

ORIGINAL ARTICLE

Socio-Cognitive Phenotypes Differentially Modulate Large-Scale Structural Covariance Networks

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Abstract

Functional neuroimaging studies have suggested the existence of 2 largely distinct social cognition networks, one for theory of mind (taking others' cognitive perspective) and another for empathy (sharing others' affective states). To address whether these networks can also be dissociated at the level of brain structure, we combined behavioral phenotyping across multiple socio-cognitive tasks with 3-Tesla MRI cortical thickness and structural covariance analysis in 270 healthy adults, recruited across 2 sites. Regional thickness mapping only provided partial support for divergent substrates, highlighting that individual differences in empathy relate to left insular-opercular thickness while no correlation between thickness and mentalizing scores was found. Conversely, structural covariance analysis showed clearly divergent network modulations by socio-cognitive and -affective phenotypes. Specifically, individual differences in theory of mind related to structural integration between temporo-parietal and dorsomedial prefrontal regions while empathy modulated the strength of dorsal anterior insula networks. Findings were robust across both recruitment sites, suggesting generalizability. At the level of structural network embedding, our study provides a double dissociation between empathy and mentalizing. Moreover, our findings suggest that structural substrates of higher-order social cognition are reflected rather in interregional networks than in the the local anatomical markup of specific regions per se.

Key words: connectivity, connectome, empathy, social brain, theory of mind

Introduction

Social cognition refers to our ability to understand each other and encompasses capacities such as empathy, the ability to share affective states of others (Singer et al. 2004; Bernhardt and Singer 2012), and theory of mind (ToM; also referred to as mentalizing), the ability to attribute mental states to others and to understand that they can differ from our own (Premack and Woodruff 1978; Frith and Frith 2003, 2006).

On a conceptual level, it is possible to discriminate between both forms of social cognition. We have previously (de Vignemont and Singer 2006) defined empathy if: 1) one is in an affective state, 2) this state is isomorphic to another's affective state, 3) this

state is elicited by the observation (or imagination) of another's affective state, 4) one knows that the other is the source of its own affective state. Empathy can, thus, be understood as the implicit sharing of subjective affect. In contrast, ToM/mentalizing is defined as inferring beliefs and intentions from another's mind (Frith and Frith 2003). Crucially, while one can discriminate between ToM on cognition and ToM on emotion (Shamay-Tsoory et al. 2005; Kalbe et al. 2010; Walter 2012), ToM does not necessarily have a "qualia," that is a feeling attached to it. On the other hand, empathy requires "sharing a feeling," that is experiencing how something feels and not just knowing about a feeling (see de Vignemont and Singer 2006; Singer and Lamm 2009).

Research in psychiatric conditions has indicated selective impairments of either forms of social cognition, with psychopaths showing atypical empathy and relatively normal ToM (Blair et al. 1997; Richell et al. 2003; Blair 2005; Pfabigan et al. 2015), while selective impairments in ToM are considered a core symptom of specific subgroups with autism (Baron-Cohen et al. 1985; Adolphs et al. 2001; Silani et al. 2008; Bird et al. 2010). In healthy participants, functional neuroimaging studies have identified substrates supporting the existence of 2 distinct large-scale networks subserving either process (Singer 2006; Bernhardt and Singer 2012; Bzdok et al. 2012; Kanske et al. 2015). Recent meta-analyses focusing on empathic activations, elicited when witnessing others either undergoing pain or suffering emotionally, localized a core network including anterior insula (AI), inferior frontal gyrus (IFG), and anterior midcingulate cortex (aMCC) (Singer et al. 2004; Jackson et al. 2006; Singer 2006; Decety and Moriguchi 2007; Fan et al. 2011; Lamm et al. 2011). Conversely, processes related to mentalizing have been shown to engage a network encompassing dorsomedial prefrontal cortex (dmPFC), posterior temporo-parietal junction (TPJ), and superior temporal gyrus/sulcus (STG/STS) (Van Overwalle and Baetens 2009; Mar 2011; Bzdok et al. 2012; Schurz et al. 2014). In addition to these group-level findings, individual differences in behavior have been found to covary with functional activations. Brain responses in AI, for example, have been shown to scale both with trial-by-trial reports of state empathy and with individual differences in empathy trait (Singer et al. 2004; Lamm et al. 2011). A recent study introduced the EmpaToM, a video paradigm probing empathizing and mentalizing at the level of behavior and brain function (Kanske et al. 2015), and could confirm brain-behavior correlations not only for empathy but also for individual differences in ToM accuracy.

Despite increasing evidence for the existence of 2 independent functional networks supporting our capacities to empathize and mentalize, understanding of how individual differences in these capacities relate to the anatomical markup of these networks is limited. Structural neuroimaging techniques, such as MRI-based cortical thickness analyses, provide a means to test whether morphological variations in selected regions predict individual differences in socio-cognitive capacities. Moreover, these measures may serve as a foundation of covariance analysis, a statistical framework that interprets interregional correlations in morphology as proxies for structural networks (Lerch and Evans 2005; Lerch et al. 2006; Alexander-Bloch et al. 2013; Evans 2013). In 94 women, we recently showed a link between covariance network embedding of dAI, but not of its thickness, and individual differences in empathic responding (Bernhardt, Klimecki, et al. 2014). These findings suggested that individual differences in socio-affective capacities are likely reflected in structural networks centered on specific regions, rather than in the structural markup of the regions per se. A network-level substrate of individual differences may reflect the necessity to combine multiple functions to come to successful socio-cognitive and -affective processing (Bernhardt and Singer 2012; Singer 2012; Stanley and Adolphs 2013). In humans, diffusion tractography (Thomas et al. 2008; Mars et al. 2012; Cerliani et al. 2012) and covariance analysis (Kelly et al. 2012; Alexander-Bloch et al. 2013; Bernhardt, Klimecki, et al. 2014; Clos et al. 2014; Valk et al. 2015) have furthermore provided consistent evidence that regions heavily involved in socio-affective and -cognitive processing, such as dAI and pTPJ, represent highly interconnected hubs with crucial importance for large-scale brain network function.

The current study assessed structural and network-level substrates of socio-cognitive phenotypes. In 270 healthy adults, we operationalized empathy and mentalizing as composite scores

across multiple tasks. The EmpaToM (Kanske et al. 2015) and Socio-affective Video tasks (Klimecki et al. 2013) were used to measure individual differences in empathy, while those for mentalizing were derived from the former paradigm and a visuo-spatial perspective-taking task (Samson et al. 2010). Individual difference measures were related to both cortical thickness and covariance strength derived from 3-Tesla MRI, to test for regional and network-level hypotheses. We expected that empathy capacity would covary with substrates in regions (or networks centered on regions) functionally relevant for socio-affective processes (dAI, aMCC, IFG), but not those playing a role in mentalizing (TPJ, dmPFC, STG/STS). Conversely, mentalizing was expected to modulate TPJ, dmPFC, and STG/STS, but not empathy-related networks.

Materials and Methods

Participants

As part of a large-scale longitudinal study (<http://resource-project.org>), we recruited 332 healthy adults (197 women, mean \pm SD = 40.7 \pm 9.2 years, 20–55 years) between April 2013 and August 2014 from the cities of Berlin and Leipzig. Samples from both cities were matched for age, sex, and various psychological markers (for details, see Singer et al. 2015).

Participant eligibility was determined through a multi-stage procedure that involved several screening and mental health questionnaires, together with a phone interview. Subsequently, a face-to-face mental health diagnostic interview with a trained clinical psychologist was scheduled. The interview included computer-assisted German versions of the Structured Clinical Interview for DSM-IV Axis-I disorders (SCID-I) (First et al. 1996), DIA-X (Wittchen and Pfister 1997), and SCID-II for Axis-II disorders (First et al. 1997; Wittchen et al. 1997). Participants were excluded if they fulfilled criteria for an Axis-I disorder within the past 2 years or if they at any point fulfilled the criteria for schizophrenia, psychotic disorders, bipolar disorder, substance dependency, or an Axis-II disorder. None of the participants was in psychiatric counseling or psychoactive drug therapy at the time of study or during the preceding 2 years. Given the relatively high lifetime prevalence of Axis-I disorders (Jacobi et al. 2004; Vazquez et al. 2011), a 2-year cutoff was chosen to avoid a non-representative, extremely homogenous sample, by excluding participants that were otherwise considered to be of normal psychosocial functioning at the time of the study. In total, ~26% of included participants had a previous diagnosis of AXIS-I disorder. No participant had a history of suffering from neurological disorders or head trauma. All included subjects underwent a diagnostic radiological evaluation to rule out the presence of mass lesions (e.g., tumors, vascular malformations).

All participants gave written and informed consent prior to participation. The study was approved by the Research Ethics Committees of the University of Leipzig and the Humboldt University in Berlin.

Measuring Individual Differences in Empathy and Mentalizing

Individual differences in empathy and mentalizing were operationalized through the calculation of composite scores across several tasks.

Empathy

A) Participants underwent the Socio-affective Video Task (SoVT; Klimecki et al. 2013), where they viewed 10–18-s long videos from

documentaries or newscasts. The total duration of the paradigm was ~12 min. Half of the videos depicted people in distress (high-emotion videos), the other half in everyday situations (low-emotion videos). After each video, participants rated on a Likert-scale (ranging from 0, none, to 10, intense) how much compassion, negative affect, and positive affect they felt. Empathy was computed as the difference between mean negative affect ratings for high and low emotion videos (affect-effect-SoVT). Other measures of the SoVT, such as positive affect and compassion, were beyond the scope of this paper.

B) An additional measure of empathy was derived from the EmpaToM, a naturalistic video paradigm (Kanske et al. 2015). Videos showed people recounting autobiographical episodes that were either emotionally negative (e.g., loss of a loved one) or neutral (e.g., commuting to work), followed by Likert-scale ratings of experienced affect and compassion. For the calculation of empathy scores in this task, we calculated the mean affect rating of high versus low emotional videos (affect-effect-EmpaToM).

Mentalizing

A) The EmpaToM (Kanske et al. 2015) task also allowed for a measurement of mentalizing capacity. Subsequent to questions on affect and compassion, questions about the mental states of people in the video assessed mentalizing in the main condition and were contrasted with questions on factual reasoning on the video's content (for examples, see [Supplementary Material S1](#)). Participants did not have to identify the emotional state of people recounting autobiographical episodes. Questions had only one correct answer, which had been validated during prestudy piloting (Kanske et al. 2015). Here, we calculated participants' error rates during the mentalizing questions after the video.

B) Participants furthermore underwent the visuo-spatial perspective-taking task introduced by Samson, Apperly, and colleagues (Samson et al. 2010), where they judged their own or someone else's visual perspective in situations where perspectives were the same (congruent conditions) or different (incongruent conditions). The degree to which participants' own perspective interfered with their judgment of another's perspective was assessed ("ego-centricity bias"). Reaction times and errors were combined to a composite score.

The empathy measures derived from both EmpaToM (Kanske et al. 2015) and SoVT (Klimecki et al. 2013) corresponded to the difference in negative affect measures during the high-emotion versus neutral condition. In the SoVT, positive and negative affect were assessed separately: one Likert-scale assessed negative-to-neutral and another positive-to-neutral. In the EmpaToM, a single scale from negative-to-neutral-to-positive assessed positive versus negative affect ratings. Despite this slight difference, negative affect measures from SoVT and EmpaToM correlated highly ($r = 0.36$, $P < 0.01$).

To obtain meaningful composites for mentalizing and empathy, principal component analysis with oblique rotations was performed on empathy (EmpaToM, SoVT) and mentalizing measures (EmpaToM, Samson Task). Following the Kaiser Criterion, we derived 2 independent factors (KMO = 0.51; Bartlett's Test of Sphericity = 43.6, $P < 0.001$; % variance explained = 62.2). The first factor (Empathy factor, explaining 34.3% of the variance) entailed the empathy ratings of the EmpaToM and the SoVT. The second factor (ToM factor, explaining 27.9% of the variance) entailed ToM performances in the EmpaToM and in the Samson Task. A previous validation study (Kanske et al. 2015) showed that negative-neutral ratings correlated between SoVT and EmpaToM across 2 samples ($N = 65$, $r = 0.37$; $N = 178$, $r = 0.36$, both $P < 0.01$). This was confirmed in the current cohort ($r = 0.34$, $P < 0.001$).

MRI Acquisition

Data were acquired on a 3-Tesla Siemens Verio (Siemens). Using a 32-channel head coil, we acquired structural images using a T1-weighted 3D-MPRAGE sequence (176 sagittal slices, repetition time [TR] = 2300 ms, echo time [TE] = 2.98 ms, inversion time [TI] = 900 ms, flip angle = 7°, field of view [FOV] = $240 \times 256 \text{ mm}^2$, matrix = 240×256 , voxel size = $1 \times 1 \times 1 \text{ mm}^3$). Task-based fMRI data acquisition and processing to localize empathy and ToM contrasts are described elsewhere (Kanske et al. 2015).

MRI-Based Cortical Thickness Measurements

We used FreeSurfer to generate cortical surface models and to measure cortical thickness from T1-weighted MRI (Version 5.1.0; <http://surfer.nmr.mgh.harvard.edu>). This pipeline has been validated against histological analysis (Rosas et al. 2002) and manual measurements (Kuperberg et al. 2003). Processing steps have been detailed elsewhere (Dale et al. 1999; Fischl et al. 1999; Han et al. 2006). Following surface extraction, sulcal and gyral features of an individual were warped to an average spherical representation, fsaverage5, which allows for accurate matching of thickness measurements across participants. Surfaces were visually inspected and inaccuracies manually corrected (S.L.V., B.C.B.). Thickness data were smoothed on tessellated surfaces using a 20-mm FWHM Gaussian kernel, which reduces measurement noise while preserving the capacity for anatomical localization, as it respects cortical topological features (Lerch and Evans 2005).

Region-of-Interest Definition

Regions-of-interest (ROIs) were defined by intersecting functional MRI activations during the EmpaToM in a subset of subjects (Kanske et al. 2015) and meta-analytical findings (Lamm et al. 2011; Mar 2011). For empathy-specific seeds, we intersected i) activations from the *emotional versus neutral* contrast of the EmpaToM and ii) a meta-analytical conjunction of cue- and picture-based empathy for pain studies (Lamm et al. 2011), resulting in 6 regions: left dAI, right dAI, left IFG, right IFG, right dlPFC, and left occipital cortex. Mentalizing-specific seeds were derived from intersecting i) activations of the *mentalizing versus factual reasoning* contrast of the EmpaToM (Kanske et al. 2015) with ii) a meta-analytical conjunction of story- and non-story-based studies (Mar 2011). This resulted in 3 seeds: left dmPFC, right dmPFC, and left TPJ. For consistency, we also included right TPJ and bilateral STG/STS using the largest corresponding cluster of Mar (2011). While not addressing all regions possibly involved in empathy and mentalizing, our approach assessed networks centered on 12 ROIs consistently participating in these processes (Supplementary Figure 1).

Statistical Analyses

Analysis was performed using SurfStat for Matlab (Worsley et al. 2009).

Behavioral Analysis

Pearson correlations assessed pairwise associations between ToM and empathy constructs.

Regional Substrates: Cortical Thickness Mapping

A linear model at each cortical surface point i assessed the effect on composite score variation on its thickness T_i :

$$T_i = \beta_0 + \beta_1 \cdot \text{Sex} + \beta_2 \cdot \text{Age} + \beta_3 \cdot C$$

In the formula above, we corrected for "Sex" and "Age," given their marked effects on brain structure (Salat et al. 2004); C

is the empathy/ToM composite. In addition to carrying out an unconstrained surface-based analysis, post-hoc assessment evaluated effects in ROIs.

Interregional Network Substrates: Covariance Mapping

To map structural networks, we correlated the thickness of each seed with thickness measures across all cortical surface points. The model fitted at surface point i was as follows:

$$T_i = \beta_0 + \beta_1 * \text{Sex} + \beta_2 * \text{Age} + \beta_3 * T_{\text{seed}}$$

where T_{seed} is the seed thickness. As before, we corrected for age and sex. To assess network modulations by individual differences in empathy/mentalizing, we fitted interaction models that included terms for seed thickness, composite score, and their parametric interaction.

$$T_i = \beta_0 + \beta_1 * \text{Sex} + \beta_2 * \text{Age} + \beta_3 * T_{\text{seed}} + \beta_4 * C + \beta_5 * (T_{\text{seed}} * C)$$

where * denotes an interaction. A positive interaction indicates higher structural covariance in individuals with higher scores; a negative interaction a weaker link.

Correction for Multiple Comparisons

Surface-based findings were corrected using random field theory (Worsley et al. 1999), controlling the probability of reporting a family-wise error to $P_{\text{FWE}} < 0.05$. ROI analyses were corrected at $P_{\text{FWE}} < 0.05$ using Bonferroni-adjustment.

Multi-site Reproducibility Assessment

We assessed robustness of findings, after splitting our cohort into similarly sized samples based on the recruitment sites.

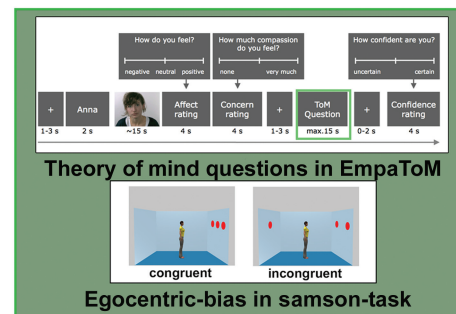
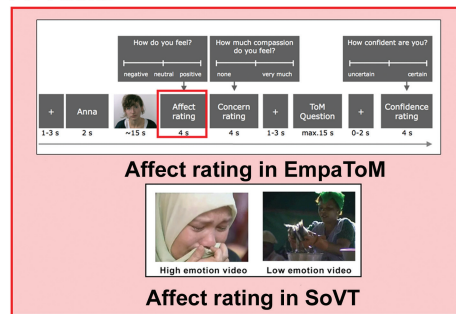
Results

Behavioral Findings

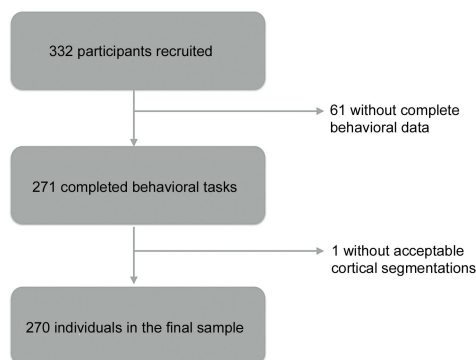
Of the initial 332 participants, we excluded those with incomplete behavioral measures in either of the composite scores ($n = 61$). Of the remaining individuals, acceptable cortical segmentations were available in all but one ($n = 270$, 156 women, mean \pm SD age = 40.9 ± 9.3 years, 20–55 years). Kolmogorov–Smirnov-tests indicated that empathy and mentalizing constructs were both normally distributed across participants. Individual differences in the empathy and mentalizing composites did not correlate ($r = 0.001$, $P > 0.2$). A lack of correlation was also observed after both variables were corrected for age, gender, or both ($r = 0.04$, $P > 0.1$) (Figure 1).

Behavioral phenotyping

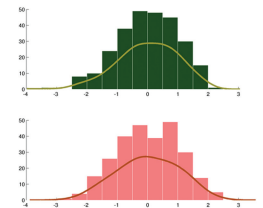
A Tasks



B Exclusion criteria



C Composite scores



D Cross-domain correlations

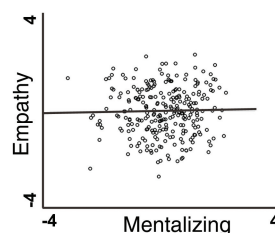


Figure 1. Behavioral phenotyping of empathy and mentalizing. (A) red/green: tasks used to generate the empathy/mentalizing construct; (B) flow chart showing subject inclusion; (C) histograms of empathy/mentalizing composite scores; (D) scatter plot showing lack of behavioral correlation between individual differences in mentalizing and empathy scores.

Regional Substrates: Cortical Thickness Mapping

Surface-based cortical thickness mapping revealed a positive relationship between empathy scores and thickness in a left-hemispheric cluster extending from fronto-insular to opercular regions ($P_{FWE} < 0.025$). In other words, individuals with high scores showed increased thickness in these regions relative to those with low scores. Surface-based findings overlapped with ROIs corresponding to left IFG and dAI ($P < 0.05$). In line with our a priori predictions, empathy-ROI thickness did not correlate with individual differences in mentalizing scores (Figure 2).

Contrary to our hypotheses, individual differences in mentalizing did not significantly relate to regional cortical thickness, neither when using surface-based nor when studying the ROIs based on intersection of ToM activations during the EmpaToM and meta-analytical findings (i.e., dmPFC, TPJ, STG/STS; $P > 0.1$).

Interregional Networks: Structural Covariance Analysis

Interregional Structural Network Substrates

Covariance analysis seeding from the ROIs revealed that each of them was embedded within a distributed, unique structural network. Bilateral dAI covaried strongly with medial and lateral prefrontal, cingulate, and insular regions, together with supramarginal cortices ($P_{FWE} < 0.025$). Conversely, TPJ thickness correlated with dorsomedial and ventrolateral prefrontal, together with posterior midline parietal, lateral temporal, and temporo-parietal thickness. Last, dmPFC thickness covaried with that of lateral prefrontal, lateral, and medial parietal, as well as inferior and anterior temporal cortices ($P_{FWE} < 0.025$) (Figure 3).

Modulation by Mentalizing and Empathizing Abilities

Assessing covariance modulations by individual differences in empathy and mentalizing revealed a divergent impact on interregional structural networks:

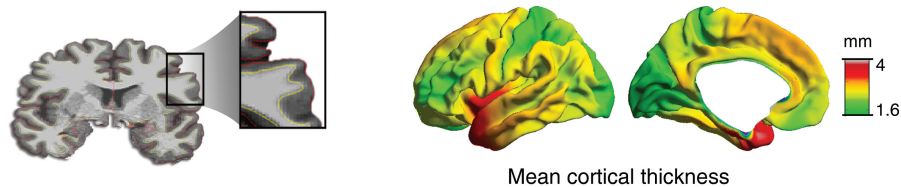
In individuals with high empathy scores, left dAI covaried more extensively with supramarginal cortices extending to the superior parietal lobule relative to those with low scores ($P_{FWE} < 0.025$). Networks centered on other empathy-related ROIs were not affected; moreover, and importantly, covariance networks of the mentalizing-related seeds (TPJ, dmPFC, STG/STS) were not modulated by empathy scores as well. In contrast to empathy scores, those for mentalizing modulated networks centered on TPJ and dmPFC. Specifically, left TPJ covariance was stronger to widespread left medial prefrontal regions encompassing dmPFC ($P_{FWE} < 0.025$) in individuals with high mentalizing scores; in accordance with these findings, dmPFC covariance networks were more marked to temporo-parietal regions including left TPJ ($P_{FWE} < 0.025$). Again, and in line with our hypotheses, covariance networks centered on mentalizing-related seeds were not affected by individual differences in empathy.

For networks centered on IFG, STG/STS, and dlPFC, please see [Supplementary Figure 2](#). These ROIs were neither modulated by individual differences in empathy nor mentalizing. Please note that covariance networks centered on aMCC, obtained from a previous meta-analysis on empathy for pain ([Lamm et al. 2011](#)), also did not show any modulations by empathy nor ToM scores.

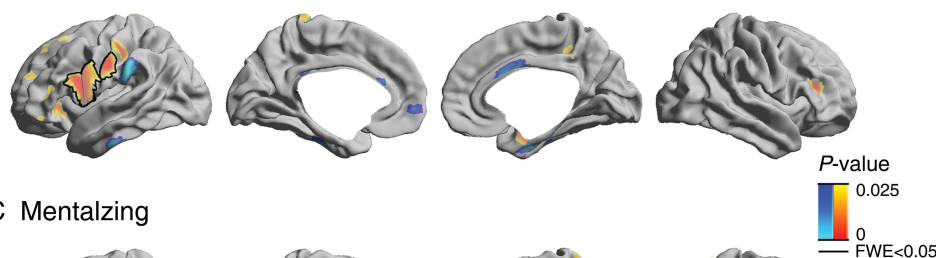
Please see [Supplementary Table 1](#) for peak MNI coordinates of reported findings. Rerunning our analysis when additionally controlling for a previous diagnosis of AXIS-I disorders yielded virtually identical results.

Regional analysis

A Cortical thickness mapping



B Structural substrates of empathy



C Mentalizing

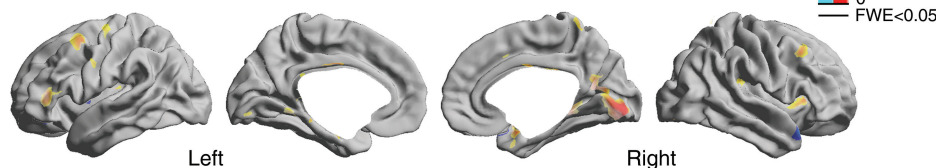


Figure 2. Regional cortical thickness substrates of social cognition. (A) Left: cortical thickness mapping schema; right: mean cortical thickness of the left hemisphere across the 270 subjects included in the study; (B) structural substrates of empathy; (C) structural substrates of mentalizing. In 2B and C, FWE-corrected clusters are outlined in black; uncorrected trends ($P < 0.025$) are shown in semitransparent.

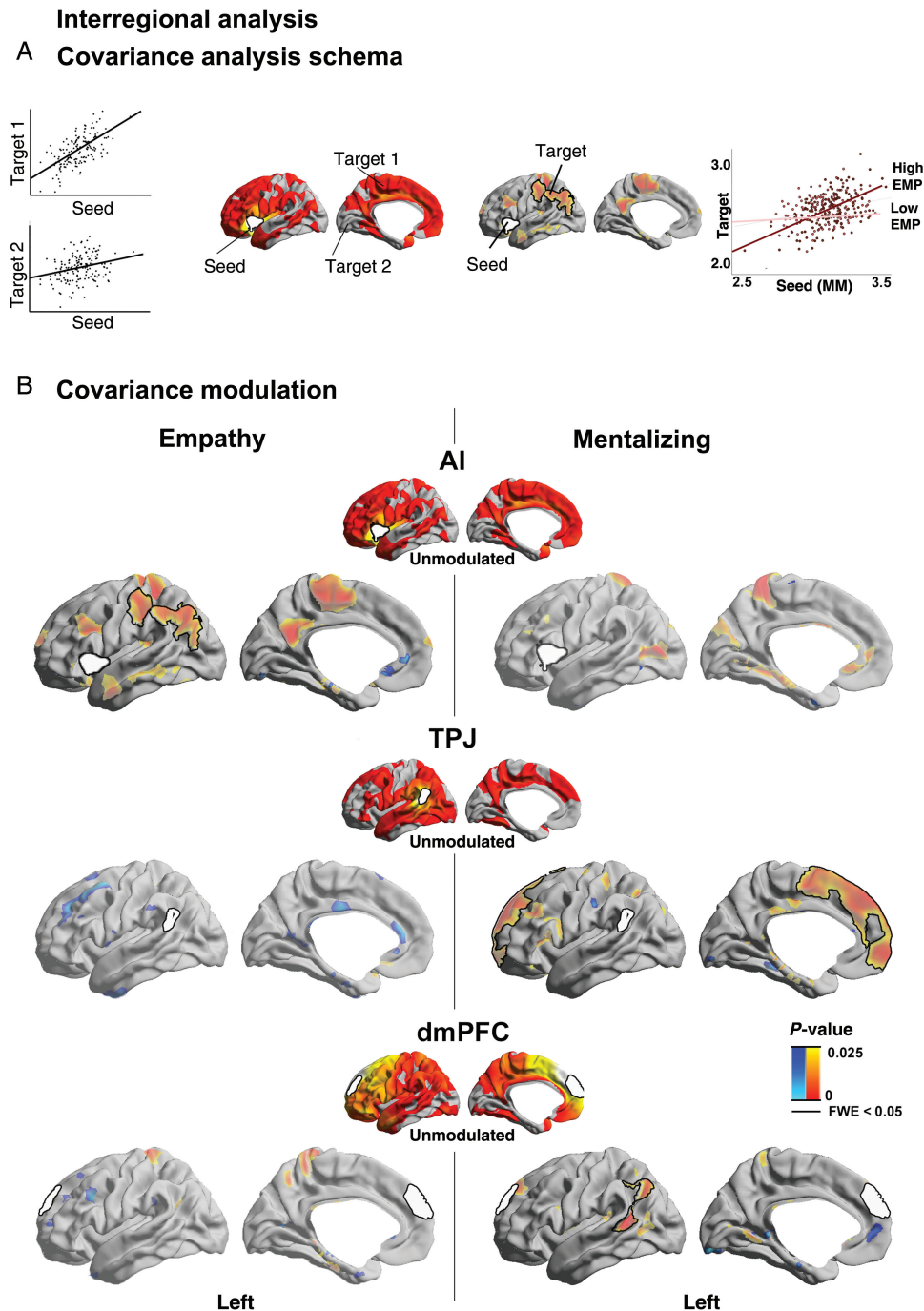


Figure 3. Interregional covariance network analysis. (A) Left: schema of covariance mapping, showing interregional covariance between a seed in the insular cortex and different target regions, thresholded at $t > 5$; Right: covariance modulation by individual differences in empathy. Here, a median split into individuals with high/low empathy illustrates the parametric modulation; (B) covariance modulation in our samples by individual differences in empathy (left) and mentalizing (right). For details on statistical thresholding, please see Figure 2. Superimposed brains in the center show simple (i.e., unmodulated) covariance, thresholded at $t > 5$. Please see [Supplementary Figure 2](#) for covariance mapping of all seeds.

Multisite Reproducibility

The above findings were consistently seen when splitting our sample with respect to recruitment site (Berlin/Leipzig). First, empathy and ToM did not correlate behaviorally in both sites (L: $r = 0.03$, $P > 0.1$; B: $r = -0.03$, $P > 0.1$). Second, as in the complete sample, regional insular-opercular thickness correlated with empathic responding in both Leipzig (post-hoc, $t = 2.77$, $P < 0.005$)

and Berlin (post-hoc, $t = 2.29$, $P < 0.02$). With respect to covariance modulations by empathy, modulations between dAI and supra-marginal cortices were robust (post-hoc, L: $t = 3.14$, $P < 0.001$; B: $t = 2.26$, $P < 0.02$). Considering modulations by mentalizing ability, findings remained robust from TPJ to dmPFC (post-hoc, L: $t = 3.0$, $P < 0.005$; B: $t = 1.44$, $P < 0.08$) and dmPFC to TPJ (post-hoc, L: $t = 3.22$, $P < 0.001$; B: $t = 2.55$, $P < 0.01$).

Discussion

Previous functional MRI findings (Kanske et al. 2015) and conceptual accounts (Singer 2006; Gonzalez-Liencre et al. 2013) have suggested independence between empathy and mentalizing as different routes of social cognition. To investigate whether individual differences in these abilities also robustly relate to divergent anatomical substrates, we adhered to several study design and analysis choices that aimed at maximizing validity and generalizability. First, we calculated individual differences by forming composites across multiple tasks (*empathy*: SoVT, EmpaToM; *mentalizing*: Samson, EmpaToM), to reduce dependency on a specific paradigm. Second, using a 3-Tesla MRI analysis approach that combined regional cortical thickness and interregional structural covariance network assessments, we could apply both hypothesis-free surface-based analysis and also target ROIs previously shown to be relevant for both processes (*empathy*: dAI, IFG, dlPFC, occipital cortex; *mentalizing*: dmPFC, TPJ, STG/STS). Notably, these ROIs were generated by intersecting functional MRI activations in a subset of participants (Kanske et al. 2015) with meta-analytical data (Lamm et al. 2011; Mar 2011), increasing functional specificity and generalizability of ROI selection.

At all analysis stages, findings confirmed our main hypotheses suggesting a divergence between affective and cognitive routes of social cognition. At the behavioral level, individual differences in empathy and mentalizing composites did not correlate, despite a high statistical power of our large-sample assessment. Moreover, evaluating regional brain structure through MRI-based cortical thickness analysis, we observed that empathic but not mentalizing capacity positively correlated to gray matter thickness extending from left fronto-insular to opercular regions. Last, and importantly, MRI covariance analysis revealed a strikingly divergent impact of empathy and mentalizing on interregional structural networks. Here, individual differences in each domain selectively modulated network organization, with left dAI covariance being modulated by empathy capacity, while networks centered on left TPJ and dmPFC were modulated by individual differences in mentalizing. Notably, left dAI networks did not scale with mentalizing scores, while left TPJ and dmPFC networks were not affected by empathy scores. Collectively, these findings, particularly those at the level of interregional covariance, indicate a dissociation of both socio-cognitive faculties. Furthermore, they advocate for a network-based approach as a sensitive analysis strategy to unveil divergent anatomical substrates of individual differences in a healthy sample. As effects were consistently seen across the 2 similarly sized and closely matched recruitment sites, confidence in the generalizability of our findings is high.

In the domain of mentalizing, while a large body of previous work has focused on developmental samples and clinical populations (Baron-Cohen et al. 1985; Frith and Frith 2003; Apperly 2013), data on structural and functional substrates are relatively limited in healthy adults. To establish a generalizable account of mentalizing, we synthesized a marker that combined cognitive and visuo-spatial perspective-taking capacity, the 2 most widely studied facets of ToM (Mar 2011; Apperly 2012; Frith and Frith 2012; Schurz et al. 2014). Despite no significant correlations between cortical thickness in any ROIs and ToM accuracy, assessing its network modulations revealed a selective effect on mentalizing- but not empathy-derived ROIs. In other words, while networks centered on regions derived from meta-analyses on functional activations during empathy tasks (i.e., dAI, IFG, aMCC) were not modulated by mentalizing scores, TPJ and

dmPFC networks were. Noteworthy, despite the use of an unconstrained surface-based analysis, covariance modulations to dmPFC with the mentalizing composite could be obtained when seeding from TPJ, and vice versa. In light of previous meta-analyses on ToM (Mar 2011; Bzdok et al. 2012; Schurz et al. 2014), our results, thus, provide direct evidence that structural network integration within the putative *mentalizing* circuitry reflects individual differences in the ability to accurately infer beliefs and intentions from other minds. It is possible that our rather broad ToM construct, encompassing both low-level visual perspective-taking and high-level mentalizing, might have contributed to the lack of correlation between regional brain structure and individual differences in ToM. Nevertheless, our findings suggest that individual differences in socio-cognitive skills may be better reflected by network-level embedding of specific regions than by their structural markup alone. Task-based functional MRI data in a subset of our sample supported this claim, by showing activations in assemblies of regions, rather than in individual loci (Kanske et al. 2015). On the other hand, as our study did not directly evaluate “affective ToM” (reasoning about other’s emotions), it was not possible to test the difference between mentalizing about others’ mental versus emotional states in the current work. Notably, while both forms of ToM rely on cognitive inferences and do not necessarily have a feeling (“qualia”) attached to it, empathy requires a “feeling with another” and is thus embodied.

Studying network modulations by individual differences in empathy, the current work identified a modulation of the loco-regional embedding of dAI, the ROI most consistently reported during previous functional MRI studies of empathy (Fan et al. 2011; Lamm et al. 2011). As the current findings were based on a large cohort of men and women across a wide age range in whom empathic responding was phenotyped across 2 different tasks, they complement our previous data restricted to young women only (Bernhardt, Klimecki, et al. 2014); in the previous study, we observed dAI network modulations by empathy state-ratings derived from single task. Notably, while this previous work emphasized modulations between dAI and mainly anterior and lateral prefrontal regions, these were only at trend levels in the current study. Conversely, we observed novel modulations between dAI and supramarginal regions, extending to inferior parietal cortices. Considering the specific link between supramarginal and insular cortices in socio-affective processing, it is of note that a recent analysis of our group in autism and alexithymia—a trait that relates to low interoceptive abilities and empathy—has identified a stronger covariance between both regions in individuals with low relative to those with high alexithymia (Bernhardt, Valk et al. 2014). Moreover, several task-based functional MRI studies, transcranial magnetic stimulation experiments, and functional connectivity analyses have indicated that the supramarginal gyrus and its connectivity profile with insular and lateral prefrontal regions contribute to affective behavior; in turn, individuals may be able to share and understand the emotional perspective of others despite their own, possibly, conflicting state (Silani et al. 2013; Steinbeis et al. 2015). The current findings, showing stronger network links in high empathizers between these regions, are, thus, in excellent agreement to these earlier results.

Several lines of research support the claim that sharing emotions may relate to largely different brain substrates than those involved in the understanding others’ mental states. In a recent behavioral and fMRI study (Kanske et al. 2015), we observed that individual differences in empathy, but not ToM (both measured via the EmpaToM), correlated with heart rate deceleration

and empathy ratings on another empathy task, the SoVT (Klimecki et al. 2013), when participants viewed others in distress. Conversely, ToM (but not empathy) measures related to visual perspective taking (Samson et al. 2010) and performance in other mentalizing tasks (Kunderman et al. 1998). Neurodevelopmental studies have suggested that ToM has evolved later in ontogeny than the ability to share affective states (Baron-Cohen et al. 2000; Eisenberg 2000; Decety and Jackson 2004; Mitchell et al. 2005; Singer 2006). Furthermore, ToM-related processes are largely localized in neocortical networks that emerged late in phylogeny, whereas empathy relates to limbic and paralimbic regions that are phylogenetically older (Giedd et al. 1999). A divergence between both domains is also suggested by the study of neurological and neuropsychiatric populations (Shamay-Tsoory et al. 2009; Bird et al. 2010; Hooker et al. 2010; Stanley and Adolphs 2013). In patients with medial frontal versus inferior frontal lesions, selective impairments in cognitive perspective taking and empathy were previously observed (Shamay-Tsoory et al. 2009). Considering autism, abundant work has suggested core impairments in ToM (Frith and Frith 2006), while empathy has been shown to be relatively preserved or—if atypical—rather related to co-occurring alexithymia in affected individuals (Capps et al. 1993; Dziobek et al. 2008; Bird et al. 2010). Our previous study could provide support for these more functionally motivated claims at the level of brain structure, by showing that autism diagnosis related to selective disruptions of covariance networks centered on the TPJ, while increased alexithymia related to the aforementioned decreased dAI covariance to supramarginal regions (Bernhardt, Valk et al. 2014). In contrast to conditions affecting socio-cognitive processing, psychopathology as well as conduct and antisocial personality disorder has frequently been suggested to specifically relate to anomalies in the affective domain, while cognitive perspective-taking abilities may be relatively intact (Dolan and Fullam 2004; Shamay-Tsoory et al. 2010; Schwenck et al. 2011; Decety et al. 2013; Meffert et al. 2013).

The evidence of dissociation of empathy and mentalizing brought forward by the current study does not necessarily imply a complete separation of both processes (Heberlein and Saxe 2005; Singer 2006). Indeed, while networks centered on the TPJ seed were not modulated by individual differences in empathy, we observed that the dAI covariance modulation by empathy scores to supramarginal regions somewhat extended to the more posterior temporo-parietal subregions thought to play a role in mentalizing. This finding at the level of structural covariance re-emphasizes the notion that different networks likely interact during complex processes underlying social cognition. This conclusion is also supported by a previous meta-analysis on fMRI studies on empathy for pain (Lamm et al. 2011), where the authors could show co-activations of ToM circuits during empathy in paradigms when participants had to infer pain in others based on abstract cues and not on the basis of emotional pictures. In that case, information about the given situation and context had to be cognitively inferred to derive the necessary information about “how much the other may suffer.” Yet, the emotional feelings of “ouch it hurts” are likely represented in interoceptive regions, which are consistently activated across multiple paradigms when contrasting high versus low emotional conditions (Fan et al. 2011; Lamm et al. 2011) and modulated by trial-by-trial differences in experienced affect (Singer et al. 2004; Kanske et al. 2015). Notably, co-activation of core empathy regions (AI, aMCC) and mentalizing networks has not always been reported. During empathy for pain paradigms, in which participants are presented with, for example, pictures of a foot in a door to elicit empathic responses, fronto-parietal

action observation networks are found to be co-activated with AI/aMCC instead. In sum, these findings suggest that, depending on a given situation, co-activation of different brain networks will allow a person to infer the necessary information needed to “share a feeling” with another person, that is to empathize with affective states of that person. These conclusions may also correspond to functional findings based on a subsample of the current cohort by Kanske and colleagues, who reported overlap of empathy and ToM specific activations in a left TPJ subregion (Kanske et al. 2015). Moreover, joint abnormalities in both domains have been suggested in several neuropsychiatric populations, including schizophrenia as well as semantic dementia (Rankin et al. 2005; Bora, Gokcen, Kayahan, et al. 2008; Bora, Gokcen, Veznedaroglu, et al. 2008; Derntl et al. 2009; Haker and Rossler 2009).

It is worth pointing out that differences in operationalization of empathy and ToM in the current work might have contributed to some of the observed divergence. Empathy was explicitly conceptualized as an affective state in the observer based on self-reports (de Vignemont and Singer 2006) that intrinsically involve a subjective component, whereas ToM was calculated based on accuracy measures. Please note, however, that previous functional work showed modulations of AI activity by empathy ratings but not by self-reports of experienced compassion; the latter modulated regions in ventral striatum (Kanske et al. 2015). In line with these findings, previous training studies could also show that training empathy induced functional plasticity in the above mentioned empathy-related brain regions involving AI and aMCC, whereas a subsequent training in compassion in the very same people induced functional plasticity in a brain network associated with affiliation and positive rather than to negative affect (Klimecki et al. 2013, 2014). These findings suggest specificity with respect to empathy and compassion ratings and their underlying brain circuitries and thus speak against confounds which may be based on differences of operationalization between measures for empathy and ToM alone. In previous functional MRI studies, insular involvement has also been shown by research studying the observation of disgusted and pleased facial expression (Jabbi et al. 2007). Conversely, Mobbs et al. (2009) noted interacting activations between the ventral striatum and anterior cingulate cortex, but not insula, in subjects experiencing vicarious reward. Recently, Silani et al. (2013) observed insula activation in empathic responses to unpleasant touch and medial orbito-frontal activations when individuals witnessed pleasant touch in others.

Given their long tradition in the field, it is important to clarify the notion of empathy used in the current work in the context of appraisal theories of emotions (Arnold 1960b, 1960a; Scherer 1984). While abundant research has indeed suggested that empathy relies on activation of feeling representations particularly in interoceptive areas, such as AI (Craig 2003, 2009; Singer et al. 2009), and that these signals are modulated by trial-by-trial ratings of negative affect and empathy (Singer et al. 2004; Kanske et al. 2015), there is nevertheless evidence that empathy-related signals in AI can also be modulated by appraisal of the context or other persons (for a review see Hein and Singer [2008]). Thus, while representation in AI may account for core affect and conscious self-experience of emotions (Craig 2003, 2009), simultaneous attentional processes, cognitive perspective taking, appraisal, and motor preparation in response to an affective episode are likely subserved by other networks co-activated with these core networks (e.g., Kanske et al. 2015; Lamm et al. 2011). Our approach is, thus, fully compatible with appraisal theories of emotion.

While amygdala and hippocampus have been associated with empathy by selected studies assessing healthy individuals and those with severe psychopathology (Carr et al. 2003; Blair 2008; Decety 2010; Decety and Michalska 2010), the 2 previous meta-analyses in the domain of empathy for pain did not specifically highlight these regions as being consistently activated across studies (Fan et al. 2011; Lamm et al. 2011). This rather inconsistent functional involvement, together with limitations of surface-based processing tools, such as FreeSurfer, to accurately segment these structures may have contributed to the lack of findings in the current work.

In sum, our study provides evidence for different routes of social cognition based on structural network analysis in a large sample of adults. To further evaluate the generalizability of findings to other affective states and mentalizing subdomains and to study the interplay of these large-scale networks, longitudinal intervention studies are recommended that allow for the assessment of causal effects related to the targeted training of socio-cognitive and socio-affective skills on brain structure, function, and behavior.

Supplementary Material

Supplementary material can be found at: <http://www.cercor.oxfordjournals.org/>.

Notes

Conflict of Interest: None declared.

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