

SEX DIFFERENCES IN THE NEUROANATOMY OF HUMAN MIRROR-NEURON SYSTEM: A Voxel-BASED MORPHOMETRIC INVESTIGATION

Y. CHENG,^{a,b,f} K.-H. CHOU,^c J. DECETY,^d I.-Y. CHEN,^a D. HUNG,^e O. J.-L. TZENG^a AND C.-P. LIN^{a*}

^aInstitute of Neuroscience, National Yang-Ming University, 155 Li-Nong Street, Sec. 2, Peitou, Taipei, Taiwan

^bDepartment of Physical Medicine and Rehabilitation, National Yang-Ming University Hospital, Yilan, Taiwan

^cInstitute of Biomedical Engineering, National Yang-Ming University, Taipei, Taiwan

^dDepartments of Psychology and Psychiatry and Center for Cognitive and Social Neuroscience, The University of Chicago, Chicago, IL, USA

^eInstitute of Cognitive Neuroscience, National Central University, Zhongli, Taiwan

^fDepartment of Research and Education, Taipei City Hospital, Taipei, Taiwan

Abstract—Females frequently perform better in empathy, interpersonal sensitivity, and emotional recognition than do males. The mirror-neuron system has been proposed to play an important role in social cognition. It remains to be clarified, however, whether the neuroanatomy underlying the human mirror neuron system exhibits sex differences. With the use of voxel-based morphometry analysis, a whole-brain unbiased technique to characterize regional cerebral volume differences in structural magnetic resonance images, concurrent with the dispositional empathy measures, we demonstrate that young adult females ($n=25$) had significantly larger gray matter volume in the pars opercularis and inferior parietal lobule than matched males ($n=25$) participants. Moreover, higher self-report scores in the emotional empathic disposition was tightly coupled with larger gray matter volume of the pars opercularis across all female and male participants ($P=0.002$). These results indicate that the existence of neuroanatomical sex differences in the human mirror-neuron system. They also suggest that the network of the human mirror-neuron system is strongly linked to empathy competence. Crown Copyright © 2009 Published by Elsevier Ltd on behalf of IBRO. All rights reserved.

Key words: voxel-based morphometry, neuroanatomy, sex differences, mirror-neuron system, empathy.

At a population level, an amount of compelling evidence supports the existence of gender differences in interpersonal sensitivity i.e. the ability to perceive and respond with care to the internal states (e.g. cognitive, affective, moti-

vational) of another, understand the antecedents of those states, and predict the subsequent events that will result (Decety and Batson, 2007). Specifically, females perform better on a variety of cognitive tasks tapping social sensitivity, emotional recognition, and verbal fluency (e.g. Hall, 1984; Hyde and Linn, 1988; Geary, 1998; Baron-Cohen et al., 1999; Kimura, 1999; McClure, 2000). The sex differences in interpersonal sensitivity seem to arise very early in ontogeny. For instance, when newborn babies are presented with either a live face or a mechanical mobile, females exhibit more looking preferences at the face whereas males prefer to look at the mechanical object (Connellan et al., 2001). Young female vervet monkeys favor playing with dolls whereas young male vervets favor toy trucks (Alexander and Hines, 2002). These findings in humans and non-human primates suggest a biological contribution for sex differences in social interest.

However, the issue of gender differences in empathy is quite controversial. The evidence for gender differences in empathy is high for self-report questionnaires of empathy in which it is obvious what is being indexed, but smaller or nonexistent for other types of indexes that are less self-evident with regard to their purpose (Eisenberg and Fabes, 1990). Moreover, adults' self-reports of empathy have been associated with indexes of social desirability in some studies (Cialdini et al., 1987). It is therefore crucial to investigate the neuroanatomic structures that underpin empathy in relation with gender differences. Such measures can provide more objective assessments of potential gender differences in social cognition.

The human mirror-neuron system (MNS) has been proposed to play an important role in social cognition by providing a neural mechanism for the understanding and imitation of action (e.g. Cheng et al., 2007b; Rizzolatti et al., 2001; Rizzolatti and Craighero, 2004; Gazzola et al., 2006; Kaplan and Iacoboni, 2006; Jabbi et al., 2007; Schulte-Rüther et al., 2007; Pfeifer et al., 2008). Single neuron recordings first indicate that mirror neurons, in the ventral premotor and posterior parietal cortices in rhesus monkey, fire when the monkey performs a specific action, and also when it observes an equivalent action performed by another individual (di Pellegrino et al., 1992; Gallese et al., 1996). Evidence for the existence of mirror neurons in humans is more indirect and mainly relies on functional neuroimaging experiments which indicate that the neural circuits involved in action execution overlap with those activated when actions are observed, as well as transcranial magnetic stimulation (TMS) and electroencephalography (EEG) studies that show changes in the excitability of the observer's brain

*Corresponding author. Tel: +886-2-28267338; fax: +886-2-28262285. E-mail address: chingpo@ntu.edu.tw (C.-P. Lin).

Abbreviations: ANCOVA, analysis of covariance; ASD, autism spectrum disorder; ECS, emotional contagion scale; EEG, electroencephalography; EETS, emotional empathic tendency scale; EQ, empathizing quotient; IRI, interpersonal reactivity index; MEG, magnetoencephalography; MNI, Montreal Neurological Institute; MNS, mirror-neuron system; MRI, magnetic resonance imaging; TIV, total intracranial volume; VBM, voxel-based morphometry.

regions that encode the execution of observed actions (see Fadiga and Craighero, 2004 for a review). It has been argued that the action–perception coupling mechanism plays a critical role in social interaction, such as action understanding and empathy (e.g. Gallese and Goldman, 1998; Preston and de Waal, 2002; Decety and Jackson, 2004; Decety and Lamm, 2006; Gu and Han, 2007; Cheng et al., 2007c). Thus, it is reasonable to speculate the MNS should differ between genders to reflect sex differences in social sensitivity. Some preliminary studies had demonstrated sex differences in the human MNS through analysis of magnetoencephalography (MEG) (Cheng et al., 2006), Hoffmann-reflex (Cheng et al., 2007a), and EEG (Cheng et al., 2008b). Female participants respond with stronger motor resonances than male participants, as indicated by spinal excitability and sensorimotor rhythms during the action observation. However, whether the human MNS also exhibits sex differences at the neuroanatomical structures remains to be determined.

The voxel-based morphometry (VBM) is a well-defined and fully automated unbiased whole-brain technique that can detect regionally specific differences in the brain structure on a voxel-by-voxel basis (Ashburner and Friston, 2000). This method has been cross-validated with region of interest measurements and functional data in a number of studies (e.g. Abell et al., 1999; Richardson et al., 1997; Krams et al., 1999; Sowell et al., 1999, 2000; Maguire et al., 2000; Mummery et al., 2000; Good et al., 2001). For instance, VBM has demonstrated larger gray matter volume within the hippocampus in taxi drivers, which accurately corroborated the link between region of interest (ROI) measures and behavioral performances (Maguire et al., 2000). It thus accepted that this technique can register and segment accurately subtle change of the brain structure in human subjects. Further, the brain structural imaging combined with off-line analysis of measures in cognitive performance can identify the neuroanatomical differences underpinning the cognitive measures of interest, irrespective of any task design constraints.

A number of sex differences in the brain structure, functional neuroimaging, and neurophysiology have been reported (e.g. Gur et al., 1999; Cahill et al., 2001; Good et al., 2001; Neubauer et al., 2002; Haier et al., 2005; Yamasue et al., 2008). There was consistently a significant sex effect on brain morphology, even after accounting for the larger global volumes of gray and white matter in males. Notably, in spite of variability in regional sex differences, females had been reported to show increased gray matter volume in the superior temporal sulcus as well as right inferior frontal gyrus. Here, the present study used VBM to clarify whether the human MNS exhibits sex-related structural differences and to examine if its core area, pars opercularis, is related to each participant's self-reported empathy performance.

EXPERIMENTAL PROCEDURES

Participants

A total of 50 healthy participants (25 females, 25 males) underwent magnetic resonance imaging (MRI) scanning with identical

imaging parameters after providing written informed consent. The study was approved by the local ethics committee (Yang-Ming University) and conducted in accordance with the Declaration of Helsinki. The female and male subgroups had matched age [27.6 years (S.D. 8.3, range 20–50) vs. 26.6 years (S.D. 10.4, range 19–49)] ($Z = -0.867$, $P = 0.386$) and education years [15.6 years (S.D. 2.8, range 12–18) vs. 15.5 years (S.D. 2.5, range 12–18)] ($Z = -0.312$, $P = 0.755$). All participants were right-handed, as determined by the Edinburgh handedness inventory (Oldfield, 1971). All participants had no history of neurological or psychiatric disorders and were free of medications at the time of testing. Participants received monetary compensation for their participation.

MRI scanning

MR scanning was performed on a 1.5 T MR system (Excite II; GE Medical Systems, Milwaukee, WI, USA) equipped with an eight-channel head coil. In order to avoid motion artifact generated during the scan, the subject's head was immobilized with cushions inside the coil after the alignment. A three-plane localizer scan was first conducted to optimize the scanning slices parallel to the anterior commissure–posterior commissure line. A three-dimensional fluid-attenuated inversion-recovery fast spoiled gradient recalled echo (FLAIR-FSPGR) was applied to obtain 124 contiguous T1-weighted structural images. The T1-weighted images were acquired with the following parameters: TR=8.548 ms, TE=1.836 ms, TI=400 ms, flip angle=15°, field of view (FOV)=26×26 cm, matrix size=256×256, yielding the in-plane resolution of 1.02×1.02 mm, and the slice thickness=1.5 mm.

Dispositional measures

Prior to MRI scanning, participants filled out a series of self-report dispositional measures of empathy including the Empathizing Quotient (EQ) (Baron-Cohen and Wheelwright, 2004), the Emotional Contagion Scale (ECS) (Doherty, 1997), the Emotional Empathic Tendency Scale (EETS) (Mehrabian and Epstein, 1972), and the Interpersonal Reactivity Index (IRI) (Davis, 1996; Siu and Shek, 2005). Statistical comparisons between the female and male groups were conducted using Mann-Whitney test.

Data processing for VBM

An optimized VBM protocol was followed for preprocessing and subsequent analysis of imaging data. This method (Ashburner and Friston, 2000; Good et al., 2001) was implemented within Matlab 6.5 (MathWorks, Natick, MA, USA) on statistical parametric mapping (SPM2; Wellcome Department of Imaging Neuroscience, London, UK; available online at <http://www.fil.ion.ucl.ac.uk/spm>) (Friston et al., 1995a,b). Preprocessing of the structural data followed a number of defined steps as the following:

Manual preprocessing. The scans were manually reoriented with the inter-hemispheric gap parallel to the vertical axis of the field of view and the anterior–posterior commissure line parallel to the horizontal axis. The origin was manually set on the anterior commissure. The reorientation matrix (six parameter rigid body transformation) was stored.

Creation of group-specific templates and priors. A group template of images was established directly from the data sets of the subjects to reduce any bias in template selection. The T1-weighted images were registered to the template image which is available in SPM2 using a 12 degrees of freedom affine transformation. All the registered T1-weighted images of the total 50 recruited subjects were then averaged and smoothed with an 8-mm gaussian kernel to generate the group template for the T1-weighted images. This group template served as the standard template among the study for further imaging analysis.

With the use of the SPM2 priors, the normalized MRI images were segmented into CSF, gray matter, and white matter compartments. Through the correction for non-uniformity in image intensity, the SPM segmentation employed a mixture model cluster analysis to identify voxel intensities that match particular tissue types in addition to the combination with priori probabilistic knowledge of the spatial distribution of tissues derived from gray and white matter, and CSF prior probability images (i.e. priors) (Ashburner and Friston, 1997). Next, CSF, gray matter and white matter images were smoothed with an 8-mm kernel and averaged to obtain the group-specific CSF, gray matter, and white matter priors for later segmentation of native MRI scans. Finally, before the segmentation, the skull was stripped from the normalized scans using Brain Extraction Tool (compiled in FSL 4.0; FMRIB Image Analysis Group, Oxford, UK; available online at www.fmrib.ox.ac.uk/fsl) to improve the segmentation quality (Smith et al., 2002).

Segmentation of native scans and deviation of optimized normalization parameters. All the original MRI native scans were segmented based on the group-specific CSF, gray matter, and white matter priors. This segmentation step involves an affine transformation of each scan to the group-specific T1 template with a subsequent back-projection into native space and an automated brain extraction procedure incorporating a segmentation step was used to remove non-brain tissue (Good et al., 2001). The extracted gray matter images and white matter images were then precisely-normalized to the group-specific gray matter and white matter template separately. The spatial normalization used the residual sum of squared differences as the matching criterion and included affine transformations and linear combination of smooth basis functions modeling global non-linear shape differences (Ashburner et al., 1997; Ashburner and Friston, 2000).

Optimized normalization and segmentation. The normalization parameters were then applied to the original structural images in native space, which is considered to reduce any contribution from non-brain voxels and affording optimal spatial normalization of gray matter and white matter. These normalized and skull-stripped structural images were re-sliced to a final voxel size of $2 \times 2 \times 2 \text{ mm}^3$ and segmented into gray and white matter and CSF partitions. The Jacobian determinants derived from the spatial normalization for the correction of volume changes were introduced during the non-linear spatial transformations, which would

modulated the partitioned gray matter images and white matter images analysis of regional differences into an absolute amount (volume) of gray and white matter. Before the voxel-wise group comparisons, an 8-mm full-width at half maximum isotropic gaussian kernel smoothed all normalized, segmented, and modulated images.

Statistic analysis

Analysis of covariance (ANCOVA). For the VBM results, ANCOVA implemented in SPM2 was employed with the individual tissue volumes as the dependent variable at each intracerebral voxel in standard space, co-varying for total intracranial volume (TIV) to uncover the voxel-wise comparison between genders in gray and white matter volume. An uncorrected P -value < 0.001 as well as a cluster size more than 30 contiguous voxels was set to putatively detect the significant between-group differences. Peak localization was driven from the coordinates from the Montreal Neurological Institute (MNI) template. We used a non-linear algorithm, provided by Matthew Brett (MRC Cognition and Brain Sciences Unit, Cambridge, UK), to transform MNI into Talairach coordinates. The localization of the peak coordinates was identified on the basis of the Talairach and Tournoux (1988) atlas.

Correlation analysis. To elucidate the neuroanatomical correlates of individual differences in empathy, partial correlation analyses with TIV as a confounding covariate were performed to correlate the dispositional empathy scores with the regional brain volumes within each sex group separately. The regional gray matter volumes were extracted from the peak coordinates showing a sex effect. The correlation analysis was also examined in the sex-combined sample to test the specificity of correlation. The threshold for statistical significance was set at $P < 0.05$ with correction for multiple comparisons.

RESULTS

Dispositional measures

The characteristics of the sample are given in Table 1. There was no significant difference between female and male participants in age, education, or handedness. The analysis of the dispositional measures revealed that there

Table 1. Characteristics and dispositional measures of the female and male subgroups

Variable	Male ($n=25$)		Female ($n=25$)		Mann-Whitney	
	Mean	S.D.	Mean	S.D.	Z Value	P
Demographics						
Age (range)	26.6 (19–49)	10.4	27.6 (20–50)	8.3	–0.867	0.386
Education years (range)	15.5 (12–18)	2.5	15.6 (12–18)	2.8	–0.312	0.755
Interpersonal Reactivity Index						
Fantasy	15.3	5.3	17.7	5.4	–1.635	0.102
Personal distress	11.5	4.6	13.6	4.5	–1.275	0.202
Perspective taking	17.3	4.3	18.4	4.2	–1.159	0.246
Empathic concern	18.9	3.4	21.1	2.5	–2.109	0.035
Emotional Contagion Scale	25.4	6.7	29.5	6.2	–2.277	0.023
Emotional Empathic Tendency Scale	12.8	18.0	29.6	15.3	–3.174	0.002
Empathizing Quotient	39.0	9.3	43.5	8.8	–1.846	0.065
Systemizing Quotient	34.0	11.1	30.3	8.7	–1.156	0.248
Global brain measures						
Total gray matter volume (ml)	616	61	586	49	–2.299	0.021
Total white matter volume (ml)	374	32	418	39	–3.910	0.000
Total intracranial volume (ml)	1034	94	959	75	–3.172	0.002

was a significant gender difference in the scores of the ECS ($Z=-2.277$, $P=0.023$), the EETS ($Z=-3.174$, $P=0.002$), and the empathic concern subscale of IRI ($Z=-2.109$, $P=0.035$). Females reported to have higher scores than males in these dispositional measures of empathy. Instead, there were no significant differences between the genders in the EQ, SQ, and other subscales of IRI.

VBM

Considering that participants' age was well matched between the enrolled female and male groups (females 27.6 ± 8.3 years, males 26.6 ± 10.4 years), we uncovered the global effects of gender in the white matter and the gray matter volume. The mean volume of gray matter was significantly larger in males (0.616 ± 0.061 l) than in females (0.586 ± 0.049 l) ($Z=-2.299$, $P=0.021$). The white matter volume also display a similar pattern (females: 0.374 ± 0.032 l; males: 0.418 ± 0.039 l) ($Z=-2.299$, $P<0.001$). Accordingly, males (1.034 ± 0.094 l) had significantly larger TIV than females (0.959 ± 0.075 l) ($Z=-3.172$, $P=0.002$). The gray-white absolute volume ratio was 1.57 for females and 1.47 for males.

In addition to the global brain volume, the regional gray matter volume also differs between the genders (Table 2). Females had larger gray matter volume than males in the social cognition network with the involvement of medial prefrontal cortex and lateral occipital cortex as well as the human MNS. Of note, females showed larger gray matter volume of the right pars opercularis and right anterior inferior parietal lobule, as the core areas of the human MNS. Instead, males significantly displayed larger gray matter volume in the amygdala, parahippocampus, and lentiform nucleus (Fig. 1).

Correlation analysis

The correlation analysis indicated that the structural volume of regions that belong to the human MNS correlates

with dispositional empathy measures (Fig. 2). Specifically, within all females and males, the gray matter volume of pars opercularis (x 54, y 6, z 26) of the right hemisphere, a key region of the human MNS showed a positive correlation with the ECS ($P=0.016$), the EETS ($P=0.002$), and the empathic concern subscale of the IRI ($P=0.040$). The gray matter volume of the right inferior parietal lobule (x 48, y -54, z 50) positively correlated with the EETS ($P=0.027$) and the IRI empathic concern scale ($P=0.048$). Moreover, the volume of right medial prefrontal cortex (x 10, y 68, z -6) had a positive correlation with the empathic concern subscale of the IRI ($P=0.002$). The other regions did not reach any significant correlation with the other empathy measures.

Within males, there was a significant correlation between the right pars opercularis volume and the EQ ($P=0.039$). The medial prefrontal cortex also correlated with the EQ ($P=0.022$) and the empathic concern of the IRI ($P=0.030$). Instead, within females, the right pars opercularis volume correlated with the fantasy scale of the IRI ($P=0.009$).

DISCUSSION

The results of the present study demonstrate that the neuroanatomical volume of regions that belong to the human MNS exhibits sex differences. In accordance with previous MEG, Hoffman-reflex, and EEG studies (Cheng et al., 2006, 2007, 2008), female participants display larger gray matter volumes than male participants in the pars opercularis and inferior parietal lobule of the right hemisphere. In addition, the gray matter volume in the core areas of the human MNS, the right pars opercularis and the right inferior parietal lobule, positively correlated with the EETS across all female and male participants. Moreover, the sex differences in the human MNS, as first noted by differential gray matter volume through VBM analysis provided here, appear in a similar direction to previous neuroanatomical studies (Hadjikhani et al., 2006; Yamasue

Table 2. Gender differences in regional brain volume

Anatomical location	Peak coordinate			Z score	FDR-corrected P	Cluster size (mm ³) ($P<0.001$)
	x	y	z			
Larger in females ($n=25$)						
Pars opercularis	54	6	26	4.21	0.005	59
Inferior parietal lobule	48	-54	50	4.83	0.002	123
Superior frontal gyrus	22	64	-8	4.04	0.007	35
Lateral occipital cortex	-42	-74	36	5.31	0.001	1280
Precentral gyrus	44	-16	40	4.17	0.006	92
Angular gyrus	42	-68	26	4.01	0.007	105
Cuneus	14	-92	-36	3.77	0.012	86
Precentral gyrus	-42	-6	56	3.68	0.015	50
Medial prefrontal cortex	-6	56	-12	3.75	0.013	30
Brainstem	4	-66	-50	4.21	0.005	270
Larger in males ($n=25$)						
Amygdala	-20	-6	-18	4.01	0.035	85
Lentiform nucleus	-28	6	2	4.42	0.034	443
Lentiform nucleus	18	8	-10	4.32	0.034	225
Parahippocampal gyrus	20	-12	-20	4.03	0.035	116

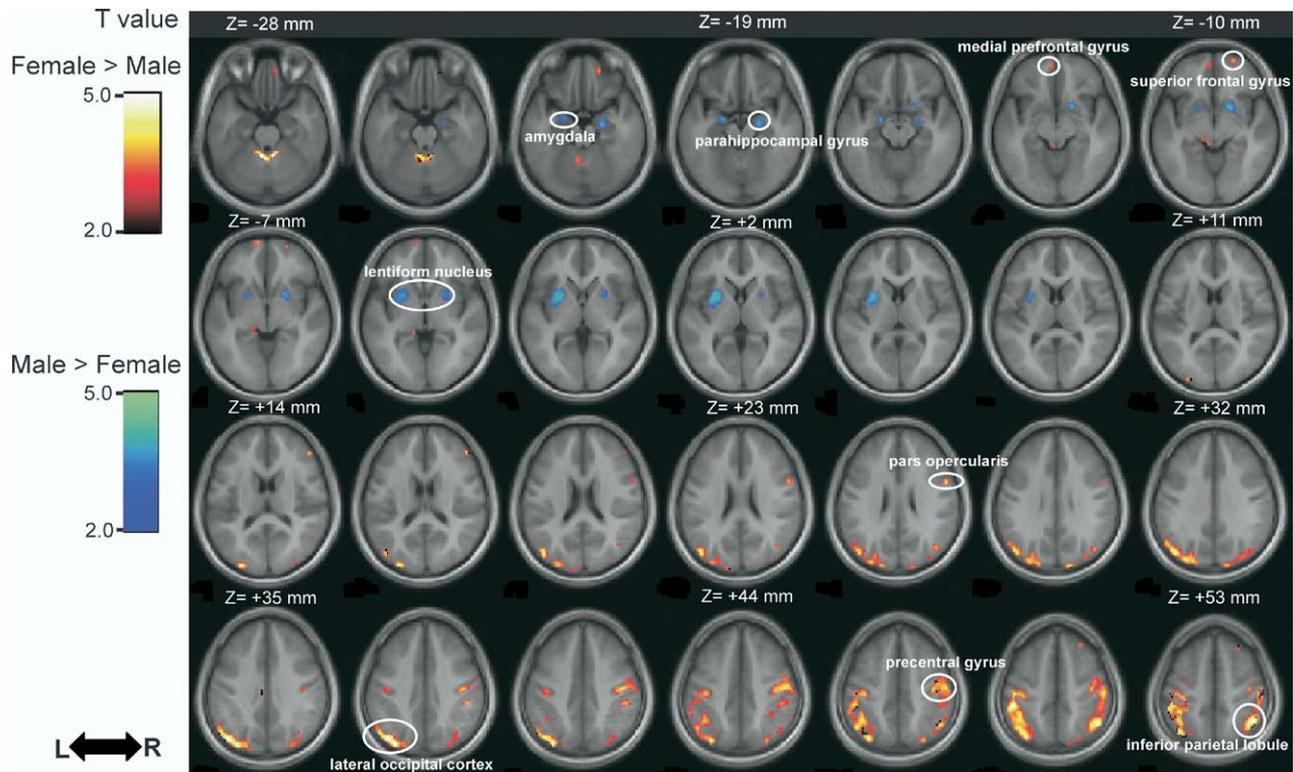


Fig. 1. Gender differences in regional brain volume. The gray matter regions showing significant sex-dimorphism were rendered onto the averaged horizontal images of the whole sample ($N=50$) (voxel threshold: uncorrected $P<0.001$). The gray matter regions that are larger for females than males are presented in red to yellow. Conversely, the gray matter regions that are larger for males are presented in blue to green. The Z-coordinate for each coronal slice in the MNI space is given in millimeters. L: left. R: right. For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.

et al., 2008). It may lend some indirect support the extreme male brain theory (Baron-Cohen et al., 2005) and may also offer some insight to the mirror neuron account in the autism spectrum disorders (ASDs) (Williams et al., 2001).

Our data concur with well-established findings of larger global brain volumes in males (e.g. Peters, 1991; Good et al., 2001). Further, we showed that the gray–white absolute volume ratio was 1.57 for females and 1.47 for males, within a range between approximately 1 and 3 from previous literature reports (e.g. Good et al., 2001; Haier et al., 2005). Besides, the present findings are consistent with previous findings of sexual dimorphism in regional brain structures. Females with larger gray matter volume of the right inferior frontal gyrus, inferior parietal lobule, and medial prefrontal cortex but males with larger amygdala and cerebellum volumes have been reported when sex differences in global brain measures were taken into account (e.g. Fredrikse et al., 1999; Good et al., 2001; Yamasue et al., 2008).

Of note, the peak coordinates in the pars opercularis and inferior parietal lobule are located within a sphere with a radius of 10 mm in the mean coordinates of the human MNS from previous functional MRI studies of observation and imitation of others actions (Nishitani et al., 2005; Chao and Martin, 2000; Buccino et al., 2001; Nishitani et al., 2005; Cheng et al., 2007a), understanding the intention of others (Villabos et al., 2005; Iacoboni et al., 2005; Dapretto et al., 2006; Kaplan and Iacoboni, 2006; Jabbi et al., 2007;

Pfeifer et al., 2008), and empathy (Carr et al., 2003; Gazzola et al., 2006; Cheng et al., 2007c; Lamm et al., 2007; Schulte-Rüther et al., 2007). Of note, the present findings are also in line with a recent VBM study, which demonstrated healthy female participants with larger gray matter volume in the social brain regions as well as the human MNS (Yamasue et al., 2008). One recent fMRI study found that females recruited more mirror neurons than males during empathic face-to-face interactions (Schulte-Rüther et al., 2008). Also, EEG evidence supported sex differences in empathy for pain (Han et al., 2008). The mu rhythms, as a reliable indicator of the mirror neurons activity within the prefrontal and parietal network, appeared sexually dimorphic (Oberman et al., 2005, 2008; Pineda, 2005; Cheng et al., 2006, 2008a). Here, the current findings disclosed sex differences in the neuroanatomical underpinnings of the human MNS at a similar location and in the same direction as these previous studies.

Our study may also contribute to understanding of some aspects of the neural pathophysiology of ASDs, characterized by impaired social reciprocity, and which has disproportionately high incidences in males (Folstein and Rosen-Sheidley, 2001). Williams et al. (2001) posited that individuals with ASD have impaired social interaction and communication because it results from consequent developmental failures of the MNS. Recent studies have demonstrated dysfunctions in the MNS of the patients with ASD

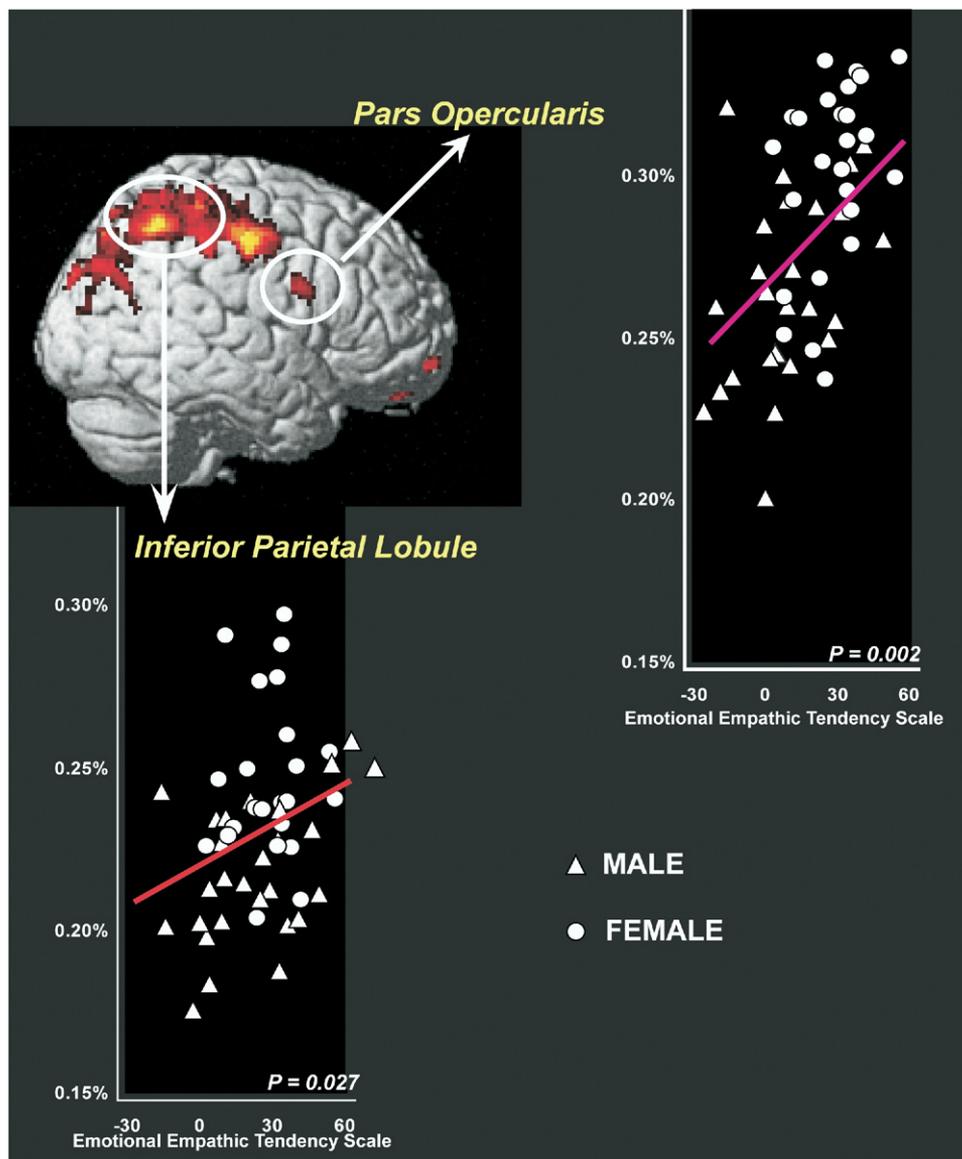


Fig. 2. Neuroanatomical correlates of the human MNS and the EETS. The horizontal axis depicts the scoring of the EETS and the vertical axis represents the ratio of the regional gray matter volume over the TIV. (A) Pars opercularis. (B) Inferior parietal lobule of the right hemisphere.

(Nishitani et al., 2004; Oberman et al., 2005; Théoret et al., 2005; Villalobos et al., 2005; Dapretto et al., 2006). Particularly, individuals with ASDs show reduced gray matter volume and cortical thickness in the inferior frontal gyrus (Abell et al., 1999; Hadjikhani et al., 2006). Here, similarly, healthy male participants showed less gray matter volume in the inferior frontal gyrus than female participants. Interestingly, Baron-Cohen et al. (2005) proposed the extreme male brain theory of autism which considers that the ASDs represent an extreme of the normal male brain profile with impaired empathizing and enhanced systemizing. It thus suggested that specific aspects of autistic neuroanatomy may be extremes of normal male neuroanatomy (Baron-Cohen et al., 2005). In our study, higher self-report scoring of empathic concern was tightly coupled with the larger gray matter volume of right pars opercularis. The current

findings may cast some light on the normal male MNS neuroanatomy, as measured with VBM, and add support to the extreme brain theory and mirror neuron account of ASDs.

Some limitations of our study should be addressed. First, the enrolled participants, mainly college students, might not be representative of the Chinese general population. Second, the current study enrolled only Chinese participants. It is likely that the pure ethnicity may contribute to the finding clarity. Also, the present findings appear similar to the findings of Yamasue et al. (2008) in only Japanese participants. Considering that ethnic differences may affect brain morphology (Zilles et al., 2001), further application to other ethnicities and a larger sample are indicated to infer the current findings to the general population.

CONCLUSION

Through VBM analysis combined with dispositional measures of empathy, our study shows that the neuroanatomical underpinnings of the human MNS exhibit gender differences. In line with our previous EEG/MEG and H-reflex studies, the results support the idea that female subjects show stronger motor resonances during action observation. Importantly, the present findings indirectly lend support to the extreme male brain theory put forward by Baron-Cohen et al. (2005), and may cast some light on the mirror-neuron dysfunction (Williams et al., 2001) in ASDs.

Acknowledgments—We gratefully acknowledge support by grants from the National Science Council (NSC 97-2752-H-010-004-PAE; NSC 97-2410-H-010-003-MY2) and Academia Sinica (AS-93-TP-C05), Taiwan. Dr. Jean Decety was supported by an NSF grant (# BCS-0718480). The authors also acknowledge support from MRI core facility in NYMU.

REFERENCES

- Abell F, Krams M, Ashburner J, Passingham R, Friston K, Frackowiak R, Happe F, Frith C, Frith U (1999) The neuroanatomy of autism: a voxel-based whole brain analysis of structural scans. *Neuroreport* 10:1647–1651.
- Alexander GM, Hines M (2002) Sex differences in response to children's toys in nonhuman primates (*Cercopithecus aethiops sabaeus*). *Evol Hum Behav* 23:467–479.
- Ashburner J, Friston KJ (1997) Multimodal image coregistration and partitioning: a unified framework. *Neuroimage* 6:209–217.
- Ashburner J, Friston KJ (2000) Voxel-based morphometry: the methods. *Neuroimage* 11:805–821.
- Baron-Cohen S, O'Riordan M, Joines R, Stone V, Plaisted K (1999) Recognition of faux pas by normally developing children with Asperger syndrome or high-functioning autism. *J Autism Dev Disord* 29:407–418.
- 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.
- Baron-Cohen S, Knickmeyer R, Belmonte MK (2005) Sex differences in the brain: implications for explaining autism. *Science* 310:819–823.
- Buccino G, Binkofski F, Fink GR, Fadiga L, Fogassi L, Gallese V, Seitz RJ, Zilles K, Rizzolatti G, Freund HJ (2001) Action observation activates premotor and parietal areas in a somatotopic manner: an fMRI study. *Eur J Neurosci* 13:400–404.
- Cahill L, Haier RJ, White NS, Fallon J, Kilpatrick J, Lawrence C, Potkin SG, Alkire MT (2001) Sex-related differences in amygdala activity during emotionally influenced memory storage. *Neurobiol Learn Mem* 75:1–9.
- 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 U S A* 100:5497–5502.
- Chao LL, Martin A (2000) Representation of manipulable man-made objects in the dorsal stream. *Neuroimage* 12:478–484.
- Cheng Y, Tzeng OJL, Decety J, Imada T, Hsieh JC (2006) Gender differences in the human mirror system: a magnetoencephalography study. *Neuroreport* 17:1115–1119.
- Cheng Y, Decety J, Lin CP, Hsieh JC, Hung D, Tzeng OJL (2007a) Sex differences in spinal excitability during observation of bipedal locomotion. *Neuroreport* 18:887–890.
- Cheng Y, Melzoff A, Decety J (2007b) Motivation modulates the activity of the human mirror-neuron system. *Cereb Cortex* 17:1979–1986.
- Cheng Y, Lin CP, Liu HL, Hsu Y, Lim K, Hung D, Decety J (2007c) Expertise modulates the perception of pain in others. *Curr Biol* 17:1708–1713.
- Cheng Y, Yang CY, Lin CP, Lee PL, Decety J (2008a) The perception of pain in others suppresses somatosensory oscillations. *Neuroimage* 40:1833–1840.
- Cheng Y, Lee PL, Yang CY, Lin CP, Hung D, Decety J (2008b) Gender differences in the mu rhythm of the human mirror-neuron system. *PLoS ONE* 3:e2113.
- Cialdini RB, Schaller M, Houlihan D, Arps K, Fultz J, Beaman AL (1987) Empathy-based helping: Is it selflessly or selfishly motivated? *J Pers Soc Psychol* 52:749–758.
- Connellan J, Baron-Cohen S, Wheelwright S, Batki A, Ahluwalia J (2001) Sex differences in human neonatal social perception. *Infant Behav Dev* 23:113–118.
- Dapretto M, Davies MS, Pfeifer JH, Scott AA, Sigman M, Bookheimer SY, Iacoboni M (2006) Understanding emotions in others: mirror neuron dysfunction in children with autism spectrum disorders. *Nat Neurosci* 9:28–30.
- Davis MH (1996) *Empathy: A social psychological approach*. Madison, WI: Westview Press.
- Decety J, Jackson PL (2004) The functional architecture of human empathy. *Behav Cogn Neurosci Rev* 3:71–100.
- Decety J, Lamm C (2006) Human empathy through the lens of social neuroscience. *Sci World J* 6:1146–1163.
- Decety J, Batson CD (2007) Social neuroscience approaches to interpersonal sensitivity. *Soc Neurosci* 2:151–157.
- di Pellegrino G, Fadiga L, Fogassi L, Gallese V, Rizzolatti G (1992) Understanding motor events: a neurophysiological study. *Exp Brain Res* 91:176–180.
- Doherty RW (1997) The emotional contagion scale: A measure of individual differences. *J Nonverbal Behav* 21:131–154.
- Eisenberg N, Fabes RA (1990) Empathy: conceptualization, measurement, and relation to prosocial behavior. *Motiv Emotion* 14:131–149.
- Fadiga L, Craighero L (2004) Electrophysiology of action representation. *J Clin Neurophysiol* 21:157–169.
- Folstein SE, Rosen-Sheidley B (2001) Genetics of autism: complex aetiology for a heterogeneous disorder. *Nat Rev Genet* 2:943–955.
- Frederikse ME, Lu A, Aylward E, Barta P, Peralson G (1999) Sex differences in the inferior parietal lobule. *Cereb Cortex* 9:896–901.
- Friston KJ, Frith CD, Frackowiak RS, Turner R (1995a) Characterizing dynamic brain responses with fMRI: a multivariate approach. *Neuroimage* 2:166–172.
- Friston KJ, Frith CD, Turner R, Frackowiak RS (1995b) Characterizing evoked hemodynamics with fMRI. *Neuroimage* 2:157–165.
- Gallese V, Fadiga L, Fogassi L, Rizzolatti G (1996) Action recognition in the premotor cortex. *Brain* 119:593–609.
- Gallese V, Goldman A (1998) Mirror neurons and the simulation theory of mind-reading. *Trends Cogn Sci* 2:493–501.
- Gazzola V, Aziz-Zadeh L, Keysers C (2006) Empathy and the somatotopic auditory mirror system in humans. *Curr Biol* 16:1824–1829.
- Geary DC (1998) *Male, female: the evolution of human sex differences*. Washington, DC: American Psychological Association.
- Good CD, Johnsrude I, Ashburner J, Henson RNA, Friston KJ, Frackowiak RSJ (2001) Cerebral asymmetry and the effects of sex and handedness on brain structure: a voxel-based morphometric analysis of 465 normal adult human brains. *Neuroimage* 14:685–700.
- Gu X, Han S (2007) Attention and reality constraints on the neural processes of empathy for pain. *Neuroimage* 36:256–267.
- Gur RC, Turetsky BI, Matsui M, Yan M, Bilker W, Hughett P, Gur RE (1999) Sex differences in brain gray and white matter in healthy young adults: correlations with cognitive performance. *J Neurosci* 19:4065–4072.
- Hadjikhani N, Joseph RM, Snyder J, Tager-Flusberg H (2006) Anatomical differences in the mirror neuron system and social cognition. *Cereb Cortex* 16:1276–1282.

- Haier RJ, Jung RE, Yeo RA, Head K, Alkire MT (2005) The neuroanatomy of general intelligence: sex matters. *Neuroimage* 25:320–327.
- Hall JA (1984) *Nonverbal sex differences*. Baltimore: Johns Hopkins University Press.
- Han S, Fan Y, Mao L (2008) Gender difference in empathy for pain: an electrophysiological investigation. *Brain Res* 1196:85–93.
- Hyde J, Linn M (1988) Gender differences in verbal ability: a meta-analysis. *Psychol Bull* 104:53–69.
- Iacoboni M, Molnar-Szakacs I, Gallese V, Buccino G, Mazziotta JC, Rizzolatti G (2005) Grasping the intentions of others with one's own mirror neuron system. *PLoS Biol* 3:e79.
- Jabbi M, Swart M, Keysers C (2007) Empathy for positive and negative emotions in the gustatory cortex. *Neuroimage* 34:1744–1753.
- Kaplan JT, Iacoboni M (2006) Getting a grip on other minds: mirror neurons, intention understanding, and cognitive empathy. *Soc Neurosci* 1:175–183.
- Kimura D (1999) *Sex and cognition*. Cambridge, MA: Massachusetts Institute of Technology Press.
- Krams M, Quinton R, Ashburner J, Friston KJ, Frackowiak RS, Bouloux PM, Passingham RE (1999) Kallmann's syndrome: mirror movements associated with bilateral corticospinal track hypertrophy. *Neurology* 52:816–822.
- 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.
- Maguire EA, Gadian DG, Johnsrude IS, Good CD, Ashburner J, Frackowiak RSJ, Frith CD (2000) Navigation-related structural change in the hippocampi of taxi drivers. *Proc Natl Acad Sci U S A* 97:4398–4403.
- McClure EB (2000) A meta-analytic review of sex differences in facial expression processing and their development in infants, children, and adolescents. *Psychol Bull* 126:424–453.
- Mehrabian A, Epstein N (1972) A measure of emotional empathy. *J Pers* 40:525–543.
- Mumery CJ, Patterson K, Price CJ, Ashburner J, Frackowiak RS, Hodges JR (2000) A voxel-based morphometry study of semantic dementia: relationship between temporal lobe atrophy and semantic memory. *Ann Neurol* 47:36–45.
- Neubauer AC, Fink A, Schrausser DG (2002) Intelligence and neural efficiency: the influence of task content and sex on the brain-IQ relationship. *Intelligence* 30:515–536.
- Nishitani N, Schurmann M, Amunts K, Hari R (2005) Broca's region: from action to language. *Physiology* 20:60–69.
- Nishitani N, Avikainen S, Hari R (2004) Abnormal imitation-related cortical activation sequence in Asperger's syndrome. *Ann Neurol* 55:558–562.
- Oberman LM, Hubbard EM, McCleery JP, Altschuler EL, Ramachandran VS, Pineda JA (2005) EEG evidence for mirror neuron dysfunction in autism spectrum disorders. *Brain Res Cogn Brain Res* 24:190–198.
- Oberman LM, Ramachandran VS, Pineda JA (2008) Modulation of mu suppression in children with autism spectrum disorders in response to familiar or unfamiliar stimuli: the mirror neuron hypothesis. *Neuropsychologia* 46:1558–1565.
- Oldfield RC (1971) The assessment and analysis of handedness: the Edinburgh Inventory. *Neuropsychologia* 9:97–113.
- Peters M (1991) Sex differences in the human brain size and the general meaning of differences in brain size. *Can J Psychol* 45:507–522.
- Pfeifer JH, Iacoboni M, Mazziotta JC, Dapretto M (2008) Mirroring others' emotions relates to empathy and interpersonal competence in children. *Neuroimage* 39:2076–2085.
- Pineda JA (2005) The functional significance of mu rhythms: translating "seeing" and "hearing" into "doing." *Brain Res Brain Res Rev* 50:57–68.
- Preston SD, de Waal FBM (2002) Empathy: its ultimate and proximate bases. *Behav Brain Sci* 25:1–71.
- Richardson MP, Friston KJ, Sisodiya SM, Koepp MJ, Ashburner J, Free SL, Brooks DJ, Duncan JS (1997) Cortical grey matter and benzodiazepine receptors in malformations of cortical development. A voxel-based comparison of structural and functional imaging data. *Brain* 120:1961–1973.
- Rizzolatti G, Fogassi L, Gallese V (2001) Neurophysiological mechanisms underlying the understanding and imitation of action. *Nat Rev Neurosci* 2:661–670.
- Rizzolatti G, Craighero L (2004) The mirror-neuron system. *Annu Rev Neurosci* 27:169–192.
- Schulte-Rüther M, Markowitsch HJ, Fink GR, Piefke M (2007) Mirror neuron and theory of mind mechanisms involved in face-to-face interactions: a functional magnetic resonance imaging approach to empathy. *J Cogn Neurosci* 19:1354–1372.
- Schulte-Rüther M, Markowitsch HJ, Shah NJ, Fink FR, Piefke M (2008) Gender differences in brain networks supporting empathy. *Neuroimage* 42(1):393–403.
- Siu AMH, Shek DTL (2005) Validation of the Interpersonal Reactivity Index in a Chinese context. *Res Social Work Prac* 15:118.
- Smith SM, Zhang Y, Jenkinson M, Chen J, Matthew PM, Federico A, De Stefano N (2002) Accurate, robust, and automated longitudinal and cross-sectional brain change analysis. *Neuroimage* 17:479–489.
- Sowell ER, Thompson PM, Holmes CJ, Batth R, Jernigan TL, Toga AW (1999) Localizing age-related changes in brain structure between childhood and adolescence using statistical parametric mapping. *Neuroimage* 9:587–597.
- Sowell ER, Levitt J, Thompson PM, Holmes CJ, Blanton RE, Kornsand DS, Caplan R, McCracken J, Asarnow R, Toga AW (2000) Brain abnormalities in early-onset schizophrenia spectrum disorder observed with statistical parametric mapping of structural magnetic resonance images. *Am J Psychiatry* 157:1475–1484.
- Talairach J, Tournoux P (1988) *Co-planar stereotaxic atlas of the human brain*. New York: Thieme.
- Théoret H, Hallogan E, Kobayashi M, Fregni F, Tager-Flusberg H, Pascual-Leone A (2005) Impaired motor facilitation during action observation in individuals with autism spectrum disorder. *Curr Biol* 15:R84–R85.
- Villabos ME, Mizuno A, Dahl BC, Kemmotsu N, Müller RA (2005) Reduced functional connectivity between V1 and inferior frontal cortex associated with visuomotor performance in autism. *Neuroimage* 25:916–925.
- Williams JHG, Whiten A, Suddendorf T, Perrett DI (2001) Imitation, mirror neurons and autism. *Neurosci Biobehav Rev* 25:287–295.
- Yamasue H, Abe O, Suga M, Yamada H, Rogers MA, Aoki S, Kato N, Kasai K (2008) Sex-linked neuroanatomical basis of human altruistic cooperativeness. *Cereb Cortex* 18:2331–2340.
- Zilles K, Kawashima R, Dabringhaus A, Fukuda H, Schormann T (2001) Hemispheric shape of European and Japanese brains: 3-D MRI analysis of intersubject variability, ethnical, and gender differences. *Neuroimage* 13:262–271.