

A limitation of this study is that the group of PDD participants was small, as then was the two subgroups. Therefore, future study should involve a larger number of participants. In addition, the profiles of the control group participants lacked important information. For example, no accurate IQ information was available, although because the average IQ of the PDD group participants was higher than 100 and no correlation was found between IQ and mind-reading performance, the influence of IQ appears to be limited. In future studies, the IQ, age and education level of the control group should be matched to those of the PDD group. Moreover, the participants in this study were all male. Given that gender differences on mind-reading tasks have been reported (Baron-Cohen, Wheelwright, Skinner, et al., 2001; Baron-Cohen, 2003; Golan et al., 2006; Rutherford et al., 2002; Wakabayashi & Katsumata, in press), future work should include female participants. Finally, the tasks used in this study were created from clips from a TV drama, which resulted in somewhat uncontrolled categories of emotions. Thus, future use of controlled categories of emotions to examine performance differences among groups divided by diagnosis should contribute to identifying those emotions and mental states that are relatively easier for adults with HFA to recognize.

5. Conclusions

Using the new visual and auditory tasks, this study compared the performance of subgroups of PDD divided according to DSM-IV-TR diagnostic criteria in order to clarify the difference in mind-reading abilities among the subgroups. The results demonstrated that on both the visual and auditory tasks, individuals with HFA experienced the greatest difficulty in understanding the complicated emotions and mental states of others. In contrast, the results suggest that the mind-reading abilities of adults with AS and PDD-NOS did not differ much from those without PDD. Taken together, complex mind-reading tasks appear to be effective for distinguishing individuals with HFA from those with AS or PDD-NOS. Clinically, adults with HFA who are not able to understand easily others' thoughts and emotions will likely encounter problems in social relationships. Individuals with AS or PDD-NOS will likewise experience such problems, but for different reasons: although they might well be able to understand others' emotions and thoughts, they will likely have difficulty knowing how to adapt their own social behavior. The support offered to individuals of different PDD subgroups may need to be differentiated accordingly.

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Reduced Acetylcholinesterase Activity in the Fusiform Gyrus in Adults With Autism Spectrum Disorders

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Context: Both neuropsychological and functional magnetic resonance imaging studies have shown deficiencies in face perception in subjects with autism spectrum disorders (ASD). The fusiform gyrus has been regarded as the key structure in face perception. The cholinergic system is known to regulate the function of the visual pathway, including the fusiform gyrus.

Objectives: To determine whether central acetylcholinesterase activity, a marker for the cholinergic system, is altered in ASD and whether the alteration in acetylcholinesterase activity, if any, is correlated with their social functioning.

Design: Using positron emission tomography and a radiotracer, *N*-[¹¹C]methyl-4-piperidyl acetate ([¹¹C]MP4A), regional cerebrocortical acetylcholinesterase activities were estimated by reference tissue-based linear least-squares analysis and expressed in terms of the rate constant *k*₃. Current and childhood autism symptoms in the adult subjects with ASD were assessed by the Autism Diagnostic Observation Schedule and the Autism Diagnostic Interview-Revised, respectively. Voxel-based analyses as well as region of interest-based methods were used for be-

tween-subject analysis and within-subject correlation analysis with respect to clinical variables.

Setting: Participants recruited from the community.

Participants: Twenty adult subjects with ASD (14 male and 6 female; age range, 18-33 years; mean [SD] intelligence quotient, 91.6 [4.3]) and 20 age-, sex-, and intelligence quotient-matched healthy controls.

Results: Both voxel- and region of interest-based analyses revealed significantly lower [¹¹C]MP4A *k*₃ values in the bilateral fusiform gyri of subjects with ASD than in those of controls (*P* < .05, corrected). The fusiform *k*₃ values in subjects with ASD were negatively correlated with their social disabilities as assessed by Autism Diagnostic Observation Schedule as well as Autism Diagnostic Interview-Revised.

Conclusions: The results suggest that a deficit in cholinergic innervations of the fusiform gyrus, which can be observed in adults with ASD, may be related to not only current but also childhood impairment of social functioning.

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AUTISM SPECTRUM DISORDERS (ASD), comprising autistic disorder, Asperger disorder, and pervasive developmental disorder not otherwise specified, are characterized by impairment in both social interaction and communication as well as by restricted or repetitive behaviors and interests.¹ Although individuals with ASD also have significant deficits in face perception,^{2,3} this aspect is not included in the current diagnostic criteria.¹ Because of the fundamental role of face processing in social interactions, it has been hypothesized that abnormalities in the neural circuitry involved in face processing contribute to social disabilities in ASD.

It is well recognized from functional magnetic resonance imaging (fMRI) studies that a specific region of the fusiform gyrus called the fusiform face area (FFA) is consistently active during face viewing in typically developing individuals.^{4,5} The FFA activity in face processing is known to be dominated by the right hemisphere,⁶ and the functional volume of the right FFA, defined by fMRI during face viewing, may increase with age.⁷ Most previous fMRI studies have found that subjects with ASD lack FFA activation in response to strangers' faces,⁸⁻¹⁰ although subsequent studies have shown that differences in FFA activation between typically developing and autistic people may

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be mediated by task demand,^{11,12} familiarity,^{13,14} or the amount of time spent fixating on the eyes.¹⁵ The FFA hypofunction, especially in the right hemisphere, that occurs when children and adults with ASD view strangers' faces, is the best-replicated fMRI abnormality.^{14,16} This phenomenon may arise from neuropathological abnormalities in the fusiform gyrus in ASD; in a recent post-mortem study by van Kooten et al,¹⁷ compared with controls, patients with autism showed significantly lower neuron densities in layer III, total neuron numbers in layers III, V, and VI, and mean perikaryal volumes of neurons in layers V and VI in the fusiform gyrus.

Several neurotransmitters including acetylcholine, dopamine, noradrenaline, and serotonin have been found to play important roles in cortical activity.^{18,19} In the visual cortex, acetylcholine makes the greatest contribution to the biophysical properties of the neurons and synaptic efficacy, although the involvement of noradrenaline and serotonin is also implicated.¹⁹ Evidence of the critical effect of acetylcholine on fusiform activity has been derived from the results of fMRI and positron emission tomography (PET) studies, which have demonstrated that pharmacological manipulation of cholinergic activity can alter the function of the fusiform gyrus; scopolamine reduced fusiform activity in individuals who performed a long-term encoding task,²⁰⁻²³ while cholinergic enhancement by the cholinesterase inhibitor physostigmine augmented the relative neuronal response in the middle fusiform gyrus during emotional processing.²⁴ These findings suggest that abnormalities in cholinergic function could occur in the fusiform gyrus in individuals with ASD and that such abnormalities would be associated with social disability. To test this hypothesis, we assessed acetylcholinesterase (AChE) activity, a marker for the central cholinergic system,²⁵ in adult individuals with ASD and age- and sex-matched controls by PET and the radioactive tracer *N*-[¹¹C]methylpiperidin-4-yl acetate ([¹¹C]MP4A), which is an analog of acetylcholine and is selectively hydrolyzed by AChE.^{26,27} Furthermore, we examined the clinico-biomarker relationship by comparing clinical variables with regional [¹¹C]MP4A PET data in subjects with ASD. Because previous studies describe right-hemisphere dominance in fusiform hypofunction during face processing^{14,16} and unaltered choline acetyltransferase activities in the postmortem parietal and frontal cortices²⁸ in autism, we predicted that abnormalities in AChE activity measured by [¹¹C]MP4A PET would be less prominent or not altered in the cerebral cortex, other than the right-hemisphere fusiform gyrus, in subjects with ASD.

METHODS

SUBJECTS

Twenty subjects with ASD (14 male and 6 female; mean [SD] age, 23.5 [4.3] years; age range, 18-33 years) and 20 age- and sex-matched control subjects (14 male and 6 female; mean [SD] age, 23.1 [4.2] years; age range, 19-34 years) participated in this study. All of the participants were right-handed and had an intelligence quotient greater than 70. None of the participants were tobacco smokers or taking any medication, including psychotropic drugs.

All of the subjects with ASD were diagnosed by 2 trained child psychiatrists (K.N. and T.S.) according to the DSM-IV.¹ The subjects with ASD did not have any other psychiatric comorbidity disorders, as confirmed by applying the Structured Clinical Interview for DSM-IV axis I disorders.²⁹ In addition, they had no notable dysmorphology, neurocutaneous abnormalities, significant neurologic deficits, history of epileptic seizures, or disorders known to be associated with autism such as fragile X syndrome, neurofibromatosis, or tuberous sclerosis. The Autism Diagnostic Observation Schedule (ADOS)³⁰ module 4 and Autism Diagnostic Interview-Revised (ADI-R)³¹ were used to evaluate current and childhood autism symptoms, respectively, by trained clinicians (K.J.T. and K.M., respectively). Fifteen of 20 subjects with ASD were diagnosed with autistic disorder and remaining 5 were considered to have pervasive developmental disorder not otherwise specified according to the ADOS scores, although all 20 subjects met ADI-R criteria of autism disorder. All control subjects were found to be mentally and physically healthy according to comprehensive assessments of their medical histories and neuropsychiatric examinations. The study was approved by the local ethics committees. Written informed consent was obtained from each of the participants.

MRI AND PET PROCEDURES

As described elsewhere,^{32,33} we performed 3-dimensional MRI scans using a 0.3-T MRI unit (model MRP7000AD; Hitachi Medical, Tokyo, Japan) and PET scans with a high-resolution brain PET scanner with the ability to yield 47 PET images simultaneously (model SHR-12000; Hamamatsu Photonics, Shizuoka, Japan). Details in image acquisition and preprocessing procedures are described in the online-only material (eAppendix 1; <http://www.archgenpsychiatry.com>). The MRI measurements and a mobile PET gantry allowed us to reconstruct PET images parallel to the anterior-posterior intercommissural line without resectioning. Using this approach, we were able to allocate a region of interest (ROI) to the target area of the PET image.³³ Before dynamic PET scanning, a 20-minute transmission scan was performed for attenuation correction using a ⁶⁸Ge/⁶⁸Ga source with the participant's head fixed by means of a radiosurgery-purpose thermoplastic face mask. Then, after a bolus intravenous injection of a 380-MBq dose of [¹¹C]MP4A, 32 serial PET scans (time frames, 4 × 30 seconds, 20 × 60 seconds, and 8 × 300 seconds) were performed for 62 minutes. No sedatives were administered during either the MRI or the PET scan.

IMAGING DATA ANALYSIS

Regional cerebrocortical AChE activities were estimated using PMOD 2.95 software (PMOD Technologies, Zurich, Switzerland). Production of parametric k_3 images was based on the reference tissue model designated for [¹¹C]MP4A k_3 value quantification,³⁴ and the ROI analysis was based on the reference tissue-based linear least-squares method³⁵ (eAppendix). In brief, a target cortical region and the cerebellum as a reference region were delineated on MRIs from each participant and transferred onto PET images. The regional k_3 value, representing the rate of tracer hydrolysis by AChE, and the R_1 value, which is the delivery of the tracer in the target region relative to the reference and reflects regional cerebral blood flow, were calculated using multilinear regression from time-activity curves from the target and reference regions.³⁵ The R_1 value is important for ruling out the effect of regional cerebral blood flow on the regional k_3 value. Using the PMOD, whole-brain parametric maps of k_3 and R_1 were generated. We masked extracerebral structures by demarcating cerebral regions on MRIs for further analysis of the k_3 and R_1 parametric maps.

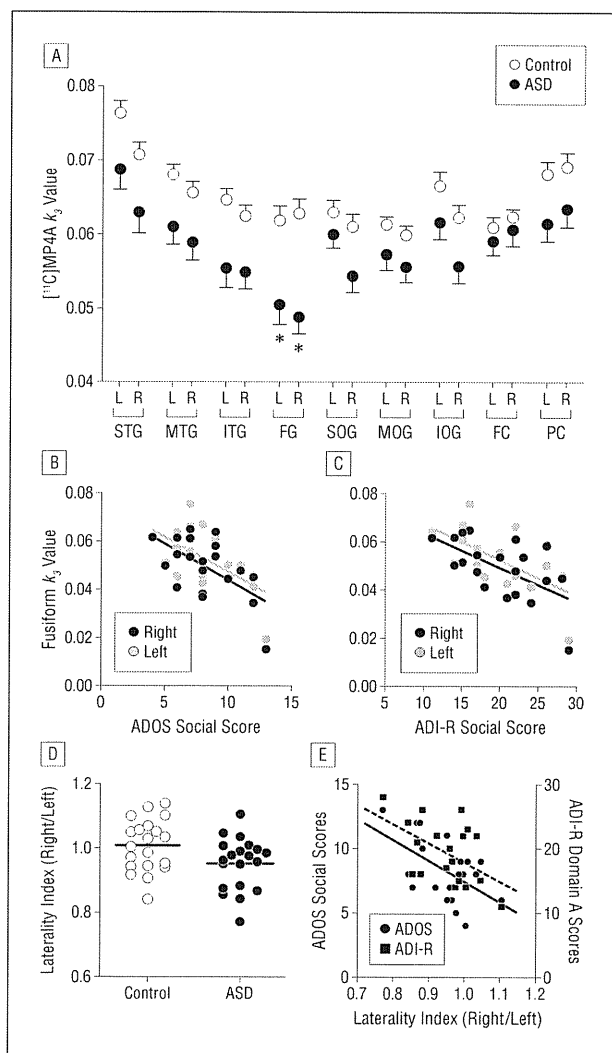


Figure 1. Results of region of interest–based analysis. A, Mean regional brain M -[^{11}C]methylpiperidin-4-yl acetate ([^{11}C]MP4A) k_3 values in controls and subjects with autism spectrum disorder (ASD). Subjects with ASD had significantly lower k_3 values in the bilateral fusiform gyri compared with controls. Error bars represent the standard error of the mean. Note the significance ($P < .01$ by post hoc Bonferroni test following 2-way analysis of variance). Correlation between [^{11}C]MP4A k_3 values in the fusiform gyrus and social scores of the ADOS (B) and ADI-R (C) is shown. Values of [^{11}C]MP4A k_3 in both the right and left fusiform gyri were significantly and negatively correlated with the Autism Diagnostic Observation Schedule (ADOS) social scores (A) as well as the Autism Diagnostic Interview–Revised (ADI-R) domain A scores (B). D, The mean laterality index (right to left ratio) of the fusiform k_3 values in controls and subjects with ASD is shown. E, Correlation between laterality index of fusiform k_3 and social scores of ADOS or ADI-R in subjects with ASD is also shown. ADI-R indicates Autism Diagnostic Interview–Revised; ADOS, Autism Diagnostic Observation Schedule; FC, dorsolateral prefrontal cortex; FG, fusiform gyrus; IOG, inferior occipital gyrus; ITG, inferior temporal gyrus; MOG, middle occipital gyrus; MTG, middle temporal gyrus; PC, parietal cortex (angular gyrus); SOG, superior occipital gyrus; and STG, superior temporal gyrus.

VOXEL-BASED IMAGE ANALYSIS

We performed voxel-based whole-brain analyses using statistical parametric mapping software (SPM5; Wellcome Department of Cognitive Neurology, Institute of Neurology, London, England). In the SPM analysis of [^{11}C]MP4A k_3 and R_1 parametric maps, between-group comparisons were performed to investigate regional differences in each value, using the t test for each voxel. The SPM analyses were performed without proportional scaling of k_3 and R_1 values. Correlations be-

tween k_3 and R_1 values were examined on a voxel-by-voxel basis using the Biological Parametric Mapping toolbox.³⁶ The Biological Parametric Mapping toolbox examines any correlation voxelwise between multimodal images that are coregistered and aligned within the same space (ie, Montréal Neurological Institute space). To test the effect of tracer delivery (R_1) on the metabolic rate (k_3), an analysis of covariance was performed using the k_3 map as the primary modality and the corresponding R_1 map as the regressor using the Biological Parametric Mapping toolbox. In addition, we performed exploratory correlation analyses between the regional changes in [^{11}C]MP4A k_3 values and the severity of social disabilities in subjects with ASD. Age and sex were treated as covariates, and the scores on the ADOS and ADIR were considered to be variables of interest. To test hypotheses about the regional specific effects of these variables, the estimates were compared using 2 linear contrasts (positive or negative correlation).

ROI-BASED ANALYSIS

In addition to the voxel-based analysis that is suitable for an exploratory examination of tracer distribution altered in the brain, we performed ROI-based analysis because it enabled us to generate quantitative differences in [^{11}C]MP4A k_3 and R_1 values in specific regions. Manual delineation on individual MRI scans in ROI-based approaches is often biased by the variability between raters and side differences in ROI size, whereby direct case-control comparability is compromised. Therefore, we chose to delineate ROIs by application of a standardized ROI template based on the Anatomical Automated Labeling atlas³⁷ fitting the Montréal Neurological Institute standard brain. Both the k_3 and R_1 parametric maps were normalized to the Montréal Neurological Institute space by applying a nonlinear iterative algorithm using PMOD software. Then we chose ROIs of 9 brain areas bilaterally including visual processing pathways (the fusiform gyrus, superior, middle, and inferior temporal gyri, and the superior, middle, and inferior occipital gyri), dorsolateral prefrontal cortex (Brodmann area 9), and parietal cortex (angular gyrus, Brodmann area 39). Averaged k_3 and R_1 values for each ROI were obtained. To determine whether there is laterality in the regional k_3 values, we calculated a laterality index (right k_3 /left k_3) in bilateral fusiform ROIs in the 2 groups.

STATISTICAL ANALYSIS

Demographic and clinical variables were compared between the ASD and control groups using the unpaired t test using statistical software (SPSS version 17J; SPSS Japan Inc, Tokyo, Japan). In the voxel-based analyses, the results were corrected for multiple comparisons of whole-brain analysis at a significance level of $P < .05$ (false discovery rate). The significance level was determined using a voxel-level threshold of $P < .001$. In ROI-based analyses, we tested the main effect of the diagnosis of ASD on [^{11}C]MP4A k_3 or R_1 values derived from 9 brain regions using 2-way analysis of variance followed by post hoc Bonferroni test. We further conducted an analysis of covariance using the k_3 value as the independent variable and the corresponding R_1 value as the covariate in ROIs on the fusiform gyrus, based on the results of the 2-way analysis of variance (Figure 1A). In the laterality analysis, an unpaired t test was used for the comparison between the 2 groups. Evaluation of relationships between the regional k_3 values from each ROI and ADI-R or ADOS scores among subjects with ASD was performed with the Pearson r correlation coefficient. Statistical significance was set at $P < .05$.

RESULTS

The characteristics of all the participants are summarized in **Table 1**. There was no significant difference in the distribution of age or the sex ratio. The difference in intelligence quotient between the 2 groups did not reach statistical significance ($t = 1.43$; $P = .16$). In quantitative PET brain imaging, the motion artifact is the important degrading factor. Therefore, we fixed the head of each participant using a thermoplastic face mask, observed participants carefully during each scan, and confirmed that all of the participants had remained immobilized. Another major confounding factor in PET image analysis is the partial volume effect (PVE) that can be observed in measuring small brain structures and lead to an underestimation of tracer activity. The present results were generated without PVE correction. To minimize PVE, we used a high-resolution brain-purpose PET scanner for data acquisition and MRI data for image analysis, the latter of which allowed us to select the brain loci with no extraparenchymal spaces to estimate k_3 value, an index of AChE activity, and R_1 , an index of tracer delivery, with reference tissue-based linear least-squares analysis³⁴ of dynamic [¹¹C]MP4A PET images. When we conducted an additional volumetric brain morphometry study using a 3-T scanner on the participants of the MP4A PET study, there was no significant difference in whole-brain or regional gray matter volumes between subjects with ASD and controls (eAppendix 2, eTable, eFigure 1 and eFigure 2).

VOXEL-BASED WHOLE-BRAIN ANALYSIS

We first obtained parametric maps of k_3 and R_1 values of ASD and control subjects. **Figure 2A** illustrates normalized and averaged [¹¹C]MP4A k_3 parametric maps from control subjects and subjects with ASD. The ASD group showed significant reductions in [¹¹C]MP4A k_3 values in ventral portion of the bilateral temporal lobes compared with the control group (Figure 1B). There was no voxel where [¹¹C]MP4A k_3 values were greater in subjects with ASD than in controls. In contrast, there was no significant difference in R_1 values in the whole brain between groups (eFigure 3 and eFigure 4). Although it was found that R_1 values did not differ significantly between the ASD and control groups, to exclude further a possible adverse effect of the [¹¹C]MP4A delivery on its retention, we conducted an analysis of covariance using the k_3 map as the primary modality and the corresponding R_1 map as the regressor. After controlling the effect of R_1 value, the reduction in [¹¹C]MP4A k_3 values in the ASD group was still significant within the fusiform gyrus bilaterally (Figure 1C; $P < .05$, corrected).

We further examined the possible relationships between [¹¹C]MP4A k_3 values and clinical features in subjects with ASD (**Table 2**). Figure 1D shows a cluster on the fusiform gyrus in which the [¹¹C]MP4A k_3 values were significantly negatively correlated with the ADOS social score ($P < .05$, corrected). Figure 1E indicates a cluster on the fusiform gyrus in which a significantly negative correlation between the [¹¹C]MP4A k_3 values and the ADI-R domain A (social) score was noted ($P < .05$, cor-

Table 1. Demographic Characteristics of the Participants

Characteristic	Mean (SD) [Range]	
	Control (n = 20)	ASD (n = 20)
Male:female, No.	14:6	14:6
Age, y	23.1 (4.2) [19-32]	23.5 (4.3) [18-33]
WAIS-III, full IQ	100.5 (19.4) [70-136]	91.6 (19.7) [70-140]
ADOS score		
Social	NA	8.6 (2.3) [5-13]
Communication	NA	4.3 (1.9) [2-8]
Stereotype	NA	0.8 (0.9) [0-3]
ADI-R score, Domain		
A (social)	NA	20.0 (5.2) [11-29]
B (communication)	NA	14.8 (5.0) [9-23]
C (stereotype)	NA	5.2 (2.3) [4-13]

Abbreviations: ADI-R, Autism Diagnostic Interview-Revised; ADOS, Autism Diagnostic Observation Schedule; ASD, autism spectrum disorder; NA, not applicable; WAIS-III, Wechsler Adult Intelligence Scale, 3rd edition.

rected). Clusters associated with the ADOS social score (Figure 1D) and the ADI-R social score (Figure 1E) were located within the clusters shown in Figure 1C. The other scores in the ADOS and ADI-R did not correlate significantly with [¹¹C]MP4A k_3 values (data not shown).

ROI ANALYSIS

The results of analyses of multiple ROIs are shown in Figure 2. Consistent with the findings derived from the voxel-based analysis, [¹¹C]MP4A k_3 values in the bilateral fusiform gyri in subjects with ASD were significantly lower than the corresponding values in control subjects (Figure 2A; $t = 4.91$, $P < .001$ for the right; $t = 3.98$, $P = .002$ for the left). There was no difference in [¹¹C]MP4A R_1 values between subjects with ASD and controls in either side of the fusiform gyrus (eFigure 5; $t = 1.47$, $P = .15$ for the right; $t = 1.66$, $P = .10$ for the left). Analysis of covariance showed that differences in k_3 values between the 2 groups were significant in bilateral fusiform ROIs after controlling the effect of R_1 value ($F_{1,37} = 12.51$, $P = .001$ for the right; $F_{1,37} = 6.78$, $P = .01$ for the left).

Examination of the correlation between [¹¹C]MP4A k_3 values in the bilateral fusiform gyri and the clinical characteristics revealed that the [¹¹C]MP4A k_3 values were significantly negatively correlated with social scores of both the ADOS (Pearson $r = -0.559$, $P = .009$ for the right; $r = -0.512$, $P = .02$ for the left) and ADI-R ($r = -0.594$, $P = .007$ for the right; $r = -0.572$, $P = .008$ for the left) (Figure 2B for ADOS and Figure 2C for ADI-R). No correlation was found between [¹¹C]MP4A k_3 values in the fusiform gyrus and other scores of the ADOS or the ADI-R (data not shown). Values of [¹¹C]MP4A k_3 in ROIs other than the fusiform gyrus did not correlate significantly with any ADOS or ADIR scores (data not shown).

Results from the laterality analysis of [¹¹C]MP4A k_3 values in the fusiform gyrus are shown in Figure 2, D and E. The group mean of the laterality index, a right to left ratio of the k_3 value, in subjects with ASD was significantly lower than that of controls ($t = 2.21$; $P = .03$). The laterality index was weakly but significantly and negatively correlated with ADOS social scores (Pearson

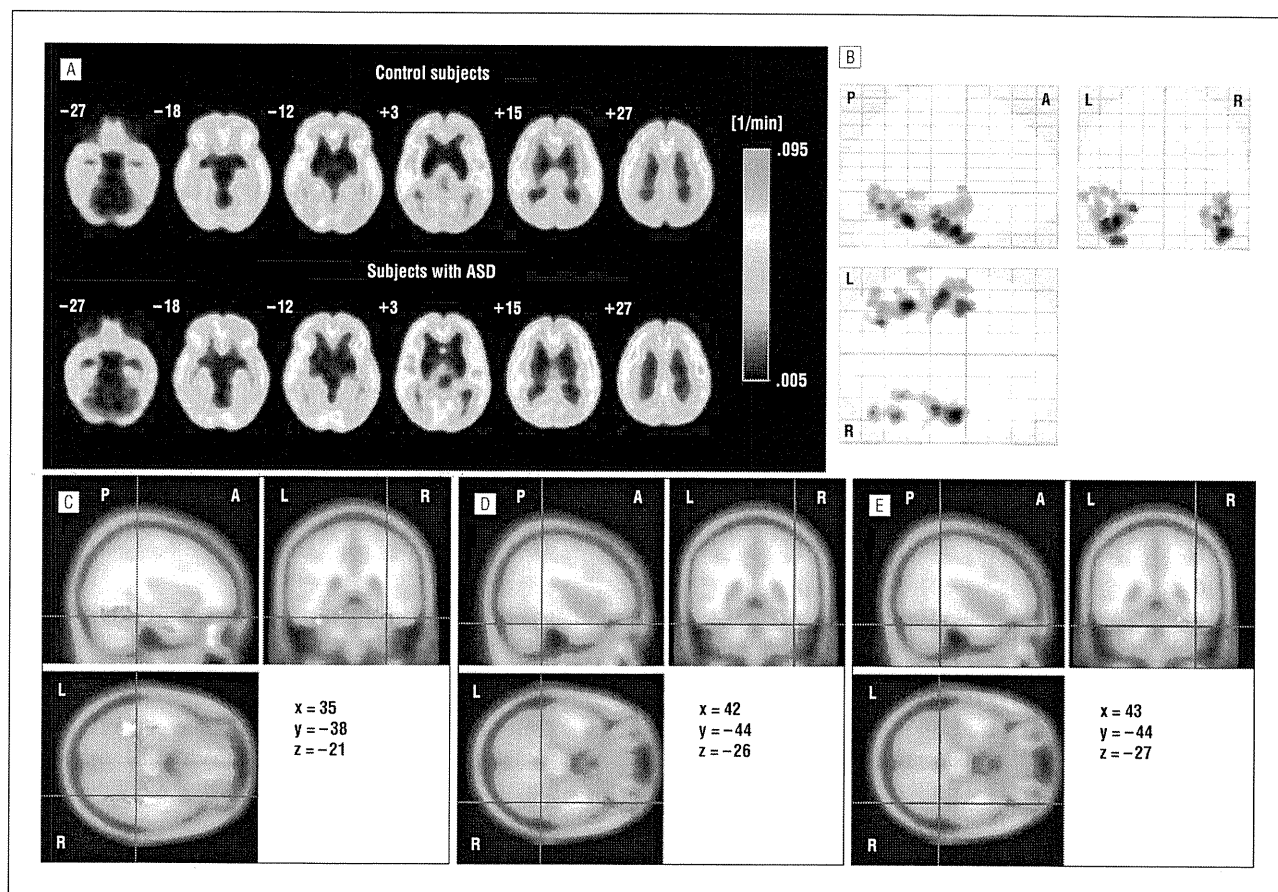


Figure 2. Results of the whole-brain voxel-based statistical parametric mapping analysis of the *N*-[¹¹C]methylpiperidin-4-yl acetate ([¹¹C]MP4A) k_3 value distribution maps. A, Normalized and averaged [¹¹C]MP4A k_3 parametric maps from control subjects and subjects with autism spectrum disorders (ASD) are shown. B, Areas with significantly reduced [¹¹C]MP4A k_3 values in subjects with ASD compared with those in controls ($P < .05$, corrected) are rendered on glass brains. C, Results from analyses of covariance are shown. Areas with significantly lower [¹¹C]MP4A k_3 values in the ASD group than in the control group ($P < .05$, corrected) are indicated. The location of a cluster with significant negative correlations between [¹¹C]MP4A k_3 values and Autism Diagnostic Observation Schedule social scores (D) or Autism Diagnostic Interview-Revised social scores (E) in subjects with ASD ($P < .05$, corrected) is shown. The locations are rendered on the standard-brain T1 template. A indicates anterior; P, posterior;

$r = -0.508$; $P = .02$) as well as ADI-R domain A scores ($r = -0.505$; $P = .02$) (Figure 2E).

COMMENTS

Adults with ASD had significantly and locally reduced [¹¹C]MP4A k_3 values, a representative measure of the hydrolytic activity of AChE in the bilateral fusiform gyri, with no significant change in [¹¹C]MP4A k_3 values in the other cortical areas. As mentioned previously, motion during PET and PVE are potential confounding factors that influence the results of PET analysis. In this study, however, we confirmed that all of the participants had remained immobilized during each PET scan by fixing the head of each participant. An additional volumetric brain morphometry study showed no significant difference in whole-brain or regional gray matter volumes between subjects with ASD and controls (eAppendix 2, eTable, eFigure 1 and eFigure 2). Therefore, the obtained PET data may correctly represent the condition in the brain. Acetylcholinesterase is most abundant along cholinergic pathways, where it terminates neurotransmission through the rapid hydrolysis of acetylcholine. Although AChE has a very good correspondence with choline acetyltransfer-

ase, the enzyme that synthesizes acetylcholine, several other cortical AChE-rich neurons have no choline acetyltransferase activity and are classified as noncholinergic but cholinceptive.^{38,39} However, the AChE-rich cortical axons in the adult brain are almost exclusively cholinergic, arise mostly from the basal forebrain, and contain AChE that is transported anterogradely from cholinergic perikarya in the basal forebrain.⁴⁰⁻⁴² Therefore, the present result of reduction in the [¹¹C]MP4A k_3 values localized in the bilateral fusiform gyri suggests that presynaptic cholinergic innervation of a specific cortical region is selectively impaired in adult individuals with ASD. Previously, Perry et al²⁸ measured cholinergic enzyme activity as well as the levels of muscarinic and nicotinic receptors in the frontal and parietal cortices in deceased adults with autism and found no change in the activities of AChE and choline acetyltransferase, although there were decreases in some types of muscarinic and nicotinic receptors. The results of Perry et al²⁸ may support our contention that the presynaptic cholinergic innervations of the cortex, other than the restricted region of the fusiform gyrus, are intact in ASD. Serotonergic and dopaminergic, as well as cholinergic, innervations may play important roles in the regulation

Table 2. Clusters Where [¹¹C]MP4A k_3 Values Significantly Correlated With Social Scores From ADOS and ADI-R in Subjects With ASD in the Fusiform Gyrus^a

Hemisphere	Cluster Size	F	x	y	z
Negatively Correlated With ADOS Social Scores					
R	58	29.92	42	-44	-26
L	16	24.92	-46	-52	-20
R	20	23.78	24	-60	-20
R	38	19.65	24	-46	-16
L	14	16.89	-28	-74	-16
Negatively Correlated With ADI-R A (Social) Scores					
R	267	32.78	38	-46	-24
L	36	28.70	-46	-52	-20
L	59	16.53	-28	-76	-16
R	39	15.55	24	-80	-16

Abbreviations: [¹¹C]MP4A, *N*-[¹¹C]methylpiperidin-4-yl acetate; ADI-R, Autism Diagnostic Interview-Revised; ADOS, Autism Diagnostic Observation Schedule; ASD, autism spectrum disorder; NA, not applicable.

^a*P* < .05, corrected; cluster extent threshold, 10 voxels.

of cortical activity in the visual area.¹⁹ However, our recent PET study in which brain serotonin and dopamine transporter bindings were evaluated in adults with high-functioning autism showed no changes in the serotonergic or dopaminergic terminals in the fusiform gyrus.³² Therefore, the deficit in the fusiform gyri of individuals with ASD may be relatively specific to the cholinergic neurotransmission, although more study of the influences of other neurotransmitters, such as noradrenaline, is necessary. In our ROI-based analysis, AChE activities tended to be lower in the ASD groups than in the controls across all of the ROIs tested, although it reached significance only in the bilateral fusiform gyri after correction for multiple comparisons. It may be possible that the cholinergic transmission is globally impaired in ASD. Further study is therefore required on the subject.

When the relationship between the [¹¹C]MP4A k_3 value and the diagnostic algorithm scores from the ADOS and ADI-R was examined in each side of the fusiform gyrus, lower levels of the k_3 value in both fusiform gyri were found to be associated with more severe social reciprocity, as evaluated by the ADOS and ADI-R. The ADOS social score reflects the current social function, while the ADI-R social (domain A) scoring is based on early social development. Therefore, a deficit in cholinergic innervation of the fusiform gyri, which can be observed in adults with ASD, may be related not only to the current but also the childhood impairment of social functioning. The participation of the fusiform gyrus in this regard may be more predominant in the right than the left hemisphere, since our laterality analysis showed that the individual laterality indices were negatively correlated with social scores from the ADOS and ADI-R. It is currently unknown whether children with ASD have abnormalities in cholinergic innervations of the fusiform gyri. However, a lack of interest in the human face is a major symptom of autism and is evident as early as the first year of life,⁴³ suggesting the emergence of a functional impairment of the face-processing system, including the FFA within the fusiform gyrus, in the early development of ASD. Although speculative, the association of the current deficit in cholinergic innervations of the fusiform gyri with

the present and early impairment of social functioning may reflect the existence of the cholinergic insult in the early development of ASD, persisting into adulthood. Recently, Nacewicz et al⁴⁴ demonstrated that a smaller amygdala exhibits more significant impairment in social reciprocity as determined by the ADI-R. When Kleinhans et al,⁴⁵ using the fMRI technique, investigated functional connectivity within the limbic system during face identification in high-functioning adults with ASD, abnormal functional connectivity between the right fusiform gyrus and the left amygdala was associated with ADI-R social scores in childhood. At this time, it is unclear whether cholinergic transmission impairment in the right-hemispheric fusiform gyrus is involved in the time-independent association described by Nacewicz et al⁴⁴ and Kleinhans et al.⁴⁵

A previous neuropathological study of autism described significant reductions in neuron density in layer III, total neuron numbers in layers III, V, and VI, and mean perikaryal volumes of neurons in layers V and VI in the fusiform gyrus.¹⁷ The neuropathological changes may be specific to the fusiform gyrus because none of these alterations were found in the primary visual cortex or in the whole cerebral cortex.¹⁷ The pyramidal cells in layers III and V have been suggested to be cholinceptive.^{40,46-51} Because acetylcholine is known to play an important role in the regulation of both structural and functional maturation of cortical circuits,^{18,52,53} and because the modulatory effect of acetylcholine seems to depend on the level of AChE activity,⁵⁴ we suppose that the reduced AChE activity in the fusiform gyrus observed here may partly contribute to the reduction in the number of cholinceptive neurons in layers III and V.

Our study has some limitations. The small sample size renders the data presented here preliminary, and a larger study with more ASD subjects will be necessary. However, recruitment for the current study was limited to a group of high-functioning subjects with ASD, none of whom were given psychotropic drugs, and all were able to complete PET examination without sedation. Therefore, our data are free from possible confounding factors and thus reflect a certain common pathology among

people with ASD. Another methodological issue is that the absence of PVE correction using a low-resolution PET camera would affect quantitative values such as k_3 .⁵⁵ One solution is the use of a higher-resolution PET camera. Compatible with the reported high-resolution human PET scanner,⁵⁵ our PET camera has an intrinsic 2.9-mm resolution, which previously allowed us to evaluate the change in tracer accumulation in a small region such as the mid-brain.⁵⁶ The fusiform is actually larger than the mid-brain, and it was reported that the fusiform cortex is thicker in ASD than in controls.⁵⁷ Thus, the use of a high-resolution brain-purpose PET camera and MRI-guided ROI determination on the thicker cortical region could minimize the PVE issue in the present study. It was reported that hypometabolism exceeded atrophy in most altered structures in Alzheimer disease.⁵⁸ Although the disease is different, that observation suggests that the present [¹¹C]MP4A k_3 reduction reflects the pathophysiology of ASD rather than the atrophy.

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Correction

Error in Figure Citations and Legend. In the Original Article "Reduced Acetylcholinesterase Activity in the Fusiform Gyrus in Adults With Autism Spectrum Disorders" by Suzuki et al, published in the March 2011 issue of the *Archives* (2011;68(3):306-313), some figure citations and some parts of the legend are incorrect. Though the first figure citations (those in boldface) are correct, all subsequent ones are incorrect. Thus, Figure 1 should be Figure 2 and Figure 2 should be Figure 1 in these citations. Also, in the legend of Figure 1, lines 11 and 12, (A) and (B) should be (B) and (C), respectively. The Suzuki et al article was corrected online.

日本における成人期 ADHD の疫学調査 — Adult ADHD self report scale-screener (ASRS-screener) 陽性群の特長について —

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Summary

Adult ADHD self report scale-screener (ASRS-screener) を用いて、静岡県浜松市の 18 歳から 49 歳の男女 10,000 人を対象として疫学調査を行った。その結果、3,910 名から調査協力が得られ、回収率は 39.1% であった。調査協力者のうち 196 名が screening において陽性となり、成人期 ADHD の疑いがある陽性群となった。この陽性群と陰性群について、さまざまな観点から比較を行ったところ、性別、年齢家族構成、結婚歴、職業、世帯の合計年収、現在の健康状態、通院の有無、過去 1 年での悩み事やストレスの有無において有意差がみとめられ、いずれの項目についても、陽性群の方が顕著に否定的な特徴がみられた。

キーワード：adult attention deficit/hyperactivity disorder, adult ADHD self report scale-screener (ASRS-screener), epidemiology, screening

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I. 背景

注意欠陥／多動性障害は、1960 年代に微細脳損傷症候群 (minimal brain damage syndrome : MBD) と呼ばれていた。これは脳損傷児の行動特徴として、情緒変動性、落ち着きのなさ、衝動性、注意転導性、しつこさなどを見出し脳の微細な損傷が中枢神経系に機能不全をもたらし、注意と知覚の特異的障害となって、読み、綴、計算を習得する学習能力を損なうと仮定した。1962 年には微細な脳損傷の存在を客観的に証明することが困難ということで、微細脳機能不全症候群と定義された。また同じ時期に、多動が目立つ子どもを hyperactive child syndrome と呼ぶようになった (中村ら, 2008)。臨床的観察から多動は児童期に限られており、青年期には常に軽快すると、1970 年代半ばまでは考えられていた。その頃 Wender は子どものころに多動性障害と診断された大人の cohorts 研究を行い始めた。1987 年 DSM-III-R (アメリカ医学会の診断基準) において多動性障害は注意欠陥／多動性障害 (attention-deficit / hyperactivity disorder : ADHD) と定義された。しかしながら DSM-III-R では成人期の注意欠陥／多動性障害は定義として含まれなかった (Adler, 2008)。次第に多動性障害の予後に対する研究が行われた。青年期までの予後研究は、精神病理が持続することを一様に示してい

る。予後の全体的なパターンは、児童期の症状、落ち着きのなさや集中力の障害が持続することと、約25%に反社会的行動が発生することである。多動児は成人しても、多動、集中力の症状が残存し、反社会的な人格障害、薬物依存をより多く有し続ける。学業成績に関しては、成人した元多動児は、友人たちよりも成績が不良で学校の不適応があり、学校を早くやめ、学力試験での成績が不良である (Klein & Mannuzza, 1991)。そして、学童期の ADHD は学校場面やそれに関する場面での問題が主であるが、成人期の ADHD は問題が多義に広がる傾向があることが特徴的である。例えば、働く場面においても困難さを示す。上司との人間関係の不適切さ、仕事の締め切りを守れないこと、長期欠勤などがさまざまな仕事の中で派生し、いくつもの仕事につくことになる。そしてますます仕事に関する困難さがまして経済的にも困ることになる。さらに成人期 ADHD は事故を起こしやすく、医療機関を頻回に受診し、健康上の問題を抱えることが多い (Stein, 2008)。

欧米での成人期 ADHD の有病率は4%程度とされており (Kessler ら, 2009)、成人期においても決して稀な障害ではない。このことから、近年では、ADHD は児童期のみの問題ではなく、生涯を通じた問題という認識が一般化しつつある。このように、欧米では児童期だけでなく、成人期の ADHD も注目され、有益な知見が蓄積されつつある。

しかしながら、わが国においては、成人期 ADHD に関していえば、欧米の知見が紹介されているにすぎない。そのため、成人期 ADHD がどのような特徴を示すかといったことは明確にはされておらず、臨床現場での経験に頼る部分が多い。

そこで、本研究では、欧米の研究と比較可能な規模での成人期 ADHD の疫学調査を実施した。ここでは、その調査の screening 検査の結果を分析し、screening において陽性となった調査協力者の特徴について明らかにする。

II. 方法

1. 調査協力者

静岡県浜松市を研究フィールドとした。浜松市は、人口約81万人の政令指定都市であり、主要産業都市は楽器、オートバイ、自動車部品、繊維などの製造を中心として、農業(茶、みかん、菊など)、漁業(ふぐ、うなぎなど)が盛んな都市である。本研究では、浜松市に在住する18歳から49歳までの男女の中から、無作為に10,000人を抽出し、調査対象者とした。その際、3歳刻みの8つの年齢帯および性別から16のグループを構成し、各グループの人数を住民基本台帳の人口按分をもとに算出した。

2. 調査内容

(1) デモグラフィックデータ

性別、年齢(18歳から49歳を3歳刻みで8区分にした)、居住地域(区)、家族構成、結婚歴、職業、世帯の合計年収(200万未満～1000万以上を5段階に区切ったものと「分からない」)の7項目である。

(2) adult ADHD self report scale-screener (ASRS-screener)

ASRS-screener は、Kessler ら (2005) によって、WHO の尺度として開発されたものであり、日本を含む多くの言語に翻訳されており、無償で使用することができる尺度である。DSM-IV の診断基準 A に準拠した内容の6項目から構成される。対象者が自身の過去6ヵ月を振り返り、どの程度の頻度でそれぞれの項目に記述された症状を経験しているかを5段階(0～4点)で評定する形式である。

screener は、項目ごとに基準となる頻度が設定されており、基準を超えている項目数を加算して screening 得点を算出する。screening 得点は0～6点の間をとる。それがカットオフ値である4点以上であれば、成人期 ADHD の可能性があり、さらに詳細な検討を行う必要があることを示唆する。具体的には、項目1～3までは、それぞれ、時々、頻繁、非常に頻繁という回答である場合にその数をカウントし、項目4～6の場合は、頻繁、非常に頻繁とい

う回答である場合にその数をカウントすることになる。例えば、項目1に「時々」、項目2に「頻繁」、項目3に「時々」、項目4に「めったにない」、項目5に「全くない」、項目6に「頻繁」となる場合は、4つが該当することになり、screenerに陽性(positive)と判断されることになる。

(3) 健康についての質問項目

現在の健康状態(4段階)、現在の通院の有無、通院している病気の種類(複数回答)、飲酒と喫煙の状況、過去1年間での悩み事やストレス(4段階評価)、悩みやストレスの内容の6項目を尋ねた。

3. 手続と実施時期

以上の調査内容を記載した調査用紙を作成し、調査対象者の自宅に郵送した。回収は、浜松医科大学が行った。調査は、2010年1月から3月の期間に行った。

4. 倫理面への配慮

調査用紙に調査の趣旨や内容について十分に説明した文面を記載し、インフォームドコンセントに配慮した。また、本調査は浜松市と共催で実施し、得られた回答は調査の目的以外では使用せず、市の成人期 ADHD 対策の推進に活用される事も記載した。さらに、調査協力者に結果を還元するために、希望者に結果の報告と無料相談を実施することも記載した。なお、本研究におけるデータ解析、公表については浜松医科大学倫理委員会の承認を得て行われた。

Ⅲ. 結果

1. 調査協力者の人数

10,000人を受作為抽出して選んだ調査対象者のうち、協力を得られたのは3,910名であった。したがって、回収率は39.1%である。

2. 標本の代表性の確認

標本の代表性を確認するため、調査対象者の母集団である浜松市における性別の割合と標本における

表1 性別ごとの調査母集団と標本の内訳と比較

	母集団	標本	$\chi^2(df)$	ϕ
男	166940 (51.9)	1655 (42.4)	138.2*** (1)	.02
女	154651 (48.1)	2244 (57.6)		
合計	321591 (100)	3899 (100)		

上段：度数(人)，下段：(%)

*** $p < .001$

性別の割合の比較を行った(表1)。なお、年齢情報に欠損のみられた者が11名いたため、その11名は分析から除外した。その結果、母集団では男性の方が女性よりも割合が若干多いのに対して、標本ではその割合が逆転し、女性の方が男性よりも有意に多かった($\chi^2(1) = 138.2 (p < .001)$)。このことから、本研究で得られたデータは、母集団の人口割合と比べて女性の割合が若干多いデータであるといえる。

次に、年齢帯および居住区について、母集団における割合と標本における割合の比較を、性別ごとに行った(表2)。その結果、年齢帯については、男女ともに χ^2 値が有意となり、母集団と標本では年齢帯の割合に差があった。どの年齢帯において期待度数からの差が大きいかを検討するために残差分析を行ったところ、男性では22～25歳と26～29歳において標本の割合が小さく、46～49歳において標本の割合が大きかった。女性では、18～21歳と22～25歳において標本の割合が小さく、38～41歳と46～49歳において標本の割合が大きいという結果であった。ただし、 χ^2 値はデータ数が多いことによって些細な割合の偏りでも有意となる傾向があるため、年齢帯における母集団と標本のずれはそれほど極端なものではない。実際に、男女とも各年齢帯の割合は極端に偏っているわけではなく、連関係数 ϕ の値も極めて小さいものであった($\phi = .02$)。

同様に居住区についても男女ごとに分析を行ったところ、男性では χ^2 値が有意とならず、居住区の割合において母集団と標本には差がなかった。女性

表2 性別・年齢帯ごとおよび性別・居住区ごとの調査母集団と標本の内訳と性別ごとの比較

		男			女			合計	
		母集団	標本	残差分析	母集団	標本	残差分析	母集団	標本
年齢帯	18-21 歳	16698 (10.0)	155 (9.4)	<i>n.s.</i>	15804 (10.2)	180 (8.0)	↓↓	32502 (10.1)	335 (8.6)
	22-25 歳	18317 (11.0)	135 (8.2)	↓↓	17024 (11.0)	194 (8.7)	↓↓	35341 (11.0)	329 (8.5)
	26-29 歳	20186 (12.1)	159 (9.6)	↓↓	18262 (11.8)	256 (11.4)	<i>n.s.</i>	38448 (12.0)	415 (10.7)
	30-33 歳	23569 (14.1)	224 (13.6)	<i>n.s.</i>	21814 (14.1)	302 (13.5)	<i>n.s.</i>	45383 (14.1)	526 (13.5)
	34-37 歳	24366 (14.6)	251 (15.2)	<i>n.s.</i>	22611 (14.6)	356 (15.9)	<i>n.s.</i>	46977 (14.6)	607 (15.6)
	38-41 歳	22938 (13.7)	243 (14.7)	<i>n.s.</i>	21120 (13.7)	342 (15.3)	↑↑	44058 (13.7)	585 (15.0)
	42-45 歳	20920 (12.5)	225 (13.6)	<i>n.s.</i>	19221 (12.4)	294 (13.1)	<i>n.s.</i>	40141 (12.5)	519 (13.3)
	46-49 歳	19946 (11.9)	260 (15.7)	↑↑	18795 (12.2)	315 (14.1)	↑↑	38741 (12.0)	575 (14.8)
	合計	166940 (100)	1652 (100)		154651 (100)	2239 (100)		321591 (100)	3891 (100)
$\chi^2(df)$		43.6(7)***			36.4(7)***				
ϕ		.02			.02				
居住区	中区	122757 (30.7)	485 (29.3)	<i>n.s.</i>	122196 (30.2)	703 (31.4)	<i>n.s.</i>	244953 (30.5)	1188 (30.5)
	東区	62910 (15.7)	264 (16.0)	<i>n.s.</i>	62833 (15.5)	360 (16.1)	<i>n.s.</i>	125743 (15.6)	624 (16.0)
	南区	51734 (12.9)	216 (13.1)	<i>n.s.</i>	51508 (12.7)	266 (11.9)	<i>n.s.</i>	103242 (12.8)	482 (12.4)
	西区	54303 (13.6)	250 (15.1)	<i>n.s.</i>	55603 (13.8)	329 (14.7)	<i>n.s.</i>	109906 (13.7)	579 (14.9)
	北区	46984 (11.8)	189 (11.4)	<i>n.s.</i>	48846 (12.1)	274 (12.2)	<i>n.s.</i>	95830 (11.9)	463 (11.9)
	浜北区	42996 (10.8)	178 (10.8)	<i>n.s.</i>	43842 (10.8)	248 (11.1)	<i>n.s.</i>	86838 (10.8)	426 (10.9)
	天竜区	18020 (4.5)	73 (4.4)	<i>n.s.</i>	19500 (4.8)	62 (2.8)	↓↓	37520 (4.7)	135 (3.5)
	合計	399704 (100)	1655 (100)		404328 (100)	2242 (100)		804032 (100)	3897 (100)
	$\chi^2(df)$		4.1(6)			23.8(6)**			
ϕ		.00			.01				

上段：度数(人)，下段：(%)

*** $p < .001$, ** $p < .01$

↑ 標本の度数が母集団の人口按分にもとづく期待度数よりも大きいことを意味する。

↓ 標本の度数が母集団の人口按分にもとづく期待度数よりも小さいことを意味する。

では、 χ^2 値が有意となり、母集団と標本に差がみられた。残差分析の結果、天竜区のみにおいて標本の度数が母集団の割合の期待度数よりも有意に低かった。ただし、年齢帯の場合と同様に、居住区に

においても母集団からの極端な偏りはみられず、連関係数 ϕ の値も極めて小さいものであった ($\phi = .00$)。

この結果から、本研究で分析対象とするデータは、性別においては母集団と比較して女性の割合が若干

表3 調査協力者のASRS-screener への回答と各項目のscreening 基準該当者の人数

	選択肢への回答 ^{1,2}					全体	各項目の screening 基準該当者
	全くない	めったに ない	時々	ひんぱん ひんぱん	非常に ひんぱん		
(1) 物事を行うにあたって、 難関は乗り越えたのに、最後の詳細をまとめて 仕上げるのが困難だったことが、どのくらいの頻度でありましたか。	941 (24.3)	1907 (49.2)	872 (22.5)	127 (3.3)	30 (0.8)	3,877 (100)	1029 (26.5)
(2) 計画性を要する仕事を行う際に、 作業を順序立てるのが困難だったこと が、どのくらいの頻度でありましたか。	1016 (26.1)	1802 (46.4)	861 (22.2)	166 (4.3)	41 (1.1)	3,886 (100)	1068 (27.5)
(3) 約束や用事を忘れたことが、どのくらいの頻度でありましたか。	914 (23.5)	1960 (50.4)	889 (22.8)	100 (2.6)	29 (0.7)	3,892 (100)	1018 (26.2)
(4) じっくり考えなければならない作業がある際に、 その作業に取りかかるのを 避けたり遅らせようとしたりしたことが、どのくらいの頻度でありましたか。	690 (17.8)	1544 (39.7)	1321 (34.0)	266 (6.8)	66 (1.7)	3,887 (100)	332 (8.5)
(5) 長時間座っていなければならない時に、 手足を揺すったり身もだえした りしたことが、どのくらいの頻度でありましたか。	1641 (42.2)	1423 (36.6)	616 (15.8)	163 (4.2)	47 (1.2)	3,890 (100)	210 (5.4)
(6) まるでモーターに動かされているように、 異常に活動的だったり、何かしな ければという衝動に駆られたりしたことが、どのくらいの頻度でありましたか。	1855 (47.7)	1309 (33.7)	550 (14.1)	135 (3.5)	41 (1.1)	3,890 (100)	176 (4.5)

¹ 上段：度数／下段：(%)

² ボールドは、screening の際に回答者のチェックをカウントする箇所

多いものの、年齢帯および居住区においては、母集団をほぼ代表するデータとして扱うことができる。

3. ASRS-screener の結果

まず、ASRS-screener が尺度としての信頼性を有しているかを検討するために、各項目の粗点からCronbachの α 係数を算出した。その結果、 $\alpha = .77$ であり、Kesslerら(2005)と同様に、6項目という比較的少ない項目数ながら満足しうる値が得られた。よって、本研究においても、ASRS-screenerは内的整合性という面での信頼性を備えていることが明らかになった。そこで、ASRS-screenerの粗点を合計したASRS-screener尺度得点とその平均値を算出したところ、平均値 = 6.18点 (SD = 3.56)であった。

次に、ASRS-screenerへの回答と、各項目のscreening基準を満たした者の度数を表3に示した。前述したように、ASRS-screenerは、項目によって異なるscreening基準を設定している。

各項目の基準を満たした者の人数に着目すると、本研究では、項目(1)~(3)においては、いずれも1000人以上(26.2%~27.5%)であった。一方、項目(4)~(6)の基準を満たした者はそれぞれ、332名(8.5%)、210名(5.4%)、176名(4.5%)であっ

表4 調査協力者のscreening得点と基準を満たした者の度数(%)

ASRSのscreening得点(点)	度数(人)	(%)
0	1932	(49.4)
1	903	(23.1)
2	573	(14.7)
3	306	(7.8)
4	132	(3.4)
5	51	(1.3)
6	13	(0.3)
合計	3910	(100)
screening基準を満たす者	196	(5.0)

た。

各調査協力者について、ASRS-screenerの各項目に設定された基準を満たした数を合計し、screening得点を算出した(表4)。screeningのカットオフ値となる4点では132名(3.4%)、5点では51名(1.3%)、6点では13名(0.3%)が該当していた。よって、カットオフ値4点以上でありscreening陽性となった者は196名(5.0%)であった。

4. screening陽性者の特徴

screeningにおいて陽性になった者の特徴を明ら

かにするため、デモグラフィックデータや健康調査項目について、陽性群と陰性群の人数比の比較を行った。

(1) 性別、年齢帯、居住地域

性別、年齢帯および居住地域と screening 結果（陽性／陰性）との関連を検討した結果を表5に示した。 χ^2 検定の結果、性別において0.1%水準で有意、年齢帯においては1%水準で有意となり、性別と年齢帯が screening における陽性／陰性と関連があることが示唆された。性別については、男性に多かった。年齢帯については、どの年齢帯において人数比に差がみられるかを検討するために残差分析を行ったところ、「22～25歳」と、「26～29歳」において陽性群の度数が有意に期待度数よりも大きく、「46～49歳」においては、有意に小さいことが明らかになった。すなわち、20歳代の比較的若い層においては陽性群が多く、40歳代の比較的高年齢層においては少ないことを示唆している。居住地域については、 χ^2 値は有意とならず、関連がないことが示唆された。

(2) 結婚歴、家族構成、職業、世帯の合計収入

結婚歴、家族構成、職業および世帯の合計収入についても同様に検討した結果を表6に示した。いずれにおいても、 χ^2 値は有意となり、結婚歴、家族構成および世帯の合計収入においては0.1%水準で有意、職業においては1%水準で有意となり、関連があることが示唆された。

残差分析の結果、家族構成においては「ひとり暮らし」と「あなた（あなた夫婦）と親」においては、陽性群の度数が期待度数よりも多く、「あなた（あなた夫婦）と子」においては小さいことが明らかになった。このことから、陽性群ほどひとり暮らしや調査協力者（調査協力者夫婦）と親の家族形態である率が高く、子ども（と夫婦）と暮らしている家族形態である率が低いことが示唆された。結婚歴においては、「未婚」において陽性群の度数が有意に期待度数よりも大きく、逆に「既婚」において小さかった。このことから、陽性群ほど未婚者である率が高く、既婚者である率が低いことが示唆された。

職業については、「勤めている」と「無職」において陽性群の度数が期待度数よりも有意に大きく、「パート・アルバイト」と「専業主婦・主夫」においては小さいことが明らかになった。このことは、陽性群であるほど勤めているか無職である率が高く、パート・アルバイトとして働いていたり、あるいは結婚して主婦や主夫として家庭に入っていたりする率が低いことを示唆している。世帯の合計収入については、「200万円未満」において陽性群の度数が有意に期待度数よりも大きく、「700～1000万円未満」において小さいことが明らかになった。このことは、陽性群に低所得者層が多く、比較的高い所得の層には少ないことを示唆している。

(3) 飲酒・喫煙習慣、現在の健康状態、過去一年間での悩み事やストレス、通院状況

飲酒・喫煙習慣、現在の健康状態、過去一年間での悩み事やストレスおよび通院状況についても同様に検討した結果を表7に示した。現在の健康状態と過去一年間での悩み事やストレスにおいて χ^2 値が0.1%水準で有意となり、通院状況においては5%水準で有意となったことから、これらの変数と screening 結果との間に関連が示唆された。飲酒・喫煙状況においては χ^2 値は有意とならず、関連はみられなかった。通院状況については、陽性群に通院している人が多いことが示唆された。現在の健康状態と過去一年間での悩み事やストレスについては残差分析の結果、「あまり健康ではない」と「健康ではない」では陽性群の度数が有意に期待度数よりも大きく、「健康である」では小さかった。このことから、陽性群ほどより不健康な状態にあると感じていることが示唆された。「よくあった」において通過群の度数が有意に期待度数よりも大きかった。また、過去一年間での悩み事やストレスでは、「よくあった」において陽性群の度数が有意に期待度数よりも大きく、「あまりなかった」と「たまにあった」において小さかった。このことから、陽性群ほど悩み事やストレスを多く抱えている傾向があることが示唆された。

表5 性別, 年齢帯, 居住区における screening 陽性群と陰性群の比較

		陰性	陽性	合計	χ^2 (df)	残差分析
性別	男性	1540 (41.6)	115 (58.7)	1655 (42)	22.24 *** (1)	—
	女性	2163 (58.4)	81 (41.3)	2244 (58)		
	合計	3703 (100)	196 (100)	3899 (100)		
年齢帯	18-21 歳	312 (8.4)	23 (11.7)	335 (9)	22.09 ** (7)	<i>n.s.</i>
	22-25 歳	305 (8.2)	25 (12.8)	330 (8)		2.21 ↑
	26-29 歳	384 (10.4)	33 (16.8)	417 (11)		2.85 ↑
	30-33 歳	502 (13.6)	24 (12.2)	526 (13)		<i>n.s.</i>
	34-37 歳	578 (15.6)	30 (15.3)	608 (16)		<i>n.s.</i>
	38-41 歳	561 (15.2)	25 (12.8)	586 (15)		<i>n.s.</i>
	42-45 歳	501 (13.5)	18 (9.2)	519 (13)		<i>n.s.</i>
	46-49 歳	558 (15.1)	18 (9.2)	576 (15)		-2.27 ↓
	合計	3701 (100)	196 (100)	3897 (100)		
居住区	中区	1128 (30.4)	60 (30.6)	1188 (30)	3.38 <i>n.s.</i> (6)	<i>n.s.</i>
	東区	593 (16.0)	32 (16.3)	625 (16)		<i>n.s.</i>
	南区	462 (12.5)	23 (11.7)	485 (12)		<i>n.s.</i>
	西区	551 (14.9)	30 (15.3)	581 (15)		<i>n.s.</i>
	北区	435 (11.7)	28 (14.3)	463 (12)		<i>n.s.</i>
	浜北区	411 (11.1)	15 (7.7)	426 (11)		<i>n.s.</i>
	天竜区	127 (3.4)	8 (4.1)	135 (3)		<i>n.s.</i>
	合計	3707 (100)	196 (100)	3903 (100)		

上段：度数(人), 下段：(%)

*** $p < .001$, ** $p < .01$

↑陽性者の度数が期待度数よりも大きいことを意味する。

↓陽性者の度数が期待度数よりも小さいことを意味する。

表6 結婚歴、家族構成、職業、収入におけるscreening 陽性群と陰性群の比較

		陰性	陽性	合計	$\chi^2(df)$	残差分析	
結婚歴	既婚(同居)	2172 (58.7)	83 (42.6)	2255 (58)	24.18 *** (5)	-4.44 ↓	
	既婚(別居)	112 (3.0)	6 (3.1)	118 (3)		n.s.	
	未婚	1259 (34.0)	99 (50.8)	1358 (35)		4.78 ↑	
	死別	11 (0.3)	0 (0)	11		n.s.	
	離別	135 (3.6)	6 (3.1)	141 (4)		n.s.	
	同棲	12 (0.3)	1 (0.5)	13 (0)		n.s.	
	合計	3701 (100)	195 (100)	3896 (100)			
家族構成	ひとり暮らし	289 (7.8)	27 (13.8)	316 (8)	26.38 *** (5)	2.99 ↑	
	夫婦のみ	314 (8.5)	16 (8.2)	330 (8)		n.s.	
	あなた(あなた夫婦)と親	700 (18.9)	57 (29.2)	757 (19)		3.51 ↑	
	あなた(あなた夫婦)と子	1355 (36.6)	49 (25.1)	1404 (36)		-3.29 ↓	
	あなたを含めて三世代	798 (21.5)	35 (17.9)	833 (21)		n.s.	
	その他	248 (6.7)	11 (5.6)	259 (7)		n.s.	
	合計	3704 (100)	195 (100)	3899 (100)			
職業	勤めている(常勤)	1934 (52.3)	117 (59.7)	2051 (53)	24.74 ** (6)	2.03 ↑	
	パート・アルバイト	621 (16.8)	18 (9.2)	639 (16)		-2.80 ↓	
	自営業	180 (4.9)	9 (4.6)	189 (5)		n.s.	
	自由業	16 (0.4)	2 (1.0)	18 (0)		n.s.	
	専業主婦・主夫	522 (14.1)	14 (7.1)	536 (14)		-2.76 ↓	
	無職	149 (4.0)	15 (7.7)	164 (4)		2.46 ↑	
	学生	279 (7.5)	21 (10.7)	300 (8)		n.s.	
	合計	3701 (100.0)	196 (100.0)	3897 (100)			
収入(世帯合計)	200万円未満	215 (5.8)	24 (12.4)	239 (6)	23.58 *** (5)	3.69 ↑	
	200～400万円未満	839 (22.8)	43 (22.3)	882 (23)		n.s.	
	400～700万円未満	1341 (36.4)	64 (33.2)	1405 (36)		n.s.	
	700～1000万円未満	637 (17.3)	18 (9.3)	655 (17)		-2.90 ↓	
	1000万円以上	295 (80)	19 (98)	314 (8)		n.s.	
	わからない	360 (9.8)	25 (13.0)	385 (10)			
	合計	3687 (100)	193 (100)	3880 (100)			

上段：度数(人)，下段(%)

*** $p < .001$, ** $p < .01$

↑陽性者の度数が期待度数よりも大きいことを意味する。

↓陽性者の度数が期待度数よりも小さいことを意味する。

表7 飲酒・喫煙習慣, 1年間での悩み事やストレス, 健康状態, 通院状況におけるscreening 陽性群と陰性群の比較

		陰性	陽性	合計	$\chi^2(df)$	残差分析
飲酒, 喫煙習慣	飲酒のみ	1344 (36.4)	59 (30.3)	1403 (36)	6.16 <i>n.s.</i> (3)	
	喫煙のみ	291 (7.9)	19 (9.7)	310 (8)		
	飲酒と喫煙両方	529 (14.3)	38 (19.5)	567 (15)		
	飲酒・喫煙はしない	1528 (41.4)	79 (40.5)	1607 (41)		
	合計	3692 (100)	195 (100)	3887 (100)		
1年間での 悩み事やストレス	まったくなかった	58 (1.6)	1 (0.5)	59 (2)	85.12 *** (3)	<i>n.s.</i>
	あまりなかった	599 (16.2)	15 (7.7)	614 (16)		-3.18 ↓
	たまにあった	1648 (44.6)	41 (21.0)	1689 (43)		-6.46 ↓
	よくあった	1393 (37.7)	138 (70.8)	1531 (39)		9.22 ↑
	合計	3698 (100)	195 (100)	3893 (100)		
健康状態	健康である	2070 (55.8)	70 (35.7)	2140 (55)	81.66 *** (3)	-5.52 ↓
	まあまあ健康である	1427 (38.5)	89 (45.4)	1516 (39)		<i>n.s.</i>
	あまり健康でない	167 (4.5)	23 (11.7)	190 (5)		4.58 ↑
	健康ではない	43 (1.2)	14 (7.1)	57 (1)		6.80 ↑
	合計	3707 (100)	196 (100)	3903 (100)		
通院状況	通院している	852 (23.0)	58 (29.7)	910 (23)	4.71 * (1)	—
	通院していない	2853 (77.0)	137 (70.3)	2990 (77)		
	合計	3705 (100)	195 (100)	3900 (100)		

上段：度数(人), 下段：(%)

*** $p < .001$, * $p < .05$

↑陽性者の度数が期待度数よりも大きいことを意味する。

↓陽性者の度数が期待度数よりも小さいことを意味する。