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Original Article

Inhibitory Function and Working Memory in Attention Deficit/Hyperactivity Disorder and Pervasive Developmental Disorders: Does a Continuous Cognitive Gradient Explain ADHD and PDD Traits?

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To clarify the relationship between attention deficit/hyperactivity disorder (AD/HD) and pervasive developmental disorders (PDD), we investigated the common features and differences of these disorders in neuropsychological profiles. The subjects were 4 groups of Japanese boys aged 6 to 15 years, categorized by diagnosis: AD/HD (n = 20), PDD with comorbid AD/HD (PDD+: n = 16), PDD without comorbid AD/HD (PDD−: n = 8), and typically developing (n = 60). We evaluated executive function (EF) through verbal and visuospatial memory tasks, the Go/NoGo task, and the color-word matching Stroop task. We performed a categorical analysis to estimate the effects of the 3 disorders on EF and a dimensional analysis to estimate the effects of symptom scales on EF. We found that the AD/HD and PDD+ subjects had negative effects on verbal working memory and intra-individual response variability. The severity of these impairments was positively correlated with the inattentiveness score. The subjects with a PDD+ or PDD− diagnosis had poorer scores on interference control; the severity of this impairment was correlated with the PDD symptom score. Impairments in visuospatial working memory were detected in the AD/HD and PDD− groups but not in the PDD+ group. Impairments in inhibition of the pre-potent response were noted in all 3 categories. AD/HD and PDD share neuropsychological features, though each disorder has a specific impairment pattern. Our findings partially support the idea that AD/HD and PDD are on a spectrum.

Key words: attention deficit/hyperactivity disorder, pervasive developmental disorder, executive function, working memory, color-word matching Stroop task

Although the current Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) [1] does not allow the diagnosis of co-morbid attention deficit/hyperactivity disorder (AD/HD) in patients with pervasive developmental disorder (PDD), the symptoms of AD/HD and those of PDD often overlap. Therefore, some researchers have proposed that the diagnosis of AD/HD be permitted in PDD patients [2, 3].

The neuropsychological bases of AD/HD and PDD

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have been investigated by numerous researchers. Many previous studies have shown that inhibition, planning, and working memory functions are impaired in individuals with AD/HD [4, 5]. Impairment of the inhibitory function has long been considered a primary neuropsychological defect in AD/HD [6]. Meta-analytic studies have reported that impairment of the inhibitory function had a larger effect than that of other impairments in executive functions [4]. However, in the purely inattentive type of AD/HD, a relationship between symptoms and impairment in working memory was reported [7].

Similarly, many researchers have reported impaired flexibility and planning functions in individuals with PDD [8]. With regard to the inhibitory function, some studies showed that inhibition of the pre-potent response was impaired in PDD patients. However, other studies showed no definitive abnormalities in interference control functions, as examined by the Stroop task and other similar tasks [9]. There are several reports related to the impaired spatial working memory in PDD patients, but the results of previous studies were not consistent in regard to verbal working memory [10–12].

The disturbance in executive functions has attracted a significant amount of research attention. Considering the significant overlap between the symptoms of AD/HD and those of PDD, the symptoms of these 2 conditions may arise from dysfunctions in executive functions that are common to both conditions, as well as some disorder-specific dysfunctions. Although some studies have investigated the differences in the executive function profiles among children with AD/HD, children with PDD and typically developing children, the results have been inconsistent [13–18]. One cause of this inconsistency may be that the co-morbidity of AD/HD in PDD patients was not considered in most studies. Only a few studies considered AD/HD and PDD to be on the same disease continuum and took AD/HD-related symptoms in PDD patients into consideration [19].

This study focused on the symptom overlap between AD/HD and PDD and aimed to clarify the relationship between these 2 disorders by investigating the similarities and differences in their neuropsychological features, with a focus on inhibitory and working memory functions.

Subjects and Methods

The subjects were Japanese boys from 6 to 15 years of age with normal intelligence: 20 boys with AD/HD, 24 with PDD, and 60 typically developing (TD) boys as the control group. Since previous studies showed a gender difference in some neuropsychological aspects such as inhibitory control [20], studying boys and girls separately is desirable as it enables better interpretation of results. In this study, we focused on boys. The 2 patient groups had been scored on the Wechsler Intelligence Scale for Children-III (WISC-III, Japanese version: Nihon Bunkakagakusya Ltd., Tokyo, Japan) within a year prior to this study, and all members of each patient group had full-scale IQ (FIQ) scores of 80 or higher. Patients with epilepsy, cerebral palsy, severe visual impairment, and past history of severe central nervous system infections or cerebral vascular diseases were excluded.

We recruited subjects with AD/HD or PDD from among the patients who visited the Okayama University Hospital clinic treating developmental and behavioral problems from April 2007 to March 2011. The diagnoses of AD/HD and PDD were made by experienced child neurologists based on the criteria of the DSM-IV after one to three 90-min sessions with the patients and their parents. As a condition of diagnosing PDD not otherwise specified (PDD-NOS), according to the DSM-IV the patients should have one or more applicable items in at least 1 of 3 domains of autism diagnostic criteria: (1) qualitative impairment in social interaction, (2) qualitative impairments in communication, and (3) restricted, repetitive, and stereotyped patterns of behavior, interests, and activities.

In the patients diagnosed with PDD, we also evaluated AD/HD-related symptoms according to the DSM-IV. The PDD group ($n = 24$) consisted of 3 boys with autistic disorder, 3 with Asperger's disorder, and 18 with PDD not otherwise specified (NOS). Sixteen of these 24 patients (3 with autistic disorder, 2 with Asperger's disorder, and 11 with PDD-NOS) met the AD/HD diagnostic criteria.

When diagnosing AD/HD, we also evaluated PDD-related symptoms based on the DSM-IV. If a patient could be diagnosed as having PDD, we gave priority to the diagnosis of PDD over the diagnosis of AD/HD. The AD/HD group ($n = 20$) consisted of 4 boys with combined-type AD/HD and 16 with predominantly

inattentive type. There were no patients with predominantly hyperactive-impulsive type AD/HD.

The TD group consisted of 60 healthy boys attending elementary schools or junior high schools in Okayama prefecture. They participated in this study as volunteers. We confirmed that they had no history of developmental or behavioral problems by means of a parent-reported questionnaire at the time of participation. TD boys were excluded when their scores on the Autistic Spectrum Screening Questionnaire, Japanese version (ASSQ-R) or the revised AD/HD rating scale (AD/HD-RS) were outliers.

If patients were prescribed methylphenidate (MPH), we had the patients not take the MPH for 24 h before they underwent the neuropsychological tests. We did not restrict other medications. Written informed consent was obtained from all participants and/or their parents at the time of this study. After participating in this study, all subjects received a book coupon as an expression of our gratitude. This study was approved by the Ethical Committee of the Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences.

Neuropsychological tasks. We administered 5 types of memory tasks and 2 types of inhibition tasks to each subject. To evaluate memory function in detail, we used 3 verbal memory tasks and 2 visuospatial memory tasks. One of the verbal tasks and one of the visuospatial tasks were relatively simple passive tasks, and the remaining memory tasks were dual tasks involving both storage and active processing components of memory. Of the 2 inhibition tasks, one assessed inhibition of the pre-potent response and the other assessed interference control. All tasks other than the digit span test were prepared using E-Prime 1.0 neuropsychological software (Psychology Software Tools, Inc., Sharpsburg, PA, USA) and were administered on a laptop computer with a 12-inch LCD touch screen panel (Lenovo Thinkpad x60 tablet). Subject responses were collected using a stylus pen attached to the notebook computer or the buttons on a Serial Response Box (SR Box), which was included with the E-Prime software package. Each subject was examined in a quiet room while he was seated on a chair. The notebook computer and the SR Box were placed in front of the subject.

1. Digit span task

As one of the verbal memory tasks, we used the digit span subtest of the WISC-III. Forward span was administered as a simple passive task, and backward span as a complex active task. If a subject had been given the WISC-III within 1 year, we used the digit span score from the previous test session in this study.

2. Reading span test (RST)

As another measure of verbal working memory, the Reading Span Test (RST) [21] was administered. We prepared our own age-appropriate sentences for the RST. The "target word" was placed at random positions in the stimulus sentences. The subject was instructed not only to read each sentence aloud but also to memorize a target word underlined in red. Several sentences were presented one after another in a set. After reading all of the sentences in a set, the subject was asked to recall all of the target words included in the set. The span level indicated the number of sentences in each set. This started at 2 and could increase to as high as 5. When a subject passed 3 out of 5 trials at one span level, he proceeded to the next span level. Every time a subject passed a span level, he received 1 point. If a subject gave 2 correct answers out of 5 trials, he received 0.5 point at that span level. The evaluated score was the span score, defined as the sum of these points (0 to 5 points).

3. Visuospatial span task (VST)

To measure visuospatial short-term memory, we used the visuospatial span task (VST) [22]. Circles (memory stimuli) were presented one at a time in a 4×4 matrix on the computer screen. Each stimulus was displayed for 2 s on the screen. After all stimuli in each trial were presented, the subject was instructed to touch the locations in which these memory stimuli had appeared in an empty matrix on the touch screen, using a stylus pen. The span level indicated the number of circles in each set. This started at 2, increased after 2 trials, and ranged up to a maximum of 9. The test terminated when the subject erred in both trials at a particular span level. The evaluated score was the span score, defined as the highest span level in which the subject passed at least one trial (0 to 9 points).

4. Visuospatial working memory test (VWT)

To measure visuospatial working memory, we used the visuospatial working memory test (VWT) [23]. In this complex dual task, the subject was presented with 3 circles serially in contiguous cells in a 4×4 matrix and asked to immediately make an alignment

judgment in which they had to decide whether the positions of the 3 circles were along the same line. After several alignment judgment tasks, the subject was directed to recall the position of the last circles in each set. The span level indicates the number of alignment judgment tasks in each set. When a subject passed 3 out of 5 trials at the same span level, that subject proceeded to the next span level. The span level started at 2 and could increase as high as 5. The evaluated score was the span score, defined as the highest span level in which the subject passed 3 out of 5 trials (0 to 5 points).

5. Go/NoGo task (Go/NoGo)

To examine inhibition of the pre-potent response, we used the Go/NoGo task [24]. Three pictures were repeatedly presented at random on the screen. One of the 3 was the "NoGo" stimulus, and the other 2 were the "Go" stimuli. Each stimulus was displayed for 500 ms followed by a random interval (blank screen) that was either 1,000, 1,500, or 2,000 ms. This task consisted of 3 blocks, and each block consisted of 100 trials. The subject took a 10-sec break between each block. Forty-five out of 300 stimuli were "NoGo" stimuli. The subject was instructed to push the button as fast as possible when a "Go" stimulus was presented, and not to respond to a "NoGo" stimulus.

The evaluated scores were the rate of omission errors (% omission), the rate of commission errors (% commission), the mean reaction time (mean RT) to the Go stimulus, and the coefficient of variation (CV). The CV was calculated according to the following formula:

(standard deviation of RT to Go stimuli)/(mean RT to Go stimuli)

Responses with reaction times of less than 110 ms were considered to be anticipation errors and were omitted from the analysis. Though we intended to program E-Prime to set the window time for response acquisition at 1,400 ms, the actual window time was 500 ms due to an inadequacy of the program.

6. Color-word matching stroop task (cwmStroop)

To examine interference control competence, we used the color-word matching Stroop task (cwmStroop) [25]. Two rows of letters appeared on the screen. Letters in the upper row were printed in red, blue, yellow, or green font. Letters in the lower row consisted of color names in Japanese, namely, "あか [aka] (red)," "あお[ao] (blue)," "きいろ[kiiro] (yellow)," and "みどり[midori] (green)" displayed in black font. The letters in the lower row were presented 100 ms after those in the upper row. Subjects were required to judge whether the font color of the letters in the upper row corresponded to the color word in the lower row, and pushed one of 2 buttons ("1" for yes, "2" for no) as fast as possible. These stimuli were presented for a maximum of 4 sec until a subject responded.

For incongruent trials, the top row consisted of the color names printed in different colors. For congruent trials, the top row consisted of the color names printed in the same color. For the neutral condition, the top row consisted of "XXX." This task consisted of 4 blocks, with each block consisting of 30 trials (10 trials in each of the 3 conditions). After each trial, a blank screen was displayed for 100 ms. The subject took a 30-sec break between each block. In half of the trials in each condition, the color of the letters in the upper row corresponded to the color names in the lower row. The evaluated scores were the ratio of correct answers and the mean RT in the incongruent condition.

Questionnaires. We asked the parents of all participants to fill out 3 questionnaires: the Autistic Spectrum Screening Questionnaire, Japanese version (ASSQ-R) [26, 27], the AD/HD Rating Scale-Revised (AD/HD-RS-R), and our original questionnaire on problems with vision or hearing and past history of diseases or developmental problems. The ASSQ-R is composed of 27 questions pertaining to behavioral problems that are common among patients with PDD. Each item is rated on a 3-point scale, ranging from 0 (normal) and 1 (slightly abnormal) to 2 (definitely abnormal). The total ASSQ-R score ranges from 0 to 54 points.

For the AD/HD-RS-R, we translated the original AD/HD Rating Scale-IV for parents [28] into Japanese, and added some typical examples of abnormal behavior related to each item on the questionnaire to help parents answer. The AD/HD-RS-R is composed of nine items related to inattention and nine items related to hyperactivity and impulsivity. Each item is rated on a 4-point scale, ranging from 0 (never or rarely) to 3 (very often). The total AD/HD-RS-R score ranges from 0 to 54 points and includes an inat-

tention score (0 to 27 points) and a hyperactivity/impulsivity score (0 to 27 points).

Data analysis. We analyzed the relations between the clinical symptoms and the scores on our test battery using 2 approaches: the categorical approach and the dimensional approach. In the categorical approach, the participants were divided into 4 groups: PDD children with AD/HD symptoms that met the DSM-IV criteria of AD/HD (PDD+), PDD children without AD/HD symptoms (PDD−), children with AD/HD only (AD/HD), and TD children. Each disorder category was defined as a dummy variable; namely, a subject was assigned a value of 1 if he belonged to the particular disorder category (AD/HD, PDD+, PDD−) and 0 if he did not. All 3 of these variables were 0 in TD (the control group). We performed a standardized multiple linear regression analysis with these 3 dummy variables and age as independent variables and the scores of each task as dependent variables.

We used a one-way analysis of variance (ANOVA) to compare mean age among the 4 groups and to compare mean IQs among the 3 patient groups (AD/HD, PDD+, and PDD−), followed by *t*-test with the Bonferroni correction as a post-hoc multiple comparison.

In the dimensional approach, we used the number of items corresponding to the clinical symptoms listed in the DSM-IV diagnostic criteria of AD/HD or autistic disorder as a symptom scale. The symptom scale for AD/HD consists of 2 parts: a scale of inattentive symptoms and a scale of hyperactive/impulsive symptoms. We performed a standardized multiple linear regression analysis with the age of subjects and the 3 symptom scales (inattentive, hyperactive/impulsive, PDD) as independent variables and the scores of each task as dependent variables. For the TD group, we did not clinically evaluate behavior based on the DSM-IV. Instead, we calculated 3 symptom scales based on the AD/HD-RS-R and ASSQ-R scores. Because 9 inattentive symptoms are listed in the DSM-IV and the maximum inattention score on the AD/HD-RS-R is 27, the scale of inattentive symptoms was calculated according to the following formula:

$$9 \times (\text{inattention score of AD/HD-RS-R})/27$$

In the same way, the scale of hyperactive/impulsive symptoms was calculated according to the following formula:

$$9 \times (\text{hyperactivity/impulsivity score of AD/HD-RS-R})/27$$

Because 12 autism symptoms are listed in the DSM-IV and the maximum score on the ASSQ-R is 54, the scale of PDD symptoms was calculated according to the following formula:

$$12 \times (\text{total score of ASSQ-R})/54$$

Each result of these formulas was rounded off to the nearest integer. All statistical analyses were performed using SPSS version 17 for Windows.

Results

The mean and standard deviation (SD) of age, verbal IQ (VIQ), performance IQ (PIQ), and full-scale IQ (FIQ) in each group as well as handedness and details of medication at the time of the present examination are shown in Table 1. There was no significant difference in age among the 4 groups, and no significant difference in VIQ, PIQ, and FIQ among the 3 patient groups. Additionally, the mean, median, and range of the 3 symptom scales (*i.e.*, inattention, hyperactivity/impulsivity, and PDD) of each group are shown in Table 2.

Effects of categorical factors on executive functions. With 3 dummy variables and age as independent variables and the scores of each task as dependent variables, the adjusted coefficients of determination (R^2) and standardized partial regression coefficients (β) of multiple regression equations were calculated and are shown in Table 3.

1. Verbal working memory

No significant effect of diagnostic category on the forward recall scores in the digit span task was found. The AD/HD group showed significantly lower backward recall scores ($\beta = -0.222$, $p = 0.012$), and the PDD+ groups tended to show lower backward recall scores ($\beta = -0.171$, $p = 0.052$).

In the RST, the AD/HD subjects produced significantly lower span scores ($\beta = -0.220$, $p = 0.010$), as did the PDD+ subjects ($\beta = -0.266$, $p = 0.002$).

2. Visuospatial working memory

Table 1 Chronological ages, medication, and IQs of the subjects

	AD/HD	PDD+	PDD−	TD
N (Left-handed)	20 (1)	16 (2)	8 (0)	60 (4)
Age (years)	10.3 ± 2.1	9.7 ± 1.9	11.2 ± 2.4	10.1 ± 2.4
MPH	7	5	0	0
SSRI	1	0	1	0
Antipsychotics	1	1	2	0
VIQ	95.7 ± 9.8	94.4 ± 8.7	94.9 ± 9.5	not done
PIQ	102.1 ± 10.2	94.3 ± 9.8	95.8 ± 9.3	not done
FIQ	98.7 ± 8.7	93.9 ± 8.4	95.0 ± 7.8	not done

AD/HD, attention deficit/hyperactivity disorder; PDD+, pervasive developmental disorder with comorbid AD/HD; PDD−, pervasive developmental disorder without comorbid AD/HD; TD, typical development; MPH, methylphenidate; SSRI, selective serotonin reuptake inhibitors; VIQ, verbal IQ; PIQ, performance IQ; FIQ, full-scale IQ.

Table 2 Symptom scale scores of each group

Symptom scales		AD/HD	PDD+	PDD−	TD
inattentive	mean	7.3	7.1	2.8	1.2
	median	7.0	7.0	2.5	1.0
	range	6.0–9.0	6.0–9.0	0–5.0	0–3.7
hyperactive/impulsive	mean	3.1	3.5	0.9	0.6
	median	2.5	3.5	0.5	0.3
	range	0–9.0	0–7.0	0–3.0	0–3.3
PDD	mean	0.6	4.6	4.0	0.6
	median	0	4.0	3.5	0.2
	range	0–3.0	2.0–9.0	3.0–6.0	0–2.2

AD/HD, attention deficit/hyperactivity disorder; PDD, pervasive developmental disorder; PDD+, pervasive developmental disorder with comorbid AD/HD; PDD−, pervasive developmental disorder without comorbid AD/HD; TD, typical development.

On the VST, the boys with AD/HD had significantly lower span scores ($\beta = -0.178$, $p = 0.045$). A tendency for lower span scores on the VST was also observed in the PDD+ group ($\beta = -0.162$, $p = 0.068$) and the PDD− group ($\beta = -0.164$, $p = 0.063$).

On the VWT, the boys with AD/HD had significantly lower span scores ($\beta = -0.188$, $p = 0.01$), as did the children with PDD− ($\beta = -0.200$, $p = 0.006$). The PDD+ group tended to have lower span scores ($\beta = -0.137$, $p = 0.057$).

3. Inhibition of the pre-potent response and interference control

With respect to the Go/NoGo task, the subjects with AD/HD ($\beta = 0.282$, $p = 0.005$), PDD+ ($\beta = 0.239$, $p = 0.016$), or PDD− ($\beta = 0.233$, $p = 0.018$) made significantly more commission errors. However, the diagnostic category had no effect on the percentage of omission errors. The mean RT tended to be shorter in the AD/HD group ($\beta = -0.167$, $p = 0.066$) and the PDD+ group ($\beta = -0.174$, $p = 0.056$). The CV was significantly higher in the AD/HD ($\beta = 0.231$, $p = 0.018$) and PDD+ ($\beta = 0.382$, $p < 0.001$) groups.

For the cwmStroop task, the PDD− subjects tended to have a reduced percentage of correct answers in the incongruent condition ($\beta = -0.178$, $p = -0.057$). The subjects with PDD+ showed significantly prolonged mean RTs in the incongruent condition ($\beta = 0.221$, $p = 0.001$).

Effects of symptom scales on executive functions. With the 3 symptom scales (inattentive, hyperactive/impulsive, and PDD) and age as independent variables and the scores of each task as dependent variables, we calculated the adjusted coefficients of determination (R^2) and standardized partial regres-

Table 3 Effects of diagnostic categories on executive functions

Dependent variables	Adjusted R^2	Partial regression coefficients (β)			
		Age	group		
			AD/HD	PDD+	PDD−
Digit span					
Forward recall	0.357**	0.598**	0.035	−0.125	−0.053
Backward recall	0.275**	0.498**	−0.222*	−0.171#	−0.080
RST					
Span score	0.356**	0.538**	−0.220**	−0.266*	−0.094
VST					
Span score	0.265**	0.502**	−0.178*	−0.162#	−0.164#
VWT					
Span score	0.513**	0.707**	−0.188**	−0.137#	−0.200**
Go/NoGo					
% commission	0.095**	−0.030	0.282**	0.239*	0.233*
% omission	0.462**	−0.687**	−0.015	0.056	−0.004
Correct mean RT	0.230**	−0.467**	−0.167#	−0.174#	−0.038
Correct CV	0.122**	0.008	0.231*	0.382**	0.083
cwmStroop					
Incongruent accuracy	0.172**	0.419**	0.006	−0.118	−0.178#
Incongruent mean RT	0.631**	−0.766**	0.002	0.221*	0.102

**$p < 0.01$, *$p < 0.05$, #$p < 0.10$

R^2, coefficient of determination; RST, reading span task; VST, visuo-spatial span task; VWT, visuo-spatial working memory test; RT, reaction time; CV, coefficient of variation.

sion coefficients (β) of multiple regression equations; the results are shown in Table 4.

1. Verbal working memory

In the digit span task, no significant effect of any of the 3 symptom scales on forward recall scores was found. In contrast, negative associations were noted between the score on the inattentive symptom scale and the backward recall score on the digit span task as well as the span score in the RST. As the inattentive symptom scale score increased, the backward recall score on the digit span task ($\beta = -0.335$, $p = 0.01$) and the span score in the RST ($\beta = -0.408$, $p = 0.001$) decreased significantly. The other 2 symptom scales (hyperactive/impulsive and PDD) had no effect on the backward recall score or the span score in the RST.

2. Spatial working memory

No significant effect of any of the 3 symptom scales on the span score of the VST or the VWT was found.

3. Inhibition of the pre-potent response and interference control

Our results indicated a positive association between the inattentive symptom scale score and the CV in the Go/NoGo task. As the inattentive symptom scale score increased, the CV increased significantly ($\beta = 0.351$, $p = 0.015$). In addition, as the inattentive symptom scale score increased, the % commission in the Go/NoGo task tended to increase ($\beta = 0.248$, $p = 0.094$). No significant effect of the inattentive symptom scale on the other scores in the Go/NoGo task was noted. There was no significant effect of the hyperactivity/impulsivity symptom scale or the PDD-related symptom scale on the scores in the Go/NoGo task.

No significant effect of the inattentive or hyperactivity/impulsivity symptom scale on the scores in the cwmStroop task was noted. We found a positive association between the PDD-related symptom scale score and the mean RT in the cwmStroop task. As the PDD-related symptom scale score increased, the mean RT in the incongruent condition increased significantly ($\beta = 0.176$, $p = 0.009$).

Table 4 Effects of symptom scales on executive functions

Dependent variables	Adjusted R^2	Partial regression coefficients (β)			
		Age	Symptom scale		
			inattentive	hyperactive/impulsive	PDD
Digit span					
Forward recall	0.346**	0.609**	−0.063	0.048	−0.072
Backward recall	0.280**	0.507**	−0.335*	0.091	0.079
RST					
Span score	0.373**	0.564**	−0.408**	0.165	−0.038
VST					
Span score	0.235**	0.451**	−0.195	0.048	−0.012
VWT					
Span score	0.484**	0.683**	−0.179	0.000	−0.029
Go/NoGo					
% commission	0.053	−0.007	0.248#	−0.003	0.099
% omission	0.466**	−0.711	0.116	−0.126	−0.005
Correct mean RT	0.224**	−0.478**	−0.102	−0.093	−0.036
Correct CV	0.110*	−0.016	0.351*	−0.094	0.154
cwmStroop					
Incongruent accuracy	0.151**	0.426**	−0.058	0.150	−0.099
Incongruent mean RT	0.630**	−0.774**	0.112	−0.033	0.176**

**$p < 0.01$, *$p < 0.05$, #$p < 0.10$

R^2, coefficient of determination; RST, reading span task; VST, visuo-spatial span task; VWT, visuo-spatial working memory test; RT, reaction time; CV, coefficient of variation.

Discussion

Here we investigated executive functions, focusing on working memory and inhibition control, both of which have been reported to be associated with AD/HD [4]. In addition to subjects with AD/HD, we also evaluated the symptoms of AD/HD according to DSM-IV criteria in subjects with PDD. We classified the subjects with PDD into a PDD+ group with AD/HD symptoms and a PDD− group without. In this way, we could investigate the relationships between executive functions and AD/HD-related symptoms in subjects with PDD as well as those with AD/HD.

Verbal working memory was impaired in the subjects with AD/HD symptoms (*i.e.*, the AD/HD and PDD+ groups). Further, the more inattentive symptoms a subject had, the more likely it was that the subject's verbal working memory was disturbed. These results indicated a relationship between AD/HD-related symptoms (inattention scores) and impairment of verbal working memory. Considering that a previous study showed a high co-morbidity of reading disability in patients with AD/HD [29], it is necessary to take into account the possible effect of reading ability on the RST scores. In the RST, a subject's ability to remember words is expected to decrease when the subject has reading difficulty. However, in the present study the score on the backward digit span task, which does not involve reading letters, was also found to be correlated with AD/HD symptoms or the diagnosis of AD/HD. We therefore suspect that the inattentive symptoms themselves are related to impairment of the verbal working memory function. Other recent studies have also shown a relationship between verbal working memory and inattention [30].

As for spatial working memory tasks, the boys diagnosed with AD/HD had significantly lower span scores on both the VST and the VWT. The boys with the diagnosis of PDD− had significantly lower span scores on the VWT, but only marginally lower span

scores on the VST. In contrast, the boys with PDD+ (*i.e.*, PDD+AD/HD) showed only slightly lower span scores on both the VST and VWT. Willcutt *et al.* performed a meta-analysis regarding spatial working memory in patients with AD/HD [4]. Six of the 8 studies analyzed indicated that patients with AD/HD had significantly lower scores than those in the control group, and the 6 studies showed a medium weighted mean effect size. These studies yielded results similar to ours, and thus it is likely that AD/HD is related to the impairment of spatial working memory.

Several research groups have studied spatial working memory in patients with PDD using the spatial working memory task from the Cambridge Neuropsychological Test Automated Battery (CANTAB) [17, 19, 31, 32]. With the exception of the study by Happe *et al.* [17], the studies found a significant relation between PDD and impairment of spatial working memory. Among them, Sinzig *et al.* [19] adopted the same diagnostic categories that we used. Their findings indicated that their 2 patient groups (corresponding to our AD/HD and PDD− groups) showed more errors than the control group, but the remaining patient group (corresponding to our PDD+ group) showed no significant abnormalities. In our study and theirs, a diagnosis of PDD+ did not result in significantly lower VST or VWT scores. Thus, it seems likely that the degree of spatial working memory impairment in the present PDD+ group is milder than that in the AD/HD group or the PDD− group. Although the data are difficult to interpret, it is interesting to note that the present subjects with PDD+ (who have symptoms of both AD/HD and PDD) showed milder impairment of spatial working memory than the other 2 groups. The pathological conditions of AD/HD and PDD may interact with each other in a complicated manner.

The % commission in the Go/NoGo task is a measure of the inhibitory function of the pre-potent response. Several studies of Go/NoGo task scores among typically developing children and patients with AD/HD or PDD have been reported [14, 17, 19]: all of them found significantly higher rates of commission errors or false alarms in patients with AD/HD, but their results with regard to PDD were not compatible. In our study, a diagnosis in any of the 3 categories, AD/HD, PDD+, or PDD−, significantly increased the % commission. The standardized partial regression coefficients were fairly similar among the 3 diagnostic categories as well. Thus, impairment of the inhibitory function for the pre-potent response is likely to be commonly associated with both AD/HD and PDD. Many previous studies have reported that patients with AD/HD show high rates of omission errors [4], but in the present study neither the AD/HD diagnosis nor the PDD diagnosis had any effect on the % omission. Because of the short time window for response acquisition in our Go/NoGo task, responses with reaction times longer than 500 ms were erroneously judged as omission errors. This may have led to our negative result.

The reaction time CV is one of the indexes used to measure intra-individual variability of responses. The Go/NoGo task and the continuous performance test have been widely used to examine the high levels of intra-individual variability in patients with AD/HD [33]. In the present study, the CV was higher in both the AD/HD group and the PDD+ group compared to the TD group, and as the inattentive symptom scale score increased, the CV increased significantly. This result suggests that inattentive symptoms may be related to increased intra-individual response variability.

Regarding the cwmStroop task, the PDD+ subjects showed significantly prolonged mean RTs, and the PDD− subjects achieved low scores in the incongruent condition, with marginal significance. In the dimensional approach, as the PDD-related symptom scale scores increased, the mean RTs in the incongruent condition increased significantly. These results indicate that an impairment of the cognitive process tapped by the cwmStroop task may be related to symptoms of PDD. However, most previous studies that used the classical Stroop task found no impairment in interference control in patients with PDD [9].

In patients with AD/HD, on the other hand, many previous studies using the classical Stroop task found lower scores and longer reaction times [34]. In the cwmStroop task adopted in the present study, subjects matched 2 attributes of different stimuli. In contrast, subjects performing the classical Stroop task generate a verbal response to match one attribute of a stimulus. Consequently, the response preparation process and interference control process are affected mutually and are not separable in the classical Stroop

task, whereas the 2 processes are separated in the cwmStroop [35]. CwmStroop is more suitable to purely assess interference control ability, because the results of the classical Stroop task reflect both interference control and motor preparation and the inhibition of motor responses. This may be the basis of the discrepancy between the results of our study and those of previous studies using the classical Stroop task.

Adams *et al.* reported that patients with PDD showed significant impairment on a modified flanker resistant to distractor task that assesses interference control function; these patients showed intact prepotent response inhibition on the stop-signal response inhibition task [36]. Those results and our present findings indicate that impairment of interference control at a conceptual level in patients with PDD may play an important role in the cognitive processes of patients with PDD.

The relationships between scores on the test batteries and our 3 diagnostic categories are shown in Fig. 1. The patients with AD/HD symptoms (*i.e.*, the AD/HD and PDD+ groups) showed impairments in verbal working memory and increased intra-individual variability. On the other hand, the patients with PDD symptoms (the PDD and PDD+ groups) showed impairments in interference control. Accordingly, impairments in response inhibition were common features in AD/HD and PDD traits.

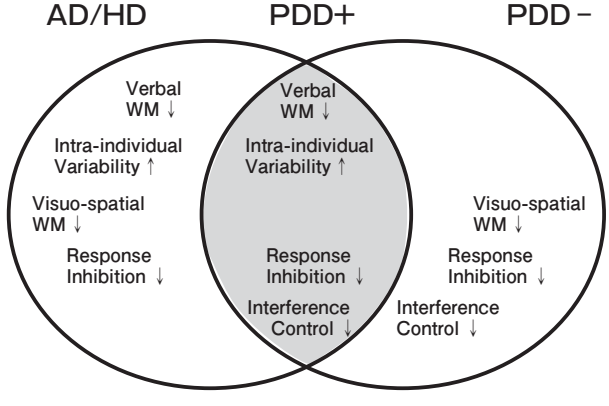

Fig. 1 Summary of executive function deficits in boys with AD/HD (n = 20), PDD with comorbid AD/HD (PDD+: n = 16), PDD without comorbid AD/HD (PDD−: n = 8), and in the typically developing (TD; n = 60) group. Impairment of verbal working memory and intra-individual variability were traits specific to the AD/HD category, while that of interference control was specific to PDD. Impairment of visuospatial working memory and response inhibition, on the other hand, were common features of both AD/HD and PDD.
WM, working memory.

From a neuropsychological perspective, AD/HD and PDD have some common features, though each disorder has a specific impairment pattern, and PDD+ often shows overlap with some characteristics of PDD and some of AD/HD. However, it seems that PDD+ is not a simple combination of AD/HD and PDD in terms of cognitive functions. Impairments of visuospatial working memory were observed in the present AD/HD and PDD groups but not in the PDD+ groups. Further studies focused on the other cognitive functions and the symptoms of individuals with PDD+ are required to clarify the details of this interesting group.

There are some study limitations. We examined only working memory and inhibitory functions. Other executive functions such as "planning," which could relate to both AD/HD and PDD [4, 8], and "set shifting," which could relate to PDD [8], should be researched in the future using both categorical and dimensional approaches. Secondly, many of our subjects were being treated with medications. We restricted the use of methylphenidate (MPH) for 24 h before the neuropsychological testing, because MPH is thought to improve the executive functions of patients with AD/HD [37]. The neuropsychological effects of risperidone (RIS), which is often prescribed to patients with PDD, remain unclear, though it was reported that RIS improved the function of working memory in patients with PDD [38]. The neuropsychological effects of selective serotonin reuptake inhibitors are also unknown. In this study, although we eliminated the short-term effects of MPH, the possibility remained that executive functions may have been affected by other medications.

References

1. American psychiatric association: Diagnostic and statistical manual of mental disorders DSM-IV-TR 4th ED, American Psychiatric Press, Washington, DC, (2000).
2. Hattori J, Ogino T, Abiru K, Nakano K, Oka M and Ohtsuka Y: Are pervasive developmental disorders and attention-deficit/hyperactivity disorder distinct disorders? Brain Dev (2006) 28: 371–374.
3. Murray MJ: Attention-deficit/hyperactivity disorder in the context of autism spectrum disorders. Curr Psychiatry Rep (2010) 12: 382–388.
4. Willcutt EG, Doyle AE, Nigg JT, Faraone SV and Pennington BF:

Validity of the executive function theory of attention-deficit/hyperactivity disorder: a meta-analytic review. Biol Psychiatry (2005) 57: 1336–1346.
5. Homack S and Riccio CA: A meta-analysis of the sensitivity and specificity of the Stroop color and word test with children. Arch Clin Neuropsychol (2004) 19: 725–743.
6. Barkley RA: Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. Psychol Bull (1997) 121: 65–94.
7. Kofler MJ, Rapport MD, Bolden J, Sarver DE and Rainker JS: ADHD and working memory: the impact of central executive deficits and exceeding storage/rehearsal capacity on observed inattentive behavior. J Abnorm Child Psychol (2010) 38: 149–161.
8. Hill EL: Executive dysfunction in autism. Trends Cogn Sci (2004) 8: 26–32.
9. O'Hearn K, Asato M, Ordaz S and Luna B: Neurodevelopment and executive function in autism. Dev Psychopathol (2008) 20: 1103–1132.
10. Bennetto L, Pennington BF and Rogers SJ: Intact and impaired memory functions in autism. Child Dev (1996) 67: 1816–1835.
11. Williams DL, Goldstein G, Carpenter PA and Minshew NJ: Verbal and spatial working memory in autism. J Autism Dev Disord (2005) 35: 747–756.
12. Gabig CS: Verbal working memory and story retelling in school-age children with autism. Lang Speech Hear Serv Sch (2008) 39: 498–511.
13. Ozonoff S and Jensen J: Brief report: specific executive function profiles in three neurodevelopmental disorders. J Autism Dev Disord (1999) 29: 171–177.
14. Nyden A, Gillberg C, Hjelmquist E and Heimann M: Executive function/attention deficits in boys with Asperger syndrome, attention disorder and reading/writing disorder. Autism (1999) 3: 213–228.
15. Geurts HM, Verte S, Oosterlaan J, Roeyers H and Sergeant JA: How specific are executive functioning deficits in attention deficit hyperactivity disorder and autism? J Child Psychol Psychiatry (2004) 45: 836–854.
16. Goldberg MC, Mostofsky SH, Cutting LE, Mahone EM, Astor BC, Denckla MB and Landa RJ: Subtle executive impairment in children with autism and children with ADHD. J Autism Dev Disord (2005) 35: 279–293.
17. Happe F, Booth R, Charlton R and Hughes C: Executive function deficits in autism spectrum disorders and attention-deficit/hyperactivity disorder: examining profiles across domains and ages. Brain Cogn (2006) 61: 25–39.
18. Johnson KA, Robertson IH, Kelly SP, Silk TJ, Barry E, Daibhis A, Watchorn A, Keavey M, Fitzgerald M, Gallagher L, Gill M and Bellgrove MA: Dissociation in performance of children with ADHD and high-functioning autism on a task of sustained attention. Neuropsychologia (2007) 45: 2234–2245.
19. Sinzig J, Morsch D, Bruning N, Schmidt MH and Lehmkuhl G: Inhibition, flexibility, working memory and planning in autism spectrum disorders with and without comorbid ADHD-symptoms. Child Adolesc Psychiatry Ment Health (2008) 2: 4.
20. Kochanska G, Murray K, Jacques TY, Koenig AL and Vandegeest KA: Inhibitory control in young children and its role in emerging internalization. Child Dev (1996) 67: 490–507.
21. Osaka M and Osaka N: Working memory capacity related to reading: measurement with the Japanese version of reading span test. Shinrigaku Kenkyu (Tokyo) (2004) 65: 339–345 (in Japanese).
22. Westerberg H, Hirvikoski T, Forssberg H and Klingberg T: Visuospatial working memory span: a sensitive measure of cognitive deficits in children with ADHD. Child Neuropsychol (2004) 10: 1 55–161.
23. Mammarella IC and Cornoldi C: Difficulties in the control of irrelevant visuospatial information in children with visuospatial learning disabilities. Acta Psychol (Amst) (2005) 118: 211–228.
24. Booth JR, Burman DD, Meyer JR, Lei Z, Trommer BL, Davenport ND, Li W, Parrish TB, Gitelman DR and Mesulam MM: Neural development of selective attention and response inhibition. Neuroimage (2003) 20: 737–751.
25. Schroeter ML, Zysset S, Wahl M and von Cramon DY: Prefrontal activation due to Stroop interference increases during development--an event-related fNIRS study. Neuroimage (2004) 23: 1317–1325.
26. Ehlers S, Gillberg C, Wing LS: A screening questionnaire for Asperger syndrome and other high-functioning autism spectrum disorders in school age children. J Autism Dev Disord (1999) 29: 129–141.
27. Ii T, Hayashi E, Hirose Y and Tojo Y: The high-functioning autism spectrum screening questionnaire. Reports of Grants-in-Aid for Scientific Research (B) (2) (#13410042) (2003) (in Japanese).
28. DuPaul GJ, Power TJ, Anastopoulos AD and Reid R: ADHD Rating Scale-IV. Checklists, norms, and clinical interpretation, The Guilford Press, New York, (1998).
29. Germano E, Gagliano A and Curatolo P: Comorbidity of ADHD and dyslexia. Dev Neuropsychol (2010) 35: 475–493.
30. Rogers M, Hwang H, Toplak M, Weiss M and Tannock R: Inattention, working memory, and academic achievement in adolescents referred for attention deficit/hyperactivity disorder (ADHD). Child Neuropsychol (2011) 17: 444–458.
31. Landa RJ and Goldberg MC: Language, social, and executive functions in high functioning autism: a continuum of performance. J Autism Dev Disord (2005) 35: 557–573.
32. Steele SD, Minshew NJ, Luna B and Sweeney JA: Spatial working memory deficits in autism. J Autism Dev Disord (2007) 37: 605–612.
33. Klein C, Wendling K, Huettner P, Ruder H and Peper M: Intra-subject variability in attention-deficit hyperactivity disorder. Biol Psychiatry (2006) 60: 1088–1097.
34. Lansbergen MM, Kenemans JL and van Engeland H: Stroop interference and attention-deficit/hyperactivity disorder: a review and meta-analysis. Neuropsychology (2007) 21: 251–262.
35. Zysset S, Muller K, Lohmann G and von Cramon DY: Color-word matching stroop task: separating interference and response conflict. Neuroimage (2001) 13: 29–36.
36. Adams NC and Jarrold C: Inhibition in autism: children with autism have difficulty inhibiting irrelevant distractors but not prepotent responses. J Autism Dev Disord (2012) 42: 1052–1063.
37. Swanson J, Baler RD and Volkow ND: Understanding the effects of stimulant medications on cognition in individuals with attention-deficit hyperactivity disorder: a decade of progress. Neuropsychopharmacology (2011) 36: 207–226.
38. Troost PW, Althaus M, Lahuis BE, Buitelaar JK, Minderaa RB and Hoekstra PJ: Neuropsychological effects of risperidone in children with pervasive developmental disorders: a blinded discontinuation study. J Child Adolesc Psychopharmacol (2006) 16: 561–573.