Excessive hemodynamic activity in the superior frontal cortex during the flanker task in children with attention deficit hyperactivity disorder

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Near-infrared spectroscopy studies in children with attention deficit hyperactivity disorder (ADHD) have shown excessive prefrontal activity responsible for coping with interference. However, it is possible that the previous results were influenced by verbal, reading, and memory developments. The flanker task is an interference task that does not require a verbal response, reading, or memorization. We examined activity in the superior frontal cortex (SFC) during the flanker task in 12 children with ADHD and 14 children with typical development using near-infrared spectroscopy. SFC activity was significantly greater in children with ADHD than in those with typical development. The results showed excessive interference coping activity in children with ADHD irrespective of verbal, reading, and memory development. Moreover, SFC activity was positively correlated with the inattention subscale score of the ADHD rating scale. We suggest that children with ADHD need greater SFC activation to cope with interference, and the inefficient mechanism is demanding and hard to sustain, which causes inattention symptoms of children with ADHD. *NeuroReport* **00:000–000**

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Introduction

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by age-inappropriate levels of inattention, hyperactivity, and impulsivity [1]. Being 'easily distracted' is one of the inattention symptoms defined by the *Diagnostic and Statistical Manual of Mental Disorders*, 5th ed. (DSM-5) [1]. In experimental settings, the symptom is associated with impaired performance in interference tasks [2,3], such as the flanker task or the Stroop task. Several cognitive mechanisms operate in interference tasks. Such tasks are associated with prefrontal areas, such as the superior frontal cortex (SFC), the inferior frontal cortex (IFC), and the dorsolateral prefrontal cortex (DLPFC) [4,5]. Previous studies showed that prefrontal areas are functionally and structurally impaired in children with ADHD [6–8]. Thus, altered activity in prefrontal areas during interference tasks may be associated with the inattention symptoms of children with ADHD.

Near-infrared spectroscopy (NIRS) is a noninvasive method of recording neural activity. NIRS is not very sensitive to movement artifact; thus, participants can move freely. Because hyperactivity is an ADHD symptom [1], NIRS is suitable for examining neural activity in children with ADHD. NIRS experiments found elevated activity in prefrontal areas of children with ADHD during the Stroop task [9,10]. Activity in the left prefrontal cortex was greater in the right prefrontal cortex for children with ADHD in the reverse Stroop task, whereas no difference was found in children with typical development (TD) [11]. In children with ADHD, activity in the prefrontal cortex was elevated for the presentation of distractors in a working memory task [12]. These results suggest excessive activity of prefrontal areas responsible for coping with interference in children with ADHD.

However, the Stroop task requires verbal and reading abilities [2], and working memory tasks obviously require working memory. Thus, it is possible that the previous findings were influenced by verbal, reading, and memory developments. In the flanker task, a target arrow is presented with flanker arrows pointing in a different direction, and the inconsistency causes the interference. Thus, the flanker task does not require a verbal response, reading, or memorization. This is advantageous for the study of interference control in children with ADHD [2]. In addition, the flanker task showed atypical brain activity in children with ADHD in studies with event-related potentials [13] and a functional MRI [14].

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Therefore, we examined prefrontal activity during the flanker task in children with ADHD and those with TD using NIRS.

Participants and methods

Participants

This study included 12 children with ADHD and 14 children with TD (Table 1). The children's parents provided written informed consent before the experiments. The study was approved by the ethics committees of the National Center of Neurology and Psychiatry (A2011-003) and Kurume University Hospital (07045). The children's ages ranged between 8 and 11 years. Children with ADHD were recruited from among the participants of summer treatment programs in Kurume, Japan. The diagnosis of ADHD was confirmed by a pediatric neurologist (Y.Y.) according to the DSM-5 [1]. Children with TD were recruited from an after-school care center. Their parents did not report any neurological or psychiatric illnesses. The children with ADHD and those with TD were similar in age ($P > 0.32$). We assessed intellectual ability using Raven's colored progressive matrices and found no significant between-group difference ($P > 0.60$).

Stimuli and procedure

An arrow version of the flanker task was performed using E-Prime 2.0 (Psychology Software Tools Inc., Sharpsburg, Pennsylvania, USA). Stimuli consisted of arrays of five arrows, which were classified into compatible (i.e. <<<<<, >>>>>) and incompatible (i.e. >><>>, <<><<) stimuli on the basis of whether the central arrow pointed in the same direction as the flanker arrows. For each stimulus, participants were asked to press a button with their thumb corresponding to the direction of the central arrow.

For the NIRS analysis, we used an experimental design featuring alternated baseline and activation periods. Thus, we presented alternating compatible (i.e. baseline) 12-trial blocks and incompatible (i.e. activation) 12-trial blocks in each session (Fig. 1a). The session consisted of three compatible and two incompatible blocks, with the first block in the session always being compatible. Each stimulus was presented for 500 ms on a PC monitor (visual angle = 1.39° × 8.33°) and the stimulus color was green. The stimulus onset asynchrony was set to 2500 ms. Participants performed two sessions after a practice session comprising four compatible and four incompatible trials.

Table 1 Characteristics of children with attention deficit hyperactive disorder and typical development

	TD (mean ± SD)	ADHD (mean ± SD)
Sex: male (female)	10 (4)	11 (1)
Handedness: right (left)	13 (1)	11 (1)
Age	9.50 ± 1.06	9.92 ± 1.05
RCPM correctness	28.43 ± 3.74	29.09 ± 4.99
RCPM response time	224.86 ± 43.17	236.91 ± 64.93
ADHD-RS: inattention	NA	14.25 ± 3.36
ADHD-RS: hyperactivity–impulsivity	NA	9.25 ± 3.31

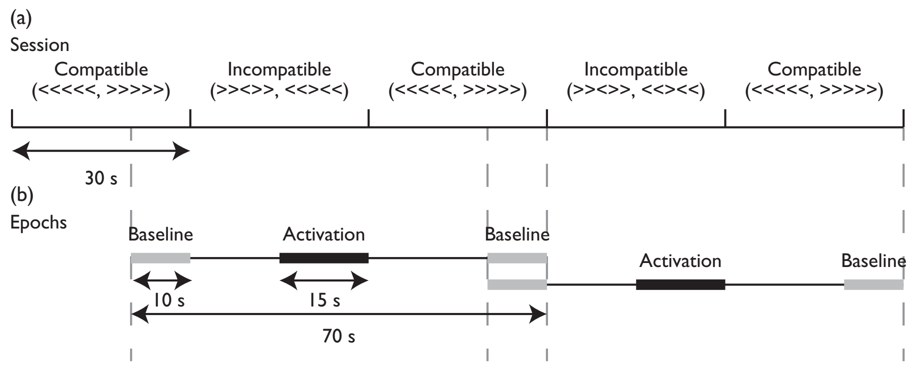
ADHD, attention deficit hyperactivity disorder; ADHD-RS, attention deficit hyperactivity disorder rating scale; NA, not available; RCPM, Raven's colored progressive matrices; TD, typical development.

Near-infrared spectroscopy recordings and analyses

NIRS data were sampled at 1.53 Hz using an OEG-16 head module (Spectratec Inc., Tokyo, Japan). Six emitters and six detectors were arranged in a 2 × 6 matrix, resulting in data acquisition from 16 locations (Fig. 2). The distance between the detector and the emitter was 30 mm. The lower corners of the array were placed at F7 and F8 and the center point of bottom was placed at Fpz according to the 10–20 system.

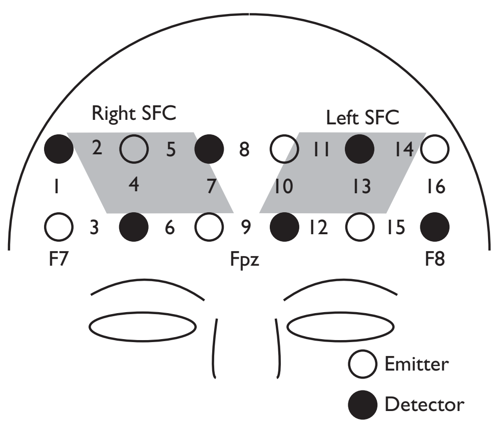
The data were analyzed using OEG-16 software V3.0 (Spectratec Inc., Tokyo, Japan) and MATLAB 2010Ra (Mathworks Inc., Natick, Massachusetts, USA). NIRS data were low-pass filtered offline at 0.05 Hz. We obtained the changes in oxyhemoglobin (ΔoxyHb) and deoxyhemoglobin (ΔdeoxyHb) concentrations from all 16 channels of NIRS data. Using a hemodynamic signal separation method [15], we separated NIRS signals into functional and systemic components. The method assumes that ΔoxyHb and ΔdeoxyHb are negatively correlated in the functional component, which is associated with cerebral cortex activity, whereas they are positively correlated in the systemic component, which is related to activity in superficial tissues. We then excluded the systemic component. For simplicity, we used only ΔoxyHb because it has a fixed linear relationship with ΔdeoxyHb in the functional component. Epochs were extracted from periods 10 s before and 60 s after the beginning of incompatible blocks (Fig. 1b). ΔoxyHb signals were baseline-corrected using the linear fitting method on the basis of the first 10 s and the last 10 s of the epoch (Fig. 1b). We manually excluded epochs containing task-irrelevant signal changes greater than ± 0.1 mM/mm (e.g. head-moving artifacts) and at least two epochs were averaged for each participant (TD = 2.50 ± 0.53, ADHD = 2.33 ± 0.49). The locations corresponding to the left and right SFCs (Brodmann areas 9 and 10) [16] were averaged (right: channels: 2, 4, 5, 7; left channels: 10, 11, 13, 14) because the SFC is activated when incompatible stimuli are successively presented in the flanker task [4,5]. ΔoxyHb increased gradually after the beginning of the incompatible block, although the activation was unclear in the block's early period. Thus, we used the mean value of a period from 15 to 30 s after the beginning of the incompatible blocks for statistical analysis. We defined statistical significance as P value less than 0.05.

Fig. 1



(a) Session, (b) Epochs.

Fig. 2



Channel locations. Numbers represent channels of near-infrared spectroscopy. SFC, superior frontal cortex.

Attention deficit hyperactivity disorder symptoms

We used a Japanese version of the ADHD Rating Scale IV [17] to evaluate the levels of ADHD symptoms. ADHD Rating Scale IV consists of 18 items divided into two subscales: inattention (nine items) and hyperactivity–impulsivity (nine items). The parents of children with ADHD were asked to rate the children's behavior using a four-point Likert scale ranging from 0 to 3. We used the summed score of each subscale for the correlational analysis.

Results

Behavioral data

Table 2 shows the correct response times and incorrect response rates for compatible and incompatible stimuli in children with TD and those with ADHD. We carried out analyses of variance on correct response times and incorrect response rates for group (TD, ADHD) and condition (compatible, incompatible). The correct response time was significantly longer for incompatible stimuli than compatible ones ($F_{1,24}=81.29$, $P<0.001$). We did not find a significant main effect of group or the interaction of group and condition ($P>0.20$). The incorrect response rate was significantly higher for incompatible stimuli than compatible ones ($F_{1,24}=24.69$, $P<0.001$). There was a significant interaction between group and condition ($F_{1,24}=4.49$, $P=0.04$), where the incorrect response rate was significantly higher for the incompatible stimulus than the compatible one in both children with TD and those with ADHD ($P<0.001$). However, the differences between groups were not significant for either the compatible stimulus or the incompatible one ($P>0.05$).

Near-infrared spectroscopy data

Figure 3 shows ΔoxyHb waveforms for children with TD and those with ADHD. ΔoxyHb values in the SFCs were higher in children with ADHD than in those with TD, with a notable difference in the left SFC (Fig. 3). An analysis of variance was carried out on ΔoxyHb values for group (TD, ADHD) and region (left, right). We found a significant main effect of group ($F_{1,24}=4.58$, $P=0.04$) and a significant interaction between group and condition ($F_{1,24}=4.50$, $P=0.04$). Simple-effect analyses showed that the difference between the groups was significant in the left SFC ($F_{1,24}=7.40$, $P=0.01$), but not in the right SFC ($F_{1,24}=1.17$, $P=0.29$). The left SFC had a significantly higher ΔoxyHb value than the right SFC in children with ADHD ($F_{1,24}=5.16$, $P=0.04$), but not in children with TD ($F_{1,24}=0.74$, $P=0.40$). There was no main effect of region ($F_{1,24}=0.73$, $P=0.40$).

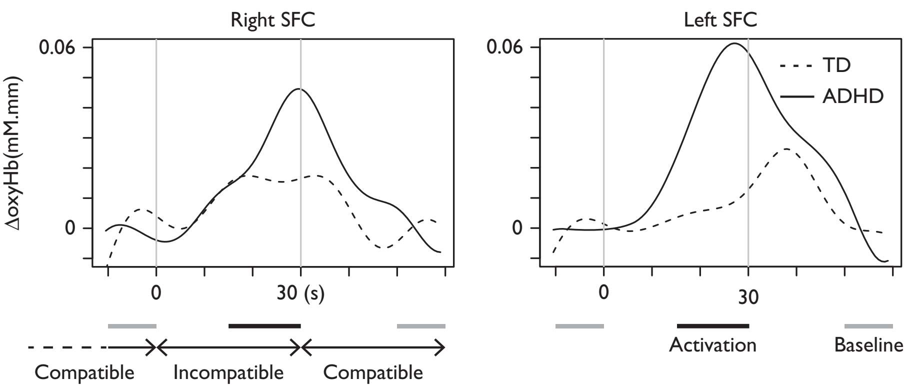
ΔoxyHb values in the SFCs were significantly correlated with scores on the inattention subscale (right: $r=0.58$, $P<0.05$; left: right: $r=0.58$, $P<0.05$). There were no significant correlations between ΔoxyHb values in the SFCs and scores on the hyperactive–impulsive subscale (right: $r=0.43$, $P=0.16$; left: right: $r=0.49$, $P=0.10$).

Table 2 **Behavioral results**

	TD (mean ± SD)		ADHD (mean ± SD)	
	Compatible	Incompatible	Compatible	Incompatible
Correct response time (ms)	561.07 ± 118.56	674.09 ± 144.04	598.40 ± 74.26	747.40 ± 95.52
Incorrect response rate (%)	2.38 ± 3.13	5.68 ± 5.10	2.02 ± 2.36	10.23 ± 7.22

ADHD, attention deficit hyperactivity disorder; TD, typical development.

Fig. 3



Waveforms of changes in oxyhemoglobin (ΔoxyHb) in superior frontal cortices (SFCs) during the flanker task in children with attention deficit hyperactive disorder (ADHD) and those with typical development (TD).

Discussion

Previous NIRS studies have shown increased activation of prefrontal areas during the Stroop task and a working memory task involving distractors in children with ADHD [9,10,12]. However, it is possible that the previous results were influenced by verbal, reading, and memory development. The flanker task does not require a verbal response, reading, or memorization. We measured SFC activity during the flanker task in children with ADHD and those with TD. Left SFC activity during the flanker task was greater in children with ADHD than in those with TD. Thus, our results confirmed that excessive activity in children with ADHD was independent of verbal, reading, and memory development. We therefore suggest that children with ADHD need greater prefrontal activation to cope with interference because their neural mechanism for handling interference is inefficient.

Left SFC activity was greater than right SFC activity in children with ADHD, but no difference was found in children with TD. Yasumura *et al.* [11] also reported greater activity in the left prefrontal cortex than in the right one in children with ADHD. A meta-analysis of functional MRI studies showed that left prefrontal cortex activation was greater in individuals with ADHD than in controls [18]. These findings suggest that an inefficient neural mechanism in individuals with ADHD results in compensatory and excessive activation of the left prefrontal area.

Contrary to our results, previous studies frequently reported hypoactivation of prefrontal areas such as DLPFC and IFC in children with ADHD [18,19]. The two known types of cognitive control are reactive control and proactive control [20]. Reactive control refers to transient cognitive control after cognitively demanding events (e.g. the incompatible stimulus) and is associated with the DLPFC and IFC [4,5]. Proactive control represents a maintenance of attention in preparation for cognitively demanding events and is associated with the SFC [4,5]. As incompatible stimuli were successively presented in the current study, participants could anticipate them. We therefore suggest that our task mainly involved proactive control. Therefore, our results suggest that children with ADHD have an inefficient neural mechanism for proactive control, whereas previous reports led us to speculate that these children's dysfunctional regions might be associated with reactive control.

Greater SFC activity was related to stronger inattention symptoms in children with ADHD. We suggest that an inefficient mechanism for proactive control makes it demanding and hard to sustain, which causes inattention symptoms. Several studies have shown that ventral striatal activity in reward anticipation tasks is reduced in individuals with ADHD and that it is correlated with hyperactivity–impulsivity symptoms, but not inattention symptoms [21,22]. Hence, cognitive functions (e.g. proactive control and reward anticipation) might be differently associated with inattention symptoms and hyperactivity–impulsivity symptoms. We expect that future studies will clarify the association between cognitive functions and ADHD symptoms.

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Conflicts of interest

There are no conflicts of interest.

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