Investigating prefrontal hemodynamic responses in ADHD subtypes: A fNIRS study

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Abstract

The purpose of the present study was to examine the hemodynamic response and reaction time (RT) in healty children and attention deficit hyperactivity disorder (ADHD) subtypes as measured by functional near infrared spectroscopy (fNIRS) during the auditory oddball attention task. The sample was made up of 40 children divided into four groups: control group (n=14), inattenttive subtype (ADHD-I; n=9), hyperactive-impulsive subtype (ADHD-HI; n=6), and combined subtype (ADHD-C; n=11). Right prefrontal cortex heamodynamic responses and groups performance on RT was compared between subtypes and between controls and subtypes. fNIRS indicated that while control subjects exhibited higher activation than all ADHD subtypes; ADHD subtypes did not differ from one another. Relative to control subjects, longer RT observed in all ADHD subtypes. ADHD-I group showed significantly longer RTs compared to ADHD-HI and ADHD-C group. These results suggest a novel path of significant interest concerning reliable evaluation of fNIRS and RT studies in ADHD.

1. Introduction

ADHD is one of the most common psychiatric disorders in school age children, which is characterized by inattention, hyperactivity and impulsivity symptoms. ADHD diagnoses can be further categorized into three different subtypes, including persistent inattention (ADHD-I), hyperactivity-impulsivity (ADHD-H), or a combination of both (ADHD-C) according to Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [1]. Although in the current clinical view, these three subtypes belong to the same diagnostic entity, the subtypes can be distinguished from each other on inattention symptoms, event-related brain activation, inhibitory control and responsiveness to stimulant medication [2-3]. The distinctiveness of the ADHD subtypes on neuroimaging measures is not clear. Thus, the current study focuses on the neuroimaging profiles of ADHD subtypes using functional near infrared spectroscopy (fNIRS).

fNIRS, which assesses functional activity in the brain by monitoring changes in the concentrations of oxygenated and deoxygenated hemoglobin, is advantageous as it is highly sensitive, cost-effective, and does not restrict a user's range of motion [4]. Various fNIRS studies have sought to assess the hemodynamic changes of ADHD patients [5-6]. Because the prefrontal cortex (PFC) is associated with the level of alertness and attention [7], these studies particularly focussed on alterations in PFC activity during a cognitive task and consistently showed atypical hemodynamic response in children with ADHD. In this study we invastigated ADHDs' frontal brain functions during an auditory stimulation with heamodynamic changes specifically in oxy-Hb.

Another more consistent findings in the ADHD neuropsychology literature is that these children demonstrate, slower and more variable reaction times (RT)s compared to typically-developing children on a number of different tasks. [8]. Studies have demonstrated that increased RT variability in ADHD is mostly related to extremely slow responses that are caused by periodic lapses of attention in goal-directed processing [9]. The literature is inconsistent with respect to differences between ADHD subtypes in terms of inhibitory control, with some showing longer RT or increased commission errors in children with ADHD-C, some showing slower processing speed in the ADHD-I subtype and others failing to find subtype differences on one or more of these measures [10]. Given the inconsistencies in results of neurocognitive studies of the ADHD-I and ADHD-C subtypes, the use of fNIRS may help to resolve continuing controversy concerning whether these subtypes are variants of the same condition or completely different disorders. The present study carefully selected groups of ADHD participants to provide an accurate separation of ADHD subtypes and examined differences between them in terms of oxygenation of PFC and RT to target stimuli during a auditory oddball attention task.

2. Methods

2.1 Participants: In this study, participants were comprised of 40 children that were classified into four groups: control group children with a mean age of 10.33 (n = 14; SD = 2.12; range 7-12 years); group (ADHD-I) with a mean age of 9.66 (n = 9; SD = 2.95; range 7-12 years); group (ADHD-HI) with a mean age of 8.16 (n = 6; SD = 0.75; range 7-12 years); and group ADHD-C, with a mean age of 10.00 (n = 11; SD = 1.61; range 7-12 years). Groups of ADHD subtypes were carefully identified using DSM IV criteria and they were not receiving any kind of pharmacological treatment. Controls underwent a standard clinical assessment comprising neurological, endocrine and psychiatric evaluations and no history of psychiatric or neurological disorder, were enrolled in the study. Participants were all right handed, Turkish and had normal hearing functions. The Wechsler Intelligence Scale for Children-Revised (WISC-R)[11] full IQ scores of subjects were all over 80. The research protocol was approved by the ethics committees of the University of Erciyes and was in accordance with the latest version of the Declaration of Helsinki. All participants provided child assent and their parents gave written informed consent after comprehensive explanation of the procedures. ADHD children and control did not differ statistically in terms of age, years of education, IQ and gender ($p>0.05$).

2.2 Task: In this study 128 standard (2000 Hz) and 32 target (1500 Hz) auditory stimuli were presented in a random order with duration of 160 s (Superlab 4.0). The interstimulus intervals (ISI) were randomized between 1250 and 2500 msec. Prior to the first run of the oddball task, the participants were told that they would need to listen for a defined auditory target stimulus (1500 Hz), presented through headphones, and to respond by pressing a button. They were asked not to move, speak, or blink too much, and to look at a fixed point in order to avoid noises and stabilize the blood flow in all channels.

2.3 fNIRS data acquisition and Pre-Processing : In the present study, we used a 16 channel (CH) continuous wave fNIRS system that has 4 LED type light sources at 2 wavelengths of 730 nm and 850 nm and 10 photo detectors seperated from the sources by 2.5 cm as illustrated in Figure 1 (a). Relative changes in hemodynamic responses in terms of oxy-Hb were calculated using the modified Beer–Lambert law [12]. The sampling frequency was 2Hz. Data processing began with the removal of heart pulsation, respiration and movement artifacts from the raw fNIRS intensity measurements by using a low-pass filter with a cut-off set to 0.14 Hz [4]. Then data of each channel were averaged across 32 target responses for each subject. Target responses identified 3 s before the target stimuli period onset to 10 s after the target stimuli. Grand average of integrated oxy-Hb for all target responses belongs to one participant of each group are illustrated in figure 2. RT of participants to 32 target stimuli detected with Matlab R2015a automatically by calculating the period between the emerging of the target stimulus and the subject's motor response. Mean RT for each participant was computed by averaging RTs.

2.4 Region of interest (ROI): In consistent with previous studies (see results) the analyses of fNIRS revealed that compared to healthy controls, ADHD children (in all subtypes), showed reduced increases in the concentration of oxy-Hb particulary for channels located in right PFC. So we focused on (CHs 9,10,11,12,13,14,15,16) the channels that were located in right PFC (Fig. 1). We calculated the average of the integral value of oxy-hb for selected ROI for each participant.

2.5 Statistical Analysis: We conducted a statistical comparison of participant characteristics for each group using two-tailed paired t-tests. We compared the variables between the ADHD subtypes and the control group using a student's t-test. Differences were considered to be significant if they had a probability of less than 0.05. All the statistical analyses were performed using the SPSS 16.0 for Windows software.

3. Results

fNIRS indicated that while control subjects exhibited higher activation than all ADHD subtypes; ADHD subtypes did not differ from one another. All ADHD subtypes showed longer RT ($p<0.001$) than controls. ADHD-I group showed significantly longer RTs compared to ADHD-HI and ADHD-C group. Statistical analysis results are illustrated in Table 1, Table 2 and Table 3 seperately

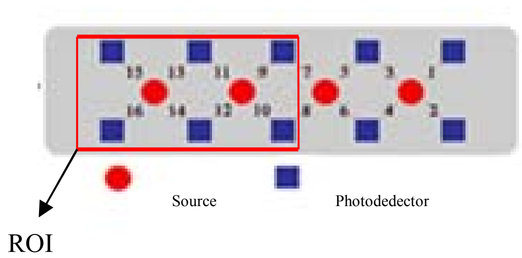

Fig. 1. The source-detector, channel locations on the fNIR probe and locations of ROIs

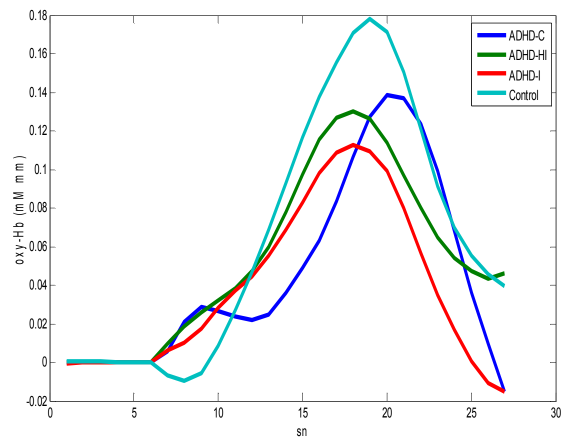

Fig.2: The average of target responses of oxy- Hb signal of ADHD subtypes and control in right PFC

Table 1: Values of variables for each group (mean±standart deviation)

	Control	ADHD-I	ADHD-HI	ADHD-C
Oxy-Hb	1.87±0.72	1.02±0.5	1.021±0.65	1.21±0.51
RT(ms)	513±77.7	1046±379	728.4±376.5	717±225

Table 2: Comparison between controls and ADHD subtypes

	Control vs. ADHD-I		**Control vs. ADHD-HI**		**Control vs. ADHD-C**	
	t	p	t	p	t	p
Oxy-Hb	3.36	0.003*	2.4	0.025*	2.57	0.017*
RT	5.34	0.000*	2.18	0.042*	3.25	0.003*

Table 3: Comparison between ADHD subtypes

	ADHD-I vs ADHD-C		**ADHD-I vs ADHD-HI**		**ADHD-C vs ADHD-HI**	
	t	p	t	p	t	p
Oxy-Hb	0.96	0.348	0.007	0.994	0.72	0.486
RT	2.29	0.035*	1.55	0.147	0.06	0.948

* significant

4. Conclusions

The present study was aimed to investigate whether ADHD subtypes and healthy controls differ in terms of RT and oxygenation of PFC during an auditory oddball attention task. In consistent with previous studies [13-15] the analyses of fNIRS revealed that compared to healthy controls, ADHD children (in all subtypes), showed reduced increases in the concentration of oxy-Hb particulary for channels located in right PFC. ADHD subtypes did not differ from one another in terms of concentration of oxy-Hb. Additionally, although these differences were non-significant, the ADHD-I group obtained lower oxy-hbo values compared the other subtypes. This findings is cohorent to previous studies and would agree with the fact that inattentive symptomatology is common to all subtypes of ADHD [16].

Recently, right prefrontal activation served as an objective neuro functional biomarker for fNIRS measurement in ADHD patients in many studies[13,14]. So we focused on this region. Amoung fNIRS measures we analysed oxy-Hb signal because of its higher sensitivity to changes in cerebral blood flow than that of deoxy-Hb and total-Hb signals [17-18] The oxy-Hb has been identified as a discriminatory feature for ADHD and controls, in many previous fNIRS studies [13-15]. We selected an easy, short task contains standard and target paradigm with random squence that can be appropriate for ADHD children. This current study was one of few studies using the selective auditory attention task to investigate the fNIRS in ADHD children.

The studies on ADHD subtypes indicate that the executive and non-executive findings in ADHD subtypes are, at least, inconsistent. The distinctiveness of the ADHD subtypes on neuropsychological measures is not clear-cut. Barkley (1997) had hypothesised differences between these subgroups of ADHD in terms of executive functions, memory, and focussed attention [19]. Seidman (2006) reviewed differences between subtypes of ADHD in terms of neuropsychological tests and concluded that there were more similarities than differences between subtypes [20]. Solanto et all observed no significant group differences between subgroups of ADHD in task (go/no-go paradigm) performance in fMRI, similarly [21]. Given the inconsistencies in results of neurocognitive studies of the ADHD subtypes, the use of fNIRS helped to resolve continuing controversy concerning whether these subtypes are variants of the same condition or completely different disorders. The fNIRS results showed these subtypes are variants of the same condition.

In RT results; relative to control subjects, longer RT observed in all ADHD subtypes. ADHD-I group showed significantly longer RTs compared to ADHD-HI and ADHD-C groups. The results are consistent with previous studies [8]. Barkley (2001) has indicated that ADHD-I reflecting impaired speed of processing compared to ADHD-C [19]. This study will bring a novel path of significant interest concerning reliable evaluation of fNIRS studies and reaction time evaluation in ADHD. A limitation of the present study was that an ADHD-HI group was less compared the others. This subtype diagnosis is far less common than those for the other two subtypes.

7. References

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