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Prefrontal Abnormality in Children with ADHD during Cognitive Interference Control: a Functional NIRS Study

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Abstract **Aim:** Children with attention-deficit/hyperactivity disorder (ADHD) show cognitive impairments such as disrupted attention and impaired learning and memory. The multi-source interference task (MSIT) combines multiple dimensions of cognitive interference and recruits the cingulo-frontal-parietal cognitive/attention network. The aim of this study was to determine whether children with ADHD show fronto-parietal dysfunction during the MSIT by using functional near-infrared spectroscopy (NIRS). **Methods:** Nineteen boys with ADHD and 14 age- and IQ-matched controls were studied. We measured oxygenated hemoglobin concentration ([oxy-Hb]) changes in the fronto-parietal region by using a 46-channel functional NIRS imaging system. The behavioral performance and mean [oxy-Hb] of the two groups during the MSIT were compared.**Results:** The behavioral data of the MSIT were not significantly different between the two groups. Compared to the control group, the ADHD group showed higher [oxy-Hb] changes in the left dorsolateral prefrontal region (ADHD, $0.17 \times 10^{-1} \pm 0.11$; control, $-0.65 \times 10^{-1} \pm 0.62 \times 10^{-1}$; $P = 0.02$). **Conclusion:** Our results suggest that compared to controls, children with ADHD have abnormal prefrontal activation in response to multiple interference control, in order to achieve favorable outcomes of cognitive demand. These findings may provide insights into the pathophysiology of ADHD.

Key words: attention-deficit/hyperactivity disorder, dorsolateral prefrontal cortex, hemodynamic response, multi-source interference, near-infrared spectroscopy.

Supplementary Table. List of abbreviations in the text

ADHD	Attention-deficit/hyperactivity disorder
MSIT	multi-source interference task
DLPFC	dorsolateral prefrontal cortex
Functional MRI	functional magnetic resonance imaging
Functional NIRS	functional near-infrared spectroscopy
ADHD-RS	ADHD Rating Scale
CBCL	Child Behavior Checklist
GAF	Global Assessment of Functioning
FDR	False discovery rate

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a developmental/behavioral disorder characterized by age-inappropriate symptoms of inattention, impulsiveness, and hyperactivity. ADHD symptoms persist into adulthood in 65% of the cases of childhood ADHD.[1] Despite this high level of morbidity, the pathophysiology of ADHD remains unknown.

Individuals with ADHD show impaired executive functioning, including deficits in response to inhibition, set shifting, interference, planning, and working memory.[2,3] A systematic review of the executive function using the Flanker and Simon task suggests that children with ADHD show deficits in interference control relative to controls.[4] Bush et al.[5] developed the multi-source interference task (MSIT) that combined multiple dimensions of cognitive interference (i.e., Stroop tasks, Eriksen Flanker-type tasks, and Simon effect task variants) with decision-making, target detection, novelty detection, error detection, response selection, stimulus/response competition, and task difficulty. The MSIT is designed to effect functional activation of the dorsal anterior midcingulate cortex, dorsolateral prefrontal cortex (DLPFC), and parietal cortex in the cingulo-frontal-parietal cognitive/attention network, which plays a critical role in attention and cognitive processing.[5] Functional magnetic resonance imaging (MRI) studies using the MSIT have been reported in adults with ADHD;[6,7] for instance, adults with ADHD who were treated with methylphenidate showed greater activation of the dorsal anterior midcingulate cortex during the MSIT than did those treated with placebo.[6] To our knowledge, there has been no functional neuroimaging study using the MSIT in children with ADHD.

Functional near-infrared spectroscopy (NIRS), an optical method for measuring changes in brain oxygenation, is noninvasive and relatively insensitive to motion artifacts, making it suitable for measuring brain functions in children with ADHD. Similar to functional NIRS studies in adults with schizophrenia and depression,[8,9] studies in children with ADHD have reportedly increased, but with inconsistent findings; one reported that children with ADHD were not significant difference of prefrontal activation compared with controls, whereas others show decreased activation of the frontal area compared with controls.[10-12] However, to our knowledge, no functional NIRS study has evaluated the fronto-parietal function in children with ADHD.

The aim of this study was to determine whether children with ADHD show prefrontal and parietal dysfunction during the MSIT, by using functional NIRS. We hypothesized that compared to control children, children with ADHD would show poor task performance and functional abnormalities in the prefrontal and parietal regions during the MSIT, and that these abnormalities would be associated with the severity of ADHD.

Methods

Subjects

Participants were 19 boys with ADHD and 14 controls. The patients were recruited from 2 sites-Yamaguchi University Hospital and Hiroshima City Child Guidance and Clinic Center. Children with ADHD were diagnosed

according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision criteria by clinical interview and clinical conference by child and adolescent psychiatrists. The patients were also administered the International Neuropsychiatric Interview for Children and Adolescents, Japanese version[13] to confirm the diagnosis and evaluate comorbid psychiatric illnesses. Any child with ADHD who had a comorbid pervasive disorder or other psychiatric disorder such as mood disorders, anxiety disorders, or conduct disorders was excluded from this study. All control subjects were screened by the International Neuropsychiatric Interview for Children and Adolescents, Japanese version. Control subjects with first- or second-degree relatives with any psychiatric disorders were excluded from this study. All participants had a full IQ score of 85 or more in the Wechsler Intelligence Scale for Children-Third Edition and were right-handed.[14] Parents scored the puberty status of their child based on the Pubertal Development Scale.[15] The socioeconomic status of parents was assessed by the Hollingshead Index of Socioeconomic Status.[16] All participants received a physical examination and blood tests to rule out medical illnesses. Medical conditions such as metabolic illnesses, liver disease, kidney problems, or respiratory problems were also grounds for exclusion.

Children with ADHD were evaluated for behavioral symptoms using the ADHD Rating Scale (ADHD-RS)-IV-Japanese Version.[17] The home version of this rating scale was scored by parents, and the school version was completed by homeroom teachers. ADHD-RS evaluates the severity of ADHD symptoms and the higher score indicates more severe ADHD symptoms.

We assessed behavior using the Child Behavior Checklist (CBCL), an internationally validated questionnaire for emotional and behavioral problems for children between ages 4 and18 years.[18] The CBCL queries parents about their child's behavior over the past 6 months and aggregates those data into T scores. The CBCL provides Internalizing and Externalizing summary scores reported as sex- and age-normed T-scores. High T-scores indicate severe and frequent behavioral problems and T-scores ≥ 64 on either scales are considered to be in the clinical range.[18] At the beginning of the study, 15 of the children with ADHD were medicated with methylphenidate (mean ± SD; 22.3 ± 9.7 mg), 1 with atomoxetine (40.0 ± 10.0 mg), 1 with both drugs, and 1 was on methylphenidate, atomoxetine and aripiprazole. One child was medication naïve. Because children with ADHD were medicated at school on weekdays, we studied medicated patients to clarify their brain dysfunction in their day-to-day life and could not ethically allow them to stop taking medication in order to participate in the study.

The study was approved by the Institutional Review Board of Yamaguchi University Hospital and the ethics committee in Hiroshima City Child Guidance and Clinic Center. After completely describing the study to subjects, written informed consent from parents and assent from children were obtained.

Task description

We assembled a MSIT task for functional NIRS study using Presentation software according to the original protocol.[5] Participants viewed a set of 3 digits on a computer screen and were instructed to report, via pressing a control-pad, the identity of the number that was different from the other 2 numbers (Fig. 1). For the baseline task, the distracters are zeroes and the target number (1, 2, or 3) is always placed congruently with its position on the pad. In the interference (activation) task, the distracters are other numbers (1, 2, or 3), and the target number (1, 2, or 3) is never placed congruently with their positions on the pad. The task design included a 30-s pre-task (the baseline task), a 40-s interference task, and an 80-s post-task (the baseline task) period. The sets of numbers are changed every 2 seconds. The instructions appear for 11 s before each trial. We verified that participants correctly learned the task when they participated in the practice session, which consisted of 6 trials of the baseline task and 8 trials of the interference task.

NIRS measurement

During the MSIT, we measured the oxygenated hemoglobin concentration ([oxy-Hb]) changes in the fronto-parietal region

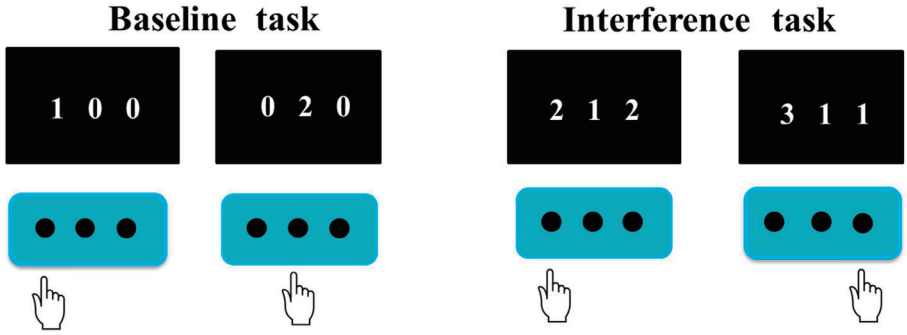

Figure 1. Example of a multi-source interference task
The distracters are the zeroes, and target numbers (1, 2, or 3) are always placed congruently with their position on the pad in the baseline task. In the interference task, the distracters are other numbers (1, 2, or 3), and target numbers (1, 2, or 3) are never placed congruently with their position on the pad in the MSIT. The hand indicates the correct choice.

using a 46-channel NIRS imaging system (ETG-4000, Hitachi Medical Corporation, Tokyo, Japan). Subjects sat in a comfortable chair without any restraints on their bodies. Their eyes were open throughout the measurements. The device uses near-infrared light at 2 wavelengths (695 nm and 830 nm) and [oxy-Hb] was estimated from the detected changes of the near-infrared light on the basis of the Beer-Lambert law.[19] We used a head-cap with 2 folders; 1 folder had 22 channels placed on the frontal region, and the other had 24 channels placed on the parietal region. The lowest probe line was set along the Fp1-Fp2 line and the middle probe of the line was set at the FPz as defined by the International 10-20 system used for electroencephalography. The inter-probe distance was 30 mm. The device is said to measure points at a depth of 20-30 mm below the scalp, which corresponds to the surface of the cerebral cortex.[20] Time resolution was set at 100 ms. Linear fitting using [oxy-Hb] data of the pre- and post-task was applied for baseline correction: the pre-task baseline was determined as the mean across the last 10 s in the 30-s pre task period and the post-task baseline was determined as the mean across the last 5 s in the 80-s post task period.[21] The moving average method was used to exclude short-term motion artifacts in the analyzed data (moving average window: 5 s). Although the relevance of deoxygenated hemoglobin concentration has not been established, [oxy-Hb] changes are reportedly strongly correlated with the blood-oxygenation level-dependent signal changes of functional MRI.[22] Thus, we used the changes in [oxy-Hb] during the MSIT for the analysis. The value of [oxy-Hb] was in mmol·mm.[19] The anatomical regions were estimated using a virtual registration method and the Platform for Optical Topography Analysis Tools (http://www.jichi.ac.jp/brainlab/tools.html).[23]

Statistical analyses

The mean reaction time, the cognitive interference effect (reaction time of the interference task - reaction time of the baseline task)[5], and the accuracy (%) of the MSIT were compared between children with ADHD and control children using Student's *t*-test. Pearson's correlation coefficient was used for the correlation between the task-performance, the dose of methylphenidate, and the scores of CBCL, Global Assessment of Functioning (GAF), and ADHD-RS in children with ADHD.

To screen channels activated by the MSIT, we compared the mean [oxy-Hb] changes of the pre-task (10 s before the interference task) and interference task for each channel in control children using paired Samples *t* test.[24] Significance was defined as false discovery rate (FDR) correction set at $P < 0.05$ based on the application of FDR (P_{FDR}) for functional NIRS analyses.[25] A channel with significant change in control children was

defined as "an effective channel". We also compared the mean [oxy-Hb] changes of the pre-task and interference task for each channel in children with ADHD. For the effective channels, the mean [oxy-Hb] changes in the interference task were compared between children with ADHD and control children using Student's *t*-test. At the effective channels that showed significant differences between the 2 groups, we also tested the correlation between the mean [oxy-Hb] during the task and clinical variables, including the dose of methylphenidate and the scores of CBCL, GAF, and ADHD-RS, in children with ADHD using Pearson's correlation coefficient.

Results

The clinical and demographic details of subjects are shown in Table 1. There were no significant differences between children with ADHD and control children in body mass index, pubertal development score, or Hollingshead Index of Socioeconomic Status. Compared to control children, children with ADHD showed significantly higher internalizing and externalizing T scores in the CBCL (t = -4.83, $P < 0.01$; t = -4.94, $P < 0.01$) and significantly lower scores on the GAF (t = 9.93, $P < 0.01$).

Table 1. Clinical and demographic characteristics of participants

	ADHD children (n = 19)	Control children (n = 14)	t	P
Age (years)	8.2 ± 1.0	8.2 ± 1.6	0.01	0.99
WISC				
Full IQ	107.1 ± 12.4	107.4 ± 14.1	0.05	0.96
BMI	16.0 ± 2.4	15.5 ± 1.1	-0.81	0.43
Pubertal development score	5.3 ± 0.6	5.6 ± 0.8	1.35	0.19
SES				
Father	34.6 ± 10.1	41.5 ± 11.9	1.79	0.08
Mother	29.2 ± 11.8	36.9 ± 11.2	1.91	0.07
ADHD-RS, Home version				
Total	27.6 ± 9.1	N.A.	N.A.	N.A.
Inattention	15.1 ± 5.2	N.A.	N.A.	N.A.
Hyperactivity- impulsivity	12.5 ± 4.6	N.A.	N.A.	N.A.
ADHD-RS, School version				
Total	18.1 ± 10.6	N.A.	N.A.	N.A.
Inattention	9.4 ± 5.9	N.A.	N.A.	N.A.
Hyperactivity- impulsivity	8.7 ± 5.7	N.A.	N.A.	N.A.
CBCL				
Internalizing T	61.4 ± 9.1	49.3 ± 5.2	-4.83	< 0.01
Externalizing T	69.2 ± 12.1	50.2 ± 9.1	-4.94	< 0.01
GAF	75.0 ± 10.0	98.3 ± 2.1	9.93	< 0.01

SES, Hollingshead Socio-Economic Status; ADHD-RS, ADHD Rating Scale-IV; CBCL, Child Behavior Checklist; GAF, Global Assessment of Functioning; WISC, Wechsler Intelligence Scale for Children-Third edition.

Table 2. Performance on Multi-Source Interference Task

	ADHD children	Control children	t	P
Reaction time (ms)	1040.9 ± 176.7	1077.1 ± 157.9	0.61	0.55
Interference effect (ms)	341.2 ± 199.0	360.5 ± 212.3	0.27	0.79
Accuracy (%)	62.1 ± 23.1	71.3 ± 19.8	1.19	0.24

Data were presented as mean ± SD. Group differences tested with Student's *t*-test.

Behavioral data

There were no significant differences between children with and without ADHD for the reaction time, the cognitive interference effect, or accuracy (% correct) (Table 2). The 3 performances were not significantly correlated with clinical variables including the scores for CBCL, GAF, ADHD-RS, and dose of methylphenidate in children with ADHD.

Functional NIRS

There were significant differences in [oxy-Hb] changes between the pre-task and the interference task in 2 channels in control subjects; e.g., channel #6 (the pre-task, $-0.11 \times 10^{-2} \pm 0.20 \times 10^{-2}$; the interference task, $-0.65 \times 10^{-1} \pm 0.62 \times 10^{-1}$; $t = 3.88$, $P_{FDR} = 0.002$, Cohen's $d = -1.46$) and #2 (the pre-task, mean ± SD, $-0.48 \times 10^{-3} \pm 0.15 \times 10^{-2}$; the interference task, $-0.75 \times 10^{-3} \pm 0.75 \times 10^{-1}$; $t = 3.74$, $P_{FDR} = 0.002$, Cohen's $d = -1.41$). The two channels were defined as "effective channel". The [oxy-Hb] during the interference task in these channels was decreased compared that during the pre-task. Children with ADHD did not show any channel with significant differences between the pre-task and the interference task. The mean [oxy-Hb] change was significantly different between children with and without ADHD in channel #6, ($0.17 \times 10^{-1} \pm 0.11$, $-0.65 \times 10^{-1} \pm 0.62 \times 10^{-1}$, respectively; $t = -2.44$, $P = 0.02$, Cohen's $d = 0.89$) but not in channel #2 ($-0.35 \times 10^{-1} \pm 0.14$, $-0.75 \pm 0.75 \times 10^{-1}$, respectively; $t = 0.35$, $P = 0.35$, Cohen's $d = 0.38$). Fig. 2 shows the grand average waveforms of [oxy-Hb] changes in the fronto-parietal region during the MSIT in children with or without ADHD. The brain area in channel #6 was estimated to encompass 100% of the left DLPFC by Platform for Optical Topography Analysis Tools (Fig. 3).

The [oxy-Hb] changes in channel #6 during the task did not significantly correlate with clinical variables in children with ADHD, including the dose of methylphenidate, the score of CBCL, GAF score, and the ADHD-RS score.

Discussion

Children with ADHD demonstrated similar behavioral performance on the MSIT and abnormal activity in the left DLPFC when compared to control children. The control children showed decreased [oxy-Hb] in the left DLPFC (channel #6) while the children with ADHD did not. As the NIRS instrument measures relative changes in [oxy-Hb], we defined the [oxy-Hb] changes during the interference task of control children as "normal" in the current study. Therefore, we interpreted that the left DLPFC in children with ADHD was relatively overactivated during the task compared to that in control children. The abnormal activity of the DLPFC was not associated with ADHD severity, behavioral problem, or medication load in the patients with ADHD. The results suggest that in the regions which are recruited by multiple cognitive interference, the brain activity of children with ADHD is different from that of control children for being successful in behavioral performance and this abnormality is independent of ADHD severity.

To date, 2 functional NIRS studies on children with ADHD have used other cognitive interference tasks such as the Stroop color-word task.[10,11] In one study demonstrated that boys with ADHD showed higher [deoxy-Hb] in the right DLPFC than did control boys, but the task performance and [oxy-Hb] changes in both the DLPFC were not significantly different between the 2 groups.[11] The authors of this study interpreted the results to mean that patients with ADHD have a compensatory activation of the right DLPFC. A second study, patients with ADHD had lower task performance and a smaller change in [oxy-Hb] in the prefrontal cortex than the controls,[10] which was interpreted to mean that the prefrontal brain activation in patients with ADHD might be insufficient to fulfill all functions during the task. In light of the previous findings, the results of the current study suggest that children with ADHD may show more activation in the left DLPFC in order to achieve comparable success in cognitive and behavioral performance to that of control children.

We also showed that the left DLPFC activity during the interference task was independent of severity of ADHD. A prior functional NIRS study on patients with ADHD

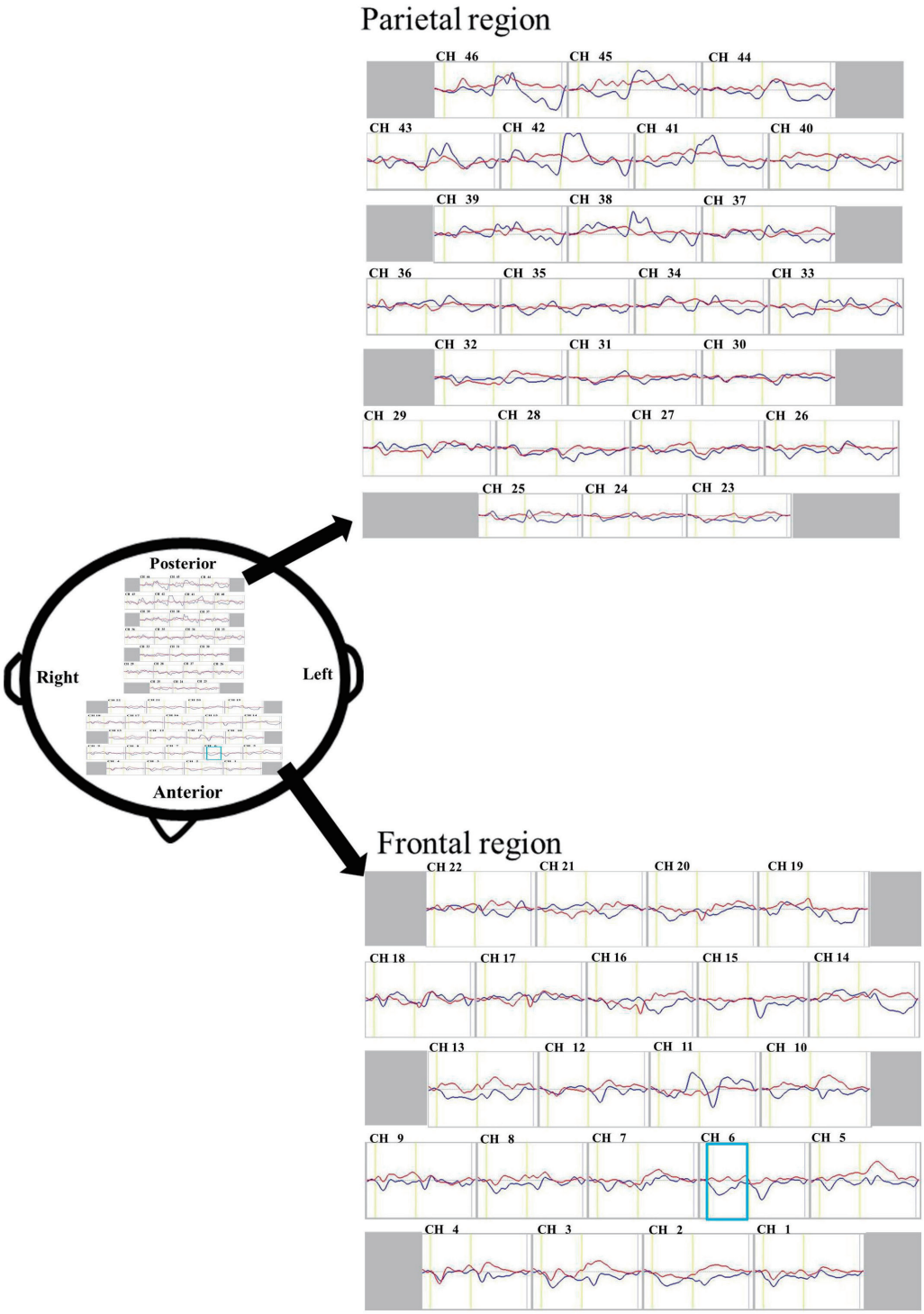

Figure 2. Grand average waveforms of [oxy-Hb] changes during the MSIT in the frontal and parietal regions in children with ADHD and control children.

The lower figure on the right represents channels #1 to #22 in the frontal region and the upper figure on the right represents channels #23 to #46 in the parietal region. The red line represents the grand average waveforms of [oxy-Hb] in children with ADHD and the blue line represents the grand average waveforms of [oxy-Hb] in control children. The period of the interference task in the MSIT is between the yellow lines. Turquoise boxes indicates channel #6 with a significant difference in [oxy-Hb] between children with and without ADHD.

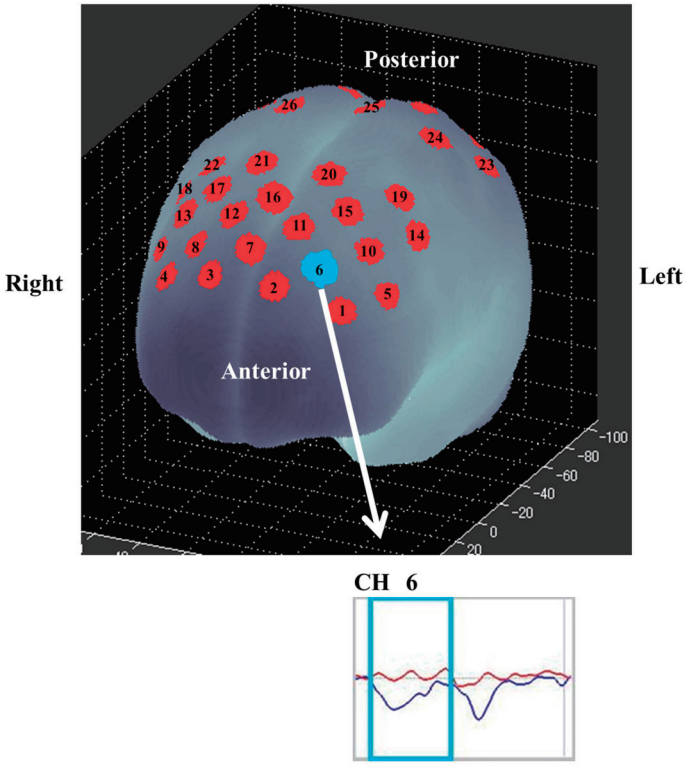

Figure 3. Anatomical location of channel #6 superimposed on a 3D-MRI model of a brain.

The number in patches represents the name of the channel. Turquoise patches indicates channel #6 with a significant difference in [oxy-Hb] between children with and without ADHD. Grand average waveforms of [oxy-Hb] changes in channel #6 show a significant difference between children with ADHD and control children. The red line represents the grand average waveforms of [oxy-Hb] in children with ADHD and the blue line represents the grand average waveforms of [oxy-Hb] in control children.

showed a negative correlation between the right lateral prefrontal cortex activity and the severity of attention deficit.[26] However, the differences between our results should be cautiously interpreted because there were methodological differences among the previous and current studies in utilizing the NIRS instrument, including the number of NIRS channels, the analysis of NIRS data, and the presence of psychiatric comorbidities and medications. Further functional NIRS studies of ADHD are required to test the association between brain function and clinical symptoms.

Functional abnormalities of the DLPFC in patients with ADHD are evident in functional MRI studies.[27,28] Boys with ADHD had reduced activation relative to healthy controls in the left DLPFC during a sustained attention task.[28] A meta-analysis of 55 functional MRI studies revealed that children with ADHD showed hyperactivation in the posterior cingulate and angular gyrus, and hypoactivation in frontal regions.[29] One study reported that boys with ADHD had hypoactivation of the bilateral DLPFC compared to control boys.[30] Another study demonstrated that patients with ADHD showed hypoactivation of the left DLPFC compared to the control subjects.[28] Although it has not been concluded that patients with ADHD show abnormal functioning of the DLPFC on the right, left or both sides, it is evident that abnormal DLPFC function is observed in patients with ADHD. The results in the current study further support this data. The functional neuroimaging studies and the current study provide the evidence that patients with

ADHD show abnormalities in the prefrontal activity including that of the DLPFC, which is involved in the pathophysiology of ADHD.

In the present study, we observed no significant differences in the activation of the parietal region during the MSIT between children with and without ADHD. A functional MRI study of the MSIT showed hyperactivation of the parietal cortex in medicated adults with ADHD compared to non-medicated ones.[6] However, this study did not report the depth of the activated regions in the parietal lobe, whether surface or deep areas.[6] Therefore, functional NIRS would be unable to detect the activation of the parietal region if the MSIT activates deep areas of the region. It is also possible that there is a developmental difference, such that children with ADHD do not activate parietal regions during the MSIT as adults with ADHD do. To resolve these issues, more functional MRI and NIRS studies on children with ADHD need to test the parietal function using the MSIT.

One consideration in interpreting the results of our study is the finding that methylphenidate allows frontal regions to become active in children with ADHD. A functional NIRS study on children with ADHD reported that the patients showed hyperactivation in the middle frontal region during a Go/NoGo task in the post-treated condition of methylphenidate compared to the pre-treated condition.[12] Other studies report that methylphenidate allows abnormal prefrontal function to be normalized, meaning that medicated patients with ADHD show comparable prefrontal activation to healthy subjects.[31,32] However, to our knowledge, there has been no study to show hyperactivation of prefrontal cortex in patients with ADHD treated with stimulants when compared to healthy subjects. Although the present study demonstrated that the mean [oxy-Hb] change in the left DLPFC and behavioral performance during the MSIT were not associated with methylphenidate load, and patients taking different medications have shown different neurological responses,[7] we cannot exclude the possibility that the medication is masking the brain dysfunction in children with ADHD. Future functional NIRS studies comparing pre- and post-treatment of methylphenidate in medication-naïve children with ADHD will help address this issue.

Other methodological limitations should be noted. First, the sample size was relatively small and may have limited our ability to demonstrate the results although the size of the effects in the functional NIRS results was relatively large. Second, because there is admittedly no other study using the MSIT in children, it is uncertain whether the task actually addresses specific processing pertinent to the executive function, and its neuroanatomical specificity remains speculative.

Nonetheless, the present study provides evidence that children with ADHD show abnormal activation of the DLPFC in response to interference control in order to achieve favorable outcomes of cognitive demand, and this abnormality is independent of the severity of ADHD. These findings may provide insights into the pathophysiology of ADHD.

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Conflict of Interest

The authors state no conflict of interest.

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References

1. Mannuzza, S., Klein, R.G., Moulton, J.L., 3rd.: Persistence of Attention-Deficit/Hyperactivity Disorder into adulthood: what have we learned from the prospective follow-up studies? *J. Atten. Disord.*, **7**: 93-100, 2003.
2. Schwartz, K., Verhaeghen, P.: ADHD and Stroop interference from age 9 to age 41 years: a meta-analysis of developmental effects. *Psychol. Med.*, **38**, 1607-1616, 2008.
3. Sonuga-Barke, E.J.: The dual pathway model of AD/HD: an elaboration of neurodevelopmental characteristics. *Neurosci.*

Biobehav. Rev., **27**: 593-604, 2003.
4. Mullane, J.C., Corkum, P.V., Klein, R.M., McLaughlin, E.: Interference control in children with and without ADHD: a systematic review of Flanker and Simon task performance. *Child Neuropsychol.*, **15**: 321-342, 2009.
5. Bush, G., Shin, L.M.: The Multi-Source Interference Task: an fMRI task that reliably activates the cingulo-frontal-parietal cognitive/attention network. *Nat. Protoc.*, **1**: 308-313, 2006.
6. Bush, G., Spencer, T.J., Holmes, J., Shin ,L.M., Valera, E.M., Seidman, L.J., Makris, N., Surman, C., Aleardi, M., Mick, E., Biederman, J.: Functional magnetic resonance imaging of methylphenidate and placebo in attention-deficit/hyperactivity disorder during the multi-source interference task. *Arch. Gen. Psychiatry*, **65**: 102-114, 2008.
7. Bush, G., Holmes, J., Shin, L.M., Surman, C., Makris, N., Mick, E., Seidman, L.J., Biederman, J.: Atomoxetine increases fronto-parietal functional MRI activation in attention-deficit/hyperactivity disorder: A pilot study. *Psychiatry Res.*, **211**: 88-91, 2013.
8. Matsubara, T., Matsuo, K., Nakashima, M. Nakano, M., Harada, K., Watanuki, T., Egashira, K., Watanabe, Y.: Prefrontal activation in response to emotional words in patients with bipolar disorder and major depressive disorder. *Neuroimage*, **85 Pt 1**: 489-497, 2014.
9. Kinou, M., Takizawa, R., Marumo, K., Kawasaki, S., Kawakubo, Y., Fukuda, M., Kasai, K.: Differential spatiotemporal characteristics of the prefrontal hemodynamic response and their association with functional impairment in schizophrenia and major depression. *Schizophr. Res.*, **150**: 459-467, 2013.
10. Negoro, H., Sawada, M., Iida, J., Ota, T., Tanaka, S., Kishimoto, T.: Prefrontal dysfunction in attention-deficit/hyperactivity disorder as measured by near-infrared spectroscopy. *Child Psychiatry Hum. Dev.*, **41**: 193-203, 2010.
11. Jourdan, Moser, S., Cutini, S., Weber, P., Schroeter, M.L.: Right prefrontal brain activation due to Stroop interference is altered in attention-deficit hyperactivity disorder - A functional near-infrared spectroscopy study. *Psychiatry Res.*, **173**: 190-195, 2009.
12. Monden, Y., Dan, H., Nagashima, M., Dan, I., Tsuzuki, D., Kyutoku, Y., Gunji, Y., Yamagata, T., Watanabe, E., Momoi, M.Y.: Right prefrontal activation as a neuro-functional biomarker for monitoring acute effects of methylphenidate in ADHD children: An fNIRS study. *Neuroimage: Clinical.*, **1**: 131-140, 2012.
13. Otsubo, T., Tanaka, K., Koda, R., Shinoda, J., Sano, N., Tanaka, S., Aoyama, H., Mimura, M., Kamijima, K.: Reliability and validity of Japanese version of the Mini-International Neuropsychiatric Interview. *Psychiatry Clin. Neurosci.*, **59**: 517-526, 2005.
14. Oldfield, R.C.: The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia*, **9**: 97-113, 1971.
15. Petersen, A., Crockett, L., Richards, M., Richards, M., Boxer, A.: A self-report measure of pubertal status: reliability, validity, and initial norms. *J. Youth Adolesc.*, **17**: 117-133, 1988.
16. Hollingshead, A.B.: *Two Factor Index of Social Position*. Mimeo. New Haven, Connecticut, Yale University, 1957.
17. Yamazaki, K.: *ADHD-RS-IV Japanese versions. Japanese guideline for the diagnosis and treatment of attention deficit hyperactivity disorder (ADHD). In:* Kanbayashi, Y., Saito, K., Kita, M. (eds.), Jiho Press, Tokyo, 2003.
18. Achenbach, T.M., Rescorla, L.A.: *Manual for the ASEBA school-age forms & profiles*, University of Vermont, Research Center for Children, Youth, and Families., Burlington, VT, 2001.
19. Yamashita, Y., Maki, A., Ito, Y., Watanabe, E., Koizumi, H.: Noninvasive near - infrared topography of human brain activity using intensity modulation spectroscopy. *Opt. Eng.*, **35**: 1046-1049, 1996.
20. Okada, E., Delpy, D.T.: Near-Infrared Light Propagation in an Adult Head Model. II. Effect of Superficial Tissue Thickness on the Sensitivity of the Near-Infrared Spectroscopy Signal. *applied optics.*, **42**: 2915-2922, 2003.

21. Kameyama, M., Fukuda, M., Yamagishi, Y., Sato, T., Uehara, T., Ito, M., Suto, T., Mikuni, M.: Frontal lobe function in bipolar disorder: a multichannel near-infrared spectroscopy study. *Neuroimage*, **29**: 172-184, 2006.
22. Strangman, G., Culver, J.P., Thompson, J.H., Boas, D.A.: A quantitative comparison of simultaneous BOLD fMRI and NIRS recordings during functional brain activation. *Neuroimage*, **17**: 719-731, 2002.
23. Tsuzuki, D., Jurcak, V., Singh, A.K., Okamoto, M., Watanabe, E., Dan, I.: Virtual spatial registration of stand-alone fNIRS data to MNI space. *Neuroimage*, **34**: 1506-1518, 2007.
24. Marumo, K., Takizawa, R., Kinou, M., Kawasaki, S., Kawakubo, Y., Fukuda, M., Kasai, K.: Functional abnormalities in the left ventrolateral prefrontal cortex during a semantic fluency task, and their association with thought disorder in patients with schizophrenia. *Neuroimage*, **85 Pt 1**: 518-526, 2014.
25. Singh, A.K., Dan, I.: Exploring the false discovery rate in multichannel NIRS. *Neuroimage*, 33: 542-549, 2006.
26. Yasumura, A., Kokubo, N., Yamamoto, H., Yasumura, Y., Nakagawa ,E., Kaga, M., Hiraki, K., Inagaki, M.: Neurobehavioral and hemodynamic evaluation of Stroop and reverse Stroop interference in children with attention-deficit/hyperactivity disorder. *Brain Dev.*, **36**: 97-106, 2014.
27. Cubillo, A., Halari, R., Smith, A., Taylor, E., Rubia, K.: A review of fronto-striatal and fronto-cortical brain abnormalities in children and adults with Attention Deficit Hyperactivity Disorder (ADHD) and new evidence for dysfunction in adults with ADHD during motivation and attention. *Cortex*, **48**: 194-215, 2012.
28. Christakou, A., Murphy, C.M., Chantiluke, K., Cubillo, A.I., Smith, A.B., Giampietro, V., Daly, E., Ecker, C., Robertson, D.; MRC, AIMS, consortium, Murphy, D.G., Rubia, K.: Disorder-specific functional abnormalities during sustained attention in youth with Attention Deficit Hyperactivity Disorder (ADHD) and with autism. *Mol. Psychiatry*, **18**: 236-244, 2013.
29. Cortese, S., Kelly, C., Chabernaud, C., Proal, E., Di, Martino, A., Milham, M.P., Castellanos, F.X.: Toward Systems Neuroscience of ADHD: A Meta-Analysis of 55 fMRI Studies. *Am. J. Psychiatry* , **169**: 1038-1055, 2012.
30. Cubillo, A., Smith, A.B., Barrett, N., Giampietro, V., Brammer, M., Simmons, A., Rubia, K.: Drug-specific laterality effects on frontal lobe activation of atomoxetine and methylphenidate in attention deficit hyperactivity disorder boys during working memory. *Psychol. Med.*, **44**: 633-646, 2014.
31. Rubia, K., Halari, R., Mohammad, A.M., Taylor, E., Brammer, M.: Methylphenidate normalizes frontocingulate underactivation during error processing in attention-deficit/hyperactivity disorder. *Biol. Psychiatry*, **70**: 255-262, 2011.
32. Cubillo, A., Smith, A.B., Barrett, N., Giampietro, V., Brammer, M.J., Simmons, A., Rubia, K.: Shared and Drug-Specific Effects of Atomoxetine and Methylphenidate on Inhibitory Brain Dysfunction in Medication-Naive ADHD Boys. *Cereb. Cortex*, **24**: 174-185, 2014.