Table 2. Results of the Whole-Brain Voxel-Based Statistical Parametric Mapping Analyses of [^{11}C](+)McN-5652 and [^{11}C]WIN-35,428 Binding Parameters[a]

Brain Area	Coordinates			Voxel Level	
	x	y	z	Corrected *P* Value	*z* Score
	[^{11}C](+)McN-5652 Binding				
Decrease in binding in the autistic vs control groups					
Frontal region					
Left middle frontal cortex, BA 6	−52	10	48	<.001	6.86
Left superior frontal cortex, BA 10	−16	54	−4	<.001	5.93
Left medial frontal cortex, BA 10	−12	46	10	<.001	5.82
Left middle frontal cortex, BA 11	−30	38	−18	<.001	5.63
Right superior frontal cortex, BA 10	18	70	−2	.001	5.40
Right medial frontal cortex, BA 25	6	26	−18	.002	5.23
Left inferior frontal cortex, BA 47	−34	32	−6	.002	5.19
Right superior frontal cortex, BA 11	20	52	−14	.004	5.11
Left subcallosal cortex, BA 25	−4	8	−12	.005	5.05
Temporal region					
Left superior temporal cortex, BA 22	−68	−6	6	<.001	6.54
Right inferior temporal cortex, BA 20	38	−8	−44	<.001	6.53
Left middle temporal cortices, BA 21	−70	−12	−8	<.001	6.20
Right inferior temporal cortex, BA 20	48	−22	−32	<.001	6.01
Left inferior temporal cortex, BA 37	−58	−56	−8	.001	5.48
Left fusiform cortex, BA 37	−34	−54	−12	.001	5.39
Right superior temporal cortex, BA 38	42	18	−20	.001	5.34
Left orbitofrontal cortex, BA 11	−6	40	−22	.002	5.21
Right orbitofrontal cortex, BA 11	8	44	−20	.003	5.19
Right superior temporal cortex, BA 22	50	4	2	.004	5.11
Right middle temporal cortex, BA 21	56	0	−12	.006	5.01
Right postcentral cortex, BA 5	44	−56	64	.006	5.00
Limbic region					
Left hippocampus	−28	−36	−6	<.001	6.02
Left parahippocampal cortex, BA 19	−40	−48	−4	<.001	5.70
Right anterior cingulate cortex, BA 24	2	26	8	.001	5.34
Right cingulate cortex, BA 23	6	−20	24	.004	5.11
Parietal region					
Left inferior parietal cortex, BA 40	−62	−46	−52	<.001	6.82
Right inferior parietal cortex, BA 39	46	−66	42	<.001	6.18
Right precuneus cortex, BA 19	10	−88	44	<.001	5.72
Left superior parietal cortex, BA 7	−30	−56	46	.002	5.22

(continued)

wise between-group comparisons were performed to investigate regional differences in the binding levels of [^{11}C](+)McN-5652 and [^{11}C]WIN-35,428. Correlation analyses were conducted between the 5 clinical behavior scores (Faux Pas Test, Y-BOCS, HAM-A, HAM-D, and AQ) and the total voxel analysis of the whole brain by using SPM analysis within the autistic group. To avert the risk of a type I error, the levels of statistical significance for the voxel and cluster analyses were set at $P<.05$ after allowing for multiple comparisons. In addition, we performed ROI analysis to examine whether regional serotonin and dopamine binding covaried in autistic individuals. Based on the results of the SPM analysis, we restricted the ROI analysis to the orbitofrontal area, where pronounced disturbances were present in the binding of serotonin and dopamine transporters (**Table 2**). In this analysis, the Pearson product moment correlation coefficient was computed. $P<.05$ was considered statistically significant.

RESULTS

The demographic and clinical variables of the participants are shown in Table 1. The mean Faux Pas Test score was significantly lower in the autistic participants than in the controls ($P<.001$).

COMPARISON OF SEROTONIN TRANSPORTER BINDING BETWEEN GROUPS

The SPM results showed significant reductions in the [^{11}C](+)McN-5652 distribution volume throughout the global brain in the autistic group compared with the control group ($P<.05$, corrected), with the reductions being most pronounced in the frontal, temporal, parietal, and occipital lobes; in the limbic and subcortical regions; and in the cerebellum (Table 2 and **Figure 2**A).

CORRELATES OF SEROTONIN TRANSPORTER WITH CLINICAL CHARACTERISTICS IN AUTISTIC PARTICIPANTS

The [^{11}C](+)McN-5652 distribution volume in the anterior cingulate cortex, the cingulate cortex, and the posterior cingulate cortex extending to the precuneus had a significantly positive correlation with the scores of the Faux Pas Test ($P<.05$, corrected) (Table 2 and Figure 2B).

Table 2. Results of the Whole-Brain Voxel-Based Statistical Parametric Mapping Analyses of [^{11}C](+)McN-5652 and [^{11}C]WIN-35,428 Binding Parameters[a] (continued)

Brain Area	Coordinates			Voxel Level	
	x	y	z	Corrected *P* Value	*z* Score
	[^{11}C](+)McN-5652 Binding				
Decrease in binding in the autistic vs control groups					
Occipital region					
Right lingual cortex, BA 18	30	−74	−6	<.001	6.02
Left inferior occipital cortex, BA 19	−32	−76	0	<.001	5.64
Left lingual cortex, BA 18	0	−74	−4	.001	5.50
Right occipital cortex, BA 19	50	−82	10	.006	4.98
Subcortical region					
Left claustrum	−28	10	−4	<.001	5.79
Right lentiform nucleus/putamen	23	3	7	<.001	5.59
Left midbrain	−2	−20	−8	<.001	5.52
Right thalamus	6	−18	0	<.001	5.46
Right midbrain	6	−18	−9	.001	5.44
Right caudate	16	−2	18	.001	5.43
Left lentiform nucleus/putamen	−26	−24	−2	.001	5.42
Left thalamus	−12	−16	2	.002	5.20
Left pons	−4	−12	−26	.002	5.18
Left midbrain	−12	−18	−12	.003	5.14
Left insula, BA 13	−30	20	4	.006	5.00
Cerebellum					
Left dentate nucleus	−20	−50	−34	<.001	5.81
Left lobule VIII	−24	−56	−42	<.001	5.62
Right lobule VIII	10	−68	−34	.001	5.51
Right lobule VI	18	−56	−30	.001	5.45
Right lobule VI	28	−52	−36	.003	5.18
Brain regions correlated with reduction in the Faux Pas Test score in autistic participants					
Right posterior cingulate cortex, BA 30	18	−50	16	<.001	7.61
Left posterior cingulate cortex, BA 30	−16	−54	12	<.001	6.91
Anterior cingulate cortex, BA 32	−8	40	16	<.001	6.61
Cingulate cortex, BA 24	−4	−19	40	<.001	6.44
Brain region correlated with an increase in the Y-BOCS score in autistic participants					
Thalamus	4	−25	3	<.001	6.96
	[^{11}C]WIN-35,428 Binding				
Increase in binding in the autistic vs control groups					
Orbitofrontal cortex, BA 11	−2	30	−10	.02	4.28

Abbreviations: BA, Brodmann area; [^{11}C](+)McN-5652, radioactive carbon (^{11}C)–labeled *trans*-1,2,3,5,6,10-β-hexahydro-6-[4-(methylthio)phenyl[pyrrolo-[2,1-a]isoquinoline; [^{11}C]WIN-35,428, ^{11}C-labeled 2β-carbomethoxy-3-β-(4-fluorophenyl)tropane; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

[a]The significance thresholds at the voxel cluster levels were $P < .05$ after correction for multiple comparisons. Coordinates are given in millimeters based on the Talairach stereotaxic brain atlas. Each location is a peak within a cluster (defined as the voxel with the highest *z* score).

We also evaluated the degree of repetitive and/or obsessive behavior and interests, which are additional clinical features of autism, using the Y-BOCS. A higher Y-BOCS score signifies more severe symptoms. There was a significant negative correlation between the Y-BOCS scores and the distribution volume of [^{11}C] (+)McN-5652 in the thalamus extending to the parahippocampal region ($P < .05$, corrected) (Table 2 and Figure 2C).

No significant correlation was found between the [^{11}C] (+)McN-5652 distribution volume and the symptom profiles of the HAM-A, HAM-D, or AQ.

COMPARISON OF DOPAMINE TRANSPORTER DISTRIBUTION BETWEEN GROUPS

The SPM analysis revealed a significant increase in [^{11}C]-WIN-35,428 binding in the medial frontal region covering the orbitofrontal cortex in the autistic group compared with the control group ($P < .05$, corrected in voxel-level analysis) (Table 2 and Figure 2D).

No significant correlation was found between [^{11}C]-WIN-35,428 binding and the symptom profiles of the Faux Pas Test, Y-BOCS, HAM-A, HAM-D, or AQ.

CORRELATION BETWEEN SEROTONIN AND DOPAMINE TRANSPORTER BINDINGS

In the ROI analysis of the orbitofrontal cortex, which showed disturbances in [^{11}C](+)McN-5652 and [^{11}C]WIN-35,428 binding in the autistic group (Figure 1C, D, G, and H), the [^{11}C](+)McN-5652 distribution volumes were significantly negatively correlated with the [^{11}C]WIN-35,428 binding potentials of the autistic group (**Figure 3**) ($r = -0.61$; $P = .004$, according to Pearson product moment correlation coefficient).

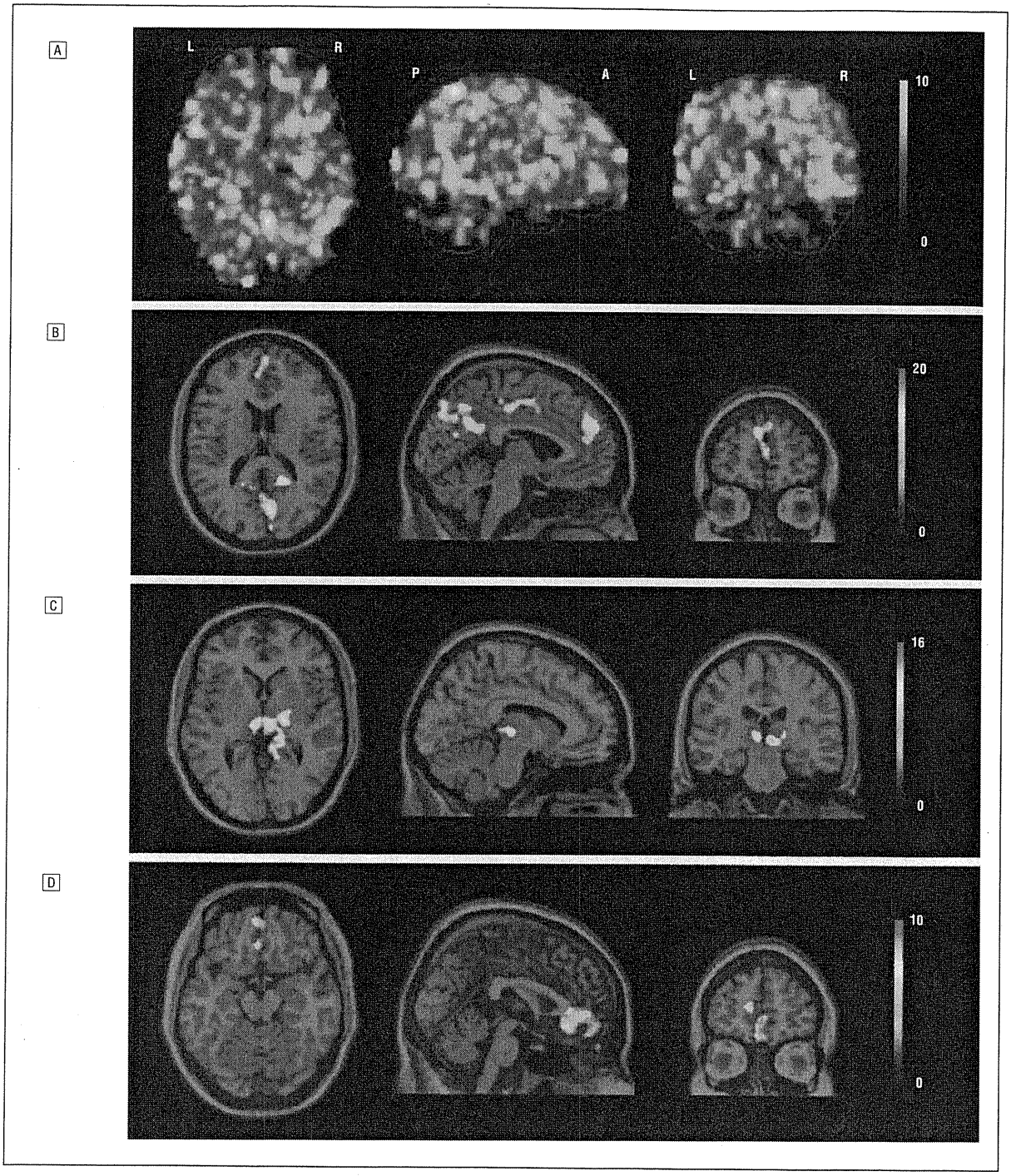

Figure 2. Statistical parametric mapping results for [^{11}C](+)McN-5652 and [^{11}C]WIN-35,428 binding. A, Glass brain images indicate extensive reduction in the [^{11}C](+)McN-5652 distribution volume in the autistic group ($P<.05$, corrected). B and C, Statistical parametric maps show brain regions in which the [^{11}C](+)McN-5652 distribution volume correlates positively with the Faux Pas Test score and negatively with the Yale-Brown Obsessive Compulsive Scale score, respectively, in autism ($P<.05$, corrected). D, A statistical parametric map showing a brain region in which the [^{11}C]WIN-35,428 ratio index is significantly higher in the autistic group than in the control group ($P<.05$, corrected). Color bars indicate T values. A indicates anterior; L, left; P, posterior; and R, right. See the legend to Figure 1 for expansion of other abbreviations.

COMMENT

The autistic participants had a significantly decreased [^{11}C](+)McN-5652 distribution volume throughout the brain, whereas they had a significantly increased [^{11}C]WIN-35,428 distribution volume in the medial region of the orbitofrontal cortex, compared with those of the controls. These results suggest the impairment of the function of the serotoninergic systems throughout the brain and the overfunctioning of the dopaminergic systems in the orbi-

tofrontal cortex of the autistic adults. However, the autistic participants studied herein are not a representative or a typical sample of the population of autistic individuals. We opted for autistic individuals with an IQ of greater than 70 in this study (ie, high-functioning individuals), although about 65% of autistic individuals are known to have an IQ of less than 70.[55] In addition, approximately 20% to 38% of autistic individuals are reported to have epilepsy.[56,57] However, in the present study, our autistic participants had no comorbidity, including epilepsy. Furthermore, our autistic participants were all drug naive. Therefore, our findings cannot be generalized to the entire population of autistic adults.

In the anterior and posterior cingulate cortices, where reduced serotonin transporter binding was noted in the autistic group, the magnitude of reduction was correlated with poor performance on the Faux Pas Test, which assesses social cognition ability. Our finding is in line with those of previous PET studies, which showed that reduced metabolism or blood flow in the cingulate cortices is associated with impairment of social cognition in autistic individuals.[58,59] Our finding is also supported by a study that used single-photon emission computed tomography and demonstrated that adults with Asperger syndrome, a clinical entity that is part of a spectrum of pervasive developmental disorders, exhibit a reduction in serotonin 2A receptor binding in the cingulate cortices and that this binding reduction is related to impaired social interaction.[60]

We also found that, in the autistic participants studied, the reduction in the serotonin transporter binding in the thalamus correlated with repetitive and/or obsessive behavior and interests as assessed by the Y-BOCS. This finding is compatible with previous studies that showed that the thalamus is the principal site for the accumulation of selective serotonin reuptake inhibitors,[61] which in turn ameliorate repetitive behaviors in some but not all autistic individuals.[15] In the present study, there was, however, no correlation in any of the other regions that have been implicated as responsible for repetitive behavior in individuals with obsessive-compulsive disorder (eg, the basal ganglia, frontal regions, and hippocampus). A prior hydrogen 1–labeled magnetic resonance spectroscopy study has shown that, in adults with Asperger syndrome, increased prefrontal *N*-acetylaspartate levels are positively correlated with obsessional behavior.[62] Furthermore, MRI studies of autistic adults have demonstrated enlargement of the caudate and putamen volumes, which is positively correlated with repetitive behaviors.[63] Repetitive behaviors have also been shown to be related to the hippocampus volume in obsessive-compulsive disorder.[64] In addition, individuals with autistic spectrum disorders were reported to have significantly higher concentrations of glutamate/glutamine and creatine/phosphocreatine in the amygdale-hippocampal region.[65] One possible explanation for the lack of correlations found in these regions (the basal ganglia, frontal regions, and hippocampus) is that impairments in the regions other than the thalamus, if any, could be accounted for by altered dysfunctions that are not related to disturbed serotonin transporter bindings per se. Nevertheless, further work is needed to determine whether the localized reduction in serotonin transporter binding in the thalamus is specific to repetitive and/or obsessive behavior and interests seen in adults with high-functioning autism.

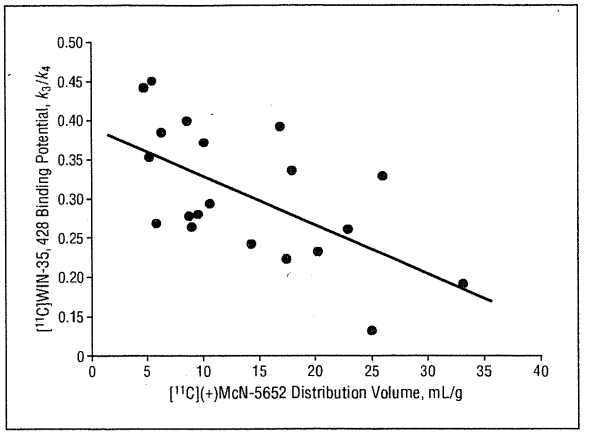

Figure 3. Correlation between [^{11}C](+)McN-5652 and [^{11}C]WIN-35,428 binding. Pearson product moment correlation analysis shows a significantly negative correlation between the [^{11}C](+)McN-5652 distribution volume and the [^{11}C]WIN-35,428 binding potential in the orbitofrontal cortex in autistic subjects (r=−0.61; P=.004; y=−0.006x+0.39). The k values represent the binding potential. See the legend to Figure 1 for other abbreviations.

Increases in peripheral serotonin levels have been the most consistent finding in autistic children.[6-10] High levels of peripheral serotonin are known to cause a loss of serotonin terminals during development, when serotonin transporters are located,[66-69] and this may happen in the brain as well. Therefore, we speculate that the reduction of serotonin transporter binding found in the brain of autistic adults in this study may stem from altered serotoninergic systems at the developmental stage. The *SLC6A* gene polymorphism has been associated with autism,[17,18] although other reports have not replicated these findings.[70,71] Because the gene polymorphism could modulate the neurodevelopment and function of the brain[19,20] and influence *SLC6A4* expression,[72,73] it may be responsible for the reduction of serotonin transporter binding that we observed in the present study.

Several limitations of our study bear mention. We repeated the SMP analysis separately for each of 5 clinical behaviors within the autistic participants, which may have led to a type I error. However, we found that 2 of the 5 clinical behaviors were correlated with the serotonin transporter bindings in particular brain regions, and, as discussed in the preceding paragraphs, these regions are considered to be critical and biologically plausible areas for involvement in these behaviors. Therefore, our results may not be attributable merely to type I error. Serotoninergic activity of the prefrontal cortical regions has been shown to correlate with aggressive behavior in humans.[74] Some autistic individuals were reported to have aggression.[75] In this context, we anticipated that our sample of autistic adults would show the relationship between reduced serotonin transporter binding and the degree of aggression. However, SPM analysis did not reveal any brain regions in which the reduced binding correlated with aggression as assessed by the AQ. This negative finding in the present study may have been because we recruited adults with high-functioning autism who were coopera-

tive with the imaging procedures. We showed correlates of alterations in the serotonin transporter binding with clinical features. Causative inference cannot be based merely on such correlations. Therefore, our findings cannot be considered conclusive. To elucidate the direct causal relationship between altered serotonin transporter binding and autism, further studies will be needed. Finally, the present study was limited by its small sample size and lack of female participants.

Dopamine transporter binding was significantly and locally increased in the medial region of the orbitofrontal cortex in our autistic participants. Our finding of overfunctioning in the dopaminergic system is compatible with previous PET studies, which showed increased striatal dopamine D_2 receptor binding in autistic children[32] and elevated dopamine synthesis and storage in the striatum and frontal cortex of adults with Asperger syndrome.[76] The orbitofrontal cortex is a key structure in the network underlying emotional regulation; dysfunction in the orbitofrontal-limbic circuit may be associated with behaviors in autism,[77] such as impulsive and aggressive behaviors.[75,78] However, the increased dopamine transporter binding was not correlated with aggression as assessed by the AQ in the present study. As mentioned in the preceding paragraphs, this may have been due to a bias arising from the selection of individuals with high-functioning autism in the present study, who are more cooperative with the PET imaging procedures than are autistic individuals as a whole. Thus, more work is needed in this regard.

When the relationship between dopamine and serotonin transporter binding was examined in our autistic participants, the dopamine transporter binding was significantly negatively correlated with that of the serotonin transporter. The mechanism underlying the interaction between the 2 transporters in the orbitofrontal region in autism is still unknown. However, some animal studies have illustrated that the number of dopaminergic neuron fibers increases in response to disruption of the serotoninergic system by a lesion in the nucleus raphe[79] and that the uptake of serotonin into dopamine neurons takes place by means of dopamine transporters.[80]

With respect to our use of [^{11}C]WIN-35,428 to evaluate dopamine transporter binding in the orbitofrontal cortex, a methodological issue should be addressed. The capability of the tracer for measuring low levels of dopamine transporter binding in the extrastriatal region is disputable. In the present study, we conducted 2 types of analytic procedures (ie, ROI method and SPM analysis) to estimate quantitative values of the orbitofrontal binding and to detect brain regions with significant changes. The difference in the shape of the time-activity curve of the orbitofrontal cortex between the groups (Figure 1G and H) and a series of our previous studies that have reported significant changes in the extrastriatal dopamine transporter binding[48,81-83] indicate the validity for the use of [^{11}C]WIN-35,428 for the purpose of the present study. This contention is also supported by our findings that the level of the orbitofrontal binding potential is higher in autistic individuals (0.27, based on our present data) than in their normal counterparts (0.19)[48] and that the magnitude of this increase (58%) is greater than the reported level of within-subject test-retest variability (9.3%).[84] Despite these accounts, a PET tracer with a much higher affinity to the extrastriatal dopamine transporter may be desirable.

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BRIEF REPORT

CINP

Metabolite alterations in the hippocampus of high-functioning adult subjects with autism

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Abstract

The aim of the present study was to investigate metabolite alterations in the hippocampal formation as they relate to aggression in high-functioning adults with autism. We measured concentrations of *N*-acetylaspartate (NAA), choline-containing compounds (Cho), and creatine plus phosphocreatine (Cr + PCr) in the hippocampal formation by proton magnetic resonance spectroscopy in 12 non-medicated male subjects with autism and 12 age- and sex-matched controls. Aggression was scored in the autistic subjects using the Buss–Perry Aggression Questionnaire. The concentrations of Cho and Cr + PCr in the hippocampal formation in autistic subjects were significantly higher than the corresponding values in control subjects, and a significant positive correlation was observed between the concentrations of these metabolites in the hippocampal formation and scores on the Buss–Perry Aggression Questionnaire in autistic subjects. Results suggest that high-functioning adult subjects with autism have abnormal metabolite concentrations in the hippocampal formation, which may in part account for their aggression.

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Key words: Aggression, autism, hippocampus, magnetic resonance spectroscopy.

Introduction

Autism is a neurodevelopmental disorder characterized by qualitative impairment of social interaction and communication, as well as by restricted repetitive and stereotyped patterns of behaviours, interests, and activities. In addition to the core features of autism, there are common comorbid psychiatric symptoms such as anxiety, depression, and aggression (Matson & Nebel-Schwalm, 2007). The presence of aggressive behaviour can reduce the effectiveness of treatment interventions, and many individuals with autism remain significantly impaired. Therefore, from a treatment perspective, it would be advantageous to clarify the underlying mechanism for the development of aggression in individuals with autism. The brain structures that are involved in the control of aggression include limbic structures such as the amygdala, hippocampus (Gregg & Siegel, 2001), and the cerebellum (Berman, 1997). Interestingly, the most significant findings from post-mortem studies of autism have been confined to regions of the limbic system and the cerebellum, e.g. reduced neuronal cell size and increased cell packing density in the hippocampus (Bauman & Kemper, 2005), shrinkage of nuclei of the amygdala (Schumann & Amaral, 2006), and reduced Purkinje cell density in the cerebellum (Bailey *et al.* 1998; Bauman & Kemper, 2005; Ritvo *et al.* 1986). However, the correlation between structural abnormalities associated with dysfunction in these structures and aggression in autism has not yet been clearly established.

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Proton magnetic resonance spectroscopy (^{1}H-MRS) is a non-invasive tool for evaluating neurochemical changes related to the clinical characteristics of psychiatric disorders. ^{1}H-MRS produces spectra that represent concentrations of *N*-acetylaspartate (NAA), a marker of neuronal integrity (Clark, 1998); choline-containing compounds (Cho), markers of cell number and/or membrane turnover (Miller *et al.* 1996); and creatine plus phosphocreatine (Cr + PCr), a marker of overall (i.e. neuronal plus glial) cellular density (Sartorius *et al.* 2008). Of the 35 post-mortem cases of autism reported in the previous studies mentioned above, 26 had died aged $\geqslant$19 yr. It is expected that ^{1}H-MRS study of the brain of autistic adults will be a helpful initial step in clarifying the involvement of the limbic system and cerebellum in the expression of aggression by individuals with autism. However, previous ^{1}H-MRS studies of the limbic system and cerebellum of autistic patients have primarily focused on children (i.e. patients aged $<$20 yr) and have been confounded by the inclusion of learning-disabled subjects and subjects with seizure disorders. In this regard, the only exception was a study by Page *et al.* (2006), in which the authors examined high-functioning adults with autism and reported a significant increase in Cr + PCr levels in the amygdala–hippocampal region. However, in that study, the relationship between neurobiological changes and clinical features was not examined. Furthermore, the putative roles of the amygdala and hippocampus in the expression of aggression appeared to differ (Gregg & Siegel, 2001), although these two regions are closely interconnected. To date, there has been no report of a ^{1}H-MRS evaluation of concentrations of metabolites in the cerebellum of adult subjects with autism.

In the present study, we hypothesized that alterations of metabolites may be present in the hippocampus and cerebellum of high-functioning adults with autism, and such metabolite alterations could be correlated with the aggression exhibited in a subset of these patients. To test these hypotheses, we recruited non-medicated, high-functioning male adults with autism in order to measure metabolite concentrations in the hippocampal formation (not including the amygdala) and cerebellum of these subjects using ^{1}H-MRS. In addition, we examined the correlation between metabolite levels and aggression in autistic adults.

Methods

The Ethics Committee of the Hamamatsu University School of Medicine approved the study. Each participant gave written informed consent after being given a complete description of the study. We conducted the Wechsler Adult Intelligence Scale – Revised (WAIS-R) to assess the intelligence quotient (IQ) of all participants. The diagnosis of autism was made according to the Japanese version of the Autism Diagnostic Interview – Revised (ADI-R; Lord *et al.* 1994) and the Autism Diagnostic Observation Schedule (ADOS; Lord *et al.* 2000). Control subjects were recruited from the community by advertisement. All autistic and control subjects were screened to exclude psychiatric illnesses (i.e. schizophrenia, affective disorders, mental retardation, and personality or behavioural disorders) by means of the Structured Clinical Interview for DSM-IV (SCID). We excluded individuals with epilepsy, with psychotropic medication, and those with mental retardation as defined by a full-scale IQ of $<$70. Twelve male subjects with autism and 12 age-matched healthy male controls were included in the present study. All participants were right-handed, as assessed by the Edinburgh Handedness Inventory (Oldfield, 1971). We evaluated aggression in the participants using the Japanese version of the Aggression Questionnaire (Ando *et al.* 1999). The original version of the Aggression Questionnaire (Buss & Perry, 1992) is a 29-item, self-administered test designed to measure aggression (i.e. physical aggression, verbal aggression, anger, and hostility) as a personality trait. The validity and reliability of the Japanese version of the Aggression Questionnaire has previously been established (Ando *et al.* 1999).

Participants were scanned using a GE 1.5 T magnetic resonance scanner at the Hamamatsu University Hospital. We selected two volumes of interest (VOIs) for each subject, i.e. the left hippocampal region and the right cerebellar hemisphere (Fig. 1*a–c*). The rationale for the selection of two VOIs was as follows: (1) since all the participants were right-handed, the left hippocampus and the right cerebellum were regarded as dominant (Jansen, 2005); (2) although there is no known direct projection from the hippocampus to the cerebellum, most of the efferents from the temporolimbic region send information to the contralateral cerebellar cortex via the cortico-ponto-cerebellar pathway (Schmahmann, 2000); and (3) left-sided abnormalities have been associated with aggression in humans (Tebartz van Elst *et al.* 2000; Zetzsche *et al.* 2007). To establish these VOIs, whole-brain images were acquired with a 3D fast-spoiled gradient-echo imaging protocol. A sagittal scout image was used to select oblique coronal slices perpendicular to the long axis of the hippocampal formation (Fig. 1*a*). A slanted rectangular VOI ($2 \times 2 \times 1.5$ cm^3) was selected such

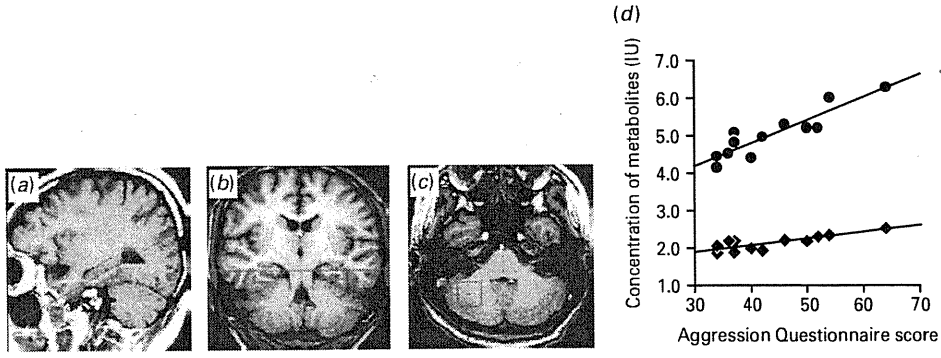

Fig. 1. (*a–c*) Locations of a 6-ml volume of interest (VOI) in the left hippocampus (*a*, *b*) and of an 8-ml VOI in the right cerebellum (*c*). (*d*) Choline-containing compounds (◆; Cho) and creatine plus phosphocreatine (●; Cr+PCr) concentrations in the hippocampus of autistic subjects. Both values showed a significant and positive correlation with the Aggression Questionnaire score (Cho: $\rho = 0.719$, $p = 0.008$; Cr+PCr: $r = 0.884$, $p < 0.001$).

that it was aligned along the long axis of the hippocampus, starting just posterior to the amygdala (Fig. 1*a*, *b*). The centre of the VOI was at the cornu ammonis of the left hippocampus; as a result, the VOI contained the hippocampus proper and a portion of the parahippocampal gyrus. A cerebellar VOI ($2 \times 2 \times 2$ cm^3) was placed on one axial image, which showed the full length of the middle cerebellar peduncle (Fig. 1*c*). To explore metabolite levels in the cerebellar cortex, we excluded the dentate nucleus from each VOI; the medial side of the VOI was just adjacent to the lateral margin of the dentate nucleus, which was determined by axial T_2-weighted images. A point-resolved spectroscopy (PRESS) spectrum [repetition time (TR) = 1500 ms, echo time (TE) = 144 ms, 256 averages] was obtained after chemical shift selective water suppression. To determine the tissue composition of the VOI, fast-spoiled gradient-echo images were segmented into white matter, gray matter, and cerebrospinal fluid (CSF) using the software package Dr View/Linux. We measured the concentrations of NAA, Cho, and Cr+PCr using the LC model algorithm and corrected the concentrations for the proportion of CSF within the VOI.

Statistical analyses were performed using two-tailed Student's *t* test, Spearman's ρ correlation coefficient, and Bonferroni's correction. The level of significance was set at $p < 0.05$.

Results

The demographic characteristics of the autistic and control subjects are shown in Table 1. There was no significant difference in the distribution of age or full-scale IQ between the two groups, indicating that subject matching was successful. As shown in Table 1, there were no significant inter-group differences in the compositions of gray matter, white matter, and CSF within either of the two VOIs. In the hippocampus, the autistic group had significantly higher concentrations of Cho ($p < 0.001$) and Cr+PCr ($p < 0.001$) compared to control subjects (Table 1). In the cerebellum, the concentration of NAA in the autistic group was significantly lower than that in the control group ($p < 0.001$, Table 1). We performed a Spearman's correlation analysis to determine whether the concentrations of Cho and Cr+PCr in the hippocampus and NAA in the cerebellum were correlated with autistic subjects' scores on the Aggression Questionnaire. Both Cho ($p = 0.008$) and Cr+PCr ($p < 0.001$) concentrations in the hippocampus, but not the NAA concentration in the cerebellum, were significantly positively correlated with the Aggression Questionnaire scores (Fig. 1*d*). There was no correlation between metabolite alterations (i.e. hippocampal Cho and Cr+PCr, and cerebellar NAA) and IQ or autistic symptoms as assessed by ADI-R (data not shown).

Discussion

In the present study, the observed increase in the Cr+PCr concentration in high-functioning subjects with autism was compatible with the results of a previous ^{1}H-MRS study by Page *et al.* (2006), who measured the concentration of this metabolite combination in the right amygdala–hippocampal complex in autistic adults of normal intelligence. We also found an elevation of Cho in the hippocampal formation (not including the amygdala) of high-functioning adults with autism, although it should be noted that the

Table 1. Demographic characteristics and ^{1}H-MRS measurements of the hippocampus and cerebellum in subjects with autism and controls

	Control ($n=12$)	Autism ($n=12$)	t value	p value
Age (yr)	22.3±1.8 (19–24)	22.0±2.2 (18–25)	0.384	0.705
Full-scale IQ	105.2±12.6 (85–125)	96.3±14.0 (71–117)	1.645	0.114
ADI-R (Diagnostic algorithm)				
(A) Social	n.a.	20.9±5.3 (12–28)		
(B) Communication				
Verbal	n.a.	14.2±5.4 (4–22)		
Non-verbal	n.a.	8.4±4.0 (2–14)		
(C) Stereotype	n.a.	5.5±2.0 (3–10)		
Aggression Questionnaire	n.a.	45.3±9.4 (34–64)		
Hippocampus				
NAA (IU)	7.79±1.57	8.14±0.84	−0.672	0.509
Cho (IU)	1.87±0.21	2.19±0.17	−4.176	<0.001*
Cr+PCr (IU)	3.80±0.97	5.16±0.59	−4.124	<0.001*
Gray matter (%)	64.5±6.9	65.6±7.3	0.394	0.866
White matter (%)	33.9±8.3	32.2±7.5	0.609	0.769
Cerebrospinal fluid (%)	1.6±2.0	2.2±1.9	0.215	0.880
Cerebellum				
NAA (IU)	9.01±0.50	8.29±0.71	3.949	<0.001*
Cho (IU)	2.12±0.18	2.07±0.22	0.505	0.618
Cr+PCr (IU)	6.08±0.56	5.85±0.63	0.909	0.373
Grey matter (%)	71.6±9.2	71.8±8.0	0.620	0.495
White matter (%)	28.2±9.2	27.7±8.9	0.154	0.448
Cerebrospinal fluid (%)	0.0±0.0	0.1±0.0	0.031	0.084

ADI-R, Autism Diagnostic Interview – Revised; n.a., not applicable. NAA, *N*-acetylaspartate; Cho, choline-containing compounds; Cr+PCr, creatine plus phosphocreatine; IU, institutional unit.
Values are expressed as means±S.D. (range).
* Statistically significant difference, as determined by two-tailed Student's t test.

study by Page *et al.* (2006) did not demonstrate such changes in Cho level. The discrepancy between the two studies presumably may reflect a difference in VOI placement, i.e. the Page *et al.* study included the amygdala, whereas our study did not. The ^{1}H-MRS Cho peak is known to be caused by free choline, phosphocholine (components of membrane synthesis), and glycerophosphocholine (a product of the degradation of membrane phosphatidylcholine). Therefore, an increase in the Cho concentration has been interpreted as representing increased membrane synthesis and/or membrane disruption in processes including tumour growth, demyelinization, and gliosis (Miller *et al.* 1996). An elevation of Cr+PCr on ^{1}H-MRS reflects high-energy phosphate metabolism (Sartorius *et al.* 2008). Therefore, the elevation of Cho and Cr+PCr levels observed here suggests active, viable neuronal turnover in the hippocampal region of autistic adults. Previous structural MRI studies (Rojas *et al.* 2004; Schumann *et al.* 2004) have demonstrated enlarged hippocampal volume in autistic adults of normal intelligence. However, since in our sample no changes were observed in the NAA concentration in the hippocampal region, it remains unclear whether or not elevated Cho and Cr+PCr levels are associated with changes in hippocampal volume. Further studies are required to clarify this issue.

Both Cho and Cr+PCr concentrations in the left hippocampal region were significantly and positively correlated with trait aggression, as assessed by the Aggression Questionnaire administered to our adult subjects with autism. To the best of our knowledge, this is the first report to describe a link between metabolite alterations in the hippocampal formation and a clinical feature of autism. There is no available data to account for the mechanism by which the hippocampus affects the trait of aggression in autism. However, the accumulated evidence does suggest that the hippocampal formation modulates aggression in animals. For instance, electrical stimulation of the

dorsal or ventral hippocampus has been shown to inhibit or facilitate, respectively, aggressive behaviour in cats (Gregg & Siegel, 2001). Electrophysiological recordings have revealed that aggressive behaviours are associated with increased frequency in hippocampal discharge patterns in rabbits (Fontani & Vegni, 1990). Furthermore, the present findings agree with the results of previous clinical studies indicating that left hemispheric lesions may be associated with a higher risk for the development of aggression (Tebartz van Elst *et al.* 2000). Zetzsche *et al.* (2007) reported that increased lifetime aggression in patients with borderline personality disorder was significantly correlated with volume of the left, but not the right, hippocampus. Taken together, these findings suggest that the elevations in the Cho and Cr + PCr concentrations observed here reflect altered function in the hippocampal formation, which in turn was found to be associated with aggression in adult subjects with autism. Since it is still unclear whether the functional alterations in the hippocampal formation are causative of aggression in people with autism, further studies are needed.

As assessed by ^{1}H-MRS, the concentration of NAA in the cerebellum was significantly lower in autistic adults than controls. This finding is comparable with that of previous ^{1}H-MRS studies of autistic children, who exhibited a similar reduction in metabolite concentrations in the cerebellum (Chugani *et al.* 1999; Otsuka *et al.* 1999). Since post-mortem studies have repeatedly demonstrated decreased Purkinje cell density in the cerebellum (Bailey *et al.* 1998; Bauman & Kemper, 2005; Ritvo *et al.* 1986), and since a decrease in the ^{1}H-MRS NAA peak is a putative marker of neuronal loss (Clark, 1998), it is possible that the decreased NAA concentration observed here reflects a relative decrease in the number of Purkinje cells in the cerebellum of high-functioning subjects with autism.

There are some limitations of our study. The small sample size renders the data presented here preliminary, and a larger study with more subjects with autism will be necessary. However, recruitment for the present study was limited to a group of high-functioning subjects with autism, all of whom were given no psychotropic drugs, and all were able to complete magnetic resonance spectroscopy without sedation. Therefore, we believe that our data are free from possible confounding factors and thus may reflect a certain common pathology in people with autism. Other limitations of this study include the following: (1) the lack of an assessment of the right hippocampal formation; (2) inclusion of not only the hippocampus proper, but also the parahippocampal gyrus in the hippocampal VOI; and (3) a relatively short TR acquisition period in the ^{1}H-MRS method, which could have affected metabolite levels. Furthermore, we did not include autistic adults without aggression as a comparison group, which might have been useful to test our hypothesis. These limitations should be factored into any interpretation of the present results. Nevertheless, in the existing literature, few studies to date have combined results from neuropsychological tests with neurometabolic levels in specific brain areas, which is a main advantage of our study.

In conclusion, although the sample size was small, our findings suggest that high-functioning people with autism have metabolite alterations in the cerebellum and hippocampus, and the latter in particular may play an important role in the expression of aggression in individuals with autism.

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Statement of Interest

None.

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特集：ADHD(Attention-Deficit/Hyperactivity Disorder)をめぐって

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現状と課題

児童青年精神医学とその近接領域　51(2)；67—76（2010）

注意欠如・多動性障害（ADHD）のわが国特有な課題を中心に現状を示すとともに現在のところ回答がない重要な課題を明らかにすることを目的に，概念の形成史，現在の概念，診断，治療の各領域を展望した。その際著者が意識したのは，精神障害への治療・支援とはその症状に対してだけ向かうものではなく，その障害を持つ当事者一人一人の生き方全体を対象として行われるべきものであり，横断面への支援だけではなく，時間経過の中で当事者と支援の相互性の中で変化していくプロセスに伴走することが重要であるという一点である。そのような全体的な支援を提供するためには，その基盤となる診断そのものが各当事者の個人的問題としてのADHDを，正確に診断できるとともに，当事者のADHDもその一部としているに過ぎない人格特性全体を包括的にとらえることを目指すものでなければならない。わが国においてADHD診療が国際的基準を意識した構造化されたものをめざすようになってから日はまだ浅く，ようやく国際的標準とされる医療を追いかけはじめたところである。臨床ガイドラインは第3版となってようやく臨床応用に耐えるものに近づいてきたが，まだまだ明確な推奨を示せないでいる分野が多いのもわが国の現実である。

Key words：attention-deficit/hyperactivity disorder, history, concept, diagnosis, treatment

Ⅰ．ADHD概念小史

わが国の児童精神科領域における臨床家の関心を独占しているかの感がある「発達障害」の一角を占める注意欠如・多動性障害 Attention-Deficit/Hyperactivity Disorder（以下ADHDと略記）は，近年の広汎性発達障害 Pervasive Developmental Disorders（以下PDDと略記）概念のわが国特有な拡大に基づく過剰診断傾向の陰に隠れてやや目立たない位置に退いているようにも見える。しかし実際にはADHD概念は，この間の生物学的研究の成果や複数の適応薬剤の登場という事情もあって，病因，主症状，治療の各領域で一定の均一性を持った包括的疾病概念として凝集性を高めつつある。

現在ADHDと呼ばれているような障害が最近になって突然あらわれたものでないことはいうまでもない。その歴史的な変遷過程をBarkleyの教科書（Barkley, 2006）を参考に振り返ってみたい。

医学的疾患単位として現在のADHD概念に相通じる特徴を持つ子どもに関する学術的記載は，1902年にLancetに掲載されたStillによる攻撃的で反抗的になりやすい43例の子どもについての講義録まで遡ることができる。Stillが描いた状態像と類似の特徴を示している子どもについての論考は1908年のTredgoldの論文にあるような「早期に発生した軽度で検出されていない脳損傷」を持つ子どもという仮説へと展開し，後の微細脳損傷（MBD）理論を予感させる流れを作り出した。それとは別に，1917年頃の流行性脳炎の多発を経験した北米大陸では，その後遺症研究を通じて「脳炎後行動障害」概念の検討が進み，脳損傷が明確にならない多動，衝動性，不注意の背景にも脳損傷関連の器質性

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要因を想定する観点が打ちたてられていった。

しかし，以上のような仮説の前提となる脳損傷が，当時の脳科学研究の方法では証明できないという限界の前に，1949年にはGesellとAmatrudaが，また1959年にはKnoblockとPassamanickが蓋然性としての脳器質性障害という意味での「微細脳損傷 minimal brain（ないし minimal cerebral）damage（MBD）」という概念を提唱した。しかし，証明できない脳器質性障害を前提とするこの概念には批判も多く，1962年に英国オクスフォードで開催されたこの問題に関する小児神経学領域の国際研究会において，脳器質性障害ではなく，形態的変化を伴わない脳機能障害を病態とする「微細脳機能障害 minimal brain dysfunction（MBD）」という概念への修正が提案され，わが国でも一旦はこの概念が受け入れられた。

しかし1960年代を通じて，MBD概念はその根拠となるはずの脳機能障害が同定できないまま，徐々に疾患概念としての凝集性に疑問を持たれるようになっていった。

それに代わって優勢になってきたのは，病因としての脳機能障害の解明という難題から離れ，多動性を障害規定の中心に据え，その多動性が前景に立ち，しかも病因を明確に見出すことのできない子どもを「多動児 hyperkinetic child あるいは hyperactive child」と呼ぼうという症候群の観点である。1968年に米国で出版された精神障害の分類と診断基準の第2版（DSM-II）はこのような観点を採用し，Still以来注目されてきた多動で落着きなく，衝動的な子どもを「児童思春期の行動障害」という障害グループに属する「児童思春期の多動反応 hyperkinetic reaction of childhood and adolescence」という概念で規定することを提案している。1977年になって，WHOの提案する疾病分類であるICD-9はこの疾患を「多動症候群 hyperkinetic syndrome」と名づけることを提案した。

1970年代に入ると，このような子どもの基本的特徴に，多動性とは別に注意集中時間の極端な短さや集中力の乏しさを含めるべきであるとする研究結果が提出されるようになり，後に「注意欠如 attention-deficit」と記載されることになる注意機能や実行機能の障害に注目が集まるようになっていった。1980年に米国精神医学会が作成したDSM-IIIは，このような成果を継承する形で「注意欠如障害 attention-deficit disorder（ADD）」という概念にまとめ，現在のADHD概念につながる道を切りひらいた。このDSM-IIIはADD概念を「多動を伴うもの」と「多動を伴わないもの」の二種類の下位分類に分けている。

1987年に出版されたDSM-IIIの改訂版（DSM-III-R）は，DSM-IIIで認めた不注意だけを主症状として多動性と衝動性を伴わない群を障害の枠組みから排除し，多動性，衝動性，不注意をすべて具えた状態像を示すものだけを「注意欠如多動性障害 Attention-Deficit Hyperactivity Disorder（ADHD）」と呼ぶという大きな変更を加えた。1992年に発刊されたWHOのICD-10に掲載されている「多動性障害 hyperkinetic disorders」は，このDSM-III-Rの考え方と同じように，不注意だけが前景に出た状態像を排除した障害概念としており，当時は国際的にこの枠組みで決着したと思われた。

ところが1994年に出版された米国のDSM-IVは，不注意，多動性，衝動性を3主症状に定めるというDSM-III-Rの定義を継承したうえで，それら3症状の組み合わせによって不注意優勢型，多動衝動性優勢型，混合型の3種類の下位分類を持つ「注意欠如・多動性障害 Attention-Deficit/Hyperactivity Disorder（ADHD）」という障害概念を新たに提唱するという再々度の修正を行った。この修正によりDSM-IVは，「多動を伴わないADD」を含んだ障害概念を提案したDSM-IIIの観点に回帰したことになる。

DSM-IVのこの修正により，DSM-III-RとICD-10の共存していた7年間，分類の受け皿をほぼ失い，障害として宙に浮いてしまった注意障害を中心とする状態像がADHDの枠組みに入れられ，障害として再認知されることとなっ

た。この考え方は2000年のDSM-IV-TRの登場に際しても継承されており，すでに16年にわたって不注意のみが前景に出た障害もADHDとしてとらえる立場での研究成果と臨床経験の蓄積が続けられている。

こうしたADHD概念のわが国での発展経過は多難なものであったといっても過言ではない。リタリン問題との関係もあって，最近までその障害概念の正当性を問う批判的議論がなされる状況が続いていた。しかし，ADHD概念にぴったりあてはまる子どもは，MBD時代から一定の規模で存在しており，状態像の深刻度においても無視できない臨床上の対象であることは，一線の児童精神科医や小児神経科医にとって自明のことであった。

1998年にマスメディアがこの障害に注目した報道を連続的に行ったことを機に，わが国でもADHDは障害として社会的注目を集め，医療界においてもようやく疾患概念として認知されるようになってきた。翌1999年には厚生労働省「精神・神経疾患研究委託事業」の一環としてADHDのガイドライン作成に取り組む研究班（主任研究者：上林靖子）が組まれ，その3年間の研究の成果をまとめる形で，2003年にはわが国初のADHDの診断・治療ガイドライン（上林ら，2003）が出版された。2005年には発達障害者支援法が施行され，法の対象たる発達障害の代表的障害の一つとしてADHDが明記されたこともあり，徐々に我が国の社会に受け入れられていった。そして2007年にコンサータ，2009年にストラテラと相次いでADHDの子どもを対象とするADHD治療薬が認可されるにおよび，わが国においてもADHDは障害概念として確実に定着したのではないだろうか。

II．ADHD概念をめぐる現状と問題点

現在世界的にADHD概念の標準となっているDSM-IVが，活動性と注意の障害として規定したICD-10の多動性障害（DSM-IVでは混合型ADHDにあたる）に加えて，不注意と表現される注意機能の単独障害もADHDに含める形で成立していることはすでに述べた。ADHDは多動性，衝動性，不注意が三大主症状とされているが，DSM-IVでもICD-10でも多動性と衝動性は一つにくくられ，症候論的には多動性・衝動性と不注意という二大主症状の存在で規定されている。したがって，ADHDは「著しい多動性・衝動性と不注意の二大主症状のどちらか，あるいは両方を持ち，それによって社会機能や学習機能などの著しい障害が生じており，同時に主症状がPDD，統合失調症，気分障害，反応性愛着障害など他の精神障害の症状の一部として出現しているのではない障害」であると定義できるだろう。

いうまでもなく，現在の操作的診断体系による精神障害の概念は原則として病因を含まずに定義されており，あくまで現象面での均質性と，各障害を規定する諸条件を満たしていることで診断されるということになっている。ADHDも例外ではなく，DSM-IV-TRの解説にも小児虐待やネグレクトと，鉛中毒などの神経毒への暴露，脳炎，子宮内での薬物への暴露，精神遅滞などが既往として存在するかもしれないといった記述や，ADHDの子どもの一親等の親族に一般人口より発現が多いといった記述があり，遺伝的要因や胎生期や早期幼児期での外因，あるいは早期幼児期の虐待などが病因となる可能性を示唆してはいるものの，明言を避けている。

障害概念としてADHDが持つ重要な課題が一つある。我が国の発達障害者支援法はADHDをPDDと並ぶ主たる対象障害として挙げているが，国際障害分類であるDSM-IVもICD-10もADHDを発達障害とは認めていないという事実である。

DSM-IVはADHDをPDDや学習障害とともに「通常，幼児期，小児期，または青年期に初めて診断される障害」に含めているものの，PDDや学習障害と同列ではなく，反抗挑戦性障害や素行障害とともに「注意欠如および破壊的行動障害」に含まれるいち障害という位置に置いており，PDDや学習障害等の発達障害と一線を画した配列となっている。ICD-10は，発達障

表1 ICD-10のF8「心理的発達の障害」の共通点（World Health Organization, 1992）

（a）	発症は常に乳幼児期あるいは小児期である
（b）	中枢神経系の生物学的成熟に深く関係した機能発達の障害あるいは遅滞である
（c）	精神障害の多くを特徴づけている寛解や再発が見られない，安定した経過である

害を主として規定する「F8 心理的発達障害」にはPDDと学習障害系の諸障害だけを含め，ADHDは「F9 小児期および青年期に通常発症する行動および情緒の障害」に素行障害などとともに分類している。

しかし，心理的発達障害を規定する特徴としてICD-10があげた3条件（表1）については，齊藤（2007）がすでに指摘したように，ADHDもまた満たしていることはほぼ確実である。このため筆者も加わったわが国の診断・治療ガイドライン第3版（齊藤ら，2008）では診断・評価ガイドラインの最初に「ADHDは不注意，多動性，衝動性の三種の主症状によって定義され，基本的には生来的な脳機能障害が発現の主要因である精神障害を意味している。わが国の発達障害者支援法ではADHDは発達障害を構成する一障害と位置づけられており，本ガイドラインもそれに準じてADHDを発達障害と位置づける」という定義に関する考え方を示した。

Ⅲ. ADHDの診断をめぐる現状と課題

ADHDの診断・評価は概念をめぐる問題でも述べたように操作的診断体系に沿った評価を行うことが求められている。図1はDSM-Ⅳの診断基準をアルゴリズムとして示したものである。このアルゴリズムにしたがった診断を確実に実行するために構造化面接や半構造化面接に使用する質問紙が多数開発されているが，わが国で公刊されているガイドライン（齊藤ら，2008）でも『ADHDの診断・評価用フォーム』を掲載し，その使用を推奨している。これはDSM-Ⅳにしたがって質問していく形の半構造化面接で，ADHDだけでなく，反抗挑戦性障害，素行障害，PDDに属する各障害などのADHDと関連の深い諸障害を診断するフォームとなっている。

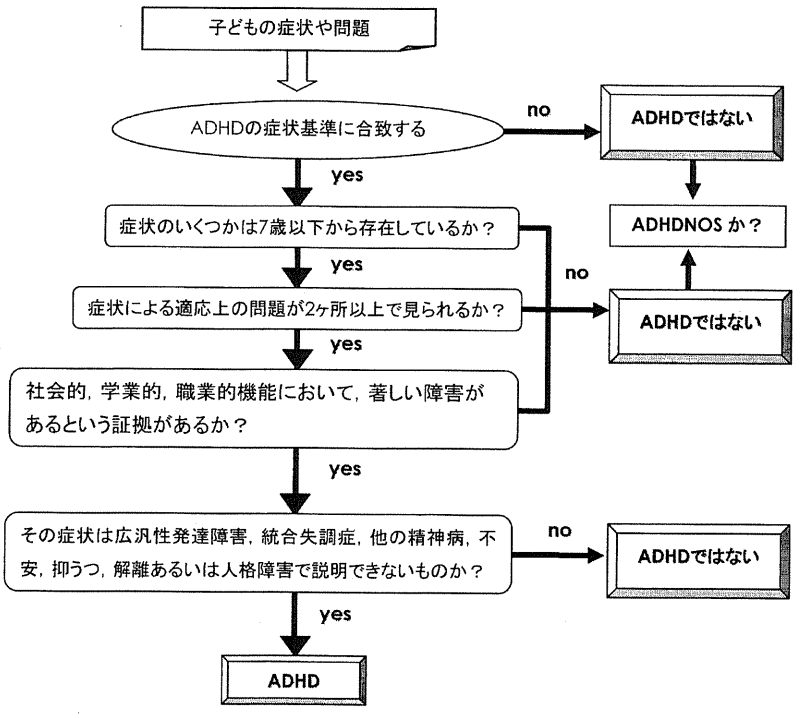

図1 DSM-Ⅳに準拠したADHDの診断アルゴリズム（齊藤ら，2008より改変）

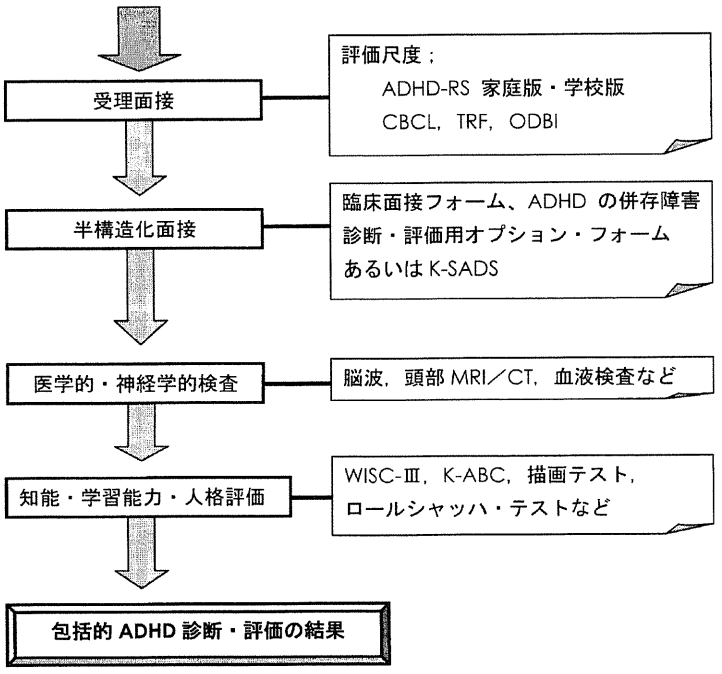

図2 ADHDの評価・検査フローチャート
（齋藤ら，2008）

さらに，ADHDは併存精神障害が非常に多いことで知られている。診断として，ADHDおよびその周辺の障害を評価するだけでは，ADHDの全体像を把握するには不完全といわざるをえない。したがって，前記ガイドラインでは『ADHDの診断・評価用フォーム』に加えて，『ADHDの併存障害診断・評価用オプション・フォーム』を掲載した。これは各種の不安障害，気分障害，適応障害，反応性愛着障害，学習障害，チック障害などを診断する質問表を中心とするフォームで，これら2種類のフォームを用いることで，取りこぼしなく併存障害の有無を査定できる組み合わせになっている。同じような機能を持つ診断用フォームにはK-SADSなどもあり，主として研究領域で用いられることが多い。それに対して，『ADHDの併存障害診断・評価用オプション・フォーム』は，あくまで臨床的な使い勝手のよさをめざしたフォームであり，過度に完全主義的とはしない構成となっている。

とはいうものの，このような操作的診断法にしたがった半構造化面接は，2種類のフォームの量からもわかるとおり，実施にはかなりの長時間を要するため，それが臨床現場での使用をためらわせる大きな要因となっている。

さらにADHDの総合的・包括的評価を通じたADHD児・者の全体像の把握のために，中枢神経系の代謝疾患や変性疾患，あるいは感染症や腫瘍といった器質性疾患との鑑別や，知的発達の水準，認知機能の特性，形成されつつある人格構造などを個々に評価するために必要な諸検査を行わなければならない（図2）。これらをきちんと実施し結果を得るために要する検査機器と時間，さらには実施と結果の分析に必要な人材を用意することは，臨床の第一線を担う医師や医療機関では難しい場合が多い。しかし，こうした推奨されている診断ツールをきちんと用い，ガイドラインに基づいて評価を進めていく手順を省略することは，それだけ診断者の主観の関与する余地が大きくなり，見逃しや過剰診断の危険を増大させることになる。

本来，操作的診断法により症候に規定された障害概念である多くの精神障害は，典型的な症候の組み合わせを中心に診断基準が定められている。しかし，臨床場面で実際に見出す各症候は，必ずしも鮮明な輪郭線で区切られたもので

はなく，他の症候や無症候との間に非常に曖昧で幅広い移行ゾーンあるいは境界ゾーンを持っており，その有無の判断に迷うことが多い。

ADHDの場合には，その曖昧さへの対応策の一つとして，ADHDの重症度を数量化するために開発されたDuPaulら(1998)による「ADHD評価スケール(ADHD-RS)」などを用いて，診断をいくらかでも客観化しようとする試みが行われている。いうまでもなく診察場面は，子どもにとって非日常的で特殊な場であるため，環境の影響を受けやすいADHDの子どもの通常の状態像を観察し評価する場として，必ずしも適切ではない。親や教師が家庭や学校での症状を評価するADHD-RSは，診断医にとって家庭や学校での状況を把握する重要な資料となることと思われる。

しかし，このようなチェックリストは客観的な指標としてあまりにも曖昧な部分を含んでいることもまた確かである。評価を行った親や教師はチェックのための評価基準について訓練を受けた専門家ではなく，あくまでADHD-RSの文章に刺激されて反応を返しているにすぎない。したがって，個々のチェックの基準は評価者の価値観や感情に大きく支配されるだろうし，症状チェックの結果は評価者である親や教師と被評価対象である子どもとの関係性を色濃く反映したものとなるだろう。

このようなADHD-RSの最も有効な使用目的は，一人の子どものADHD症状の推移や治療的介入によるその変化を時間経過に沿って観察することである。診断という絶対的評価において参考にする際には，その結果にはあくまで相対的な意義しかないことを心得て利用すべきである。

以上から，ADHDの診断には何らかの客観的指標，すなわち生物学的指標（biological marker）が求められていることは明らかである。ADHDを対象にしたCPT（continuous performance test）やアクチグラフを用いた研究，あるいは脳画像研究などはこれまでも行われており，一定の知見は得られるものの，ADHDを特異的に指すような指標とする決め手に欠け，現在そのような指標はないとされている。

しかし，脳機能をめぐる検索法や描出法の近年における急速な進歩は，例えば事象関連電位や機能画像研究の領域で，あるいは認知機能検査，中でも注意機能検査の世界でADHDに特有な所見が発見されつつある。

「この所見が陽性ならADHDである」といった高い水準の生物学的指標は今後も見出されない可能性が高いものの，「生物学的指標の①と②と③が陽性なのでADHDである蓋然性は高い」，「診断面接やADHD-RSの結果を支持する生物学的指標④の結果である」といった形式でADHD診断の堅牢性を高める指標は遠からず見出されるのではないだろうか。さらには，ADHDとされた子どもの治療を組み立てる際の治療技法の選択に利用できる生物学的指標が明らかにされたら，臨床的な意義は非常に大きいものがあるだろう。

ADHDの診断をめぐるわが国特有な問題として，「虐待を発症要因とするADHD」という概念が成立するか否かという問題について触れておきたい。すでに述べたように，DSM-IV-TRの解説部分で虐待やネグレクト（わが国では虐待の一部に入れられている）の既往を持つ事例もあるという記述があることから，存在すると考えても不合理とはいえないだろう。一方，障害概念について述べたところで触れたように，ADHDを生来性の体質的障害，すなわち発達障害に含めるわが国のとらえ方からすれば，虐待によるものは明らかに二次性の障害であり，反応性愛着障害などのような虐待関連精神障害の症状の一部ととらえるほうが自然である。

しかし，もし早期幼児期における虐待によってADHDの脳機能障害と同質の障害を負うことがあきらかとなれば，虐待はADHDを生じさせる重要な要因ととらえることが可能となる。この点についても今後さらに良質のエビデンスを提供できるような研究や症例検討が必要である。

Ⅳ．ADHDの治療をめぐる現状と課題

1．薬物療法をめぐって

ADHDの体系的な治療・支援はまだまだ緒についたばかりというのがわが国の現状であろう。MBDと呼ばれた時代から児童精神科や小児神経科の領域では多動で衝動的な子どもの薬物療法は試みられてきたが，不注意だけが著しい子どもにはDSM-IIIのADD概念の登場まで薬物療法についての関心は乏しかった。またわが国では，諸外国における薬物療法が中枢刺激薬を中心としたものであることは専門家の間で知られていたが，中枢刺激薬の代表的薬剤であるmethylphenidate製剤のリタリンは乱用や副作用に対する警戒心から，子どもへの使用に抵抗があるという状況が長く続いていた。いうまでもなくわが国でリタリンは，MBDの時代はいうに及ばず，ADHDの時代になっても，一度も適応薬として承認されたことはない。

それでも，1990年代からADHDへのリタリンの投与は増加していき，専門家の間で広く使われるようになっていった。ADHDを診療対象としている日本児童青年精神医学会および日本小児神経学会の医師会員を対象として2001年に行った全国調査では，有効回答者487名のうち84％にあたる409名がADHDの薬物療法を行っており，そのうちの89％がリタリンを最もよく処方する薬物としていた（上林ら，2002）。さらに3年後の2004年，齊藤ら（2006）は同様の調査を日本児童青年精神医学会の医師会員と日本小児神経学会専門医を対象に実施し，ADHDの薬物療法を有効回答者700名のうち93％の医師が行っており，併存障害のないADHDへの第一選択薬を問う質問への有効回答者530名のうち96％がリタリンを挙げていた。こうした結果を反映させる形でADHDの診断・治療ガイドラインの改定版（齊藤ら，2006）では，適応外処方であることを当事者に明確にすることを前提にfirst lineの薬剤としてmethylphenidate（当時はリタリン）を推奨することを初めて明記した。

その後現在までの数年間に，ADHDの薬物療法をめぐる環境は急激な変化を示した。2007年末にはリタリンがナルコレプシーに限った適応薬となり，ADHD治療やうつ病には用いることができなくなった。その替わりとして2007年12月にはmethylphenidateの徐放剤であるコンサータが正式な適応薬（ただし18歳未満の子どもに限局された適応）として承認された。さらに，2009年6月には選択的ノルアドレナリン再取り込み阻害薬であるatomoxetine製剤のストラテラが18歳未満のADHDを適応とする薬剤として承認され，販売を開始した。

現在薬物療法ではコンサータが丸2年の使用経験を，ストラテラが半年の使用経験を積み重ねてきており，まもなくこれら2適応薬の臨床的評価も定まってくるものと思われる。それまでは2008年に出版された診断・治療ガイドラインの第3版（齊藤ら，2008）で示したアルゴリズム（図3）に沿った両薬剤の使用が適切と考える。

このアルゴリズムでは両薬剤の併用を認めており，現実にすでにかなり多くの事例で併用が行われていると聞く。両薬剤の特性を生かして双方の欠点を埋めあうような使用には一定の合理性も考えられるが，最初に投与した薬剤の効果を，用量を上げながらきちんと見極めることをせずに，少量投与で効果を不十分と評価し，安易に両者の併用に向かうことは薬物療法として推奨できない。いずれにしても両薬剤のどちらが第一選択薬でどちらが第二選択薬かという課題は非常にデリケートな問題であり，今少し臨床経験を蓄積したうえで，臨床家の実感に沿って決めていくべきものであろう。現在は両薬剤をfirst lineと位置づけている。

ところでADHDの薬物療法についてのわが国における最大の課題は両適応薬が18歳未満の子どもにしか承認されていないという点にある。すでに見てきたように，ADHDは生涯にわたる障害であるがゆえに発達障害に含まれるべきなのであって，18歳で薬物療法を終えることのできない事例はけっして少なくないはずであ