



## Smaller insula and inferior frontal volumes in young adults with pervasive developmental disorders

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### ARTICLE INFO

#### Article history:

Received 2 October 2009

Revised 15 January 2010

Accepted 25 January 2010

Available online 1 February 2010

#### Keywords:

Pervasive developmental disorders (PDD)

Autistic spectrum disorders (ASD)

Voxel-based morphometry (VBM)

Insula

Inferior frontal gyrus (IFG)

Mirror neuron system (MNS)

### ABSTRACT

Enlarged head circumference and increased brain weight have been reported in infants with pervasive developmental disorders (PDD), and volumetric studies suggest that children with PDD have abnormally enlarged brain volumes. However, little is known about brain volume abnormalities in young adults with PDD. We explored gray matter (GM) volume in young adults with PDD. T1-weighted volumetric images were acquired with a 3-T magnetic resonance scanner from 32 males with high-functioning PDD ( $23.8 \pm 4.2$  years; Full Scale Intelligence Quotient [FSIQ] =  $101.6 \pm 15.6$ ) and 40 age-matched normal male control subjects ( $22.5 \pm 4.3$  years; FSIQ =  $109.7 \pm 7.9$ ). Regional GM volumes were compared between the two groups using voxel-based morphometry (VBM) with the Diffeomorphic Anatomical Registration using Exponentiated Lie algebra (DARTEL). Compared with the control group, the high-functioning PDD group showed significantly less GM in the right insula, the right inferior frontal gyrus, and the right inferior parietal lobule. A conservative threshold confirmed considerably smaller volumes in the right insula and inferior frontal gyrus. In these areas, negative correlations were found between Autism Spectrum Quotient scores and GM volume, although no significant correlations were found between each subject's FSIQ and GM volume. No regions showed greater GM volumes in the high-functioning PDD group. The insular cortex, which works as a relay area for multiple neurocognitive systems, may be one of the key regions underlying the complex clinical features of PDD. These smaller GM volumes in high-functioning PDD subjects may reflect the clinical features of PDD itself, rather than FSIQ.

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### Introduction

Autistic disorder and Asperger's disorder are considered pervasive developmental disorders (PDD) (DSM-IV; American Psychiatric Association, 2000) or autistic spectrum disorders (ASD) (Wing et al., 2002). Research has addressed the epidemiology of the increasing

prevalence of these disorders (Baird et al., 2006). Individuals with PDD have core impairments in reciprocal social interactions, abnormal development and use of language, repetitive and ritualized behaviors, and a narrow range of interests (Kanner, 1943; Asperger, 1944). The etiology of PDD is still unknown.

Neuroimaging (Dapretto et al., 2006) and pathological studies (Bauman and Kemper, 2005) have revealed both global and local morphological changes in the brain in PDD. Measures of head circumference (Courchesne et al., 2004; Hazlett et al., 2005; Dawson et al., 2007) and postmortem studies (Courchesne et al., 1999) have

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reported enlarged head circumference and greater brain weight in infants with PDD. PDD individuals show larger total brain volume or larger local gray matter (GM) volumes (Carper et al., 2002; Hazlett et al., 2005; Redcay and Courchesne, 2005) in the caudate nucleus (Langen et al., 2007) and frontal and temporal regions (Hazlett et al., 2006). These structural differences were not prominent in adult patients (Amaral et al., 2008). It is still unclear whether the brain enlargement is limited to early development (Courchesne et al., 1999, 2001; Redcay and Courchesne, 2005; Dawson et al., 2007) or continues into adulthood (Courchesne et al., 1999). On the other hand, several studies have reported smaller local GM volumes in fronto-striatal and cerebellar regions (McAlonan et al., 2002) and the superior temporal sulcus (STS) (Boddaert et al., 2004). Both enlarged GM volumes in some areas and smaller volumes in other areas have also been reported (Rojas et al., 2006; Ke et al., 2008).

These apparently discrepant findings suggest that the time course of brain development, rather than the final product, may be abnormal in PDD (Amaral et al., 2008). Thus, age is a confounding factor for volumetric studies of PDD. Another confounding factor is functionality, as measured by the intelligence quotient (IQ). Lotspeich et al. (2004) reported that a low-functioning autistic group showed larger GM volumes than groups with Asperger syndrome, high-functioning autism, and control subjects. Therefore, it is essential to control for subjects' age and IQ when investigating the relationship between the clinical features of PDD and morphological abnormalities. Importantly, the social reciprocity problems that characterize the PDD group from infancy persist through childhood and adolescence into adult life (Billstedt et al., 2007). Thus, fine-grained clinico-morphological analysis in young adults with PDD and normal IQ enables the neural substrates responsible for impaired social interaction to be investigated.

The purpose of the current study was to explore GM volume abnormalities in young adults with high-functioning PDD (i.e., PDD subjects with normal IQs) using voxel-based morphometry (VBM).

## Materials and methods

### Subjects

Thirty-three males with high-functioning PDD were recruited at the Department of Neuropsychiatry, University of Fukui Hospital, Japan, and the Department of Psychiatry and Neurobiology, Kanazawa University Hospital, Japan. Author T.M. diagnosed the participants based on the classifications in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV; American Psychiatric Association, 2000) and standardized criteria using the Diagnostic Interview for Social and Communication Disorders (DISCO) (Wing et al., 2002). Author T.M. was trained in the diagnosis of PDD under Dr. Tokio Uchiyama and was qualified to use the DISCO (DISCO Japanese edition, 2007). It has been suggested that the DISCO has good psychometric properties (Nygren et al., 2009; Posserud et al., 2009). Further, it contains items on early development and a section on activities of daily life, thus giving the interviewer some idea of the level of functioning in several different aspects of daily life, and not only social functioning and communication (Posserud et al., 2009). The high-functioning PDD group consisted of 18 participants with high-functioning autistic disorder and 15 with Asperger's disorder. One individual with autistic disorder was excluded after MRI examination due to motion artifact. The data from the remaining 32 male individuals with PDD (mean age  $23.8 \pm 4.2$  years old, 17–32 range) were used in the present study (Table 1). In total, 40 age-matched normal male volunteers (mean age  $22.5 \pm 4.3$  years old, 18–34 range) were recruited from the local community (Table 1). Subjects were excluded if they had a history of major medical or neurological illness including epilepsy, significant head trauma, or a lifetime history of alcohol or drug dependence. They were screened to exclude individuals who had a first-degree relative

**Table 1**  
Demographic data and rating scale scores.

Subject	Control subjects	PDD subjects	T-value	P
Number	40 Males	32 Males		
Handedness <sup>b</sup> (right/left)	38/2	30/2		
Age at examination	22.5 ± 4.3	23.8 ± 4.2	1.40	0.16
WAIS-III: full scale IQ <sup>c</sup>	109.7 ± 7.9	101.6 ± 15.6	2.77	0.01 <sup>a</sup>
WAIS-III: verbal IQ <sup>c</sup>	111.9 ± 8.0	108.3 ± 17.5	1.06	0.29
WAIS-III: performance IQ <sup>c</sup>	105.1 ± 9.0	93.4 ± 15.4	3.72	<0.01 <sup>a</sup>
AQ: total score	17.1 ± 5.8	32.0 ± 5.7	10.81	<0.01 <sup>a</sup>
AQ: social skill scores	2.9 ± 2.3	7.0 ± 2.5	7.18	<0.01 <sup>a</sup>
AQ: attention switching scores	4.6 ± 2.2	7.4 ± 1.3	6.31	<0.01 <sup>a</sup>
AQ: attention to detail scores	4.5 ± 2.0	5.6 ± 2.5	2.05	0.04 <sup>a</sup>
AQ: communication scores	2.7 ± 2.0	6.5 ± 2.6	7.02	<0.01 <sup>a</sup>
AQ: imagination scores	2.5 ± 1.4	5.6 ± 2.2	7.17	<0.01 <sup>a</sup>

Values are mean ± SD.

PDD, pervasive developmental disorders; WAIS-III, Wechsler Adult Intelligence Scale—Third Edition; AQ, Autism Spectrum Quotient.

<sup>a</sup>  $P < 0.05$ , with independent-samples *t*-test, compared between control subjects and PDD subjects.

<sup>b</sup> Assessed by the Edinburgh handedness inventory (Oldfield, 1971).

<sup>c</sup> WAIS-III was performed by 33 control subjects and all 32 PDD subjects.

with an axis I disorder, based on the DSM-IV criteria. IQ assessments were carried out using the Wechsler Adult Intelligence Scale-III (WAIS-III; Wechsler, 1997). All participants' full-scale IQ (FSIQ) scores were  $>80$ , and the mean FSIQ scores of each group were  $>100$ . The Autism Spectrum Quotient (AQ; Baron-Cohen et al., 2001) was used to quantify autistic traits (Table 1). Although the AQ (PDD,  $32.0 \pm 5.7$ ; controls,  $17.1 \pm 5.8$ ) is not diagnostic, it is a useful support of diagnosis because it has been validated in a clinical sample (Woodbury-Smith et al., 2005). Among the participants with PDD, 29 of 32 (90.6%) scored above the cutoff point ( $=26$ ) for Asperger's disorder or high-functioning autism (Woodbury-Smith et al., 2005), compared with only one individual in the control group (2.5%). The protocol used for this study was approved by the ethics committee of the University of Fukui. After a complete explanation of the study, written informed consent was obtained from each subject.

### MRI acquisition and processing

Brain magnetic resonance (MR) images were acquired using a 3.0-T scanner (Signa Horizon; General Electric Medical Systems, Milwaukee, Wisconsin). T1-weighted volumetric three-dimensional inversion recovery-prepared fast spoiled gradient recalled (3D IR FSPGR) acquisition in the steady-state MRI scans (repetition time [TR] = 11.3 ms, echo time [TE] = 5.3 ms, first inversion time [TI] = 700 ms, second TI = 400 ms, flip angle  $10^\circ$ , number of excitations = 1,  $320 \times 192$  matrix, auto-zero-fill interpolation [ZIP] 512, 200–220 axial slices of 1.6-mm thickness with 0.8 mm overlap, voxel size =  $0.75 \times 1.25 \times 1.6$  mm) were obtained as in our previous study (Narita et al., 2009).

### VBM–DARTEL analysis

We conducted VBM to investigate the differences in the volumes of GM, white matter (WM), and cerebrospinal fluid (CSF) between the high-functioning PDD group and the control group. T1-weighted volumetric images were analyzed with SPM5 (<http://www.fil.ion.ucl.ac.uk/spm>) implemented in Matlab 2008a (Math Works, Natick, MA, USA) using the VBM5.1 method (<http://dbm.neuro.uni-jena.de/vbm>) with the default parameters. We used the Diffeomorphic Anatomical Registration using Exponentiated Lie algebra (DARTEL) (Ashburner, 2007) SPM5 toolbox, which creates a study-specific template and then performs segmentations using the study-specific template. This technique, being more deformable, notably improves the realignment of small inner structures (Yassa and Stark, 2009). The VBM

preprocessing included five steps (Bergouignan et al., 2009): (1) checking for scanner artifacts and gross anatomical abnormalities for each subject; (2) setting the image origin to the anterior commissure; (3) using the Hidden Markov Random Field (HMRF) option in the segmentation part of the VBM5 toolbox to minimize the noise level of the segmentation; (4) using the DARTEL toolbox to produce a high-dimensional normalization protocol, following John Ashburner's chapter in its standard version including the MNI space transformation (Ashburner, 2007); (5) checking for homogeneity across the sample and using standard smoothing (i.e., 8 mm). After this preprocessing, we obtained smoothed, modulated, normalized data that were used for the statistical analysis. The aim of the modulation step was to render the final VBM statistics reflective of the "volume" differences rather than the "concentration" differences in GM (Ashburner and Friston, 2000).

### Statistical comparison

Data analysis was conducted in three steps. First, estimates of the absolute GM, WM, and CSF volumes were obtained after the automatic brain segmentation procedure had been carried out by VBM5.1. The total intracranial volume (ICV) was calculated as the sum of the volumes of the GM, WM, and CSF. Statistical analyses were carried out using SPSS (Windows version 17; SPSS Japan Inc., Tokyo, Japan). To assess the differences between the groups in segmented brain volumes, we conducted multivariate analysis of covariance (MANCOVA), with group (PDD and control) as a between-subject factor, and segmented brain regional absolute volume (GM, WM and CSF) as a within-subject factor, and age and ICV as covariates. The statistical significance level was set at  $P < 0.05$ .

Second, for the GM analysis, the normalized, modulated, and smoothed GM image segments in each group were entered into a voxel-wise two-sample  $t$ -test analysis in SPM5. An absolute threshold mask of 0.30 was used to avoid possible edge effects around the border between GM and WM. The statistical threshold was set at a false discovery rate (FDR) of  $P < 0.05$  (FDR-corrected  $P < 0.05$ ). GM volume and age were included as nuisance covariates. In the same way, we separately compared the regional brain volumes of the subgroup with high-functioning autistic disorder and the control group, and the Asperger's disorder subgroup and the control group. We also performed a correction for multiple comparisons with the inference test based on the theory of Gaussian fields (Friston et al., 1996) at the cluster level, because of the increased sensitivity to spatially extended signal changes (Hayasaka et al., 2004). However, when images are nonstationary, the cluster-size distribution varies depending on local smoothness. Worsley et al. (1999) and Hayasaka et al. (2004) recently proposed the adjustment of cluster sizes according to the local roughness of the images. This local roughness is provided in SPM5 as the resel per voxel (RPV) image and is used to warp or flatten the image into an isotropic data space. Using the VBM toolbox that implements the method of Hayasaka et al. (2004), we analyzed our data with a smoothness adjustment ( $P < 0.05$ , cluster level).

Next, we determined whether each subject's FSIQ or AQ score correlated with the smaller GM volumes in the right insula and the right IFG of the high-functioning PDD subjects. To do this, we calculated the correlation coefficients between the GM volumes in these areas and the FSIQ or AQ total scores at the threshold of  $P < 0.005$  using SPSS17.

## Results

### Differences in whole-brain volumes

The segmented brain regional absolute volumes were estimated (GM:  $713.9 \pm 47.2$  and  $716.2 \pm 58.8$ ; WM:  $512.8 \pm 50.1$  and  $520.2 \pm$

**Table 2**  
Means, SDs, and group comparisons of brain volumes.

Subject	Control subjects	PDD subjects	MANCOVA covariates: age, ICV $P$
Characteristics	( $n = 40$ )	( $n = 32$ )	
Absolute volume ( $\text{cm}^3$ )			
Gray matter (GM)	$713.9 \pm 47.2$	$716.2 \pm 58.8$	0.52
White matter (WM)	$512.8 \pm 50.1$	$520.2 \pm 43.6$	0.26
Cerebrospinal fluid (CSF)	$334.2 \pm 50.9$	$364.1 \pm 53.5$	0.15
Intracranial volume (ICV)	$1560.8 \pm 102.6$	$1600.5 \pm 104.6$	NA

Values are mean  $\pm$  SD.

PDD, pervasive developmental disorders.

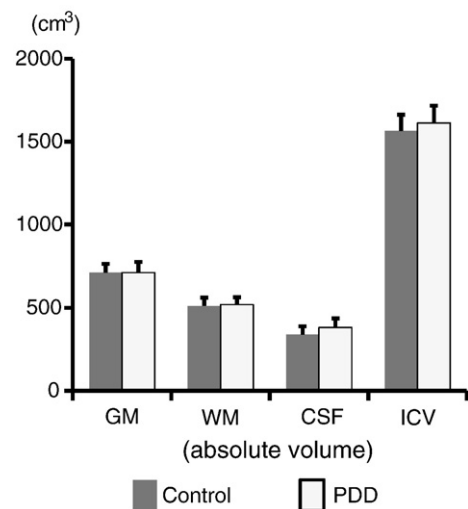
MANCOVA, multivariate analysis of covariance.

$43.6$ ; CSF:  $334.2 \pm 50.9$  and  $364.1 \pm 53.5$ ) in both the control and high-functioning PDD groups, respectively (Table 2, Fig. 1). The results of the MANCOVA analysis for group differences, covarying for age and ICV, revealed no significant differences (GM:  $F = 0.4$ ,  $df = 1,68$ ,  $P = 0.52$ ; WM:  $F = 1.3$ ,  $df = 1,68$ ,  $P = 0.26$ ; CSF:  $F = 2.2$ ,  $df = 1,68$ ,  $P = 0.15$ ) (Table 2). Therefore, there were no significant differences in overall GM volumes between the two groups.

### Local GM volume differences (VBM-DARTEL)

The high-functioning PDD group showed significantly less regional GM volume in the right anterior and posterior insula (FDR-corrected  $P = 0.039$ ), the right inferior frontal gyrus (IFG, Brodmann area [BA] 45, FDR-corrected  $P = 0.039$ ), and the right inferior parietal lobule (IPL) including the intraparietal sulcus (BA 40, FDR-corrected  $P = 0.045$ ) compared with the control group (Table 3, Fig. 2). At the adjusted cluster level (corrected  $P < 0.05$ , cluster level), the right insula and the right IFG were significantly smaller in the high-functioning PDD group (Table 3). The high-functioning PDD group did not show greater GM volumes than the control group in any brain regions.

Although the high-functioning autistic disorder subgroup showed a tendency to have smaller regional GM volumes in the right insula (FDR-corrected  $P = 0.052$ ;  $x = 50$ ,  $y = -14$ ,  $z = 4$ ) and the right IFG (FDR-corrected  $P = 0.052$ ;  $x = 58$ ,  $y = 20$ ,  $z = 10$ ) compared with the



**Fig. 1.** The absolute volumes of gray matter (GM), white matter (WM), cerebrospinal fluid (CSF), and intracranial volume (ICV) in the high-functioning PDD group and the control group. Multivariate analysis of covariance (MANCOVA) with age and ICV entered as covariates revealed no significant differences in any of these measures between the two groups.

**Table 3**  
Areas showing significant differences in GM volume between the PDD group and the control group using VBM–DARTEL analysis.

Area	BA	Cluster level (non-stationary)		Peak coordinates <sup>a</sup>			Voxel level	
		<i>P</i> corrected	<i>K</i> voxels	<i>x</i>	<i>y</i>	<i>z</i>	<i>T</i> -value	<i>P</i> FDR-corrected
Control>PDD								
R insula (anterior+ posterior)*		0.002	90	44	−12	10	4.91	0.039
R insula (anterior)		0.116	15	44	4	2	4.45	0.039
R insula (anterior)		0.059	12	46	14	−4	4.38	0.039
R inferior frontal gyrus (IFG)*	45	0.017	26	58	20	10	5.25	0.039
R inferior parietal	40	0.315	2	30	−38	58	4.20	0.045
PDD>Control								
No suprathreshold clusters								

PDD, pervasive developmental disorders.

BA, Brodmann area; L, left; R, right.

<sup>a</sup> *x*, *y*, *z*, stereotaxic coordinates as given in the Montreal Neurological Institute Atlas. The statistical threshold was set at  $P < 0.05$ , FDR-corrected for multiple comparisons.

\*  $P < 0.05$ , corrected for multiple comparisons at the cluster level (non-stationary) using the VBM toolbox (Hayasaka et al., 2004).

control group, there were no significant differences in regional brain volumes between participants with high-functioning autistic disorder or Asperger's disorder and controls when the groups were compared separately.

#### Interaction between GM volume and full-scale IQ or AQ total scores

In all subjects, there were no significant correlations between each subject's FSIQ and the GM volumes of the right insula ( $r = 0.314$ ,  $P = 0.011$ ;  $x = 44$ ,  $y = -12$ ,  $z = 10$ ) or the right IFG ( $r = 0.286$ ,  $P = 0.021$ ;  $x = 58$ ,  $y = 20$ ,  $z = 10$ ) (Fig. 3). However, there were significant negative correlations between each subject's AQ total score and the GM volumes of the right insula ( $r = -0.398$ ,  $P = 0.001$ ) and the right IFG ( $r = -0.404$ ,  $P < 0.001$ ) in all subjects (Fig. 3).

In the high-functioning PDD group, there were no significant correlations between either FSIQ and the GM volumes of the right insula ( $r = 0.239$ ,  $P = 0.188$ ) or the right IFG ( $r = 0.264$ ,  $P = 0.145$ ), or the AQ total score and the GM volumes of the right insula ( $r = 0.171$ ,  $P = 0.350$ ) or the right IFG ( $r = 0.067$ ,  $P = 0.714$ ) (Fig. 3). In the control group, there were no significant correlations between each subject's FSIQ and the GM volumes of the right insula ( $r = 0.149$ ,  $P = 0.409$ ) or the right IFG ( $r = -0.003$ ,  $P = 0.988$ ), or between each subject's AQ total score and the GM volumes of the right insula ( $r = -0.390$ ,  $P = 0.013$ ) or the right IFG ( $r = -0.246$ ,  $P = 0.126$ ) (Fig. 3). There were no significant differences in the slopes of these relationships between the groups ( $P > 0.05$ ; Fig. 3).

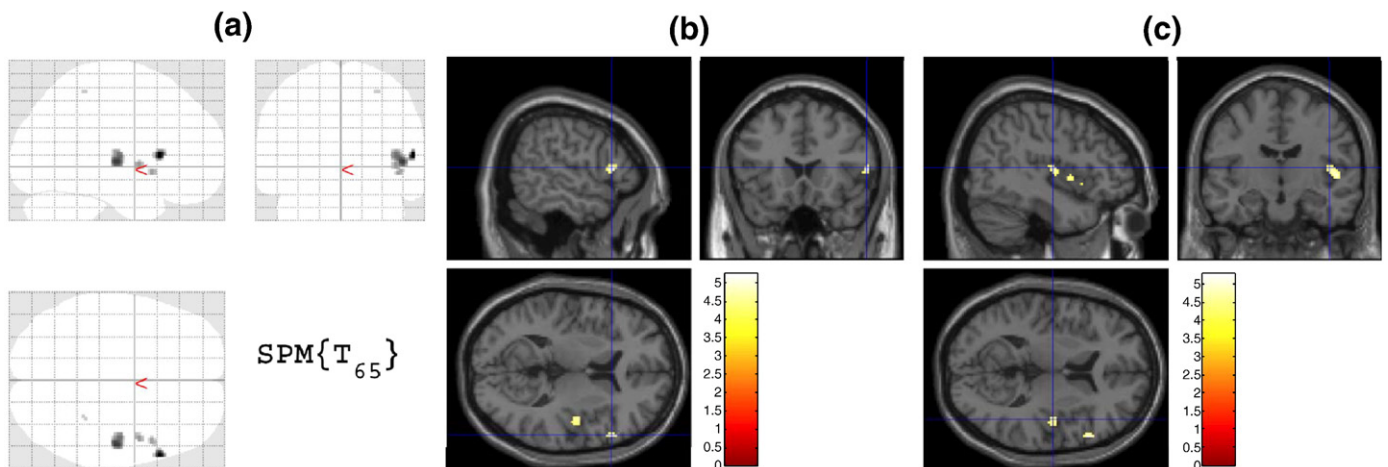
## Discussion

### Less local gray matter volume

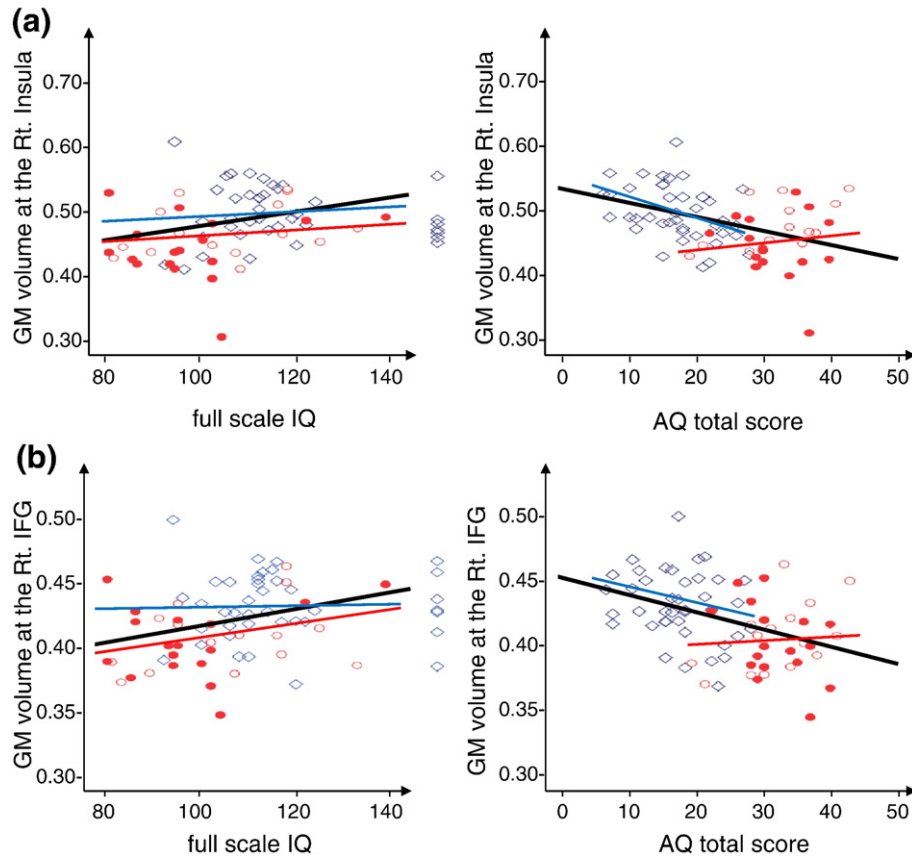
The present study showed significantly smaller local GM volumes in the right IFG, IPL, and insula of high-functioning young adults with PDD and normal IQ compared with control participants. There was no significant between-group difference in the whole absolute GM volume. Our finding of smaller local, rather than overall, GM volumes in young adults with PDD is consistent with a review by Amaral et al. (2008) that reported that whole GM volumes were within the normal range in the majority of adults with PDD. Although there were no significant correlations between FSIQ and the GM volumes of the right insula or the right IFG (Fig. 3), negative correlations were found between total AQ scores and the GM volumes in these areas. These findings suggest that smaller GM volumes in high-functioning PDD subjects reflect the clinical features of PDD itself, rather than FSIQ.

### Right IFG and IPL

The right IFG and IPL, where smaller GM volumes were found in high-functioning PDD subjects, are part of the mirror neuron system (MNS). Non-human primate studies have identified a particular class of visuomotor neurons, called mirror neurons, in area F5, which is the human analogue of part of the inferior frontal gyrus. Mirror neurons discharge both when a monkey performs a particular action and when it observes another individual (monkey or human) performing a



**Fig. 2.** (a) Brain regions showing smaller local GM volumes in high-functioning PDD individuals compared with control subjects projected onto the canonical VBM–DARTEL image. Adjustments have been made for GM volume and age ( $P < 0.05$ , corrected for multiple comparisons using FDR). The GM volumes of (b) the right inferior frontal gyrus and (c) the right insula were significantly smaller in the high-functioning PDD group at the adjusted cluster level ( $P < 0.05$ , corrected for multiple comparisons).



**Fig. 3.** Scatter plots portraying the relationships between GM volumes in (a) the right insula and (b) the right IFG and full scale IQ (left) and the AQ total scores (right) in all subjects. The solid red dots represent the subjects with high-functioning autistic disorder, and the open red dots indicate the subjects with Asperger's disorder. The open blue diamonds represent control subjects. In the left panel, the blue diamond on the right side represents the seven subjects for whom full-scale IQ scores were not measured. The slopes indicate the correlations in all subjects (black line), the high-functioning PDD group (red line), or the control group (blue line).

similar action (see Rizzolatti and Craighero, 2004, for a review). In humans, neuroimaging studies have revealed similar activation patterns in the IFG and IPL, which are usually considered constituents of the MNS. The human MNS is activated during the observation and imitation of others' actions (Rizzolatti and Craighero, 2004; Nishitani et al., 2005; Iacoboni and Dapretto, 2006) and is thought to be one of the key elements facilitating the early imitation of actions, the development of language, executive functions, and many components of the theory of mind in the developing child (Frith and Frith, 1999; Williams et al., 2001).

Our finding of smaller IFG volumes in the high-functioning PDD group is consistent with previous anatomical studies in PDD (Abell et al., 1999; McAlonan et al., 2005; Hadjikhani et al., 2006). Hadjikhani et al. (2006) directly measured cortical thickness and found that GM volumes in the IFG and IPL were smaller in high-functioning PDD participants.

Neuroimaging data also support a functional impairment of the right IFG in PDD. During the imitation of emotional expressions, functional MRI revealed that ASD children showed less activation in the right IFG, even though the control and ASD groups performed the tasks equally well (Dapretto et al., 2006). Subjects with Asperger syndrome also displayed delayed and diminished activation in the IFG, particularly in the right hemisphere, during the imitation of lip formations (Nishitani et al., 2004). Finally, disrupted functional connectivity between frontal and parietal areas has been reported in PDD subjects (Nishitani et al., 2004; Just et al., 2007).

As the IFG is part of the MNS, some authors have suggested that MNS dysfunction results in impaired social interaction, one of the core symptoms of PDD (Williams et al., 2001; Iacoboni and Dapretto, 2006). The present findings support this idea.

### Insula

To our knowledge, this is the first report showing smaller insula volumes in PDD. The insular cortex, which has reciprocal projections to areas of the limbic system such as the amygdala, plays a crucial role in emotional and various cognitive functions as a component of the "limbic integration cortex" (Augustine, 1996). Additionally, the insula plays a fundamental role in the critical relay from action representation to emotion, together with the IFG, superior temporal cortex, and amygdala (Mesulam and Mufson, 1982; Carr et al., 2003).

It is suggested that healthy individuals rely upon the MNS interfacing with the limbic system via the insula, whereby the meaning of the imitated (or observed) emotion is directly felt and hence understood (Carr et al., 2003; Dapretto et al., 2006). Thus, this structure could be described as an interface between the frontal component of the MNS and the limbic system, which enables the translation of an observed or imitated facial emotional expression into its internal emotional significance, i.e., empathy (Mesulam and Mufson, 1982; Augustine, 1996; Carr et al., 2003; Dapretto et al., 2006).

The GM volumes of the right insula and IFG were different between the two groups, and they were negatively correlated with each subject's AQ total score. These findings suggest that the right insula and IFG are related to the clinical features of PDD, which are represented by the AQ (i.e., poor social skill, poor attention-switching/strong focus of attention, exceptional attention to detail, poor communication skill, poor imagination; Baron-Cohen et al., 2001). In particular, the social reciprocity problems that characterize the PDD group from infancy persist through childhood and adolescence into

adult life (Billstedt et al., 2007). PDD individuals have specific delays and difficulties in the ability to discriminate emotions from eye expressions and tend to make less eye contact. They have an impaired drive to identify the emotions and thoughts of others and to respond with an appropriate emotion (i.e., impaired empathy; Baron-Cohen, 2002). In functional neuroimaging studies of PDD subjects, insular dysfunction has been reported, including hypo-perfusion in the bilateral insulae in a  $^{99m}\text{Tc}$ -ECD-SPECT study (Ohnishi et al., 2000) and insufficient activation of the right insula and IFG during an empathizing task in a functional MRI study (Baron-Cohen et al., 1999). Taken together, the findings of the present study indicate that the smaller volumes in the insula and IFG in PDD subjects contribute to the clinical symptoms of PDD.

Smaller volumes in the IFG and insular cortices may also explain the impairment in self-consciousness in PDD. High-functioning PDD individuals lack self-consciousness when performing an incidental memory task (Toichi et al., 2002). The self-reference effect works through enhanced semantic retrieval and selection processes (Klein and Loftus, 1988). The area around the IFG has been shown to be important in semantic retrieval and selection processes (Badre et al., 2005). In contrast, the right posterior insula was activated when the afferent input matched subjects' own actions in a positron emission tomography (PET) study (Farrer et al., 2003). These findings were interpreted as evidence that the right posterior insula plays an important role in integrating signals related to self-awareness and establishing a boundary between self and others (Saxe et al., 2007). As more self-focused PDD subjects are better at empathy tasks (Lombardo et al., 2007), the same neural substrates might underlie impaired empathy and self-consciousness in PDD. Williams (2008) suggested that impaired empathy and self-consciousness in PDD patients may be related to MNS dysfunction. Our colleagues (Morita et al., 2008) found significantly increased activation of the right IFG and bilateral insulae in the "own face" task compared with the "other's face" task. These previous findings, together with the results of the present study, suggest that the insula may be one of the key regions in PDD pathogenesis.

#### Limitations of the present study

Although there were over 70 subjects in the present study, the sample size was still small. However, to offset the small sample size, we used the VBM-DARTEL method, which provides study-specific templates and increases statistical power and sensitivity to real differences. A larger longitudinal study of PDD subjects with well-characterized clinical features will be necessary to confirm our preliminary results.

#### Conclusion

In conclusion, we found smaller local GM volumes in the insular cortex and right IFG in young male adults with high-functioning PDD. The smaller volumes in these areas were related to AQ scores rather than IQ scores. Since the insula works as a relay area for multiple neurocognitive systems engaged in empathy, social interaction, imagination, imitation, and self-consciousness, it may be one of the key regions underlying the complex clinical features of PDD. Although further studies are needed, the present study provides valuable data to improve our understanding of the pathogenesis and brain morphological changes in PDD.

#### Acknowledgments

This study was funded in part by the Fukui Prefectural Government's Grant-in-Aid for Collaboration Research Projects and Grants-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (17100003, 17209040, 21791120, and 21220005). **Part of this study is the result of the project "Development of biomarker**

**candidates for social behavior", which was carried out under the Strategic Research Program for Brain Sciences by the Ministry of Education, Culture, Sports, Science and Technology of Japan.**

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