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Original Article

Sex difference in trait empathy is encoded in the human anterior insula

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Females are considered the more empathic sex. This conventional view, however, has been challenged in the past few decades with mixed findings. These heterogeneous findings could be caused by the fact that empathy is a complex and multifaceted construct. To clarify whether sex differences exist in certain dimensions of empathy and whether they are associated with specific neural bases, this study measured trait empathy using the interpersonal reactivity index (IRI) and collected brain structural and functional magnetic resonance imaging data in a large sample of healthy participants (206 males vs. 302 females). We found that females scored higher in the personal distress (PD) subscale than males, but they were comparable to males in other IRI subscales. Sex difference in PD was encoded by brain structural (e.g. gray matter volume in left anterior insula [AI]) and functional (e.g. resting-state functional connectivity between left AI and temporoparietal junction/inferior frontal gyrus) characteristics. Notably, the relationship between sex and PD was indirect-only and serially mediated by AI-associated structural and functional characteristics. Altogether, our results suggested that sex difference existed in self-oriented affective empathy (i.e. PD) and highlighted the importance of the AI, both structurally and functionally, in mediating the sex difference in trait empathy.

Key words: empathy; gray matter volume (GMV); insula; resting-state functional connectivity (rs-FC); sex difference.

Introduction

Empathy is a complex and multifaceted construct (Decety and Ickes 2009), which mainly reflects one's innate ability to perceive, understand, and share the emotional states of others (Shamay-Tsoory 2011; Bernhardt and Singer 2012). As an essential social ability, empathy has drawn lots of attention from researchers during the past decades, and its neural mechanisms have been thoroughly explored. Specifically, the dorsal anterior cingulate cortex (ACC), anterior middle cingulate cortex, supplementary motor area, and bilateral anterior insula (AI) are considered as the core network in empathy (Fan et al. 2011). Both the parietofrontal mirror system (i.e. the parietal lobe and inferior frontal gyrus [IFG]) and limbic mirror system (i.e. the insula and anterior mesial frontal cortex) are involved in the recognition of affective behaviors, facial actions, motor actions, and intention coding (Cattaneo and Rizzolatti 2009; Iacoboni 2009).

Notably, the debate on the sex differences in empathy is nothing new (Eisenberg and Lennon 1983; Rueckert 2011; Christov-Moore et al. 2014). Typically, females are considered the more empathic sex (Baron-Cohen et al. 2005; Mestre-Escriva et al. 2009), deriving from the stereotypical perception that females are more emotionally responsive and more likely to care for others than males. Indeed, females often score higher than males on self-report empathy scales (Baron-Cohen and Wheelwright 2004; Cheng et al. 2008; Rueckert and Naybar 2008; Luo et al. 2018; Li et al. 2021) and show more empathic responses neurologically when seeing others suffer (Proverbio et al. 2009), even though those in pain or distress are hostile (Fukushima and Hiraki 2006) or disgraceful (Singer et al. 2006). From an evolutionary perspective, sex differences in empathy may reflect an asymmetry in the sexes' parental investment in primitive conditions; that is, females are more likely than males to be the primary caretaker of children (Wood and Eagly 2002). However, this traditional view has been challenged in the past few decades with more and more contradictory results (Cheng et al. 2009; Dores et al. 2021). For example, an image-based meta-analysis of 9 independent functional magnetic resonance imaging (MRI) investigations on empathy for pain provided null evidence for sex-specific activation differences (Lamm et al. 2011).

In our opinion, whether sex differences in empathy exist largely depend on which dimension of empathy is triggered and how it is assessed. Briefly, empathy consists of at least 2 related but distinct components, including an affective component through which people vicariously share others' internal states and a cognitive component whereby people adopt other's point of view (Zaki and Ochsner 2012; Weisz and Cikara 2021). Studies tapping into different dimensions of empathy might yield contradictory results. This claim is well supported by neuroimaging studies, in which the neural activity accompanying affective and cognitive empathy seems not overlapping. In general, affective empathy mainly engages the ACC, AI, and IFG, while cognitive empathy mainly engages the ventromedial prefrontal cortex (vmPFC),

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inferior parietal lobule (IPL), and temporoparietal junction (TPJ) (de Waal and Preston 2017; Lamm et al. 2019; Kogler et al. 2020). In other words, different components of empathy are subserved by distinct neural systems (Zaki and Ochsner 2012).

Given the dissociation between different components of empathy, it is possible that the sex difference in empathy can be observed in one dimension but not the other (Cheng et al. 2009; Dores et al. 2021). For instance, a survey targeting Chinese college students showed sex differences in affective empathy but not in cognitive empathy (Jiang et al. 2021). Notably, similar findings were also observed in Western medical students (Guilera et al. 2019). Therefore, it is necessary to distinguish different components when taking on the investigations of sex differences in empathy. In the meantime, a number of studies using neuroimaging techniques have been conducted to explore the neural correlates of sex differences in empathy with various experimental tasks (Han et al. 2008; Schulte-Ruther et al. 2008; Cheng et al. 2009). However, most of them adopted a relatively small sample size (all less than 50 subjects), which might be insufficient to explore the differences in empathy between males and females (Christov-Moore et al. 2014). Moreover, most of these neuroimaging studies focused on individuals' state empathic responses in a specific circumstance, limiting the generalizability of results. In contrast, trait empathy is less likely to be influenced by contextual factors, as it is mainly assessed by self-report scales and reflects the tendencies to share and understand the internal states of others (Van der Graaff et al. 2016).

To address the above issues, in the present study, we assessed sex differences in different components of trait empathy and their neural basis in a large sample of 508 healthy participants (206 males vs. 302 females). Individual level of trait empathy was assessed by a self-report measure of the Chinese version of the interpersonal reactivity index (IRI-C; Zhang et al. 2010), which distinguishes four dimensions of empathy, that is, perspective taking (PT), fantasy (FS), empathic concern (EC), and personal distress (PD). The structural and functional neural basis of sex difference in trait empathy were quantified using structural and functional MRI. The relationship between trait empathy and brain structure and function was explored using a series of partial correlation analyses. Moreover, we built a theoretical model to quantify their mediation relationship using structural equation modeling. As such, the present study would broaden our understanding of the neural mechanism underlying the sex differences in trait empathy.

Materials and methods

Participants

A total of 508 healthy participants were recruited in this study. All included participants reported no history of neurological or psychiatric illness. None had safety contradictions for MRI and no history of alcohol or drug abuse. The experiment was approved by the local ethics committee. Written informed consent was obtained from each participant before the experiment, and all participants received monetary compensation after their participation.

Demographic information and questionnaires

Basic demographic information, including age, sex, handedness, and years of education, was collected from all participants upon arrival at the laboratory. To assess the trait empathy, all participants were instructed to fulfill the IRI-C. The IRI-C includes 22 items divided into four subscales: PT, FS, EC, and PD. Specifically, PT assesses the tendency to adopt another's perspective; FS reflects the tendency to transpose oneself into the emotional states of fictional characters in books, movies, and plays; EC measures the "other-oriented" feelings of warmth, compassion, and concern toward observed others; PD describes the "self-oriented" own feelings of fear, apprehension, and uneasiness at witnessing the negative experiences of others (Davis 1980).

Considering that trait empathy was associated with depression (Yan et al. 2021), anxiety (Pittelkow et al. 2021), and personality (Guilera et al. 2019), the trait scale of State-Trait Anxiety Inventory (STAI_T; Shek 1988), the Beck Depression Inventory (BDI; Beck et al. 1988), and the NEO Five-Factor Inventory (NEO FFI; Costa and McCrae 1992) were also collected. The STAI_T is a subscale of the State-Trait Anxiety Inventory, which includes 20 items to assess the degree of dispositional anxiety. The BDI consists of 21 items that measure attitudes and symptoms of depression during the last week. The NEO FFI is a 60-item questionnaire that provides a quick, reliable, and accurate measure of the 5 domains of personality (i.e. Neuroticism, Extraversion, Openness to experience, Agreeableness, and Conscientiousness).

MRI data acquisition

MRI data were collected using a 3.0-Telsa MRI system (Discovery MR 750; General Electric Healthcare, Milwaukee, WI, USA) at the Brain and Cognitive Neuroscience Research Center, Liaoning Normal University, Dalian, China. A standard birdcage with an 8-channel head coil, along with restraining foam pads, was used to minimize head motion and scanner noise. High resolution T1-weighted structural images were acquired using a gradient echo (3D SPGR) sequence with the following parameters: flip angle (FA) = 8°; field of view (FOV) = 256 × 256 mm^2; matrix = 256 × 256; slice thickness = 1 mm. Ten-minutes resting-state functional MRI (fMRI) images were obtained using echo-planar-imaging (EPI) sequence with the following parameters: repetition time (TR) = 2,000 ms; echo time (TE) = 29 ms; FA = 90°; FOV = 192 × 192 mm^2; matrix = 64 × 64; slice thickness = 3 mm; slices = 43; interleaved slice ordering. During the resting-state fMRI data acquisition, the screen presented a white fixation "+" in the center of the black background. Participants were asked to relax and keep their heads still with their eyes open during the whole acquisition phase.

MRI data analyses

Voxel-based morphometry

Structural MRI images were reoriented to the anterior commissure (AC)–posterior commissure (PC) line to have the same point of origin using Statistical Parametric Mapping (SPM12; http://www.fil.ion.ucl.ac.uk/spm/software/spm12/). Then, images were preprocessed using the Computational Anatomy Toolbox (CAT12; http://dbm.neuro.uni-jena.de/cat12/) in SPM12. The preprocessing steps included denoising, skull stripping, segmentation into gray matter, white matter, and cerebrospinal fluid, and normalization to Montreal Neurological Institute (MNI) space. The ICBM space template based on East Asian brains was used in affine regularization for segmentation. Diffeomorphic Anatomical Registration using Exponentiated Lie algebra (DARTEL; Ashburner 2007) with default template obtained by standard DARTEL registration of 555 IXI subjects between 20 and 80 years was used for spatial registration. The quality of images was assessed with the built-in image-quality rating and visual check. Finally, images were spatially smoothed using a 4-mm full width half maximum (FWHM) Gaussian kernel.

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Resting-state functional connectivity

Resting-state functional images were preprocessed using Data Processing Assistant for resting-state fMRI (DPARSF; Yan and Zang 2010). The preprocessing steps included removing the first 10 volumes, slice timing with the 43rd slice as the reference slice, regressing out nuisance regressors including Friston 24 head motion parameters, white matter signals, and cerebrospinal fluid signals, regressing out an overall linear trend, co-registering T1 images to functional images, segmenting T1 images through the DARTEL method and using the East Asian template for affine regularization, normalizing functional images to the standard MNI space using DARTEL template, smoothing with a 4-mm FWHM Gaussian kernel, and filtering with a bandpass of 0.01–0.1 Hz. Participants with head motion more than 3.0 mm of maximum translation (in any direction of x, y, or z) or 3.0° of maximum rotation throughout scanning were excluded from resting-state fMRI data analyses. For the remaining participants, the mean framewise displacements (FD) of all participants were within 0.2 mm. The brain regions defined from voxel-based morphometry (VBM)-conjunction analysis were used as regions of interest (ROIs, please see the following statistical analyses for details). Voxel-wise functional connectivity analyses were conducted to calculate the correlation coefficients between the mean time series from each ROI and the time series from other voxels across the whole brain. Finally, the resultant r value maps were transformed to z-statistic maps using the Fisher's r to z transformation to allow for between-subjects comparisons.

Statistical analyses

Demographics and trait empathy

Independent-samples t-tests were used to assess sex differences in demographic information (i.e. age and years of education), trait empathy (i.e. IRI subscale scores), STAI_T, BDI, and NEO FFI. To rule out possible confounding factors of demographic information on sex difference in trait empathy (e.g. age is an important factor in the modulation of empathy, see Wieck et al. 2021; Ziaei et al. 2021), linear stepwise regression analyses were conducted with IRI subscale scores as dependent variables, while sex, age, and years of education as independent variables. All tests were 2-tailed, and the level of significance was 0.05. Bonferroni correction on P values was conducted for multiple comparisons. All statistical analyses were conducted using SPSS 25.0 (SPSS Inc., Chicago, IL, USA).

Structural and functional MRI data

Whole-brain regression analyses were conducted to assess the relationship between gray matter volume (GMV) and IRI subscale scores that showed significant sex differences. Moreover, whole-brain independent-sample t-tests were conducted to examine the GMV differences between females and males. An absolute threshold of 0.1 was used during VBM analyses. Total intracranial volume (TIV) and age (Taki et al. 2013) were used as covariates in the above statistical analyses. A conjunction analysis was performed on the statistical results of the above two analyses using the xjview toolbox (https://www.alivelearn.net/xjview), which yielded brain regions in which the GMV showed significant correlations with IRI subscale scores and significant sex differences. The brain regions obtained from the conjunction analysis were defined as the ROIs for further analyses. GMV values in each ROI were extracted from normalized, modulated, and smoothed gray matter images (regressed out age and TIV), then were used to intuitively display their relationship with IRI subscale scores for males and females.

Whole-brain regression analyses were also conducted to assess the relationship between ROI-based resting-state functional connectivity (rs-FC) and IRI subscale scores that showed significant sex differences. Moreover, whole-brain independent-sample t-tests were conducted to examine the sex difference in ROI-based rs-FC. Age was used as the covariate in the above statistical analyses since age-related differences in rs-FC were reported in previous studies (Damoiseaux 2017; Tremblay et al. 2022). A conjunction analysis was performed on the statistical results of the above 2 analyses using the xjview toolbox, which yielded brain regions in which the ROI-based rs-FC showed significant correlations with IRI subscale scores and significant sex differences. The values of ROI-based rs-FC that survived from the conjunction analysis were extracted and regressed out age to intuitively display their relationship with IRI subscale scores for males and females. For both VBM and rs-FC analyses, clusters were considered significant only if they reached a threshold of voxel-level at $P < 0.001$ and cluster-level family-wise error (FWE) corrected at $P < 0.05$.

In addition, partial correlation analyses were conducted to examine the relationship between the extracted GMV values in each ROI and its corresponding rs-FC values. Age was used as the covariate, and Bonferroni correction on P values was conducted for multiple comparisons.

Mediation analyses

To explore the influencing factors of the relationship between sex and trait empathy, we built 3 mediation models based on VBM and rs-FC results. Specifically, sex was used as the independent variable, and IRI subscale scores that showed significant sex differences were used as the dependent variable. GMV values ($n = 484$), rs-FC values ($n = 480$), and both GMV and rs-FC values ($n = 480$) were used as the mediator variable in the 3 models, respectively. The adequacy of the proposed mediation model was tested using structural equation modeling (SEM; Byrne 2016) based on maximum likelihood estimation. The model fit was assessed using the following criteria: the significance of chi-square (χ^2) statistic (P value) > 0.05, the ratio of chi-square to degrees of freedom (χ^2/df) < 3, the root-mean-square error of approximation (RMSEA) ≤ 0.06 (Hu and Bentler 1999), both the goodness-of-fit index (GFI) and the adjusted GFI (AGFI) ≥ 0.90, both the comparative fit index (CFI) and the normed fit index (NFI) ≥ 0.95 (Hooper et al. 2008). Bias-corrected 95% confidence intervals (CI) were calculated using the bootstrapping procedure (Preacher and Hayes 2008). The estimation was considered statistically significant when the 95% CI (based on 2000 bootstrap samples) excluded zero. Standardized estimate (b), standard error (SE), 95% CI, and P value were reported for both direct and indirect effects. The mediation analyses were performed using Amos 24.0 (SPSS Inc., Chicago, IL, USA).

Results

Demographics and questionnaires

Participants with incomplete data collection ($n = 7$) and those whose structural images exhibited obvious artifacts or extremely low signal-to-noise ratio ($n = 17$) were excluded from the analyses. As a result, a total sample of 484 participants was left for the VBM analyses (194 males vs. 290 females, see Table 1). Four additional participants, including 3 males and 1 female, were excluded from rs-FC analyses because of head motion larger than 3.0 mm or 3.0°. Consequently, 480 participants (191 males vs. 289

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Table 1. Descriptive statistics ($M \pm SD$) of demographic information and trait empathy for males and females.

Variables	Males ($n = 194$)	Females ($n = 290$)	χ^2/t value	P value	Cohen's d
Age (years)	22.02 ± 4.73	20.90 ± 3.00	2.92	0.004**	0.30
Education (years)	14.74 ± 2.06	14.61 ± 1.96	0.70	0.486	
Handness (left/right)	12/182	11/278	1.45	0.229	
IRI-C					
Perspective taking	13.61 ± 3.33	13.29 ± 3.34	1.02	1.000	
Fantasy	16.07 ± 4.10	16.68 ± 4.05	-1.60	0.440	
Empathic concern	16.60 ± 3.22	16.74 ± 3.79	-0.43	1.000	
Personal distress	9.59 ± 3.97	10.99 ± 3.81	-3.89	<0.001***	0.36
STAI_T	41.43 ± 9.14	41.71 ± 8.56	-0.35	0.729	
BDI	10.30 ± 7.23	9.98 ± 7.06	0.48	0.635	
NEO FFI					
Neuroticism	32.15 ± 8.71	32.87 ± 8.35	-0.90	0.367	
Extraversion	41.01 ± 7.59	41.60 ± 7.25	-0.86	0.390	
Openness to experience	39.29 ± 5.74	39.56 ± 5.16	-0.53	0.595	
Agreeableness	41.68 ± 4.96	41.62 ± 5.34	0.11	0.915	
Conscientiousness	42.18 ± 6.34	42.17 ± 5.87	0.01	0.989	

IRI-C, the Chinese version of interpersonal reactivity index; M, mean; SD, standard deviation; STAI_T, the trait scale of State-Trait Anxiety Inventory; BDI, the Beck Depression Inventory; NEO FFI, the NEO Five-Factor Inventory. ** $P < 0.01$; *** $P < 0.001$. One female did not report the handedness, 3 males and 2 females did not complete the BDI, and 3 females did not complete the NEO FFI. Bonferroni correction on P values was conducted for multiple comparisons for the IRI-C questionnaire.

females) were left for the rs-FC analyses. Additionally, 1 female did not report her handedness, 3 males and 2 females did not complete the BDI, and 3 females did not complete the NEO FFI. These missing data were excluded from the corresponding data analysis.

Whereas no significant sex differences were observed in PT ($t(482) = 1.02$, $P = 1.000$), FS ($t(482) = -1.60$, $P = 0.440$), or EC subscale scores ($t(482) = -0.43$, $P = 1.000$), a significant sex difference was observed in PD subscale scores ($t(482) = -3.89$, $P < 0.001$) (Table 1 and Fig. 1). Notably, a significant sex difference was also found in age ($t(482) = 2.92$, $P = 0.004$) but not in years of education ($t(482) = 0.70$, $P = 0.486$), and handedness ($\chi^2(1) = 1.45$, $P = 0.229$). Linear stepwise regression analysis with PD subscale score as the dependent variable, sex, age, and years of education as independent variables showed that PD subscale score was significantly modulated by sex ($t(482) = 3.89$, $P < 0.001$), but not by age ($t(482) = -1.68$, $P = 0.094$) and years of education ($t(482) = 0.85$, $P = 0.397$).

Furthermore, no significant sex differences were observed in the STAT_T ($t(482) = -0.35$, $P = 0.729$), BDI ($t(477) = 0.48$, $P = 0.635$), or any domain in the NEO FFI (Neuroticism: $t(479) = -0.90$, $P = 0.367$; Extraversion: $t(479) = -0.86$, $P = 0.390$; Openness: $t(479) = -0.53$, $P = 0.595$; Agreeableness: $t(479) = 0.11$, $P = 0.915$; Conscientiousness: $t(479) = 0.01$, $P = 0.989$).

Structural and functional MRI results

For structural MRI data, whole-brain regression analyses showed that GMV values in the left AI, left superior temporal gyrus (STG) extending into the middle temporal gyrus (MTG), and right cerebellum were significantly correlated with PD subscale scores (uncorrected $P < 0.001$ at the voxel level and FWE corrected $P < 0.05$ at the cluster level; Supplementary Fig. S1A). Whole-brain independent-sample t-test showed that a wide range of cortical areas exhibited significant differences between males and females, including the bilateral fusiform extending into the limbic system and bilateral insula, left precentral gyrus, bilateral superior frontal gyrus, and left IFG (uncorrected $P < 0.001$ at the voxel level and FWE corrected $P < 0.05$ at the cluster level; Supplementary Fig. S1B). Conjunction analysis showed that GMV values in the left AI, left STG extending into the MTG, and right cerebellum were significantly correlated with PD subscale scores and showed significant sex differences at the same time (Table 2 and Fig. 2).

For functional MRI data, whole-brain regression analyses showed that rs-FC values between the left AI and the left TPJ, as well as those between the left AI and the right IFG, were significantly correlated with PD subscale scores (uncorrected $P < 0.001$ at the voxel level and FWE corrected $P < 0.05$ at the cluster level; Supplementary Fig. S2A). No significant correlation was found for rs-FC based on the left STG extending into the MTG and the right cerebellum. Whole-brain independent-sample t-test showed that rs-FC values between the left AI and a wide range of cortical areas, including bilateral TPJ, bilateral IFG, ACC, mid-cingulate cortex (MCC), amygdala, bilateral temporal lobe, bilateral medial frontal lobe, and bilateral fusiform gyrus, exhibited significant sex differences (uncorrected $P < 0.001$ at the voxel level and FWE corrected $P < 0.05$ at the cluster level; Supplementary Fig. S2B). Conjunction analysis showed that values of rs-FC between the left AI and the left TPJ extending into the left IPL as well as between the left AI and the right IFG pars triangularis showed significant correlations with PD subscale scores and significant sex differences at the same time (Table 3 and Fig. 3).

Partial correlation analyses showed GMV values in the left AI were significantly and positively correlated with the values of rs-FC between the left AI and the left TPJ, as well as those between the left AI and the right IFG (left TPJ: $r = 0.225$, $P < 0.001$; right IFG: $r = 0.178$, $P < 0.001$) (Fig. 4).

Mediation effects

For the first mediation model (GMV values were used as the mediator variable), GMV in the left AI and left STG indirect-only mediated the relationship between sex and PD subscale scores (Supplementary Fig. S3). Specifically, sex demonstrated an indirect effect ($b = 0.19$, SE = 0.06, CI = [0.10, 0.33], $P < 0.001$), but not

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Table 2. GMV in brain regions showed significant correlations with PD subscale scores and significant sex differences ($n = 480$, 191 males vs. 289 females).

			Correlations with PD				Sex difference			
				Peak MNI coordinates				Peak MNI coordinates		
Cluster size	Hemi	Brain regions	t	X	Y	Z	t	X	Y	Z
517	L	Anterior insula	4.39	−41	5	6	8.14	−35	6	2
			4.32	−38	12	12	6.61	−42	2	2
			4.09	−38	12	2	5.98	−32	12	9
81	L	STG extending into MTG	4.36	−63	−53	18	4.84	−66	−50	15
			3.90	−66	−45	15	3.97	−63	−54	23
696	R	Cerebellum extending into fusiform	4.81	45	−66	−21	11.24	44	−72	−20
			4.48	53	−54	−41	8.91	44	−59	−24
			4.31	47	−57	−27	8.00	50	−53	−47

Clusters were considered as significant only if they reached a threshold of voxel-level $P < 0.001$ and cluster-level FWE corrected $P < 0.05$. TIV and age were included as covariates for all statistical analyses. GMV, gray matter volume; PD, personal distress; MNI, Montreal Neurological Institute; STG, superior temporal gyrus; MTG, middle temporal gyrus; FWE, family-wise error; TIV, total intracranial volume.

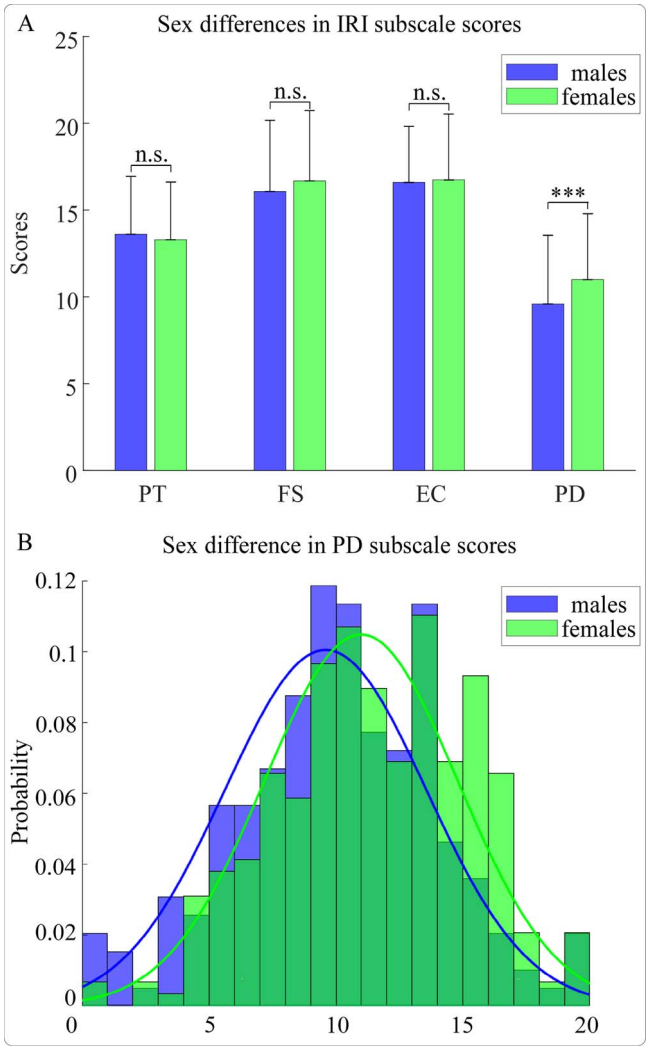

Fig. 1. Sex difference in IRI subscale scores. (A) No significant sex differences were observed in PT, FS, or EC subscale scores, while females scored higher than males in PD subscale. (B) Probability distributions of PD subscale scores for males and females. PT, perspective taking; FS, fantasy; EC, empathic concern; PD, personal distress. *** $P < 0.001$; n.s. = not significant.

a direct effect ($b = -0.02$, SE = 0.07, CI = [−0.16, 0.13], $P = 0.844$) on PD subscale scores through the GMV.

For the second mediation model (rs-FC values were used as the mediator variable), ROI-based rs-FC between the left AI and left TPJ as well as between the left AI and right IFG also indirect-only mediated the relationship between sex and PD subscale scores (Supplementary Fig. S4). Specifically, sex demonstrated an indirect effect ($b = 0.08$, SE = 0.03, CI = [0.04, 0.15], $P < 0.001$), but not a direct effect ($b = 0.09$, SE = 0.05, CI = [−0.002, 0.19], $P = 0.058$) on PD subscale scores through the rs-FC.

For the third mediation model (both GMV and rs-FC values were used as mediator variables), GMV in the left AI/left STG and the left AI-based rs-FC serially and indirect-only mediated the relationship between sex and PD subscale scores (Fig. 5; pathway 1: sex → GMV → PD, pathway 2: sex → rs-FC → PD, pathway 3: sex → GMV → rs-FC → PD). Specifically, GMV in the left AI/left STG was the mediator between sex and the AI-based rs-FC (between the left AI and left TPJ as well as between the left AI and right IFG), which in turn mediated the relationship between GMV and PD subscale scores. Statistically, sex demonstrated an indirect effect ($b = 0.24$, SE = 0.06, CI = [0.14, 0.37], $P < 0.001$), but not a direct effect ($b = -0.06$, SE = 0.07, CI = [−0.20, 0.08], $P = 0.424$) on PD subscale scores serially through the GMV and rs-FC.

Discussion

In the present study, we investigated the sex differences in trait empathy and their neural basis using both structural and functional MRI data in a large group of healthy participants. There were several salient observations from the present results. First, females scored significantly higher in the PD subscale than males, but they were comparable to males in other subscales, indicating a sex difference in self-oriented affective empathy. Second, such a difference in trait empathy was negatively correlated with GMV in the left AI, left STG, and right cerebellum. Third, the sex difference in trait empathy was also negatively correlated with the rs-FC between the left AI and the left TPJ extending into the IPL as well as between the left AI and the right IFG pars triangularis. Fourth, the relationship between sex and PD subscale was indirect-only and serially mediated by GMV in the left AI and the left AI-related rs-FC. These differences between the 2 sex groups cannot be explained by emotional traits or personality, as no sex differences were observed in these related questionnaires. Our findings provide solid evidence for the neural basis of the sex difference in the affective dimension of trait empathy (i.e. PD), which sheds new light on the debate of the sex differences in empathy.

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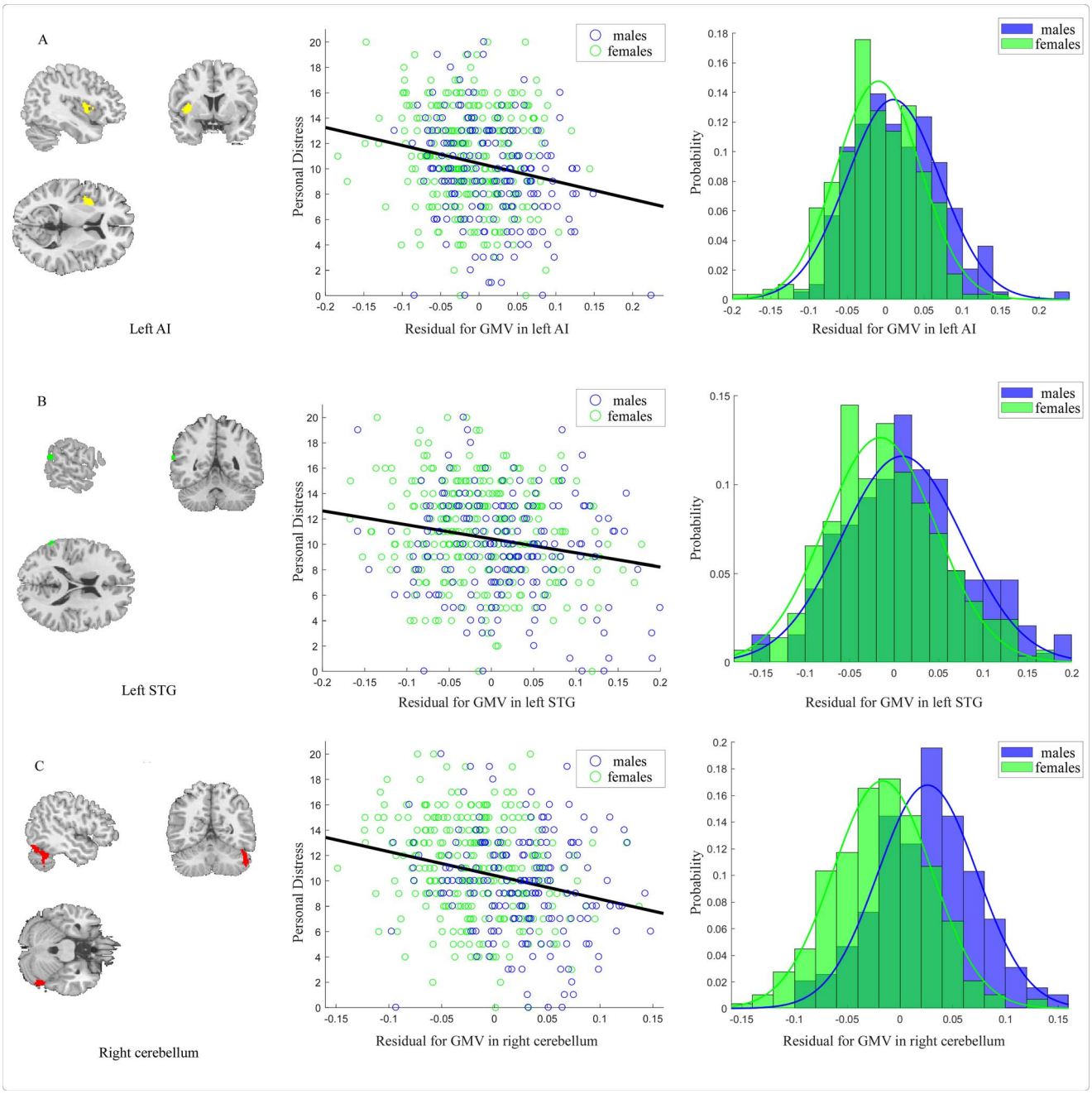

Fig. 2. Brain regions in which the GMV values showed significant correlations with PD subscale scores and significant sex differences. GMV values in the left AI (A), left STG (B), and right cerebellum (C), showed significant negative correlations with PD subscale scores, were significantly larger for males than females. Note that brain regions displayed in the left column were defined based on the conjunction analysis. Dot plots (middle column) and probability distribution maps (right column) were used to intuitively display the relationships between GMV values after controlling age and TIV and IRI subscale scores for males and females. GMV, gray matter volume; AI, anterior insula; STG, superior temporal gyrus; PD, personal distress; TIV, total intracranial volume.

In line with previous studies demonstrating a sex difference in the affective dimension of empathy (Proverbio et al. 2009; Groen et al. 2013), females reported higher PD scores than males in the present study. This finding can be accounted for by the evolutionary basis of empathy—parenting behavior (Decety et al. 2012). As the dominant caregivers in most species, it is necessary for females to be more sensitive to perceive the inner states of their offspring and respond with emotional expressions of hunger, pain, distress, or fear (Decety and Holvoet 2021). A study, in which 74% of the data on caregivers were from mothers, showed that sick child's level of pain behavior had a strong influence on caregivers' pain estimations, which in turn could be explained by PD (Caes et al. 2017). From this perspective, it is reasonable that females are more likely to experience feelings of discomfort and anxiety when witnessing the negative experiences of others (Proverbio et al. 2009). On the other hand, we did not find a sex difference in the EC subscale, which measures one's tendency to experience feelings of warmth, compassion, and concern for others undergoing negative experiences (Davis 1980). This finding suggests a comparable other-orientated trait empathy between females

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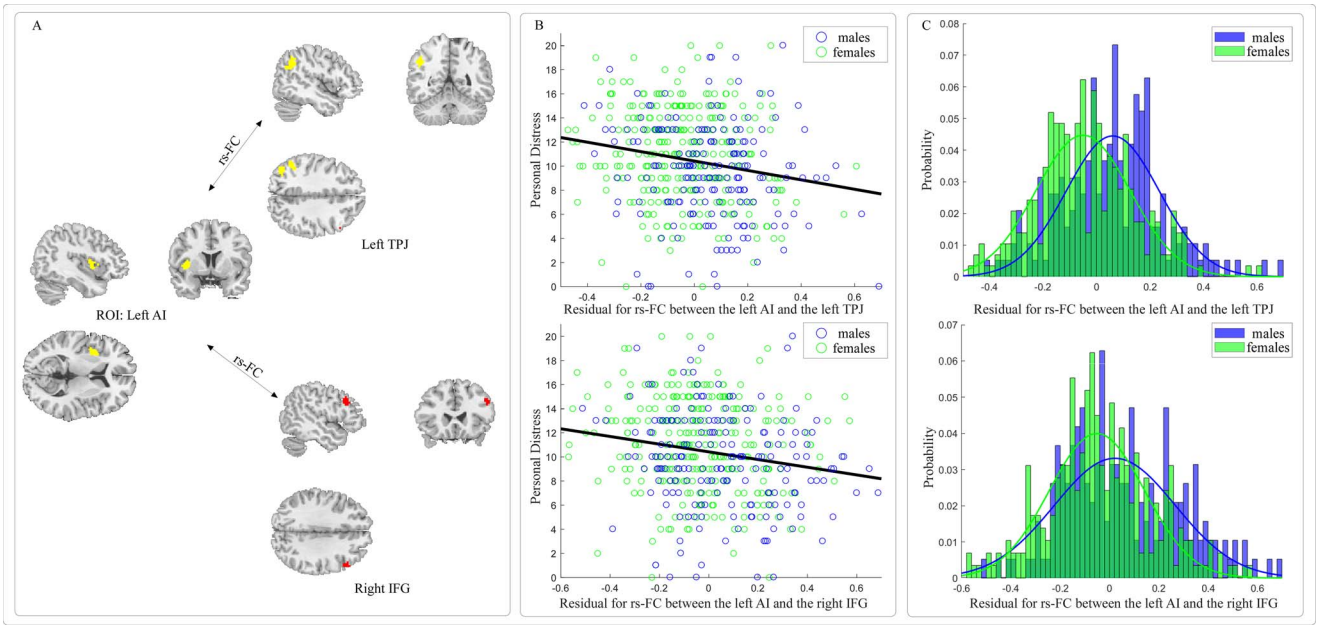

Fig. 3. Rs-FC showed significant correlations with PD subscale scores and significant sex differences. Rs-FC values between the left AI and the left TPJ, as well as between the left AI and the right IFG (A), showed significant negative correlations with PD subscale scores (B), were significantly larger for males than females (C). Note that brain regions displayed in (A) were defined based on the conjunction analysis. Dot plots (B) and probability distribution maps (C) were used to intuitively display the relationships between rs-FC values after controlling age and IRI subscale scores for males and females. AI, anterior insula; TPJ, temporoparietal junction; IFG, inferior frontal gyrus; rs-FC, resting-state functional connectivity; PD, personal distress.

Table 3. rs-FC showed significant correlations with PD subscale scores and significant sex differences ($n = 480$, 191 males vs. 289 females).

				Correlations with PD				Sex difference			
					Peak MNI coordinates				Peak MNI coordinates		
ROI	Cluster size	Hemi	Brain regions	*t*	X	Y	Z	*t*	X	Y	Z
Left AI	125	L	TPJ extending into IPL	4.24	−48	−54	36	5.84	−33	−69	42
				3.93	−42	−69	42	4.93	−54	−63	42
				3.23	−54	−63	42	4.54	−45	−54	33
	30	R	IFG pars triangularis	3.88	51	21	33	4.63	48	24	33
				3.33	42	21	24				

Clusters were considered as significant only if they reached a threshold of voxel-level $P < 0.001$ and cluster-level FWE corrected $P < 0.05$. Age was included as a covariate for all statistical analyses. Rs-FC, resting-state functional connectivity; PD, personal distress; ROI, region of interest; MNI, Montreal Neurological Institute; AI, anterior insula; TPJ, temporoparietal junction; IPL, inferior parietal lobule; IFG, inferior frontal gyrus; FWE, family-wise error.

and males. Indeed, although PD and EC are both considered as affective empathy, they are two distinct feelings (feeling *with* vs. feeling *for*)—PD is self-orientated and makes self's emotion more negatively (Williams et al. 2014), while EC is other-orientated and usually results in sustained functioning and helping behaviors (FeldmanHall et al. 2015; Berry et al. 2018; Coyne et al. 2018; Weisz and Cikara 2021). Therefore, it would be necessary to distinguish these two sub-dimensions in affective empathy in future research.

In line with our findings in self-report trait empathy, we identified the left AI as the key region that showed a significant correlation with PD subscale scores and a significant difference between females and males. The insula plays a crucial role in the generation of a wide range of subjective feelings and emotions, including vicarious emotional states (Craig 2009; see Fan et al. 2011 for meta-analysis results; Masten et al. 2011). Notably, it has been suggested that the processing of emotional stimuli was predominantly associated with the left AI (Duerden et al. 2013), a brain area consistently activated in the affective–perceptual empathy (Fan et al. 2011) and specifically involved in empathy toward others' physical pain (Ding et al. 2020). For instance, either viewing painful pictures versus neutral pictures (Gu et al. 2010) or the empathic feelings for a loved one receiving a painful stimulation were associated with stronger AI activation (Singer et al. 2004). Additionally, our results suggested that the left AI played a more significant role than the right AI in sex differences in the affective dimension of trait empathy. In our opinion, these results are in line with previous findings about the lateralization of affective processing in the insula, that is, emotional stimuli predominantly activated the left AI (Gu et al. 2010; Duerden et al. 2013).

In the present study, we observed that the GMV values in the left AI, left STG, and right cerebellum were negatively correlated with PD subscale scores (Fig. 2). Notably, the negative correlations between brain morphometry in empathy-related brain regions and trait empathy were also observed in several previous studies (Banissy et al. 2012; Takeuchi et al. 2014; Luo et al. 2018; Li et al. 2020). Moreover, negative correlations between GMV and cognitive performance were frequently observed in other cognitive neuroscience fields (Hyde et al. 2006; Hyde et al. 2007; Kanai et al. 2011), and these negative correlations were

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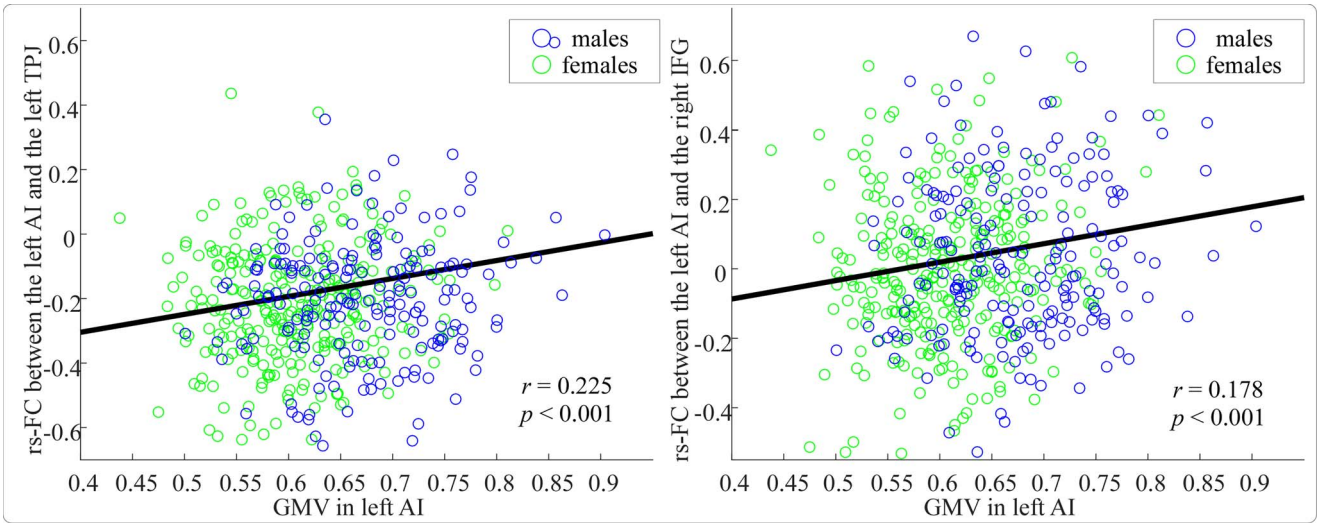

Fig. 4. Correlations between GMV in the left AI and AI-related rs-FC. GMV in the left AI was significantly correlated with the rs-FC between the left AI and the left TPJ (A) as well as between the left AI and the right IFG (B). GMV, gray matter volume; AI, anterior insula; rs-FC, resting-state functional connectivity; TPJ, temporoparietal junction; IFG, inferior frontal gyrus.

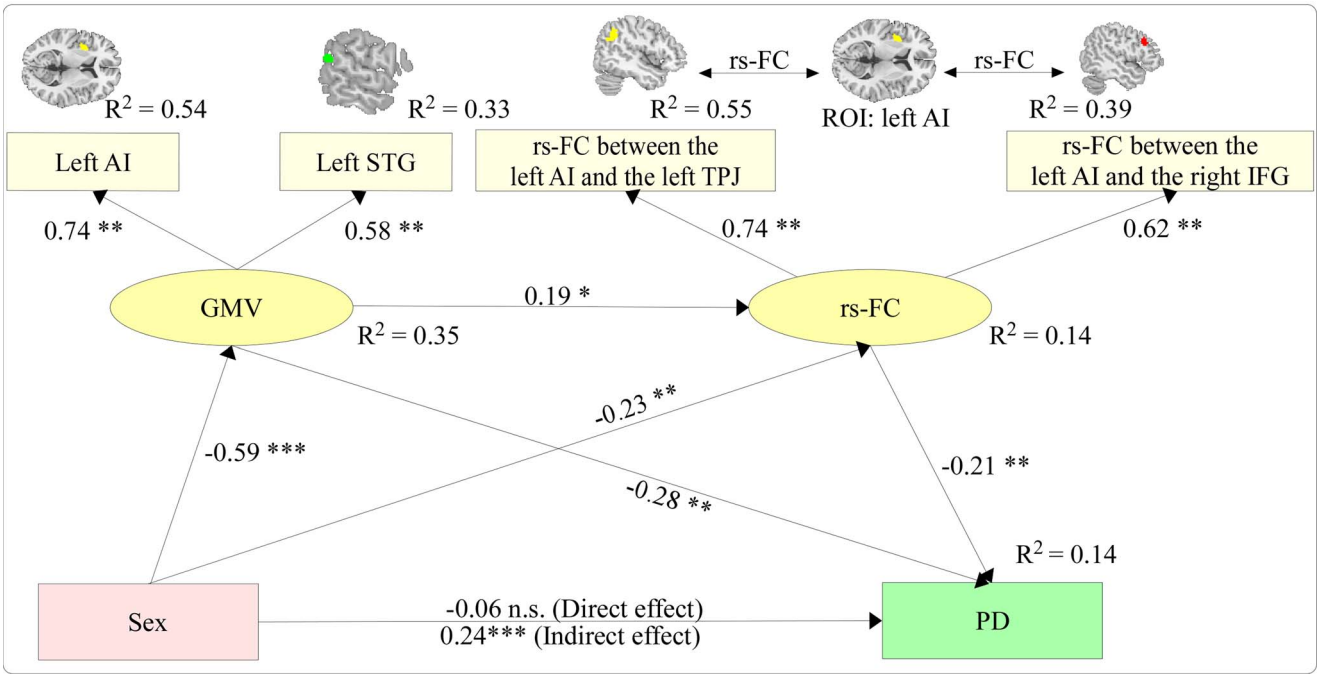

Fig. 5. GMV in the left AI/left STG and AI-related rs-FC mediated the relationship between sex and PD subscale scores. The relationship between sex and PD subscale scores was indirect-only and serially mediated by GMV in the left AI/left STG and AI-related rs-FC. The final model fit the data well and exhibited adequate fit indices: χ^2 (5) =8.933, $P = 0.112$, $\chi^2/df = 1.787$, RMSEA = 0.041, GFI = 0.994, AGFI = 0.974, CFI = 0.990, NFI = 0.979. Standardized regression weights and squared multiple correlation coefficients were shown for the model. GMV, gray matter volume; PD, personal distress; rs-FC, resting-state functional connectivity; AI, anterior insula; STG, superior temporal gyrus; TPJ, temporoparietal junction; IFG, inferior frontal gyrus. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; n.s. = not significant.

explained from a developmental perspective (Kanai and Rees 2011). During brain maturation, the synapses and neurons in the cortex decrease with the pruning processing, which results in the improvement of the computational efficacy of the cortex. As a result, the reduction in GMV at the macroscopic level that would reflect synaptic and neuronal pruning processes leads to more efficient cognitive processing (Kanai and Rees 2011). Importantly, most subjects recruited in the present study are in their adolescent stage (Table 1), which also reinforces the rationality of explaining our negative correlations from the development perspective.

The rs-FC results provide another line of evidence suggesting the core function of the AI in the sex difference in PD. Specifically, rs-FC between the left AI and the left TPJ as well as between the left AI and the right IFG pars triangularis showed a significant correlation with PD subscale scores and a significant difference between females and males. Notably, previous studies suggested that the left TPJ and right IFG played an important role in empathy

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for pain in addition to the AI (Schulte-Ruther et al. 2008; Bzdok et al. 2012; Li et al. 2021). The right IFG, as a part of the human mirror neuron system (Iacoboni et al. 1999; Rizzolatti and Craighero 2004), allows immediate experience sharing between observers and others by simulating on own neural circuit for observed action, thereby facilitating empathy (Iacoboni 2009) and emotion regulation (Naor et al. 2020). Moreover, the left TPJ involves reasoning about the contents of another person's mind (Saxe and Kanwisher 2003) and plays a vital role in distinguishing between the self and others (Decety and Sommerville 2003). For instance, Schulte-Ruther et al. (2008) found that males showed increased activation in the left TPJ (but not the right TPJ) than females during the attribution of emotion to oneself, reflecting a more cognitively driven access to one's own feelings in response to the emotions of other people in males. Thus, with more information perceived by the left AI and stronger functional connectivity between the left AI and left TPJ, males differentiated self-other more clearly, which may result in less PD.

In short, given the important role of the AI in the generation of emotion from action representation (Carr et al. 2003), of the right IFG in action representation, and of the left TPJ in self-other distinction (Schulte-Ruther et al. 2008), one may expect to observe a strong link among these regions when investigating empathy. In agreement with this prediction, we observed that PD subscale scores were negatively correlated with GMV in the left AI, rs-FC between the left AI and left TPJ, and rs-FC between the left AI and right IFG. Additionally, the structural (i.e. GMV) and functional (i.e. rs-FC) features were positively correlated. Due to their significant correlations, we observed that the relationship between sex and PD subscale was indirect-only and serially mediated by GMV in the left AI and the left AI-related rs-FC. Specifically, males had greater GMV in the left AI, stronger left AI-left TPJ rs-FC, stronger left AI-right IFG rs-FC, but lower PD subscale scores. In other words, for females, the less information observed from action representation, the less self-other differentiated, the more PD generated.

In conclusion, the present study provided solid evidence showing that sex differences existed in self-oriented affective empathy (i.e. PD), and such a difference is mediated by the GMV in the left AI/left STG and rs-FC between the left AI and the left TPJ/right IFG. Our findings highlight the importance of the left AI in empathic distress, which might serve as the neural basis underlying the sex differences in trait empathy. Further, these findings may help explain sex-differentiated social behaviors that affect the distribution of social roles in both nonindustrial and industrial societies (Cejka and Eagly 1999; Wood and Eagly 2002).

Supplementary material

Supplementary material is available at *Cerebral Cortex* online.

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