STAFF AWARENESS AND EXPERIENCE OF TOURETTE SYNDROME —DIFFERENCE BETWEEN TEACHERS IN SPECIAL NEEDS EDUCATION AND REGULAR EDUCATION—

Maiko NONAKA, Natsumi KIKUCHI
Graduate School of Education, The University of Tokyo
Toshiaki KONO
Department of Mental Health Policy and Evaluation, National Institute of Mental Health
Takafumi SHIMADA
Department of Neuropsychiatry, Graduate School of Medicine, The University of Tokyo
Hitoshi KUWABARA, Yukiko KANO
Department of Child Neuropsychiatry, Graduate School of Medicine, The University of Tokyo

This study was designed to compare awareness and experience of Tourette Syndrome (TS) between teachers in special needs education (SpEd) and regular education (ReEd). Methods: Questionnaire survey of 168 SpEd teachers and 109 ReEd teachers. Results: Fewer ReEd teachers were familiar with the term "Tourette Syndrome" (18%) compared to teachers of SpEd classes (36%). In each group, more than 70% of the teachers had the experience of being in charge of students with tics, with more than half those teachers having paid some form of special consideration to such students. Knowledge of "TS" was significantly associated with the experience of providing special care for students with tics, regardless of group. SpEd teachers tended to adopt a direct approach, as in attempts to monitor and minimize their stress, while more ReEd teachers took steps addressing the student's environment, including collaboration with other staff and parents. Discussion: There appears to be a considerable number of students with tics in the school setting, with teachers having traditionally cared for them in ways adjusting to the class configuration. However, the survey also conveyed underlying needs for more information on TS among the teachers, particularly for those working in ReEd.

Corresponding Author's Address:
Y. Kano
Department of Child Neuropsychiatry, Graduate School of Medicine, The University of Tokyo
7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, JAPAN

Child Psychiatry Hum Dev (2010) 41:193–203
DOI 10.1007/s10578-009-0160-y

ORIGINAL ARTICLE

Prefrontal Dysfunction in Attention-Deficit/Hyperactivity Disorder as Measured by Near-Infrared Spectroscopy

Hideki Negoro · Masayuki Sawada · Junzo Iida · Toyosaku Ota · Shohei Tanaka · Toshifumi Kishimoto

Published online: 14 October 2009

Abstract Recent developments in near-infrared spectroscopy (NIRS) have enabled non-invasive clarification of brain functions in psychiatric disorders with measurement of hemoglobin concentrations as cerebral blood volume. Twenty medication-naïve children with attention-deficit/hyperactivity disorder (ADHD) and 20 age- and sex-matched healthy control subjects participated in the present study after giving consent. The relative concentrations of oxyhemoglobin (oxy-Hb) were measured with frontal probes every 0.1 s during the Stroop color-word task, using 24-channel NIRS machines. During the Stroop color-word task, the oxy-Hb changes in the control group were significantly larger than that in the ADHD group in the inferior prefrontal cortex, especially in the inferior lateral prefrontal cortex bilaterally. The Stroop color-word task used with NIRS may be one useful measurement to assess prefrontal brain dysfunction in ADHD children.

Keywords Near-infrared spectroscopy · Attention-deficit/hyperactivity disorder · Stroop color-word task · Prefrontal dysfunction

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a central nervous system (CNS) disorder estimated to occur in 3–7% of school-age children [1]. Functional brain abnormality has been reported in ADHD patients. A mean regional I-123 IMP single photon emission computed tomography (SPECT) region of interest (ROI) count ratios (left to right) study demonstrated that the ADHD patients had greater overall hemispheric I-123 IMP uptake

H. Negoro · M. Sawada (✉) · T. Ota · S. Tanaka · T. Kishimoto
Department of Psychiatry, Nara Medical University School of Medicine, 840 Shijocho Kashihara, Nara 634-8522, Japan
e-mail: sawao.com28@mopera.net

M. Sawada
Hannan Hospital, Osaka, Japan

J. Iida
Nara Medical University School of Nursing, Nara, Japan

asymmetry, with less activity in the left frontal and left parietal regions, in comparison with control patients [2]. Bush et al. [3] also reported anterior cingulate cortex dysfunction in ADHD using the counting Stroop during functional magnetic resonance imaging (fMRI). With regard to working memory tasks, Schweitzer et al. [4] compared regional cerebral blood flow (rCBF) changes in six adult patients with ADHD and six healthy controls using [15O] H_2O positron emission tomography (PET) studies and indicated that task-related changes in rCBF in the healthy controls were more prominent in the frontal and temporal regions. Thus, it is possible that ADHD patients have functional frontal dysfunction.

However, functional brain imaging methodologies, such as PET, SPECT, and fMRI have the disadvantage of requiring large apparatuses, which prevents their use in a bedside setting for diagnostic and treatment purposes. Furthermore, these functional brain imaging methodologies do not offer high time resolution. By contrast, multi-channel near-infrared spectroscopy (NIRS) systems have recently been developed to allow non-invasive and bedside functional mapping of the cerebral cortex, with a high time resolution [5–7].

Some NIRS studies in ADHD patients have been performed using several executive function tasks. Weber et al. [8] examined prefrontal dysfunction in ADHD children as measured by NIRS and determined cerebral hemodynamic changes in response to an executive function task (trail-making test) in 11 children with ADHD and 9 healthy age- and sex-matched controls. They found that both groups showed increases in oxyhemoglobin (oxy-Hb) and CBV, but only the controls showed an additional increase in total-Hb in the left prefrontal region. Another report examined lateral prefrontal activation in 13 adult patients with ADHD and 13 healthy age- and sex-matched controls during a working memory task (n-back task) [9]. They showed that ADHD patients exhibited reduced task-related increases in the concentration of oxy-Hb in NIRS channels located over the ventrolateral prefrontal cortex, confirming previous findings of prefrontal cortical and working memory deficits in ADHD patients and arguing for a specific impairment of this clinical group in a particular working memory component. Schecklmann et al. [10] examined executive functions in 14 ADHD adults and 14 healthy age- and sex-matched controls using verbal fluency tasks. They reported that ADHD patients had a lower magnitude of oxygenation and a significant negative correlation of brain activity with performance, indicating that these results might be interpreted as an expression of a benefit in the ADHD group. Thus, functional prefrontal dysfunction in ADHD patients has been reported using NIRS.

Schroeter et al. [11] examined hemodynamic responses during incongruent, congruent, and neutral trials of the Stroop task using NIRS in 14 adult healthy controls and reported that the hemodynamic response was stronger during incongruent trials compared with congruent and neutral trials of the Stroop task in the lateral prefrontal cortex bilaterally. Thus, the stronger hemodynamic response was interpreted as stronger brain activation during incongruent trials of the Stroop task because of interference.

To our knowledge, however, there is no report examining the hemodynamic response in healthy children and functional prefrontal dysfunction in ADHD children as measured by NIRS using the Stroop task. Thus, we examined two points in the present study: (1) whether brain activation in healthy children during the Stroop color-word task is similar to healthy adults as measured by NIRS and (2) whether functional prefrontal dysfunction in ADHD children is found during the Stroop color-word task as measured by NIRS. We therefore used multichannel NIRS machines to examine the frontal characteristics of rCBV changes during the Stroop color-word task in ADHD children and age- and sex-matched control subjects.

Methods

Subjects

Twenty subjects (18 boys and 2 girls), aged 6–13 years and diagnosed with ADHD according to DSM-IV [12], were compared with 20 age- and sex-matched healthy control subjects (17 boys and 3 girls), aged 6–13 years (Table 1).

The subjects with ADHD, who had no history of developmental disorder treatment, consulted an experienced pediatric psychiatrist at the Department of Psychiatry of Nara Medical University with a chief complaint of attention deficit, hyperactivity, or impulsiveness. The subjects with ADHD underwent a standard clinical assessment comprising a psychiatric evaluation, a structured diagnostic interview, a cognitive battery, and a medical history. Two experienced pediatric psychiatrists confirmed the diagnosis of ADHD according to DSM-IV [12]. Thus, 20 subjects with ADHD who had no previous medication were enrolled in the present study. Of them, two subjects had comorbid obsessive compulsive disorder (OCD), and one subject had comorbid oppositional defiant disorder (ODD).

Healthy control subjects were recruited from local elementary schools. They also underwent a standard clinical assessment comprising a psychiatric evaluation, a structured diagnostic interview, a cognitive battery, and a medical history. Thus, 20 healthy control subjects, who were not confirmed ADHD and had no history of psychiatric or neurological disorder, were enrolled in the present study.

The Wechsler Intelligence Scale for Children-Third Edition (WISC-III) full IQ scores of subjects were all over 70. All subjects were right-handed and Japanese. This study was approved by the Institutional Review Board of Nara Medical University Hospital. Written informed consent was obtained from all subjects and/or their parents before the study.

Table 1 Characteristics of the subjects

	ADHD Mean (SD)	Control Mean (SD)	*P* value
Sex [M:F]	20 [18:2]	20 [17:3]	0.64
Age	9.55 (1.93)	9.35 (2.13)	0.76
WISC-III	99.60 (11.28)	97.65 (9.61)	0.56
ARI	15.10 (5.06)	1.65 (1.79)	<0.001[$]
ARH	12.05 (3.98)	0.40 (0.88)	<0.001[$]
ARF	27.15 (7.16)	2.05 (2.35)	<0.001[$]
SCWC-1	29.30 (8.39)	36.15 (7.50)	0.0097***
SCWC-2	31.70 (10.59)	39.40 (9.84)	0.022*
SCWC-3	29.75 (9.98)	36.25 (9.66)	0.043*

Group differences tested with *t* tests

ADHD Attention-deficit/hyperactivity disorder, *M* male, *F* female, *WISC-III* Wechsler Intelligence Scale for Children-Third Edition, *ARI* ADHD RS IV-J Inattention subscale's scores, *ARH* ADHD RS IV-J Hyperactivity–Impulsivity subscale's scores, *ARF* ADHD RS IV-J Full scores, *SCWC-1* Stroop color-word task number of correct answers first time, *SCWC-2* Stroop color-word task number of correct answers second time, *SCWC-3* Stroop color-word task number of correct answers third time

$*P < 0.05$; $**P < 0.02$; $***P < 0.01$; $^{\$}\ P < 0.001$

Assessment of ADHD Symptoms

ADHD Rating Scale-IV-Japanese Version (ADHD RS-IV-J, Home Version) [13] was used to evaluate ADHD behavior symptoms in ADHD children. ADHD RS-IV-J consists of 18 items regarding attention-deficit, hyperactivity, or impulsiveness, each scored on a 0–3 point scale. The total scores were calculated by adding the scores of the 18 items. The Inattention subscale's scores were calculated by adding the scores of the 9 odd-numbered items. The Hyperactivity–Impulsivity subscale's scores were calculated by adding the scores of the 9 even-numbered items. The full score, Hyperactivity–Impulsivity subscale's score, and Inattention subscale's score of ADHD RS-IV-J were 54, 27, and 27 points, respectively; it is generally considered that the higher an ADHD RS-IV-J score, the more severe the ADHD symptoms.

Twenty-six subjects (23 boys and 3 girls) diagnosed with ADHD were compared with 11 healthy control subjects (6 boys and 5 girls) to estimate the utility of ADHD RS-IV-J (Home Version). ADHD RS-IV-J exhibited a high level of reliability (Cronbach's alpha coefficient of internal consistency reliability, 0.92). The intra-class correlation was judged to be very high because the score was 0.97. The scores estimated by their mothers were significantly correlated to the scores estimated by the experienced pediatric psychiatrists (Spearman's ρ, 0.92). Furthermore, 2,709 boys (aged 6–15 years) and 2,870 girls (aged 6–15 years) were estimated by their parents using ADHD RS-IV-J (Home Version). In boys, the mean score was 6.68 (SD, 6.91; median, 5; 90th percentile, 16). In girls, the mean score was 4.38 (SD, 5.17; median, 3; 90th percentile, 11). The cutoff score of the full scoring of ADHD RS-IV-J (Home Version) was established as 14–16 points from these results.

All subjects underwent assessment for ADHD RS-IV-J (Table 1). As shown in Table 1, the scores of ADHD RS IV-J Inattention subscale's scores (ARI), ADHD RS IV-J Hyperactivity–Impulsivity subscale's scores (ARH), and ADHD RS IV-J Full scores (ARF) in the ADHD group were significantly higher than those in the control group. The ARF scores of all ADHD subjects were over 16; those of all the control subjects were under 7.

The Stroop Color-Word Task

We reproduced the Stroop task according to the method previously described [14]. The Stroop task consisted of two pages stapled together. Each page had 100 items in 5 columns of 20 items. Items on the first page were the color words RED, GREEN, and BLUE in black ink. Items on the second page were the words RED, GREEN, and BLUE printed in red, green, or blue ink, with the limitation that the word and ink could not match. On the two pages, the items were randomly distributed, except that no item within a column could follow itself.

Before the task, examiners instructed subjects as follows: "These are tests of how quickly you can read the words on the first page, and the colors on the second page. After we say 'begin,' you are to read down the columns, starting with the first one, saying the words/colors to yourself as quickly as you can. After you finish the first column, go on to the next and so on. After you have read the paper for 45 s, we will turn the page. Then you will read the turned paper again. And we will repeat this process with you."

We combined those two pages and made the Stroop color-word task simple and easy because the subjects were school-age children, including 6 year olds. The Stroop color-word task consisted of the first page (p1) and the second page (p2). The Stroop color-word task consisted of a 45-s p1 task, a 45-s p2 task (the color-word task first time), a 45-s p1 task, a 45-s p2 task (the color-word task second time), a 45-s p1 task, a 45-s p2 task (the color-word task third time), and a 45-s p1 task. We made the 45-s p1 task as the baseline task. We also counted the number of correct answers each time. We named them as follows: Stroop color-word task number of correct answers first time (SCWC-1), second time (SCWC-2), and third time (SCWC-3). Examiners who were blind to diagnoses measured the Stroop color-word task. As shown in Table 1, the SCWC-1, SCWC-2, and SCWC-3 of the ADHD group were significantly lower than those of the control group.

NIRS Measurements

The oxy-Hb increase and deoxyhemoglobin (deoxy-Hb) decrease in NIRS have been shown to reflect cortical activation. In animal studies, oxy-Hb is the most sensitive indicator of rCBF because the direction of change in deoxy-Hb is determined by the degree of changes in venous blood oxygenation and volume [15]. Therefore, we decided to focus on changes in oxy-Hb. In this study, oxy-Hb was measured with a 24-channel NIRS machine (Hitachi ETG-100, Hitachi Medical Corporation, Tokyo, Japan) at two wavelengths of near-infrared light (760 and 840 nm), the absorption of which was measured. Oxy-Hb was calculated as previously described [4]. The interprobe distance of the machine was 3.0 cm, and it was determined that the machine measures points 2–3 cm beneath the scalp, i.e., the surface of the cerebral cortices [16, 17].

The NIRS probes were placed on the subject's frontal regions, and arranged to measure the relative concentrations of Hb changes at 24 measurement points in an 8 × 8 cm area, with the lowest probes positioned along the Fp1–Fp2 line according to the international 10/20 system used in electroencephalography. The correspondence of the probe positions and the measurement points on the cerebral cortex were confirmed by superimposition of the probe positions on an MRI of a three-dimensionally reconstructed cerebral cortex of a representative subject in the control group (Fig. 1). The absorption of near-infrared light was measured with a time resolution of 0.1 s. The obtained data were analyzed with the "integral mode": the pre-task baseline was determined as the mean across 10 s just before

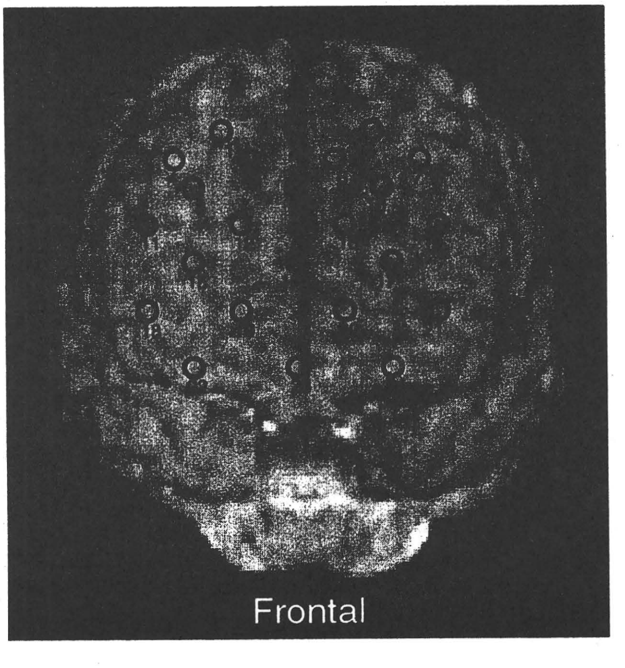

Fig. 1 Cortical projection of near-infrared spectroscopy (NIRS) measurement points. The points were mapped onto anatomical frontal brain using MRIcro software (MRIcro: developed by Dr Chris Rorden, available at http://www.mricro.com). *Numbers* denote channel numbers for points of measurement

the task period; the post-task baseline was determined as the mean across 25 s after the task period; and linear fitting was performed on the data between the two baselines. Moving average methods were used to exclude short-term motion artifacts in the analyzed data (moving average window, 5 s).

We tried to exclude motion artifacts by closely monitoring artifact-evoking body movements, such as neck movements, strong biting, and blinking (identified as most influential in the preliminary artifact-evoking study), and by instructing the subjects to avoid these movements during the NIRS measurements. Examiners who were blind to diagnoses measured NIRS.

Statistical Analyses

Oxy-Hb changes were compared between each of the two groups with Student's *t*-tests using the grand average waveforms every 0.1 s in each channel. This analysis enabled more detailed comparison of oxy-Hb changes along the time course of the task. Data analyses were conducted using MATLAB 6.5.2 (Mathworks, Natick, MA, USA) and Topo Signal Processing type-G version 2.05 (Hitachi Medical Corporation, Tokyo, Japan). OT-A4 version 1.63 K (Hitachi Medical Corporation, Tokyo, Japan) was used for overlap display of the grand average waveforms in both groups in Fig. 2 and was used to calculate mean oxy-Hb measurements in Table 3. SPSS 16.0 J for Windows (SPSS, Tokyo, Japan) was used for statistical analysis.

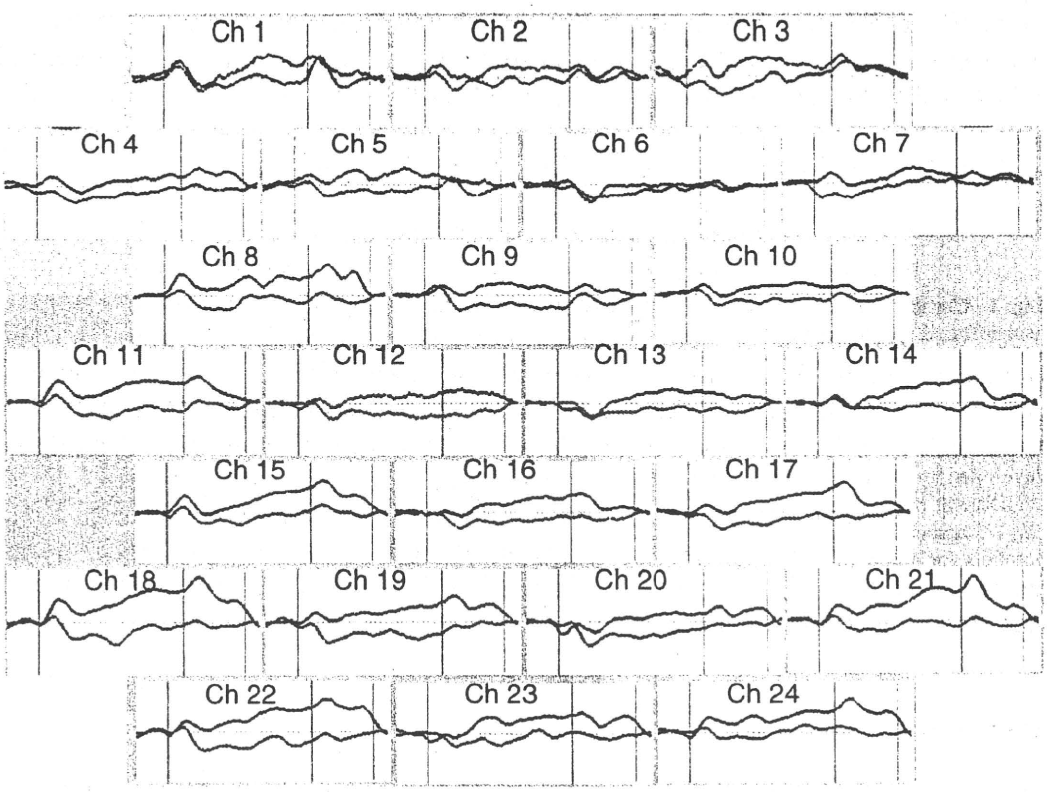

Fig. 2 Grand average waveforms of oxyhemoglobin (oxy-Hb) concentration changes during the Stroop color-word task in both groups. Grand average waveform of oxy-Hb in the attention-deficit/hyperactivity disorder (ADHD) group is the *red line*, and grand average waveform of oxy-Hb in the control group is the *blue line*. The task conducts between *light green lines*

Table 2 Correlations between Stroop task and characteristics of the subjects

	ADHD			Control		
	SCWC-1	SCWC-2	SCWC-3	SCWC-1	SCWC-2	SCWC-3
Age	0.547**	0.519**	0.433	0.777§	0.763§	0.726§
WISC-III	0.088	0.037	−0.069	−0.058	0.196	0.273
ARI	0.22	0.222	−0.091	−0.288	−0.216	−0.193
ARH	−0.052	−0.108	−0.205	−0.152	−0.156	−0.297
ARF	0.068	0.064	−0.217	−0.295	−0.221	−0.215

Correlations between Stroop task and characteristics of the subjects tested with Spearman's correlation test

ADHD Attention-deficit/hyperactivity disorder, *M* male, *F* female, *WISC-III* Wechsler Intelligence Scale for Children-Third Edition, *ARI* ADHD RS IV-J Inattention subscale's scores, *ARH* ADHD RS IV-J Hyperactivity–Impulsivity subscale's scores, *ARF* ADHD RS IV-J Full scores, *SCWC-1* Stroop color-word task number of correct answers first time, *SCWC-2* Stroop color-word task number of correct answers second time, *SCWC-3* Stroop color-word task number of correct answers third time

* $P < 0.05$; ** $P < 0.02$; *** $P < 0.01$; § $P < 0.001$

Results

Correlations Between Stroop Task and Characteristics of the Subjects

Spearman's ρ correlations between the scores of SCWC and age, WISC-III, and the scores of ADHD RS IV-J can be seen in Table 2. In both groups, there are positive correlations between the scores of SCWC and age; there are no correlations between the scores of SCWC and WISC-III and between the scores of SCWC and the scores of ADHD RS IV-J.

NIRS Data of the Subjects During the Stroop Color-Word Task

The grand average waveforms of oxy-Hb concentration changes during the Stroop color-word task in both groups can be seen in Fig. 2. The grand average waveform of oxy-Hb concentration change in the control group increased during the task period. On the other hand, that of the ADHD group did not change much. The mean oxy-Hb measurements from task to post-task period in all 24 channels can be seen in Table 3. Group differences were tested with Bonferroni correction. From task to post-task period, the mean oxy-Hb of the ADHD group was significantly smaller than that in the control group in channels 18, 21, and 22. Topographic presentation of the t value of oxy-Hb comparison between the control group and the ADHD group during the Stroop color task can be seen in Fig. 3. The oxy-Hb changes in the control group were significantly greater than that of the ADHD group during the task period in the inferior prefrontal cortex, especially in the inferior lateral prefrontal cortex bilaterally.

Discussion

Until now, there have been few reports examining prefrontal dysfunction in ADHD children as measured by NIRS. In one, cerebral hemodynamic changes were examined in response to an executive function task (trail-making test) in 11 children with ADHD and 9 healthy age- and sex-matched controls [8]. In that study, both groups showed increases in

Table 3 Mean oxyhemoglobin (oxy-Hb) measurements from task to post-task period in 24 channels

	Control		ADHD		Statistical analysis
	Mean (mMmm)	SD (mMmm)	Mean (mMmm)	SD (mMmm)	
Ch1	0.0231	0.02957	−0.0031	0.04273	NS
Ch2	0.0172	0.05376	−0.0061	0.02842	NS
Ch3	0.0274	0.04375	−0.0037	0.05009	NS
Ch4	0.0185	0.03762	−0.0175	0.04418	NS
Ch5	0.0212	0.03208	−0.0134	0.03826	NS
Ch6	−0.0090	0.03770	−0.0141	0.03425	NS
Ch7	0.0152	0.04812	−0.0079	0.05385	NS
Ch8	0.0444	0.10645	−0.0138	0.03051	*
Ch9	0.0137	0.03206	−0.0211	0.02840	NS
Ch10	0.0147	0.03342	−0.0159	0.03312	NS
Ch11	0.0355	0.02300	−0.0167	0.03325	NS
Ch12	0.0128	0.02828	−0.0278	0.04339	NS
Ch13	0.0051	0.02990	−0.0190	0.03809	NS
Ch14	0.0249	0.02102	−0.0116	0.03667	NS
Ch15	0.0379	0.02859	−0.0078	0.03673	NS
Ch16	0.0176	0.03181	−0.0208	0.03619	NS
Ch17	0.0300	0.03126	−0.0196	0.03569	NS
Ch18	0.0647	0.06864	−0.0189	0.06022	§
Ch19	0.0311	0.05739	−0.0261	0.03934	*
Ch20	0.0094	0.03978	−0.0256	0.04434	NS
Ch21	0.0529	0.04550	−0.0122	0.03573	§
Ch22	0.0465	0.05556	−0.0256	0.05184	§
Ch23	0.0299	0.04915	−0.0123	0.05563	NS
Ch24	0.0478	0.04947	−0.0012	0.04019	NS

Group differences were tested with Bonferroni correction

* $P < 0.1$; ** $P < 0.05$; *** $P < 0.01$; § $P < 0.001$

oxy-Hb and CBV, but only the controls showed an additional increase in total-Hb in the left prefrontal region. In the present study, we used the Stroop color-word task to estimate prefrontal function because the inferior frontal gyrus has been described as one of the regions most strongly related to Stroop interference [18]. To the best of our knowledge, there are no other studies using the Stroop task to examine prefrontal dysfunction in children with ADHD as measured by NIRS.

With respect to the relationship between ADHD and the Stroop task, Schwartz and Verhaeghen [19] examined 25 studies that reported data on the Stroop color word task in children and adults with ADHD and in age-matched controls. ADHD individuals were found to be 1.14 times slower on average than age-matched controls in both the color and the color-word condition, while the Stroop interference effect appeared to be immune to age in both groups. Similar results were obtained in the present study. SCWC-1, SCWC-2, and SCWC-3 of the ADHD group were significantly lower than those of the control group. Furthermore, we examined Spearman's ρ correlations between the scores of SCWC and age, WISC-III, and the scores of ADHD RS IV-J, which indicated that there are positive

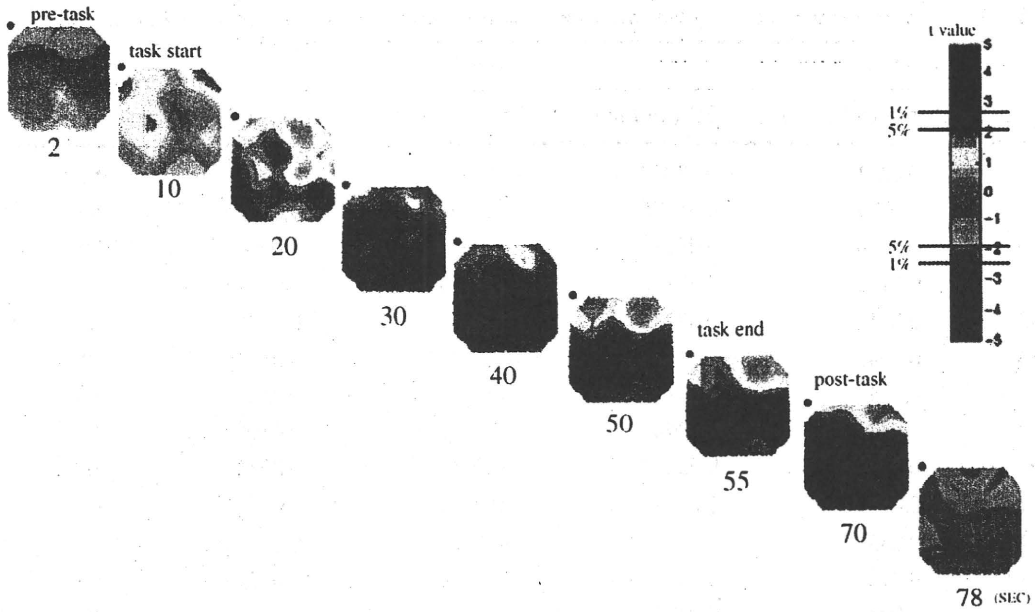

Fig. 3 Topographic presentation of the *t* value of oxyhemoglobin (oxy-Hb) comparison between the control group and the attention-deficit/hyperactivity disorder (ADHD) group during the Stroop color-word task. The *t* value of oxy-Hb for the control and ADHD group is presented as a topographic map along the time course of the task (from top to bottom). The *red*, *green*, and *blue* areas in the topographs indicate positive, zero, and negative *t* values, with 2.0 and 2.7 for 5% and 1% statistical significance levels, respectively

correlations between the scores of SCWC and age in both the groups. These data suggest that our Stroop color-word task may be a useful task for estimating ADHD symptoms.

Despite the relationship between the Stroop color-word task and NIRS, there are few studies that have examined the relationship. Ehlis et al. [20] investigated 10 healthy subjects by means of multi-channel NIRS during performance of congruent and incongruent trials of the Stroop color-word task. In that study, oxy-Hb and total-Hb changes indicated specific activation for interference trials in inferior-frontal areas of the left hemisphere. However, the influences of the Stroop color-word task in inferior-frontal areas of the right hemisphere were not examined. As previously mentioned, the other study [11] reported the hemodynamic response in the lateral prefrontal cortex bilaterally.

However, these two studies reported that oxy-Hb change in adult healthy subjects indicated specific activation during the Stroop color-word task in inferior-frontal areas. In the present study, we found that oxy-Hb change in 20 healthy children indicated specific activation during the Stroop color-word task in the inferior prefrontal cortex, especially in the inferior lateral prefrontal cortex bilaterally, supporting the Schroeter et al study. We therefore found prefrontal brain activation in healthy children during the Stroop color-word task as well as in healthy adults using NIRS, which was interpreted as a result of Stroop interference in children as well as in adults.

We also discussed the comparison between the ADHD group and the control group. We found that oxy-Hb changes in 20 ADHD children were smaller than those in 20 healthy children during the Stroop color-word task in the inferior prefrontal cortex, especially in the inferior lateral prefrontal cortex bilaterally. As shown in Table 1, SCWC-1, SCWC-2, and SCWC-3 of the ADHD group were significantly lower than those of the control group. These data suggest that the prefrontal brain activation in the ADHD children may not fulfill function well during the Stroop color-word task. indicating that ADHD children have some problems in the inferior prefrontal cortex, especially in the inferior lateral prefrontal cortex bilaterally, which has been described as one of the regions most strongly related to Stroop interference.

In the present study, we had two restrictions: NIRS has disadvantages compared with other methodologies [7]. The main disadvantage of NIRS is that it enables measurement of Hb concentration changes only as relative values, not as absolute values. We made the Stroop task that had the first page as the base task to overcome these potential problems. Furthermore, we measured Hb concentration changes from the activation task to the base task and performed the task three times to average potential accidental changes and prevent the subjects from being tired. The other restriction was the inclusion of subjects with comorbidity (i.e., two subjects had comorbid OCD; one subjects had comorbid ODD). Future studies are needed to compare between pure ADHD children and ADHD children with comorbid disorders (e.g. OCD, ODD, and PDD).

Finally, our findings of prefrontal dysfunction in ADHD by NIRS involved a large group, allowing for high confidence in the data. The Stroop color-word task may be a very useful tool when measuring prefrontal dysfunction in ADHD using NIRS, and multi-channel NIRS systems may be one very useful measurement to assess brain function, especially for children, because multi-channel NIRS systems can provide handy, non-invasive, and bedside-functional mapping of the cerebral cortex at much shorter measurement time (about 5 min) than other functional brain imaging methodologies. Future studies are needed to determine the effect of osmotic-release methylphenidate (MPH) treatment on ADHD children using NIRS by comparing before and after osmotic-release MPH treatment.

Summary

The purpose of the present study was to examine the hemodynamic response in healthy children and functional prefrontal dysfunction in ADHD children as measured by NIRS using the Stroop task. Therefore, 20 medication-naïve children with ADHD and 20 age- and sex-matched healthy control subjects participated in the present study. The relative concentrations of oxy-Hb were measured with frontal probes every 0.1 s during the Stroop color-word task, using 24-channel NIRS machines. Findings indicate that ADHD children have some problems in the inferior prefrontal cortex, especially in the inferior lateral prefrontal cortex bilaterally, which has been described as one of the regions most strongly related to Stroop interference. Finally, the Stroop color-word task during NIRS may be one useful measurement to assess prefrontal brain dysfunction in ADHD children. Furthermore, multi-channel NIRS systems may be one very useful measurement to assess brain function, especially for children, because multi-channel NIRS systems can provide handy, non-invasive, and bedside-functional mapping of the cerebral cortex at much shorter measurement time (about 5 min) than other functional brain imaging methodologies.

Acknowledgements The authors would like to thank Hitachi Medical Corporation for the ETG-100 equipment and the skilled technical and methodical support. This work was funded by Research Grant (20B-6) for Nervous and Mental Disorders from the Ministry of Health, Labor and Welfare, Japan.

References

1. American Psychiatric Association (2000) Diagnostic and statistical manual of mental disorders, 4th edn. Text revision (DSM-IV-TR). American Psychiatric Association, Washington, DC

2. Sieg KG, Gaffney GR, Preston DF, Hellings JA (1995) SPECT brain imaging abnormalities in attention deficit hyperactivity disorder. Clin Nucl Med 20:55–60
3. Bush G, Frazier JA, Rauch SL et al (1999) Anterior cingulate cortex dysfunction in attention-deficit/hyperactivity disorder revealed by fMRI and the counting Stroop. Biol Psychiatry 45:1542–1552
4. Schweitzer JB, Faber TL, Grafton ST, Tune LE, Hoffman JM, Kilts CD (2000) Alterations in the functional anatomy of working memory in adult attention-deficit/hyperactivity disorder. Am J Psychiatry 157:278–280
5. Koizumi H, Yamashita Y, Maki A et al (1999) Higher-order brain function analysis by transcranial dynamic NIRS imaging. J Biomed Opt 4:403–413
6. Maki A, Yamashita Y, Ito Y, Watanabe E, Mayanagi Y, Koizumi H (1995) Spatial and temporal analysis of human motor activity using non-invasive NIR topography. Med Phys 22:1997–2005
7. Yamashita Y, Maki A, Koizumi H (1996) Near-infrared topographic measurement system: Imaging of absorbers localized in a scattering medium. Rev Sci Instrum 67:730–732
8. Weber P, Lütschg J, Fahnenstich H (2005) Cerebral hemodynamic changes in response to an executive function task in children with attention-deficit hyperactivity disorder measured by near-infrared spectroscopy. J Dev Behav Pediatr 26:105–111
9. Ehlis AC, Bahne CG, Jacob CP, Herrmann MJ, Fallgatter AJ (2008) Reduced lateral prefrontal activation in adult patients with attention-deficit/hyperactivity disorder (ADHD) during a working memory task: a functional near-infrared spectroscopy (fNIRS) study. J Psychiatr Res 42:1060–1067
10. Schecklmann M, Ehlis AC, Plichta MM et al (2009) Diminished prefrontal oxygenation with normal and above-average verbal fluency performance in adult ADHD. J Psychiatr Res 43:98–106
11. Schroeter ML, Zysset S, Kupka T, Kruggel F, Yves von Cramon D (2002) Near-infrared spectroscopy can detect brain activity during a color-word matching Stroop task in an event-related design. Hum Brain Mapp 17:61–71
12. American Psychiatric Association (1994) Diagnostic and statistical manual of mental disorders, 4th edn. American Psychiatric Press, Washington, DC
13. Yamazaki K (2003) ADHD-RS-IV Japanese versions. In: Kanbayashi Y, Saito K, Kita M (eds) Japanese guideline for the diagnosis and treatment of attention deficit hyperactivity disorder (ADHD). Jiho, Tokyo, pp 48–54
14. Goldman CJ (1975) A group version of the Stroop color and word test. J Pers Assess 39:386–388
15. Hoshi Y, Kobayashi N, Tamura M (2001) Interpretation of near-infrared spectroscopy signals: A study with a newly developed perfused rat brain model. J Appl Physiol 90:1657–1662
16. Hock C, Villringer K, Müller-Spahn F et al (1997) Decrease in parietal cerebral hemoglobin oxygenation during performance of a verbal fluency task in patients with Alzheimer's disease monitored by simultaneous rCBF-PET measurements. Brain Res 755:293–303
17. Toronov V, Webb A, Choi JH et al (2001) Investigation of human brain hemodynamics by simultaneous near-infrared spectroscopy and functional magnetic resonance imaging. Med Phys 28:521–527
18. Laird AR, McMillan KM, Lancaster JL et al (2005) A comparison of label-based review and ALE meta-analysis in the Stroop task. Hum Brain Mapp 25:6–21
19. Schwartz K, Verhaeghen P (2008) ADHD and Stroop interference from age 9 to age 41 years: a meta-analysis of developmental effects. Psychol Med 29:1–10
20. Ehlis AC, Herrmann MJ, Wagener A, Fallgatter AJ (2005) Multi-channel near-infrared spectroscopy detects specific inferior-frontal activation during incongruent Stroop trials. Biol Psychol 69:315–331

doi:10.1111/j.1440-1819.2010.02134.x

Regular Article

Effects of osmotic-release methylphenidate in attention-deficit/hyperactivity disorder as measured by event-related potentials

Masayuki Sawada, MD,[1,2]* Junzo Iida, MD, PhD,[3] Toyosaku Ota, MD,[1] Hideki Negoro, MD, PhD,[4] Shohei Tanaka, MA,[1] Miyuki Sadamatsu, MD, PhD[1] and Toshifumi Kishimoto, MD, PhD[1]

[1]*Department of Psychiatry, Nara Medical University School of Medicine,* [2]*Hannan Hospital,* [3]*Nara Medical University School of Nursing and* [4]*Nara University of Education, Nara, Japan*

Aim: Attention-deficit/hyperactivity disorder (ADHD) is a relatively common central nervous system disorder in school-age children, which may involve a specific disorder in cognition and/or information processing. Event-related potentials (ERP) are commonly used as physiological measures of cognitive function as they are easily measured and non-invasive. Thus, in the present study, we examined the effects of osmotic-release methylphenidate (MPH) (Concerta), a common treatment for childhood attention-deficit/hyperactivity disorder (ADHD), in ADHD children as measured by ERP.

Methods: Ten ADHD children participated after giving consent. Based on the guidelines for evoked potential measurement, mismatch negativity (MMN) and P300 were obtained by auditory odd-ball tasks. We measured both MMN and P300 in the drug-naive condition and after intake of osmotic-release MPH.

Results: The MMN amplitudes after intake of osmotic-release MPH were significantly greater than those in the drug-naive situation at Pz and C4. The P300 amplitudes after intake of osmotic-release MPH were significantly greater than those in the drug-naive situation at Cz and Pz.

Conclusion: MMN and P300 are sensitive tools for measuring the pharmacological effects of osmotic-release MPH in ADHD children.

Key words: attention-deficit/hyperactivity disorder, event-related potentials, methylphenidate, mismatch negativity, P300.

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) is a central nervous system (CNS) disorder estimated to occur in 3–7% of school-age children,[1] and is considered to involve a specific disorder in cognition and/or information processing. Event-related potentials (ERP) are commonly used as physiological measures of cognitive function as they are easily measured and non-invasive. For instance, ERP have been used to examine cognitive disturbance in children with developmental disorder, and an early negative ERP has been shown to be strongly-related to attention deficit.

The mismatch negativity (MMN), which functions in a distinctive stimulus discrimination process that utilizes sensory memory of prior stimuli, is considered an important mechanism for rapid detection of changes in the outer world, except those concerning consciousness.[2] As such, MMN reflects an automatic cerebral discrimination process, not under-attentive control. We previously reported that the amplitudes of both P300 and MMN were smaller in ADHD patients than in healthy subjects.[3]

*Correspondence: Masayuki Sawada, MD, Department of Psychiatry, Nara Medical University School of Medicine, 840 Shijocho Kashihara, Nara 634-8522, Japan.
Email: sawao.com28@mopera.net
Received 19 October 2009; revised 9 July 2010; accepted 19 July 2010.*

With respect to the impulsivity observed in ADHD patients, we previously reported that the Hyperactivity-Impulsivity subscale score of the ADHD Rating Scale-IV-Japanese version (ADHD RS-IV-J) (Home Version)[4] had a significantly strong positive correlation with the latency of MMN, and had a significant strong negative correlation with the amplitude of MMN, in predominantly hyperactive-impulsive type ADHD subjects.[5] In other words, the more severe the impulsivity of ADHD subjects, the longer the MMN latency and the lower the MNN amplitude. Thus, ADHD children may have difficulty in referring to previous stimuli, causing increased sensitivity to and augmented anxiety about stimuli, which may account for the exhibited impulsivity.

Stimulating medications are commonly used for treatment of ADHD symptoms. Methylphenidate (MPH), for instance, has been used in ADHD children since 1937.[6] In Japan, osmotic-release MPH (Concerta) was recently accepted as a treatment medication for ADHD children. Several studies have demonstrated a reduced P300 in ADHD children, which was normalized following MPH medication.[7–9] However, to the best of our knowledge the effects of osmotic-release MPH on MMN in ADHD children have not been described. Thus, in the present study we examined the effects of MPH on MMN and P300, and on ameliorating cognitive function, especially attention function, in ADHD children.

METHODS

Subjects

Ten children (nine boys, one girl) aged 7–13 years and diagnosed as ADHD based on DSM-IV,[10] participated in the present study. The subjects with ADHD, who had no history of developmental disorder treatment, consulted an experienced pediatric psychiatrist (M. S., T. O., or H. N.) at the Department of Psychiatry of Nara Medical University with the chief complaint of attention deficit, hyperactivity, or impulsiveness. The subjects with ADHD underwent a standard clinical assessment comprising a psychiatric evaluation, a structured diagnostic interview, a cognitive battery, and a medical history. Two experienced pediatric psychiatrists (J. I., H. N.) confirmed the diagnosis of ADHD according to DSM-IV.[10]

The Wechsler Intelligence Scale for Children-Third Edition (WISC-III) full IQ scores of all subjects were over 70. All patients were Japanese and right-handed. In ADHD subjects, the severity of ADHD symptoms and latencies and amplitudes of ERP (MMN, P300) were estimated both before and after (8–12 weeks) osmotic-release MPH treatment at the same time of day (10.00–11.00 hours). ADHD subjects were treated with osmotic-release MPH as soon as possible after baseline ERP. The dose of osmotic-release MPH treatment ranged from 18 to 54 mg (mean ± SD, 33.3 ± 10.4 mg). The characteristics of the subjects can be seen in Table 1. This study was approved by the Institutional Review Board of Nara Medical University Hospital. Written informed consent was obtained from all subjects and/or their parents prior to the study.

Procedures

ADHD assessment

We used the ADHD RS-IV-J (Home Version)[4] to evaluate ADHD symptoms in ADHD children. It is generally considered that the higher an ADHD RS-IV-J score, the more severe the ADHD symptoms. All subjects underwent ADHD RS-IV-J assessment before and after osmotic-release MPH treatment (Table 1). In ADHD children the ADHD RS-IV-J full scores (ARF), ADHD RS-IV-J inattention subscales scores (ARI), and the ADHD RS-IV-J hyperactivity-impulsivity subscales scores (ARH) were significantly higher before osmotic-release MPH treatment than those after osmotic-release MPH treatment.

Event-related potentials

Measurements

Based on the guidelines for evoked potential measurement, MMN and P300 were obtained by auditory odd-ball tasks. An NEC Multi Stim II (NEC, Tokyo, Japan) was used as the auditory stimulus system.

MMN

Tone bursts at 1000 Hz standard stimuli ($P = 0.9$) and at 1100 Hz deviant stimuli ($P = 0.1$) (each stimulus lasted 50 ms) were presented at 500-ms intervals and at 80-dB intensities. The infrequent and frequent stimuli were given in random order via headphones. The MMN was measured while the children, as instructed, were reading books or magazines of their choice, without paying particular attention to the auditory stimuli given.

Table 1. Subjects characteristics

Sex	Boy	%	Girl	%	
(n = 10)	9	90	1	10	
	Mean		SD		
Age (years)	9.3		1.9		
WISC-III	100.5		15.3		
Concerta dose (mg)	33.3		10.4		

	Before Concerta treatment		After Concerta treatment			
	Mean	SD	Mean	SD	t value (d.f. = 9)	P-value
ARF	31.1	8	11.9	5.6	9.826	<0.001
ARI	17.5	5.5	8.3	3.1	6.209	<0.001
ARH	13.6	3.6	3.6	3.8	8.135	<0.001

ARF, Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Japanese version full scores; ARH, Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Japanese version hyperactivity-impulsivity subscale scores; ARI, Attention-Deficit/Hyperactivity Disorder Rating Scale-IV-Japanese version inattention subscale scores; WISC-III, Wechsler Intelligence Scale for Children-Third Edition.

P300

Infrequent target stimuli were presented as tone bursts at 2000 Hz ($P = 0.2$) and frequent non-target stimuli as bursts at 1000 Hz ($P = 0.8$), with each stimulus lasting 50 ms. Both types of stimuli were given at intervals of 1.5 s and an intensity of 80 dB. The infrequent and frequent stimuli were given in random order via headphones. The children were instructed to pay attention to the target stimuli with their eyes open, and to press the button as quickly as possible when each target stimulus was delivered.

Recording and analyses

ERP were recorded with an MEB 2200 (NIHON KOHDEN, Tokyo, Japan). Electroencephalograms (EEG) were obtained at Fz, Cz, C3, C4, and Pz positions on the scalp using disk electrodes. The bilateral ear lobes were used as the reference electrode sites. The resistance of the electrodes was set at ≤5 kΩ. MMN was analyzed during the period between the 30-ms pre-stimulus and the 360-ms post-stimulus. P300 was analyzed during the period between 50 ms pre-stimulus and 750 ms post-stimulus. Artifact-free responses to the stimuli were added and averaged after EEG amplitude data ≥100 μV and eye movements were removed. To prevent the subjects from getting tired of, or used to, performing the tasks, each trial was conducted only once.

MMN

Fifty responses to infrequent deviant stimuli and 450 responses to frequent standard stimuli were averaged separately. The waveform of the frequent standard stimuli responses was subtracted from that of the infrequent deviant stimuli responses. From the subtraction waveform, MMN was identified as a negative wave with a peak latency from 100 to 250 ms. MMN latency and amplitude were measured.

P300

Thirty responses to infrequent target stimuli were averaged. Of the ERP obtained, P300 was identified as a positive wave with a peak latency from 250 to 550 ms. P300 latency and amplitude were also measured.

Statistical analyses

Statistical comparison of subject characteristics between the two groups was performed by two-tailed paired *t*-test. The latencies and amplitudes of both P300 and MMN were compared between before treatment and after treatment by two-tailed paired *t*-test. SPSS 17.0 J for Windows (SPSS, Tokyo, Japan) was used for all analyses.

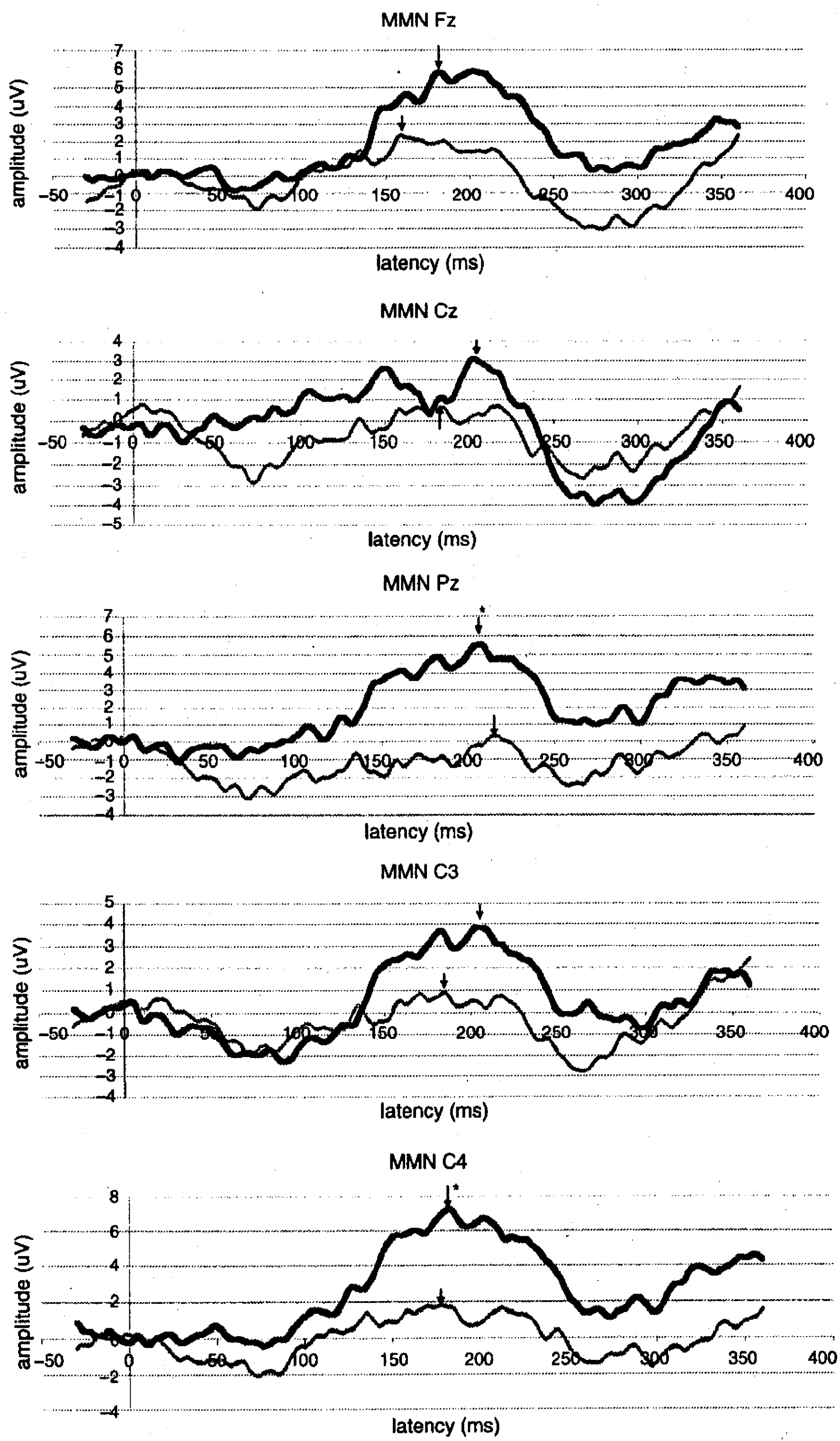

Figure 1. Grand average mismatch negativity (MMN) from attention-deficit/hyperactivity disorder children (▬▬) before and (▬▬) after Concerta treatment conditions. MMN is shown by arrows. *$P < 0.05$.

Table 2. Amplitudes and latencies of mismatch negativity (MMN) and P300

	Before Concerta treatment		After Concerta treatment			
	Mean	SD	Mean	SD	t value (df = 9)	P-value
MMN amplitude (uV)						
Fz	4.2	4.2	9.1	9.1	−1.79	0.107
Cz	3.6	4	6.4	11.5	−0.829	0.429
Pz	2.2	5	8.1	6.4	−2.442	0.037*
C3	3.5	4.8	5.6	6.6	−0.88	0.402
C4	4.5	3.5	9	5.4	−2.718	0.024*
MMN latency (ms)						
Fz	173.1	36.3	188.1	33.2	−1.096	0.302
Cz	185	36.4	193	30.1	−0.558	0.591
Pz	192.8	34.2	192.4	32.3	0.033	0.974
C3	191.4	35.9	191	27.9	0.038	0.97
C4	187.5	31.6	180.9	33.4	0.613	0.555
P300 amplitude (uV)						
Fz	−8.5	16.3	−20.8	16.8	1.643	0.135
Cz	−11.2	11.2	−28.1	17.7	2.785	0.021*
Pz	−17	6.7	−33.3	19.8	2.317	0.046*
C3	−10.7	9.2	−19.2	11.3	2.056	0.07
C4	−11	10.5	−20	12.3	2.192	0.056
P300 latency (ms)						
Fz	376.7	68.1	383.4	54.4	−0.36	0.727
Cz	388.7	67.8	383.4	57.4	0.366	0.723
Pz	357.8	58.2	360.9	68.4	−0.233	0.821
C3	355.1	55.5	373.2	57.5	−0.882	0.401
C4	361.8	53.8	358.7	58.1	0.181	0.861

*$P < 0.05$.

RESULTS

MMN

The grand average MMN from ADHD children after osmotic-release MPH treatment was greater than that before treatment (Fig. 1). The exact figures of amplitudes and latencies are listed in Table 2. The mean MMN amplitudes from ADHD children at Pz and C4 after osmotic-release MPH treatment were significantly greater than those before treatment (Table 2).

P300

The grand average P300 from ADHD children after osmotic-release MPH treatment was greater than that before treatment (Fig. 2). The exact figures of amplitudes and latencies are listed in Table 2. The mean P300 amplitudes from ADHD children at Cz and Pz after osmotic-release MPH treatment were significantly greater than those before treatment (Table 2).

DISCUSSION

In the present study, although there seemed to be visual differences in most electrodes for both MMN and P300 following osmotic-release MPH treatment in ADHD children, significant increases in MMN or P300 amplitudes after osmotic-release MPH treatment were only observed in Pz and C4 or Cz and Pz. These discrepancies may relate to the small sample size and large standard deviation in the present study.

P300 is a potential generated in the final stage of sensory and cognitive processing. The improvement in P300 following osmotic-release MPH treatment in ADHD children is consistent with previous studies.[7–9] As disturbance of the P300 component has been previously suggested as an indicator of impaired cognition,[11,12] these data suggest that cognitive function in

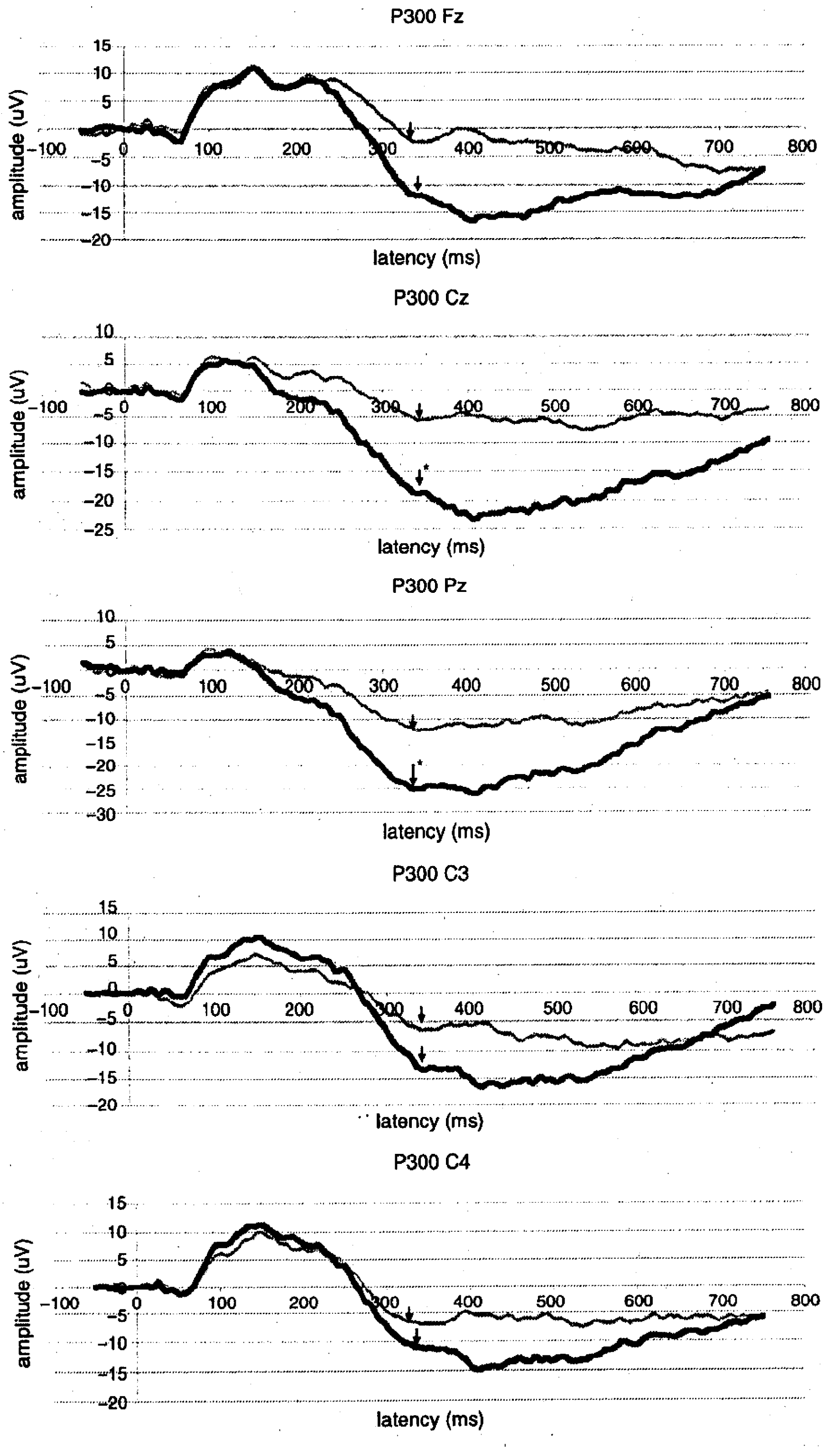

Figure 2. Grand average P300 from attention-deficit/hyperactivity disorder children (▬▬) before and (▬▬) after Concerta treatment conditions. P300 is shown by arrows. $*P < 0.05$.

ADHD children was ameliorated by osmotic-release MPH treatment. However, P300 is likely to be affected by the cognitive factors present prior to P300 generation, thus limiting the significance of investigations employing solely P300 recordings. As such, we also evaluated MMN in ADHD children in the present study, the pre-P300 potentials that reflect information processing itself.[3,5]

In the present study, we reported that MMN amplitudes were increased after osmotic-release MPH treatment in ADHD children, suggesting that the automatic cerebral discrimination process might be ameliorated by osmotic-release MPH treatment, which in turn may have reduced the impulsiveness and hyperactivity in ADHD children.

With respect to the laterality of cerebral dysfunction in ADHD, it was proposed that ADHD children exhibit dysfunction in a right-sided frontal-striatal system.[13] This comprehensive morphometric analysis was consistent with the hypothesized dysfunction of right-sided prefrontal-striatal systems in ADHD children.[14] Furthermore, in an event-related functional magnetic resonance imaging (fMRI) study, ADHD children exhibited less right-sided activation in the anterior cingulate gyrus during alerting (one of the attentional networks) relative to controls.[15]

In the present study, there was no difference between the left (C3) and right (C4) P300 amplitudes or MMN amplitudes either before or after treatment, and there was no difference between the left (C3) and right (C4) P300 and MMN latencies either before or after treatment. However, the MMN amplitude after osmotic-release MPH treatment was significantly greater than that in the drug-naive situation at C4. Thus, we suggest that the right hemisphere may be competent following MPH treatment with respect to MMN.

There were two limitations to our study. First, the sample size was small. However, we examined 10 ADHD children who had no history of developmental disorder treatment, and our data showed significant changes. Second, we had no placebo-control subjects. Future studies with large samples and placebo-control subjects as measured by ERP are required to determine whether cognitive function in ADHD children was ameliorated by osmotic-release MPH treatment. In conclusion, the results of the present study suggest that both MMN and P300 are sensitive tools for measuring the pharmacological effects of osmotic-release MPH in ADHD children.

ACKNOWLEDGMENTS

This work was supported by a Grant for International Health Research (127-A) from the Ministry of Health, Labor and Welfare, Japan.

REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 4th. edn. Text Rev. American Psychiatric Association, Washington, DC, 2000.
2. Jonkman LM, Kemner C, Verbaten MN *et al.* Event-related potentials and performance of attention-deficit hyperactivity disorder: Children and normal controls in auditory and visual selective attention tasks. *Biol. Psychiatry* 1997; 41: 595–611.
3. Ito N, Iida J, Iwasaka H, Negoro H, Kishimoto T. Study of event-related potentials in attention-deficit/hyperactivity disorder. *Jpn J. Child Adolesc. Psychiatry* 2003; 44 (Suppl.): 101–111.
4. Yamazaki K. ADHD-RS-IV Japanese version. In: Kanbayashi Y, Saito K, Kita M (eds). *Japanese Guideline for the Diagnosis and Treatment of Attention Deficit Hyperactivity Disorder (ADHD)*. Jiho, Tokyo, 2003; 48–54 (in Japanese).
5. Sawada M, Iida J, Negoro H *et al.* Impulsivity of attention deficit/hyperactivity disorder (ADHD) and mismatch negativity (MMN). *Jpn J. Psychiatry Treat.* 2006; 21: 987–991 (in Japanese).
6. Bradley C. The behavior of children receiving Benzedrine. *Am. J. Psychiatry* 1937; 94: 577–585.
7. Klorman R. Cognitive event-related potentials in attention deficit disorder. *J. Learn. Disabil.* 1991; 24: 130–140.
8. Lopez J, Lopez V, Rojas D *et al.* Effect of psychostimulants on distinct attentional parameters in attentional deficit/hyperactivity disorder. *Biol. Res.* 2004; 37: 461–468.
9. Seifert J, Scheuerpflug P, Zillessen KE, Fallgatter A, Warnke A. Electrophysiological investigation of the effectiveness of methylphenidate in children with and without ADHD. *J. Neural Transm.* 2003; 110: 821–829.
10. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 4th edn. American Psychiatric Association, Washington, DC, 1994.
11. Näätänen R. The role of attention in auditory information processing as revealed by event-related potentials and other brain measures of cognitive function. *Behav. Brain Sci.* 1990; 12: 201–288.
12. Hillyard SA, Hink RF, Schwent VL, Picton TW. Electrical signs of selective attention in the human brain. *Science* 1973; 182: 177–180.
13. Heilman KM, Voeller KK, Nadeau SE. A possible pathophysiologic substrate of attention deficit hyperactivity disorder. *J. Child Neurol.* 1991; 6 (Suppl.): 76–81.

14. Castellanos FX, Giedd JN, Marsh WL *et al.* Quantitative brain magnetic resonance imaging in attention-deficit hyperactivity disorder. *Arch. Gen. Psychiatry* 1996; 53: 607–616.
15. Konrad K, Neufang S, Hanisch C, Fink GR, Herpertz-Dahlmann B. Dysfunctional attentional networks in children with attention deficit/hyperactivity disorder: Evidence from an event-related functional magnetic resonance imaging study. *Biol. Psychiatry* 2006; 59: 643–651.