Reduced Gray Matter Volume of Pars Opercularis Is Associated with Impaired Social Communication in High-Functioning Autism Spectrum Disorders

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Background: Recent literature suggests that the inferior frontal gyrus, especially its posterior portion, has an important role in imitation and social reciprocity and in the pathophysiology of their disturbance in autism spectrum disorders (ASD). However, the structural abnormality of this region has not fully been clarified in subjects with ASD.

Methods: Here we obtained magnetic resonance images from 13 right-handed men with high-functioning ASD (Asperger disorder [$n = 10$] or autism [$n = 3$]) and from 11 age-, parental socioeconomic background-, and intelligence quotient-matched right-handed typical men. A reliable manual tracing methodology was employed to measure the gray matter volume of the pars opercularis, corresponding to Brodmann area 44, and the pars triangularis, corresponding to Brodmann area 45.

Results: A significant gray matter volume reduction of both the pars opercularis and triangularis was found bilaterally in the subjects with ASD compared with the typical control subjects. The effect size seemed to be larger for pars opercularis (1.25) than for pars triangularis (.90). The reduced volume of right as well as total pars opercularis showed a significant association with the increased severity of social communication problems in the ASD group.

Conclusions: The current findings support an important role of pars opercularis, a center of the mirror neuron system, in the pathophysiology of ASD.

Key Words: Autism, Asperger disorder, human mirror neuron system, MRI, social dysfunction

Dysfunction in social reciprocity is the core feature of autism-spectrum disorders (ASD). It is common, regardless of age, intellectual ability, and subtype, including autistic disorder, Asperger's disorder, and pervasive developmental disorder not otherwise specified (1,2). Its brain structural substrates, however, have yet to be clarified.

Brain regions contributing to human mirror neuron system (MNS) might be a candidate locus for social reciprocity deficits in ASD (3). The MNS enables the modeling of behavior of other people through a mechanism of embodied simulation, an internal representation of body states associated with actions and emotions. The inferior frontal gyrus (IFG) and the right superior parietal lobule constitute core regions of human MNS. These regions are activated with the observation of a movement made by another individual as well as the execution of the identical movement as imitative behavior (4,5). Among subregions of IFG, the pars opercularis—which mainly consists of Brodmann area 44 (BA44)—might be particularly involved in human MNS (6). Literature suggests that the BA44 is strongly involved in action imitation and is the orchestrator of the human MNS and social interaction (7–9). Several functional magnetic resonance imaging (MRI) studies have focused on the pars opercularis as a possible neural substrate of social reciprocity deficits in ASD (10,11).

Brain structural abnormalities have also been documented in IFG of subjects with ASD. Hadjikhani *et al.* (12) used an automated technique of analysis that measures the thickness of the cerebral cortex and compared a group of 14 high-functioning subjects with ASD with matched control subjects. They found local decreases of cortical thickness (CT) in the pars opercularis in the ASD group. Abell *et al.* (13) found decreases of gray matter density in the left IFG with voxel-based morphometry (VBM). Levitt *et al.* (14), employing parametric mesh-based analytic techniques to create maps of major sulci, reported anterior shifting of inferior frontal sulci in individuals with autism. Nodahl *et al.* (15), with a surface-based morphometry, showed that autism subjects had a prominent shape abnormality centered on pars opercularis that was associated with a sulcal depth difference in the anterior insula and frontal operculum. Applying these automated techniques to the structural assessment of IFG, however, might have methodological limitations, because significant individual variation of the gyral pattern of IFG has been pointed out (16). The VBM might not detect very small and localized gray-matter volume reductions, because false-positive or false-negative VBM findings might arise from changes in the shape or displacement of structures in the course of spatial normalization (17). Spatial normalization could result in the misclassification of gyri with significant individual variation (18).

In contrast, no manual-tracing study has reported volume reduction of posterior IFG. A few studies have measured the IFG volume in ASD; however, they failed to find a significant volume change relative to typically developed control subjects (19–21). In the present study, we adopted a more sophisticated method of manual tracing for pars opercularis and triangularis than those employed in the prior studies. We considered anatomical variation

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Table 1. Demographic Characteristics of Study Participants

Variables	Subjects with ASD ($n = 13$)		Control Subjects ($n = 11$)		*t* Test	
	Mean	SD	Mean	SD	*t*	*p*
Age (range)	28.5 (18–49)	10.2	29.1 (24–33)	3.1	−.20	.85
SES	3.5	1.4	1.6	.5	4.48	<.001
Parental SES	2.3	.9	2.1	.5	.73	.48
IQ (range)	95.5 (77–121)	12.2	101.7 (79–119)	12.7	1.22	.24
CARS Total Score	28.8	8.6				
Social communication	8.7	2.4				
Social interaction	4.1	1.2				
Stereotypies and sensory abnormalities	6.5	1.6				
Emotional reaction	8.3	2.1				

ASD, autism spectrum disorder; SES, socioeconomic status, assessed with the Hollingshead (higher scores indicate lower status); CARS, Childhood Autism Rating Scale.

of pars opercularis and triangularis according to a precise operational definition (see Methods and Materials).

Accordingly, the aims of this study were: 1) to assess whether there is gray matter volume reduction of IFG subregions in high-functioning adults with ASD compared with matched healthy control subjects; and 2) to identify differential clinical correlates of pars opercularis and triangularis morphology, particularly the correlation between the volume of pars opercularis and severity of disrupted social communication and reciprocity, in subjects with ASD.

Methods and Materials

Subjects

Thirteen male subjects with Asperger disorder ($n = 10$) or high-functioning autism ($n = 3$) were recruited from the Department of Neuropsychiatry, University of Tokyo Hospital, Japan. Diagnosis of autism spectrum disorders was determined according to strict DSM-IV criteria by a trained child-adolescent psychiatrist (clinical experience > 5 years; HK). The severity was assessed with the Childhood Autism Rating Scale (CARS) (22). Factor scores of CARS were calculated with the four factor structures identified by principal axis factor analysis (23). Eleven age-, gender-, intelligence quotient (IQ)-, and parental socioeconomic status (SES)-matched typical participants were employed as control subjects. The autistic trait in the control subjects was screened with Autism spectrum quotient (24), because the autistic trait could be observed in some degree also in typically developed people. The maximum total score of Autism spectrum quotient was 20 in the control subjects ($n = 10$, mean = 13.7 [minimum–maximum: 7–20], SD = 4.4; data were not available for one subject), whereas the cutoff threshold was defined as 34 points (24). The IQ was assessed with full-scale of the Wechsler Adult Intelligence Scale Revised version for 12 of 13 subjects with ASD and 7 of 11 control subjects, whereas the remaining subjects were assessed with the short version of the Wechsler Adult Intelligence Scale Revised version (25). Full-scale IQ > 75 was the cutoff for high-functioning autism (26). The SES was assessed with the Hollingshead scale (27). Seven of 13 subjects with ASD were medication-free. Two with ASD had taken antipsychotic, anti-Parkinson, antidepressant, and anxiolytic medications. One with ASD had taken antipsychotic, anti-Parkinson, and anxiolytic medications. One with ASD had taken antipsychotic and anxiolytic medications. Two with ASD had taken antidepressant and anxiolytic medications.

There were no significant differences between the ASD and control groups in age, IQ, and parental SES, although the ASD group had significantly lower self-SES than control subjects. The typical control subjects were interviewed by a trained psychiatrist (HY) to be screened for the presence or absence of neuropsychiatric disorders through the Structured Clinical Interview for DSM-IV Axis I Disorder Nonpatient Edition (28,29). All the participants were right-handed, determined with the Edinburgh Inventory (30); with a laterality index of > .8 as the cutoff for right-handedness. The demographic characteristics of the participants are shown in Table 1.

The exclusion criteria for both groups were current or past neurological illness, traumatic brain injury with any known cognitive consequences or loss of consciousness for more than 5 min, a history of electroconvulsive therapy, and substance abuse or addiction. An additional exclusion criterion for the control group was a history of psychiatric disease or a family history of axis I disorder in their first-degree relatives. The ethics committee of the University of Tokyo Hospital approved this study (No. 397). After a complete explanation of the study to the subjects, written informed consent was obtained from every participant.

MRI Acquisition

The methods of MRI acquisition have been described in detail elsewhere (31,32) and in Supplement 1.

Definition of Region of Interest. The pars opercularis and triangularis gray matter regions of interest (ROIs) were outlined manually with a software package for medical image analysis (3D Slicer; software available at http://www.slicer.org). The manual tracing procedure for data of all participants was completed by a trained rater (SY) without knowledge of diagnosis or participant information. The anatomical landmarks to delineate pars opercularis and triangularis with 3-dimensional information were the same as our recent study (33), which was developed on the basis of previous studies examining IFG (16,34) and our earlier studies with 3-dimensional information in other ROIs (35,36) (Figure 1). The detailed definition of ROI was described elsewhere (33); also see Supplement 1.

Anatomical Variations of Inferior Frontal Subregions. As significant individual variability of gyral and sulcal pattern of inferior frontal subregions was identified, we categorized the variants of respective pars opercularis and triangularis into two subtypes—a relatively simple scheme in comparison with more elaborate categorization employed previously (37).

Pars Opercularis. One gyral/sulcal pattern was most common, constituting 21 of 24 cases in the left hemisphere and all 24 cases in the right hemisphere. This pattern was labeled pars opercularis-