Brain & Development 41 (2019) 577–586

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Original article

Age-related differences in frontal lobe function in children with ADHD

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Received 31 August 2018; received in revised form 13 March 2019; accepted 14 March 2019

Abstract

Background: The neural correlates of executive function disorders are thought to be predominantly localized within the prefrontal cortex (PFC). However, no study to date has investigated changes in this system across different age groups in children with attention deficit hyperactivity disorder (ADHD). Thus, this study aimed to explore changes in PFC function in children with ADHD.

Methods: Study participants included typically developing (TD) children ($n = 140$) and children with ADHD ($n = 67$) of primary school age. Behavioral executive functions and their neural basis were evaluated between the TD children and children with ADHD and also across different age periods (younger and older children). To examine executive function, inhibitory control was assessed using the reverse Stroop task, and PFC near-infrared spectroscopic measurements were used to investigate the neural mechanisms involved.

Results: Both ADHD symptoms and the ability to inhibit color interference improved with age. Compared to TD children, children with ADHD demonstrated decreased activation of the right and middle PFC across all age groups. Interestingly, the left PFC appeared to play a compensatory role.

Conclusion: Children with ADHD exhibited changes in PFC function that varied with age. Longitudinal studies are required to assess the potential of using PFC function as an early biomarker of ADHD.

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https://doi.org/10.1016/j.braindev.2019.03.006
0387-7604/

Keywords: Attention deficit hyperactivity disorder (ADHD); Children with ADHD; Frontal lobe function; Prefrontal cortex (PFC); Near-infrared spectroscopy (NIRS); Inhibitory control; Reverse Stroop task (RST)

1. Introduction

Attention deficit hyperactivity disorder (ADHD) is a developmental, behavioral disorder of inhibitory control. Previous research has focused on antisocial and maladaptive problem behaviors within ADHD, which reflects the conceptualization of the disorder prior to publication of the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5). However, focus has since progressed to more central causes, and ADHD is currently considered to be a developmental disorder induced by brain dysfunction [1]. In the DSM-5, ADHD is categorized with autism spectrum disorder (ASD) and other neurodevelopmental disorders that are considered to be caused by specific brain dysfunction [2].

The primary clinical symptoms of ADHD include inattention and hyperactivity/impulsivity [2], and many studies support the notion that executive function disorders are at the core of ADHD symptoms [3]. Executive functions require higher complex cognitive and behavioral processes that are necessary to effectively execute goal-directed behaviors. These functions are generally accepted to be mediated by the prefrontal cortex (PFC) [4,5]. It has been suggested that clinical ADHD symptoms strongly relate to disruption of inhibitory control, which represents one element of the complex mix of executive functions [5]. Such functions are necessary for intentionally suppressing inappropriate and predominant behavior in specific situations.

Methods that enable quantitative assessment of brain function may ultimately assist in the differential diagnosis of ADHD and the development of therapeutic interventions. However, since most children with ADHD present with hyperactivity and other behavioral problems, it can be challenging to use techniques like functional magnetic resonance imaging (fMRI), which are highly vulnerable to motion artifacts and require prolonged periods of participant co-operation. For this reason, fMRI and similar imaging techniques are often performed in sleeping child participants, precluding the evaluation of waking functions. An alternative imaging method, near-infrared spectroscopy (NIRS), enables measurement of neural blood flow even if the child moves his or her head. Since NIRS can provide an index of PFC function [6], it is highly suitable as a proxy measure of some functional brain characteristics in children with ADHD.

Previous studies have investigated the role of inhibitory control in ADHD, but few have focused on differences in brain function between typically developing (TD) children and those with ADHD during functional tasks, which might ultimately aid the diagnosis of this disorder [7]. To address this, in a previous study, we sought to determine whether it would be possible to reliably differentiate between TD children and children with ADHD or ASD by analyzing PFC activity during executive function interference inhibition tasks, such as the Stroop task (ST) or reverse Stroop task (RST) [8]. The results indicated a deficit in inhibitory control of color interference in children with ADHD compared to the TD and ASD groups. In addition, inhibitory control deficits were found to relate to inattention severity with regard to right PFC activity. Finally, these data strongly endorsed the RST as a valid approach for identifying children with ADHD.

Subjective behavioral assessments indicate that impulsivity and hyperactivity decrease with age, but that inattention tends to persist into adulthood [9]. Moreover, ST studies have found that interference inhibition capacity matures during childhood [10]. Furthermore, the PFC, which has been implicated in interference inhibition, continues to develop as TD children grow into adulthood [11]. However, to the best of our knowledge, no study to date has carefully evaluated changes in PFC function at different ages in children with ADHD. Ultimately, identifying neural changes in this vulnerable population might pave the way for early diagnoses and treatment.

As a critical next step towards developing a marker for the diagnosis of ADHD, a large sample of Japanese children was recruited through a multi-site collaboration for assessment. Two age groups of primary school children with ADHD (but no other comorbid conditions) and age-matched groups of TD children were assessed for inhibitory control of interference and PFC activity using NIRS during the RST. In addition, the validated 26-item, Japanese version of the Swanson, Nolan, and Pelham scale, version IV (SNAP-IV) rating scale [12] was completed by the parent/guardian as a subjective index of the three common subscales of ADHD severity. Age effects were evaluated between the ADHD and TD groups. In addition, structural equation modeling (SEM) was used to describe the relationships between PFC function and ADHD symptom severity.

2. Methods

2.1. Recruitment and participants

A total of 299 primary school children were recruited through one of seven collaborative institutions in Japan.

Table 1
Participant group characteristics. Mean (standard deviation) and [range] or percent values for demographics and clinical scales.

	ADHD		TD	
	Younger	Older	Younger	Older
N	38	29	68	72
Age	8.49 (.85)	11.11 (.63)	8.41 (.88)	11.23 (.63)
	[6.75–9.92]	[10.17–12.25]	[6.50–9.92]	[10.00–12.50]
Handedness (r)	86.8%	89.7%	89.7%	93.1%
Gender (m)	84.2%	89.7%	54.4%	38.9%
Raven's Colored Progressive Matrices	28.21 (4.07)	30.31 (3.72)	29.13 (3.00)	31.0 (3.11)

The exclusion criteria for both groups were as follows: severe comorbidities such as ASD or learning disabilities; difficulties in performing or completing the experimental tasks; and/or NIRS values varying by more than 3 standard deviations (SD) from the sample mean. After exclusion, a total of 207 children participated in the study. The characteristics of the participants are described in Table 1. Some of the subjects included in these analyses also participated in our earlier study [8].

Sixty-seven children with ADHD participated in the present study (younger group: $n = 38$, 8.49 ± 0.85 years; older group: $n = 29$, 11.11 ± 0.63 years). ADHD was diagnosed by a pediatric neurologist specializing in developmental disorders based on DSM-IV-TR and DSM-5 criteria [2]. All children in the ADHD group were administered the Wechsler Intelligence Scale for Children (WISC)-III or WISC-IV and all scored a Full Intelligence Quotient (IQ) or Full Scale IQ of 80 or higher [13,14]. Forty-one of the children with ADHD had been prescribed methylphenidate (MPH), atomoxetine (ATX), or risperidone (RIS) (younger group: *MPH: n = 18, ATX: n = 3*; older group: *MPH: n = 14, ATX: n = 5, RIS: n = 1*). Children taking stimulant medication for their ADHD underwent a 24-hr washout period before their assessment. In addition, 140 TD children participated in the study (younger group: $n = 68$, 8.41 ± 0.88 years; older group: $n = 72$, 11.23 ± 0.63 years). None of the TD children had been diagnosed with ADHD or any other developmental disability, nor were they on any medications to treat a comorbid condition or chronic illness.

Children with ADHD and TD children were matched within the two age groups with regard to age (younger: $t(104) = .44$, $p = .66$; older: $t(99) = .82$, $p = .41$), handedness (younger: $\chi2 = .199$, $p = .75$, older: $\chi2 = .328$, $p = .69$), and non-verbal intelligence on the Raven's Colored Progressive Matrices (RCPM) [15] (younger: $t(104) = 1.33$, $p = .19$; older: $t(99) = .95$, $p = .34$). The ADHD group included significantly more male than female participants (younger: $\chi2 = 9.53$, $p = .003$, older: $\chi2 = 21.42$, $p < .001$). For colorblind examination, we used a paper-based Stroop examination in advance. There was no one with color blindness.

All participants and their parents/guardians provided written informed consent prior to participation. The study was approved by the Institutional Review Board, National Center of Neurology and Psychiatry, Japan.

2.2. Subjective ADHD severity scale

To examine correlations between age and ADHD severity, and to ensure that TD children did not experience ADHD symptoms, all parents/guardians completed the Japanese version of the 26-item SNAP-IV [12]. The SNAP-IV includes subscales with items relating to inattention, hyperactivity/impulsivity, and oppositional defiant disorder from the DSM-IV, and Conners Index Questionnaire [16]. Higher scores indicate greater problems within each sub-score. The Japanese version demonstrates good test–re-test reliability (intra-class correlation = 0.752–0.822) and high internal consistency (Cronbach's $\alpha = 0.933$–0.952) [16].

2.3. Reverse Stroop task

The RST was administered to examine participants' ability to inhibit color interference. The details of this protocol and analyses have been previously reported [8]. Briefly, the participants sat approximately 50 cm in front of a 15-inch liquid crystal display (LCD) screen with a gray background and responded to tasks using a touch panel screen. All RST prompt words were in Japanese. For the RST, participants were required to select the color that matched the meaning of the central word. For example, when the word "green" was displayed in red font at the center of the LCD screen, the correct choice was the corner patch colored green. The task consisted of a neutral condition (Supplemental Fig. S1a) and an incongruent condition (Supplemental Fig. S1b). In the neutral condition, the central word was a color name in black font, whereas in the incongruent condition, the central word was presented in a font color different from the word (e.g., "green" in red font). In the incongruent condition, the font color was incongruent with the central word meaning and therefore interfered with the choice of matching colored patch.

In all tasks, the font colors used were red, yellow, white, and green. Each task lasted for 30 s, beginning with a 10 s rest period during which the participants were required to stare at a central white circle. During each 30 s task, new stimuli appeared on the screen 5 s after the subject's response. Two separate task sessions were conducted, each consisting of one congruent and one incongruent task. The order of task presentation was counterbalanced for each participant. The color and word at the center as well as the colors of the four corner patches and the order of the corner words varied randomly between trials. All participants used their index finger for choice selection.

2.4. NIRS recordings

While participants performed the RST, PFC neural activity was recorded by measuring changes in oxygenated hemoglobin (oxy-Hb) levels using a multichannel NIRS system (OEG-16®; Spectratech Inc., Tokyo, Japan). The details of this protocol have been previously described [8]. Briefly, near-infrared laser diodes with two wavelengths (approximately 770 and 840 nm) were used to emit near-infrared light. The re-emitted light was detected with avalanche photodiodes located 30 mm from the emitters. The temporal resolution of acquisition was approximately 0.65 s. The system measures oxy-Hb at a depth of approximately 30 mm below the scalp. In our system, six emitters and six detectors were placed at alternate points on a grid, enabling the detection of signals from 16 channel locations between these probes (Fig. 1). The center of the probe matrix was placed on Fpz using the International 10–10 system, and the bottom left and right corners were located around F7 and F8, respectively [8,17]. NIRS signals were sent to a data collection computer. To increase the signal-to-noise ratio, each recording was converted to a z-score to compare traces across the participants and channels [6,8,18]. The z-score was calculated using the mean and SD of oxy-Hb during the last 6 s of the rest period. Recordings more than 2 SD away from the mean were excluded because these were likely to be contaminated by motion artifacts. The average signal for each channel during the last 20 s of the RST was used to compare regional neural activity between groups. In addition, signals from channels 11–16 were averaged to obtain left PFC activity, channels 7–10 were averaged to obtain middle PFC activity, and channels 1–6 were averaged to obtain right PFC activity.

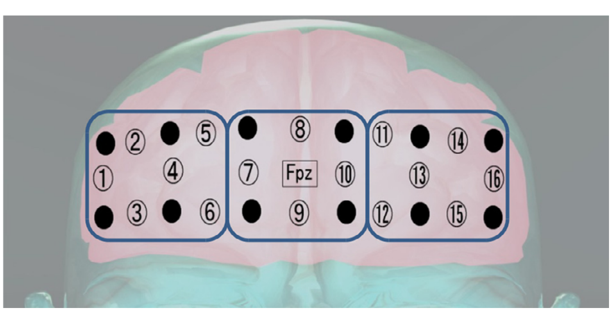

Fig. 1. Emitter and probe configuration for near-infrared spectroscopy (NIRS). The NIRS system was attached to the prefrontal area. The center of the probe matrix was placed on Fpz (using the international 10–20 system). The blue outlined boxes represent placement locations for the right, middle, and left prefrontal cortex (PFC), respectively. The black circles represent probe locations, which enabled recording from 16 channels between the respective probes. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

2.5. Statistical analyses

SPSS Statistics v21, Amos v21, and MATLAB R2013a were used for statistical analysis. Correlations between age and the three SNAP-IV sub-scores (inattention, hyperactivity/impulsivity, and oppositional defiance) were examined. In addition, 2 (age: younger vs. older) × 2 (diagnosis: TD vs. ADHD) distribution analyses were performed for SNAP-IV sub-score measures; the RST interference rate; and changes in left, middle, and right PFC activity. A two-way analysis of variance (ANOVA) was conducted for group comparisons, and multiple comparisons were carried out after applying a Bonferroni correction. Statistical significance was determined at a p value $<.005$. Correlation analyses were conducted using Pearson product-moment correlation coefficients.

3. Results

3.1. ADHD severity

Age-related variation was first examined with regard to inattention scores in children with ADHD and TD children (Fig. 2a). No significant correlation was observed between age and inattention within either the ADHD or TD groups (ADHD: $r = -0.203$, $p = .099$; TD: $r = -.050$, $p = .558$). However, a distribution analysis of diagnosis (TD vs. ADHD) within the younger or older age groups indicated a main effect of diagnosis, with TD children scoring significantly lower on inattention than children with ADHD in both the younger and older age groups (main effect: ADHD × TD: $F(3,203) = 210.29$, $p < .001$, partial $\eta 2 = .509$; multiple comparisons: younger: $p < .001$, older: $p < .001$). A main effect of age was also observed within the ADHD group, with older children scoring lower on inattention than younger children (main effect: younger × older: $F(3,203) = 4.83$, $p = .029$, partial $\eta 2 = .023$; multiple comparisons: ADHD: $p = .023$, TD: $p = .580$). No interaction was identified between diagnosis and age group (interaction: $F(3,203) = 2.46$, $p = .118$, partial $\eta 2 = .012$).

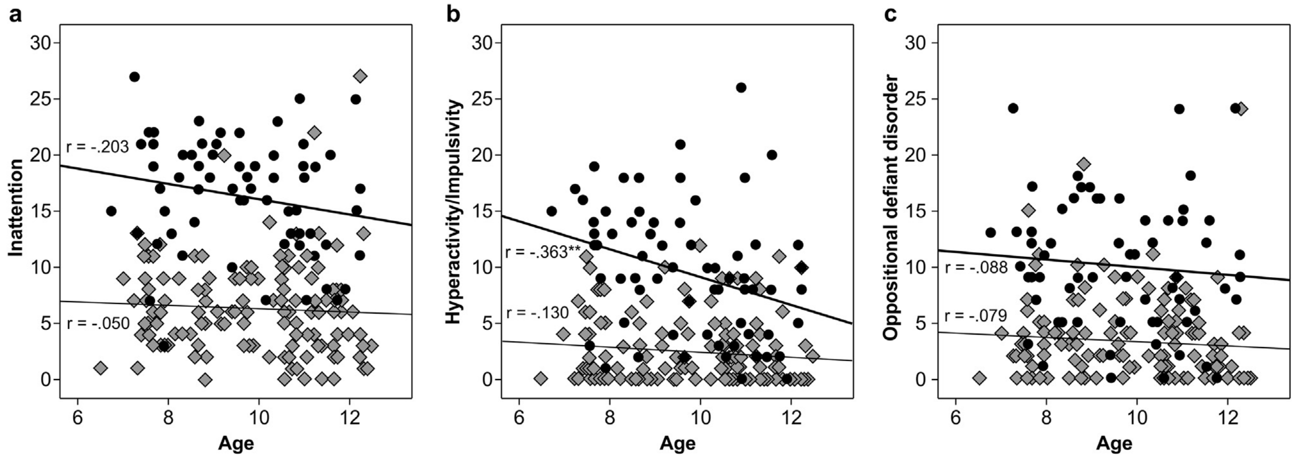

Fig. 2. Correlation between age and Swanson, Nolan, and Pelham scale, version IV (SNAP-IV) inattention scores. Displayed are the plots of children of various ages with attention deficit hyperactivity disorder (ADHD) (black circle) or typically developing (TD) children (gray diamond) with Inattention (a), Hyperactivity/Impulsivity (b), and Oppositional Defiant Disorder (c). Statistical significance was determined at $^{**}p < 0.01$ using Pearson's correlation.

Next, age-related variations were investigated with regard to hyperactivity/impulsivity scores in children with ADHD and TD children (Fig. 2b). A significant, negative correlation was identified for age and hyperactivity/impulsivity among children with ADHD but not TD children (ADHD: $r = -.363$, $p = .002$; TD: $r = -.130$, $p = .091$). The distribution analysis of the diagnosis and age groups indicated a main effect of diagnosis, with TD children scoring significantly lower on hyperactivity/impulsivity than children with ADHD in both the younger and older groups (main effect: ADHD × TD: $F(3,203) = 135.41$, $p < .001$, partial $\eta 2 = .400$; multiple comparisons: younger: $p < .001$, older: $p < .001$). A main effect of age was also observed, with older children scoring lower on hyperactivity/impulsivity than younger children in the ADHD, but not the TD, group (main effect: younger × older: $F(3,203) = 14.75$, $p < .001$, partial $\eta 2 = .068$; multiple comparisons: ADHD: $p < .001$, TD: $p = .577$). In addition, a significant interaction was identified between diagnosis and age group (interaction: $F(3,203) = 10.29$, $p = .002$, partial $\eta 2 = .048$).

Finally, age-related variations in oppositional defiant scores were examined (Fig. 2c). No significant correlation was observed between oppositional defiant scores and age in either the ADHD or TD group (ADHD: $r = -.088$, $p = .481$; TD: $r = -.079$, $p = .355$). The distribution analysis of diagnosis and age groups indicated a main effect of diagnosis, with TD children scoring significantly lower on oppositional defiance than children with ADHD in both the younger and older groups (main effect: ADHD × TD: $F(3,203) = 93.18$, $p < .001$, partial $\eta 2 = .315$; multiple comparisons: younger: $p < .001$, older: $p < .001$). However, a main effect was not observed for age (main effect: younger × older: $F(3,203) = 1.30$, $p = .256$, partial $\eta 2 = .006$; multiple comparisons: TD = .331, ADHD: $p = .477$). In addition, no interaction was observed between diagnosis and age group (interaction: $F(3,203) = .001$, $p = .971$, partial $\eta 2 < .001$).

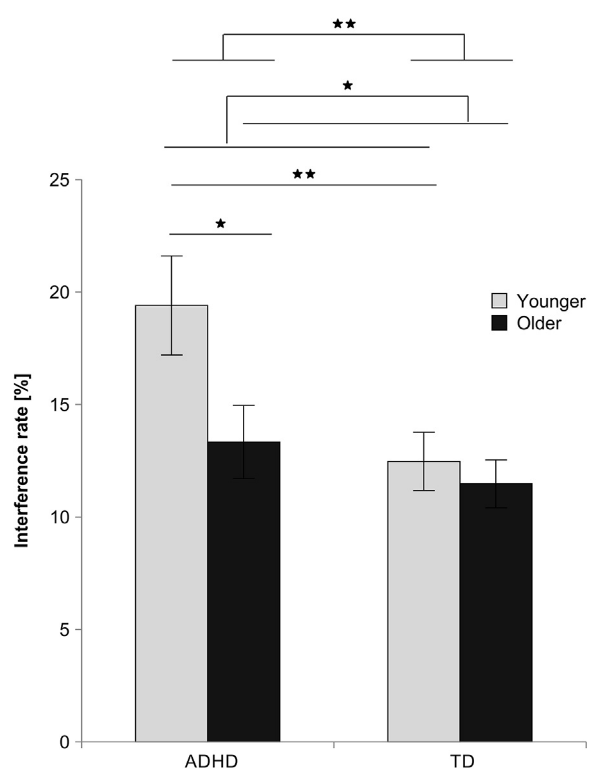

Fig. 3. Behavioral results of the reverse Stroop task (RST). Displayed are the interference rates for children with attention deficit hyperactivity disorder (ADHD) and typically developing (TD) children from two age groups during the RST. Error bars indicate standard error of mean. Statistical significance was determined at $^{*}p < 0.05$ and $^{**}p < 0.01$ using a two-way ANOVA with Bonferroni post hoc analysis.

3.2. Reverse Stroop task

The authors have previously demonstrated that interference rates in the RST can be effectively used as an index of interference inhibition capacity [8]. In the entire sample, a significant correlation was identified between inference rate and age (r = −.199, $p = .004$). When analyzing the individual groups, it became apparent that the overall association was driven by the ADHD group (r = −0.325, $p = .007$), and no significant correlation was present within the TD group (r = −.117, $p = .169$). The age-specific difference in test results (Fig. 3) indicated a main effect of diagnosis, with TD children scoring significantly lower on interference with inhibition capacity than children with ADHD in the younger, but not the older, group (main effect: ADHD × TD: $F(3,203) = 7.83$, $p = .006$, partial η2 = .037; multiple comparisons: younger: $p = .001$, older: $p = .423$). A main effect was also observed for age, with older children demonstrating significantly lower interference with inhibition capacity than younger children in the ADHD group (main effect: younger × older: $F(3,203) = 5.06$, $p = .026$, partial η2 = .024; multiple comparisons: ADHD: $p = .020$, TD: $p = .577$). A significant interaction was not observed between diagnosis and age group relative to interference inhibition capacity (interaction: $F(3,203) = 2.61$, $p = .108$, partial η2 = .013). In addition, a significant, negative correlation was identified between age and interference rate within the ADHD group (ADHD: $r = -.325$, $p = .007$; TD: $r = -.117$, $p = .169$).

3.3. Prefrontal cortex function

There was no main effect of diagnosis for the left PFC (Fig. 4a), but TD children exhibited significantly higher left PFC function than children with ADHD in the younger, but not the older, group (main effect: ADHD × TD: $F(3,203) = 3.13$, $p = .078$, partial η2 = .015; multiple comparisons: younger: $p = .021$, older: $p = .792$). A main effect of age was identified, with older children demonstrating significantly higher left PFC function than younger children, but only within the ADHD group (main effect: younger × older: $F(3,203) = 4.49$, $p = .035$, partial η2 = .022; multiple comparisons: ADHD: $p = .035$, TD: $p = .515$). Furthermore, no significant interaction was observed between diagnosis and age group (interaction: $F(3,203) = 1.91$, $p = .169$, partial η2 = .009).

There was a main effect of diagnosis for the middle PFC (Fig. 4b), with TD children demonstrating significantly higher middle PFC function than children with ADHD among both younger and older subjects (main effect: ADHD × TD: $F(3,203) = 12.88$, $p < .001$, partial η2 = .060; multiple comparisons: younger: $p = .034$, older: $p = .004$). While a main effect was not observed for age, older subjects had significantly higher middle PFC function than younger subjects, but only within the TD group (main effect: younger × older: $F(3,203) = 2.83$, $p = .094$, partial η2 = .014; multiple comparisons: ADHD: $p = .547$, TD: $p = .037$). Furthermore, no interaction was observed between diagnosis and age group (interaction: $F(3,203) = .474$, $p = .492$, partial η2 = .002).

There was a main effect of diagnosis for the right PFC (Fig. 4c), with TD children having significantly higher right PFC function than children with ADHD, but only within the older group (main effect: ADHD × TD: $F(3,203) = 5.60$, $p = .019$, partial η2 = .027; multiple comparisons: younger: $p = .422$, older: $p = .014$). A main effect was not observed for age, but older children had significantly higher right PFC function than

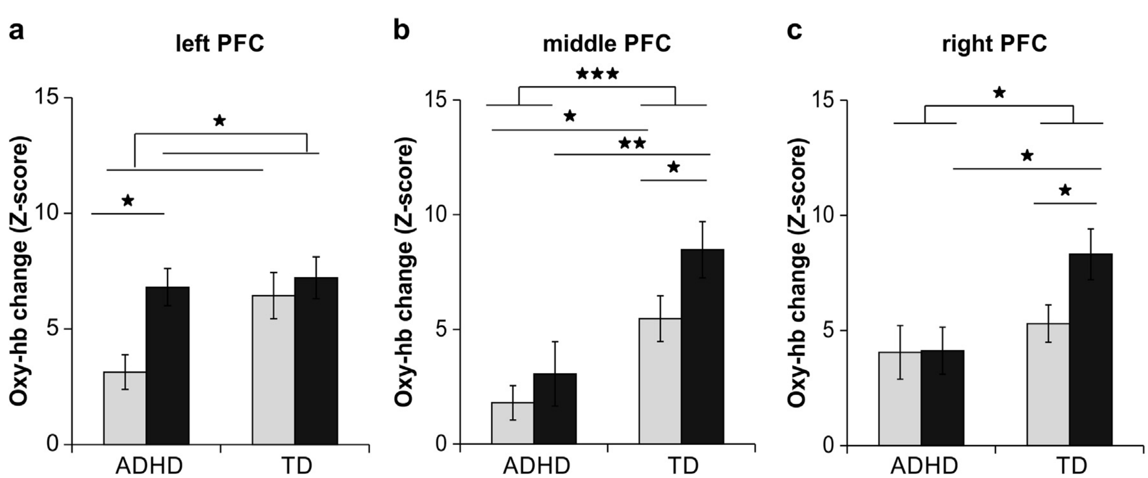

Fig. 4. Mean z-score of oxygenated hemoglobin (oxy-Hb) changes during the trial period. Near-infrared spectroscopy (NIRS) was used in children with attention deficit hyperactivity disorder (ADHD) and typically developing (TD) children from two age groups to measure activation in the left prefrontal cortex (PFC) (a), the middle PFC (b), and the right PFC (c). Error bars indicate standard error of mean. Statistical significance was determined at $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$ using a two-way ANOVA with Bonferroni post hoc analysis.

younger children within the TD group (main effect: younger × older: $F(3,203) = 1.80$, $p = .181$, partial $\eta 2 = .009$; multiple comparisons: ADHD: $p = .969$, TD: $p = .022$). A significant interaction was not observed between diagnosis and age group (interaction: $F(3,203) = 1.63$, $p = .203$, partial $\eta 2 = .008$).

To examine any left-right brain differences, the left and right PFC regions were compared within each group using the Student's *t*-test (two-tailed). The results revealed a higher activation in the left PFC compared to the right PFC only among older children with ADHD (TD younger: $t(67) = 1.53$, $p = .130$; TD older: $t(71) = 1.31$, $p = .195$; ADHD younger: $t(37) = .850$, $p = .401$; ADHD older: $t(28) = 2.23$, $p = .034$).

Changes in brain function during RST tasks, as measured by NIRS, are displayed topographically in Fig. 5. The 30 s of the RST interference condition being tested is shown topographically for every 10 s. The relationships between task performance and ADHD measures were also assessed. First, the correlations between PFC activation areas and SNAP-IV sub-scores were determined among the whole sample ($n = 207$). The correlations were as follows: between the left PFC and inattention ($r = -.112$, $p = .107$), impulsivity/hyperactivity ($r = -.156$, $p = .025$), and oppositional defiance disorder (ODD) ($r = -.168$, $p = .015$); between the middle PFC and inattention ($r = -.153$, $p = .028$), impulsivity/hyperactivity ($r = -.176$, $p = .011$), and ODD ($r = -.189$, $p = .006$); and between the right PFC and inattention ($r = -.124$, $p = .076$), impulsivity/hyperactivity ($r = -.116$, $p = .095$), and ODD ($r = -.125$, $p = .073$). Correlations between the RST interference rate and SNAP-IV sub-scores in the whole sample were statistically significant for inattention ($r = .199$, $p = .004$), impulsivity/hyperactivity ($r = .203$, $p = .003$), and ODD ($r = .144$, $p = .039$).

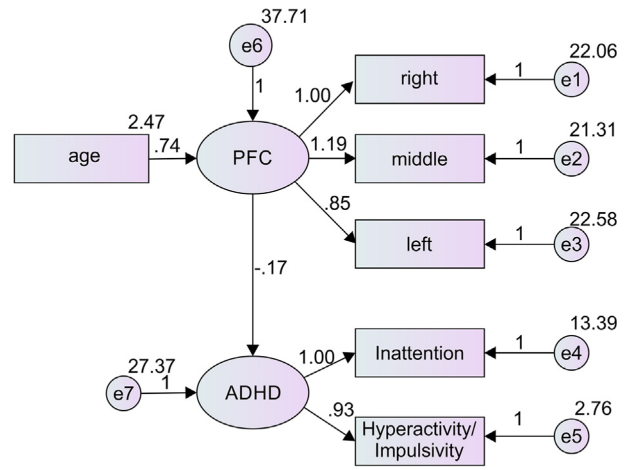

Fig. 6. Path diagram for the structural equation model to examine the relationship between prefrontal cortex (PFC) function and attention deficit hyperactivity disorder (ADHD) severity. Standardized estimates e1–e7 represent the error using covariance structure analysis.

3.4. Structural equation modeling

SEM was used to model the relationship between PFC function and ADHD severity (Fig. 6). The results indicated significant standardized estimates at a 5% level in all cases. The goodness of fit indices (GFI = .984, AGFI = .958, CFI = .995, and RMSEA = .036) demonstrated a high model fit. The coefficient from PFC to ADHD was −0.17, confirming that high PFC activation is associated with a lower severity of ADHD indices.

4. Discussion

Evaluations of subjective SNAP-IV surveys demonstrated that while indices of inattention and hyperactivity/impulsivity were lower in older children with

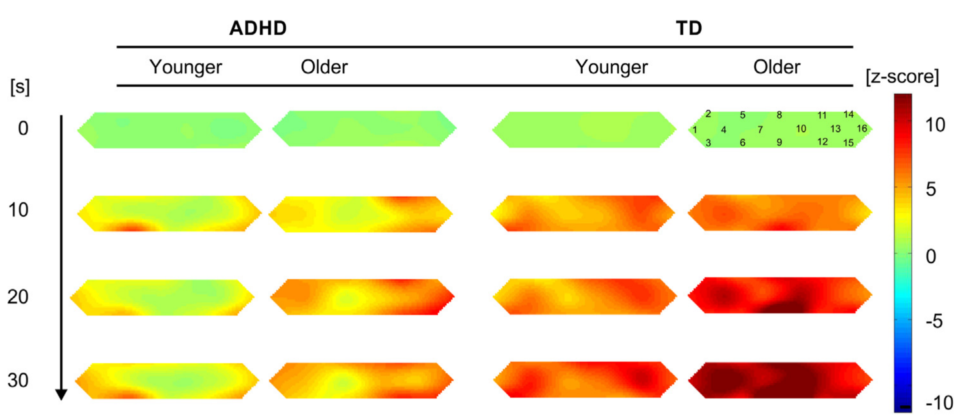

Fig. 5. Mean z-score changes in oxygenated hemoglobin (oxy-Hb) measured by near-infrared spectroscopy (NIRS) during the reverse Stroop task (RST). Pseudocolor images plot regional changes in oxy-Hb across the prefrontal cortex for typically developing (TD) children (right) and children with attention deficit hyperactivity disorder (ADHD) (left). Values on the fourth image of the first row indicate the channel locations.

ADHD, discrepancies also existed within the TD group. For ODD, no age differences were observed in either group; however, the findings for the TD and ADHD groups differed. Nonetheless, since an interaction was only observed for hyperactivity/impulsivity, and because hyperactivity/impulsivity correlated negatively with age in the ADHD group, hyperactivity/impulsivity might be influenced to a greater extent by age than inattention.

Previous studies have reported that the RST interference rate relates strongly to inhibitory control, dysfunction of which is a core symptom of ADHD [19,20]. The current results also suggest that children with ADHD might have weaker inhibitory control. Moreover, the cumulative findings of a lower interference rate in older children and a negative correlation between age and interference rate suggest that inhibitory control might improve with age.

Previous studies have reported regional activation of the PFC during the performance of certain tasks [19]. In addition, age-related changes in PFC activation are also thought to arise in a region-specific fashion [21]. To examine changes in PFC function, the PFC was divided into left, middle, and right regions, and the changes in standardized oxy-Hb levels were quantified within each region. Distribution analyses of diagnosis and age were used for each region (Fig. 4).

Frontal lobe-based inhibitory control of interference is thought to develop as TD children progress into adulthood [5]. In the current study, age-related differences were identified in the right and middle PFC between age groups in early childhood. While the right PFC has been strongly linked to inhibitory control, the current findings suggest that in TD children, age-related changes in right PFC functioning might closely relate to concurrent differences in inhibitory control [22]. Moreover, the frontal pole is located in the middle PFC, which has been linked to predicting the future and evaluating past decisions [2,23], and might be involved in monitoring during inhibitory tasks. In contrast to TD children, age-related changes in right and middle PFC functioning were not found among children with ADHD. However, within the ADHD group, age-related differences in left PFC functioning were identified that were not observed in TD children. Based on these cumulative data, we speculate that in children with ADHD the left PFC might play a compensatory role during development. Compensatory brain function has been reported in both patients with aphasia, among whom the inferior hemisphere functions as the language area, and in those with learning disorders (which, like ADHD are considered developmental disorders) [24]. The RST not only requires subjects to inhibit color interference, but also requires them to retain the meaning of words [25]. Broca's area, which is involved in processing language information, is located in the left PFC [26]. In children with ADHD, the ability to retain language information (i.e., word meaning) might develop in the left PFC to compensate for the relative weakness of the right and middle PFC, which are involved in inhibitory control.

The SEM model used in this study, which features a high goodness of fit, suggests that the PFC is involved in the core ADHD symptom profile. This supports the hypothesis that the PFC is implicated in disorders of executive function (i.e., the core symptoms) in children with ADHD, and further suggests that PFC dysfunction should be targeted as a potential early and objective marker of ADHD [4,27,28]. The next step in this process will require longitudinal assessment to determine whether the age differences found herein reflect a developmental change. It will then be possible to investigate whether a protocol such as ours can be used for early interventional work. Further, since failures in the frontal lobe-corpus striatum system and intra-cerebral network problems have been proposed as a potential explanation for ADHD, developmental changes in circuits outside the PFC also require longitudinal evaluation [29].

The ST and RST are commonly used to assess inhibitory control [7,30], wherein the ST serves as an index of inhibitory control against Stroop interference, which occurs when conflict arises between language and color information. For example, a card is presented with text spelling the word "Yellow," on which the text is printed in the color red, and the subject's task is to correctly say/select "Red." The semantic meaning of the text frequently causes interference (i.e., meaning interference) with the subject's ability to correctly respond. By contrast, in the RST, the subject is required to select the color associated with the meaning of the word (yellow). In this context, the color of the text causes the interference (color interference). Both tasks can be administered using either a verbal response or a matching format. With verbal responses, the indices include the fluency and accuracy of the spoken answers; with matching responses, the indices include the speed and accuracy of pointing or otherwise indicating answers. Verbal responses produce almost no reverse Stroop interference (color interference) compared to Stroop interference (meaning interference). In contrast to verbal responses, matching responses (in which the colored patch signified by the word is selected from several patches) are known to produce reverse Stroop interference [22,30]. Therefore, when the RST is administered to children with ADHD or ADHD symptoms, it is possible to observe ADHD-specific characteristics not observed with the ST [31]. In a previous study, we used the RST to discriminate effectively between children with ADHD or ASD and TD children [8].

A correlation has also previously been reported between ADHD and disorders of working memory (an additional element of executive function). According to Westerberg et al. [32] disparities in non-verbal working memory tasks tend to arise with age in TD children and in those with ADHD. However, age-related changes in PFC function in children with ADHD have not been previously reported. To the best of our knowledge, this is the first study to examine regional PFC activation in children with ADHD and TD children at different ages.

A potential limitation of this study includes the impact of medications used to treat ADHD. However, while children receiving medication were included in our sample, distinct age differences were still identified between TD children and those with ADHD, supporting the notion that either the effects of age were strong enough to mitigate the variance accounted for by medication, or that the impact of medication was marginal. There were no significant differences between medicated clinical group and medication-naïve clinical group in behavioral and brain indices (Supplemental Table S1). Nevertheless, comparison with a medication-naïve clinical group would be valuable. Importantly, longitudinal assessments are needed to confirm the developmental nature of such changes, and experimental designs alone may be able to answer questions relating to causality. Finally, we were unable to both retain statistical power and divide our samples into more narrow age-ranges. In the future, as with any developmental study, the youngest age groups should be included to the greatest extent possible and comparable standardized assessments validated for their inclusion.

5. Conclusion

Specific age changes in inhibitory control occur in the PFC of children with ADHD. These results suggest that cognitive interference inhibition tasks and assessment of PFC function by NIRS should be considered valuable for refining the characteristics of ADHD and therefore for improving early diagnosis and subsequent treatment.

Acknowledgements

We would like to thank the following people for their co-operation in collecting data: Dr. Shingo Oana, Department of Pediatrics, Tokyo Medical University; Dr. Yoshimi Kaga, Department of Pediatrics, University of Yamanashi; Dr. Kotaro Yuge, Department of Pediatrics & Child Health, Kurume University; Dr. Yoriko Okamoto, Graduate School of Regional Sciences, Tottori University; and Dr. Chikaho Naka, Department of Special Needs Education, Tokyo Gakugei University. Editorial support, in the form of medical writing based on authors' detailed directions, collating author comments, copyediting, fact checking, and referencing, was provided by Cactus Communications.

Role of the funding source

This work was supported in part by the TMC Young Investigator Fellowship and an Intramural Research Grant (25-6; Clinical Research for Diagnostic and Therapeutic Innovations in Developmental Disorders) for Neurological and Psychiatric Disorders of the National Center of Neurology and Psychiatry (NCNP); a Grant-in-Aid for Young Scientists (A) from JSPS KAKENHI (15H05405 to Akira Yasumura), and a Grant-in-Aid for Challenging Exploratory Research from JSPS KAKENHI (15K13167 to Akira Yasumura).

Conflict of interest

The authors declare no conflict of interest.

Data statement

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.braindev.2019.03.006.

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