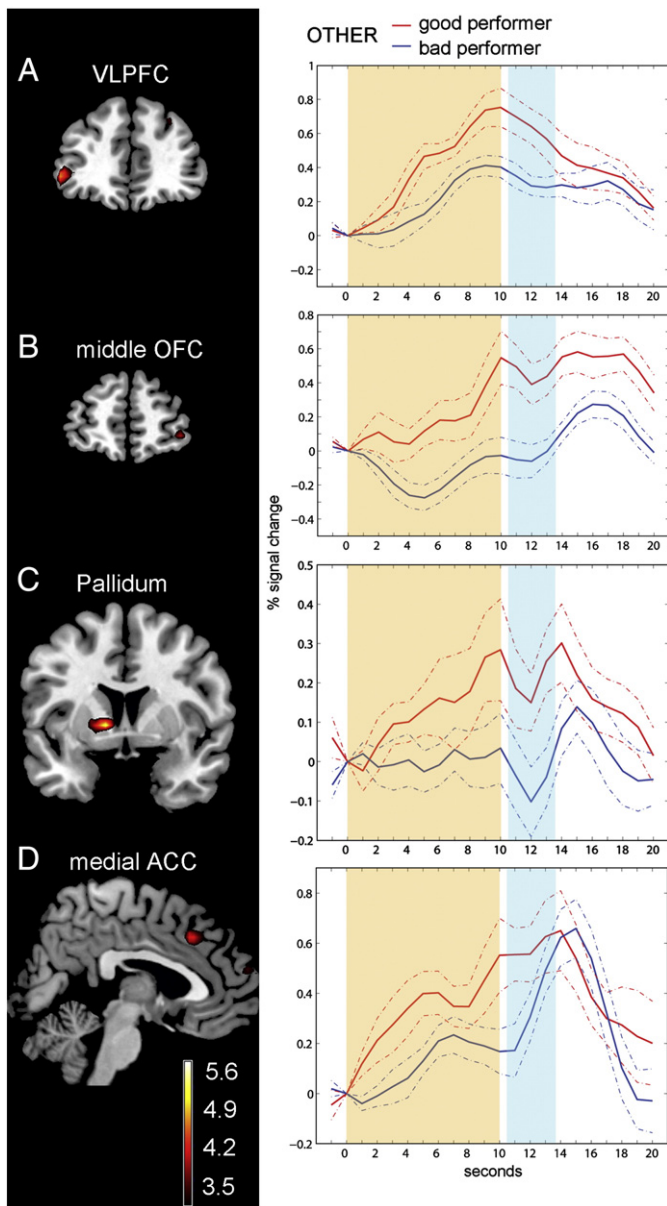


Fig. 4. Differential activation for successful versus unsuccessful performers in taking the third-person perspective is plotted at the left side and average time courses (in seconds) of these areas are plotted at the right side of the figure: left ventrolateral PFC (A: $x = -51$, $y = 44$, $z = -2$), right middle OFC (B: $x = 42$, $y = 56$, $z = -5$), left pallidum (C: $x = -12$, $y = 5$, $z = 1$) and right medial ACC (D: $x = 3$, $y = 26$, $z = 40$). The t -values of the activations are given in the adjacent color bar. The red time-courses are for the *OtherGood* and the blue for *OtherBad* condition. Dotted lines indicate the standard error of the mean. The light apricot background depicts the time range (10 s) in which the picture was presented, whereas the blue background stands for the rating phase (3 s).

the pain-matrix and previously found to be important for the *Self* condition, while this area has been linked with imagined pain from a first-person perspective (Jackson et al., 2006; Lamm et al., 2007).

Successful perspective taking, independent of the perspective task (*SelfGood* and *OtherGood*), involves the right DLPFC and left VLPFC, left OFC and bilateral inferior frontal operculum. The DLPFC and VLPFC have been reported to participate in the circuitry of emotion regulation and to contribute to cognitive and emotional control processes (Davidson et al., 2003; Decety and Jackson, 2004; Olsson and Ochsner, 2008). Suggesting that perspective taking modulates empathic responsiveness by means of top-down process, for either *Self* or *Other*, including emotion regulation and control.

Conclusion

Several studies have stressed key differences between the *Self* and *Other* perspectives underlining a special interest in the distinction between imagining *Self* versus imagining the *Other* (Decety and Jackson, 2004; Jackson et al., 2006; Ruby and Decety, 2004). Concomitantly, we demonstrated that depending on the adopted perspective, neural activity associated with empathic concern or self agency was elicited during the observation of pain in others, as previously reported (Jackson et al., 2006; Lamm et al., 2007; Ruby and Decety, 2004). Nevertheless, we were able to show differential cortical activity between both perspectives. While self-perspective appears to be fast, more intuitive and mainly requires mechanisms underlying ownership, adopting the perspective of the *Other* revealed more complicated neural mechanisms, which engage in regulatory processes and attribution of mental states enabling empathic experience. Analyses investigating perspective taking between successful (*OtherGood*, *SelfGood*) and unsuccessful (*OtherBad*, *SelfBad*) performers showed that with better perspective taking performance during the *Other* condition increased brain activity in regions underlying emotional and cognitive regulation. The gained knowledge of the specific areas involved in the different aspects of empathy could help to facilitate treatment for people with developmental (autism) or emotional (psychopaths) disorders. With real-time fMRI neurofeedback subjects can learn to regulate the BOLD activity in specific brain areas (Veit et al., 2012), making it possible to maintain or maybe even restore the ability of cognitive and emotional perspective taking.

The present findings demonstrate that empathy for pain is mediated by complex neural mechanisms underlying cognitive and emotional processes. On one hand, an individual needs to successfully adopt the perspective of the other, while at the same time regulatory and monitoring processes of the emotions themselves are required in order to enable a successful shared experience of the affective state of the other person. Nevertheless, the present data shows that both automatically shared neural mechanisms as well as distinct control processes contribute to the experience of empathy.

Conflict of interest statement

All authors report having no financial, personal, or organizational conflict of interest with the work in this manuscript.

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.neuroimage.2012.10.003>.

Table 3
Conjunction of *Other* and *Self*.

Region (Brodmann's area)	Lat	t -value	MNI coordinate		
			x	y	z
Middle occipital gyrus	R	9.93	30	-73	4
Calcarine	R	9.72	15	-94	1
Middle orbitofrontal gyrus	L	6.86	-36	44	-11
Inferior orbitofrontal gyrus	L	6.43	-48	44	-5
Middle temporal gyrus	L	6.75	-57	-49	1
Supplementary motor area (BA8)	L	6.64	-6	20	49
Dorsal anterior cingulate cortex*	L	5.43	-12	23	31
Medial anterior cingulate cortex*	R	4.96	9	17	40
Inferior frontal operculum	L	6.38	-51	11	7
Inferior frontal operculum (BA44)	R	6.33	60	17	1
Inferior frontal triangular gyrus (BA 46)	R	6.05	54	41	1
Middle frontal gyrus (BA9)	L	6.24	-42	41	25
Middle orbitofrontal gyrus	R	6.24	36	44	-11
Inferior orbitofrontal gyrus	L	5.93	-27	26	-14
Inferior temporal gyrus	L	5.77	-45	-43	-17

$p < 0.05$ FWE corrected for the whole brain, * $p < 0.05$ FWE corrected for predefined region-of-interest R = right, L = left.

Acknowledgments

This work was supported by the European Commission 7th Framework Programme (FP7), Marie Curie Initial Training Networks: ITN-LAN [PITN-GA-2008-214570]. We are grateful to Dr. Colleen Dockery for comments on an earlier version of the manuscript.

References

- Allison, T., Puce, A., McCarthy, G., 2000. Social perception from visual cues: role of the STS region. *Trends Cogn. Sci.* 4, 267–278.
- Batson, C.D., 2009. These things called empathy: eight related but distinct phenomena. *The Social Neuroscience of Empathy*. MIT Press, Cambridge, MA, US, pp. 3–15.
- Corradi-Dell'Acqua, C., Hofstetter, C., Vuilleumier, P., 2011. Felt and seen pain evoke the same local patterns of cortical activity in insular and cingulate cortex. *J. Neurosci.* 31, 17996–18006.
- Davidson, R.J., Pizzagalli, D., Nitschke, J.B., Kalin, N.H., 2003. Parsing the subcomponents of emotion and disorders of emotion: perspective from affective neuroscience. *Handbook of Affective Sciences*. Oxford Press, New York.
- Davis, M.H., 1980. A multidimensional approach to individual differences in empathy. *JSAS Cat. Sel. Doc. Psychol.* 10, 85.
- Davis, M., Franzoi, S.L., 1991. Stability and change in adolescent self-consciousness and empathy. *J. Res. Pers.* 25, 70–87.
- Decety, J., Jackson, P.L., 2004. The functional architecture of human empathy. *Behav. Cogn. Neurosci. Rev.* 3, 71–100.
- Decety, J., Lamm, C., 2006. Human empathy through the lens of social neuroscience. *Sci. World J.* 6, 1146–1163.
- Decety, J., Porges, E.C., 2011. Imagining being the agent of actions that carry different moral consequences: an fMRI study. *Neuropsychologia* 49, 2994–3001.
- Eippert, F., Veit, R., Weiskopf, N., Erb, M., Birbaumer, N., Anders, S., 2007. Regulation of emotional responses elicited by threat-related stimuli. *Hum. Brain Mapp.* 28, 409–423.
- 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. *J. Pers. Soc. Psychol.* 66, 776–797.
- Frith, C.D., Frith, U., 1999. Interacting minds – a biological basis. *Science* 286, 1692–1695.
- Gallagher, H.L., Frith, C.D., 2003. Functional imaging of 'theory of mind'. *Trends Cogn. Sci.* 7, 77–83.
- Gilbert, S.J., Spengler, S., Simons, J.S., Steele, J.D., Lawrie, S.M., Frith, C.D., Burgess, P.W., 2006. Functional specialization within rostral prefrontal cortex (area 10): a meta-analysis. *J. Cogn. Neurosci.* 18, 932–948.
- Glascher, J., 2009. Visualization of group inference data in functional neuroimaging. *Neuroinformatics* 7, 73–82.
- Hodges, S.D., Klein, K.J.K., 2001. Regulating the costs of empathy: the price of being human. *J. Socio-Econ.* 30, 437–452.
- Holm, S., 1979. A simple sequentially rejective multiple test procedure. *Scand. J. Stat.* 6, 65–70.
- Hynes, C.A., Baird, A.A., Grafton, S.T., 2006. Differential role of the orbital frontal lobe in emotional versus cognitive perspective-taking. *Neuropsychologia* 44, 374–383.
- 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., Brunet, E., Meltzoff, A.N., Decety, J., 2006. Empathy examined through the neural mechanisms involved in imagining how I feel versus how you feel pain. *Neuropsychologia* 44, 752–761.
- Kalisch, R., 2009. The functional neuroanatomy of reappraisal: time matters. *Neurosci. Biobehav. Rev.* 33, 1215–1226.
- Karim, A.A., Schneider, M., Lotze, M., Veit, R., Sauseng, P., Braun, C., Birbaumer, N., 2010. The truth about lying: inhibition of the anterior prefrontal cortex improves deceptive behavior. *Cereb. Cortex* 20, 205–213.
- Lamm, C., Batson, C.D., Decety, J., 2007. The neural substrate of human empathy: effects of perspective-taking and cognitive appraisal. *J. Cogn. Neurosci.* 19, 42–58.
- Lamm, C., Decety, J., Singer, T., 2011. Meta-analytic evidence for common and distinct neural networks associated with directly experienced pain and empathy for pain. *NeuroImage* 54, 2492–2502.
- Lawrence, E.J., Shaw, P., Giampietro, V.P., Surguladze, S., Brammer, M.J., David, A.S., 2006. The role of 'shared representations' in social perception and empathy: an fMRI study. *NeuroImage* 29, 1173–1184.
- Leiberg, S., Eippert, F., Veit, R., Anders, S., 2012. Intentional social distance regulation alters affective responses towards victims of violence: an fMRI study. *Hum. Brain Mapp.* 33, 2464–2476.
- Moll, J., Zahn, R., de Oliveira-Souza, R., Krueger, F., Grafman, J., 2005. Opinion: the neural basis of human moral cognition. *Nat. Rev. Neurosci.* 6, 799–809.
- Moriguchi, Y., Decety, J., Ohnishi, T., Maeda, M., Mori, T., Nemoto, K., Matsuda, H., Komaki, G., 2007. Empathy and judging other's pain: an fMRI study of alexithymia. *Cereb. Cortex* 17, 2223–2234.
- Nichols, T., Brett, M., Andersson, J., Wager, T., Poline, J.B., 2005. Valid conjunction inference with the minimum statistic. *NeuroImage* 25, 653–660.
- Ochsner, K.N., Knierim, K., Ludlow, D.H., Hanelin, J., Ramachandran, T., Glover, G., Mackey, S.C., 2004a. Reflecting upon feelings: an fMRI study of neural systems supporting the attribution of emotion to self and other. *J. Cogn. Neurosci.* 16, 1746–1772.
- Ochsner, K.N., Ray, R.D., Cooper, J.C., Robertson, E.R., Chopra, S., Gabrieli, J.D., Gross, J.J., 2004b. For better or for worse: neural systems supporting the cognitive down- and up-regulation of negative emotion. *NeuroImage* 23, 483–499.
- Ochsner, K.N., Zaki, J., Hanelin, J., Ludlow, D.H., Knierim, K., Ramachandran, T., Glover, G.H., Mackey, S.C., 2008. Your pain or mine? Common and distinct neural systems supporting the perception of pain in self and other. *Soc. Cogn. Affect. Neurosci.* 3, 144–160.
- Oldfield, R.C., 1971. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9, 97–113.
- Olsson, A., Ochsner, K.N., 2008. The role of social cognition in emotion. *Trends Cogn. Sci.* 12, 65–71.
- Paulus, C., 2009. Der Saarbrücker Persönlichkeitsfragebogen SPF(IRI) zur Messung von Empathie: Psychometrische Evaluation der deutschen Version des Interpersonal Reactivity Index.
- Ruby, P., Decety, J., 2004. How would you feel versus how do you think she would feel? A neuroimaging study of perspective-taking with social emotions. *J. Cogn. Neurosci.* 16, 988–999.
- 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.
- Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., Joliot, M., 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *NeuroImage* 15, 273–289.
- Veit, R., Singh, V., Sitaram, R., Caria, A., Rauss, K., Birbaumer, N., 2012. Using real-time fMRI to learn voluntary regulation of the anterior insula in the presence of threat-related stimuli. *Soc. Cogn. Affect. Neurosci.* 7, 623–634.
- Wager, T.D., Davidson, M.L., Hughes, B.L., Lindquist, M.A., Ochsner, K.N., 2008. Prefrontal-subcortical pathways mediating successful emotion regulation. *Neuron* 59, 1037–1050.
- 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. *Soc. Neurosci.* 2, 276–291.