Altered frontal pole development affects self-generated spatial working memory in ADHD

（ADHD 児における自発性空間ワーキングメモリ施行時の前頭葉の活動：

NIRS を用いた発達的変化の検討）

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Altered frontal pole development affects self-generated spatial working memory in ADHD

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Abstract

Background: Spatial working memory (SWM) dysfunction is a feature of attention deficit hyperactivity disorder (ADHD). Previous studies suggested that behavioral performance in self-generated SWM improves through development in children with and without ADHD. Nevertheless, developmental changes in the neural underpinnings of self-generated SWM are unknown.

Method: Using near-infrared spectroscopy, hemodynamic activity in the prefrontal cortex (PFC) was measured in 30 children with ADHD (9.5 ± 1.6 years-old) and 35 TD children (9.0 ± 1.6 years-old) while they performed a self-generated SWM task. We then investigated correlations between age and behavioral performance, and between age and hemodynamic activity in the PFC for each group.

Results: Both groups showed a negative correlation with age and number of errors [ADHD: $r(28) = -0.37$, $p = 0.040$; TD: $r(33) = -0.59$, $p < 0.001$], indicating that self-generated SWM improves through development. The TD group showed a positive correlation between age and oxygenated hemoglobin in the frontal pole [10ch: $r(33) = 0.41$, $p = 0.013$; 11ch; $r(33) = 0.44$, $p = 0.008$] and bilateral lateral PFC [4ch: $r(33) = 0.34$, $p = 0.049$; 13ch; $r(33) = 0.54$, $p = 0.001$], while no significant correlation was found in the ADHD group. Furthermore, regression slopes for the frontal pole significantly differed between the TD and ADHD groups [10ch: $t(61) = 2.35$, $p = 0.021$; 11ch: $t(61) = 2.05$, $p = 0.044$].

Conclusion: Children with ADHD showed abnormalities in functional maturation of the frontal pole, which plays a role in manipulating and maintaining information associated with self-generated behavior.

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Keywords: Attention deficit hyperactivity disorder (ADHD); Cambridge Automated Neuropsychological Battery (CANTAB®); Near-infrared spectroscopy (NIRS); Self-generated spatial working memory (SWM); Development; Prefrontal cortex (PFC)

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is defined as age-inappropriate behavior, with core symptoms of inattention, impulsivity, and hyperactivity [1]. Individuals with ADHD have difficulty in self-directed behavior toward solving a problem or achieving a future goal [2]. Such difficulty is considered to be induced by deficits in executive function (EF) [2], which is an overarching term referring to a neuropsychological process that enables cognitive, emotional, and physical self-control [3]. Previous studies have shown that dysfunction of EF could predict subsequent academic and occupational functioning [4]. Therefore, EF dysfunction in children with ADHD, which could lead to difficulty in self-directed behavior, is associated with various outcomes in each developmental stage, such as academic or occupational status.

EF is considered to include various components such as working memory (WM), response inhibition, cognitive flexibility, and planning. Among the various EF components, a deficit in working memory has been proposed to be the origin of the core symptoms of ADHD [5]. WM is a limited-capacity system responsible for maintaining and manipulating cognitive representations of stimuli, searching for same or similar stimuli in memory, and maintaining appropriate behavior responses [6]. Although there are several types of WM (e.g., verbal or auditory), a number of recent behavioral studies have examined spatial working memory (SWM) in children with ADHD [7–9] using tasks requiring maintenance and manipulation of spatial information of visually presented objects. In a meta-analysis, Kasper et al. [10] found that individuals with ADHD show lower SWM task performance than TD individuals [10]. In these studies, SWM ability of individuals with ADHD was frequently examined by the n-back task or the SWM set of the Cambridge Neuropsychological Test Automated Battery (CANTAB®). Although both tasks require maintenance and manipulation of spatial information, sources of the spatial information in each task are different. For example, during the n-back task, which is an externally generated task, experimenters provide subjects with information related to object locations; thus, subjects are required to maintain and manipulate externally generated spatial information. In contrast, the memorization of object locations is dependent on both externally generated information and one's own behavior during a self-generated task [11]; this is also true for behavior performed during the SWM battery of the CANTAB®. Because the functions (i.e., sources of visuo-spatial information) in the self- and externally generated SWM tasks are different, it has been considered that children with ADHD might experience different problems when performing two tasks.

Although previous studies have shown that children with ADHD have trouble with both self- [7–9] and externally [12,13] generated SWM tasks, it has been suggested that developmental changes in behavioral performances are different between the two tasks [14,15]. For example, Westerberg et al. [15] conducted a cross-sectional study to compare developmental changes in behavioral performance on an externally generated SWM task (i.e., spatial span task) between individuals with and without ADHD (aged 8–15-years-old). They showed that improvement of behavioral performance during development was greater in the typically developed (TD) group than in the ADHD group [15]. On the other hand, Coghill et al. [14] conducted a longitudinal study to examine developmental changes in behavioral performance on the SWM battery of the CANTAB®, a self-generated SWM task, for boys with and without ADHD from 10 to 14-years-old. Interestingly, their group found that boys with ADHD and TD showed equivalent improvement in SWM performance through development [14]. These findings suggest the possibility that the developmental trajectory related to different brain activities varies between these two tasks.

Although examining the developmental trajectory of brain activities during SWM tasks is relevant for elucidating the pathophysiology of ADHD, which will providing important information for selecting treatment strategies including pharmacotherapy, only two studies have examined developmental changes in brain activity during an externally generated SWM task [12,13]. For TD children, it is believed that activation in the lateral prefrontal cortex (PFC), which is relevant for maintaining and manipulating information during a WM task, increases through development during externally-generated SWM tasks [16–18]. Electroencephalogram (EEG) studies have shown different functional maturation in the PFC during externally generated SWM tasks between individuals with ADHD and TD individuals [12,13]. For instance, Myatchin et al. [13] showed that TD children tend to exhibit decreases in within-subject variability in terms of EEG amplitude in the frontal area, reflecting fluctuations in the intensity of task-relevant processing. In contrast, they observed delayed decrements in within-subject EEG amplitude variability in the frontal area for individuals with ADHD. These findings suggest that delayed functional maturation in the lateral PFC of children with ADHD might lead to abnormal developmental changes in SWM ability during externally generated tasks. With regard to self-generated tasks, Christoff et al. [11] have suggested that, along with the lateral PFC, the frontal pole is needed when self-generated information is evaluated and manipulated. If functional maturation in the lateral PFC or the frontal pole contributes to improvement of self-generated SWM behavioral performance through childhood development [14,19–21], activation in the lateral PFC and the frontal pole might change through development in both children with and without ADHD. However, despite the importance of elucidating the cause of difficulty in self-directed behavior in ADHD, no studies have examined developmental changes in neural responses of the PFC during self-generated SWM tasks in children with and without ADHD.

We utilized the SWM battery of the CANTAB® as the self-generated SWM task, and since the method requires a touch screen for the presentation of visual stimuli and correcting responses, we could not examine brain activity using a magnetic resonance imaging (MRI) scanner. Because near-infrared spectroscopy (NIRS) only requires the use of a relatively small device, which is suitable for touch screen technology [22–24], we utilized NIRS to examine activation in the PFC. Previous NIRS studies found abnormal activation in the PFC for individuals with ADHD performing EF tasks such as a response inhibition task [25–27], and spatial working memory task [24]. Thus, NIRS is a powerful tool to detect PFC dysfunction in individuals with ADHD.

In the present study, we examined developmental changes in the activation of the PFC in children with ADHD and TD children while they performed self-generated SWM tasks. During the experiment, participants performed the SWM battery of the CANTAB® while oxyhemoglobin [oxy-Hb] concentration was measured by NIRS. At first, we investigated correlations between age and behavioral performance, and between age and [oxy-Hb] for each group. We then compared regression slopes between children with ADHD and TD children to determine if developmental trajectories in behavioral performance, as well as activation in the PFC, were altered in children with ADHD.

2. Methods

2.1. Participants

Thirty boys with ADHD and 35 TD boys participated in this study (Table 1). Participants were excluded if they had major sensory handicaps (e.g., paralysis, deafness, and blindness), a history of brain damage, epilepsy, or a low full-scale intelligence quotient (FSIQ) (<80). The protocol used for this study was approved by the ethics committee of the University of Fukui and the Tokyo University of Social Welfare (25-99 and 23-03, respectively). The study was conducted in accordance with the Declaration of Helsinki. After a complete explanation of the study, written informed consent was obtained from all participants and their parents. For all participants, we measured intelligence quotient (IQ) scores using the Wechsler Intelligence Scale for children (WISC-IV) (Japanese WISC-IV Publication Committee), and severity of ADHD symptoms using the Japanese version of the ADHD-Rating Scale-IV [28], which has been validated in a clinical sample [29].

2.1.1. ADHD group

Thirty boys with ADHD (age range, 7–13 years; mean age, 9.5 ± 1.6 years) were recruited from the outpatient unit at the Department of Child and Adolescent Psychological Medicine of University of Fukui Hospital and Hiratani Clinic for Developmental Disorders of

Table 1
Characteristics of participants.

	ADHD	TD	*t* values	*p* values
Number	30	35		
Age	9.5 ± 1.6	9.0 ± 1.6	1.33	0.188
FSIQ	100.5 ± 13.3	106.4 ± 10.7	−1.98	0.052
ADHD-RS-IV				
Total score	26.3 ± 13.8	5.7 ± 4.2	8.42	<0.001*
Inattention score	17.6 ± 9.5	3.9 ± 3.1	8.08	<0.001*
Hyperactivity and impulsivity score	12.7 ± 7.3	1.9 ± 1.7	8.48	<0.001*
Comorbidity				
Learning disorder	5	0		

ADHD, attention deficit/hyperactivity disorder; TD, typical development; FSIQ, full scale intelligence quotient; ADHD-RS-IV, ADHD-Rating Scale-IV [21].
Age, FSIQ score, and ADHD-RS-IV scores are shown as mean ± SD.
* $p < 0.01$ with independent-sample *t*-test comparing ADHD and TD.

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Table 2
SWM battery of the CANTAB® score.

	ADHD	TD	t value	p value
SWM (between errors score)	25.2 ± 11.3	21.1 ± 12.3	1.38	0.171

ADHD, attention deficit/hyperactivity disorder; TD, typical development; SWM, spatial working memory.
Between errors score is shown as mean ± SD. Independent-sample t-test comparing ADHD and TD.

Table 3
Correlation between age and [oxy-Hb].

	ADHD		TD	
	r	p value	r	p value
2ch	−0.09	0.634	−0.30	0.082
3ch	0.12	0.518	0.17	0.319
4ch	0.02	0.907	0.34	0.049*
5ch	0.17	0.351	0.02	0.907
6ch	0.20	0.279	−0.08	0.662
7ch	0.26	0.164	0.25	0.151
8ch	−0.01	0.956	0.02	0.900
9ch	0.10	0.601	0.08	0.648
10ch	−0.15	0.422	0.41	0.013*
11ch	−0.10	0.590	0.44	0.008**
12ch	0.00	0.989	−0.15	0.390
13ch	0.22	0.249	0.54	0.001**
14ch	0.05	0.808	−0.10	0.565
15ch	0.19	0.315	0.30	0.077

ADHD, attention deficit/hyperactivity disorder; TD, typical development.
*$p < 0.05$, **$p < 0.01$ with correlation analysis between age and integration value of [oxy-Hb] for each group.

Children. Three pediatric neurologists (S.T., A.T., and M.H.) diagnosed participants based on Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) classifications [1]. None of the participants with ADHD had ODD, anxiety disorder, or autism spectrum disorder (ASD). However, five participants with ADHD had learning disorders. Although all participants with ADHD received methylphenidate via an osmotically controlled release oral delivery system (OROS), participants ceased taking all medications 24 h prior to the start of the experiment.

2.1.2. TD group

Thirty-five TD boys (age range, 7–13 years; mean age, 9.0 ± 1.6 years) were recruited from the local community as healthy controls. Children were not included if they had any psychiatric diagnosis or had family members with social- or attention-related problems. To exclude the presence of ADHD or ASD, all TD participants underwent an extensive child psychiatric examination, which was conducted by a pediatric neurologist according to DSM-5 criteria.

2.1.3. Index comparisons between groups

There was no significant group difference in age [$t(63) = 1.33$, $p = 0.188$] and FSIQ [$t(63) = -1.98$, $p = 0.052$], while the ADHD Rating Scale-IV (ADHD-RS-IV) total score [$t(63) = 8.42$, $p < 0.001$], inattention score [$t(63) = 8.08$, $p < 0.001$], and hyperactive and impulsivity score [$t(63) = 8.48$, $p < 0.001$] was significantly higher in the ADHD group than in the TD group. There were no significant correlations between age and FSIQ [ADHD: $r(28) = 0.24$, $p = 0.190$; TD: $r(33) = 0.12$, $p = 0.483$], and between age and ADHD-RS-IV total score [ADHD: $r(28) = -0.06$, $p = 0.766$; TD: $r(33) = -0.29$, $p = 0.090$] in each group. Therefore, intellectual ability and ADHD severity were ruled out as confounding factors, which allowed us to compare [oxy-Hb] between ADHD and TD, and to test the relationship between brain activation and age.

2.2. Experimental procedure

2.2.1. Experimental setup

We employed the SWM battery of the CANTAB® as a self-generated SWM task (Fig. 1) to assess developmental changes in self-generated SWM and activation in the PFC. During the SWM battery, participants were shown a number of colored squares (boxes) displayed on a touch screen and were required to find a blue token hidden within one of the boxes. Once the token was found, it was moved to another box. Participants were informed that the token would not be moved to the same place; therefore, they had to resist returning to a box where a token had previously been found. Returning to an empty box where a target had already been found was referred to as a "between error". Because previous behavioral studies have suggested that individuals with ADHD face severe difficulty when eight boxes are presented in the task (versus 6 or 4) [8,30,31], we measured behavioral performance and neural response using eight boxes.

2.2.2. NIRS

While participants performed the SWM battery of the CANTAB®, the relative concentration of [oxy-Hb] and deoxyhemoglobin was measured using a multichannel NIRS system (OEG-16; Spectratech Inc., Tokyo, Japan). In this system, near-infrared laser diodes with two different wavelengths (approximately 770 and 840 nm) were used to emit near-infrared light. The re-emitted light was detected with avalanche photodiodes that were located 30 mm from the emitters. The temporal resolution of acquisition was 0.65 s. The system measures oxy-Hb at a depth of approximately 30 nm below the scalp [32]. In this system, six emitters and six detectors were placed at alternate points on a 2×6 grid, enabling us to detect signals in 16 channels. The center of the probe matrix was placed on Fpz (International 10–20 system) [33], and the bottom left and bottom right corners were located around F7 and F8, respectively, as previously reported [34].

2.3. Data analysis

2.3.1. Behavioral data

In order to examine if self-generated SWM ability improved through development, we conducted a correlation analysis between age and between errors made by ADHD and TD groups. We then compared the regression slopes between ADHD and TD groups to test for differences in developmental changes.

2.3.2. NIRS data

Because participants were young children and their head circumference was small, the right edge of the 1ch and the left edge of the 16ch were excluded from the analysis. As a previous study reported oxy-Hb as a more sensitive indicator of brain activation [34], we focused on changes in oxy-Hb. The measurement principles used in this study were based on the modified Beer–Lambert law, for which [oxy-Hb] is calculated from changes in light attenuation at a given measurement point [35]. In this study, we conducted 8 boxes after 4 boxes and 6 boxes to enable the SWM battery of the CANTAB® to be conducted. Because the duration between the 8 boxes and 6 boxes was short, we set the start point without any duration as the baseline. We then calculated the integration value of [oxy-Hb] within 30 s from the start of the SWM battery using BRain Analyzer (BR systems, Tokyo, Japan). Similar to the behavioral data analysis, we performed a correlation analysis between age and integration value of [oxy-Hb] for each group, and then compared the two regression slopes between ADHD and TD groups.

3. Results

3.1. Behavioral results

Between errors during the eight-box SWM battery for all participants are shown in Table 2 and Fig. 2. Between errors for the ADHD and TD groups were 25.2 ± 11.3 and 21.1 ± 12.3, respectively. Both ADHD and TD groups showed a negative correlation with between errors and age [ADHD: $r(28) = -0.38$, $p = 0.040$; TD: $r(33) = -0.59$, $p < 0.001$] (Fig. 2). There was no significant group difference in these slopes [$t(61) = -1.13$, $p = 0.262$]. An independent t-test did not reveal a significant group difference with regard to errors

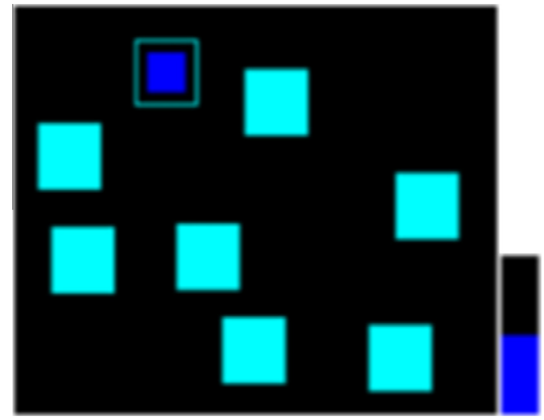

Fig. 1. Spatial working memory (SWM) battery of the CANTAB®. The SWM of the CANTAB® is a self-generated task that is based on foraging behavior. Participants are required to search an array for a hidden token without revising locations where tokens had been previously found. SWM, spatial working memory; CANTAB®, Cambridge Automated Neuropsychological Battery.

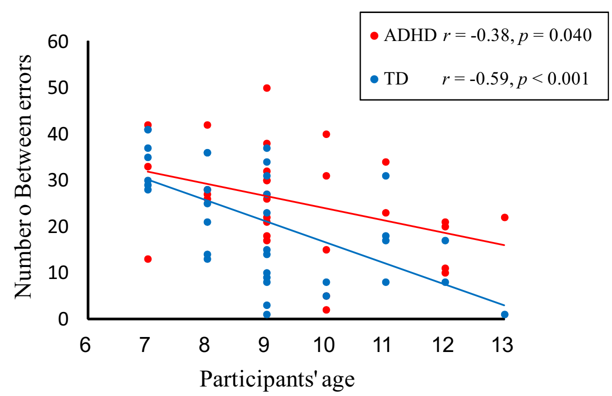

Fig. 2. Correlations between age and between errors. Regression lines for the ADHD group (red line) and TD group (blue line), respectively. ADHD, attention deficit/hyperactivity disorder; TD, typical development.

[$t(63) = 1.38$, $p = 0.171$]. However, when we conducted an analysis of covariate (ANCOVA) to exclude the effect of age, there was a significant difference between ADHD and TD groups [$F(1,62) = 5.29$, $p = 0.025$], indicating that between errors in the ADHD group were significantly higher than those in TD group. Collectively, both groups showed a developmental improvement of behavioral performance, although self-generated SWM ability was slightly lower in the ADHD group.

3.2. NIRS results

3.2.1. Correlation analysis between age and [oxy-Hb]

For the TD group, integration values of [oxy-Hb] were significantly correlated with age in 4ch and 13ch corresponding to the bilateral lateral PFC [36] [4ch: $r(33) = 0.34$, $p = 0.049$; 13ch: $r(33) = 0.54$, $p = 0.001$]

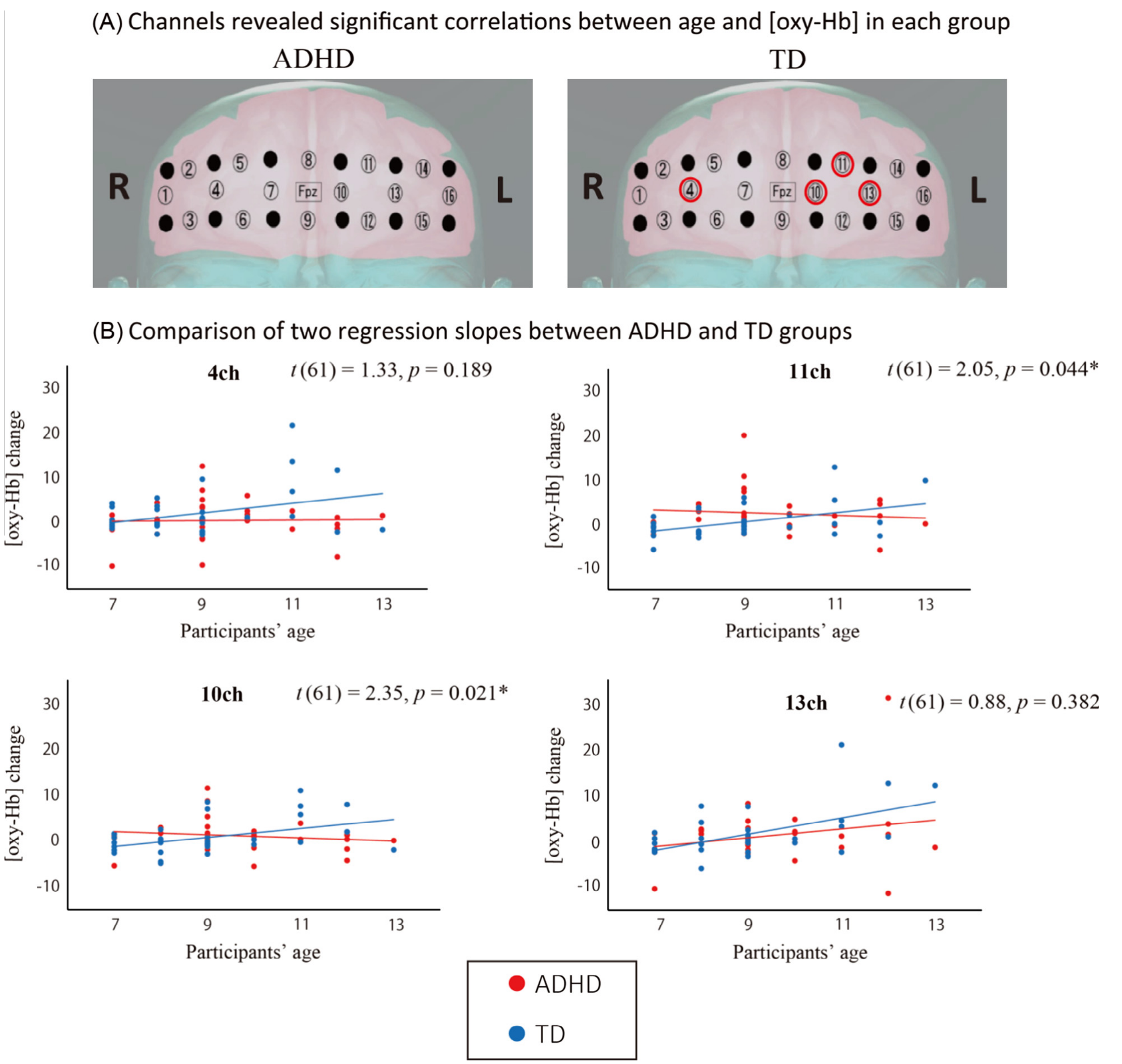

Fig. 3. Developmental changes of integration values of [oxy-Hb] during performance of a self-generated SWM task for the ADHD and TD groups. (A) Channels revealed significant correlations between age and [oxy-Hb] in each group. Red circle shows channels with significant correlations between age and [oxy-Hb]. (B) Comparison of two regression slopes between ADHD and TD groups. Regression lines for the ADHD group (red line) and TD group (blue line), respectively, are shown. oxy-Hb, oxyhemoglobin; ADHD, attention deficit/hyperactivity disorder; TD; typical development $^{*}p < 0.05$.

and in 10ch and 11ch corresponding to the frontal pole [36] [10ch: $r(33) = 0.41$, $p = 0.013$; 11ch: $r(33) = 0.44$, $p = 0.008$] (Table 3 and Fig. 3A). On the other hand, none of the channels showed significant correlations with age for the ADHD group (Table 3 and Fig. 3A). Within channels showed a significant correlation between age and integration value of [oxy-Hb] for the TD group [4ch: $r(33) = 0.34$, $p = 0.049$; 10ch: $r(33) = 0.41$, $p = 0.013$; 11ch: $r(33) = 0.44$, $p = 0.008$; 13ch: $r(33) = 0.54$, $p = 0.001$], and a comparison of slopes between ADHD and TD groups revealed significant differences in 10ch and 11ch [10ch: $t(61) = 2.35$, $p = 0.021$; 11ch: $t(61) = 2.05$, $p = 0.044$], but not in 4ch and 13ch [4ch: $t(61) = 1.33$, $p = 0.189$; 13ch: $t(61) = 0.88$, $p = 0.382$] (Fig. 3B).

3.2.2. Group differences in [oxy-Hb] of older participants (10-years-old)

Similar to the present study, previous studies also showed that young TD children (until around 10-years-old) did not exhibit enough PFC activation [16–18]; therefore, we examined whether older TD participants (over 10-years-old) showed stronger activation in the frontal pole (i.e., 10 and 11ch) than older ADHD participants. An independent t-test revealed that the mean integration value of [oxy-Hb] was higher in the TD group than in the ADHD group in the 10ch [$t(19) = -2.33$, $p = 0.031$], while no significant difference was found in the 11ch [$t(19) = -1.02$, $p = 0.321$].

4. Discussion

In the present study, both TD and ADHD groups showed a negative correlation between age and number of errors. In addition, our study showed that SWM performance was higher in the TD group than in the ADHD group when we excluded the effect of age. Thus, both children with and without ADHD showed improved SWM performance during self-generated SWM tasks through development; however, children with ADHD exhibited lower ability. On the other hand, the two groups showed different developmental changes in terms of neural response. The TD group showed a positive correlation between age and the integration value of [oxy-Hb] in the frontal pole and bilateral lateral PFC, while no significant correlation was found in the ADHD group. Furthermore, regression slopes for the frontal pole significantly differed between TD and ADHD groups. To the best of our knowledge, this is the first study to examine developmental changes in PFC activation during self-generated SWM tasks in both children with ADHD and TD children.

4.1. Behavioral performance

Our study showed significant improvements in behavioral performance of both ADHD and TD groups through development, and this developmental trajectory was not different. In cross-sectional studies such as the one conducted in the present report, it is important to consider confounding factors such as intellectual ability and severity of ADHD symptoms. However, participants' FSIQ was not different between groups. Moreover, FSIQ and ADHD-RS score were not correlated with age. Thus, the improvement of scores in SWM tasks cannot be explained by intellectual ability or the severity of ADHD symptoms. Therefore, our findings imply that both children with and without ADHD show equivalent improvements in SWM ability during self-generated SWM tasks. Similar to our findings, previous studies have reported improvements in self-generated SWM performance through development in both TD children [19–21] and children with ADHD [14]. In addition, our results showed that SWM performance was lower in the ADHD group than in the TD group when we exclude the effect of age. Previous studies have also reported lower SWM performance not only for children with ADHD [7–9], but also for adults with ADHD [30,31] during self-generated SWM tasks. These studies suggest that lower self-generated SWM ability continues into adolescence and adulthood. Collectively, our results confirmed that both children with ADHD and TD children improve SWM performance during self-generated SWM tasks, but that children with ADHD exhibit lower ability.

4.2. NIRS

4.2.1. Increased activation in the PFC of TD children

Our results showed that activation in the bilateral lateral PFC and frontal pole of TD children increased through development. As discussed in the previous paragraph, individual intellectual ability and severity of ADHD symptoms cannot explain the developmental changes that we observed. Considering that the lateral PFC and frontal pole play an important role in externally and self-generated information [11], our results suggest that functional maturation in regions associated with visuo-spatial information processing occur during school-age in TD children. Further, this might contribute to the improvement in self-generated SWM ability.

Similar to the present study, previous functional MRI studies using externally generated SWM tasks have consistently reported an increase in lateral PFC activation with age in TD children [16–18]. Because an increase in activation was found in the lateral PFC in both externally and self-generated SWM tasks, functional maturation in the lateral PFC (i.e., maintaining and manipulating externally generated information) could contribute to developmental changes in behavioral performance. In contrast, these studies also showed no change in activation in the frontal pole of TD boys [16–18]. Thus, increased activation in the frontal pole through development was only found during self-generated SWM tasks. Based on these findings, we speculate that functional maturation in the lateral PFC contributes to the improvement of externally and self-generated SWM tasks, while functional maturation in the frontal pole is only relevant for the improvement of self-generated SWM tasks.

While some previous studies have not shown developmental changes in frontal pole activation [16,17], Schweinsburg et al. [18] reported that TD boys show developmental decreases in activation of the frontal pole during an externally generated SWM task. Thus, the present study suggests that a developmental increase in activation of the frontal pole is specific to self-generated SWM tasks. It is possible that functional maturation not only in the lateral PFC but also in the frontal pole could be relevant for improvements in self-generated SWM.

4.2.2. No changes in activation of the PFC for children with ADHD

In contrast to the TD group, children with ADHD showed no developmental changes in activation of the lateral PFC and frontal pole. Furthermore, we found a significant group difference in the developmental trajectory of activation of the frontal pole (i.e., 10ch and 11ch), and older TD participants (over 10-years-old) showed stronger activation in the frontal pole (i.e., 10ch) than older ADHD participants. Because there were fewer children in the ADHD group ($n = 30$) than in the TD group ($n = 35$), the lack of significant correlation between age and integration of [oxy-Hb] may have been caused by the smaller sample size for the ADHD group. However, this is unlikely because even if the sample size was 35 (the same sample size as the TD group), a correlation coefficient equal to or greater than 0.33 would be required for $p < 0.05$, and the maximum r value for each channel in the ADHD group was 0.26, which was well below 0.33. As discussed above, individual intellectual ability and severity of ADHD symptoms cannot be confounding factors of the results. Therefore, our results suggest that children with ADHD have abnormalities in functional maturation of the frontal pole associated with self-generated SWM. The abnormal developmental changes associated with activation in the PFC might be related to delayed anatomical maturation for children with ADHD. For instance, Shaw et al. conducted a longitudinal structural MRI study to examine the developmental trajectory of cortical thickness for children with ADHD and TD children [34]. They found a similar order of cortical maturation between children with and without ADHD in that primary sensory areas attained peak cortical thickness before polymodal, higher-order association areas. However, children with ADHD showed significant delays in attaining peak cortical thickness in the PFC [34], indicating that anatomical maturation in the PFC is delayed in children with ADHD as compared to TD children. Based on these findings, we speculate that delayed anatomical maturation leads to abnormal developmental changes of activation in the PFC for children with ADHD during self-generated SWM tasks.

Despite the lack of increased activation in the PFC, the ADHD group showed significant improvements in SWM performance. These findings imply that, for children with ADHD, increased activation in other brain regions might contribute to the improved SWM seen through development. Although the current literature focuses on activation of the PFC during self-generated SWM tasks for individuals with ADHD, neuroimaging studies examining various executive functions or WM have reported compensatory brain activation in regions other than the PFC, including the occipital region [37], middle and superior temporal gyri [38], posterior cingulate [38] and supplementary motor area [39]. For instance, Schweitzer et al. [37] conducted a positron emission tomography study to compare regional cerebral flow (rCBF) changes for individuals with and without ADHD during an auditory working memory task (Paced Auditory Serial Addition Task (PASAT)). During the PASAT, single-digit numbers are presented binaurally and subjects are instructed to add each number to the preceding number and vocalize their answers. While task-related changes in rCBF in TD individuals were more prominent in the frontal and temporal regions, individuals with ADHD showed more widespread activation that was primarily located in the occipital regions. These results suggest that individuals with ADHD use alternative strategies and brain regions during a working memory task due to impaired PFC functioning. Based on these findings, we speculate that acquiring compensatory functions in the other regions induces improvement of self-generated SWM performance for children with ADHD.

4.2.3. Limitations and future studies

Six limitations of the present study should be noted. First, all participants with ADHD were being chronically administered methylphenidate, which they ceased taking at least 24 h prior to the experimental task; therefore, developmental changes in SWM performance and activation of the PFC might have been due to, or altered by, chronic administration of methylphenidate. Some studies have suggested that psychostimulant treatment, which includes methylphenidate, may normalize brain structure. For example, Nakao et al. [40] reported that psychostimulant treatment correlates with increasing (i.e., more normal) gray matter volume in the basal ganglia. On the other hand, Semrud et al. [41] reported that the anterior cingulate cortex (ACC) volume is significantly smaller in a treated naïve ADHD group than in treated ADHD and control groups. Thus, they suggested a relationship between previous treatment history and volumetric changes of the ACC in children with ADHD. Along with the PFC, these brain areas (i.e., basal ganglia and ACC) also play an important role in WM. Thus, it is possible that the improvements in SWM of children with ADHD in the present study were due to normalization of brain development by methylphenidate treatment. To elucidate purely developmental changes in SWM performance and PFC activation in children with ADHD, examination of drug-naïve participants is needed. Second, because of the limited age group in the present study (7–13 years), we were unable to examine whether inactivation of the PFC during the self-generated SWM task continued to adulthood. Myatchin et al. [13] have shown greater variability in EEG amplitude for children with ADHD than for TD children in younger (13–14 years), but not older (15–16 years) participants. Therefore, activation of the PFC during self-generated SWM tasks in children with

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ADHD might increase with older age. Examination of PFC activation during self-generated SWM tasks in adolescents with ADHD is necessary to elucidate this question. Third, we utilized a cross-sectional study in which individual differences might have been a confounding factor. Therefore, a longitudinal study is necessary to depict more accurate developmental changes. Fourth, in the present study we focused only on activation of the PFC. Therefore, we were unable to examine other brain regions, which might have shown compensatory activation. Additional NIRS approaches that can measure activation in the whole brain or other neuroimaging techniques such as functional MRI and magnetoencephalography (MEG) will better address this question. Fifth, we set the start point as the baseline, although previous NIRS studies set a baseline period with a certain length of time before the task period. Because two previous NIRS studies utilized very short baseline times (i.e., 1–2 s) and recovery and post periods were not set [42,43], it is unlikely that our definition of baseline was a critical problem in the present study. However, because the validity of setting a baseline without a duration has not been confirmed, future research is needed to verify the validity of our analysis method. Sixth, although Sato et al. [44] demonstrated that temporal changes in NIRS signals in the activated area were significantly correlated with the BOLD signals in the gray matter rather than with skin blood flow measured by laser Doppler, several NIRS studies have suggested that subcutaneous blood flow can be a confounding factor for task-related changes in NIRS signals [45,46]. In the present study, we did not measure skin blood flow; therefore, we cannot rule out the possibility that skin blood flow affected the results of present study. Thus, the replication of the present findings in the absence of skin blood flow is necessary.

5. Conclusion

Our study showed that while SWM ability improved in both ADHD and TD groups through development, children with ADHD exhibited lower ability. We also found that children with ADHD showed abnormalities in the functional maturation of the frontal pole, which plays a role in manipulating and maintaining information from self-generated behavior.

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