Gender differences in brain networks supporting empathy

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Females frequently score higher on standard tests of empathy, social sensitivity, and emotion recognition than do males. It remains to be clarified, however, whether these gender differences are associated with gender specific neural mechanisms of emotional social cognition. We investigated gender differences in an emotion attribution task using functional magnetic resonance imaging. Subjects either focused on their own emotional response to emotion expressing faces (SELF-task) or evaluated the emotional state expressed by the faces (OTHER-task). Behaviorally, females rated SELF-related emotions significantly stronger than males. Across the sexes, SELF- and OTHER-related processing of facial expressions activated a network of medial and lateral prefrontal, temporal, and parietal brain regions involved in emotional perspective taking. During SELF-related processing, females recruited the right inferior frontal cortex and superior temporal sulcus stronger than males. In contrast, there was increased neural activity in the left temporoparietal junction in males (relative to females). When performing the OTHER-task, females showed increased activation of the right inferior frontal cortex while there were no differential activations in males. The data suggest that females recruit areas containing mirror neurons to a higher degree than males during both SELF- and OTHER-related processing in empathic face-to-face interactions. This may underlie facilitated emotional "contagion" in females. Together with the observation that males differentially rely on the left temporoparietal junction (an area mediating the distinction between the SELF and OTHERS) the data suggest that females and males rely on different strategies when assessing their own emotions in response to other people.
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Introduction

Behavioral studies suggest that females often perform better in emotional tasks than males. For example, several studies report a female advantage in the decoding of non-verbal emotional cues both in adults and children (see Hall, 1978; Hall et al., 2000; McClure, 2000 for reviews). Consistently, studies of affective arousal and expression of emotion (e.g., in response to the emotions of other people) demonstrate superior performance of females over males. In these experiments, facial electromyography (EMG; Dimberg and Lundquist, 1990; Schwartz, 1980), ratings of video-taped facial expressions (Kring and Gordon, 1998), self-reports (Kring et al., 1994), and diverse other measures of non-verbal expression of emotion were used (see, for example, Brody and Hall, 2000 for a review). Women are also reported to display higher complexity and differentiation in their articulation of emotional experiences (Barrett et al., 2000), and to score higher than males on self-report measures of empathy (e.g., Davis, 1996; Baron-Cohen and Wheelwright, 2004). It is in good accordance with these findings that psychiatric disorders such as autism spectrum disease, conduct disorder, and antisocial personality disorder, which are often characterized by a lack of empathy, are far more common among males (Chakrabarti and Baron-Cohen, 2006).

Neuroimaging studies show regional gender effects of the neurofunctional mechanisms of emotion and cognition in some brain areas (e.g., Piefke et al., 2005; Azim et al., 2005; George et al., 1996; Hofer et al., 2006; Killgore and Yurgelun-Todd, 2001). In particular, there is evidence for a gender-related differential laterality of brain functions, albeit inconsistent patterns of lateralization in distinct regions have been reported (Cahill et al., 2001; Piefke et al., 2005). These findings suggest that males and females may use, at least in part, different strategies of cognitive and emotional processing which may contribute to gender differences in empathy. To date, however, functional neuroimaging data on gender differences in empathy remain scarce. To our knowledge, there is currently only one study which specifically addressed this issue. Singer et al. (2006) observed in a study of empathy for pain of other people that both sexes showed activation

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of similar brain areas during both the self-experience of pain and the observation of painful stimulation of others. In males (but not females), however, this effect was absent for persons who were perceived as behaving unfairly. This finding suggests that empathic reactions may be differentially mediated by social–cognitive inferences in males and females.

Some authors refer to empathy as the capacity of sharing other people's feelings (see, for example, Singer, 2006). However, in our approach empathy is considered as a complex multidimensional psychological construct which comprises several psychological processes. In its broadest definition empathy can be described as a reaction to observed emotional states in other people which may include (i) cognitive components like perspective taking, mentalizing or self–other distinction, and (ii) emotional components such as resonance with the emotions of others and the generation of an appropriate emotional response (see, for example, Davis, 1996; Ickes, 1997; Decety and Jackson, 2004). The cognitive component of empathy is closely linked to theory of mind (ToM), that is, the metacognitive ability to represent mental states such as beliefs, intentions, and desires of other people (Premack and Woodruff, 1978). By neuroimaging studies, the temporoparietal junction (TPJ), the medial prefrontal cortex (MPFC), and the temporal poles have been related to ToM abilities (see, for example, Frith and Frith, 2003; Vogeley and Fink, 2003 for reviews). However, gender differences in neurofunctional networks supporting ToM have not been reported, yet. Behavioral studies of gender differences in ToM abilities in adults have yielded inconsistent results. Some authors reported a female advantage (e.g., Baron-Cohen et al., 1997), while others did not find evidence for differences in ToM performance between the sexes (e.g., Jarrold et al., 2000), or showed superior ToM abilities in males (Russell et al., 2007). Likewise, only few developmental studies demonstrated that girls outperform boys in ToM tasks in early childhood (e.g., Cutting, 1999).

With respect to the emotional aspect of empathy in a face-to-face situation, a "mirror mechanism" has been proposed. For example, EMG experiments demonstrated that muscles involved in the creation of emotional facial expressions also respond during the observation of faces expressing emotions (Dimberg and Thunberg, 1998; Dimberg et al., 2000). Neuroimaging studies indicate that this mechanism might be related to the operation of the human mirror neuron system (hMNS; Schulte-Rüther et al., 2007; Carr et al., 2003) which has been suggested to constitute the neural basis of the observer's resonance with the emotional state of another individual (Gallese, 2003). Neuroimaging evidence furthermore suggests that a mirror neuron system comprising parts of the inferior frontal and posterior parietal cortices (e.g., Iacoboni et al., 1999; Koski et al., 2003) also exists in humans, and that its operation can be generalized to other domains such as the inference of intentions (Iacoboni et al., 2005) and emotions of other people (Carr et al., 2003). Consistent with this assumption, we have recently shown that the amount of activation in inferior frontal cortex during the empathy-related attribution of emotions to oneself and other persons in a face-to-face situation is correlated with individual empathic ability in healthy volunteers (Schulte-Rüther et al., 2007). In line with these data, deficits in empathic behavior and other forms of social–emotional processing might be related to a deficient hMNS. For example, Dapretto et al. (2006) demonstrated that in individuals with autism (who often have difficulties in the expression and understanding of emotions) diminished activation of the inferior frontal cortex during the observation and imitation of facial expressions is correlated with symptom severity.

To date, neuroimaging data on gender effects on the brain mechanisms of empathic behavior in emotional face-to-face interactions are not available. Here, we re-analyzed data of a previous functional magnetic resonance imaging (fMRI) study (Schulte-Rüther et al., 2007) for gender differences in empathic behavior and the underlying neurofunctional mechanisms. In that study, we measured changes of brain activation during a task which tapped empathy in that it required emotional perspective taking in an experimental face-to-face situation. Facial expressions of angry and fearful emotions were used as stimulus materials. Participants indicated either the emotional state of a presented facial expression or their own emotional response to the face. Responses were made by choosing emotional descriptions from a list of adjectives describing emotional states. This procedure was used in order to provide a frame of reference for emotional ToM reasoning about the emotional state of others or oneself and is thereby more interactive than simple emotion recognition from faces (see, for example, Critchley et al., 2000) or mere observation of emotional faces (Carr et al., 2003). The emotional task of the employed paradigm was thus not restricted to a merely perceptual decision on facial expressions of emotion. Rather, it was based on the evaluation and understanding of more complex emotional states suitable to evoke ToM reasoning. Such tasks have been used before to study emotional aspects of ToM (e.g., Baron-Cohen et al., 1997, 1999). Importantly, an interpersonal context in which empathic social cognition could emerge was constructed by the demands of switching between the self- and the other-perspective. We hypothesized that females would show a stronger recruitment of areas which are part of the human mirror neuron system when inferring their own or the emotions of other people which may account for the better emotional and empathic abilities of females (compared to males).

Materials and methods

Participants

Twenty-six right-handed subjects (12 males, mean age±SD= 24.4±3.0 years; 14 females, mean age±SD=24.8±3.7 years) participated in the study which was approved by the local ethics committee. They were native speaker of German language. Participants were screened medically to rule out the use of medication affecting the CNS, a history of neurological or psychiatric disorders, head trauma, substance abuse, or other serious medical conditions. To control for sufficient abilities of verbalizing emotional states, subjects were screened for alexithymia using the German version of the Toronto-Alexithymia-Scale (TAS-26; Kupfer et al., 2001). Subjects underwent neuropsychological testing including standard measures of IQ, working memory, and attention.

Experimental paradigm

The experimental procedures of the present study are described in detail in Schulte-Rüther et al. (2007; see also Fig. 1). In short, subjects viewed synthetic emotional faces expressing either fear or anger. They were asked to either concentrate on their own feelings that emerged when they were looking at an emotional facial expression (SELF-task), or evaluate the emotional state expressed by a stimulus face (OTHER-task). After the presentation of each face, a list of four one or two word descriptions appeared on the screen. The task of the subjects was to choose from this list of
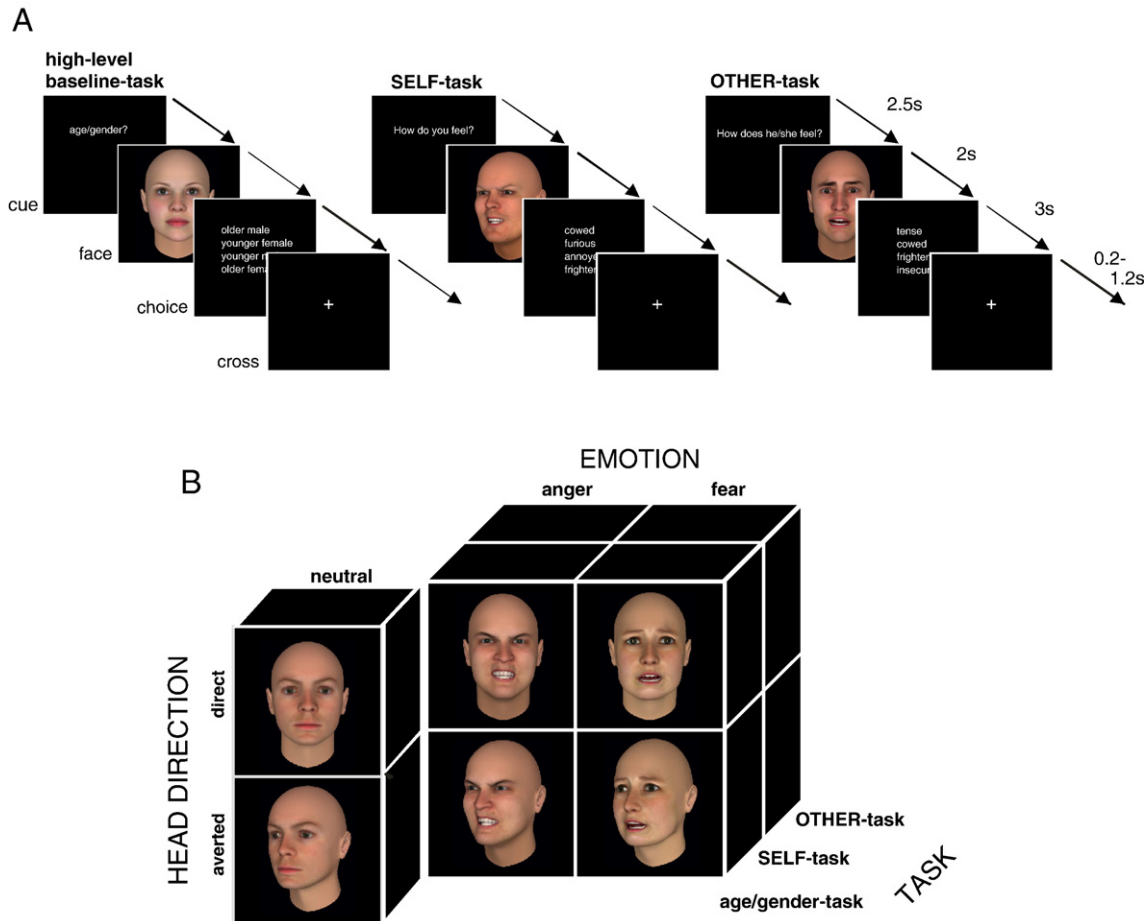
Fig. 1. Experimental paradigm. A. Time course of stimulus presentation. Trials were presented block wise for the self-, other-, and the high-level baseline task with each block consisting of four trials. Within each block emotion category and gaze direction varied pseudo-randomized by trial. The instruction cue was given only at the beginning of each block. B. Experimental factors and examples of face stimuli. Figure is taken from Schulte-Rüther et al. (2007), reproduced by permission of MIT Press.

words the description which best depicted either the emotional state expressed by the preceding face (OTHER-task) or the own emotional response of the subject to the stimulus face (SELF-task). The choice options were not simple categorical choices of emotions (e.g. "angry, fearful, sad, or happy"). Rather, they denoted more complex emotional states and thus required a more fine-grained and complex evaluation of the observed person's emotional state which is more likely to evoke ToM reasoning (Baron-Cohen et al., 1997, 1999). The emotional adjectives used for these judgments were randomly drawn from a set of words depending on the experimental condition (see Schulte-Rüther et al., 2007, for a complete list of the words). Words of choice had been generated in a separate behavioral pilot study and were matched for word length, arousal, and positivity across tasks and stimulus conditions. In this pilot study, subjects performed the same task as described above, but had to generate the emotional words instead of choosing from a word list. During the fMRI measurement subjects made their choices using their right hand and a four-button response device. Besides the factor TASK (SELF- or OTHER-perspective), two additional factors were varied systematically. These were EMOTION (angry or fearful faces) and HEAD DIRECTION (stimulus face directed towards the observer or averted by ~45°). A gender and age decision task on neutral faces (also with direct or

averted head direction) was included as a high-level baseline condition. For this task, the verbal labels "older male", "older female", "younger male", and "younger female" were used as choice options, presented in randomly varying order. The three tasks (SELF, OTHER, high-level baseline) alternated block wise in a pseudo-randomized counterbalanced order. Each block consisted of a series of four trials and was cued by a preceding verbal instruction. For stimulus presentation and response collection, the software Presentation 9.0 (Neurobehavioral Systems, Albany, CA, USA; http://www.neurobs.com) was used.

MR technical parameters

Subjects were scanned with a Siemens Magnetom SONATA whole-body system (Erlangen, Germany) at 1.5 T using a standard radio frequency head coil. Gradient-echo, echoplanar T2*-weighted images (EPI) were acquired using blood-oxygen-level-dependent (BOLD) contrast (TE = 66 ms, TR 3020 ms, α = 90°, FOV = 200 mm, voxel size = 3.1 × 3.1 × 4 mm^2, matrix size = 64 × 64, 30 slices). After functional neuroimaging, high-resolution anatomical images were acquired using a T1-weighted 3D magnetization-prepared, rapid acquisition gradient echo (MP-RAGE) pulse sequence.

Preprocessing of imaging data and single subject statistical analysis were accomplished using SPM2 (Wellcome Department of Imaging Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk/spm) implemented in MATLAB 6.5 (The Mathworks Inc., Natick, MA, USA. We used exactly the same processing steps as described in detail in Schulte-Rüther et al. (2007) to ensure comparability of the results with this earlier study. However, for the analysis of gender differences, a second-level analysis was performed with SPM5 because this version of SPM can handle within-group and between-group covariance components which are estimated for the non-sphericity correction (Glaser and Friston, 2003) to accommodate for breeches of sphericity assumptions in a mixed ANOVA design. Parameter estimates for each task-related regressor were included separately for each group (males and females) in a flexible factorial ANOVA model (with subjects treated as random effects).

Specific effects at each voxel were tested by applying appropriate linear contrasts to the parameter estimates. Common effects across the sexes were assessed by calculating the simple effects of TASK (SELF- and OTHER-task each versus the high-level baseline). Resulting SPMs were thresholded at $p < 0.05$ (FWE-corrected for multiple comparisons, voxel level). Gender-related differences were assessed within the set of voxels activated in the respective contrast across the whole group ($p < 0.001$ voxel level, uncorrected). Due to the strict character of the analysis (second-level analysis based on a random-effects model) and the predicted small effect size, a moderate height threshold was used for the analysis of gender effects ($p < 0.001$, uncorrected for multiple comparisons (with an extent threshold of 5 voxels). Resulting SPM_T maps were superimposed onto a group mean MR image which was calculated from the normalized anatomical T1-images of each subject (see above). Anatomical localization procedures are detailed in Schulte-Rüther et al. (2007). A region of interest approach was used to target regions for which we had a specific a-priori hypothesis. Anatomical ROI maps for BA 44/45 were created using a probabilistic cytoarchitectonic atlas (Eickhoff et al., 2005). Maps for the STS and TPJ region were created with the software WFU Pickatlas (v2.3) (Maldjian et al., 2003). These maps which provide anatomical details were combined (logical AND) with functional SPMs of the respective contrasts across the whole group (thresholded at $p < 0.001$, uncorrected) to create ROI masks of reliable activation across the whole group for each specific contrast within

a certain region. Masks were used for small volume corrections (SVC) in the regions of interest.

Pre- and post-scanning procedures

Before entering the MR scanner, subjects were familiarized with the experimental setup. Immediately after scanning, they completed a debriefing questionnaire on the naturalness of stimulus faces, intensity of observed (OTHER-task) and evoked emotion (SELF-task), as well as the levels of difficulty of the SELF-, OTHER-, and high-level baseline tasks for each emotion and head direction condition. Additionally, in two separate runs each single stimulus face was rated for the intensity of feelings (i) evoked in the participants and (ii) expressed by the face stimulus. The order of both runs was counterbalanced across subjects. For the ratings, each face was shown again on a computer screen (in the same order in that the faces had appeared during the MR experiment) and subjects accomplished ratings of the faces' emotion intensity on a 6-point scale.

Gender-specific differences in the post-scanning data, reaction times during scanning, and neuropsychological test scores were assessed using appropriate statistical tests. In these comparisons, parametric tests (*t*-test, ANOVA) were only used if Kolmogorov–Smirnov tests indicated approximately normal distribution, otherwise non-parametric tests were applied.

To assess correlations between neural activation and individual empathic abilities (as assessed by the BEES, see above) or self-reports of evoked emotions (post-scanning procedure), individual parameter estimates of regressors coding for the SELF- and OTHER-tasks were extracted for regions previously implicated in the hMNS at voxels showing peak activation in the "SELF"- and "OTHER"-task (for the common effect irrespective of gender). Individual means of these parameter estimates were correlated with

Table 1
Results of the neuropsychological testing

	Male $n = 12$	Female $n = 14$	t $df = 24$	p (2-sided)
DS-F (WMS-R)	9.08±1.92	8.21±1.72	1.215	0.236
DS-B (WMS-R)	8.33±2.42	8.64±2.17	−0.344	0.734
IQ (LPS)*	108.80±4.33	110.71±5.22	−1.033	0.312
CON (d2)	177.75±32.42	183.43±38.04	−0.406	0.689
TAS	2.52±0.46	2.24±0.47	1.511	0.144
ECS	17.0±3.41	19.42±4.24	−1.591	0.125
BEES	19.83±23.52	60.21±21.88	−4.533	*<0.001*

Males' and females' group mean values and results of the statistical comparison between the sexes (Student's *t*-test for independent samples) are given for several administered tests. Abbreviations: CON = Concentration performance value, d2 = d2 Test of Attention, DS-F = digit span forward, DS-B = digit span backward, WMS-R = Wechsler-Memory-Scale (German revised version; (Härting et al., 2000)), IQ = Intelligence quotient, LPS = Leistungsprüfsystem; *IQ is estimated from the results of 4 LPS subtests.

Table 2
Post-scanning questionnaire results

	Male $n = 12$	Female $n = 14$	Z	p
Difficulty to identify emotional expression	2.69±0.51	2.70±0.52	−0.131	0.913
Difficulty to identify own emotion	3.40±3.14	3.14±0.79	−1.145	0.263
Difficulty of age/gender decision	2.61±0.66	2.73±0.59	−0.723	0.484
Naturalness of emotional faces	3.00±0.95	2.89±0.71	−0.546	0.599
Naturalness of neutral faces	3.06±0.99[1]	2.86±0.59	−1.295	0.207
Intensity of observed emotional expression	3.71±0.40	3.36±0.62	−1.516	0.932[#]
Intensity of own emotion	2.65±0.49	3.01±0.66	−1.677	<0.05[#]

Comparison of mean ratings (±SD) given by males and females on items of the post-scanning questionnaire (see Materials and methods). Rating scales ranging from 1 to 5 were used for the judgment of the naturalness of faces (1=very unnatural, 2=unnatural, 3=moderately natural, 4=natural, 5=very natural), task difficulty (1=very easy, 2=easy, 3=moderate, 4=difficult, 5=very difficult), and perceived/evoked emotional intensity (1=none, 2=weak, 3=moderate, 4=strong, 5=very strong). [1]$n = 9$, due to missing data. Z and p refer to Mann–Whitney *U*-Tests which were performed on the data. [#]Refers to 1-tailed significance for comparisons with a directed a-priori hypothesis (females>males), other *p*-values indicate 2-tailed significance values.

Table 3
Simple effects of the SELF- and the OTHER-task (relative to the high-level baseline condition)

Anatomical region	H	BA	SELF versus high-level baseline				OTHER versus high-level baseline			
			x	y	z	t	x	y	z	t
Inferior frontal gyrus	L	47	−48	28	−10	15.16	−48	28	−8	13.55
Inferior frontal gyrus	L	44/45	−54	24	12	15.15	−54	24	14	12.17
Inferior frontal gyrus	R	47	54	30	−6	6.99	56	32	0	5.21*
Inferior frontal gyrus	R	45	60	26	14	5.87	60	28	16	4.53*
Superior temporal sulcus	L	21	−62	−46	2	13.44	−62	−46	2	10.98
Temporoparietal junction	L	21/22/39	−56	−58	16	12.66				
Superior temporal sulcus	R	21	50	−24	−12	6.77	52	−32	−2	5.64
Middle temporal gyrus	L	20/21	−54	2	−28	6.83	−50	−20	−14	5.43
Fusiform gyrus	L	20/37					−44	−46	−20	5.67
Temporal pole	L	20/38	−50	10	−36	7.57	−48	12	−36	4.80*
Temporal pole	R	20/38	46	16	−38	6.56	46	16	−36	5.74
Superior frontal gyrus pars medialis	L	9/10	−8	60	32	11.23	−8	54	42	7.61
Middle frontal gyrus	L	6/9	−44	8	50	10.35	−44	8	52	6.56
Supplementary motor area	L	6/8	−6	18	64	9.52	−6	18	64	6.16
Posterior cingulate cortex	L	23	−10	−48	32	8.21				

Peaks of differential brain activation for the comparisons between the SELF- and the high-level baseline task, and the OTHER- and the high-level baseline task. Statistical height threshold: $p < 0.05$ corrected for multiple comparisons across the whole brain; extent threshold: 5 voxels (except *$p < 0.05$ small volume correction; t refers to highest t-value within a region of significant activation; x, y, z coordinates are given in MNI space. H = hemisphere, L = left, R = right; BA = Brodmann Area.

behavioral measures using Spearman's rank order correlation coefficient (Spearman's Rho).

Results

Behavioral data

Neuropsychological tests and questionnaires

Mean scores of neuropsychological tests and questionnaires for male and female participants involved in the present study are summarized in Table 1. Individual scores on these scales were within the range of reference population norms for all tests administered and did not show significant differences between the sexes, except for the Balanced Emotional Empathy Scale (BEES; Mehrabian, 1997), a self-report scale measuring empathic abilities on which females scored significantly higher than males.

Reaction times during scanning

ANOVAs were calculated using TASK, EMOTION and HEAD DIRECTION as within- and GENDER as between-subject factor.

The comparison of EMOTION and HEAD DIRECTION did not show a significant main effect or interaction (neither with GENDER nor with each other), but there was a significant main effect of TASK. Paired post-hoc t-tests revealed that across gender, subjects responded faster in the high-level baseline task than both experimental tasks and faster in the OTHER-task relative to the SELF-task ($p < 0.001$ for each comparison).

Post-scanning questionnaire and post-scanning rating of stimulus faces

Mann–Whitney U-Tests were performed to assess gender differences in the post-scanning debriefing data. There were neither gender differences in the questionnaire ratings of naturalness of emotional ($Z = −0.546$, $p = 0.599$) and neutral faces ($Z = −1.295$, $p = 0.207$), nor in the difficulty ratings of the SELF-task ($Z = −1.145$, $p = 0.263$), the OTHER-task ($Z = −0.131$, $p = 0.913$), and the high-level baseline task ($Z = −0.723$, $p = 0.484$). Females rated the intensity of their own emotions during the experiment (SELF-task) significantly higher than males ($Z = −1.677$, $p < 0.05$, 1-tailed), but ratings of the perceived emotional

Table 4
Correlations between mirror neuron activation in the SELF/OTHER task and individual empathy scores (BEES)

Anatomical region	MNI-coordinates			Spearman's Rho					
				All		Male		Female	
	x	y	z	BEES	intens	BEES	intens	BEES	intens
Left inferior frontal gyrus pars triangularis	−54	24	12	0.569**	0.354*	0.452#	0.469#	0.516*	0.097
Right inferior frontal gyrus pars triangularis[1]	60	26	14	0.531**	0.407*	0.501*	0.587*	0.688**	0.143
Left superior temporal sulcus	−62	−46	2	0.482**	0.365*	0.410#	0.434#	0.451#	0.203
Right superior temporal sulcus	52	−32	−2	0.165	0.021	−0.259	0.133	0.257	−0.101

Covariation of measures of empathic abilities, ratings of emotional experience and brain activation for regions activated in both the SELF- and the OTHER-task (each compared to the high-level baseline).
Values indicate Spearman rank order correlation coefficient (Spearman's Rho), **$p < 0.01$, *$p < 0.05$, #Trend towards significance ($p < 0.1$). BEES = Balanced Emotional Empathy Scale, intens = intensity rating of own evoked emotion during the task. All = correlations were calculated across the whole group of participants; male, female = correlations were performed across the respective subgroup. All regions were significantly activated in both SELF- and OTHER-task ($p < 0.05$, FWE-corrected; except [1]$p < 0.05$, FWE corrected across a small volume of interest).

intensity of stimulus facial expressions did not differ significantly between sexes ($Z=-1.516$, $p=0.932$, 1-tailed). Post-scanning questionnaire results of males and females are given in Table 2.

When presented again with each stimulus face after the fMRI experiment, females showed a tendency to rate their own emotion in response to a stimulus face higher than males (Mann–Whitney U-Test, $Z=-1.492$, $p=0.072$, 1-tailed), while this was not the case

for the ratings of the emotion intensity expressed by the facial stimuli ($Z=-0.489$, $p=0.320$, 1-tailed).

FMRI data

Common brain activations in both males and females

Across sexes, areas of significant differential activation in both the SELF- and the OTHER-task (relative to the high-level baseline) were
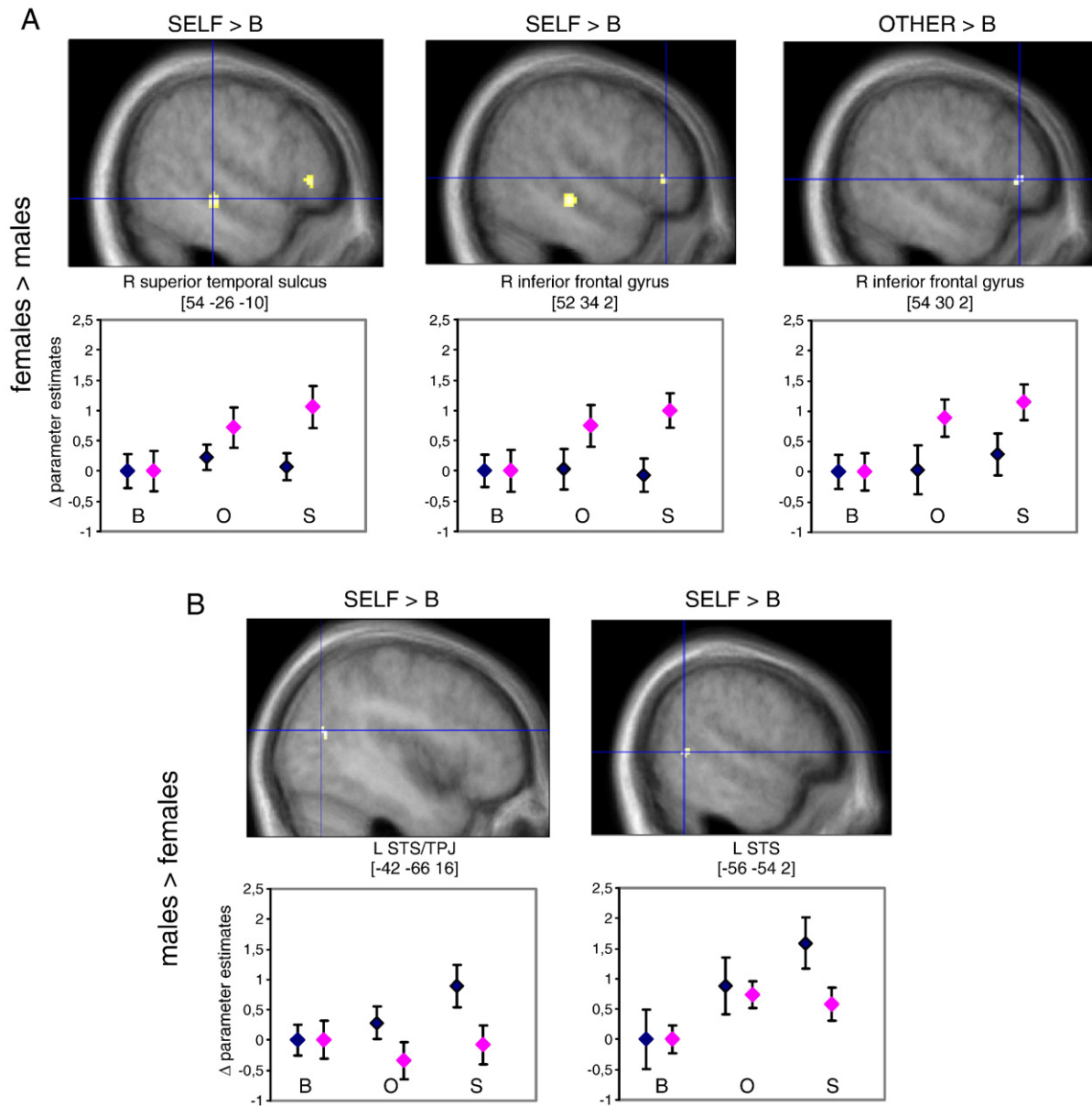

Fig. 2. Gender differences in brain activations related to the SELF- and the OTHER-task (each compared to the high-level baseline). Statistically significant ($p<0.001$, uncorrected) gender-related differential brain activations related to performance of females (A) and males (B) during the SELF- and the OTHER-task are superimposed on a mean normalized anatomical image (see Materials and methods). There is statistically significant differential activation in females (relative to males) for the contrast of the SELF- versus the high-level baseline task in the right inferior frontal gyrus and the right STS. For the contrast between the OTHER- and the high-level baseline task, females differentially recruit the right inferior frontal gyrus. In males (relative to females), there is activation of the STS and the TPJ for the comparison between the SELF- and the high-level baseline. There are no differential activations for the contrast between the OTHER- and the high-level baseline task in males. Condition specific parameter estimates (reflecting the relative contribution of each condition to the amplitude of the adjusted BOLD signal relative to the fitted mean in the respective brain region) were extracted at the given MNI coordinates. Plots show the mean and standard errors of Δ parameter estimates (relative to the mean of the high-level baseline for the respective group; magenta = females, blue = males; scaling in arbitrary units). S = SELF-task, O = OTHER-task, and B = high-level baseline task.

located in the superior temporal sulcus (STS), inferior frontal gyrus, and temporal poles bilaterally, in the left medial prefrontal cortex (MPFC), middle frontal gyrus, pre-supplementary motor area (pre-SMA), and right cerebellum. Additional activation in the comparison of SELF versus high-level baseline was observed bilaterally in the temporoparietal junction (TPJ), precuneus/posterior cingulate cortex, and MPFC. The contrast between the SELF- versus the OTHER-task revealed activations in the TPJ, MPFC, posterior cingulate cortex/precuneus, inferior frontal gyrus, and pre-SMA bilaterally, in the left middle frontal gyrus, and right cerebellum in both sexes. The inverse contrast (OTHER- versus SELF-task) did not show significant differential activations. Common brain activations in both males and females are summarized in Table 3.

Covariance of neural activation and behavioral measures

Covariance between neural activation in areas implicated in the hMNS and behavioral measures of empathy and experienced emotion are summarized in Table 4. Over the whole group (males and females combined) significant correlations were found in the inferior frontal gyrus (bilaterally) and the left STS for both the measure of empathy (BEES) and the ratings of experienced emotion. Separate analyses for males and females showed a similar correlational trend, however, within these subgroups not all correlations reached statistical significance.

Gender effects on brain activations

Gender differences in brain activation patterns were observed only for the simple effects of the SELF- and OTHER-tasks (each versus high-level baseline) and the main effect of the SELF-task versus the OTHER-task. Since relative changes in neural activity related to the complex contrasts (interactions; main effects) cannot be interpreted easily with reference to the group variable GENDER, we here restrict

our report to the simple effects of the SELF- and the OTHER-task which may provide a more transparent view of differences between the sexes in the neural mechanisms of empathy. In the comparison of the SELF- versus the high-level baseline task, females (relative to males) showed a stronger activation of right inferior frontal cortex (BA 45), right STS, and right cerebellum. In contrast, males (relative to females) showed stronger activation of the left TPJ. The comparison of OTHER-task versus the high-level baseline condition revealed stronger activations in the inferior frontal cortex (BA 45) in females (compared to males). There were no differential activations in males (relative to females) for this contrast. Gender-related differential activations related to these contrasts are illustrated in Fig. 2. The anatomical regions in which task-related effects of gender were observed and the respective MNI coordinates are further specified in Table 5.

To rule out the possibility that differential activations in the SELF-task (relative to the high-level baseline) could be more related to individual differences in emotional experience rather than to gender differences per se, self-reports of one's own intensity of emotions (as derived from the stimulus-specific ratings and the post-scanning debriefing questionnaire) were included as covariates in the same flexible factorial ANOVA model described above. These analyses yielded identical coordinates of significant peak activation for the contrast of SELF-task versus high-level baseline.

Discussion

The present fMRI study investigated gender-related differences in brain regions supporting the ability of empathy. A key aspect of empathy in interpersonal interactions is that it typically emerges in a dyadic social situation where the emotions of another person directly influence the perceiver's own emotional state. Although such social situations are difficult to implement in the restricted environment of an fMRI experiment, the current paradigm is well applicable to investigate this specific component of interpersonal face-to-face interaction. It creates an interactive and interpersonal context in which empathy is likely to emerge.

Our data show that regions involved in the human mirror neuron system (in particular, the inferior frontal gyrus, BA 44/45) are recruited during emotional perspective taking in both males and females, but activation is stronger in females in the right inferior frontal gyrus and right STS. Furthermore, males demonstrate increased activation during the attribution of emotion to themselves in the TPJ, an area which has been related to cognitive processes of perspective taking and the distinction of the self- and the other-perspective. Gender-related differential activations were located in the right hemisphere in females, and in the left hemisphere in males. This finding is in accordance with previous reports about differences between the sexes in the lateralization of brain functions. For example, Piefke et al. (2005) showed a corresponding gender-related differential lateralization (right in females, left in males) of local brain activations during the recollection of emotional autobiographical episodes. However, findings of sex-specific lateralization effects are inconsistent, yet. They are likely to depend on the task and stimuli employed in each study (Wager et al., 2003). For example, Cahill et al. (2001) reported a gender-related left–right lateralization of amygdala involvement in the memory-related processing of negatively valenced film clips with the opposite pattern of laterality (see also Canli et al., 2002). Estrogen is in particular supposed to modulate this functional hemispheric lateralization (McEwen et al., 1998; Williams, 1998; Wisniewski, 1998), yielding both differences in neuropsychological task per-

Table 5

Gender differences in brain activations related to the SELF- and the OTHER-task (relative to the high-level baseline condition)

Contrast and anatomical region	MNI-coordinates						
	H	BA	k	x	y	z	t
Simple effect of the SELF-task							
Interaction (SELF_f – B_f) – (SELF_m – B_m)							
Inferior frontal gyrus pars triangularis	R	45	56	52	34	2	3.80*
Superior temporal sulcus	R	21	15	54	−26	−10	4.27*
Cerebellum	R		20	12	−86	−46	3.78
Interaction (SELF_m – B_m) – (SELF_f – B_f)							
Superior temporal sulcus/TPJ	L	21/39	10	−42	−66	16	3.78
Middle temporal gyrus/STS	L	21	20	−56	−54	2	3.62
Simple effect of the OTHER-task							
Interaction (OTHER_f – B_f) – (OTHER_m – B_m)							
Inferior frontal gyrus pars triangularis	R	45	8	54	30	2	3.58*

Peaks of differential brain activations in males and females associated with the simple effects of the SELF- and the OTHER-task ($p < 0.001$ uncorrected, extent threshold 5 voxels). *Small volume correction ($p < 0.05$, FWE) for the respective brain region (see Materials and methods section). t refers to highest t-score within a region; x, y, z coordinates are given in the MNI-coordinate space. H = hemisphere; L = left; R = right; BA = Brodmann Area; k = number of activated voxels per cluster; f = female; m = male; SELF = SELF-task; OTHER = OTHER-task; B = high-level baseline task.

formance between males and females and variation in cognitive performance across the menstrual cycle in females (Dietrich et al., 2001). We did not control for estrogen levels in the present study. Therefore, our data cannot contribute to this issue.

Mirror mechanisms in empathic face-to-face situations

During the attribution of emotion to either oneself or a stimulus face we found significant activation in both sexes in the inferior frontal gyri bilaterally (including Broca's area, BA 44/45, and its homologue in the right hemisphere) which have previously been implicated in the hMNS (Iacoboni et al., 1999). Furthermore, activation in the left inferior frontal gyrus was stronger in the SELF- than in the OTHER-task. In a previous report, we suggested that these activations may constitute the neural basis for the resonance of an observer with the emotional state of another individual (Schulte-Rüther et al., 2007). Activation in these areas was correlated with a behavioral measure of dispositional empathic abilities and the self-report of experienced emotion during the experiment, suggesting a strong interrelation between the degree of interpersonal emotional involvement and mirror neuron activation. These assumptions are in line with behavioral and neuroimaging evidence for the involvement of mirror neuron mechanisms in social interactions, for example, the detection of emotional states (Carr et al., 2003), intentions (Iacoboni et al., 2005), and the emergence of empathy (Gallese, 2003). Moreover, stronger recruitment of the hMNS and other areas involved in the control of self-related functions suggests a specific role of mirror mechanisms and cognitive control in the self-attribution of emotion.

To our knowledge, the present study is the first which demonstrates enhanced hMNS activation in emotional perspective taking in females compared to males. It is in line with our data that gender differences in the tendency to exhibit facial mimicry have previously been reported by behavioral studies (Dimberg and Lundquist, 1990). However, evidence for gender differences in the hMNS is rare. There is one MEG study showing enhanced activation of the primary motor cortex (M1) in females, but not males, during the observation of hand movements (relative to the observation of a moving dot; Cheng et al., 2006). Yet, it is still a matter of debate whether M1 activation may reflect the recruitment of mirror neuron mechanisms (Grezes and Decety, 2001). We suggest that the gender-related differences in hMNS activation observed in our present experiment are restricted to the domain of emotional social interactions, thus reflecting increased involvement of the hMNS in females (relative to males) during empathy-related face-to-face interactions. These differential activations in the hMNS cannot simply be explained as reflecting basic gender differences in emotional responsiveness, as they are still present when individual intensity of emotional experience is controlled for.

Despite growing evidence for the crucial role of specific areas in the inferior frontal cortex for the hMNS, it should be noted that functions of executive control are also known to be implemented in the inferior frontal cortex (e.g., working memory, inhibitory control, rule application, or reversal learning). Such demands typically activate a broader network additionally comprising dorsolateral prefrontal and dorsal anterior cingulate areas. Meta-analyses of PFC activation studies on various executive task demands did not find overall evidence for a specificity of distinct modules within the PFC (Duncan and Owen, 2000), but rather suggest a role for a prefrontal network in various cognitive tasks. Note, however, a distinct role for the right inferior frontal cortex has been suggested

for inhibitory control (see, for example, Aron et al., 2004). In the present study it seems unlikely that the observed gender differences can be explained by differences in inhibitory control processes. The observed correlations between individual empathic ability, emotional experience, and activation in the inferior frontal cortex speak against this possibility. Furthermore, gender differences in inhibitory control processes would most likely result in differential response times in males and females which could not be observed in the present study.

Perspective taking and theory of mind

We have previously demonstrated activation of the MPFC, TPJ, and temporal poles (Schulte-Rüther et al., 2007) during both the SELF- and OTHER-related attribution of emotion in both males and females. These regions have also been associated with ToM by other authors (see, e.g., Frith and Frith, 2003; Vogeley and Fink, 2003 for reviews). This pattern of results is consistent with other studies which investigated self- and other-related judgments and found overlapping but also distinct foci of activation within medial prefrontal areas (see, for example, Seger et al., 2004; Mitchell et al., 2006). We did not find differences in brain activation in the comparison of OTHER versus SELF. These results suggest that ToM abilities may play an equally important role in interpersonal emotional perspective taking, be it from the self- or from the other-perspective. Moreover, they are likely to be associated with more cognitive aspects of empathy. Increased activation of the TPJ in males (relative to females) during the attribution of emotion to oneself may thus reflect a more cognitively driven access to one's own feelings in response to the emotions of other people. By some studies, brain areas at the TPJ and the posterior STS have been related to the perceptual processing of socially relevant cues (e.g., biological motion and facial expressions) that might help to determine the mental states of other people (Frith and Frith, 2003). Other studies suggest that the TPJ in particular mediates the inference of the belief of other people (Saxe and Kanwisher, 2003) and plays a vital role in the distinction between the SELF and the OTHER (Decety and Sommerville, 2003). Perceptual and ToM functions might be implemented in anatomically distinct subregions of the TPJ/STS region (Schulte-Rüther et al., 2007). We accordingly suggest that the TPJ might be a component of a neural circuitry which allows for the mental separation of one's own perspective from that of another person and thus enables us to disentangle our own feelings from those observed in other people. The present data on gender differences in empathy imply that males recruit this circuitry more intensely than females when assessing their own feelings (SELF-task) in response to an observed emotional facial expression. This finding supports the view that men may have a tendency to show the sharing of emotions with others to a lesser degree than women (along with a lesser degree of own emotional experience in response to the feelings of other people; e.g., Gross and Levenson, 1993; Schwartz, 1980). This conjecture is in accordance with our behavioral data which show that females rated their own emotions in response to each stimulus face (SELF-task) significantly higher than males. Moreover, it is in line with a recent fMRI study demonstrating that automatic mirror reactions in response to pain can better be suppressed by males (relative to females) in cases where empathy appears inappropriate due to the unfair behavior of an individual (Singer et al., 2006). Note, the coordinates of the peak activation in the TPJ region and in the STS region for the comparison between males and females do not exactly

correspond to the ToM-related coordinates reported by Saxe and Kanwisher (2003). However, several other studies have identified similar coordinates of local activation during ToM reasoning or tasks requiring a self–other distinction (e.g., Gallagher et al., 2000; Castelli et al., 2000; Vogeley et al., 2001; Brunet et al., 2000).

Theory of mind, mirror neurons, and empathy

The association between ToM and mirror neuron mechanisms and their relation to empathic behavior is still under debate (see, for example, Saxe, 2006) and, clearly, further neuroimaging studies are needed to clarify this issue. However, the results of the present study suggest that distinct brain mechanisms related to ToM and to the hMNS may play an important role in empathic face-to-face situations. We could demonstrate that areas which have been related to mirror neuron mechanisms are activated and that the amount of activation is related to both dispositional empathy and the intensity of evoked emotion. These results provide evidence for the involvement of the hMNS in the emotional aspects of empathic interpersonal behavior.

Implications for behavioral gender differences in emotional processing and empathy

Our finding of gender effects on the neurofunctional bases of empathy-related emotional perspective taking makes an important contribution to the longstanding debate on differences between males and females in the domain of emotional behavior. There is much evidence from behavioral studies for a female advantage in emotional processing and expressivity (e.g., Dimberg and Lundquist, 1990; Schwartz, 1980; Kring and Gordon, 1998). Although gender effects concerning the ability of emotion perception (e.g., in simple recognition of emotions from facial displays) are sometimes weak, they have been consistently reported in both children and adults (McClure, 2000). Concerning the expressive component of emotion, findings are even more consistent across a large body of literature (e.g., EMG measures, ratings of communication accuracy, self-reports of expression, and ratings of non-verbal behavior like smiling and gesturing): females show enhanced emotional expressivity and arousal in response to the emotions of other people in comparison to males (e.g., Dimberg and Lundquist, 1990; Schwartz, 1980; see Brody and Hall, 2000 for a review). There is evidence that these differences between the sexes pertain to almost all emotion categories, including basic emotions (Kring and Gordon, 1998). These findings suggesting superior ability of females to express emotions are at least in part corroborated by our behavioral data: females rated the intensity of their own experienced emotion during the experiment higher than males did. This subjective increase of own emotional experience in females during the experiment could be related to a higher emotional arousal of women, enhanced emotional expressivity, or both (e.g., Gross and Levenson, 1993; Schwartz, 1980). Importantly, there was no gender difference in the ratings of the emotional intensity of the observed facial expressions, suggesting that the female emotional superiority exerted stronger influences on the SELF-task compared to the OTHER-task. This finding also implies that an advantage of females in emotional behavior is more pronounced in the domain of emotional responsiveness than in that of emotion perception.

Emotional responsiveness to other people is closely linked to aspects of empathic behavior (Decety and Jackson, 2004). Our

behavioral data support the hypothesis that there exist rather weak differences between males and females in the ability to recognize the emotions of other persons. In females, however, the awareness of the feelings of others is accompanied by a stronger emotional resonance, while males may retain a more cognitively driven and distant approach to the emotional state of other persons (Hoffman, 1977). Neuroimaging results of our present study provide evidence that enhanced expressivity of emotion in females may be associated with a higher degree of hMNS activation. It is conceivable that hMNS recruitment during emotional face-to-face interactions is closely related to emotional experience and expressivity. Note, however, empathy is not restricted to the sharing of the emotional state of another individual, but also requires the distinction between the self and the other (Decety and Jackson, 2004). Our previous neuroimaging data on common effects in both sexes (Schulte-Rüther et al., 2007) as well as the present analysis of gender differences support the view that TPJ is involved in the maintenance of self–other separation (Decety and Sommerville, 2003). TPJ activation was modulated by gender, with stronger TPJ recruitment in males compared to females. Taken together these results suggest that, in the service of empathy, attenuated TPJ activation might provide females with the better capability to temporarily suspend the boundaries between the SELF- and OTHER-perspective during face-to-face interactions (Hoffman, 1977). However, this conclusion needs to be validated in future studies which directly examine the strategies that the subjects apply during such tasks.

Empathizing–systemizing theory of psychological gender differences

Baron-Cohen et al. (2005) suggested that psychological gender differences can be described by the relationship between the degree of empathizing (defined as the tendency to infer mental and emotional states of others and respond with appropriate emotional feelings and behavior) and systemizing abilities (defined as the tendency to analyze the rules of a system and predict its behavior). According to this account, the "typical female" brain is characterized by a superiority of empathizing over systemizing capabilities while the "typical male" brain is supposed to show the reverse pattern. Although the present study does not make assumptions about gender differences in systemizing capabilities, our behavioral and neuroimaging data support the notion of a general gender-related difference in empathizing and provide evidence for an associated brain mechanism. On a self-report scale of empathy (BEES; Mehrabian, 1997) which is similar to the scale devised by Baron-Cohen and Wheelright (2004) female participants of the present study scored significantly higher than male participants. Note, activation of areas related to the hMNS was correlated with individual differences in empathic abilities. This correlation was significant across the whole group of participants. When males and females were analyzed separately, some correlations were also significant, for others, there was at least a trend towards statistical significance. These results extend previous findings of a general relation between empathic abilities and mirror neuron activation (Schulte-Rüther et al., 2007) in that they suggest additional modulatory effects of gender on hMNS activation.

Implications for autism

Finally, our results contribute to the current debate on the neural correlates of diminished empathic abilities in individuals with autism. The "extreme male brain theory" of autism is an extension

of the above mentioned "empathizing–systemizing theory" of typical cognitive and behavioral differences between sexes (Baron-Cohen et al., 2005). The account suggests that individuals with autism are characterized by an extreme variant of a "typical male" brain. Our results are in accordance with both approaches. We demonstrate reduced activation of the hMNS in males (relative to females) during empathy-related emotional perspective taking in a face-to-face situation. Further support comes from a study of Dapretto et al. (2006) who observed reduced activation of inferior frontal areas in autistic individuals (relative to healthy control subjects) during the observation and imitation of facial emotions which was correlated with symptom severity. Moreover, automatic mimicry (McIntosh et al., 2006) and explicit imitation of facial expressions (Rogers et al., 2003) are impaired in autistic children. Taken together, these results give rise to the assumption that a deficient mirror neuron system may play a role in autistic symptoms (Williams et al., 2001). However, evidence for a dysfunctional hMNS in autism is mixed. For example, it has been shown that the imitation and understanding of goal-directed hand actions is not impaired in autistic children (Hamilton et al., 2007). Based on the results of our present study, we suggest that reduced activation of hMNS areas does not need to be an indicator of a basic deficiency of mirror neuron mechanisms. Rather, the degree of hMNS activation may reflect normal individual and, at least in part, gender-related differences in the tendency to recruit this brain system in emotional social interactions.

Conclusions

Our data provide novel evidence for the idea that the neural networks supporting empathy are differentially modulated by gender. Results suggest that better empathic abilities of females are related to their enhanced reliance on the hMNS when assessing the emotional states of other people and their own emotional response to the feelings of others. In contrast, males show stronger recruitment of ToM associated areas. They may thus rely on a more cognitive strategy, especially when determining their own emotional response to the feelings of others.

Acknowledgments

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