Interoceptive Awareness Enhances Neural Activity During Empathy

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Abstract: Empathy is a multicomponent function that includes sensorimotor, affective, and cognitive components. Although especially the affective component may implicate interoception and interoceptive awareness, the impact of interoception on empathy has never been evaluated behaviorally or neurophysiologically. Here, we tested how a preceding period of interoceptive awareness impacts and modulates neural activity during subsequent empathy. We used functional magnetic resonance imaging (fMRI) and measured the sequential interaction between interoception and empathy using fMRI in 18 healthy subjects. We found that the preceding interoceptive awareness period significantly enhanced neural activity during empathy in bilateral anterior insula and various cortical midline regions. The enhancement of neural activity during empathy in both interoceptive and empathy networks by preceding interoceptive awareness suggests a close relationship between interoception and empathy; thereby, interoception seems to be implicated to yielding empathy. *Hum Brain Mapp 00:000–000, 2012.* © **2012 Wiley Periodicals, Inc.**

Key words: fMRI; empathy; interoceptive awareness

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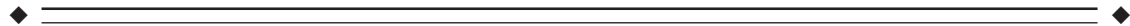
INTRODUCTION

Empathy, a phenomenon characterizing our understanding and sharing of others' feelings, is vital to everyday communication and survival in a social environment [Eisenberg and Strayer, 1987] and can be broadly defined as the experiencing of an affective or sensory state similar to that shown by a perceived individual, where one is aware as to whether the source of the state is oneself or another [Batson, 2009]. Empathy consists of both automatic affective experience and controlled cognitive processing, which are distinct but interrelated processes that may be instantiated differently in the brain [Decety and Jackson, 2004; Keysers and Gazzola, 2007; Singer, 2006; Watt, 2007]. Animal data suggest that maternal care and nurturance might reflect a kind of protoempathy [Panksepp, 1998] and might be phylogenetically coincident with the social signalling functions of emotion and the formation of social

bonds [Watt, 2007]. Such social bonding is highly relevant for an evolutionary consideration of empathy, as it has been pointed out by the hallmark work of Panksepp [1998] and Watt [2007]. Empathy thus needs to be considered within a socioevolutionary context meaning that empathic abilities are essential to the capacity to have stable attachments, with social bonding being critically enhanced by the ability to perceive the distress of a conspecific. This is being supported by imaging studies in humans investigating attachment in maternal care and romantic love and revealing a large functional overlap with regions of the empathy network [Bartels and Zeki, 2000, 2004; Lorberbaum et al., 2004]. Diminished empathic abilities and unstable or nonexistent relationships as evident in autism, sociopathy, and borderline personality disorder also suggest close ties between attachment and empathy [Baron-Cohen, 2010; Dziobek et al., 2011; Frick and White, 2008; Shamay-Tsoory et al., 2010; Watt, 2007].

Empathy studies in different domains such as pain, touch, and disgust [Wicker et al., 2003; Morrison, Lloyd, di Pellegrino, & Roberts 2004; Singer et al., 2004; Jackson, Meltzoff, and Decety 2005] have yielded a quite consistent neural network that comprises the bilateral anterior insula, the anterior cingulate cortex, the thalamus, and the medial prefrontal cortex [Fan et al., 2010, 2011; Molenberghs et al., 2011; Singer and Lamm, 2009; Decety et al., 2006; Lamm et al., 2007, 2011] that is activated during the observation as well as during the experience of the respective sensations. The simulation theory of empathy therefore proposes that humans understand the thoughts and feelings of others by using their own mind as a model. By simulating the experience of another person in our own mind, we can intuitively understand what that experience might be like [Gordon, 1986]. The discovery of mirror neurons and other "shared circuits" that are commonly activated by one's own and another's actions have been viewed as neural evidence in support of simulation theory [Gallese and Goldman, 1998; Rizzalotti, 2010]. Nonconscious neural mirroring may allow for the vicarious experience of the emotional states of others and enable the affective sharing characteristic of empathy [Decety and Jackson, 2004; Gallese, 2003; Iacoboni et al., 1999]. This idea has been supported by studies showing that imitation and observation of emotional facial expressions, which commonly activates mirror neuron and limbic regions with the insula as a relay station for transmitting action information from premotor mirror areas to limbic areas, which then process emotional content [Carr et al., 2003]. Although the role of mirror neurons in empathy has been questioned by some authors [see Watt, 2007], there is consistent and strong evidence for their involvement in the affective component of empathy, specifically in emotional contagion. It has been suggested that overt facial mimicry is related to emotional contagion [Keysers and Gazzola, 2006; Niedenthal 2007; Jabbi et al., 2007; Schulte-Ruther et al., 2007; Nummenmaa et al., 2008; Shamay-Tsoory et al., 2009].

Because especially affective states are often assumed to involve awareness of one's own bodily state, processing of bodily and thus interoceptive stimuli may be a crucial component in yielding empathy [Northoff, 2007]. This is supported by a recent electroencephalographic study that demonstrated the variation of the heartbeat-evoked potential (as cortical electrophysiological measure of interoception) during empathy [Fukushima et al., 2011]. Although this study demonstrated the dependence of interoception on empathy, it though remains unclear how the neuronal processes during empathy are modulated by interoception or more specifically during interoceptive awareness. The assumption of a close relationship between interoceptive awareness and empathy is further supported when considering the regions and neural networks recruited during both processes. Interoceptive awareness has been investigated by using a visual or auditory heartbeat feedback with the subjects' task being a synchronicity judgement about this feedback [Critchley et al., 2004; Matthias et al., 2009; Pollatos et al., 2005, 2007]. Wiebking et al. [2010, 2011] applied an interoception paradigm where subjects were asked to silently count their own heartbeat for as long as a task-type indicator was displayed. Interoceptive awareness leads to neural activity changes in the bilateral anterior insula, the anterior cingulate cortex, and the thalamus [Critchley et al., 2004, 2010; Wiebking et al., 2010, 2011]. Taken together, these results of a considerable regional overlap between empathy and interoception suggest functional interdependence. Analogously to previous studies in the visual [Kastner et al., 1999] and emotional [Bermpohl et al., 2006; Grimm et al., 2006] domains, we applied a sequential interaction design where the empathy period was preceded by periods of intero- or exteroceptive awareness. Although most previous empathy studies mainly focused on sensory qualities, and subjects were not instructed to engage (or not engage) in empathic processing, we applied an empathy task that required subjects to make empathy judgements for facial expressions and therefore specifically asked them to engage in empathic processing [Fan et al., 2011; deGreck et al., 2011]. Even though this might seem similar to an emotion recognition task [Matsumuto et al., 2000; Jehna et al., 2011], the crucial difference is the requirement of an explicit empathy judgement rather than an emotion classification.

The first aim of the study was to investigate how empathy-related neural activity in the interoceptive network is modulated by preceding interoceptive awareness. We hypothesized that the neural activity during empathy in these regions is enhanced by preceding interoceptive awareness (when compared with empathy preceded by exteroceptive awareness or empathy without any preceding awareness).

Second, we aimed to investigate whether regions of the empathy network are differentially modulated during empathy after interoceptive compared with exteroceptive awareness. We hypothesized that the preceding interoceptive awareness would significantly enhance neural activity during empathy in regions of the empathy network.

MATERIALS AND METHODS

Participants

Healthy subjects [12 women and 6 men, mean age 27 (SD 7.6)] were recruited from online study advertisements. Exclusion criteria were major medical illnesses, histories of seizures, head trauma with loss of consciousness, and pregnancy. In addition, subjects who met criteria for any psychiatric or neurologic disorder had a history of substance abuse in the previous six months or had a history of substance dependence were excluded from the study. All subjects were right-handed as assessed with the Edinburgh Handedness Inventory [Oldfield et al., 1971]. The study was carried out in accordance with the latest version of the Declaration of Helsinki and approved by the State of Zurichs' Review Board. All subjects gave written informed consent before screening.

Pictorial Stimuli

Participants viewed full-color pictures of the Japanese and Caucasian Facial Expressions of Emotions [JACFEE, Matsumoto and Ekman, 1988] picture set. The set comprises 56 photos, including eight photos each of happiness, sadness, disgust, fear, surprise, anger, and contempt. Four photos of each emotion depict posers of either Japanese or Caucasian descent (two males, two females). Fourteen of the photographs were displayed twice in our paradigm, amounting to a total stimuli number of 70. Furthermore, the experiment included eight edited photographs from the JACFEE series with unrecognizable contents. Picture contents were transformed by using a smoothing function [Gerlach et al., 2002]. The pictures were generated by Presentation® (Neurobehavioral Systems, Albany, CA) and presented via video goggles (VisuaStim digital). Participants responded by pushing a fiber-optic light sensitive key press.

Experimental Design

The functional magnetic resonance imaging (fMRI) design was "event related" and based on a paradigm introduced by Critchley et al. [2004] where subjects had to attend to intero- and exteroceptive stimuli by counting their own heartbeat and tones. The original paradigm was altered by introducing an empathy condition, a control condition with blurred photographs ("smooth"), and rest periods. This modified paradigm has been successfully applied in two previous studies [Wiebking et al., 2010, 2011]. During the interoceptive condition ("interoception"), subjects were asked to silently count their own heartbeat for as long as the task-type indicator (a black heart on a white background) was displayed (6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, and 10.0 s). After each interoceptive task presentation, subjects were asked to report the number of heartbeats counted via a simple visual scale (2 s). The marks on

the scale represented the number of heartbeats subjects counted (<7, 7–12, 13–18, and >19). Subjects gave a response about the number of heartbeats by pressing one of the four buttons of the response box. This feedback component allowed subject's attendance to the task to be monitored. Exteroceptive conditions ("exteroception") were indicated by a black musical note on a white background (6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, and 10.0 s). During the task subjects had to silently count the number of tones heard during the period the task indicator was visible. To match the difficulty of the intero- and exteroceptive task, tones were presented at an individually determined, just audible volume. Furthermore, tones were presented constantly during the duration of the whole experiment, meaning also during Interoception. Analogous to the interoceptive condition, after each exteroceptive task, subjects reported the number of tones via button press (2 s). The marks on the scale represented the number of tones subjects counted (<18, 19–-25, 26–31, and >32). Tones were presented via headphones. For the empathy and control condition, subjects were presented original or smoothed photographs from the JACFEE series, respectively (see above). Each picture was presented for 4 s and had to be judged in both conditions regarding to whether subjects could empathize with the displayed emotion (yes–no option). Both conditions were either presented after the interoceptive and exteroceptive tasks ("EaI," Empathy after Interoception; "EaE," Empathy after Exteroception; "SaI," Smooth after Interoception; "SaE," Smooth after Exteroception) or after the rest condition ("empathy" and "smooth"). Rest conditions were indicated by a black fixation cross on a white background (6.0, 6.5, 7.0, 7.5, and 8.0 s). Subjects were instructed to relax, fixate on the crosshair, and try to minimize all cognitive activity. The rest period allowed subjects to recover from the active tasks and, in addition, served as a baseline condition to distinguish between positive and negative BOLD responses [Stark and Squire, 2001]. A total of 180 trials were presented in five runs; 25 trials were presented, respectively, for "EaI," "EaE," "SaI," and "SaE." Twenty trials were presented, respectively, for "interoception," "exteroception," "empathy," and "smooth". The 70 photos of the JACFEE series were presented within the "EaI," "EaE," and "empathy" trials.

The eight different task conditions were pseudorandomized within and across the runs and their order counterbalanced across all subjects. Before the experimental session, the subjects were familiarized with the paradigm by completing a test run of eight trials.

Functional Imaging

Functional measurements were performed on a Philips Intera 3T whole-body MR unit equipped with an eight-channel Philips SENSE head coil. Functional time series were acquired with a sensitivity encoded [Pruessmann

et al., 1999] single-shot echo-planar sequence (SENSE-sshEPI). The following acquisition parameters were used in the fMRI protocol: echo time = 35 ms, field of view = 22 cm, acquisition matrix = 80 × 80, interpolated to 128 × 128, voxel size: 2.75 × 2.75 × 4 mm³, and SENSE acceleration factor R = 2.0. Using a midsaggital scout image, 32 contiguous axial slices were placed along the anterior–posterior commissure plane covering the entire brain with a TR = 3000 ms ($\theta = 82°$). The first three acquisitions were discarded due to T1 saturation effects.

Statistical Analysis

Behavioral data

Reaction times were recorded during the fMRI measurement and analyzed in an univariate ANOVA. Given that the interoceptive/exteroceptive period and the empathy/smooth period were associated with different tasks, response times were analyzed separately for the interoceptive/exteroceptive periods and periods that required an empathy rating (empathy, smooth, EaI, EaE, SaI, and SaE). Data were analyzed using SPSS 16 (SPSS, 1989–2007).

fMRI data

fMRI data were analyzed using MATLAB 6.5.1 (The Mathworks, Natick, MA) and SPM2 (Statistical Parametric Mapping software, SPM; Wellcome Department of Imaging Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk). Functional data were corrected for differences in slice acquisition time, realigned to the first volume, corrected for motion artefacts, mean adjusted by proportional scaling, normalized into standard stereotactic space (template provided by the Montreal Neurological Institute), and spatially smoothed using a 8-mm FWHM Gaussian kernel. The time series were high-pass filtered to eliminate low-frequency components (filter width 128 s) and adjusted for systematic differences across trials. Statistical analysis was performed by modeling the different conditions convolved with a hemodynamic response function as explanatory variables within the context of the general linear model on a voxel-by-voxel basis. Realignment parameters were included as additional regressors in the statistical model. A fixed-effect model at a single-subject level was performed to create images of parameter estimates, which were then used for a second-level random-effects analysis. For the fMRI data group analysis, the contrast images from the analysis of the individual participants were analyzed using one-sample t tests. Clusters of activation were identified with a global height threshold of $P < 0.001$, uncorrected and a cluster threshold of greater than 5. fMRI analyses focused on the effect of the preceding intero- or exteroceptive condition on the empathy task. For the regions of interest (ROIs) analyses of peak voxels, coordinates which were obtained in contrasts of the group analyses (Table I) were selected. ROIs were functionally

TABLE I. Summary of brain regions significantly activated during the various conditions

Region	Side	EaI > EaE	Interoception > exteroception	Empathy > smooth
Insula	R		46, 6, 6	32, 18, 8
			z: 3.87	z: 3.63
	L		−42, 0, 6	−28, 32, −8
			z: 4.33	z: 4.94
Precuneus	L	−4, −56, 28		
		z: 3.25		
PCC (bordering MPC)	L	−2, −10, 48		
		z: 3.39		
DMPFC	R	6, 44, 48		2, 18, 48
		z: 3.63		z: 5.77
SACC	R	10, 38, 26		
		z: 3.58		
Middle temporal gyrus	L	−54, −28, −16		
		z: 3.87		
MPC	R/L	8, −40, 74		
		z: 3.25		
Amygdala	R			16, −2, −20
				z: 4.34
Thalamus	L			−8, −6, 12
				z: 4.38

EaI, Empathy after Interoception; EaE, Empathy after Exteroception; PCC, posterior cingulate cortex; DMPFC, dorsomedial prefrontal cortex; SACC, supragenual anterior cingulate cortex; MPC, medial parietal cortex. The global height threshold was set to $P < 0.001$ uncorrected, the extent threshold to $k = 5$ voxels for all contrasts. The values in the table represent maximum z values with peak voxel coordinates in the MNI stereotactic space.

defined by centering spheres on the respective peak voxels with a radius of 5 mm. Analyses were carried out for the bilateral insula (46, 6, 6; −42, 0, 6; x, y, z coordinates in MNI stereotactic space), precuneus (−4, −56, 28), posterior cingulate cortex (PCC bordering to the medial parietal cortex; −2, −10, 48), dorsomedial prefrontal cortex (DMPFC; 6, 44, 48) and supragenual anterior cingulate cortex (SACC; 10, 38, 26). For the ROI analyses, percent signal changes for the different conditions were extracted for each subject separately using Marsbar (http://marsbar.sourceforge.net/). For each event, % signal changes were calculated relative to the mean signal intensity of this ROI across the whole experiment.

RESULTS

Behavioral Data

During the fMRI experiment, there was neither a significant effect of the interoceptive/exteroceptive conditions ($F(2)= 0.609, P = .436$) nor of the conditions requiring an empathy rating ($F(2)= 1.108, P = .234$) on reaction times. Inclusion of age and sex as co-variates did not have any influence on the results.
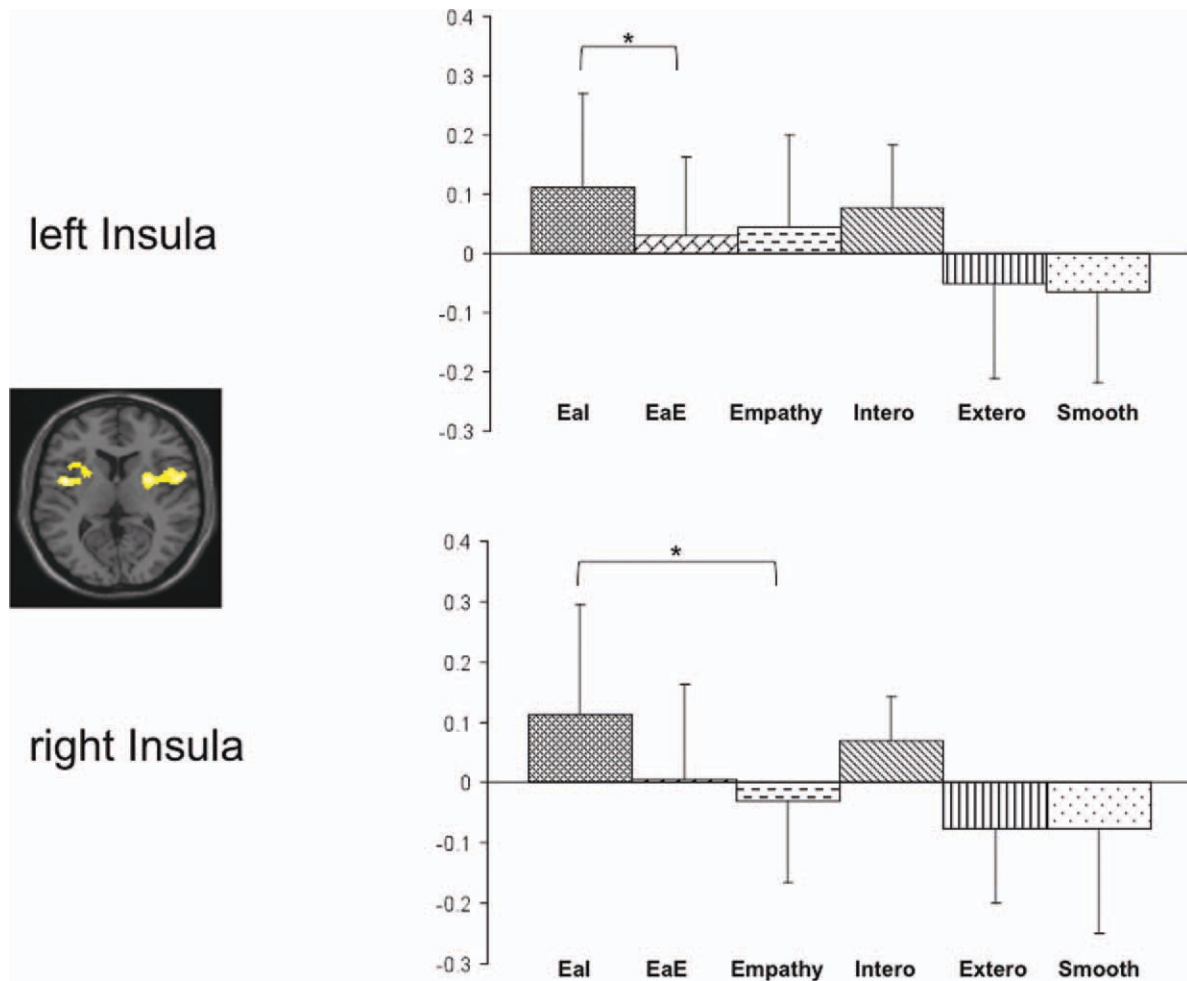
Figure 1.

Signal changes in interoceptive regions. The SPM image shows the statistical parametric (T) map for the contrast interoception > exteroception, overlaid on a single subject's normalized brain in the MNI stereotactic space ($P < 0.001$; uncorrected; $k > 5$). Bar diagrams show % signal changes during EaI, EaE, empathy, interoception, exteroception, and smooth in the bilateral insula (46, 6, 6; −42, 0, 6). Abbreviations: EaI, Empathy after Interoception; EaE, Empathy after Exteroception; Intero, interoception; Extero, exteroception. *: $P < 0.005$; **: $P < 0.001$. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

fMRI Data

Enhancement of empathy-related activity in interoceptive network by preceding interoception

For the contrast interoception > exteroception we found larger signal intensities in the bilateral insula (see Table I and Fig. 1). Pursuing a ROI approach, we then calculated the signal changes for the various empathy conditions. This yielded stronger signal changes in bilateral insula during empathy preceded by interoceptive awareness when compared with empathy following either exteroceptive awareness (left insula: $P = .021$; right insula: $P = .056$) or no awareness (right insula: $P = .021$; see Fig. 1). Interestingly, the signal changes during EaI were even stronger than those during interoception alone (see Fig. 1), even though these differences were not significant.

Enhancement of activity during EaI when compared with empathy following exteroception

After searching for signal changes in the interoceptive network, we focused on those regions that were significantly stronger activated during EaI when compared with EaE. This contrast (EaI > EaE) yielded significant signal changes in the SACC, the DMPFC, the PCC (bordering to the medial parietal cortex), and the precuneus (see Table I and Fig. 2a,b). The region-of-interest based analysis demonstrated stronger signal changes during EaI when
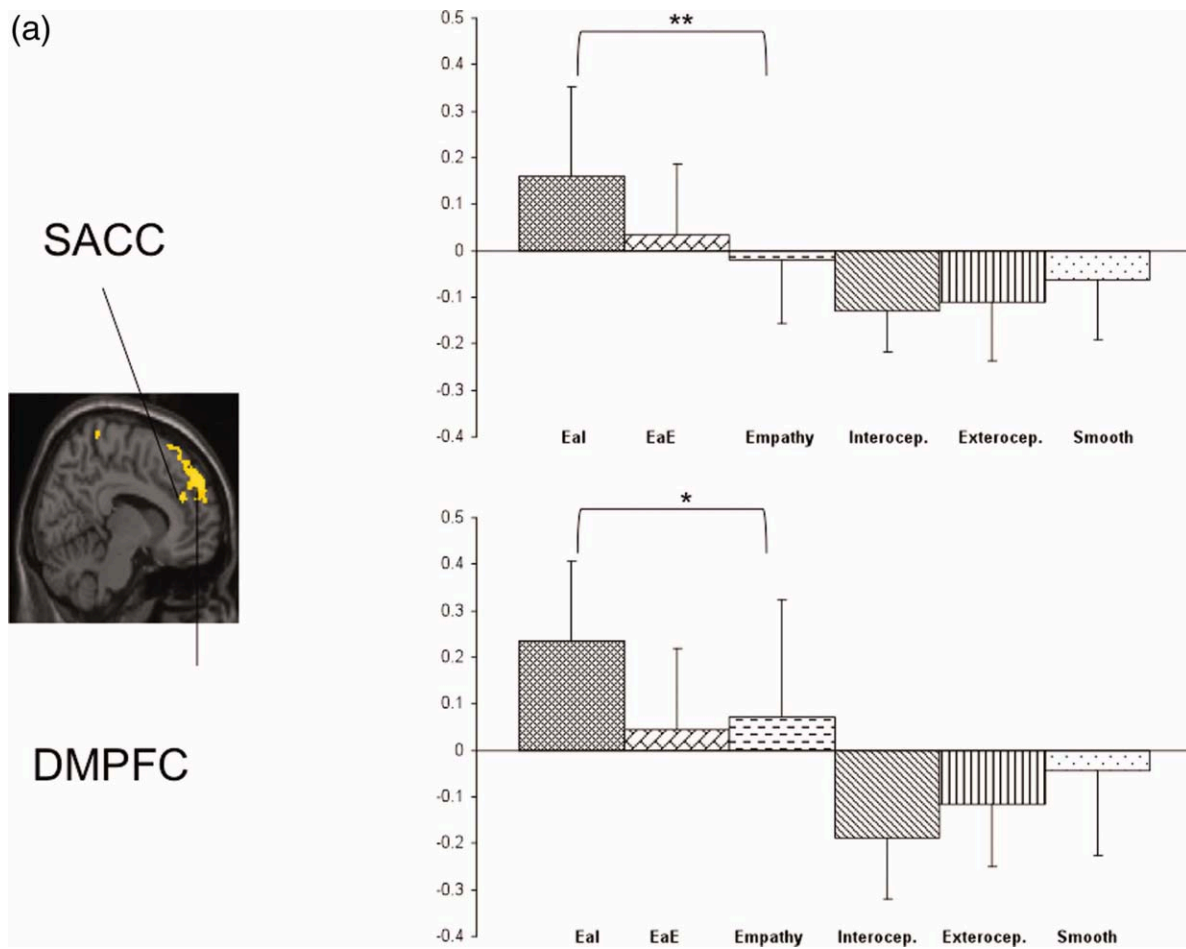
Figure 2.

Signal changes in empathy regions. (**a**) SPM image shows statistical parametric (T) map for the contrast EaI > EaE, overlaid on a single subject's normalized brain in the MNI stereotactic space ($P < 0.001$; uncorrected; $k > 5$). Bar diagrams show % signal changes in EaI, EaE, empathy, interoception, exteroception, and smooth. Bar diagrams show % signal changes in the SACC (10, 38, 26) and DMPFC (6, 44, 48). (**b**) SPM image shows statistical parametric (T) map for the contrast EaI > EaE, overlaid on a single subject's normalized brain in the MNI stereotactic space ($P < 0.001$; uncorrected; $k > 5$). Bar diagrams show % signal changes in EaI, EaE, empathy, interoception, exteroception, and smooth. Bar diagrams show % signal changes in the Precuneus (−4, −56, 28) and PCC (bordering to the medial parietal cortex) (−2, −10, 48). Abbreviations: EaI, Empathy after Interoception; EaE, Empathy after Exteroception; Intero, interoception; Extero, exteroception; SACC, supragenual anterior cingulate cortex; DMPFC, dorsomedial prefrontal cortex; PCC, posterior cingulate cortex; MPC, medial parietal cortex. *: $P < 0.005$; **: $P < 0.001$. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

compared with empathy alone (SACC: $P = .008$; DMPFC: $P = .032$) (see Fig. 2a).

DISCUSSION

Here, we investigated the relationship between interoception and empathy. Our first main finding is that a preceding interoceptive awareness period significantly enhances neural activity during empathy in those regions recruited during interoception, i.e., bilateral anterior insula. The second main finding is that preceding interoceptive awareness enhances neural activity during empathy in anterior and posterior midline regions like the SACC, DMPFC, PCC, and precuneus. Most importantly, in interoceptive and empathy-related regions, signal changes during EaI were even stronger than those during interoception and empathy alone. Taken together, our findings indicate enhancement of neural activity during empathy in both interoceptive and empathy networks by preceding interoceptive awareness. This suggests close relationship between interoception and empathy with the former being apparently implicated in yielding the latter.
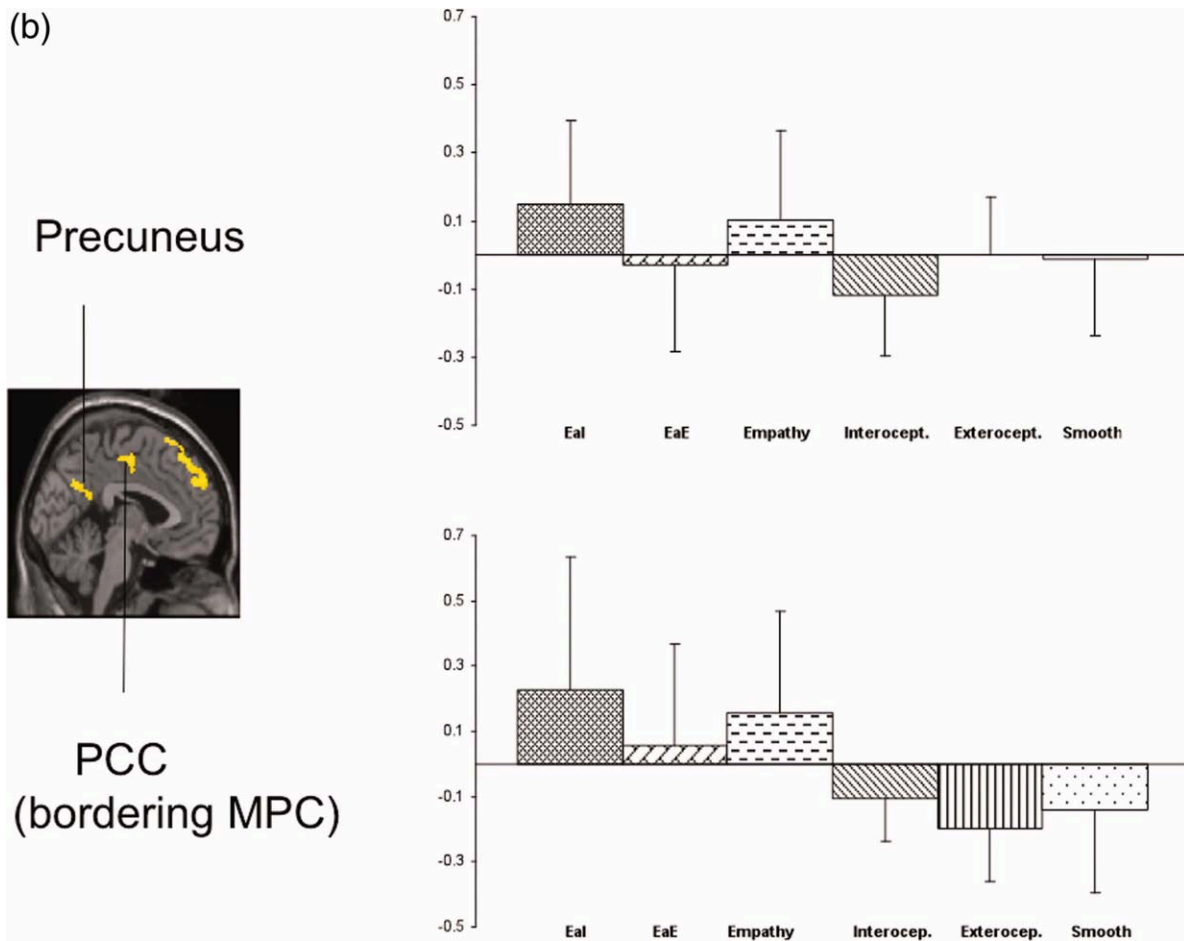
Figure 2.
(*Continued*)

Our first main finding concerns the modulation of empathy-related neural activity in interoceptive regions. Although many studies indicated recruitment of the bilateral anterior insula in both empathy [Fan et al., 2011] and interoception [Critchley et al., 2004, 2005; Wiebking et al., 2010; Craig, 2002, 2009, 2010; Paulus et al., 2007], the relationship between interoception and empathy has not been studied so far. Our results demonstrate that the neural activity in the bilateral anterior insula during empathy can be significantly enhanced by preceding interoception. More specifically, preceding interoceptive awareness enhanced neural activity during subsequent empathy when compared with either empathy with exteroceptive awareness or no preceding awareness period at all. This suggests a specific interaction of empathy with interoception, i.e., interoceptive awareness, as distinguished from exteroceptive awareness.

What does our finding imply for empathy? Empathy is considered to consist of several components including sensorimotor, affective, and cognitive functions [Fan et al.,

2010; Singer and Lamm, 2009; Decety et al., 2006; Lamm et al., 2007, 2010, 2011; Schnell et al., 2011]. The observation of emotional facial expressions commonly activates mirror neuron and limbic regions with the insula as a relay station. This nonconscious neural mirroring may allow for emotional contagion [Watt, 2007; Shamay-Tsoory, 2011] as well as for affective sharing [Decety and Jackson, 2004; Gallese, 2003; Iacoboni et al., 1999] as discussed in the simulation theory of empathy (Gordon, 1986; Gallese and Goldman, 1998]. Our study highlights the central relevance of interoceptive function. More specifically, one may be inclined to assume that the here observed enhancement of empathy-related activity in the bilateral insula by the preceding interoception indicates the implication of interoceptive function in empathy itself. Only when interoception is implicated in empathy itself, the preceding interoceptive awareness period can exert such strong enhancement effects as observed here. This is further supported by the fact that empathy following the interoceptive awareness induced stronger activity not only than the

two other empathy conditions but was also stronger than interoception alone. Hence, one may be inclined to assume that the preceding interoceptive period enhances an already existing interoceptive component in empathy itself. Because the insula and especially the anterior insula is often assumed to integrate different stimuli especially interoceptive ones [see Craig, 2002, 2009, 2010; Paulus and Stein, 2010] one may consequently assume a process we call intero–intero interaction underlying the enhancement of bilateral anterior insula activity.

In addition to the bilateral anterior insula, other regions also showed enhancement of empathy-related neural activity by preceding interoceptive awareness. This concerned especially anterior and posterior midline regions like the SACC, DMPFC, PCC, and precuneus. In addition to empathy [Fan et al., 2010], these regions have often been implicated in self-related processing, a process where stimuli are related to the own person [see Northoff et al., 2006, Qin and Northoff, 2010]. Because interoceptive stimuli stem from the own body, they may show a rather high degree of self-relatedness which in turn may account for the enhancement of neural activity in these regions by the preceding interoceptive awareness period. This however remains speculative at this point and needs to be addressed in future studies testing for the interaction between empathy, interoception, and self-relatedness.

Finally, given the supposedly central role of interoception in empathy, one may also need to reconsider empathy. Although the role of exteroceptive stimuli as coming from the other person one shows empathy with has been highlighted, the role of the interoceptive stimuli stemming from the own body remains unclear. Following our results, one may be inclined to argue that empathy may be regarded as a special form of linkage between intero- and exteroceptive stimuli thus presupposing what one may want to call intero–extero interaction. Although plenty of studies have investigated how empathy and its underlying neural activity depend on exteroceptive stimuli and the exteroceptive context [Fan et al., 2010; Singer and Lamm, 2009; Decety et al., 2006; Lamm et al., 2007, 2010, 2011; Schnell et al., 2011], no study demonstrated how the variation of interoceptive stimuli impacts empathy. On the basis of our results shown here one would hypothesize that variation of the interoceptive state of one's body also impacts the degree of neural activity and possibly the behavioral manifestation of empathy itself. This though remains to be demonstrated in the future.

Some methodological limitations need to be mentioned. First, we did not include the reverse testing of empathy modulating interoception. Future studies may want to investigate this relationship to further and better understand how interoception is implicated in empathy. Second, one needs to distinguish between interoception and interoceptive awareness with the former not necessarily entailing the latter. In our study, we targeted interoceptive awareness rather than mere interoceptive processing *per se*. Future designs may want to investigate whether both exert

differential effects on empathy including its distinct components, sensorimotor, affective, and cognitive. Third, one may want to argue that the affective component of empathy already includes the interoceptive component with our study thus showing nothing new. However, unlike in previous studies, our approach explicitly isolated the interoceptive component and investigated its impact on subsequent empathy. Future studies may therefore want to focus especially on the interaction between interoception and affect within empathy. Fourth, future studies should include an empathy questionnaire such as the Balanced Emotional Empathy Scale [Mehrabian, 1996] to provide an empathy "trait" score and allow for further investigation of the relationship between empathic abilities and specific neural activation patterns. Fifth, one might argue that interoception may have a general facilitative relationship to all forms of affect and affective experience but not a specific relationship to empathy *per se*. Future studies should investigate the impact of interoceptive awareness on other forms of emotional processing to answer this critical question. Lastly, one also needs to consider possible attention differences between the interoceptive and exteroceptive awareness conditions as well as carry-over effects of these preceding conditions on the empathy condition. Because preceding exteroceptive awareness would not only be expected to increase the attentional load to a comparable degree to interoceptive awareness and furthermore response times between these two conditions did not differ, attention differences can most likely be excluded. The same applies to carry-over effects, because the differential effect is not present yet during the preceding period of interoceptive versus exteroceptive awareness but only occurs during the subsequent empathy period.

In conclusion, we here demonstrate for the first time a direct interaction between interoception and empathy. Our data show that preceding interoceptive awareness enhances neural activity in bilateral insula and various midline regions during empathy. Our data suggest the involvement of interoceptive processing in empathy which may interact with the exteroceptive stimuli in a specific way yielding what may be called intero–extero interaction. Though tentatively, this lets one to assume that the interoceptive components may need to be considered in empathy and added to the other various components.

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