ORIGINAL

Usefulness of Near-Infrared Spectroscopy (NIRS) for evaluating drug effects and improvements in medication adherence in children with Attention Deficit Hyperactivity Disorder (ADHD)

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Abstract : The symptoms of attention deficit hyperactivity disorder (ADHD) are inattention, hyperactivity, and impulsiveness. Physicians often prescribe methylphenidate (MPH) for children with ADHD for long periods of time. The purpose of the present study was to investigate the usefulness of near-infrared spectroscopy (NIRS) for evaluating drug effects and improvements in medication adherence in children with ADHD. Subjects were 10 male children diagnosed with ADHD : average age, 9.3 years, and 10 boys with typical development : average age 9.5 years. Children with intellectual disability, autism, and obvious depressive symptoms were excluded. The present study revealed that in the ADHD group, oxy-Hb concentrations in the left and right lateral prefrontal cortex significantly increased during the execution of the Stroop color-word test in both channels when taking MPH. This method was considered to be useful for assessing drug effects on ADHD because NIRS is an objective indicator for evaluating ADHD executive dysfunction and visualizes the activation of frontal lobe function by MPH. A pediatric neurologist explained the results of NIRS while presenting images to the ADHD group, and medication adherence and the drug-taking ratio both markedly improved. Therefore, this therapeutic explanation is an effective strategy for improving medication compliance and adherence among patients. J. Med. Invest. 68 : 53–58, February, 2021

Keywords **:** *Children, ADHD (attention deficit hyperactivity disorder), NIRS (near-infrared spectroscopy), medication adherence, frontal lobe function*

INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is characterized by inattention, hyperactivity, and impulsiveness ; however, other conditions frequently co-exist with ADHD, including developmental and psychiatric disorders (1). ADHD has been identified across countries and cultures (2), and needs to be considered within the context of what is developmentally and culturally appropriate for an individual.

ADHD has been associated with the prominent disturbance of executive functions (3). Executive functions are defined as a set of neurocognitive skills that are necessary for planning, monitoring, and executing a sequence of goal-directed complex actions and include inhibition, working memory, and sustained attention (4). The frontal cortex is divided into five major functional subdivisions : the prefrontal (orbital, dorsolateral, and mesial), premotor, and motor regions : orbital prefrontal lesions are associated with social disinhibition and impulse control disorders ; dorsolateral prefrontal (DLPF) lesions are associated with organizational, planning, working memory, and attentional dysfunctions ; and mesial prefrontal lesions are linked to dysfluency and the slowing of spontaneous behaviors. The DLPF cortex has been implicated in the pathogenesis of the executive deficits observed in ADHD (5, 6).

Various interventions, including pharmacological and psychological, have been used in the treatment of ADHD (7). Methylphenidate (MPH), the most commonly administered medication for children with ADHD in many countries, is often prescribed for long periods of time (8). By inhibiting dopamine transporters, it reportedly increases dopamine concentrations in the synaptic cleft, thereby facilitating binding to receptors (9). Dopamine plays an important role in controlling processes from cognition to behavior, such as thinking and emotion in the frontal lobe and limbic system, planning actions in the basal ganglia, and selecting appropriate actions, and it also regulates executive functions in the frontal lobe (10). Forssberg *et al.* performed 3D PET scans to assess the utilization of L-[11C]-DOPA in adolescents with ADHD and found that the rate of dopamine synthesis in most brain areas was lower than in healthy controls (11). Children with ADHD need to take MPH medication continuously for a long period of time. Although adherence to medication is considered to be a key factor for the successful treatment of them, most do not adhere to their pharmacotherapy regimen (12).

In recent years, various studies (13-16) have focused on the use of near-infrared spectroscopy (NIRS), which visualizes the activity state of the brain in real time. NIRS is a method of capturing changes in cerebral blood flow caused by neural activity using near-infrared light. With NIRS, brain function may be easily and non-invasively evaluated by simply attaching a probe to the head (17). However, few studies have compared frontal lobe function between children with ADHD and those with typical development (18, 19). Furthermore, there is currently no information on the usefulness of NIRS for improving medication adherence in children with ADHD.

The present study focused on hemodynamic changes in regions of interest in the DLPF cortex before and after pharmacotherapy for ADHD and investigated whether NIRS may be used

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as an objective index for the diagnosis of ADHD and assessment of drug effects. The present study also examined whether the visualization of drug effects by NIRS increases a patient's willingness to be treated.

Therefore, the purpose of the present study was to investigate the usefulness of NIRS for evaluating drug effects and improvements in medication adherence in children with ADHD.

METHODS

Subjects

Ten male children with ADHD : average age 9.3 years (7-12 years), and 10 male children with typical development : average age 9.5 years (7-13 years), participated in the present study. The intelligence index of ADHD children was 98.5 ± 5, as evaluated by WISC-IV (the Wechsler Intelligence Scale for Children). Inclusion criteria were a clinical diagnosis of ADHD (DSM-IV (20)). Exclusion criteria were children with intellectual disability, autism, and obvious depressive symptoms.

NIRS Data Collection Period

Data were collected between July 2013 and March 2014.

NIRS Data Collection Methods

Data collection took place in the NIRS laboratory of a tertiary medical institution in a local city in Japan. Researchers carried out NIRS measurements using NIRStation near-infrared light brain function imaging OMM-3000-12.17-channel probes, which were attached to the left and right forehead.

As a stimulus task, incongruent stimuli are those in which the ink color and word differ, researchers administered the Stroop color-word test. The Stroop color-word test is one of the neuropsychological tests used to evaluate executive functions. At the time of NIRS measurements, a 60-second control task was inserted before the 60-second stimulation task, and the task was repeated five times in total. As a control task, congruent stimuli are those in which the ink color and word refer to the same color (for example the word "red" written in red). The baseline correction was set to zero at the start of the stimulus task, smoothing was performed using the Savitzky-Golay method, and averaging was conducted five times to obtain an averaging waveform. The integrated value of the average oxygenated hemoglobin (oxy-Hb) waveform during the stimulation task was calculated, and this value was used to indicate the extent to which the concentration of oxy-Hb changed.

The test was performed twice by children with ADHD ; when they took MPH medication, and when they were not taking the medication. To enable researchers to perform the examination when children were not taking MPH medication, it was done during a period of more than two weeks. Five patients were examined in the order of "non-dose" and "dose", while the remaining five were examined in the reverse order.

The first and second tests were performed at least one month apart. The ADHD-Rating Scale (RS) was used to examine the clinical effects of MPH. ADHD-RS was scored by the parents of subjects. A pediatrician explained NIRS results and Stroop task performance (correct answer rate and number of answers) to children with ADHD and their parents at the same time. Changes in the medication rate and willingness to take medication before and after the procedure were also examined. Willingness to take medication was evaluated on a numerical scale, with a response from 0 to 10. Parents were asked to report their children's medication status for one month before and after receiving explanations about test results by NIRS.

Data Analysis

The Mann-Whitney U test was used for comparisons between the ADHD group and the typical development group. The Wilcoxon signed-rank test was used to compare the ADHD group when taking and not taking MPH, as well as medication adherence in the ADHD group and the drug-taking ratio (patient compliance) before and after NIRS measurements. SPSS 18 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses. The level of significance was set to 0.05.

Ethical Considerations

Researchers obtained approval for this research study from the Tokushima University Hospital Ethics Board (No. 1671). Subjects were assured that their personal information would be protected and that the results of the study would only be reported as aggregate data and solely be used for research purposes. The purpose and procedure of the present study were explained to all subjects and their parents/guardians, and informed consent was obtained.

RESULTS

Figure 1 shows a typical example of the trend graph and extent of the change in the concentration of oxy-Hb (mapping analysis) during the execution of the Stroop color-word test in a child with typical development. In the bilateral prefrontal cortexes, particularly in ch8 (⬇) and ch27 (⬇), a marked increase was observed in the concentration of oxy-Hb. The bilateral prefrontal cortexes turned red due to an increased in the concentration of oxy-Hb. In the present study, the increase observed in the concentration of oxy-Hb was the greatest in ch8 (right) and ch27 (left) in other typically developed children. Therefore, researchers focused on these two channels and compared them with the ADHD group.

Figure 2 shows a typical example of the oxy-Hb mapping analysis during the Stroop color-word test in a child with ADHD. When not taking MPH, a slight increase was observed in the concentration of oxy-Hb in the bilateral prefrontal cortexes (Fig. 2-A). In contrast, a marked increase was noted when taking MPH (Fig. 2-B).

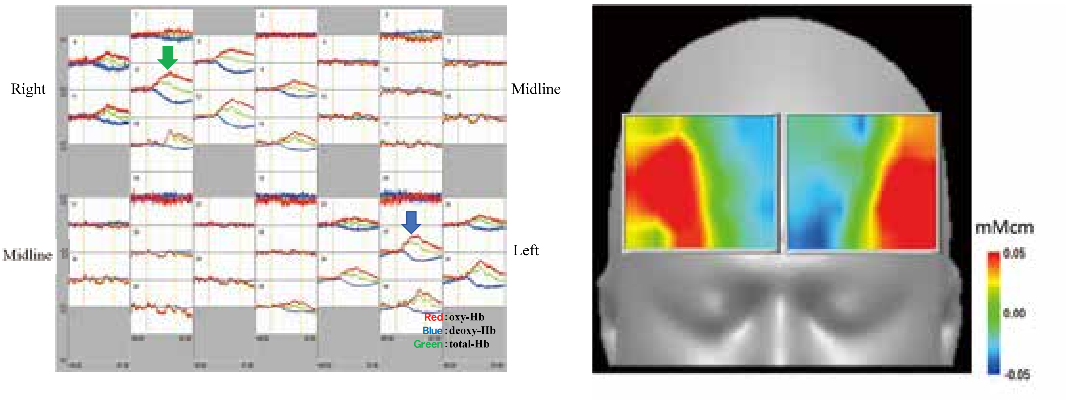
Table 1 shows the results of comparisons of oxy-Hb concentration changes during the Stroop color-word test between the ADHD group (when taking and not taking MPH) and typical development group.

In the ADHD group when MPH was not taken, increases in oxy-Hb concentrations in ch8 (right) and ch27 (left) were significantly less than in the typical development group ($p < 0.05$). No significant differences were observed in oxy-Hb concentration changes at both channels between the ADHD group when taking MPH and the typical development group.

Figure 3 shows the extent of changes in oxy-Hb concentrations in the lateral prefrontal cortexes (ch8, ch27) when the Stroop color-word test was performed in the ADHD group. In comparisons of the ADHD group when taking and not taking MPH, oxy-Hb concentrations significantly increased in both channels when taking MPH.

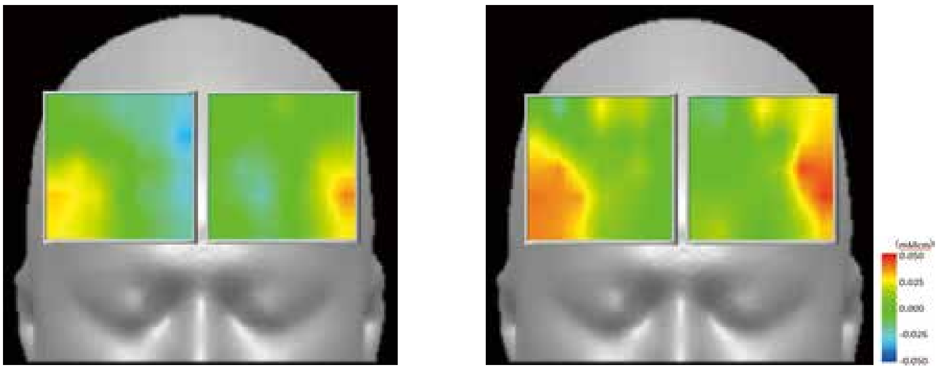
Table 2 shows the results of comparisons of performance in the Stroop color-word test between the ADHD group (when taking and not taking MPH) and typical development group. The correct answer rate ($p < 0.01$) and number of responses ($p < 0.05$) per minute during the Stroop color-word test in the ADHD group (when not taking MPH) were significantly lower than those in the typical development group.

The correct answer rate in the Stroop color-word test by the ADHD group (when taking MPH) was significantly lower than



A B

Figure 1. Typical example of a trend graph (A) and oxy-Hb mapping analysis (B) during the Stroop color-word test in a child with typical development
A : In the bilateral prefrontal cortexes, particularly in ch8 (⬇) and ch27 (⬇), a marked increase was observed in oxy-Hb concentrations. B : The bilateral prefrontal cortexes turned red due to the increase in the concentration of oxy-Hb



A B

Figure 2. Typical example of the oxy-Hb mapping analysis during the Stroop color-word test in a child with ADHD
A : When not taking MPH, a slight increase was observed in the concentration of oxy-Hb in the bilateral prefrontal cortexes. B : When taking MPH, a marked increase was noted.

Table 1. Comparison of oxy-Hb concentration changes during the Stroop color-word test between the ADHD group (when taking and not taking MPH) and typical development group

		ch8 (Right)			ch27 (Left)		
		ADHD group (N = 10)		Typical development group (N = 10)	ADHD group (N = 10)		Typical development group (N = 10)
MPH (-)	MEDIAN	0.36		0.85	0.15		0.97
	RANGE	-0.89 to 1.69		0.54 to 3.41	-0.93 to 1.73		0.66 to 4.01
	z		-1.99			-2.18	
	p		*			*	
MPH (+)	MEDIAN	0.85		0.85	1.07		0.97
	RANGE	0.50 to 1.90		0.54 to 3.41	0.30 to 1.60		0.66 to 4.01
	z		-0.36			-0.56	
	p		NS			NS	

The Mann-Whitney U test was used for comparisons between the ADHD group and typical development group. An examination was conducted when children were not taking MPH during a period of more than 2 weeks. Five patients were examined in the order of “non-dose” and “dose”, and the remaining five were examined in the reverse order. The first and second tests were performed at least one month apart. MPH (-) means not taking MPH, and MPH (+) means taking MPH, * $p < 0.05$. NS, not significant.

that by the typical development group ($p < 0.05$). In contrast, no significant differences were observed between the number of responses per minute during the Stroop color-word test between the ADHD group (when taking MPH) and typical development group.

Table 3 shows the ADHD-RS score in the ADHD group, the correct answer rate and number of responses during the Stroop color-word test when taking and not taking MPH, the evaluation score of willingness to take the drug before and after the explanation of NIRS results, and the drug-taking ratio.

Researchers compared the ADHD group when taking and not taking MPH, as well as medication adherence in the ADHD group and the drug-taking ratio (patient compliance) before and after displaying and explaining NIRS test results using images.

The ADHD group was evaluated using ADHD-RS when taking and not taking MPH, and all cases achieved better scores when taking MPH. Furthermore, the correct answer rate and number of responses during the Stroop color-word test were significantly higher when taking MPH ($p < 0.01$). Regarding changes in willingness to take medication and the rate of taking medication in the ADHD group, both were markedly improved by displaying and explaining NIRS test results using images ($p < 0.01$).

DISCUSSION

Since Barkley (21) advocated the lack of behavioral suppression as the true form of ADHD, the psychological hypothesis of ADHD based on executive dysfunction that is centered on the lateral prefrontal cortex has been widely accepted. Disorders such as decreased action restraint and the continuation of attention measured by neuropsychological tests, such as the Stroop task, go/no-go task, and working memory task, are prominently

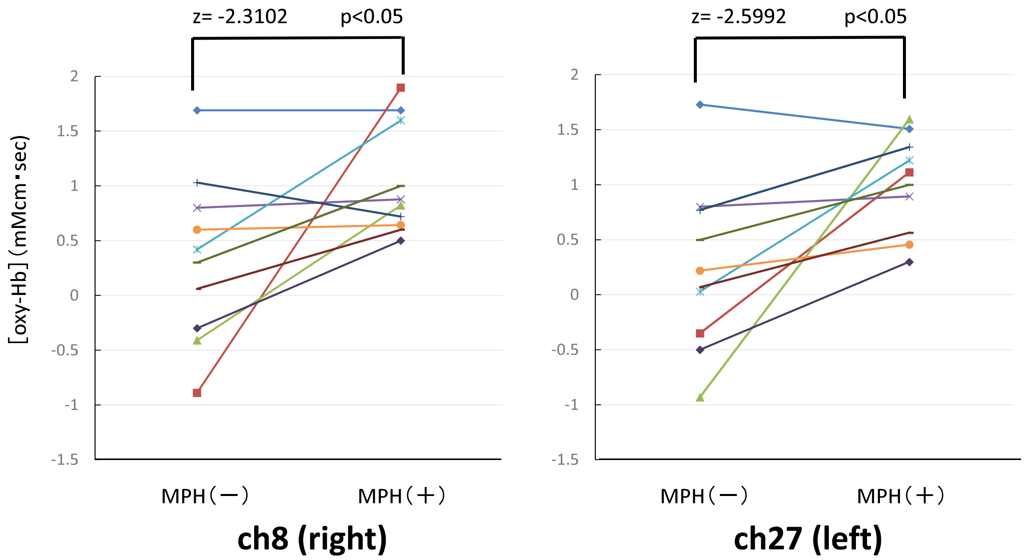


Figure 3. Oxy-Hb concentration changes in the lateral prefrontal cortex during the Stroop color-word test in the ADHD group when taking and not taking MPH
MPH (-) means not taking MPH, and MPH (+) means taking MPH. In comparisons between taking and not taking MPH, oxy-Hb concentrations significantly increased in both channels (ch8, ch27) when taking MPH.

Table 2. Comparison of performance in the Stroop color-word test between the ADHD group (when taking and not taking MPH) and typical development group

		Stroop color-word test (Correct answer rate)			Stroop color-word test (Number of responses)		
		ADHD group (N = 10)		Typical development group (N = 10)	ADHD group (N = 10)		Typical development group (N = 10)
MPH (-)	MEDIAN	85%		97%	36.35		42.88
	RANGE	67 to 93%		93 to 98%	12 to 57		30.8 to 59.5
	z		3.67			2.00	
	p		**			*	
MPH (+)	MEDIAN	92%		97%	43.75		42.88
	RANGE	74 to 96%		93 to 98%	16.2 to 59		30.8 to 59.5
	z		3.09			0.11	
	p		*			NS	

The Mann-Whitney U test was used for comparisons between the ADHD group and typical development group. An examination was conducted when children were not taking MPH during a period of more than 2 weeks. Five patients were examined in the order of “non-dose” and “dose”, and the remaining five were examined in the reverse order. The first and second tests were performed at least one month apart. MPH (-) means not taking MPH, and MPH (+) means taking MPH, ** $p < 0.01$. * $p < 0.05$. NS, not significant.

Table 3. Changes in each index in the ADHD group

(n=10)		MEDIAN	RANGE	z	p
ADHD-RS	MPH (-)	36.50	20-44	-2.81	**
	MPH (+)	17.00	8-30		
Correct answer rate	MPH (-)	85.00	67-93	-2.51	**
	MPH (+)	92.00	74-96		
Number of responses	MPH (-)	36.35	12-57	-2.55	**
	MPH (+)	43.75	16.2-59		
Willingness to take medication	Before NIRS test	5.50	1-10	-2.57	**
	After NIRS test	7.00	3-10		
Medication rate	Before NIRS test	86.50	50-100	-2.52	**
	After NIRS test	100.00	80-100		

The Wilcoxon signed-rank test, MPH (-) means not taking MPH, and MPH (+) means taking MPH, ** $p < 0.01$.

recognized in ADHD (22).

Patients with ADHD showed reduced task-related increases in the concentration of oxy-Hb in NIRS channels located over the ventro-lateral prefrontal cortex during the performance of the working memory (n-back) task (23). Negoro *et al.* also reported that oxy-Hb concentration changes in the inferior lateral prefrontal cortexes bilaterally during the Stroop color-word test were significantly greater in a control group than in an ADHD group (18).

NIRS was also used in the present study to compare the frontal lobe function of the ADHD group with that of the typical developmental group. In the NIRS test, using the Stroop color-word test, oxy-Hb concentrations in the left and right lateral prefrontal cortexes of the typical developmental group increased during the task. However, in the ADHD group, when MPH was not taken, the increases observed in oxy-Hb concentrations in the left and right lateral prefrontal cortexes were small and significantly less than those in the typical development group. Therefore, the test combination of the Stroop color-word test with NIRS was considered to be useful for assessing prefrontal brain dysfunction in children with ADHD.

Monden *et al.* (19) monitored oxy-Hb signal changes in ADHD children performing go/no-go tasks to examine inhibitory and attentional control. In control subjects, the go/no-go task recruited the right inferior and middle prefrontal gyri (IFG/MFG) ; however, this activation was absent in pre-medicated ADHD children. The reduction in right IFG/MFG activation acutely normalized after the administration of MPH.

In the present study, when the Stroop color-word test was performed by the ADHD group while taking MPH, a marked increase was observed in oxy-Hb concentrations in the left and right lateral prefrontal cortexes. Comparisons between taking and not taking MPH revealed a significantly larger change in oxy-Hb concentrations at the same site when taking MPH. Therefore, NIRS appears to be a promising tool for the detection of pharmacological-treatment biomarkers in children with ADHD.

The percentage of correct answers improved (from $p < 0.01$ to $p < 0.05$) and the number of responses per minute during the Stroop color-word test significantly increased in the ADHD group with the administration of MPH. In addition, all cases achieved better ADHD-RS scores when taking MPH. This result showed that the use of MPH was clinically effective in terms of self-control and sustaining attention.

No significant differences were observed in the number of responses per minute during the Stroop color-word test between the ADHD group taking MPH and the typical development group. However, the percentage of correct answers in the Stroop color-word test was still significantly lower in the ADHD group taking MPH than in the typical development group. These results are consistent with the findings reported by Zheng *et al.* (24). A long duration of pharmacotherapy may be required for the normalization of inhibition capacity in the Stroop color-word test in children with ADHD.

ADHD drugs, such as MPH, very effectively improve clinical symptoms. However, children with ADHD often experience difficulties taking the drug continuously for a long period of time (25). In the present study, by showing images of NIRS test results and explaining them to the children themselves, willingness to take medication significantly increased and they sustained the rate of taking medication. NIRS visualizes brain activities at the time of task execution in real time and clearly shows the effects of drugs, even for children. In the future, NIRS will be an effective means for improving willingness to control ADHD symptoms by the children themselves.

LIMITATION OF THE PRESENT STUDY

Due to the small sample size, the present results may not be generalizable. Consequently, further studies on a larger sample size are needed. Furthermore, MPH was administered to children under parental control. Their parents also understood ADHD symptom improvement levels as assessed by the ADHD-RS and NIRS test results. Therefore, it cannot be denied that parental understanding of medication efficacy may have been involved in the improvement observed in the medication rate. However, researchers confirmed improvements in a child's willingness to take medication when NIRS test results and the results of the Stroop task (correct answer rate and number of responses) were explained. Nevertheless, the willingness of a child's parents to support medication was not evaluated in the present study.

CONCLUSION

NIRS was considered to be useful for assessing the effects of drugs for ADHD because it is an objective indicator for evaluating ADHD executive dysfunction and visualizes the activation of frontal lobe function by MPH. A pediatric neurologist explained the results of NIRS while presenting images to the ADHD group, and medication adherence and the drug-taking ratio both markedly improved. Therefore, this therapeutic explanation is an effective strategy for increasing medication compliance and adherence.

CONFLICT OF INTEREST

All authors declare no actual or potential conflicts of interest associated with this study.

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