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Abstract

Background/Aims: Atomoxetine (ATX), a selective norepinephrine reuptake inhibitor, is the first approved non-stimulant drug for treatment of attention deficit/hyperactivity disorder (AD/HD). The present study examined the effects of long-term treatment with ATX on prefrontal hemodynamic activity in AD/HD children during a continuous performance task (CPT) using near-infrared spectroscopy (NIRS). *Methods:* Prefrontal hemodynamic activity was measured in 12 children with AD/HD during experimental sessions conducted before and 6 months or more after starting ATX treatment. The average maintenance dose of ATX was 1.6 mg/kg/day. Fourteen age-matched typically developing children participated as a control group. *Results:* In the control group, the CPT induced a significant increase in oxygenated hemoglobin (oxy-Hb) concentration in the bilateral dorsolateral prefrontal cortex (DLPFC). In the AD/HD group in the pre-ATX condition, the CPT did not induce a significant increase in oxy-Hb concentration in any of the NIRS channels, but induced a significant decrease in oxy-Hb concentration in the left ventrolateral prefrontal cortex (VLPFC). In the AD/HD group in the post-ATX condition, significant activation was observed in the right DLPFC and the decrease in oxy-Hb concentration in the left VLPFC disappeared. *Conclusions:* These results suggest that long-term treatment with ATX improved prefrontal hemodynamic activity in AD/HD children, and NIRS may be useful for assessment of the prefrontal hemodynamic response to ATX treatment.

Keywords: attention deficit/hyperactivity disorder, atomoxetine, near-infrared spectroscopy, prefrontal cortex, continuous performance task

1. Introduction

Attention deficit/hyperactivity disorder (AD/HD) is a developmental disorder that is characterized by age-inappropriate levels of inattention, hyperactivity, and impulsivity and affects 3% to 7% of school-aged children [1]. Although the etiology has not been fully identified, it is empirically known that these main symptoms are improved by treatment with psychostimulants such as methylphenidate (MPH) and amphetamine.

MPH, the most common treatment for AD/HD, is an indirect catecholamine agonist that blocks both dopamine and norepinephrine transporters and thereby increases extracellular levels of these neurotransmitters at synaptic sites [2]. Recent animal studies using in vivo microdialysis demonstrated that oral administration of a clinically relevant dose of MPH produced a preferential elevation in extracellular dopamine and norepinephrine within the prefrontal cortex (PFC) and subcortical regions including the striatum and nucleus accumbens, suggesting that MPH exerts therapeutic actions through enhancement of prefrontal and striatal catecholamine neurotransmission [3,4,5]. In line with these animal studies, functional magnetic resonance imaging (fMRI) studies on AD/HD children revealed that MPH increased activation of the lateral PFC and striatal regions during cognitive-attention tasks that demanded sustained attention and response inhibition, such as a go/no-go task [6] and a continuous performance task (CPT) [7].

Although the beneficial effects of MPH on AD/HD symptoms are widely accepted, it has been shown that 10% to 30% of individuals are non-responders to the psychostimulant therapy [8,9]. In addition, abuse liability and potential adverse reactions including nervousness, irritability and sleep disturbance should be taken into account when using the stimulant in AD/HD children [10].

Atomoxetine (ATX), a highly selective norepinephrine transporter inhibitor, is the first

approved non-stimulant for AD/HD treatment [11,12,13]. Comparative studies on the therapeutic effects of MPH and ATX indicated that ATX treatment for 6 weeks exerted significant symptomatic improvements in non-responders to MPH [8], demonstrating that ATX could be an alternative option for the treatment of AD/HD. Animal studies showed that acute and chronic administration of ATX preferentially increased extracellular levels of norepinephrine and dopamine in the PFC, but not in the striatum [4,5]. These results suggest that MPH and ATX may partially share therapeutic mechanisms in AD/HD treatment, especially in terms of regulatory actions of the frontal activity.

Recently, using fMRI, Schulz et al. [14] found that MPH and ATX treatments for 6–8 weeks had common therapeutic actions that decreased neural activity in the bilateral motor cortex, with an increase in response inhibition that correlated with clinical improvement. These reductions in motor cortex activation may have been produced by direct pharmacological actions via dopamine transporters and norepinephrine transporters in the motor cortex [15,16]. In addition, fMRI studies have reported that in both healthy volunteers and AD/HD patients, ATX increased activation of the ventrolateral PFC (VLPFC) and the dorsolateral PFC (DLPFC) during cognitive-attention tasks that demanded inhibitory control of a prepotent response [17,18], implying that the effects of ATX on these cortical areas resemble those of MPH. It has been suggested that the lateral PFC, particularly in the right hemisphere, plays an important role in sustained attention and top-down inhibitory control, and that patients with AD/HD show significant cognitive-attention deficits accompanied by altered functional activation of the right PFC [19,20,21]. Accordingly, measurement of cortical activity associated with sustained attention and inhibitory function may be a useful approach to evaluate the clinical effectiveness of ATX.

Recent advances in techniques for monitoring cortical hemodynamics using near-infrared spectroscopy (NIRS) have made it possible to evaluate the therapeutic effects of drugs on

patients with AD/HD in clinical settings. Compared to fMRI, NIRS is completely noninvasive and unrestricted. It can be applied in various types of experimental settings (e.g., those requiring multiple time measurements) for diverse participants including children with AD/HD [22,23,24,25]. A preliminary study using a two-channel NIRS system reported that in boys with AD/HD performing a trail-making task, the increase in total hemoglobin concentration in the right DLPFC was lower after intake of MPH than in a drug-naive situation [26]. More recently, using 44-channel NIRS, Monden et al. [23] demonstrated that acute MPH administration elicited a significant activation of the right DLPFC, and that this was correlated with improvement of response inhibition during a go/no-go task. These results suggest that NIRS was valid for assessing the prefrontal hemodynamic response to MPH treatment. Therefore, we believe that NIRS measurement of prefrontal hemodynamic activity could be a useful method by which to evaluate the clinical effectiveness of ATX.

In the present study, we used multichannel NIRS to examine the effects of ATX treatment on prefrontal hemodynamic activity in AD/HD children performing a CPT. A CPT is one of the most popular paradigms for the evaluation of sustained attention and response inhibition that has been used for medication monitoring [27]. Previous clinical trials revealed that ATX requires a longer treatment period to achieve maximal reductions in AD/HD symptoms compared to stimulants [28,29]. A recent time-course analysis of ATX treatment responses indicated that AD/HD symptoms continued to improve up to approximately 5 months after the start of treatment or beyond [30]. Thus, we measured prefrontal hemodynamic responses more than 6 months after the start of ATX treatment and compared them to prefrontal hemodynamic responses in the treatment-naive condition. Based on previous fMRI and NIRS studies, we hypothesized that in contrast to typically developing children, AD/HD children would show reduced prefrontal activity during the CPT, and ATX treatment would ameliorate the prefrontal underactivation.

2. Materials and methods

2.1. Participants

Twelve children with AD/HD (six males and six females, mean age of 9.8 years, SD = 2.3 years, range 6–13 years) participated in this study. Diagnoses based on DSM-IV-TR criteria [1] were made by an experienced pediatric neurologist (A.A.). The AD/HD Rating Scale-IV-Japanese version (AD/HD RS-IV-J) [31] was used to assess behavior symptoms. The AD/HD RS-IV-J total score before receiving ATX treatment was greater than 16 points, which is considered as the cutoff score indicating the presence of AD/HD symptoms, in all subjects (mean score of 35.2, SD = 7.1, range 18–46). The Wechsler Intelligence Scale of Children Third or Fourth Edition (WISC-III or WISC-IV) full IQ score was greater than 85 in all subjects (mean score of 99.0, SD = 10.5, range 85–113). All AD/HD participants had normal or corrected-to-normal vision and were right-handed. Demographic and clinical profiles are shown in Table 1.

All patients received ATX orally for the purpose of treatment. The starting dosage of ATX was 0.5 mg/kg/day. Dosage was increased by 0.3 mg/kg/day at intervals of 2–6 weeks until AD/HD symptoms clinically improved. The average maintenance dose was 1.6 mg/kg/day. All patients received the maintenance dose twice a day for more than 6 months. No other concurrent medications were used. In this study, the pre-ATX condition was defined as the period of no administration or of administration of only the starting dosage (0.5 mg/kg/day) of ATX, and the post-ATX condition was defined as the period more than 6 months after starting administration of the maintenance dose.

Fourteen typically developing children attending regular classes at ordinary elementary and junior high schools (five males and nine females, mean age of 9.7 years, SD = 2.8 years, range 6–15 years) participated as a control group. Participants in the AD/HD and control groups did not differ significantly regarding age (t (24) = 0.06, p = 0.950). All participants in the control group were right-handed, and had normal or corrected-to-normal vision and no history of psychiatric/neurological disorders.

Written informed consent was obtained from all participants prior to the experiments. This study was approved by the ethics committee of Asahikawa Medical University.

2.2 Task procedure

AD/HD children participated in two experimental sessions: One carried out in the pre-ATX condition and the other carried out in the post-ATX condition. The interval between sessions was between 6 months and 1 year (mean interval of 303.9 days, SD = 64.1 days, range 196–398 days). The control group participated in one experimental session and did not receive any treatment. The experiments were conducted in a small sound-shielded and dimly lit room containing a small desk and a chair. Participants sat at the table on which a notebook computer (DELL Latitude E6500, Round Rock, USA) was placed to present visual stimuli. Viewing distance was held constant at approximately 50 cm.

Figure 1a illustrates a trial sequence of the CPT. The CPT was created using Visual Basic 6.0 (Microsoft, Redmond, USA). Stimuli were presented using the computer and the participants' responses were collected on the standard keyboard. The CPT was modeled on the A-X version of the test [32,33], in which a series of random single numbers (72-point MS gothic; 0.69° wide × 1.26° high in visual angle when presented on the monitor) were presented and the participants were asked to make a response after observing a target number.

In this experiment, the target was the digit “9” immediately preceded by the digit “1”. Stimuli were presented in black, on a gray background, in the center of the screen at a constant rate of one per 1000 ms, with the stimuli appearing for the first 200 ms and a blank screen appearing for the remaining 800 ms. Participants were required to signal the detection of the target by pressing the space key with the index finger of the dominant hand as quickly as possible.

As shown in Figure 1b, each session of the CPT consisted of five blocks of 60 stimuli and each block was followed by a 30-s rest period to return to baseline, in which a blank screen was presented and participants were asked to maintain a relaxed posture with open eyes. Each block contained three target sequences (i.e., “1–9”) and response to the target was defined as a hit response. Each block also included three “false alarm” sequences, in which a number other than “9” was preceded by “1” (i.e., false alarm), and four “false target” sequences, in which a number other than “1” was followed by “9”. Response to the false alarm sequence was defined as a false alarm error, implying a failure of response inhibition or impulsivity [34]. Response to the false target sequence was termed a false target error, which may be associated with inattention. The rest of the sequences in the block were “standard” sequences consisting of two numbers other than “1” and “9”. Possible commission error responses besides false alarm and false target errors were as follows: (1) a response to “1” (alarm error), which may be associated with impulsivity, and (2) a response to a number other than “9” preceded by a number other than “1” (random error), which may be reflective of dyscontrol. Reaction time was recorded for each response.

2.3. NIRS data acquisition

Temporal changes in concentration of oxygenated hemoglobin (oxy-Hb) and deoxygenated hemoglobin (deoxy-Hb) during the CPT were measured using a 24-channel NIRS instrument (ETG-100, Hitachi Medical Corporation, Tokyo, Japan) at two wavelengths of near-infrared light (780 and 830 nm). The distance between the light emitter and detector probes was set at 30 mm to detect the hemodynamic changes on the surface of the cerebral cortex, 20–30 mm below the scalp [35,36]. Data were measured with a sampling rate of 10 Hz.

The NIRS probes were placed on the participant's forehead to cover the lateral prefrontal cortex of both hemispheres. Two sets of 3 × 3 probe holders, each of which included 12 measurement channels, were placed symmetrically on the left and right frontal area by referring to the international 10/20 system used in electroencephalography [37]. As shown in Figure 2a, the lowest probes in left and right medial columns were positioned at Fp1 and Fp2, respectively. The position of the probes on the participant's scalp was recorded using a three-dimensional digitizer (Isotrack II, Polhemus, Vermont, USA). Typical positions of the 24 measurement channels are indicated by superimposing them onto the cortical surface of a three-dimensional magnetic resonance image (Fig. 2b), and indicate that the measurement area included the superior frontal gyrus, middle frontal gyrus and inferior frontal gyrus bilaterally (Brodmann areas 9, 10, 45, 46, 47) [38].

The ETG-100 system measured change in the concentration of oxy-Hb and deoxy-Hb from the starting baseline. Individual time-course data for oxy-Hb and deoxy-Hb concentrations were averaged over the five blocks. Moving average methods were used to remove minor motion artifacts (moving average window, 10 s), and a baseline correction was performed using linear fitting based on two baseline periods: the pre-task baseline, determined as the mean across a 6-s period just before the onset of the task period, and the post-task baseline, determined as the mean across a 6-s period 12 s after the task period.

2.4. Data analyses

The percentage of hits and false alarms and mean reaction time for each response type was computed for the five blocks of the CPT during the experimental session. Because commission errors other than false alarm errors rarely occurred, the number of these minor commission errors was combined. In the AD/HD group, CPT performance and AD/HD-RS-IV-J total score were compared across the pre-ATX condition and the post-ATX condition using paired *t*-tests. CPT performance of the control group was compared to that of the AD/HD group in the pre-ATX condition using an unpaired *t*-test.

For statistical analyses of change in the concentration of oxy-Hb and deoxy-Hb, the mean values of the pre-task baseline and task period were calculated for each participant and NIRS channel. The optical path length in the NIRS method varies among individuals [39], and between-subject comparison of hemoglobin concentrations may therefore be inappropriate. Accordingly, the NIRS data were analyzed using a within-subject design, and direct comparison of hemoglobin concentrations between groups was not performed. Ten of the 24 channels (left: CH1–5 and right: CH13–17), which were located in the upper area of the probes, were affected by severe measurement noise in some participants. Because of the within-subject nature of the comparisons in the present experimental design, these 10 channels were excluded from further analyses. In the AD/HD group, the hemoglobin concentrations in the remaining 14 lower frontal channels were analyzed using a three-way repeated measures ANOVA with condition (pre-ATX condition vs. post-ATX condition), channel (14 channels, left: CH6–12 and right: CH18–24) and time segment (pre-task baseline vs. task period) as within-subject factors, followed by post hoc analysis for simple-simple main effects. In the control group, the hemoglobin concentrations were analyzed using a

two-way repeated measures ANOVA with channel (14 channels) and time segment (pre-task baseline vs. task period) as within-subject factors, followed by post hoc analysis for simple main effects.

The NIRS channels with a significant difference in oxy-Hb concentration between the pre- and the post-ATX condition in the AD/HD group, as determined by the three-way ANOVA, were selected for further analyses to examine the relations between inter-condition contrast (post-ATX condition minus pre-ATX condition) of oxy-Hb concentration and the AD/HD RS-IV-J score using Spearman's rank correlation coefficient. In addition, inter-condition contrasts of oxy-Hb concentration in the selected channels were performed using correlation analyses with retest interval (days) between the pre- and post-ATX conditions using the Spearman's method.

3. Results

3.1. Behavioral performance and AD/HD RS-IV-J score

Table 2 shows the behavioral performance in the CPT and the AD/HD-RS-IV-J total score in each condition and group. Unpaired *t*-tests revealed that there were no differences in CPT performance between the control group and the AD/HD group in the pre-ATX condition. In addition, paired *t*-tests revealed that there were no differences in CPT performance between pre- and post-ATX conditions in the AD/HD group. However, the AD/HD-RS-IV-J score was significantly lower in the post-ATX condition than in the pre-ATX condition (t (11) = 6.478, $p < 0.01$).

3.2. NIRS data

Figure 3 shows the mean relative change in oxy-Hb concentration during the task period relative to the pre-task baseline value in the control group. The two-way repeated measures ANOVA revealed a significant main effect of channel [F (13, 169) = 3.795, $p < 0.01$] and time segment [F (1, 13) = 5.025, $p < 0.05$] on oxy-Hb concentration in the control group. In addition, there was a significant interaction of channel × time segment [F (13, 169) = 3.456, $p < 0.01$]. A post hoc analysis for simple main effect (i.e., the effect of time segment on the change in oxy-Hb concentration in each channel) was conducted. The result indicated that the oxy-Hb concentration was higher in the task period than in the pre-task baseline in one channel over the left DLPFC [CH9; F (1, 182) = 10.665, $p < 0.01$] and four channels over the right DLPFC [CH19, CH21, CH22, and CH24; F (1, 182) = 4.272, $p < 0.05$, F (1, 182) = 4.306, $p < 0.05$, F (1, 182) = 17.643, $p < 0.01$, and F (1, 182) = 6.292, $p < 0.05$, respectively]. There was no main effect of channel or time segment on deoxy-Hb concentration, and no significant interaction.

Figure 4 shows the mean relative change in oxy-Hb concentration during the task period relative to the pre-task baseline value in the pre- and post-ATX conditions in the AD/HD group. The three-way repeated measures ANOVA revealed a significant main effect of channel [F (13, 143) = 2.176, $p < 0.05$] on oxy-Hb concentration. In addition, there was a significant interaction of condition × channel × time segment [F (13, 143) = 1.821, $p < 0.05$]. The post hoc analysis for simple-simple main effect (i.e., the effect of time segment on the change in oxy-Hb concentration in each channel in the pre- and post-ATX conditions) revealed that in the pre-ATX condition, the task period did not produce a significant increase in oxy-Hb concentration in any channel, but produced a significant decrease in oxy-Hb concentration in CH12, located over the left VLPFC [F (1, 308) = 4.495, $p < 0.05$]. By

contrast, in the post-ATX condition, there was a significant increase in oxy-Hb concentration relative to the pre-task baseline in two channels over the right DLPFC [CH21 and CH22; F (1, 308) = 8.760, $p < 0.01$ and F (1, 308) = 4.760, $p < 0.05$, respectively]. Additionally, the post hoc analysis for simple-simple main effect (i.e., the effect of ATX condition on the oxy-Hb concentration in task period in each channel) revealed that oxy-Hb concentration in the task period in the post-ATX condition was significantly larger than in the task period in the pre-ATX condition in three channels on the left hemisphere [CH8, CH9 and CH12; F (1, 308) = 5.399, $p < 0.05$, F (1, 308) = 7.153, $p < 0.01$, and F (1, 308) = 4.848, $p < 0.05$, respectively], and two channels on the right hemisphere [CH21 and CH22; F (1, 308) = 11.364, $p < 0.01$ and F (1, 308) = 8.956, $p < 0.01$, respectively; Fig. 5]. The three-way repeated measures ANOVA showed no significant main effect of condition, channel or time segment on deoxy-Hb concentration and no significant interactions.

We examined the relation between the activating effects induced by ATX treatment observed in five channels (CH8, 9, 12, 21 and 22) and AD/HD-RS-IV-J score. There was a moderate correlation between the increase in oxy-Hb concentration in CH22 and the decrease in AD/HD RS-IV-J score, but it was not statistically significant (Spearman's ρ = -0.438, p = 0.155). There were no significant correlations between the increase in oxy-Hb concentration in the activated channels (CH8, 9, 12, 21 and 22) and retest interval (Spearman's ρ = 0.196, 0.147, 0.028, 0.042 and -0.203, respectively, $p > 0.53$).

4. Discussion

In the present study, we investigated the effects of long-term treatment with ATX on prefrontal hemodynamic activity in AD/HD children using a 24-channel NIRS system. The

obtained results can be summarized as follows: (1) ATX treatment significantly improved AD/HD behavior symptoms assessed by AD/HD-RS-IV-J, but did not change behavioral performance on the CPT, which did not significantly differ from the performance of the control group. (2) In the pre-ATX condition, the CPT did not produce a significant increase in oxy-Hb concentration in any of the channels in the AD/HD group, but produced a robust increase in oxy-Hb concentration in the bilateral DLPFC in the control group. In the pre-ATX condition, the CPT produced a significant decrease in oxy-Hb concentration in the left VLPFC in the AD/HD group. (3) ATX treatment to the AD/HD group elicited task-related increases in oxy-Hb concentration in the right DLPFC and eliminated the decrease in oxy-Hb concentration in the left VLPFC. These findings suggest that ATX treatment improved prefrontal hemodynamic activity in AD/HD children, and that NIRS may be useful for assessment of the prefrontal hemodynamic response to ATX treatment.

In accordance with a previous study [30], significant improvements of AD/HD symptoms, evaluated using the AD/HD-RS-IV-J, were seen after more than 6 months of daily treatment with ATX. In the present study, the reduction in AD/HD-RS-IV-J total score from pre to post ATX treatment averaged 40.8%. A time-course analysis of the treatment response to ATX showed that robust improvement of symptoms, defined as ≥40% reduction from the pre-treatment AD/HD-RS-IV score, was seen after 6.5 months of treatment in 85% of study patients [30].

Behavioral performance on the CPT was not significantly improved by ATX treatment. The CPT used in the present study was modeled on the traditional A-X version used to evaluate inattention problems and impulsivity, which are reflected by high rates of omission (i.e., 1 – rate of hit responses) and commission errors (especially false alarm errors), respectively [34]. In many studies using CPTs, including the A-X version, children with AD/HD showed more errors of omission and commission than normal children, and MPH

treatment significantly reduced the rate of both error types [27,33]. We observed a slight reduction in the false alarm error rate and reaction time for hit responses with ATX treatment, but improvements were not statistically significant. The lack of effects of ATX on CPT performance in the present study may be due to a ceiling effect associated with the short task duration of the block design required for the NIRS measurement, as longer task duration requires greater concentration on CPT and other vigilance tasks [40]. In fact, we found that there were no significant differences in CPT performance between the AD/HD and control groups, suggesting that the task was too easy and did not discriminate the attention problems or impulsivity of the AD/HD children from the control group [7]. It has been reported that CPTs modified for functional neuroimaging methods such as fMRI and NIRS, which have a shorter task duration and easier presentation of stimuli than neuropsychological CPTs, often fail to statistically differentiate patients from healthy comparison groups [41,42], or placebo from MPH conditions [7]. In order to more precisely evaluate the effects of ATX on CPT performance, future research should attempt to reduce the ceiling effect by increasing task difficulty, such as by using a shorter duration of stimulus presentation or a variable inter-stimulus interval [43].

NIRS studies of healthy participants have consistently demonstrated that increases in oxy-Hb concentration in the lateral PFC are elicited by performing CPT [44] and other cognitive-attention tasks [45,46,47,48]. As predicted by these findings, healthy children in the present study showed robust activation of the bilateral DLPFC, especially in the right hemisphere, indicating that performing the CPT successfully challenged the prefrontal function involved in sustained attention and inhibitory control. By contrast, NIRS studies of AD/HD children have revealed no significant frontal activation during go/no-go tasks [22,23] and the Stroop task [24]. In accordance with these findings, AD/HD children in the pre-ATX condition did not exhibit significant prefrontal activation during the CPT. We also

found that oxy-Hb concentration in the left VLPFC (CH12) was significantly lower during the task period than during the resting baseline. This decrease in oxy-Hb concentration in the VLPFC was specific to the AD/HD group, and is consistent with previous fMRI studies reporting underactivation of the VLPFC during the CPT in AD/HD patients [7,42,49]. Recently, Christakou et al. [50] demonstrated that in AD/HD boys performing a sustained attention task, the left DLPFC was deactivated compared to a baseline task that did not require sustained attention. This deactivation was not observed in healthy controls [50]. Christakou et al. suggested that deactivation of the left DLPFC in AD/HD was associated with increased activity of a "default mode" network that comprises the medial PFC and parietal regions and is normally suppressed during tasks that require attention to external stimuli [51]. It is unclear whether the VLPFC deactivation observed in the present study was due to "overactivation" of this default mode network [50,52]. In order to confirm this hypothesis, further research is required to examine medial PFC and parietal activities during the CPT in AD/HD children compared to an age-matched control group.

In contrast to the pre-ATX condition, we observed task-related increases in oxy-Hb concentration after ATX treatment in two channels (CH21 and CH22) located over the right DLPFC. In addition to the hemodynamic change in the right DLPFC, ATX treatment canceled the task-related deactivation in the left VLPFC (CH12) and produced larger oxy-Hb responses as compared to those in the pre-ATX condition in the left DLPFC (CH8 and CH9), although these left hemisphere responses were not significant compared to the resting baseline. No significant decreases in oxy-Hb concentration were observed in any of the channels in the post-ATX condition (see Fig. 4). Of the hemodynamic changes observed from pre to post ATX treatment, only the increase in oxy-Hb concentration in CH22 was moderately correlated with the improvement in AD/HD-RS-J total score (Spearman's ρ = -0.438, n.s.), suggesting that the increased hemodynamic response in the right DLPFC partly

contributed to improvement of AD/HD symptoms. The finding of a significant effect of ATX on the underactivation of the right DLPFC replicates recent fMRI studies that demonstrated that ATX increased activation of the right DLPFC in individuals with AD/HD performing cognitive-attention tasks [18,53]. Animal studies suggest that a therapeutic dose of ATX increases the synaptic availability of norepinephrine and dopamine [4,5] and enhances neuronal firing to relevant stimuli and suppresses firing to irrelevant stimuli via alpha-adrenergic$_{2A}$ and D1 receptor actions on the dendritic spines of PFC pyramidal cells, respectively [54]. This could result in improvement of DLPFC function and, subsequently, in improvement of selective or sustained attention and inhibition [19]. Additionally, the right-lateralized effect of ATX observed in the present study may reflect the fact that the right PFC plays a more important role in the execution of attention tasks than the left PFC [19]. Indeed, the control group showed greater activation of the right DLPFC than the left DLPFC during the CPT. ATX may exert regulatory actions on right-lateralized attention networks that are mediated by norepinephrine [53, 55]. However, the underlying mechanism by which ATX predominantly modulates right DLPFC activation remains unclear. Further research should address this issue for a better understanding of therapeutic actions of ATX.

Interestingly, the activating effect of ATX on the right DLPFC is nearly identical to that observed after acute administration MPH, as demonstrated by Monden et al. [23] using NIRS. A recent fMRI study found that acute administration of both drugs to medication-naive children with AD/HD exerted normalizing effects on impaired left VLPFC activation, but only MPH had upregulation effects on right VLPFC activation [56]. However, longer-term treatment with ATX (6 weeks) exerted similar activation effects to MPH on the cognitive-attention network including the right DLPFC, parietal cortex, and caudate nucleus, among other brain regions, but not on the dorsal anterior cingulate cortex in adults with AD/HD [18]. These findings may explain why ATX requires a longer treatment period compared to MPH

[28,29]. Taken together, the results suggest that ATX treatment for a clinically relevant period improves prefrontal dysfunction in AD/HD, and that the therapeutic change in prefrontal hemodynamics can be detected by NIRS.

There are some methodological limitations to the present study that should be considered. First, no control task was performed during baseline NIRS measurement. Because the CPT is a selective and sustained attention task that requires a motor response (i.e., pressing the space key with the index finger) to an infrequent target stimulus, subjects' motor responses occur infrequently during the task period if the task is performed correctly. In the present study, each 60-s task block contained only three target stimuli. Therefore, a simple motor task requiring go-responses at constant rate is not suitable as a control task for the CPT. However, the lack of control task in the present study makes it difficult to determine the relation between the hemodynamic changes observed during performance of the task and the cognitive and behavioral components driven by the activation task. For example, some of the change in activation from pre to post ATX treatment could relate to motor and/or motivational aspects rather than to attentional and inhibitory functions. To establish the relation between cortical activation response and cognitive functions during the task, future studies should use an event-related design.

A second limitation of the present study is that the sample size did not allow statistical analyses to be performed according to AD/HD subtype (combined AD/HD, n = 8; inattentive AD/HD, n = 4). Exploratory analyses revealed that CPT performance and NIRS data did not differ between the two AD/HD subtypes, except for the percentage of false alarms in the post-ATX condition (10.83 ± 11.23 for combined AD/HD vs. 0.00 ± 0.00 for inattentive AD/HD, $p < 0.05$ with Welch's t test). There is considerable interest in understanding whether the efficacy of ATX differs for combined and inattentive AD/HD, and additional studies with a larger sample size are needed to address this issue.

Third, the effects of ATX treatment on prefrontal activation cannot be dissociated from order and developmental effects. Given the long period required for ATX treatment to achieve maximal reduction in AD/HD symptoms [30], subjects underwent two NIRS sessions: One conducted before and one conducted more than 6 months after starting ATX treatment. Although it has been suggested that multiple measurements of prefrontal hemodynamics during the same task with retest intervals of 1 week to 1 year have considerable reproducibility in healthy adults [57,58], little is known about the reliability of NIRS measures in school-aged children. Therefore, there remains a possibility that the long retest interval may have influenced prefrontal hemodynamics in the developing children included in the present study. This speculation seems unlikely because of the lack of significant correlations between retest interval and the change in prefrontal hemodynamic responses; however, further research is needed to determine the reproducibility of NIRS signals in an age-matched control group and, if possible, in AD/HD children under a placebo condition to exclude the possibility of maturation effects on prefrontal hemodynamic responses. This procedure will also help to exclude any order effect on the prefrontal hemodynamics that may occur due to multiple NIRS measurements.

In conclusion, this is, to our knowledge, the first NIRS study providing evidence that long-term treatment with ATX improves the prefrontal hemodynamic response during a cognitive-attention task in children with AD/HD. Reductions in AD/HD behavioral symptoms during ATX treatment are gradual [30]; therefore, timely evaluation of neural responses as well as behavioral assessments may provide convincing information about the efficacy of ATX treatment. The present results suggest that prefrontal hemodynamic activity measured by NIRS can be a useful indicator of neural responses to ATX treatment.

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Figure legends

Figure 1. (a) Schematic examples of a trial sequence of the CPT. Stimuli were presented at a constant rate of one per 1000 ms, with the stimuli appearing for the first 200 ms and a blank screen appearing for the remaining 800 ms. (b) The time-course of experimental session. For the AD/HD group, two sessions were carried out: One in the pre-ATX condition and one in the post-ATX condition. NIRS measurements were made from the starting baseline to the end of block 5. The duration of each session was 8 min.

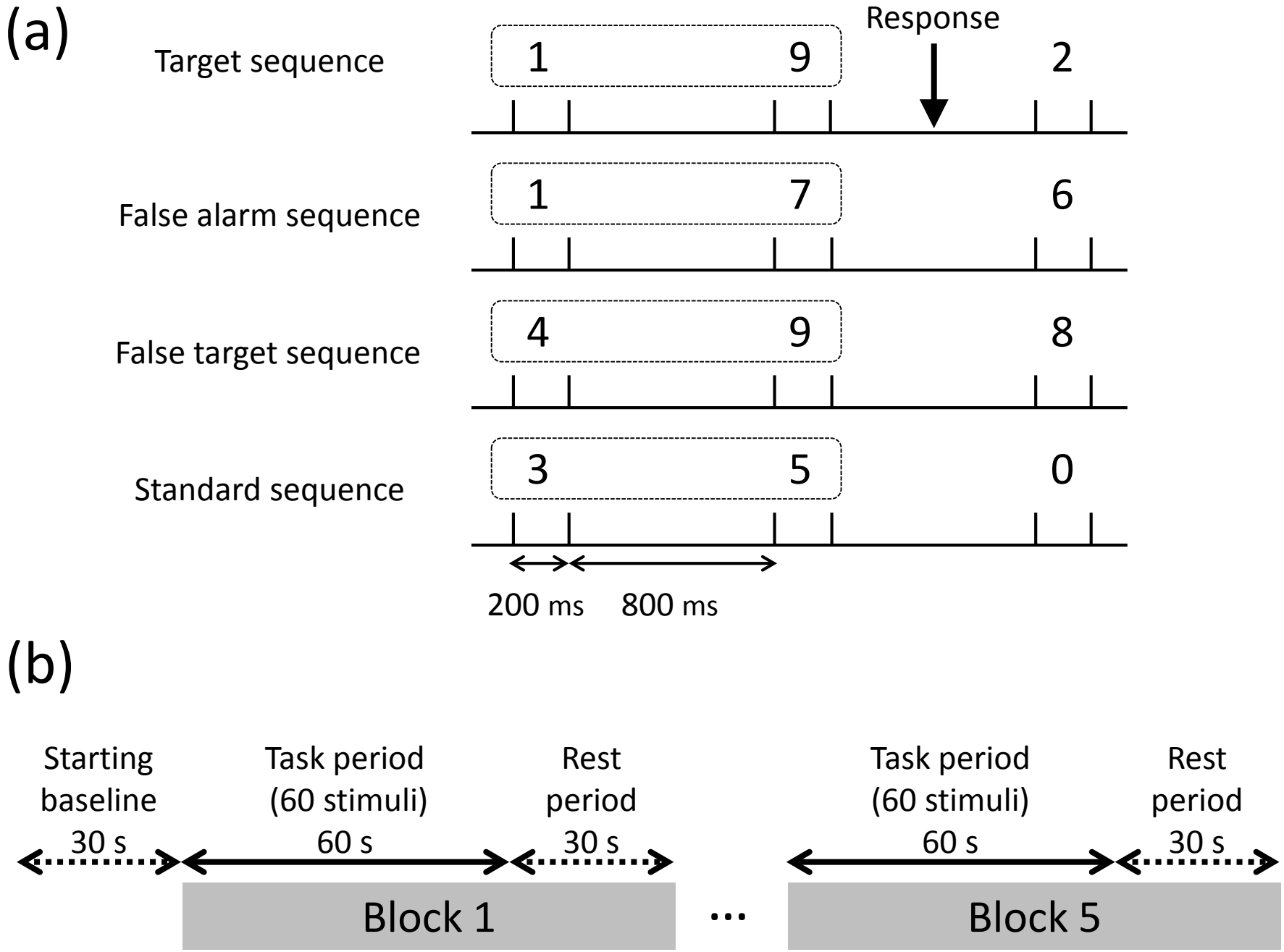
Figure 2. (a) The positions of the probes and channels as they were situated on the participant's head. The two probe holders, each of which was equipped with five laser diodes and four photodiodes (cyan dots), were located on the prefrontal regions. Open circles correspond to Fp1 and Fp2. The magenta dots with numbers represent the 24 measurement channels. (b) The positions of the 24 measurement channels (magenta dots) superimposed onto the cortical surface of a three-dimensional magnetic resonance image. Gray numbers represent channels excluded from the analyses because of measurement noise.

Figure 3. (a) The cortical surface image. Red circles indicate the position of channels that showed significant task-related activation in the control group. (b) Mean change in oxy-Hb concentration during the task period relative to the pre-task baseline in the control group. The numbers on the x-axis represent the measurement channel. * $p < 0.05$, ** $p < 0.01$.

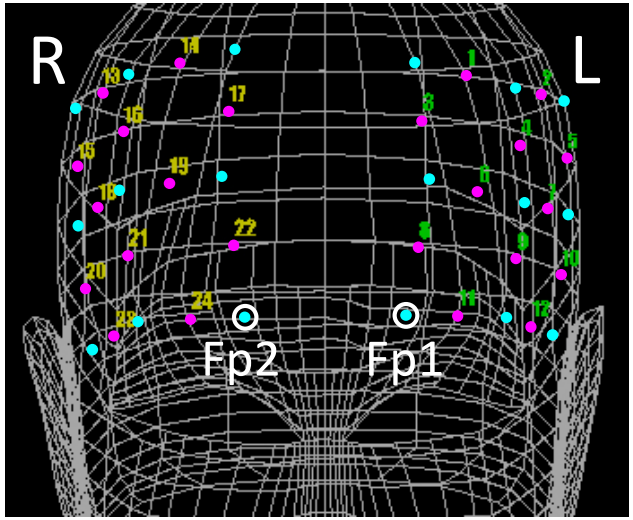
Figure 4. Mean change in oxy-Hb concentration during the task period relative to the pre-task baseline in pre- and post-ATX conditions in the AD/HD group. The numbers on the x-axis represent the measurement channels. *$p < 0.05$, ** $p < 0.01$. Red and blue circles on

the cortical surface image (left panel) indicate the positions of channels that showed significant task-related changes (red: activation, blue: deactivation).

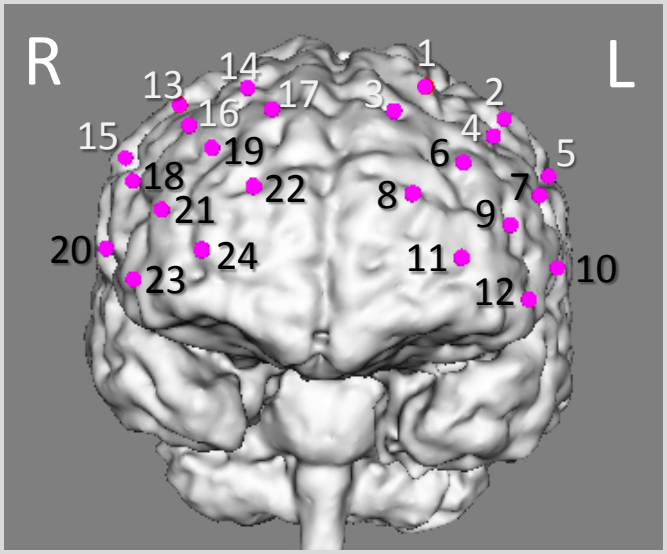
Figure 5. (a) Grand averaged waveforms of oxy- and deoxy-Hb concentrations in representative channels in which oxy-Hb concentration in the task period of the post-ATX condition was higher than in the task period of the pre-ATX condition. (b) The positions of the channels that showed a significant ATX effect (red circles).

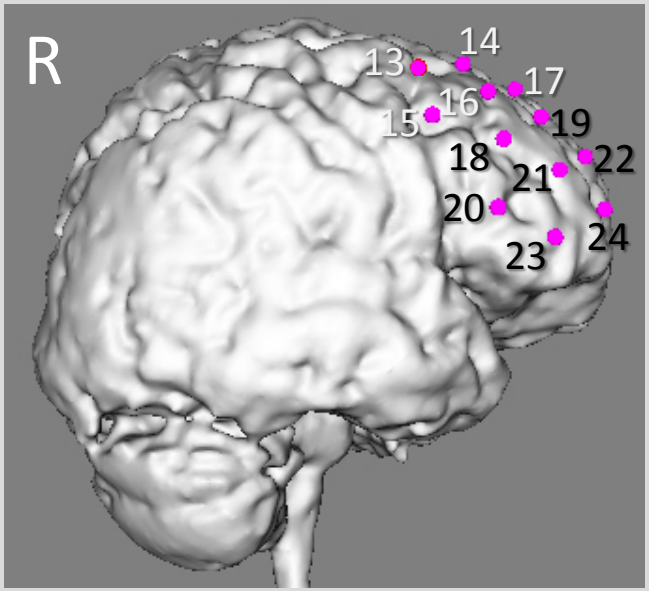

(a)
Target sequence
1
9
Response
2
False alarm sequence
1
7
6
False target sequence
4
9
8
Standard sequence
3
5
0
200 ms
800 ms
(b)
Starting baseline 30 s
Task period (60 stimuli) 60 s
Rest period 30 s
Block 1
...
Task period (60 stimuli) 60 s
Rest period 30 s
Block 5

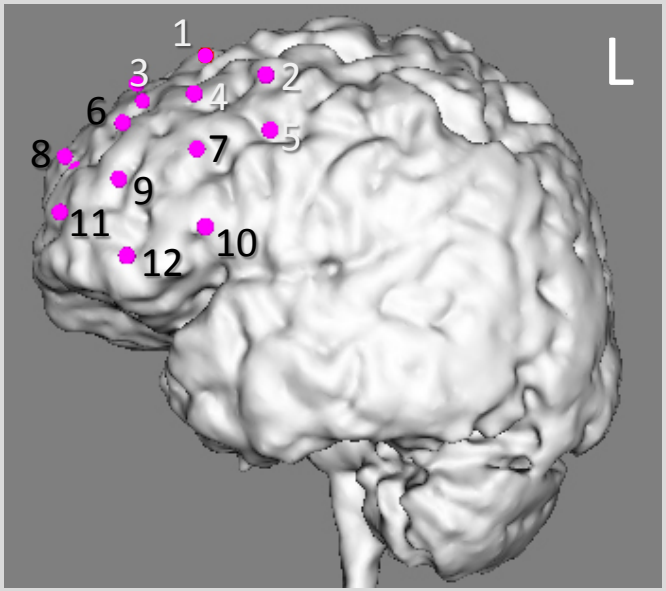
(a)


R
L
Fp2
Fp1

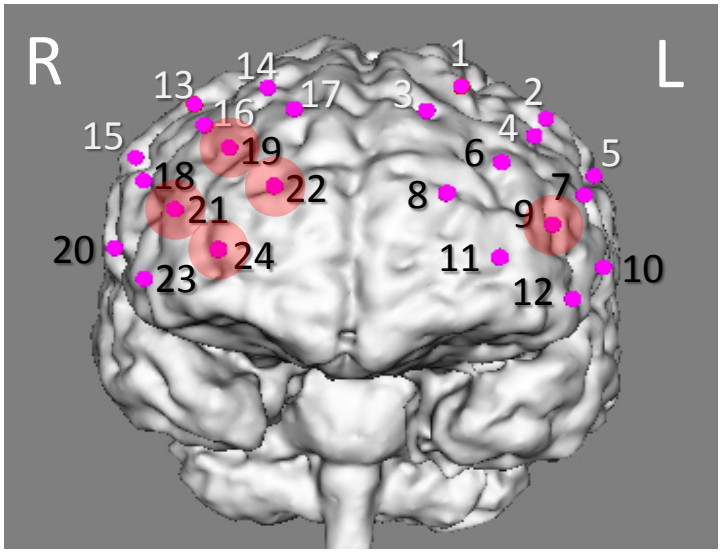
(b)


R
L
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24


R
13
14
15
16
17
18
19
20
21
22
23
24


L
1
2
3
4
5
6
7
8
9
10
11
12

(a)


R
L
1
2
3
4
5
6
7
8
9
10
11
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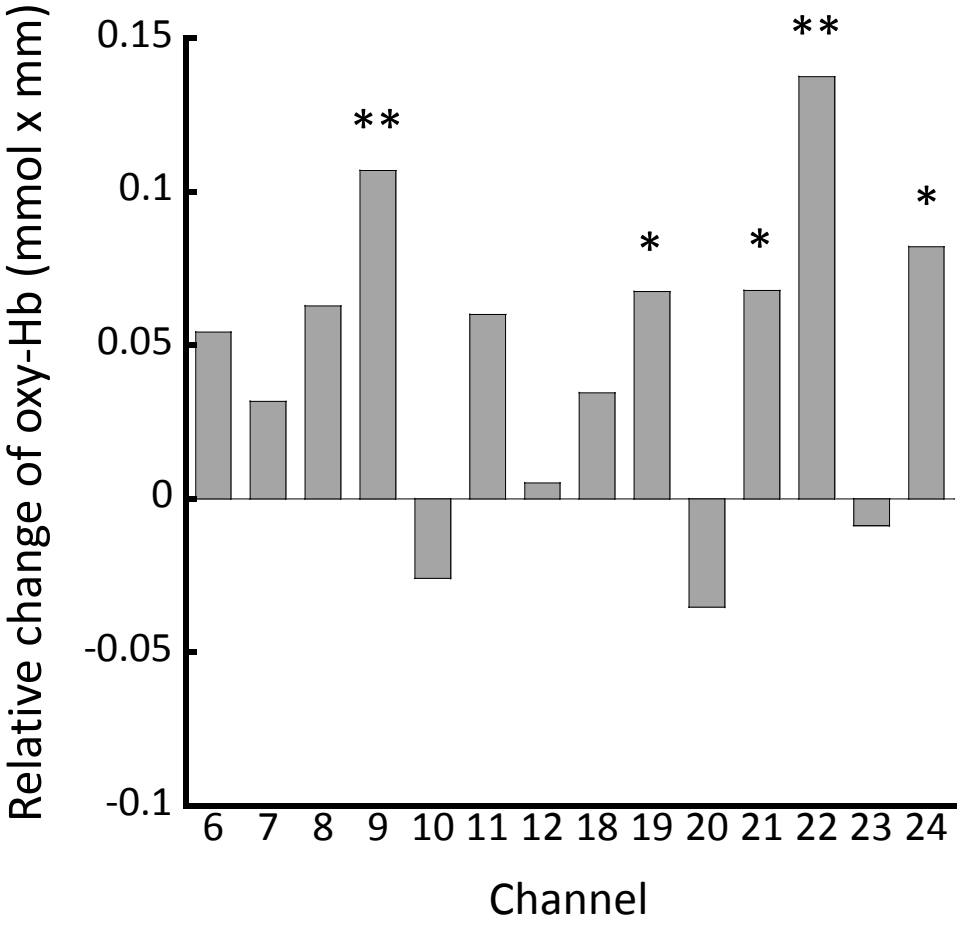
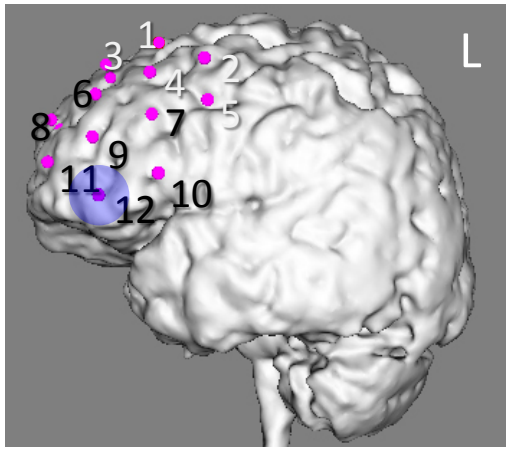
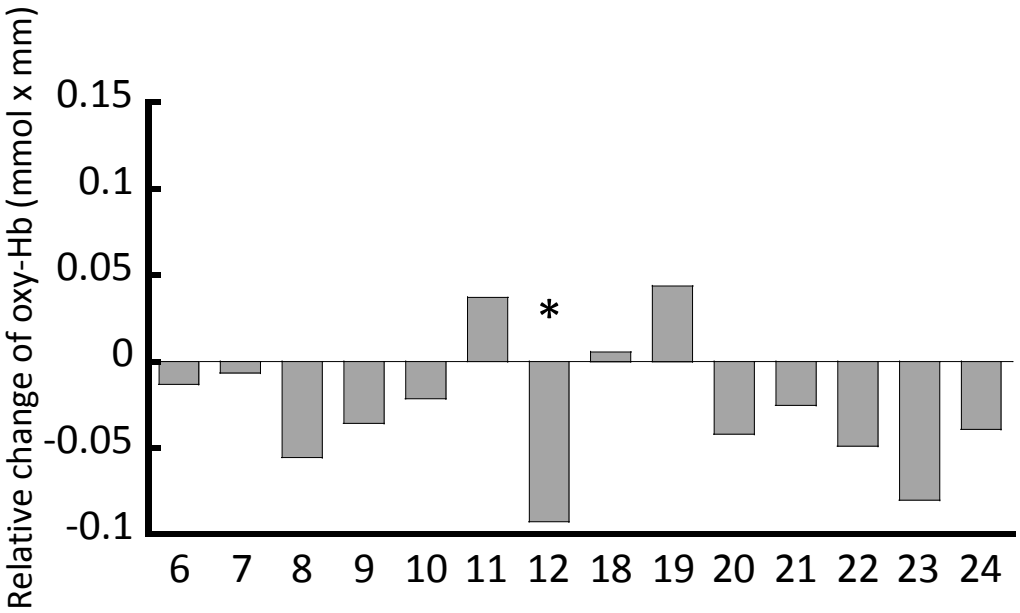
(b)

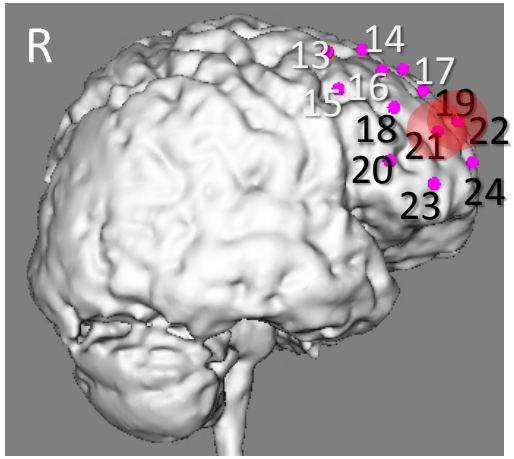

Relative change of oxy-Hb (mmol x mm)
0.15
0.1
0.05
0
-0.05
-0.1
**
*
*
**
*
6 7 8 9 10 11 12 18 19 20 21 22 23 24
Channel

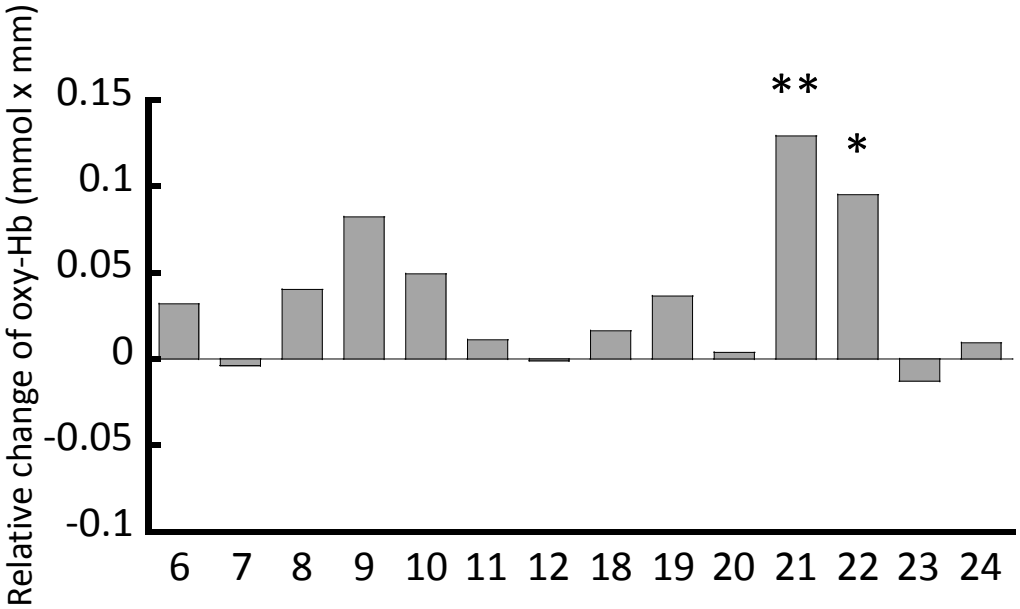
(a) Pre-ATX condition

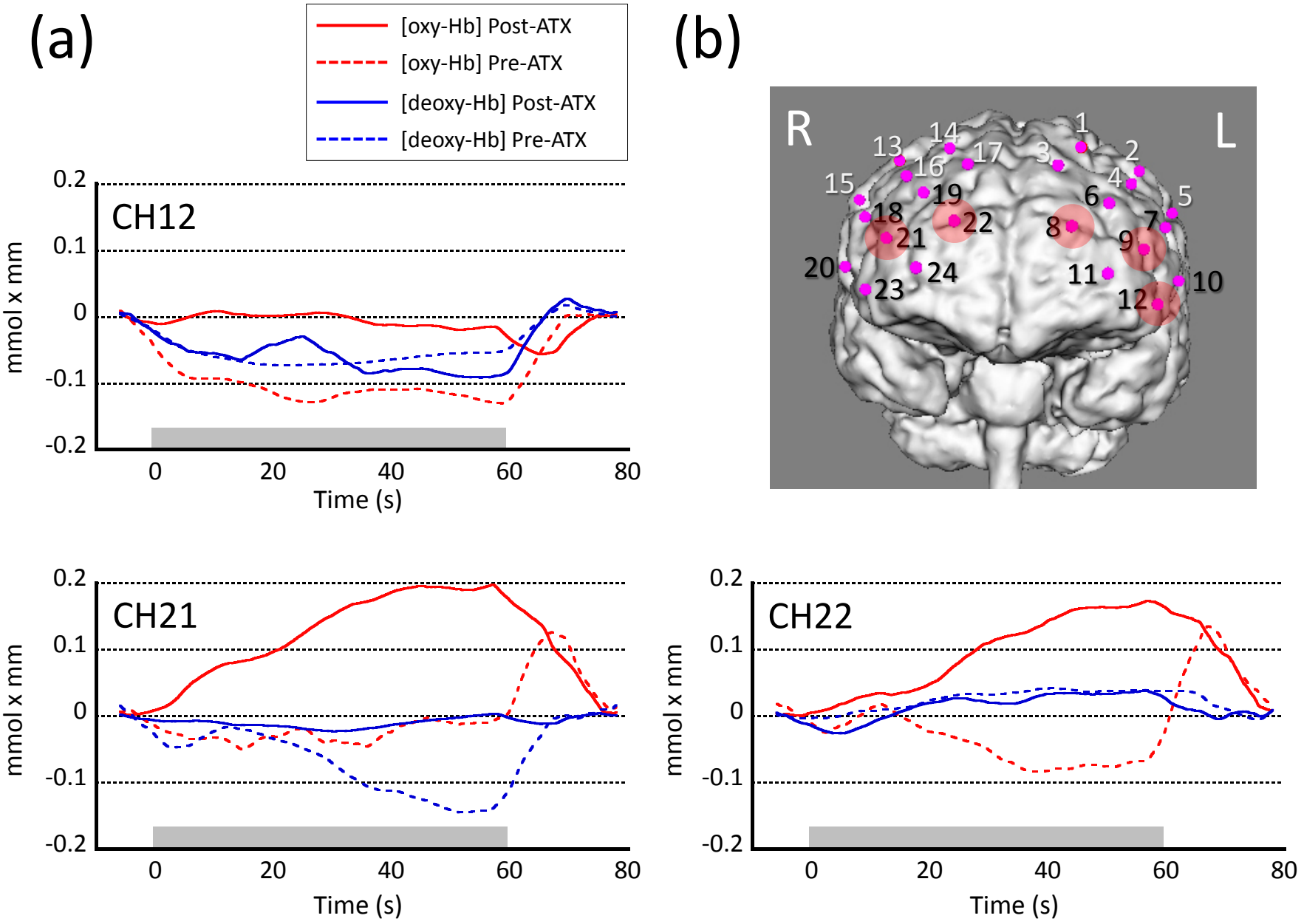




(b) Post-ATX condition






(a)
[oxy-Hb] Post-ATX
[oxy-Hb] Pre-ATX
[deoxy-Hb] Post-ATX
[deoxy-Hb] Pre-ATX
CH12
CH21
CH22
mmol x mm
Time (s)
0.2
0.1
0
-0.1
-0.2
0
20
40
60
80
(b)
R
L
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
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19
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23
24

Table 1 Demographic and clinical profiles.

Patient	Sex	Age	subtype	ATX dose (mg/kg/day)	Full IQ*	Complication
1	M	13	Combined	1.4	99	-
2	M	6	Combined	1.46	112	-
3	M	11	Inattentive	1.54	90	PDD** / Anxiety
4	M	6	Combined	1.59	107	-
5	F	12	Inattentive	1.4	85	-
6	F	7	Combined	1.8	94	-
7	F	9	Combined	1.67	85	PDD
8	F	8	Combined	1.67	113	PDD / EEG abnormalities
9	M	11	Inattentive	1.53	101	-
10	F	10	Combined	1.67	87	EEG abnormalities
11	F	10	Combined	1.8	108	-
12	M	8	Inattentive	1.72	107	-

*WISC-III or WISC-IV **Pervasive developmental disorders

Table 2 Behavioral performance and AD/HD-RS-IV-J score.

Group	Condition	Continuous performance task				AD/HD-RS-IV-J total score
		Hit (%)	Reaction time for hit (ms)	False alarm (%)	Number of minor commission errors	
Control	-	93.81 ± 9.59	394.90 ± 64.69	2.38 ± 4.97	0.14 ± 0.53	-
AD/HD	Pre-ATX	92.22 ± 10.57	382.58 ± 75.35	8.89 ± 17.13	0.92 ± 3.18	35.17 ± 7.08 **
	Post-ATX	92.78 ± 11.18	367.57 ± 106.77	7.22 ± 10.43	0.92 ± 1.73	20.00 ± 5.94

Values are given as means ± standard deviation. **p < 0.01.
Minor commission errors are as follows: false target error; alarm error; random error. For details, see Section 2.2. Task Procedure.