Structural Covariance Networks of the Dorsal Anterior Insula Predict Females′ Individual Differences in Empathic Responding

Boris C. Bernhardt[,1], Olga M. Klimecki[1], Susanne Leiberg[2] and Tania Singer[1,2]

[1]Department of Social Neuroscience, Max-Planck-Institute of Human Cognitive and Brain Sciences, D-04301 Leipzig, Germany
[2]Laboratory for Social and Economic Systems Research, Department of Economics, University of Zurich, CH-8006 Zurich, Switzerland

B.C.B and O.M.K. contributed equally to this work.

Address correspondence to Boris Bernhardt, Department of Social Neuroscience, Max-Planck-Institute of Human Cognitive and Brain Sciences, Stephanstraße 1a, D-04103 Leipzig, Germany. Email: bernhardt@cbs.mpg.de

Previous functional imaging studies have shown key roles of the dorsal anterior insula (dAI) and anterior midcingulate cortex (aMCC) in empathy for the suffering of others. The current study mapped structural covariance networks of these regions and assessed the relationship between networks and individual differences in empathic responding in 94 females. Individual differences in empathy were assessed through average state measures in response to a video task showing others' suffering, and through questionnaire-based trait measures of empathic concern. Overall, covariance patterns indicated that dAI and aMCC are principal hubs within prefrontal, temporolimbic, and midline structural covariance networks. Importantly, participants with high empathy state ratings showed increased covariance of dAI, but not aMCC, to prefrontal and limbic brain regions. This relationship was specific for empathy and could not be explained by individual differences in negative affect ratings. Regarding questionnaire-based empathic trait measures, we observed a similar, albeit weaker modulation of dAI covariance, confirming the robustness of our findings. Our analysis, thus, provides novel evidence for a specific contribution of frontolimbic structural covariance networks to individual differences in social emotions beyond negative affect.

Keywords: connectivity, cortical thickness, empathy, MRI, social emotions

Introduction

Previous functional imaging research has advanced our understanding of the neuronal underpinnings of empathy, the ability to share the feelings and sensations of others (de Vignemont and Singer 2006). In studies localizing functional correlates of empathy for pain, the dorsal anterior insula (dAI) and anterior midcingulate cortex (aMCC), in particular, have been shown to play a pivotal role in first-hand and vicarious experience of pain (Fan et al. 2011; Lamm et al. 2011). Nevertheless, accumulating findings suggest that both regions also participate in more general processing related to negative affect, and not empathy for pain specifically (Craig 2009; Singer et al. 2009; Corradi-Dell'Acqua et al. 2011; Shackman et al. 2011).

Another line of empathy research focusing on brain connectivity has suggested that empathic inferences about other people's mental states rely on the integration of affective information with other social cognitive processes such as action observation and perspective taking. In fact, previous functional connectivity studies in the domain of empathy have shown that dAI and aMCC interact with other networks involved in social cognition, such as medial prefrontal cortex (PFC) (Zaki et al. 2007) and inferior frontal gyrus of

ventrolateral PFC (Jabbi et al. 2008). Whether such interactions between dAI and aMCC and other routes of social cognition are reflected in inter-regional structural brain networks, and thus possibly relate to individual differences in empathic responding, remains unclear. Studies based on tract tracing, the gold standard for connectivity mapping, have indicated a central role of dAI and aMCC within multiple brain networks in frontolimbic, temporal, and also midline regions (Pandya et al. 1981; Mufson and Mesulam 1982). However, as these invasive techniques cannot be applied to humans, so far little is known about structural networks relating to empathy in humans.

To close this gap, we mapped structural covariance networks centered on dAI and aMCC and studied how these are modulated by individual differences in empathic responding. Specifically, we used covariance analysis of MRI-based cortical thickness measurements, a method that has previously been used to reliably map structural brain networks in vivo (Lerch et al. 2006; Bullmore and Sporns 2009; Seeley et al. 2009). Seed-regions in dAI and aMCC were identified based on a recent meta-analysis of functional studies on empathy for pain (Lamm et al. 2011). To investigate the relationship between structural covariance networks and individual differences in empathy, we calculated average empathic state ratings using a newly developed Socio-affective Video Task (SoVT) that depicts people suffering (Klimecki et al. 2012). Employing dynamic social scenes, as in the SoVT, instead of simplified and artificial stimuli might be advantageous in assessing the different component networks interacting in empathy (Zaki and Ochsner 2012). A self-report empathy trait questionnaire was also administered (Davis 1983). As evidence is accumulating that both dAI and aMCC might play a more general role in negative affect processes (Craig 2009; Singer et al. 2009; Corradi-Dell'Acqua et al. 2011; Shackman et al. 2011), we tested for the specificity of empathy-related covariance modulations by controlling for individual differences in average negative affect state ratings during the SoVT.

Materials and Methods

Subjects

We studied 94 healthy, right-handed women aged between 18 and 35 years (mean ± SD = 24.3 ± 4.17 years) from the University of Zurich and the surrounding community. Only females were recruited due to previously reported gender differences in social emotions on the behavioral and neural level (Baron-Cohen and Wheelwright 2004; Singer et al. 2006). Prior to participation, all volunteers completed an online version of the Beck Depression Inventory (BDI; Beck et al.

1996), and the Toronto Alexithymia Scale (TAS-20; Bagby et al. 1994), the latter as a measure of difficulties in experiencing and expressing feelings. To ensure that our sample population represented a normally functioning female, only volunteers with BDI <18 and TAS-20 <60 and with no contraindication for MRI were included. We, furthermore, conducted a Structured Clinical Interview for DSM-IV disorders (SCID; Wittchen et al. 1997) to screen for Axis-I and psychotic disorders via phone. Volunteers with these psychiatric illnesses were excluded.

The study was approved by the Research Ethics Committee of Zurich ("Kantonale Ethikkommission des Kantons Zürich, Spezialisierte Unterkommission Psychiatrie, Neurologie, Neurochirurgie"; E-25/2008), and was carried out in compliance with the Declaration of Helsinki. All participants gave written informed consent, were paid for their participation and were debriefed after the study was completed.

Measuring Interindividual Differences in Empathic Responding
We quantified individual differences in empathic responses through both, average empathy state ratings during the SoVT (Klimecki et al. 2012) and self-reported trait empathic concern, as measured by the Interpersonal Reactivity Index, IRI (Davis 1983) questionnaire.

Empathy Ratings During the SoVT (EMP-SoVT)
To assess average empathic state ratings, we used the newly developed Socio-affective Video Task (SoVT) which is described in detail elsewhere (Klimecki et al. 2012). It consists of 3 sets of 24 videos from documentaries or newscasts (duration 10–18 s): half of the videos depict people in distress (high emotion videos), the other half of the videos serve as a high-level baseline and depict people in everyday situations (low emotion videos). All subjects completed the SoVT during a functional MRI experiment; the functional imaging results are described elsewhere (Klimecki et al. 2012). After each video, participants were asked to rate on a Likert scale ranging from 0, none, to 10, intense, how much empathy, negative affect and positive affect they felt while watching the video. To control for each subject's individual baseline, we then calculated the mean empathy rating difference between high and low emotion videos (EMP-SoVT) and used the obtained values as regressors for subsequent statistical analysis. In a similar fashion, we calculated differences for positive affect ratings (POS-SoVT) and negative affect ratings (NEG-SoVT) as additional control covariates.

Self-Reported Questionnaire Measure of Trait Empathic Concern (IRI-EC)
All 94 subjects completed the IRI using the online survey program Unipark (Globalpark GmbH, Hurth, DE). The IRI is one of the most commonly used self-report questionnaires of dispositional empathy and contains 7 items in each of the 4 categories: empathic concern, perspective taking, personal distress, and fantasy. Each item consists of a statement to which subjects are asked to indicate on a 5-level Likert-scale whether it describes them well (scored with 4 points) or not at all (scored with 0 points). For main statistical analysis, we selected the empathic concern subscale (IRI-EC). This subscale most closely matches our and others' theoretical conception of empathy (Davis 1983; Singer 2006; Singer and Lamm 2009), as it captures feelings of sympathy and concern for unfortunate others. We thus additionally tested whether this subscale relates to structural covariance measures of dAI and aMCC. The other IRI subscales (Fantasy, Personal Distress, and Perspective Taking) were not assessed, as this also would considerably increase the amount of statistical comparisons performed.

MRI Acquisition
High-resolution T_1-weighted images were obtained using a 3-Tesla Philips Achieva whole-body magnetic resonance imaging system equipped with an 8-channel SENSE head coil (Philips Medical Systems, Best, The Netherlands). Images were acquired using a 3D-TFE pulse sequence with a flip angle of 8°. The 301 slices with a voxel size of $1.1 \times 1.1 \times 0.6 \text{ mm}^3$ were sagittally placed along the anterior–posterior commissure plane. The acquisition matrix ranged over 240×240 with a field of view of $250 \times 250 \text{ mm}^2$.

MRI-Based Cortical Thickness Measurements
We used FreeSurfer software to generate models of the cortical surface and to model cortical thickness from the T_1-weighted images (Version 5.0.0; http://surfer.nmr.mgh.harvard.edu). Previous work has validated FreeSurfer by comparing it with histological analysis (Rosas et al. 2002) and manual measurements (Kuperberg et al. 2003). The processing steps have been described in detail elsewhere (Dale et al. 1999; Fischl et al. 1999; Han et al. 2006). Following surface extraction, sulcal and gyral features across individual subjects were aligned by morphing each subject's brain to an average spherical representation that allows for accurate matching of cortical thickness measurement locations among participants, while minimizing metric distortion. The entire cortex of each participant was visually inspected and segmentation inaccuracies were manually corrected. For whole-brain analysis, thickness data were smoothed on the tessellated surfaces using a 20-mm full-with-at-half-maximum Gaussian kernel prior to statistical analysis. Selecting a surface-based kernel reduces measurement noise but preserves the capacity for anatomical localization, as it respects cortical topological features (Lerch and Evans 2005).

Seed Definition
Based on a previously published meta-analysis on empathy for pain (Lamm et al. 2011), we chose the following seed regions for structural correlation analysis: left dAI (MNI $x/y/z$: −40/22/0), right dAI (39/23/−4), and left aMCC (−2/23/40). These regions have been identified as the most consistently activated areas in a coordinate-based meta-analysis of 32 functional MRI studies that investigated the neural substrates of empathy for pain (Lamm et al. 2011). Indeed, this study of Lamm et al. (2011) showed dAI activations in 28/32 studies and 24/32 previous functional studies, while other regions were activated in <30% of assessed studies.

Thus, while not addressing all regions possibly involved in processes related to empathy (particularly those involved in the interaction between empathy and socially relevant skills, such as cognitive perspective taking or self-other distinction, including the medial prefrontal cortex or temporoparietal junction area [Saxe and Kanwisher 2003; Frith and Frith 2006]), we investigated structural networks centered on the most consistent regions. To avoid a bias to the left hemisphere for the midline region aMCC, we also seeded from the right aMCC counterpart (2/23/40), resulting in a total of 4 seed regions for all subsequent analyses. For each meta-analysis coordinate, we identified the closest surface point on the mesh representation at mid-thickness of FreeSurfer's fsaverage7 template in MNI space. In each subject, the surface-registered and smoothed cortical thickness measure was then used to construct the seed regressor.

Statistical Analyses
Analysis was performed using the SurfStat toolbox (Worsley et al. 2009) for Matlab (R2010a, The Mathworks, Natick, MA, USA).

Mapping of Structural Covariance Networks by Cortical Thickness Correlations
To map structural covariance networks involved in empathy in vivo, we correlated the cortical thickness of each seed (i.e., dAI and aMCC in left and right hemisphere) with the thickness across all surface points of the entire cortical mantle. These models were constructed by pairwise correlations of the data of all 94 participants. Following previously reported nomenclature (Lerch et al. 2006), the model fitted for the thickness T at a surface point i was

$$T_i = \beta_0 + \beta_1 T_{\text{seed}}$$

Assessment of Relationship Between Covariance Strength and Empathy State Ratings (EMP-SoVT)

We fitted linear models that included main effects of seed thickness, EMP-SoVT (i.e., the difference in mean empathy state ratings for high and low emotion videos), and the parametric interaction term between seed thickness and EMP-SoVT. The model fitted for the thickness T at a surface point i was

$$T_i = \beta_0 + \beta_1 T_{seed} + \beta_2 EMP_{SoVT} + \beta_3 (EMP_{SoVT} \times T_{seed}),$$

where × indicates an interaction between terms. While a positive interaction indicates a stronger structural correlation with EMP-SoVT, a negative interaction indicates a weaker link.

We also examined whether the interactions between structural covariance network strength and interindividual differences in EMP-SoVT were specific to empathy, or whether they could also be accounted for by negative affect ratings during the SoVT. We, thus, repeated the above analysis with NEG-SoVT (i.e., the difference in mean negative affect state ratings for high and low emotion videos) as an additional covariate in the statistical model. Moreover, using a post hoc analysis in findings of EMP-SoVT covariance modulation, we specifically assessed whether covariance strength was also modulated by NEG-SoVT.

To probe the robustness of our findings against diffuse interindividual variations in cortical thickness, the above analyses were repeated with additionally controlling for global mean thickness in the statistical model.

Assessment of Relationship Between Covariance Strength and Self-Reported Trait Empathic Concern (IRI-EC)

An analysis analogous to *"Assessment of Relationship Between Covariance Strength and Empathy State Ratings (EMP-SoVT)"* was carried out to assess the positive modulation of structural correlation strength by IRI-EC scores. This model included main effects of seed thickness, IRI-EC scores, as well as the parametric interaction term between seed thickness and IRI-EC scores. The model fitted for the thickness T at a surface point i was

$$T_i = \beta_0 + \beta_1 T_{seed} + \beta_2 IRI_{EC} + \beta_3 (IRI_{EC} \times T_{seed})$$

In regions of significant parametric interactions of seed covariance by the empathy ratings during SoVT (independently obtained from *b*), we assessed the relationship between seed covariance strength and IRI-EC scores.

Correction for Multiple Comparisons

As in previous work (Bernhardt et al. 2008; Bernhardt et al. 2010), findings from our surface-based covariance analysis were controlled using random field theory for nonisotropic images (Worsley et al. 1999). This framework strongly controlled the chance of "ever" reporting a familywise error (FWE) to be <0.05. To illustrate trends, surface maps are also shown at uncorrected threshold holds.

Results

Mapping of Empathy Networks Using Structural Covariance Analysis

Patterns of structural correlations of our seed region in left dAI encompassed large portions of lateral and medial PFC (i.e., ventromedial, ventrolateral, dorsolateral and dorsomedial PFC), cingulate (i.e., subgenual and dorsal anterior cingulate, midcingulate, and posterior cingulate), insular, medial, and lateral temporal, together with occipitotemporal, right temporoparietal, and precuneus regions in both hemispheres ($P < 0.001$, FWE) (Fig. 1).

Patterns of structural correlations from the seed in right dAI were similar to the patterns seen for the left dAI, but additionally encompassed bilateral temporopolar regions and posterior parietal midline regions ($P < 0.001$, FWE).

The seed in left aMCC was correlated with other cingulate subregions, ranging from subgenual anterior cingulate to posterior cingulate cortex ($P < 0.001$, FWE). Correlations extended to precuneus regions, as well as to a large portion of lateral PFC, right insular cortex ($P < 0.001$, FWE), and lateral temporal regions ($P < 0.03$, FWE).

Patterns of right aMCC correlations resembled those of left aMCC, but additionally encompassed extensive and bilateral lateral temporal and insular regions ($P < 0.05$, FWE).

### Relationship Between Structural Covariance and EMP-SoVT

We studied the parametric interaction between seed covariance strength and interindividual differences in empathy state ratings during the SoVT (Fig. 2). This analysis aimed to assess the relationship between structural covariance network configurations and empathic state responses. Please see the Table 1 for a detailed overview of the empathy and affect state ratings during the SoVT, as well as our recent functional work (Klimecki et al. 2012). EMP-SoVT ratings were significantly correlated with state negative affect rating differences (NEG-SoVT, $r = 0.51$, $P < 0.01$, Bonferroni-corrected), but not with state positive affect rating differences (POS-SoVT, $r = 0.03$, $P > 0.5$).

Structural correlations from our seed in left dAI to target regions in left ventrolateral and anterior PFC were positively modulated by EMP-SoVT ratings ($P < 0.05$, FWE, Fig. 2). This indicated that people with higher EMP-SoVT ratings showed a stronger structural covariance between left dAI and these regions relative to those with lower EMP-SoVT ratings. Considering covariance patterns of the right dAI seed, similar, yet more extended and bilateral effects were observed: EMP-SoVT ratings positively interacted with the covariance strength of the dAI seed to target regions in bilateral anterior and ventrolateral PFC (left: $P < 0.001$, FWE; right: $P < 0.03$, FWE). In the left hemisphere, this cluster additionally included medial PFC and anterior dorsolateral PFC regions. In the right hemisphere, we observed a separate cluster including mid- and posterior insular regions ($P < 0.02$, FWE). Contrary to our expectations, no interactions between aMCC correlations and EMP-SoVT were significant (FWE > 0.6).

Given that EMP-SoVT was significantly correlated to NEG-SoVT (see above), we carried out a series of additional analyses to assess the specificity of the above reported findings for empathy. Analyzing the modulation of dAI covariance strength by NEG-SoVT to each cluster of dAI covariance modulation by EMP-SoVT (see Fig. 2), we failed to observe any significant modulation of dAI covariance strength by NEG-SoVT ($t < 1.4$, $P > 0.1$). Moreover, statistical model comparison in each cluster between the initial interaction model that assessed parametric modulation of dAI covariance strength by EMP-SoVT and more complex models that additionally included NEG-SoVT as a nuisance regressor failed to indicate that differences in state negative affect ratings ($F < 1.24$, $P > 0.2$) significantly explain additional variance for the dAI covariance modulation by EMP-SoVT to prefrontal and mid-posterior insular regions. These additional analyses suggest that the observed results were indeed
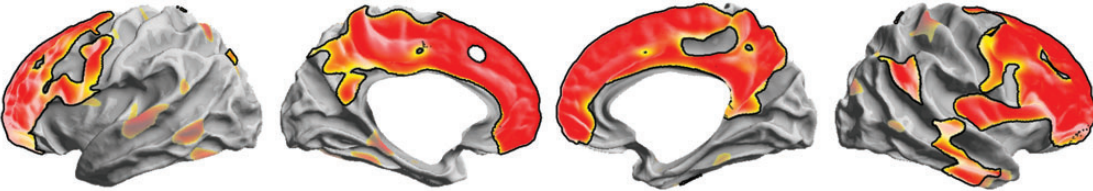
Structural covariance networks

A Left AI
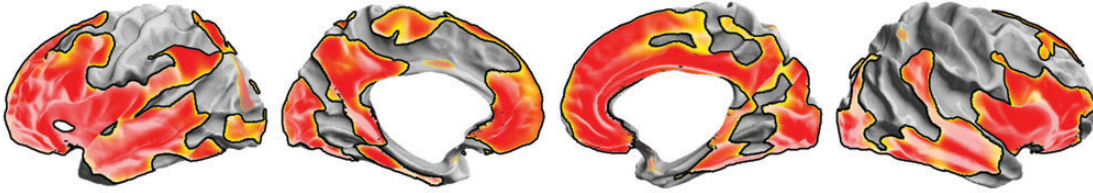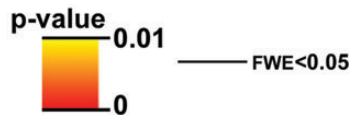

B Right AI
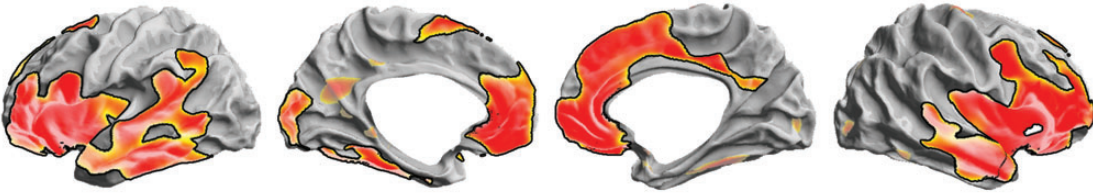
C Left aMCC

D Right aMCC

left   right

p-value
0.01
——— FWE<0.05
0

Figure 1. Structural covariance analysis seeding from (A) left dorsal anterior insula (dAI), (B) right dAI, (C) left aMCC, and (D) right aMCC in 94 females. Seed regions were identified based on a previous meta-analysis of 32 functional MRI studies on empathy for pain (Lamm et al. 2011). Significant correlations between cortical thickness in the seed and a cortical target region across the sample were interpreted as structural networks. To correct for multiple comparisons, significances have been thresholded at $P < 0.05$, FWE using random field theory for nonisotropic images (cluster threshold = 2.37, extent threshold = 1.75, black outlines). To illustrate trends, findings at $P < 0.01$, uncorrected (no black outlines, semitransparent) are also shown.

specific to empathic responses and could not be accounted for by negative affect alone.

Given that our seed regions displayed marked and widespread structural covariance with other brain networks (see Fig. 1), we furthermore tested for the robustness of these covariance modulations by EMP-SoVT when controlling for global mean thickness in the same statistical model. Specifically, a post-hoc analysis revealed robust modulations of dAI covariance by EMP-SoVT in all aforementioned clusters even when the model additionally included global mean thickness as a control covariate ($t > 3.0$, see Supplementary Figure).

Relationship Between Covariance Strength and Trait Empathic Concern (IRI-EC)

To determine whether there was a similar positive modulation of structural covariance networks by self-report trait questionnaire measures of empathic concern, we assessed the interaction between covariance strength and IRI-EC (Fig. 3). Please see Table 1 for additional details on the IRI scores. IRI-EC was positively correlated with EMP-SoVT ($r = 0.23$, $P < 0.026$), but not with NEG-SoVT ($r = 0.16$, $P > 0.1$). There was, however, no difference in the strength of correlations ($z < 0.6$, $P > 0.3$).
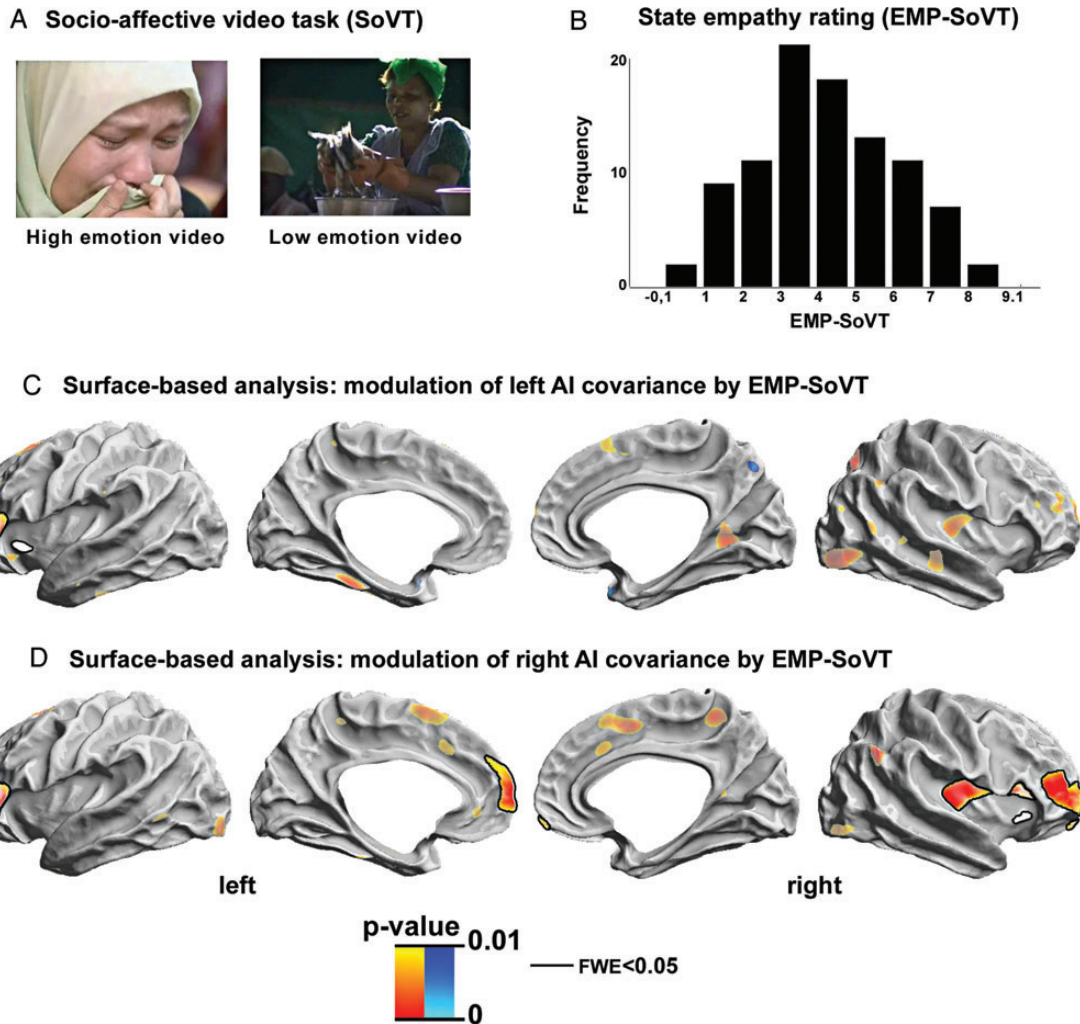
Figure 2. Interactions between the degree of structural covariance of dAI seed regions and the empathy state ratings during the socio-affective video task, SoVT (Klimecki et al. 2012). (A) Illustration of the SoVT stimuli: Participants viewed 12 high emotion videos (people in distress) and 12 low emotion videos (people in everyday situations), with each video lasting from 10 to 18 s. After each video, participants rated their subjective experience of empathy, positive affect, and negative affect. Every mini-block of 3 high or low emotion videos was followed by a fixation cross, displayed for 10 s. (B) Histogram of average EMP-SoVT ratings, which is the difference between empathy ratings during high emotion videos and low emotion videos. (C and D) Positive interactions between the degree of structural covariance to left and right dAI and EMP-SoVT ratings, indicating higher structural coupling in subjects with higher EMP-SoVT relative to those with lower EMP-SoVT. Please, see Figure 1 for details on the statistical thresholding.

Table 1

Range, mean ± SD, and median of state and trait measures of empathic and affective responding in 94 females

|	Min	Max	Mean ± SD	Median
EMP-SoVT	−0.08	9.00	4.29 ± 1.84	4.16
High emotion videos	0.67	9.75	6.78 ± 1.93	7.08
Low emotion videos	0.00	5.83	2.49 ± 1.67	2.25
POS-SoVT	−6.25	−0.50	−2.57 ± 1.32	−2.42
High emotion videos	0.00	2.83	0.59 ± 0.68	0.33
Low emotion videos	0.67	6.75	3.16 ± 1.52	2.83
NEG-SoVT	−2.00	8.50	4.78 ± 1.67	4.75
High emotion videos	0.83	9.67	6.04 ± 1.75	5.96
Low emotion videos	0.00	4.00	1.26 ± 0.92	1.00
IRI-EC	12	28	20.42 ± 3.58	20

State ratings consisted of empathy/positive affect/negative affect ratings in response to high and low emotion videos during the Socio-affective Video Task (SoVT). For the regression analysis, the difference between high and low emotion videos were calculated for each individual (EMP-SoVT/POS-SoVT/NEG-SoVT). The empathic concern subscale of the interpersonal reactivity index (IRI-EC), a self-report questionnaire, was used to measure trait empathic concern.

Analyzing the interaction between dAI and aMCC covariance and IRI-EC scores on a whole brain level, we did not observe any significant positive modulation (FWE > 0.14). In a next step, we carried out region-of-interest analyses of positive IRI-EC modulations on the covariance between dAI and significant clusters from Figure 2 (Note that these clusters were generated independently by testing on the interaction between dAI covariance and EMP-SoVT). This analysis aimed at investigating convergences between the covariance modulations based on task- and questionnaire-based empathy measures. Using these regions of interest, we observed that the covariance between the right dAI to right ventrolateral and anterior PFC was positively modulated by IRI-EC ($t = 2.1$, $P < 0.04$, uncorrected, Fig. 3). These findings indicate a stronger covariance in subjects with high IRI-EC relative to those with low total IRI-EC. No effects were found in the other clusters whose covariance to right and left dAI was modulated by interindividual differences in empathy ratings ($|t| < 1.01$, $P > 0.1$, Fig. 3).

Virtually identical patterns of findings were observed when assessing covariance modulations by the overall IRI scale instead of IRI-EC. Indeed, overall IRI also selectively modulated

ROI analysis: covariance modulation by self-reported empathic concern (IRI-EC)
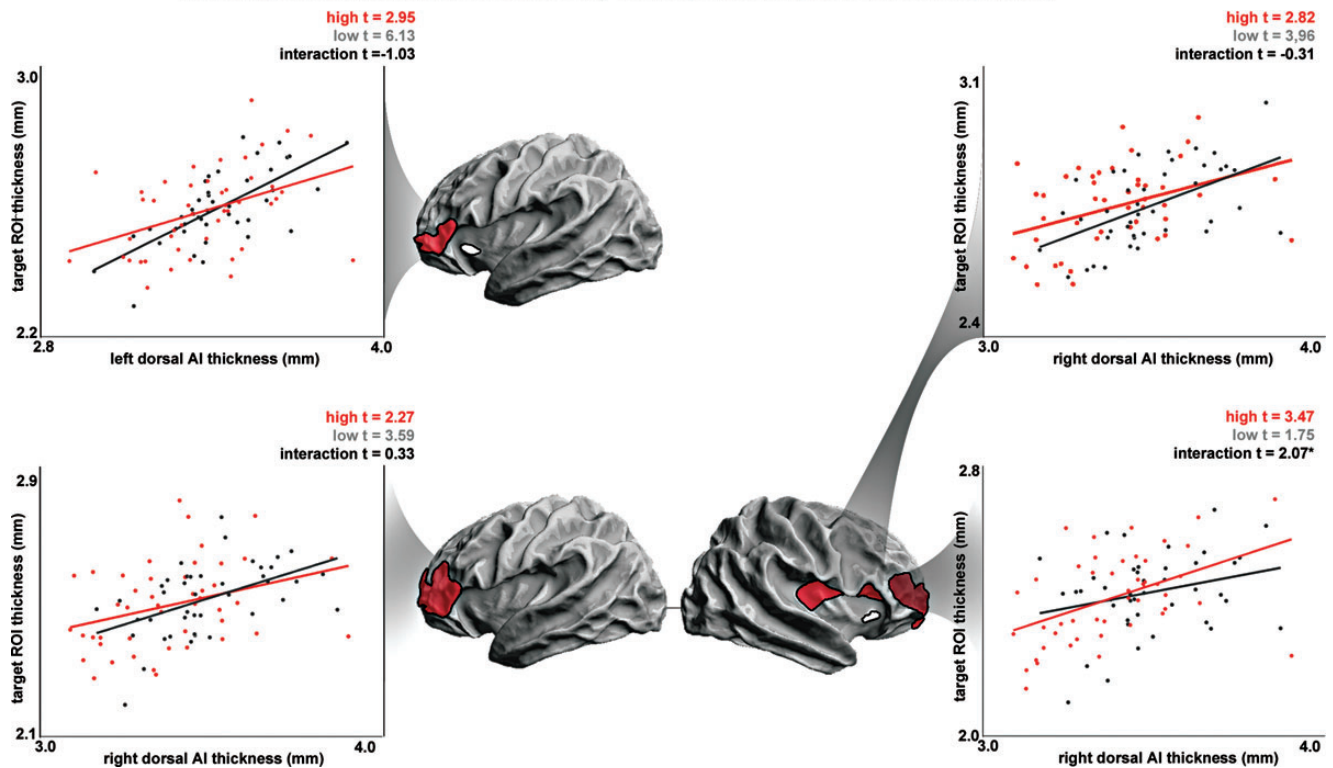
Figure 3. Interactions between the degree of structural covariance of right dAI and individual differences in self-reported trait empathy using the Interpersonal Reactivity Index, IRI (Davis 1983). Target regions were independently chosen based on the whole-brain findings of covariance modulation by EMP-SoVT (Fig. 2). To illustrate the parametric interaction effect, regression fits are also shown after the group has been split into 2 groups with $n = 47$ subjects according to the median of the IRI-EC scale (i.e., IRI-EC = 20).

covariance strength between right dAI and right ventrolateral and anterior PFC ($t = 2.44$, $P < 0.02$, uncorrected).

We also assessed the triple interaction between dAI covariance, IRI-EC, and EMP-SoVT to test whether EMP-SoVT modulates dAI networks significantly better than IRI-EC. A conjunction analysis of findings from Figure 2 and findings of a triple interaction (both at FWE < 0.05) revealed a stronger modulation of left dAI covariance networks by EMP-SoVT than IRI-EC to left ventrolateral prefrontal regions.

Lack of Simple Relationship Between Thickness and Differences in Empathic Responding

Analyzing simple correlations between individual differences in empathic responding and thickness of our seed regions did not indicate any correlations between brain structure and interindividual differences in EMP-SoVT ($t < 1.64$, $P > 0.1$, uncorrected) nor IRI-EC ($t < 1.60$ $P > 0.1$, uncorrected). In our data, simple regression analysis, thus, did not show a sufficient sensitivity to detect structural markers of individual differences in empathic responding within the dAI and aMCC themselves.

Discussion

Based on covariance analysis of MRI-based cortical thickness measurements, we assessed the relationship between structural brain networks of dAI and aMCC and individual differences in empathic responding in 94 females. We observed widespread structural correlations of dAI and aMCC to multiple frontolimbic, temporal, and midline regions. This finding extends previous anatomical and functional connectivity results to the domain of inter-regional structural covariance patterns in the brain, suggesting that these regions reflect highly integrated hubs in the brain (Mesulam and Mufson 1982; Margulies et al. 2007; Deen et al. 2011). Importantly, structural covariance of bilateral dAI but not aMCC to frontolimbic network components was related to individual differences in average empathy state ratings during a video-based task depicting people in distress (Klimecki et al. 2012) and, to a lesser extent, also to empathic concern trait scores from the IRI self-report questionnaire (Davis 1983). These results could not be accounted for by individual differences observed in negative affect ratings when subjects were exposed to distressing situations, suggesting that the observed modulation in structural covariance was specific to individual differences in empathic sensitivity of the subjects. Modulations were robust even after statistically correcting for global mean thickness in the same statistical model, indicating the observed network modulation was specific to these frontolimbic networks, and not driven by a general and diffuse global effect. Our findings, thus, provide first evidence for a contribution of specific structural frontolimbic brain networks to individual differences in social processing above and beyond individual differences in general affective reactivity.

MRI covariance analysis has been proposed to map structural networks in vivo that reflect the manifestations of persistent functional-trophic cross-talk between different brain

networks, together with common genetic, developmental, and pathological influences (Lerch et al. 2006; Bullmore and Sporns 2009; Zielinski et al. 2010; Bernhardt et al. 2011; Raznahan et al. 2011). In the present study, structural covariance networks centered on dAI and aMCC were widespread and resembled findings from tract tracing in nonhuman primates, showing insula interconnections, especially of its anterior parts, with multiple prefronal, temporolimbic, and medial and lateral parietal regions (Mesulam and Mufson 1982; Mufson and Mesulam 1982; Amaral and Price 1984; Morecraft et al. 1992; Augustine 1996), together with similarly extensive interconnections of aMCC (Pandya et al. 1981; Vogt and Pandya 1987). Moreover, covariance networks of dAI and aMCC in our participants resembled findings from previous resting-state functional connectivity analyses that studied connectional fingerprints of regions proximal to our seeds (Margulies et al. 2007; Cauda et al. 2011; Hohmann et al. 2012). These findings, thus, lend evidence from structural covariance analysis to the notion that the dAI and aMCC are important hub regions within multiple, distributed corticocortical networks, a role suitable to integrate several different functional processes hypothesized to interact in social cognition (Devinsky et al. 1995; Craig 2009; Singer et al. 2009; Kurth et al. 2010; Shackman et al. 2011; Bernhardt and Singer 2012; Chang et al. 2012; Hohmann et al. 2012).

Our main goal was to relate structural covariance networks centered on dAI and aMCC to individual differences in empathic responding. In our previous functional MRI study using the same dynamic Socio-affective Video Task, we showed that activations in dAI and aMCC correlated with empathy ratings for high emotion videos (Klimecki et al. 2012). The current study extended these findings by showing that inter-regional covariance patterns of brain structures are modulated by individual differences in empathy. This was accomplished by showing parametric modulatory effects of state and trait variables on group-level covariance networks. In fact, we were able to show that individual differences in EMP-SoVT parametrically related to the degree of structural covariance between bilateral AI, but not aMCC, and network components in frontolimbic cortices. Patterns of findings were similar when controlling for overall mean thickness in the same statistical model, suggesting that the modulation of dAI covariance was relatively specific to the observed frontolimbic network components and not driven by a general and diffuse modulation of dorsal AI covariance to all brain regions.

Importantly, these findings were specific to empathy, and could not be accounted for by differences in reported negative affect when exposed to the very same distressing scenes, as shown by our additional analysis that controlled for NEG-SoVT in the same statistical model. In other words, our current data revealed a differentiation at the level of inter-regional structural covariance networks between individual differences in empathy and more general negative affectivity; such a difference was not visible when focusing on functions of the dAI and aMCC and their relation to empathic and negative affective subjective experience alone (Klimecki et al. 2012). This differentiation at the level of inter-regional covariance is noteworthy because we did not observe any simple correlations in our seed regions with interindividual differences in empathy. Our findings, thus, did not confirm a recent voxel-based morphometric analysis that has shown correlations between IRI and gray matter estimates (Banissy et al.

2012). These findings may have been driven by differences in study groups. Indeed, while Banissy et al. (2012) studied a mixed sample of males and females, the current study was limited to assessing females only. Alternatively, given that inference in voxel-based morphometry is based on a relatively complex measure that may be driven by differences in cortical thickness, but also cortical folding, and possibly sources of misregistration and partial voluming (Ashburner and Friston 2001; Bookstein 2001; Winkler et al. 2010), our cortical thickness analysis may have offered a somewhat different assessment of local brain structure. Ultimately, our findings suggest that inter-regional network analyses—even in the structural domain—open a new avenue to better understand and possibly dissociate neural signatures of closely related socio-affective processes.

Dorsal AI networks that showed a covariance modulation by EMP-SoVT encompassed subregions of ventrolateral PFC together with lateral and medial anterior PFC, as well as limbic mid- and posterior insular cortex. Modulations were more restricted and only observed ipsilaterally for left dAI and bilaterally and more extended for right dAI, particularly to medial PFC and posterior insular regions. Whether an increased structural covariance between 2 given regions indicates the direct strengthening of a "physical" interconnection is unclear. Nevertheless, covariance analysis might be a particularly suitable technique to detect structural manifestations of persistent functional and trophic cross-talk between different brain networks and their relationship to individual differences in empathy. Interestingly, previous functional studies have indeed shown an important role of the observed target regions in social cognition processes relevant for empathy, such as emotion and action observation (Rizzolatti et al. 2001; Caspers et al. 2010; Molenberghs et al. 2012), perspective taking (Amodio and Frith 2006; Van Overwalle 2009; Bzdok et al. 2012), and emotional awareness (Craig 2002, 2009). Indeed, ventrolateral PFC subregions, such as BA44 and BA45, together with more anterior BA47 and BA10 participate in the observation of emotional facial expressions (Carr et al. 2003; Wicker et al. 2003; Leslie et al. 2004; Hennenlotter et al. 2005; Jabbi et al. 2007). BA44, a region also thought to play an important role in action observation (Rizzolatti et al. 2001; Gazzola and Keysers 2009; Caspers et al. 2010; Molenberghs et al. 2012), is also preferentially activated in empathy paradigms that use pictorial stimuli depicting others in pain (Lamm et al. 2011). Notably, previous functional MRI connectivity analysis showed increased functional coupling between frontoinsular and BA45 subregions during the observation of emotional facial expressions, suggesting an influence of such frontoinsular network interactions on empathy (Jabbi and Keysers 2008). Functional connectivity data have also suggested a specific interaction during the observation of pain in others between dAI and more anterior dorsomedial PFC (Zaki et al. 2007), one of the most consistently activated region during cognitive perspective taking (Amodio and Frith 2006; Van Overwalle 2009; Bzdok et al. 2012). Last, our finding of increased covariance between right dAI and mid-posterior insula in high empathizers may support models that relate intra-insular connectivity to empathy, interoception, and subjective awareness (Craig 2002, 2009). Altogether, our findings of dAI covariance increases to the aforementioned regions suggests that high empathizers co-engage dAI and networks involved in social cognition more frequently,

possibly leading to common morphological growth patterns. Such a hypothesis may be directly tested in longitudinal studies, which assess changes in inter-regional structural covariance patterns in subjects undergoing socio-affective training, ideally over sufficiently long periods to detect structural plasticity. Moreover, these studies may reveal further insights on a possible inter-hemispheric difference of dAI networks (Craig 2009). Such studies will ideally employ more explicit behavioral testing on processes related to action observation, perspective taking, and awareness than the current work.

We additionally tested for a modulation of structural covariance by IRI-EC scores. While we failed to observe whole brain findings, post-hoc analysis revealed IRI-EC modulations between dAI and independently generated regions of interest from the EMP-SoVT analysis. Indeed, this analysis revealed higher covariance between right dAI and anterior and ventrolateral PFC in subjects with higher self-reported trait empathic concern, although at a weaker level than state empathy. These results provide additional, questionnaire-based support that the structural integration of dAI to other networks relates to inter-individual differences in empathy.

Arguably, the lack of whole brain findings when using IRI-EC might also indicate that state empathy ratings within a computer-based task, such as EMP-SoVT, offer an increased sensitivity relative to self-report trait questionnaire measures, such as IRI. A triple interaction analysis between dAI covariance, IRI-EC, and EMP-SoVT directly confirmed this suggestion for particular AI networks, showing a more marked modulation of covariance between left dAI and left ventrolateral PFC by EMP-SoVT than by IRI-EC. A lower sensitivity of self-report questionnaire data may stem from an increased influence of factors related to self-image, social desirability, and 'cold' cognition effects. Conversely, experimental state ratings may more directly tap into immediate and 'hot' socio-affective processes and, thus, allow a more veridical assessment of empathy and its modulation. In fact, a previous meta-analysis of functional MRI studies also observed more robust modulations of dAI and aMCC activity during empathy for pain in others by state as opposed to trait scores (Lamm et al. 2011).

No noteworthy modulations of aMCC covariance strength by individual differences in empathic responding were observed. These findings support the notion that dAI, and its connectivity patterns, might play a different role in empathy than aMCC. A role of dAI in empathy may stem from the contribution of anterior insular segments to the generation of current and predictive feeling states, together with certainty computations that ultimately facilitate decision making in socio-affective contexts (Singer et al. 2009). A previous functional pattern analysis furthermore suggested that computations in dAI may more closely relate to prediction and sharing of affect, while aMCC computations rather reflect either nociceptive processing (Corradi-Dell'Acqua et al. 2011) or motor-related processes associated with pain (Morrison et al. 2007). Given the cytoarchitectonic, connectional, and functional heterogeneity of cingulate and insular cortex (Vogt et al. 2005; Margulies et al. 2007; Kurth et al. 2010; Deen et al. 2011; Shackman et al. 2011; Gallay et al. 2012), future studies are needed to provide a more comprehensive mapping of these subregions and their relationships to empathy and affect. In particular, a more detailed investigation of

differences between dAI and more ventral aspects of the anterior insula may be of interest, as this subregion is frequently involved in general emotional processing and robustly coactivated with the amygdala (Mutschler et al. 2009; Kurth et al. 2010).

Our study adds structural MRI evidence to the understanding of individual differences in empathic responding, building on previous functional MRI literature. Indeed, several functional studies have shown a relationship between empathy-related brain responses, particularly of AI, and individual differences of empathy as assessed via trait-questionnaires such as the IRI, trial-by-trial affective ratings during the functional task, or subjective state measures of empathic concern assessed just after scanning (Singer et al. 2004; Singer et al. 2006; Hein et al. 2010; Lamm et al. 2011). On the other hand, we did not address the modulation of empathy by contextual factors, such as perceived fairness (Singer et al. 2006), appraisal (Lamm, Batson et al. 2007; Lamm, Nusbaum et al. 2007; Hein and Singer 2008; Engen and Singer 2012), or perceived group membership (Hein et al. 2010). In this light, future work is needed that brings together structural brain network data, individual differences, and well as the flexibility of empathic responding in different contexts.

In summary, our findings show a contribution of inter-regional structural covariance networks in frontolimbic cortical regions to females' individual differences in empathic responding above and beyond negative affect. Thus, women with a high propensity to react empathically to the distress of others may have a stronger structural integration of dAI to other frontolimbic networks known to participate in social cognition. Ultimately, our structural covariance findings open a new methodological window to assess the complexity of brain networks underlying emotional and social processes.

References

Amaral DG, Price JL. 1984. Amygdalo-cortical projections in the monkey (Macaca fascicularis). J Comp Neurol. 230:465–496.

Amodio DM, Frith CD. 2006. Meeting of minds: the medial frontal cortex and social cognition. Nat Rev Neurosci. 7:268–277.

Ashburner J, Friston KJ. 2001. Why voxel-based morphometry should be used. Neuroimage. 14:1238–1243.

Augustine JR. 1996. Circuitry and functional aspects of the insular lobe in primates including humans. Brain Res Brain Res Rev. 22:229–244.

Bagby RM, Parker JD, Taylor GJ. 1994. The twenty-item Toronto Alexithymia Scale—I. Item selection and cross-validation of the factor structure. J Psychosom Res. 38:23–32.

Banissy MJ, Kanai R, Walsh V, Rees G. 2012. Inter-individual differences in empathy are reflected in human brain structure. Neuroimage. 62:2034–2039.

Baron-Cohen S, Wheelwright S. 2004. The empathy quotient: an investigation of adults with Asperger syndrome or high functioning autism, and normal sex differences. J Autism Dev Disord. 34:163–175.

Beck AT, Steer RA, Ball R, Ranieri W. 1996. Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients. J Pers Assess. 67:588–597.

Bernhardt BC, Bernasconi N, Concha L, Bernasconi A. 2010. Cortical thickness analysis in temporal lobe epilepsy: reproducibility and relation to outcome. Neurology. 74:1776–1784.

Bernhardt BC, Chen Z, He Y, Evans AC, Bernasconi N. 2011. Graph-theoretical analysis reveals disrupted small-world organization of cortical thickness correlation networks in temporal lobe epilepsy. Cereb Cortex. 21:2147–2157.

Bernhardt BC, Singer T. 2012. The neural basis of empathy. Annu Rev Neurosci. 35:1–23.

Bernhardt BC, Worsley KJ, Besson P, Concha L, Lerch JP, Evans AC, Bernasconi N. 2008. Mapping limbic network organization in temporal lobe epilepsy using morphometric correlations: insights on the relation between mesiotemporal connectivity and cortical atrophy. Neuroimage. 42:515–524.

Bookstein FL. 2001. 'Voxel-based morphometry' should not be used with imperfectly registered images. Neuroimage. 14:1454–1462.

Bullmore E, Sporns O. 2009. Complex brain networks: graph theoretical analysis of structural and functional systems. Nat Rev Neurosci. 10:186–198.

Bzdok D, Schilbach L, Vogeley K, Schneider K, Laird AR, Langner R, Eickhoff SB. 2012. Parsing the neural correlates of moral cognition: ALE meta-analysis on morality, theory of mind, and empathy. Brain Struct Funct. 217:783–796.

Carr L, Iacoboni M, Dubeau MC, Mazziotta JC, Lenzi GL. 2003. Neural mechanisms of empathy in humans: a relay from neural systems for imitation to limbic areas. Proc Natl Acad Sci USA. 100:5497–5502.

Caspers S, Zilles K, Laird AR, Eickhoff SB. 2010. ALE meta-analysis of action observation and imitation in the human brain. Neuroimage. 50:1148–1167.

Cauda F, D'Agata F, Sacco K, Duca S, Geminiani G, Vercelli A. 2011. Functional connectivity of the insula in the resting brain. Neuroimage. 55:8–23.

Chang LJ, Yarkoni T, Khaw MW, Sanfey AG. 2012. Decoding the role of the insula in human cognition: functional parcellation and large-scale reverse inference. Cereb Cortex. 23:739–749.

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.

Craig AD. 2002. How do you feel? Interoception: the sense of the physiological condition of the body. Nat Rev Neurosci. 3:655–666.

Craig AD. 2009. How do you feel—now? The anterior insula and human awareness. Nat Rev Neurosci. 10:59–70.

Dale AM, Fischl B, Sereno MI. 1999. Cortical surface-based analysis. I. Segmentation and surface reconstruction. Neuroimage. 9:179–194.

Davis MH. 1983. Measuring individual differences in empathy: evidence for a multidimensional approach. J Pers Soc Psychol. 44:113–126.

Deen B, Pitskel NB, Pelphrey KA. 2011. Three systems of insular functional connectivity identified with cluster analysis. Cereb Cortex. 21:1498–1506.

de Vignemont F, Singer T. 2006. The empathic brain: how, when and why? Trends Cogn Sci. 10:435–441.

Devinsky O, Morrell MJ, Vogt BA. 1995. Contributions of anterior cingulate cortex to behaviour. Brain. 118(Pt 1):279–306.

Engen HG, Singer T. 2012. Empathy circuits. Curr Opin Neurobiol. (in press).

Fan Y, Duncan NW, de Greck M, Northoff G. 2011. Is there a core neural network in empathy? An fMRI based quantitative meta-analysis. Neurosci Biobehav Rev. 35:903–911.

Fischl B, Sereno MI, Dale AM. 1999. Cortical surface-based analysis. II: Inflation, flattening, and a surface-based coordinate system. Neuroimage. 9:195–207.

Frith CD, Frith U. 2006. The neural basis of mentalizing. Neuron. 50:531–534.

Gallay DS, Gallay MN, Jeanmonod D, Rouiller EM, Morel A. 2012. The insula of Reil revisited: multiarchitectonic organization in macaque monkeys. Cereb Cortex. 22:175–190.

Gazzola V, Keysers C. 2009. The observation and execution of actions share motor and somatosensory voxels in all tested subjects: single-subject analyses of unsmoothed fMRI data. Cereb Cortex. 19:1239–1255.

Han X, Jovicich J, Salat D, van der Kouwe A, Quinn B, Czanner S, Busa E, Pacheco J, Albert M, Killiany R et al. 2006. Reliability of MRI-derived measurements of human cerebral cortical thickness: the effects of field strength, scanner upgrade and manufacturer. Neuroimage. 32:180–194.

Hein G, Silani G, Preuschoff K, Batson CD, Singer T. 2010. Neural responses to ingroup and outgroup members' suffering predict individual differences in costly helping. Neuron. 68:149–160.

Hein G, Singer T. 2008. I feel how you feel but not always: the empathic brain and its modulation. Curr Opin Neurobiol. 18:153–158.

Hennenlotter A, Schroeder U, Erhard P, Castrop F, Haslinger B, Stoecker D, Lange KW, Ceballos-Baumann AO. 2005. A common neural basis for receptive and expressive communication of pleasant facial affect. Neuroimage. 26:581–591.

Hohmann CF, Beard NA, Kari-Kari P, Jarvis N, Simmons Q. 2012. Effects of brief stress exposure during early postnatal development in Balb/CByJ mice: II. Altered cortical morphology. Dev Psychobiol. 54:723–735.

Jabbi M, Bastiaansen J, Keysers C. 2008. A common anterior insula representation of disgust observation, experience and imagination shows divergent functional connectivity pathways. PLoS One. 3: e2939.

Jabbi M, Keysers C. 2008. Inferior frontal gyrus activity triggers anterior insula response to emotional facial expressions. Emotion. 8:775–780.

Jabbi M, Swart M, Keysers C. 2007. Empathy for positive and negative emotions in the gustatory cortex. Neuroimage. 34:1744–1753.

Klimecki O, Leiberg S, Lamm C, Singer T. 2012. Functional neural plasticity and associated changes in positive affect after compassion training. Cereb Cortex. (in press).

Kuperberg GR, Broome MR, McGuire PK, David AS, Eddy M, Ozawa F, Goff D, West WC, Williams SC, van der Kouwe AJ et al. 2003. Regionally localized thinning of the cerebral cortex in schizophrenia. Arch Gen Psychiatry. 60:878–888.

Kurth F, Zilles K, Fox PT, Laird AR, Eickhoff SB. 2010. A link between the systems: functional differentiation and integration within the human insula revealed by meta-analysis. Brain Struct Funct. 214:519–534.

Lamm C, Batson CD, 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.

Lamm C, Nusbaum HC, Meltzoff AN, Decety J. 2007. What are you feeling? Using functional magnetic resonance imaging to assess

the modulation of sensory and affective responses during empathy for pain. PLoS One. 2:e1292.

Lerch JP, Evans AC. 2005. Cortical thickness analysis examined through power analysis and a population simulation. Neuroimage. 24:163–173.

Lerch JP, Worsley K, Shaw WP, Greenstein DK, Lenroot RK, Giedd J, Evans AC. 2006. Mapping anatomical correlations across cerebral cortex (MACACC) using cortical thickness from MRI. Neuroimage. 31:993–1003.

Leslie KR, Johnson-Frey SH, Grafton ST. 2004. Functional imaging of face and hand imitation: towards a motor theory of empathy. Neuroimage. 21:601–607.

Margulies DS, Kelly AM, Uddin LQ, Biswal BB, Castellanos FX, Milham MP. 2007. Mapping the functional connectivity of anterior cingulate cortex. Neuroimage. 37:579–588.

Mesulam MM, Mufson EJ. 1982. Insula of the old world monkey. III: efferent cortical output and comments on function. J Comp Neurol. 212:38–52.

Molenberghs P, Cunnington R, Mattingley JB. 2012. Brain regions with mirror properties: a meta-analysis of 125 human fMRI studies. Neurosci Biobehav Rev. 36:341–349.

Morecraft RJ, Geula C, Mesulam MM. 1992. Cytoarchitecture and neural afferents of orbitofrontal cortex in the brain of the monkey. J Comp Neurol. 323:341–358.

Morrison I, Peelen MV, Downing PE. 2007. The sight of others' pain modulates motor processing in human cingulate cortex. Cereb Cortex. 17:2214–2222.

Mufson EJ, Mesulam MM. 1982. Insula of the old world monkey. II: Afferent cortical input and comments on the claustrum. J Comp Neurol. 212:23–37.

Mutschler I, Wieckhorst B, Kowalevski S, Derix J, Wentlandt J, Schulze-Bonhage A, Ball T. 2009. Functional organization of the human anterior insular cortex. Neurosci Lett. 457:66–70.

Pandya DN, Van Hoesen GW, Mesulam MM. 1981. Efferent connections of the cingulate gyrus in the rhesus monkey. Exp Brain Res. 42:319–330.

Raznahan A, Lerch JP, Lee N, Greenstein D, Wallace GL, Stockman M, Clasen L, Shaw PW, Giedd JN. 2011. Patterns of coordinated anatomical change in human cortical development: a longitudinal neuroimaging study of maturational coupling. Neuron. 72:873–884.

Rizzolatti G, Fogassi L, Gallese V. 2001. Neurophysiological mechanisms underlying the understanding and imitation of action. Nat Rev Neurosci. 2:661–670.

Rosas HD, Liu AK, Hersch S, Glessner M, Ferrante RJ, Salat DH, van der Kouwe A, Jenkins BG, Dale AM, Fischl B. 2002. Regional and progressive thinning of the cortical ribbon in Huntington's disease. Neurology. 58:695–701.

Saxe R, Kanwisher N. 2003. People thinking about thinking people. The role of the temporo-parietal junction in 'theory of mind'. Neuroimage. 19:1835–1842.

Seeley WW, Crawford RK, Zhou J, Miller BL, Greicius MD. 2009. Neurodegenerative diseases target large-scale human brain networks. Neuron. 62:42–52.

Shackman AJ, Salomons TV, Slagter HA, Fox AS, Winter JJ, Davidson RJ. 2011. The integration of negative affect, pain and cognitive control in the cingulate cortex. Nat Rev Neurosci. 12:154–167.

Singer T. 2006. The neuronal basis and ontogeny of empathy and mind reading: review of literature and implications for future research. Neurosci Biobehav Rev. 30:855–863.

Singer T, Critchley HD, Preuschoff K. 2009. A common role of insula in feelings, empathy and uncertainty. Trends Cogn Sci. 13:334–340.

Singer T, Lamm C. 2009. The social neuroscience of empathy. Ann N Y Acad Sci. 1156:81–96.

Singer T, Seymour B, O'Doherty J, Kaube H, Dolan RJ, Frith CD. 2004. Empathy for pain involves the affective but not sensory components of pain. Science. 303:1157–1162.

Singer T, Seymour B, O'Doherty JP, Stephan KE, Dolan RJ, Frith CD. 2006. Empathic neural responses are modulated by the perceived fairness of others. Nature. 439:466–469.

Van Overwalle F. 2009. Social cognition and the brain: a meta-analysis. Hum Brain Mapp. 30:829–858.

Vogt BA, Pandya DN. 1987. Cingulate cortex of the rhesus monkey: II. cortical afferents. J Comp Neurol. 262:271–289.

Vogt BA, Vogt L, Farber NB, Bush G. 2005. Architecture and neurocytology of monkey cingulate gyrus. J Comp Neurol. 485:218–239.

Wicker B, Keysers C, Plailly J, Royet JP, Gallese V, Rizzolatti G. 2003. Both of us disgusted in My insula: the common neural basis of seeing and feeling disgust. Neuron. 40:655–664.

Wittchen H, Zaudig M, Fydrich T. 1997. SKID Strukturiertes Klinisches Interview für DSM-IV Achse I und II Handanweisung. Göttingen: Hogrefe.

Winkler AM, Kochunov P, Blangero J, Almasy L, Zilles K, Fox PT, Duggirala R, Glahn DC. 2010. Cortical thickness or grey matter volume? The importance of selecting the phenotype for imaging genetics studies. Neuroimage. 53:1135–1146.

Worsley KJ, Andermann M, Koulis T, MacDonald D, Evans AC. 1999. Detecting changes in nonisotropic images. Hum Brain Mapp. 8:98–101.

Worsley KJ, Taylor JE, Carbonell F, Chung MK, Duerden E, Bernhardt BC, Lyttelton O, Boucher M, Evans AC. 2009. SurfStat: A Matlab toolbox for the statistical analysis of univariate and multivariate surface and volumetric data using linear mixed effects models and random field theory. NeuroImage. 47 (Suppl 1):S102.

Zaki J, Ochsner K. 2012. The neuroscience of empathy: progress, pitfalls, and promise. Nat Neurosci. 15:675–680.

Zaki J, Ochsner KN, Hanelin J, Wager TD, Mackey SC. 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.

Zielinski BA, Gennatas ED, Zhou J, Seeley WW. 2010. Network-level structural covariance in the developing brain. Proc Natl Acad Sci USA. 107:18191–18196.