Sex-Linked Neuroanatomical Basis of Human Altruistic Cooperativeness

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Human altruistic cooperativeness, one of the most important components of our highly organized society, is along with a greatly enlarged brain relative to body size a spectacular outlier in the animal world. The "social-brain hypothesis" suggests that human brain expansion reflects an increased necessity for information processing to create social reciprocity and cooperation in our complex society. The present study showed that the young adult females ($n = 66$) showed greater Cooperativeness as well as larger relative global and regional gray matter volumes (GMVs) than the matched males ($n = 89$), particularly in the social-brain regions including bilateral posterior inferior frontal and left anterior medial prefrontal cortices. Moreover, in females, higher cooperativeness was tightly coupled with the larger relative total GMV and more specifically with the regional GMV in most of the regions revealing larger in female sex-dimorphism. The global and most of regional correlations between GMV and Cooperativeness were significantly specific to female. These results suggest that sexually dimorphic factors may affect the neurodevelopment of these "social-brain" regions, leading to higher cooperativeness in females. The present findings may also have an implication for the pathophysiology of autism; characterized by severe dysfunction in social reciprocity, abnormalities in social-brain, and disproportionately low probability in females.

Keywords: altruism, cooperativeness, sex difference, social brain, voxel-based morphometry

Introduction

Human altruistic cooperation is one of the most important components of our highly organized society and of what characterizes us as human (Fehr and Fischbacher 2003). The idea of reciprocity has been proposed to account for important patterns of human altruism such as that toward nonrelatives, which represent a spectacular outlier in the animal world (Gintis et al. 2003; Silk et al. 2005; Nowak and Sigmund 2005). Humans have memory systems capable of keeping complex information concerning faces and good- or bad-feelings toward people, even those who they do not encounter for years at a time. In comparison, most other species exhibit reciprocity only over very short timescales, if at all. Therefore, considerable information processing capacity is a prerequisite for reciprocal cooperativeness (Pennisi 2005).

One can postulate that the unusually large brain for our body size may be correlated with high altruistic cooperativeness in humans. In fact, evolutionary biologists have put forward the "social-brain hypothesis," which sees social complexity as a driving force for information processing capacity in brain evolution (Dunbar 1998, 2003). Although the theory was based on evidence of positive correlation between social complexity and relative neocortex volume in primates (Dunbar 1998; Reader and Laland 2002), there is no human evidence that neocortex volume correlates with indices representing human social function.

Although human altruistic cooperativeness represents a huge anomaly in the animal world, there is much individual heterogeneity in our altruistic cooperativeness. For example, although in humans an excessive deviation in this trait is observed in severe mental disorders such as autism (Soderstrom et al. 2002), one of the major factors contributing to such heterogeneity is sex difference among healthy individuals (Clutton-Brock et al. 2002). In humans, females tend to show strong cooperativeness across nations and cultures (Cloninger et al. 1993; Brandstrom et al. 2001; Farmer et al. 2003), although previous literature showed some inconsistency (Rapoport and Chammah 1965). Because human altruistic cooperativeness has recently been thought to evolve with genes (Fehr and Fischbacher 2003), relatively specific effects of X-linked genes on social cognition (Check 2005; Ross et al. 2005; Skuse 2005) may at least in part explain such sex differences in altruistic cooperativeness. Recent functional imaging studies have reported activation of posterior superior temporal gyrus (pSTG), posterior inferior frontal gyrus (pIFG), anterior medial prefrontal cortex (amPFC), anterior insula, and fusiform gyrus as neural correlates of human altruistic cooperativeness and related factors such as empathy, understanding other's emotion, and interpersonal interaction (McCabe et al. 2001; Rilling et al. 2002; Carr et al. 2003; Decety et al. 2004; Singer et al. 2004; Iacoboni et al. 2005). Furthermore, a few studies have suggested sex differences in these activations (Leibenluft et al. 2004; Azim et al. 2005; Platek et al. 2005; Singer et al. 2006). The above findings suggest it is necessary to consider the effects of sex in attempting to uncover the neuroanatomical underpinnings of human altruistic cooperativeness.

Another line of evidence has suggested that neuroanatomy is a highly heritable trait marker as estimated from magnetic resonance imaging (MRI) gray matter volume (GMV) data of twins (Baare et al. 2001; Thompson et al. 2001; Geschwind et al. 2002; Wright et al. 2002), and many studies have shown sex differences in the neuroanatomy (Gur et al. 1999; Good et al. 2001a; Luders et al. 2004). Genetic factors, which include X-linked genes, promote sex-dimorphism in brain anatomy directly by modulating early gonadal secretions (Carrer and Cambiasso 2002; Simerly 2002). Therefore, sex differences of neuroanatomy are thought to be one of the major phenotypes of X-linked genes (Arnold 2004). Furthermore, sex-dimorphism in brain anatomy may provide clues for understanding the

neural background of sex-biased probability of mental illness (Andreasen 2005; Baron-Cohen et al. 2005), whereas the behavioral correlates of sex-dimorphism in brain morphology as yet remain unclear.

Taken together, sex differences in altruistic cooperativeness and neuroanatomy might at least in part share a genetic background. Furthermore, the shared factors might influence the altruism–neuroanatomy relationship. Therefore, there are reasonable grounds to predict a sex-linked correlation between individual differences in altruistic cooperativeness and regional GMV of the social brain regions. In addition, based on the "social-brain hypothesis" (Dunbar 1998), altruistic cooperativeness is expected to correlate even with total neocortex volume. Because recent research in genetics has suggested that within-species variation precedes between species variation (Insel 2006), between-species differences in social behavior and social-brain development might suggest a link between within human individual differences in social-brain morphology and social behavior. However, little is known about the neuroanatomical basis of altruism, although a few recent studies (Moll et al. 2006; Harbaugh et al. 2007; Tankersley et al. 2007) have studied neural correlates of human altruism. For example, Tankersley et al. (2007) argued that the individual differences in activation of superior temporal sulcus associated with social learning predict individual's differences in altruism. Furthermore, the relationship between gender and neural correlates of altruism has never been studied.

The use of self-report questionnaires such as Temperament and Character Inventory (TCI) has been well-established as a means to assess individual differences in behavioral traits (Cloninger 1987; Cloninger et al. 1993). In the *Cooperativeness* subscale of TCI (C), cooperative individuals are described as socially tolerant, empathic, helpful, and compassionate (Cloninger et al. 1993). According to the original concept of Cloninger et al. (1993), temperament is independently heritable, manifest early in life, and involves preconceptual biases in perceptual memory and habit formation, whereas Character mature in adulthood and influence personal and social effectiveness by insight learning about self concepts. However, they also assumed that genetic factors are as important for 3 dimensions of character development in TCI, including C, as they are for temperament. In accordance with the theory, previous studies have reported a familiality of C (Farmer et al. 2003; Ando et al. 2004). Previous studies have reported that individuals who have less social reciprocity, such as subjects with autism-spectrum disorder (Soderstrom et al. 2002; Anckarsater et al. 2006) and with antisocial behavior (Tremblay et al. 1994; Ball et al. 1998), scored low in C. Therefore, the index seems to be suitable for a probe to index individual differences in altruistic cooperativeness.

The present study explored the neuroanatomical basis of human altruistic cooperativeness and its relationship to sex using voxel-based morphometry (VBM) (Good et al. 2001b) throughout the entire brain in healthy young adults. Therefore, the study was designed 1) to replicate the sex-dimorphism of global and regional brain morphology, 2) to identify the correlation between individual differences in C indexed by TCI and global and regional GMVs, and 3) to examine whether or not sex differences exist in the association between global and regional GMV and human altruistic cooperativeness.

Materials and Methods

Participants and Clinical Evaluation

A total of 155 Japanese right-handed (Oldfield 1971) subjects (89 male/ 66 female), mainly college students, hospital staff, and their acquaintances, participated in the study. Because the present study was concerned with trait aspects of brain morphology and personality, the age of subjects was restricted to the 3rd and 4th decades of life to minimize aging and menopausal effect on brain morphology. The participants were interviewed by a trained psychiatrist (H.Y. or M.S.) to be screened for the presence or absence of neuropsychiatric disorders through the Structured Clinical Interview for DSM-IV Axis I Disorder (American Psychiatric Association 1994), Non-patient Edition (First et al. 1997). Self- and parental-socio-economic state (SES) were assessed using the Hollingshead scale (1965). These interviews were performed on the same day as MR-scanning. The ethical committee of the University of Tokyo Hospital approved this study. After a complete explanation of the study, written informed consent was obtained from all participants. None of the subjects had a history of neuropsychiatric disorder, serious head trauma with any known cognitive consequences or loss of consciousness for more than 5 min, alcohol/substance abuse, or dependence. All participants had to have IQ greater than 75. Each subject completed a valid Japanese translation (Takeuchi et al. 1993; Kijima et al. 2000) of 240-item TCI (Cloninger 1987; Cloninger et al. 1993) within 3 months before or after MR scan. The present study focused on C subscale in TCI.

MRI Acquisition

The method of MRI acquisition was the same as that in our previous studies (Yamasue et al. 2003, 2007). Briefly, the MRI data were obtained using a 1.5-Tesla scanner (General Electric Signa Horizon Lx version 8.2, GE Medical Systems, Milwaukee, WI). Three-dimensional Fourier-transform spoiled gradient recalled acquisition with steady state was used. The repetition time was 35 ms, the echo time 7 ms with 1 repetition, the nutation angle 30°, the field of view 24 cm, and the matrix 256 × 256 (192) × 124. A trained neuroradiologist (Ha.Ya. or O.A.) evaluated the MRI scans and found no gross abnormalities in any of the subjects.

Image Processing for VBM

The same image processing for VBM as our previous study (Yamasue et al. 2007) was conducted using SPM 2 (Ashburner and Friston 2000; Good et al. 2001b) (Institute of Neurology, London, UK) running in MATLAB 7.1 (Mathworks, Sherborn, MA) in the current study. The spatial normalization to standard anatomical space was performed in a 2-stage process. In the 1st step, each image was registered to the International Consortium for Brain Mapping template (Montreal Neurological Institute, Montreal, Canada). This step applied a 12-parameter affine transformation to correct for image size and position. The normalized images of all participants were averaged and smoothed with a Gaussian kernel of 8-mm full-width at half-maximum (FWHM) and then used as a new template with reduced scanner- and population-specific bias. In the 2nd step, each image of was locally deformed to the new study-specific template using a nonlinear spatial transformation. Finally, using a modified mixture model cluster analysis, normalized images were corrected for nonuniformities in signal intensity and partitioned using a study-specific customized prior probability map into gray and white matter, cerebrospinal fluids (CSF), and background. To remove unconnected nonbrain voxels, a series of morphological erosions and dilations to the segmented images were applied (Good et al. 2001a, 2001b). In the intensity modulation step, voxel values of the segmented images were multiplied by the measure of warped and unwarped structures derived from the nolinear step of the spatial normalization. The resulting modulated gray and white matter images were smoothed with a Gaussian kernel of 12-mm FWHM.

Statistical Analysis for Global Brain Volume

Sex differences in absolute and relative volume, adjusted for individual differences in intracranial volume (ICV), of total gray matter, white

matter, CSF, and ICV calculated from optimized VBM procedure were tested using Mann–Whitney Test. Then, to test the "social-brain hypothesis," the correlation between relative total GMV and the score of C was tested using Spearman's rank-order correlation in each sex separately, because sex differences in the correlation were predicted in advance. Furthermore, sex difference in the calculated correlation was examined employing Fisher's r to z transformation. Significance level was defined at $P < 0.05$.

Statistical Analysis for Regional Brain Volume

Statistical comparison between males ($N = 89$) and females ($N = 66$) was performed using an analysis of covariance model (Friston et al. 1990). To account for global anatomical variations, ICV was treated as a confounding covariate. To test hypotheses with respect to regionally specific sex differences, the estimates were compared using 2 linear contrasts (Friston et al. 1995). The resulting set of voxel values for each contrast constituted a statistical parametric map of the t-statistic (SPM$\{t\}$). The SPM$\{t\}$ values were transformed to the normal distribution (SPM$\{z\}$) and with a threshold at $P < 0.001$. The significance of each region was corrected for multiple comparisons using false discovery rate (FDR), because previous literature suggests that multiple hypothesis testing (Bonferroni type) family-wise error correction tends to wipe out both false and true positives when applied to the entire data in neuroimaging (Genovese et al. 2002). Thus, the significance level was set at FDR-corrected $P < 0.05$.

To detect the neuroanatomical correlates of individual differences in altruism, statistical analysis was performed with ICV as a confounding covariate, and the score of C as the covariate of interest within each sex separately. To test the specificity of correlation, the correlation was also examined in the sex-combined sample. The threshold for statistical significance was also set at FDR-corrected $P < 0.05$.

Sex difference in the correlation between altruism and regional brain volume was tested for using the condition by covariates interaction analysis. The interaction analysis treated sex as condition, the score of C as covariate of interest, and ICV as the confounding covariate. Because this analysis was employed as a post hoc analysis to examine the significance of interaction between sex and altruism on the single peak coordinate showing a significant correlation with altruism, the threshold for statistical significance was set at $P < 0.05$ without correction for multiple comparisons.

Post hoc partial correlational analyses were further added for evaluating to what degree the regional correlations between C and specific areas account for the global correlation between C and relative total GMV in females, or whether the regional correlations exist beyond the global correlation. The values of regional GMV were extracted from the peak coordinates showing the regional correlation (Table 3) to test for specific effects of regional GMV after controlling for the relative total GMV effects, and for the relative total GMV effect after controlling for the regional effects.

To test whether the different areas capture independent sources of individual differences, the additional regression analyses were conducted using individual's score of C as dependent value and regional GMVs in each brain region as independent values.

Results

Demographic Characteristics

There were no significant sex differences in age, handedness, self-, or parental-SES (Hollingshead 1965). The scores of C ($P = 0.026$), reward dependence ($P = 0.007$), and self-transcendence ($P = 0.041$) were significantly higher in females than in males. (Table 1). The correlations between C and the other subscales of TCI were further examined in each sex. The Spearman's correlations between C and other items of the TCI were as follows: novelty seeking (rho = 0.004; $P = 0.98$), harm avoidance (rho = –0.257; $P = 0.038$), reward dependence (rho = 0.426, $P < 0.001$), persistence (rho = 0.0; $P = 0.99$), self-directedness (rho = 0.511, $P < 0.001$), and self-transcendence (rho = 0.281; $P = 0.022$), in female, and novelty seeking (rho = –0.037; $P = 0.73$), harm avoidance (rho = –0.413, $P < 0.001$), reward dependence (rho = 0.489, $P < 0.001$), persistence (rho = 0.384, $P < 0.001$), self-directedness (rho = 0.434, $P < 0.001$), and self-transcendence (rho = 0.347, $P = 0.001$) in male. Next, we conducted VBM analysis for exploring correlations between regional GMV and items of the TCI showing significant correlations with C ($P < 0.05$). However, the VBM analysis revealed no regions that show significant correlations with TCI scores for any items (FDR-corrected $P > 0.05$). Therefore, we did not conduct the analysis employing these TCI indices as confounding covariates.

Table 1
Subject characteristics

Variable	Male ($n = 89$)		Female ($n = 66$)		Mann–Whitney	
	Mean	SD	Mean	SD	Z value	P
Demographic variables						
Age (range)	28.9 (21–40)	4.2	28.0 (22–40)	4.3	−1.56	0.12
Handedness (range)[a]	96.0 (25–100)	11.1	96.5 (50–100)	9.0	−0.94	0.35
Socioeconomic status[b]	1.58	0.5	1.77	0.7	−1.4	0.15
Parental socioeconomic status[b]	2.15	0.6	2.11	0.6	−0.36	0.72
Temperament and Character Inventory						
Harm avoidance	15.8	7.2	16.5	6.4	−0.86	0.39
Novelty seeking	22.8	5.7	22.3	5.2	−0.65	0.51
Reward dependence	14.9	3.4	16.5	3.1	−2.68	0.007
Persistence	4.7	1.6	4.5	1.6	−0.47	0.63
Self-direcctedness	29.0	6.9	31.3	6.3	−1.9	0.051
Cooperativeness	28.4	5.5	30.3	5.4	−2.23	0.026
Self-transcendence	9.0	4.8	11.3	6.2	−2.05	0.041
Global brain measures (Fig. 1)						
Total GMV (cc)	782	57	705	47	−7.47	< 0.001
Total white matter volume (cc)	473	42	411	33	−7.99	< 0.001
Total cerebrospinal fluid volume (cc)	402	53	319	41	−8.47	< 0.001
ICV (cc)	1659	126	1436	103	−8.76	< 0.001
Gray matter/ICV	0.472	0.02	0.491	0.02	−6.26	< 0.001
White matter/ICV	0.285	0.014	0.286	0.013	−0.49	0.625
Cerebrospinal fluid/ICV	0.242	0.02	0.221	0.018	−5.80	< 0.001

[a]Determined using Edinburgh Inventory (Oldfield 1971): Scores greater than 0 indicate right-handedness. A score of 100 indicates strong right-handedness.
[b]Assessed using the Hollingshead scale (Hollingshead 1965). Higher scores indicate lower educational and/or occupational status.

Sex Difference in Global Brain Morphology

The absolute volumes of ICV, total gray matter, white matter, and CSF were significantly larger in males ($P < 0.001$). Relative total gray matter, however, was significantly larger in females ($P < 0.001$). By contrast, males had significantly larger relative total CSF volume ratio to ICV ($P < 0.001$). (Fig. 1a–c, Table 1).

Global GMV Associated with Altruistic Cooperativeness

A significant positive correlation between higher scores of C and larger relative total GMV was found in females (rho = 0.256, $P = 0.038$), whereas a homologous correlation was not found in males (rho = −0.131, $P = 0.222$). These correlations showed a significant sex difference ($Z = 2.37$, $P = 0.018$), indicating that the correlation was specific to females (Fig. 1d).

Sex Difference in Regional Brain Volumes

The VBM showed significantly larger regional GMV in females in several clusters including bilateral STG, IFG, insular cortices, occipitotemporal cortices, anterior cingulate cortices, thalamus, left parahippocampal gyrus, and medial and lateral PFC (FDR-corrected $P < 0.05$). In contrast, no voxel in the contrast showing regions larger in males than in females reached the statistical threshold, FDR-corrected $P < 0.05$. Small volume correction for multiple comparisons were then used for regions that had been predicted in advance, because previous studies have reported larger amygdala and cerebellum in males than in females (Rhyu et al. 1999; Good et al. 2001a; Goldstein et al. 2001). The regional GMVs in bilateral cerebellum and amygdala were significantly larger in males (Fig. 2 and Table 2).

Regional GMV Associated with C

In females, significant positive correlations between the score of C and regional GMV were found in 5 clusters (corrected $P < 0.05$) (Fig. 3 and Table 3). Furthermore, 3 of the 5 clusters showed significant sex and C interactions as well as significant correlation with C. Of note, all of the 3 clusters, including bilateral pIFG and left amPFC, showed a female > male sexual dimorphism as well as the female-specific correlation with C (Table 3). The regional GMV in left fusiform gyrus also showed a trend level significant female-specific correlation with C revealed by both the correlational and interaction analyses ($P = 0.072$), whereas the regional volume did not show any significant sex dimorphism. No regions showed a significantly negative correlation with scores of C in females. In contrast to the correlations in females, there was no suprathreshold gray matter voxel showing a correlation with C in males, even when a liberal threshold (uncorrected $P < 0.001$) was utilized. When both sexes combined, the correlation between C and regional GMV in right pIFG was found (peak coordinate = [54 8 8], Z-score = 3.90, uncorrected $P < 0.001$), although it did not remain statistically significant after correction for multiple comparisons (FDR-corrected $P = 0.209$).

The partial correlational analysis between C and regional GMVs remained statistically significant even after controlling for relative total GMV effect ($r > 0.335$, $P < 0.006$, df = 63). In contrast, the global correlations between C and relative total GMV did not reach the statistically significant level after controlling for regional GMV effects ($r = 0.232$, $P = 0.072$, df = 59).

The regression analyses showed positive regression coefficients for the all brain regions ($r^2 = 0.243$, $F_{5,60} = 3.85$, $P = 0.004$, coefficients = 8.9–20.8), suggesting that the each area might capture similar sources of individual differences.

Discussion

The crucial finding of the current study is that individual variability in altruistic cooperativeness showed significant
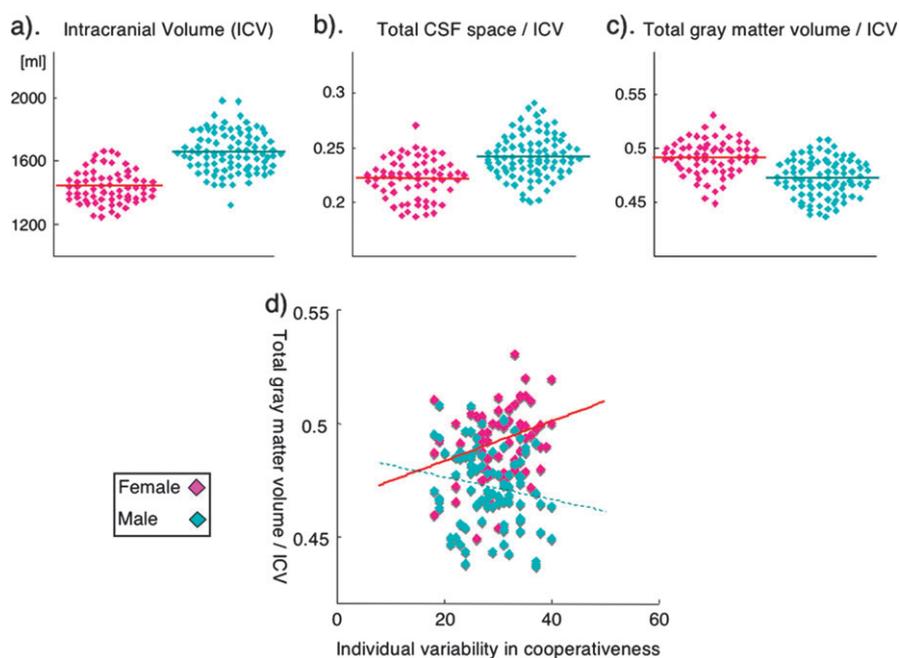

Figure 1. Sex dimorphism in global brain measures and *Cooperativeness*. Means and distributions of ICV (*a*) and total CSF space ratio to ICV (*b*) in which male participants exhibited a significantly large ratio compared to female participants ($P < 0.001$). In contrast, total gray matter ratio to ICV (*c*) is significantly larger in females ($P < 0.001$). Means are represented by solid horizontal lines drawn on each group's distribution. (*d*) Scatterplots depicting correlations between total GMV/ICV ratio and individual variability in cooperativeness in males and females. The sex difference of these correlations was statistically significant (Fisher's *r* to *z* transformation; $Z = 2.37$, $P = 0.018$).
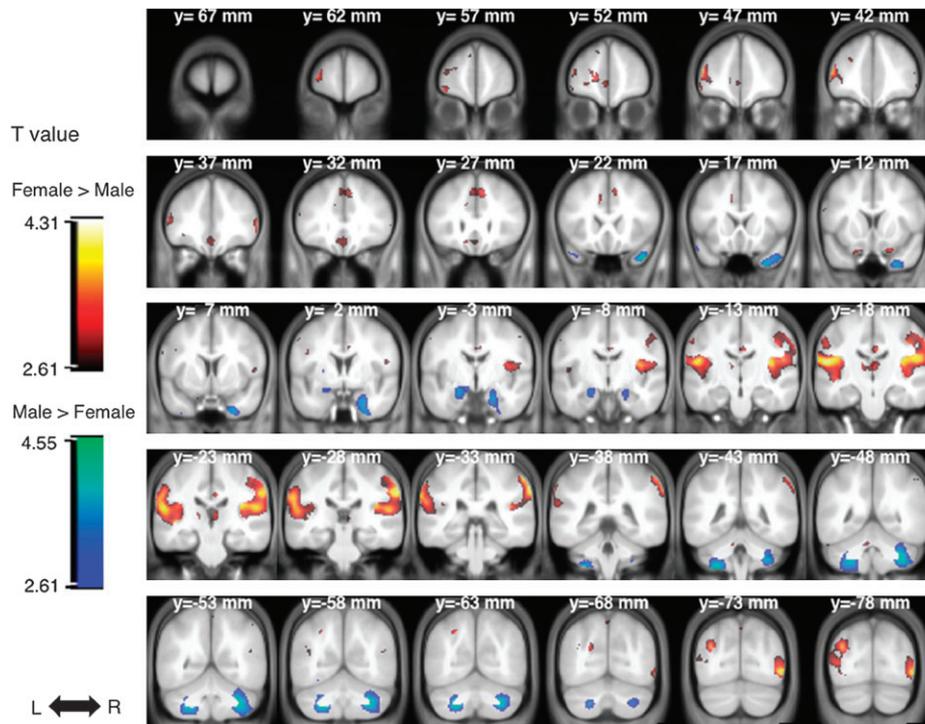
Figure 2. Sex dimorphism in regional GMV. The gray matter regions showing significant sex-dimorphism were rendered onto the averaged coronal images of the whole sample (*N* = 155) (Voxel threshold: uncorrected *P* < 0.005). The gray matter regions for which females are larger than males are presented in red ~ yellow. Conversely, the gray matter regions for which males are larger are presented in blue ~ green. The *y*-coordinate for each coronal slice in the Montreal Neurological Institute space is given in millimeters. L: left, R: right (see Table 2).

Table 2

Gender difference in regional brain volume (Fig. 2)

Anatomical location	Peak coordinate			Z score	FDR-corrected P	Cluster size (mm³) (voxel threshold: P < 0.001)
	x	y	z			
Larger in female (n = 155)						
Left STG, IFG, and insula	−56	−20	16	4.04	0.03	9160
Left occipitotemporal cortex	−36	−86	−8	4.03	0.03	984
Right occipitotemporal cortex	48	−78	−4	3.95	0.03	3384
Right STG, IFG, and insula	52	−20	20	3.89	0.03	11616
Left lateral prefrontal cortex	−45	45	12	3.78	0.03	400
Left anterior medial prefrontal	−14	52	4	3.33	0.03	64
Anterior cingulate (pregenual)	−14	52	4	3.33	0.03	64
Bilateral thalamus	2	−22	10	3.3	0.03	128
Anterior cingulate (dorsal)	8	28	42	3.23	0.03	96
Larger in male (n = 155)						
Left cerebeller hemisphere	−22	−64	−44	4.4	< 0.001 (SV 30cc[a])	3664
Right cerebeller hemisphere	30	−62	−40	4.33	0.001 (SV 30cc[a])	4976
Right amygdala	22	0	−30	3.57	0.003 (SV 3cc[a])	2848
Left amygdala	−20	−4	−20	3.54	0.004 (SV 3cc[a])	392

Note: SV: searched volume.

[a]The definitions of searched volumes were based on previous studies.

female-specific correlations with total gray matter/ICV ratio (Fig. 1*d*) and more specifically with the regional GMV in bilateral pIFG and left amPFC (Figs 1 and 3 and Tables 3). In addition, the present study replicated findings of significantly larger global and regional brain volumes in all of these regions (Good et al. 2001a) (Figs 1 and 2 and Tables 1 and 2) and higher C in females (Farmer et al. 2003). Because the other subscale of TCI showed no significant global or regional correlations with the GMV, the relationships are thought to be specific to C.

Thus, the present findings demonstrated the 1st evidence of sex-linked neuroanatomical background of human altruism.

The present study replicates previous findings of sexual dimorphism in brain structure. Although larger ICV as well as whole brain volume in males has been consistently reported (Filipek et al. 1994; Goldstein et al. 2001), larger total gray matter compositions, STG, cingulate, IFG, PFC, and thalamus in females and larger amygdala and cerebellum volumes in males have also been consistently reported when sex differences in

Table 3
Neural coorelates of Cooperativeness

Anatomical location	Peak coordinate			Z score	Correlation coefficient	FDR-corrected P	Cluster size (mm^3) (voxel threshold: P < 0.001)	Gender × Cooperativeness interaction[a] (n = 155)		Gender difference	
	x	y	z					Z score	P	Z score	P
Positive correlation in female (n = 66) (Figs 2 and 3)											Female > Male
Right pIFG	54	6	10	4.36	0.512	0.037	11 144	2.33	0.01	2.57	0.005
Left amPFC	−16	58	8	3.89	0.464	0.037	1112	3.23	0.001	2.17	0.015
Right medial parietal cortex	10	−40	62	3.81	0.455	0.037	440	n.s.	n.s.	n.s.	n.s.
Left pIFG	−56	14	0	3.56	0.429	0.046	296	3.36	< 0.001	1.96	0.025
Right precentral gyrus	56	−2	44	3.56	0.428	0.046	1904	n.s.	n.s.	n.s.	n.s.
Left fusiform gyrus	−40	−22	−22	3.14	0.382	0.072	24	3.22	0.001	n.s.	n.s.

Note: Correlation in male (n = 89) and negative correlation in female (n = 66). No suprathreshold cluster. SV: searched volume.
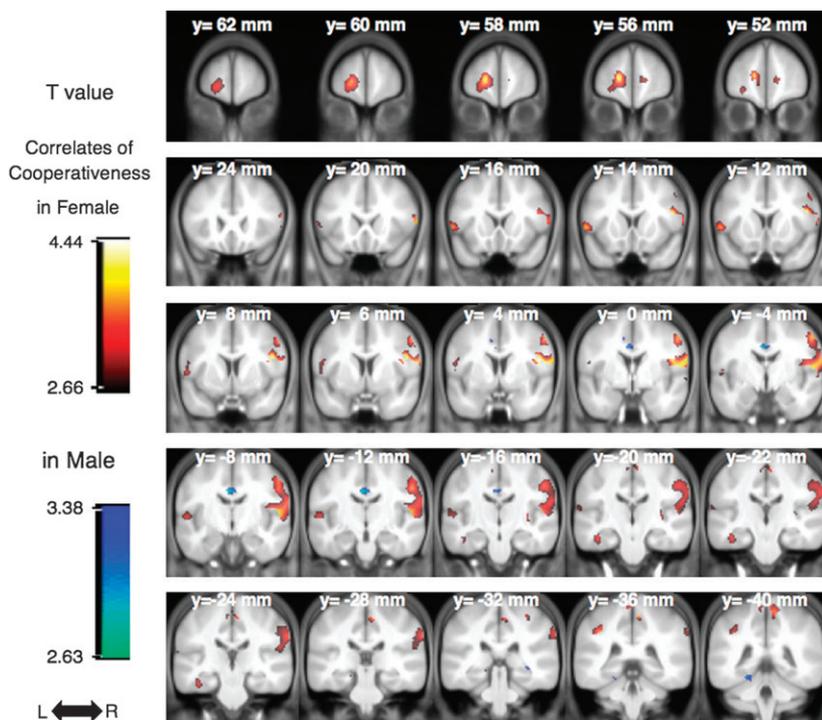[a]The interactions indicate significantly greater positive correlation in females.

Figure 3. Localized neuroanatomical correlates of *Cooperativeness*. The gray matter regions showing correlations with the individual variability of *Cooperativeness* were rendered onto the averaged images of the whole sample (N = 155) (voxel threshold: uncorrected P < 0.005). The gray matter regions where the correlation was found in females are presented in red ~ yellow. Conversely, the gray matter regions where the correlation was found in males are presented in blue ~ green. The y-coordinate for each coronal slice in the Montreal Neurological Institute space is given in millimeters. L: left, R: right (see Table 3).

global brain measures is taken into account (Jacobs et al. 1993; Schlaepfer et al. 1995; Giedd et al. 1996; Murphy et al. 1996; Paus et al. 1996; Harasty et al. 1997; Gur et al. 1999; Nopoulos et al. 2000; Good et al. 2001a). The present findings are also consistent with the suggestion that greater gyrification in females implies more cortical surface area, which may offset sex differences in global brain size (Luders et al. 2004).

In accordance with the "social-brain hypothesis" (Dunbar 1998, 2003), the current study demonstrated that larger relative total GMV showed a significant correlation with higher C in females. Although there is some evidence for a link between neural measures and various lifestyles in mammals (Harvey and Krebs 1990; Joffe and Dunbar 1997; White and Byrne 1997; De Winter and Oxnard 2001; Byrne and Corp 2004), the present study provides the 1st human evidence supporting the social-brain hypothesis. The original social-brain

hypothesis argued for the extreme development of the human brain compared with the other animals, however, the current study was conducted only with human individuals and consequently cannot conclude human superiority relative to other animals.

The voxel-by-voxel analysis further revealed localizations of neuroanatomical correlates of altruistic cooperativeness; larger regional volume in pIFG, and amPFC showed significant intensive correlations with higher altruistic cooperativeness. The location of peak coordinate in pIFG is close to those in previous studies showing neural correlates of observation and imitation of other's action (Nishitani et al. 2005), grasping intention of others (Iacoboni et al. 2005, Dapretto et al. 2006), and empathy (Carr et al. 2003; Adolphs 2003; Leslie et al. 2004). Evolution of cooperativeness occurs through social learning based on action observation and imitation of others, which

contributes to creating reciprocal altruism (Fehr and Fischbacher 2003). Therefore, it is reasonable to find neural substrates of altruistic cooperativeness in the regions known to be implicated in observation and imitation of others. Because previous studies have reported activations around the currently identified peak location of amPFC during tasks such as the attribution of emotion to self and others close to the self (Ochsner et al. 2004) and mentalizing tasks such as predicting the behavior of others (Harris et al. 2005), the region is thought to be one of the core areas for social cognition (Amodio and Frith 2006). The localization in neuroanatomical correlates of altruistic cooperativeness revealed by the present VBM is consistent with the previous functional neuroimaging studies overviewed above. In addition, the current correlations between C and neocortical regions are consistent with the "social-brain hypothesis" arguing that enlarged human neocortex volume reflects our social complexity.

Of note, all 3 clusters, including bilateral pIFG and left amPFC, demonstrating significant female-specific correlations with altruistic cooperativeness also revealed a significant female > male sex-dimorphism. The findings are in line with a previous functional imaging study, which showed greater left PFC including pIFG activation elicited by humor appreciation in females (Azim et al. 2005). A candidate for a biological mechanism shaping the sex-linked neuroanatomy–cooperativeness relationship is genetic factors, because previous studies have reported that a significant part of individual differences (e.g. 82% (33)) in GMV in healthy adults derives from genetic factors (Baare et al. 2001; Thompson et al. 2001; Geschwind et al. 2002; Wright et al. 2002). Therefore, the present findings suggest that genetic factors coding development of the social-brain influence altruistic cooperativeness more directly in females. Recent studies reported that a number of X-linked genes code mental development and social intelligence (Check 2005; Skuse 2005). Genes on sex chromosomes determine the sex of the brain in 2 ways: by acting on the gonads to induce sex differences in levels of gonadal secretions that have sex-specific effects on brain, and by acting in the brain itself to differentiate XX and XY brain cells (Arnold 2004). Thus, action of gonadal hormones has also been suggested as a key biological mechanism shaping sex differences in brain and mental development (Simerly 2002). Sexually dimorphic brain regions are rich in sex-hormone receptors, and their development may therefore be rather directly affected by sex hormones (Goldstein et al. 2001). Therefore, early gonadal–hormonal exposure interacting with neurotrophic factors (Carrer and Cambiasso 2002) might contribute to promoting a relationship between sexually dimorphic brain anatomy and sex difference in altruistic cooperativeness. Taking the above evidence into account, it seems likely that females are more likely to have more highly developed social-brain regions and altruistic cooperativeness as a phenotype of genetic factors such as X-linked genes coding gonadal secretions and social-brain development. Consistent with this notion, structural abnormalities related to X-chromosome abnormalities are found in PFC of patients with turner syndrome (Reiss et al. 1993; Good et al. 2003; Kesler et al. 2003; Molko et al. 2004; Rae et al. 2004). By contrast, it has also been suggested that current gene-based evolutionary theories cannot totally explain important patterns of human altruism, pointing to the importance of both theories of cultural evolution as well as gene-culture coevolution (Fehr and Fischbacher 2003). Therefore, altruistic

cooperativeness in males, having only 1 X-chromosome, may be more likely to be associated with nongenetic factors, such as social learning and cultural evolution.

The present findings may also contribute to uncovering the neural background of autism, a pervasive developmental disorder characterized by severe social and interpersonal dysfunction, abnormalities in social-brain, and disproportionately low probability in females (Folstein and Rosen-Sheidley 2001). Baron-Cohen (2002) proposed the extreme-male brain theory of autism that the male brain is a defined psychometrically as those individuals in whom systemizing is performed significantly better than empathizing or friendship, and that the female brain is defined as the opposite cognitive profile (Brandstrom et al. 2001; Baron-Cohen 2002; Soderstrom et al. 2002; Baron-Cohen and Wheelwright 2003, 2004; Baron-Cohen et al. 2003, 2005; Farmer et al. 2003; Lawson et al. 2004). Using these definitions, autism can be considered as an extreme of the normal male profile. Recently, the hypothesis further suggests that specific aspects of autistic neuroanatomy may also be extremes of typical male neuroanatomy (Baron-Cohen et al. 2005). The current results are consistent with this hypothesis. Previous studies using structural MRI demonstrated smaller anterior cingulate (Haznedar et al. 1997, 2000), STG, PFC (Boddaert et al. 2004; De Fosse et al. 2004; Waiter et al. 2004; McAlonan et al. 2005; Yamasue et al. 2005; Hadjikhani et al. 2006), thalamus (Tsatsanis et al. 2003), pIFG (Hadjikhani et al. 2006) and enlarged amygdala, cerebellum (Howard et al. 2000; Sparks et al. 2002) in subjects with autism-spectrum disorders. The present study revealed sex-dimorphism in brain anatomy at a similar location and in the same direction as these previous studies of individuals with autism. Thus, the current study may add supportive evidence for Baron-Cohen's extreme-male brain theory of autism at the level of brain structure. In addition, the results from partial correlational analyses support for the case that the regional correlations exist beyond the global correlation. Although the current results are inconclusive, the regionally specific association might indicate specific extreme-male brain theory of autism against very general social brain hypothesis.

Here we address the methodological considerations and limitations of our study. First, the present study includes only Japanese participants. It is possible, however, that the pure ethnicity of the present sample might contribute to the clarity of findings. Because previous studies have reported significant ethnic differences in brain morphology (Zilles et al. 2001), future replication in other ethnicities is necessary to generalize the findings. Second, the present study employed a self-report questionnaire as an index for individual variability in altruistic cooperativeness. Although the validity of questionnaires to study biological aspects of personality has been demonstrated (Cloninger 1987), future studies should confirm the findings using other indices of altruism. Third, the present study participants, who were mainly college students, hospital staff, and their acquaintances, might not be representative of the average Japanese population. Therefore, the future study should replicate the present findings in the general population recruited in a different way such as advertisements.

The present study demonstrates that females had higher altruistic cooperativeness and larger global and regional GMV than males, and that these were tightly interrelated in females only. These regions included pIFG, and amPFC, participating in the social-brain regions and/or human mirror neuron system.

The findings at least partly support the "social-brain hypothesis" (Dunbar 1998, 2003) and suggest an important role of X-linked genes on social cognition (Skuse 2005). Moreover, the present results may also be consistent with the extreme-male brain theory of autism (Baron-Cohen 2002).

Notes

Conflict of Interest: None declared.

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