博士学位論文

Assessment of executive function using the Behavior Rating Inventory of Executive Function (BRIEF) and the Cambridge Neuropsychological Test Automated Battery (CANTAB) in young children with attention deficit/hyperactivity disorder, inattention type

（BRIEF と CANTAB を用いた注意欠如多動性障害不注意優勢型の子どもの実行機能の評価）

平成 25 年

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Assessment of executive function using the Behavior Rating Inventory of Executive Function (BRIEF) and the Cambridge Neuropsychological Test Automated Battery (CANTAB) in young children with attention deficit/hyperactivity disorder, inattention type

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Abstract: Attention deficit/hyperactivity disorder, predominantly inattentive subtype (AD/HD-I) is one of subtypes of AD/HD. Previous studies found that poor academic performance was the most common problem of children with AD/HD-I. Moreover a higher prevalence of substance dependence/abuse disorders and higher percentage experienced neurological disorders were reported in adults with this disorder. However AD/HD-I has a high risk of being overlooked due to the lack of objective measurement. To avoid these problems, it is necessary to find out children with AD/HD-I and start to intervene them early in life. AD/HD is reported to have deficits in executive function (EF), however, there have been no consistent findings regarding the presence and the characteristics of EDF in ADHD-I to date. To clarify EDF of AD/HD-I, we analyzed EF in children with AD/HD-I by using two tests designed to evaluate inhibition and working memory from CANTAB together with the BRIEF, a parent-rated scale. We found significant differences in many outcome measures of these CANTAB tests and most scales of the BRIEF between AD/HD-I and control children, indicating the presence of EDF in AD/HD-I. In addition, correlations between these tools were identified, especially in scales for working memory. We also examined predictors that distinguish AD/HD-I from controls by using discriminant analysis.

In summary, outcome measures of CANTAB and the BRIEF are considered to be useful for determining AD/HD-I in young children.

Introduction

Attention deficit/hyperactivity disorder (AD/HD) is classified into three subtypes: combined type (AD/HD-C), predominantly inattentive subtype (AD/HD-I), and predominantly hyperactive-impulsive type (AD/HD-H)[1]. AD/HD-I is characterized by prominent symptoms of inattention (e.g., failing to pay close attention to details, making careless mistakes in schoolwork, or having difficulty sustaining attention or organizing tasks and play activities) but with less prominent symptoms of hyperactivity and impulsivity. Regarding prevalence, the DSM-IV field trials reported a higher rate of AD/HD-C (55%) compared to AD/HD-I (27%), whereas in population-based studies, AD/HD-I has consistently been found to be the most prevalent of the three AD/HD subtypes[2]. There is consensus among researchers that the rate of AD/HD-H in children is low[2]. Previous studies found that poor academic performance was the most common problem of children meeting the criteria for AD/HD-I[3], and that high inattention strongly predicted lack of a high school diploma at 22–23 years of age[4], and that childhood attention measures predicted academic achievement[5]. In addition, Murphy, Barkley, and Bush reported that young adults with AD/HD-I had a higher prevalence of alcohol and cannabis dependence/abuse disorders and a higher percentage experienced dysthymia, somatization, obsessive-compulsive symptoms, interpersonal sensitivity, depression, hostility, anxiety, paranoid ideation, and psychoticism than controls[6]. This evidence highlights the importance of early detection and proper intervention for children with AD/HD-I. However, without objective measurement, many children with AD/HD-I are overlooked more often than those with AD/HD-C and AD/HD-H.

On the basis of existing literature, AD/HD is being considered cognitively heterogeneous[7]. Sonuga-Barke and Nigg proposed multiple developmental pathways in AD/HD, illustrating the mechanism of symptoms with the delay aversion model[8,9]. Most recently, Sonuga-Barke, Bitsakou, and Thompson proposed an additional hypothesis of temporal processing deficits in AD/HD[10]. Among these hypotheses, the most influential and established is the Executive Dysfunction (EDF) Hypothesis. Executive function (EF) is a broad term that refers to cognitive skills that regulate behavior, cognition, and emotion to attain future goals[11,12]. Klorman et al. suggested that EDF was not recognized in AD/HD-I[13], and Barkley postulated that AD/HD-H and AD/HD-C are associated with EDF, but AD/HD-I is not[14]. However, some researchers found that children with AD/HD-I and AD/HD-C had similar profiles of neuropsychological impairments[15,16]. In addition, Diamond proposed that the core problem of EF in AD/HD-I is in working memory[17], and Schmitz et al. revealed impairments in working memory and inhibition in AD/HD-I subjects[18]. Thus, there have been no consistent findings regarding the presence and the characteristics of EDF in AD/HD-I to date.

Many measures can be used to evaluate EF, including performance-based and parent-rated scales. BRIEF was developed to assess EF from behaviors of daily life in school-aged children and has been used in children with traumatic brain injury, autistic spectrum disorders (ASD), AD/HD, and so on[19]. Jarratt, Riccio, and Siekierski reported significant differences between AD/HD and control groups in all subscales of the BRIEF[20]. Bodnar, Prahme, Cutting, Denckla, and Mahone administered the Tests of Variables of Attention (TOVA) and Conner's Continuous Performance Test-II (Conner's CPT-II) as performance-based measures to assess inhibitory control together with the BRIEF in children and adolescents with AD/HD as well as other conditions, such as disruptive behavioral disorder, reading disorder, and Tourette syndrome[21]. They found that the BRIEF appeared to measure different elements of inhibitory control than those assessed by TOVA and Conner's CPT-II. Ultimately, they concluded that both kinds of measures should be incorporated in the evaluation of EF in children.

CANTAB[22], a computer-administered battery originally developed to diagnose dementia in the aged[23,24], has been used with children because it has the following 4 advantages: (1) even young children are motivated to do many tests, (2) examiners merely following documented instructions do not affect participants' performance, (3) it does not require verbal communication ability, and (4) many outcome measures are integrated and computed automatically. The CANTAB has been used with children with developmental disorders such as ASD and AD/HD. For example, Goldberg et al. used the Stockings of Cambridge (SOC; analogous to the Tower of London Test), Intra-Dimensional/Extra-Dimensional Shift Task (ID/ED; analogous to the Wisconsin Card Sorting Test), and Spatial Working Memory (SWM) test to investigate the specificity of EDF in 8- to 12-year-old children with high-functioning autism or AD/HD as well as controls[25]. No significant differences in SOC or ID/ED among the 3 groups were found. However, children with AD/HD made significantly more errors compared to the control group on the most difficult problems of SWM only. Happé, Booth, Charlton, and Hughes compared the EF of children aged between 8 and 16 years with ASD or AD/HD to that of controls by using the ID/ED, SOC, and SWM[26]. They found significant differences in SWM outcome measures between controls and children with AD/HD aged 8 to 10. No differences were found in ID/ED and SOC among ASD, AD/HD, and control groups.

We focused on AD/HD-I because early detection is often difficult in spite of the burden of the defects children may bear. There were 3 main purposes of the current study. The first was to examine the presence and characteristics of EDF in young children with AD/HD-I by using the CANTAB as a performance-based measure and the BRIEF as a parent-rated scale. As previously mentioned, the presence of EDF in AD/HD-I remains controversial, and specific deficits in EF related to AD/HD-I remain unclear. The second was to evaluate the consistency of the CANTAB and BRIEF data, and the third, to evaluate the effectiveness of these objective measures to detect children with AD/HD-I.

Method

Participants

The clinical group consisted of 10 boys and 9 girls with AD/HD-I (mean age 8.6 ± 1.8 years) who were diagnosed according to the DSM-IV-TR criteria at Osaka University Hospital. The diagnosis was supported by ADHD-Rating Scales (ADHD-RS) for caregivers as well as teachers[27]. The children's intellectual quotients (IQs) were assessed using the Wechsler Intelligence Scale for Children, 3rd version (WISC-III); all of their IQs were greater than 70, and the average Full Scale IQ was 96.6. ADHD-RS revealed high scores for inattention with low scores for hyperactivity, confirming the DSM-IV diagnosis of AD/HD-I. None of the AD/HD-I children had a history of brain trauma or neurological diseases, learning disorder, mental retardation, or comorbidity reported by pediatricians. On the first visit to the hospital, pediatricians interviewed caregivers to obtain relevant information, and they were asked to fill out the BRIEF and ADHD-RS while the children completed the two CANTAB subtasks individually in a quiet room. They started with SWM and then worked on the Stop Signal Task (SST). Later, the children completed the WISC-III.

A sex- and age-matched control group was recruited from the community and consisted of 20 boys and 18 girls with a mean age of 8.8 ± 1.4 years. All of the children in the control group were enrolled in regular classes at local elementary schools; none was reported to have a learning disorder or any history of neurological or mental illness. The assessments for the control group were completed at community centers with the same procedure used for the clinical group. While the children completed the CANTAB, caregivers filled out the BRIEF.

An independent t-test comparing the ages of the clinical group and the control group revealed no significant group difference (p = .624). Demographic information is shown in Table 1.

Table 1: Demographic Characteristics.

Demographic Variables	Clinical	Control
N	19	38
Gender (M/F)	10/9	20/18
Age (years)	8.6± 1.8	8.8±1.4
FIQ (WISC-III)	96.6±15.1	-
ADHD-RS		
Inattention	14.8±7.1	-
Hyperactivity	6.4±4.9	-

*1 FIQ: Full-scale IQ of WISC-III.
*2 The cut-off values of male and female inattention were set at 13–18 and 10–11, respectively.
*3 The cut-off values of male and female hyperactivity were set at 13–15 and 8–11, respectively.

This study was approved by the Institutional Review Board of Osaka University Hospital. Informed consent was obtained from subjects' caregivers before conducting the tests.

Instruments

The CANTAB

Among the 23 subtasks comprising the CANTAB, the SWM and SST were selected for two reasons[22]. First, children at this age are completely able to perform these tasks, whereas the SOC and IED are too difficult for some children. Second, these 2 tasks are designed to assess working memory and inhibition, respectively, which are considered to be the main EF deficits in AD/HD-I[15,17].

SWM is a self-ordered search task that assesses spatial working memory for spatial stimuli. Participants are presented with a number of boxes and are told to find blue tokens hidden beneath one of them. Once a token is found in a box, the same box will not hold a token again. After a participant finds all of the tokens, the next set of boxes is presented. The number of boxes increases from 3 to 4, 6, and then 8. Three primary kinds of outcome measures were used in this study. First, "Between Errors (n boxes)" were recorded when a participant opened a box where a token had already been found in an n-box trial. Between Errors were computed by adding the scores of Between Errors with 4, 6, and 8 boxes. Second, "Within Errors" were recorded when a participant opened an empty box more than twice within a single search sequence. Finally, “Strategy Score” refers to the ability of a participant to search for a token effectively (i.e., beginning a search sequence with a particular box to avoid skipping over it, applying the same search sequence to avoid opening the same box, etc.). Strategy Score was computed only with the 6- and 8-box trials. Higher scores mean that a subject found tokens in a more effective way.

In the SST, a circle initially appeared, followed by an arrow inside the circle 400 ms later. Subjects were then required to press the button in the same direction of the arrow as quickly as possible. In 25% of the trials, an auditory stop signal beep was emitted at various delays following the go stimulus. When the stop signal beep was emitted, the subject is instructed not to press any button. Four basic outcome measures were used in this task. First, a “Direction Error” was recorded when a subject pressed the wrong button. Second, “Proportion of Successful Stops” was calculated as the percentage a subject was able to successfully stop responding after the beep. Third, “Standard Deviation on Correct Reaction Time on GO Trials” (SD on Correct RT on GO Trials) was also calculated. Fourth, the “Stop Signal Delay” (SSD) was measured as the time from the onset of the arrow stimulus to the emission of the stop signal beep. The SSD varies in the trials because the timing of the auditory stop signal changes throughout the test depending on the subject’s past performance. The average time taken by the subjects to successfully inhibit their responses was recorded. Finally, the “Stop Signal Reaction Time” (SSRT) was calculated as follows: SSRT = mean reaction time − SSD. The SSRT refers to the time it takes to internally suppress a response. Raw scores were used to analyze the SWM and SST.

The BRIEF

As in the original version of the BRIEF, the Japanese version contains 86 items; 73 are used to assess 8 clinical scales: Inhibit, Shift, Emotion Control, Initiate, Working Memory, Plan/Organize, Organization of Materials, and Monitor. The first 3 scales combine to form the Behavior Regulation Index (BRI), and the remainder, the Metacognition Index (MI). The Global Executive Composite (GEC) can be obtained by summing scores of all 8 clinical scales[19]. Each question is answered using a 3-point response format: “never,” “sometimes,” or “often.” Results are reported as age- and sex-normalized T-scores, which were used in this study. Higher T-scores indicate more severe EDF.

Data analysis

First, the Mann-Whitney U test was used to test group differences in SWM, SST, and BRIEF. Second, Spearman rank-correlation coefficients were calculated to examine interrelationships among subscales of SWM, SST, and BRIEF. Finally, a discriminant analysis was conducted to predict whether a child has AD/HD-I. Using this method, cross-validation was completed by classifying each case according to functions driven from all cases other than that case. Variables were entered using a step-wise procedure. Predictor variables that were used in this study were the strategy score of SWM, direction errors on stop and go trials, SSRT of the SST, and GEC of the BRIEF. These were chosen because they have consistently distinguished between diagnostic groups and were not correlated significantly each other. All analyses were performed using PASW Statistics v. 18.0 (IBM Japan, Tokyo.).

Results

There were significant differences between the clinical and control groups in Between Errors (total, 4, 6, and 8 boxes; $p < .01$, .05, .01, and .01, respectively), Strategy Score of SWM ($p < .05$), Direction Errors ($p < .01$), and SD Correct RT on GO Trials of SST ($p < .05$: Table 2). However, there were no differences in Within Errors of SWM and Successful Stops, SSD and SSRT of SST between the clinical and control groups.

Table 2: Median (range) by group in CANTAB

		Clinical	Control	p value	
SWM	Within Errors	1 (0-2)	0.5 (0-1)	.230	
	Between Errors	48 (41.5-58)	32 (20-45.25)	.001	**
	Between Errors (4)	1 (0-3)	0 (0-0.75)	.015	*
	Between Errors (6)	14 (11-19)	6.5 (1.25-13)	.003	**
	Between Errors (8)	34 (28-36.5)	24.5 (17-32)	.006	**
	Strategy Score	37 (35-39)	35 (32-37.75)	.028	*
SST	Direction Errors	4 (2-13.5)	1.5 (0.25-4)	.008	**
	Successful Stops	0.54 (0.50-0.60)	0.55 (0.49-0.61)	.525	
	Sd on correct RT on GO	225.75 (192.97-313.23)	179.62 (156.2-231.77)	.034	*
	SSD(50%)	315.78 (225.75-1010.4)	362.17 (284.34-439.53)	.210	
	SSRT	303.1 (238.44-335.57)	267.52 (241.39-316.18)	.370	

Note. Raw score was used. Sd on correct RT on GO trials: Standard deviation on correct RT on GO trials, SSD: Stop Signal Delay, SSRT: Stop Signal Reaction Time Significant differences were determined with the Mann-whitney U test. *p < .05, **p < .01

Table 3 shows that there were highly significant differences of $p < .01$ and $p < .05$ between the clinical and control groups in all of the BRIEF clinical subscales, BRI, MI, and GEC.

Table 3: Median (range) by group in BRIEF

	Clinical	Control	*p* value
Inhibit	48 (42-55)	40 (38-42)	.001 **
Shift	53 (47-63.5)	43 (39-50)	.001 **
Emotion Control	47 (42-49)	40 (36-45)	.012 *
Initiate	61 (47-67.5)	40 (38-49.75)	.000 **
Working Memory	59 (53-64)	41 (38-46.25)	.000 **
Plan/Organize	63 (55-69)	42 (37.25-46)	.000 **
Org.of Materials	56 (46-64.5)	42 (39-48.75)	.000 **
Monitor	62 (52-69.5)	38 (34-50)	.000 **
BRI	48 (46-53)	39 (36-47)	.001 **
MI	62 (51.5-68.5)	39 (35.25-46)	.000 **
GEC	61 (52.5-65)	38 (35-44.5)	.000 **

Note. T score was used. Org. of Materials: Organization of Materials, BRI: Behavior Regulation Index, MI: Metacognition Index, GEC: Global Executive Composite Significant differences were determined with the Mann-whitney U test. $*p < .05$, $**p < .01$

Correlations between subscales of SWM/SST and the BRIEF are presented in Table 4. Among SWM outcome measures, Between Errors was significantly correlated with Shift and Working Memory of BRIEF (r = .270 and .286, respectively, all p's < .05). Between Errors (4) was significantly correlated with Working Memory, Organization of Materials, and Monitor (r = .319, .261, and .271, respectively, all p's < .05). Between Errors (6) was significantly correlated with Working Memory (r = .308, p < .05) and Between Errors (8) was significantly correlated with Emotion Control (r = .267, p < .05). The correlation between Strategy Score and Inhibit was also statistically significant (r = .282, p < .05). In regard to SST outcome measures, Direction Errors was significantly correlated with Inhibit, Emotion Control, Initiate, and Monitor (r = .263, .304, .285, and .307, respectively, all p's < .05). The other subscales of the SST were not correlated with any outcome measures of the BRIEF.

Table 4: Spearman Correlations Between SWM Scales, SST Scales and BRIEF Scales

SWM \ BRIEF	Inhibit	Shift	Emotion Control	Initiate	WM	Plan/ Organize	Org. of Materials	Monitor
Within Errors	.009	.152	.197	.270 *	.204	.113	.259	.058
Between Errors	.223	.270 *	.260	.184	.286 *	.184	.137	.230
Between Errors (4)	.230	.205	.139	.248	.319 *	.214	.261 *	.271 *
Between Errors (6)	.216	.217	.198	.128	.308 *	.170	.140	.202
Between Errors (8)	.187	.230	.267 *	.161	.196	.153	.084	.178
Strategy Score	.282 *	.173	.156	.101	.216	.208	.091	.227
SST \ BRIEF	**Inhibit**	**Shift**	**Emotion Control**	**Initiate**	**WM**	**Plan/ Organize**	**Org. of Materials**	**Monitor**
Direction Errors	.263 *	.248	.304 *	.285 *	.223	.173	.119	.307 *
Successful Stops	-.065	-.089	-.181	-.134	-.083	-.052	.012	-.101
Sd on correct RT on GO tri	.212	.057	-.034	.050	.259	.248	.155	.200
SSD(50%)	-.136	-.122	-.236	-.132	-.177	-.138	-.016	-.208
SSRT	.186	.132	.022	-.027	.135	.150	.067	.247

Note. WM: Working Memory, Org. of Materials: Organization of Materials, Sd on correct RT on GO trials: Standard deviation on correct RT on GO trials, SSD: Stop Signal Delay, SSRT: Stop Signal Reaction Time Raw score of CANTAB and T score of BRIEF were used. $*p < .05$, $**p < .01$

Concerning the standardized canonical discriminant function coefficients, GEC was the highest among the 4 predictor variables examined (Fig. 1).

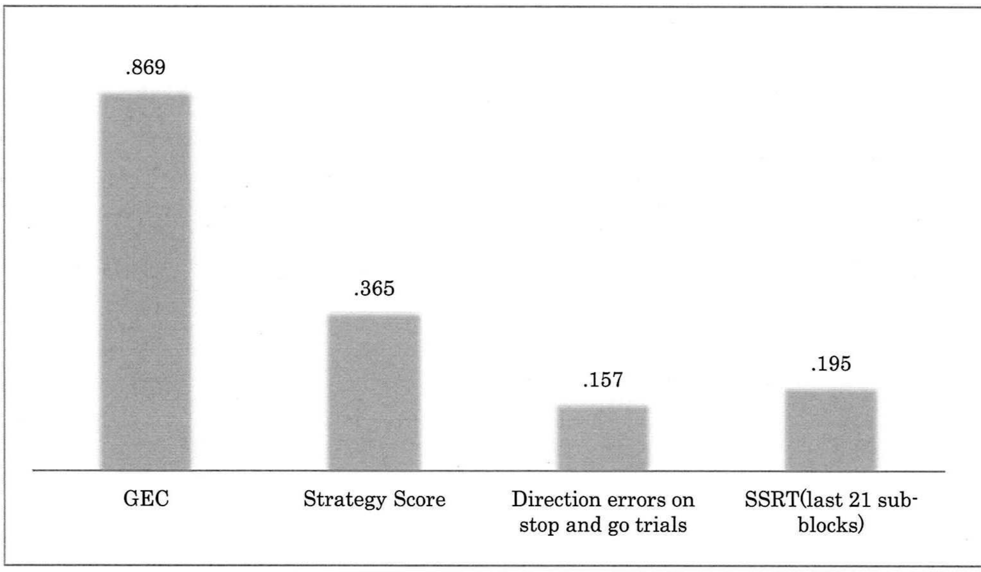

Fig. 1 Standardized Canonical Discriminant Function Coefficients

The cross-validation classification revealed that 79.0% of the original group was correctly classified into the clinical group or control group. The control group was classified with better accuracy (89.5%) than the clinical group (68.4%; Table 5).

Table 5: Classification Results

		group	Predicted Group Membership		Total
			Clinical	Control	
Original	Count	Clinical	14	5	19
		Control	3	35	38
	%	Clinical	73.7	26.3	100.0
		Control	7.9	92.1	100.0
Cross-validated	Count	Clinical	13	6	19
		Control	4	34	38
	%	Clinical	68.4	31.6	100.0
		Control	10.5	89.5	100.0

Note. Percentage of cross-validated grouped cases correctly classified was calculated as average of 68.4 and 89.5, that is, 79.0%

Discussion

In the current study, performance-based CANTAB tasks and the parent-rated BRIEF were administered to children with AD/HD-I and controls. Significant inter-group differences were found in Between Errors (total and 4-, 6-, and 8-box) and Strategy Score. Barnett et al. reported that Between Errors, but neither Within Errors nor Strategy Score of SWM, was significantly higher in children with AD/HD than controls[28]. In the study by Goldberg et al., children with AD/HD made significantly more errors compared to controls on only the most difficult (8-box) problems[25]. The slightly different and more distinct findings in our study may be explained by the hypothesis that children with AD/HD-I performed worse than children with other subtypes of AD/HD on SWM.

For the SST from the CANTAB, which was used for the first time with children with AD/HD-I in the present study, the results showed significant differences between the two groups in Direction Errors and the Standard Deviation on Correct RT on GO Trials scale. Direction Errors reflect deficits in sustained attention, and this may explain why a significant difference existed between the two groups. Standard Deviation on Correct RT on GO Trials was larger in the clinical group than in the control group in this study, which was associated with the hypothesis that a larger standard deviation in speed of responding is one of the characteristics of inattention[29].

Our study revealed significant differences between the AD/HD-I and control groups on all of the BRIEF scales. Gioia, Isquith, Kenworthy, and Barton previously reported that AD/HD-I subjects exhibited higher scores than controls on all of the clinical scales of the BRIEF except the Shift scale[30]. Therefore, it could be concluded that EDF is present in AD/HD-I, and most, if not all, BRIEF clinical scales might be useful for detecting children with AD/HD-I.

Among the correlations of outcome measures of SWM in the CANTAB, the correlation of Between Errors (total and 4 and 6 boxes) and BRIEF Working Memory was significant. This result might confirm that the BRIEF Working Memory and Between Errors of SWM assess the same component of working memory of AD/HD-I subjects that was observed in daily life and neuropsychological performance in clinical settings.

Additionally, SWM outcome measures were significantly correlated with the other BRIEF scales, including Inhibit, Shift, Emotional Control, Initiate, Organization of Materials, and Monitor. Toplak, Bucciarelli, Jain, and Tannock found significant correlations between the digit span and spatial span subtests from the WISC-III and several scales from the BRIEF in addition to the working memory scale[31]. This finding is concordant with ours in that working memory in performance-based tasks and the BRIEF were strongly correlated, but not correlated in any specific way.

This might be explained by results of several functional neuroimaging studies on cognitive deficits in AD/HD. For instance, McNab et al. demonstrated that the neural correlations between inhibition and working memory overlapped in the right inferior frontal gyrus[32]. In addition, Turner, Blackwell, Dowson, McLean, and Sahakian suggested that fronto-striatal brain dysfunction in AD/HD may underlie many neurocognitive deficits, such as attentional and executive impairments[33]. This could imply that impairment of working memory may accompany or underlie other impairments of EF.

In addition, the correlations between Direction Errors, which may represent the impairment in sustained attention and/or inhibition, and Inhibit, Emotion Control, Initiate, and Monitor in the BRIEF were significant (Table 4). This might coincide with Barkley's assumption that impairment of inhibition affects self-regulation of affect-motivation-arousal, internalization of speech, and reconstitution[14]. There was no correlation between the other outcome measures of SST and BRIEF subscales.

This is the first report using SWM and the SST of the CANTAB as performance-based measures and the BRIEF as a parent-rated scale to assess the cognitive deficiencies of young children with AD/HD-I. The BRIEF successfully differentiated AD/HD-I subjects from the controls. In addition, some subscales of the BRIEF and some outcome measures of SWM and SST were strongly correlated, especially in scales for working memory.

In summary, the BRIEF, Between Errors (total and n boxes), Strategy Score of SWM and the Direction Errors of SST are considered to be useful for determining AD/HD-I in young children, which will help us to start successful intervention early in life.

Limitations

In this study, typical or normal development in children in the control groups was not confirmed by child neurologists or psychiatrists and was not backed up by assessment with AD/HD-RS and WISC-III.

Although the prevalence of AD/HD in boys is about twice that reported in girls[2], the gender ratio was 10:9 in both the clinical and control group in this study.

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謝辞

本論文を作成するにあたり、多くのご支援とご指導を賜りました本研究科こころの発達神経科学講座　谷池雅子教授、毛利育子准教授、下野九理子講師、子どものこころの分子統御機構研究センターの職員の皆様に心より感謝申し上げます。

学位論文審査において貴重なご助言を賜りました主査の本研究科こころの発達神経科学講座　片山泰一教授、副査の本研究科こころの相互認知科学講座　棟居俊夫教授、同副査の本研究科こころの発達神経科学講座　酒井佐枝子准教授に心より感謝申し上げます。

本研究を計画、遂行し学位論文にまとめるにあたり、谷池雅子教授、毛利育子准教授には、日々の研究のみならず、終始暖かい激励と多大なご指導、ご支援を賜りましたことを記すとともに、深甚の謝意を表します。

本研究の実施にあたりご協力いただきました大阪大学附属病院小児科の先生方、職員の皆様に心より感謝申し上げます。

加えて、ボランティアのお子さま、ご家族の皆様からの多大なご協力を賜り、本研究を遂行することができましたことをここに記すとともに心より感謝申し上げます。

3 年間の大学院生活中、ともに励まし合い、切磋琢磨して過ごした本研究科一期生の志澤美保さん、諏訪絵里子さん、松嵜順子さんをはじめとする同期の皆様、および院生の皆様の存在があって本研究を遂行することができました。心より感謝申し上げます。

最後に、ここまでの道のりを応援してくださった家族、関係者の皆様に深い感謝の意を表して謝辞といたします。

平成 24 年 11 月