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NeuroImage: Clinical 4 (2014) 53–63

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Prefrontal activation during inhibitory control measured by near-infrared spectroscopy for differentiating between autism spectrum disorders and attention deficit hyperactivity disorder in adults ☆

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ARTICLE INFO

Article history:
Received 23 June 2013
Received in revised form 2 October 2013
Accepted 3 October 2013
Available online 26 October 2013

Keywords:
Autism spectrum disorders
Attention deficit hyperactivity disorder
Near-infrared spectroscopy
Inhibitory control
Stop signal task

ABSTRACT

The differential diagnosis of autism spectrum disorders (ASDs) and attention deficit hyperactivity disorder (ADHD) based solely on symptomatic and behavioral assessments can be difficult, even for experts. Thus, the development of a neuroimaging marker that differentiates ASDs from ADHD would be an important contribution to this field. We assessed the differences in prefrontal activation between adults with ASDs and ADHD using an entirely non-invasive and portable neuroimaging tool, near-infrared spectroscopy. This study included 21 drug-naïve adults with ASDs, 19 drug-naïve adults with ADHD, and 21 healthy subjects matched for age, sex, and IQ. Oxygenated hemoglobin concentration changes in the prefrontal cortex were assessed during a stop signal task and a verbal fluency task. During the stop signal task, compared to the control group, the ASDs group exhibited lower activation in a broad prefrontal area, whereas the ADHD group showed underactivation of the right premotor area, right presupplementary motor area, and bilateral dorsolateral prefrontal cortices. Significant differences were observed in the left ventrolateral prefrontal cortex between the ASDs and ADHD groups during the stop signal task. The leave-one-out cross-validation method using mean oxygenated hemoglobin changes yielded a classification accuracy of 81.4% during inhibitory control. These results were task specific, as the brain activation pattern observed during the verbal fluency task did not differentiate the ASDs and ADHD groups significantly. This study therefore provides evidence of a difference in left ventrolateral prefrontal activation during inhibitory control between adults with ASDs and ADHD. Thus, near-infrared spectroscopy may be useful as an auxiliary tool for the differential diagnosis of such developmental disorders.

1. Introduction

The differential diagnosis of the 2 commonest types of neurodevelopmental disorders, autism spectrum disorders (ASDs) and attention deficit hyperactivity disorder (ADHD), can be difficult. ASDs are characterized by impairments in social skills and communication, as well as repetitive interests and activities (American Psychiatric Association, 2000; Stigler et al., 2011). ADHD is characterized by symptoms of inattention, hyperactivity, and impulsivity (American Psychiatric Association, 2000). These conditions often share symptoms of inattention, hyperactivity, impulsivity, and neuropsychological deficits in inhibitory control (Willcutt et al., 2005; Corbett et al., 2009). Thus, misclassification between ASDs and ADHD may occur in clinical settings, particularly in cases of ASDs with comorbid ADHD symptoms. Because the clinical symptoms of high-functioning ASDs and ADHD of adulthood have been modified according to environmental and

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http://dx.doi.org/10.1016/j.nicl.2013.10.002

developmental factors (Nylander et al., 2013; Lehnhardt et al., 2012; Hofvander et al., 2009; Michielsen et al., 2013), it is more difficult to establish a differential diagnosis of ASDs and ADHD in adults.

These misclassifications may lead to a suboptimal treatment strategy. For example, the administration of methylphenidate (MPH), which is a common treatment for childhood ADHD (Whalen et al., 1989; Barkley et al., 2005; Newcorn et al., 2008; Jensen et al., 2007), to children with ASDs and comorbid ADHD symptoms is frequently associated with adverse effects (i.e., social withdrawal, irritability, and stereotypy) severe enough to warrant treatment discontinuation (Autism Network, 2005; Di Martino et al., 2004). Despite the insufficient study of the benefits and adverse effects of MPH in adults with ASDs and ADHD symptoms, MPH is often administered in these cases, even without evidence of its efficacy, because it is the first line of pharmacological treatment for adult ADHD (Kooij et al., 2010; Atkinson and Hollis, 2010). Other treatments are more appropriate for adult ASDs, such as selective serotonin reuptake inhibitors (Williams et al., 2010a), risperidone (McDougle et al., 1998), and cognitive behavioral therapy (White et al., 2009; Lang et al., 2010).

The inhibitory dysfunction observed in the two disorders may have different neurobiological bases, despite similar symptomatic and neuropsychological manifestations.

Stop signal and go/no-go tasks are commonly used tasks to detect inhibitory control in neuroimaging studies. The stop signal task creates a higher load on response inhibition processes compared to the go/no-go task, in that it involves the retraction of a response that has already been triggered by a go signal (Rubia et al., 2001). Go/no-go tasks have a higher load on response selection, due to the a priori knowledge about whether or not to respond to the presentation of specific categorical stimuli (Rubia et al., 2001).

Studies of children with ASDs have revealed no significant differences compared to healthy children in the stop signal task (Ozonoff and Strayer, 1997) but lower performance in the go/no-go task (Happé et al., 2006). Inhibitory motor control as assessed by the stop signal task has been studied extensively in ADHD. The meta-analysis revealed a significant difference in stop latency (stop signal reaction time) between ADHD patients and matched controls in both children and adults (Lijffijt et al., 2005), while children with ADHD had lower performance compared to healthy controls in the go/no-go task (Happé et al., 2006; Raymaekers et al., 2007).

Most previous neuropsychological and neuroimaging studies comparing ADHD with ASDs were performed in children. Neuropsychological studies have found that the ASDs group can have either better (Ozonoff and Jensen, 1999; Geurts et al., 2004; Happé et al., 2006) or poorer (Corbett et al., 2009) inhibitory control than the ADHD group. However, some studies showed little difference in executive function profiles between ADHD and ASDs (Goldberg et al., 2005; Verté et al., 2006). The only neuropsychological study performed in adult patients revealed significant differences between ADHD and ASDs in the Stroop task. However, using the Hayling Sentence Completion Test, which assesses verbal response inhibition, it was found that adults with ADHD did not exhibit more severe impairments compared to those with ASDs (Johnston et al., 2011).

Thus, the development of an inhibitory-task-related neurophysiological index as an auxiliary tool for the differential diagnosis of ASDs and ADHD in adults would be an important contribution to this field. Recent functional magnetic resonance imaging (fMRI) and event-related potential studies have revealed differences between children with ASDs and ADHD (Christakou et al., 2012; Malisza et al., 2011; Kemner et al., 1995; Groen et al., 2008). To date, however, no studies have directly compared adults with ASDs to those with ADHD using functional neuroimaging or neurophysiological indices.

Ideally, a diagnostic index should be developed using a neuroimaging tool that is suitable for application in clinical settings. Near-infrared spectroscopy (NIRS) is an optical neuroimaging technique that allows the non-invasive measurement of changes in the concentrations of oxygenated and deoxygenated hemoglobin ([oxy-Hb] and [deoxy-Hb], respectively), thus reflecting regional cerebral blood volume (Hoshi and Tamura, 1993; Villringer et al., 1993). NIRS is safe and portable and allows the examination of subjects in a natural sitting position. The resolution of NIRS for detecting time-course alterations in brain activation in the prefrontal cortex (PFC) is finer than that of fMRI. Therefore, NIRS could be applied as an auxiliary diagnosis tool in clinical psychiatry.

Our research aim was to determine whether prefrontal NIRS signals recorded during an inhibitory control task differed between adults with ASDs and those with ADHD. In this study, we used a stop signal task (SST) to detect brain activation associated with inhibitory control. We chose the letter version of the verbal fluency task (VFT) as a control index of prefrontal function to test whether the findings were task specific. We hypothesized that adults with ASDs and ADHD would exhibit differential prefrontal NIRS signals during the SST, and that both groups of patients would show activation of the PFC compared to the control group. Further, we hypothesized that during the VFT, both groups would show a similarly reduced activation of the PFC compared to the control group.

2. Materials and methods

2.1. Participants

Twenty-one adults with ASDs, 19 adults with ADHD, and 21 healthy control (HC) subjects participated in the study (Table 1). We recruited 26 adults with ASDs and 25 adults with ADHD from the outpatient clinic at the Department of Neuropsychiatry, University of Tokyo Hospital, Japan, and from community clinics. After recruitment of the patient group, some individuals were recruited in the control group in order to match patients for age, sex, and IQ. As a result, all participating subjects were matched for age, sex, and IQ (Table 1). All subjects gave written informed consent in accordance with the Declaration of Helsinki after a complete explanation of the study. The ethics committee of the University of Tokyo Hospital approved this study (approval no.: 630-6). The diagnoses of ASDs and ADHD were established in accordance with the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) based on comprehensive clinical assessments performed by at least 2 trained child psychiatrists (YK, HK, and AI). We included participants in this study only when at least 2 of the 3 child psychiatrists had seen patients and given consistent diagnoses. Current and lifetime DSM-IV diagnoses, other than ASDs/ADHD, were ruled out based on a consensus decision using information gained from independent clinical interviews, other available clinical data, and from the Mini-International Neuropsychiatric Interview (MINI). The exclusion criteria for all groups were as follows: full-scale IQ <70, neurological illness, genetic disorders, traumatic brain injury with any known cognitive consequences or loss of consciousness for more than 5 min, a history of electroconvulsive therapy, a history of treatment with stimulants or other psychiatric medication, alcohol/substance abuse or addiction, bipolar disorder, and schizophrenia. An additional exclusion criterion for the control group was personal history of a psychiatric disease, as assessed using the MINI, or a family history of psychiatric disease among their first-degree relatives.

None of the adults with ASDs or ADHD had been treated with stimulants or other psychiatric medication. In Japan, MPH was approved only for treatment of children with ADHD in 2007, and it cannot be used for treating adult ADHD in Japan. Therefore, MPH cannot be used even for cases with severe ADHD symptoms.

The HC group was also free of medication. To the extent possible, we obtained childhood information from a person who knew the patient in childhood (usually the mother). At the time of the recruitment of the subjects, the usage of the Autism Diagnostic Interview, Revised (ADI-R), Autism Diagnostic Observation Schedule (ADOS), and Conners' Adult ADHD Diagnostic Interview for DSM-IV™ (CAADID) was extremely limited in Japan. Before we finished recruitment, we obtained permission

Table 1
Characteristics and task performance.

	ASDs ($n = 21$)	ADHD ($n = 19$)	HC ($n = 21$)		Comparison		
	Mean (SD)	Mean (SD)	Mean (SD)	*P*	Post-hoc *P*		
					ASDs:HC	ADHD:HC	ASDs:ADHD
Age, years	30.8 (7.2)	30.6 (7.4)	28.8 (5.5)	0.60			
Sex, men/women	8 13	11 8	13 8	0.26			
IQ	105.1 (14.6)	102.6 (16.6)	109.0 (5.6)	0.25			
SST (all trials), %	80.8 (11.6)	78.9 (13.8)	84.9 (9.3)	0.26			
SST (stop trials), %	49.2 (38.4)	56.1 (26.3)	65.6 (23.6)	0.22			
SST (go trials), %	94.3 (7.2)	87.7 (20.2)	92.7 (9.8)	0.27			
MRT (SST), ms	498.0 (102.7)	539.1 (100.4)	558.1 (75.8)	0.11			
VFT, words	16.0 (4.3)	15.5 (4.5)	16.9 (4.4)	0.60			
ASRS	3.2 (1.8)	5.2 (0.8)	1.3 (1.1)	<0.01	<0.01	<0.01	<0.01
WURS	53.1 (23.2)	62.1 (20.0)	17.5 (9.3)	<0.01	<0.01	<0.01	0.39
AQ total score	33.5 (7.9)	27.6 (5.5)	13.4 (4.2)	<0.01	<0.01	<0.01	0.02
GAF	51.8 (13.2)	58.8 (10.7)	84.6 (3.1)	<0.01	<0.01	<0.01	0.45
Subtype	Asperger, 5; PDD NOS, 16	ADHD, 11; ADD, 8					

ASDs, autism spectrum disorders; ADHD, attention deficit hyperactivity disorder; HC, healthy control subjects; Asperger, Asperger syndrome; PDD, pervasive developmental disorder; NOS, pervasive developmental disorder - not otherwise specified; IQ, intelligence quotient; SST, stop signal task; MRT, mean reaction time; VFT, verbal fluency task; ASRS, The World Health Organization (WHO) Adult ADHD Inhibitory-Report Scale; WURS, Wender Utah Rating Scale; AQ, autism spectrum quotient; GAF, Global Assessment of Functioning.

to use the ADI-R, ADOS, and CAADID, which were administered by child psychiatrists and psychologists (HK, YK, and AI) to 6 participants (3 ASDs and 3 ADHD participants). The conventional diagnosis was coincident with the diagnosis obtained using ADI-R, ADOS, and CAADID in these 6 participants.

All participants were self-reported right-handers, as assessed using the Edinburgh score (>70) (Oldfield, 1971). The IQ scores of subjects with ASDs and ADHD were obtained using the Wechsler Adult Intelligence Scale-Revised (WAIS-R), Japanese version. The IQ scores of the HCs were estimated using the Japanese version of the National Adult Reading Test (JART) (Matsuoka et al., 2006). Although the JART can measure IQ accurately in HC participants, the test is problematic for participants with ASDs and ADHD because of the well-known imbalances in their intellectual abilities.

A self-reported screening scale was used to assess ADHD symptoms; the World Health Organization (WHO) Adult ADHD Self-Report Scale (ASRS), which was developed in conjunction with the revision of the WHO Composite International Diagnostic Interview (CIDI) (cutoff >3). The Japanese version of the Wender Utah Rating Scale (WURS), which is a self-reporting instrument that is used to identify childhood tendencies toward ADHD retrospectively (cutoff >46) (Matsumoto et al., 2005), was also used. We used these 2 scales in the ASDs and ADHD groups.

We applied the Autism Spectrum Quotient (AQ), as obtained from a self-reported questionnaire, to quantify autistic symptoms in all participants (Baron-Cohen et al., 2001; Wakabayashi et al., 2006). The AQ comprises 50 questions, with 10 questions assessing each of 5 different areas: social skills, attention switching, attention to detail, communication, and imagination. Scores range from 0 to 50 (cutoff >32).

2.2. Task procedure

Hemoglobin concentration ([Hb]) changes were measured during 2 cognitive activation tasks. Subjects sat on a comfortable chair with their eyes open throughout the NIRS measurements and were instructed to minimize movements such as head movements, strong biting, and eye blinking. The sequence of the following 2 tasks was counterbalanced across the subjects.

2.2.1. SST

The cognitive activation task included a 30 s pre-SST, an 81 s SST, and an 80 s post-SST period (Fig. 1A). We selected the block design for the cognitive activation task. In the pre- and post-SST periods (Fig. 1B), the participants were instructed to indicate the direction of an image of a dog (left or right) by pressing a button as quickly as possible. Participants performed 20 trials during the pre-task period and 30 trials during the post-task period. The mean reaction time was calculated automatically during the pre-task period. The image of a dog was displayed for 0.5 s. Between presentation of the images of dogs, a cross shape was shown for 0.4–1.0 s.

During the SST (Fig. 1C), participants were instructed to respond to the "GO" stimulus as quickly as possible during the "GO" trials, and to try to withhold their response on the "STOP" trials (short beep). "STOP" signals were given under 3 conditions of delay after the "GO" stimulus was presented (ΔT equal to mean reaction time [MRT], MRT − 100 ms, and MRT − 250 ms). We used these 3 conditions of delay to avoid the usual tendency to delay the Go response. The subjects performed 21 "GO" trials and 9 "STOP" trials during the SST. We used the total number of correct responses (the number of correct inhibitions plus the number of correct responses to the direction of the dog) divided by the total number of trials as a measure of task performance. We also used the success rate of stop trials and go trials in SST period as a measure of task performance.

2.2.2. VFT

The VFT, which was presented as described previously (Takizawa et al., 2008, 2009), included a 30 s pre-VFT, a 60 s VFT (letter version), and a 70 s post-VFT period. In the pre- and post-task baseline periods, the subjects were instructed to repeat Japanese vowels (/a/, /i/, /u/, /e/, and /o/) aloud. This was intended to correct the data during the fluency task with regard to activation due to vocalization. During the VFT period, participants were instructed to generate as many Japanese words beginning with a designated syllable as possible. This approach is commonly used in the Japanese letter version of the VFT, as Japanese words inevitably begin with a vowel or a consonant–vowel syllable. The 3 initial syllables (first: /to/, /a/, or /na/; second: /i/, /ki/, or /se/; third: /ta/, /o/, or /ha/) were presented in an order that was counterbalanced among the subjects and changed every 20 s during the 60 s task period, to reduce the time during which the subjects remained silent. The subjects were instructed by an auditory cue at the start and end of the task and when the syllable was changed. The total number of correct words generated during the 60 s activation period was used as a measure of task performance.

2.3. NIRS measurement

Relative [oxy-Hb] and [deoxy-Hb] changes were monitored using a 52-channel NIRS machine (Hitachi ETG-4000) at 2 wavelengths of

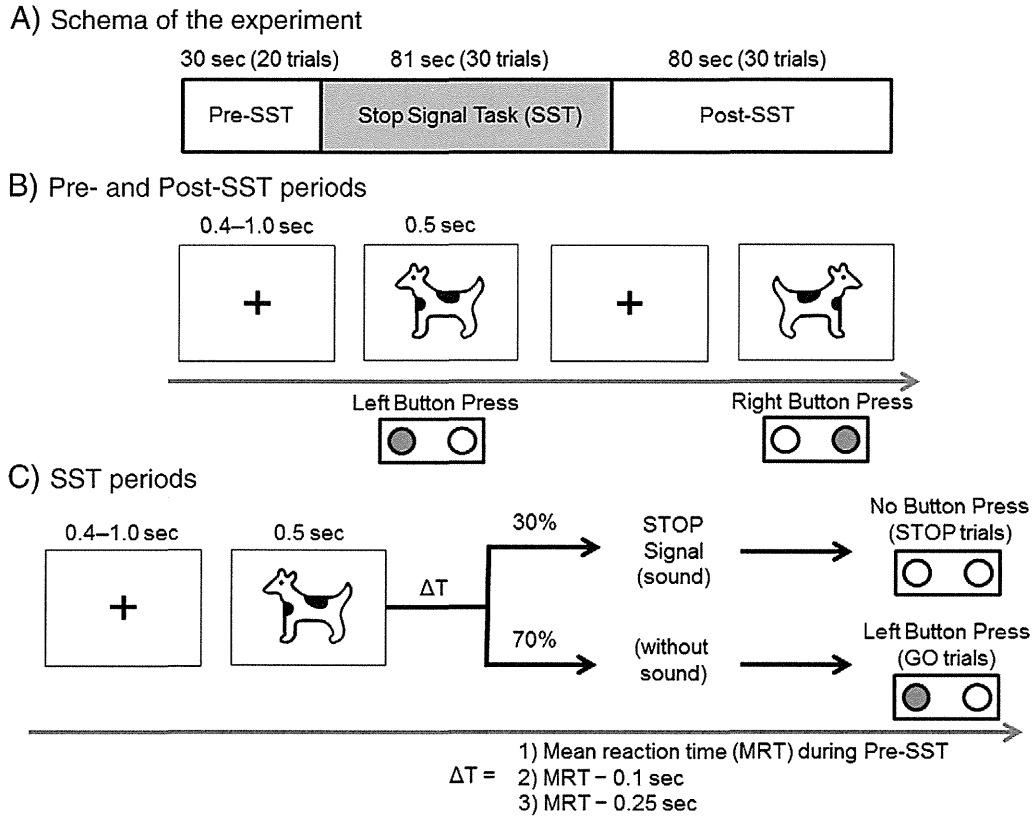

Fig. 1. Schematic representation of the stop signal task. Auditory "STOP" signals were given under 3 conditions of delay (ΔT equal to the mean reaction time [MRT], MRT − 100 ms, and MRT − 250 ms) after the "GO" stimulus was presented.

near-infrared light (695 and 830 nm) based on the modified Beer–Lambert law. The distance between pairs of light source and detector probes was set at 3 cm, and each measurement area between pairs of source/detector probes was defined as a "channel." The probes of the NIRS machine were arranged in 3 × 11 shells and placed on the subject's frontal area. The lowest probes were positioned along the T3–Fpz–T4 line, according to the international 10/20 system. As described previously (Takizawa et al., 2008), this arrangement of the probes is able to detect [Hb] changes in the surface regions of the PFC on bilateral sides (dorsolateral PFC [DLPFC; Brodmann areas (BA) 9 and 46], ventrolateral PFC [VLPFC; BA44, 45, and 47], and frontopolar PFC [; BA10]), and the temporal cortex. To estimate the cortical localization of each channel, we used the virtual registration method (Tsuzuki et al., 2007; Tzourio-Mazoyer et al., 2002), which enables the probabilistic registration of NIRS data onto the Montreal Neurological Institute (MNI) coordinate space without data on magnetic resonance images or probe positions (Fig. 2).

The sampling rate was set to 10 Hz. The pre-task period value was determined as the mean value over a 10 s period just prior to the task period, and the post-task period value was determined as the mean value over the last 10 s of the post-task period. Linear fitting was performed using data from the pre- and post-task periods. The moving average method was used to remove any short-term motion artifacts (moving average window, 5 s). The time resolution of the NIRS apparatus was set at 0.1 s and changes were analyzed using the first-order correction to exclude changes unrelated to the task, such as very slow oscillations or baseline drifts. To acquire a stable baseline, a 20 s non-measured period was included in the 30 s pre-task period; NIRS measurement started in the last 10 s of the pre-task period. Because the NIRS signal was sometimes unstable at the start of the pre-task period, the pre-task baseline was determined as the mean across the last 10 s of the this period, the post-task baseline was determined as the mean across the last 10 s of the post-task period, and a linear fitting was performed on the basis of data between the 2 baselines according to previous NIRS studies (Takizawa et al., 2008; Marumo et al., 2013).

Despite the application of these artifact-rejection methods, visible artifacts sometimes remained in the waveforms. We therefore used a

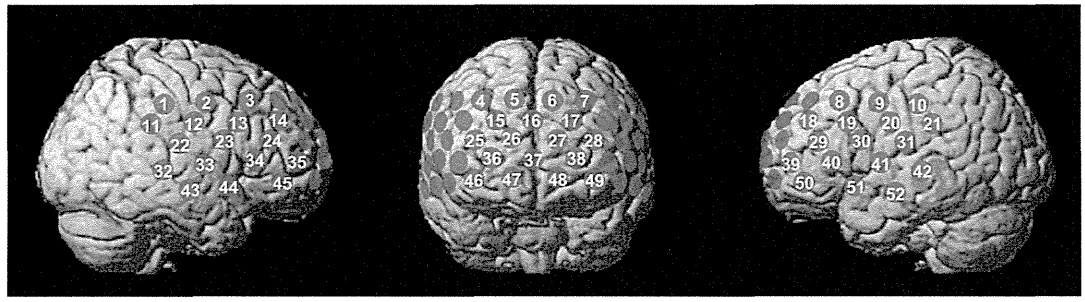

Fig. 2. Locations of the near-infrared spectroscopy (NIRS) probes. The locations of NIRS measurements (channels) were estimated probabilistically and labeled anatomically in the standard brain space (LBPA40) according to Tsuzuki et al. (2007).

computed rejection program (see Inline Supplementary material A.1) that automatically rejected channels that included waveforms with prominent artifacts. Because we excluded the rejected channels from further analyses, the number of available channels varied among individuals.

Finally, the [oxy-Hb] and [deoxy-Hb] data obtained for each channel were averaged for the task period and the [task + post-task] period, respectively. We chose these 2 NIRS signals to detect the time course of [oxy-Hb] and [deoxy-Hb] changes during cognitive tasks.

2.4. Statistical analyses

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) 18 software (SPSS Inc., Tokyo, Japan).

2.4.1. Clinical scale and task performance

Between-group differences in the scores for clinical scales and task performance were tested using a 1-way analysis of variance (ANOVA) and Tukey's honestly significant difference (HSD) test as a post-hoc analysis. A chi-squared test was used for testing sex differences. Clinical and behavioral results were considered significant at $P < 0.05$.

2.4.2. NIRS data

We focused on the mean [oxy-Hb], as the [oxy-Hb] increase is assumed to reflect cognitive activation more directly than does the [deoxy-Hb] decrease, as shown by a stronger correlation of [oxy-Hb] with the blood-oxygenation-level-dependent signal measured by fMRI (Strangman et al., 2002) and by results of animal studies (Hoshi et al., 2001).

For the SST and VFT, mean [oxy-Hb] values were analyzed via one-way ANOVA using the mean [oxy-Hb] as the dependent variable and the diagnosis (ASDs, ADHD, or HC) as the independent variable for each period (the task period or the [task + post-task] period) and for each channel. A false-discovery rate (FDR) correction for multiple comparisons (52 channels) was applied. We set the value for the maximum FDR to 0.05, to allow no more than 5% false positives on average (Singh and Dan, 2006). The mean [oxy-Hb] values were then analyzed using Tukey's HSD test, as a post-hoc analysis, for each period and for each channel.

2.4.3. Classification and cross-validation

The individual expression values were defined as the mean [oxy-Hb] values during the task (or task + post-task) period. We submitted the resulting individual expression values to a parametric Fisher's linear discriminant analysis classification algorithm (Ponseti et al., 2012) in order to discriminate the ASDs from the ADHD group, the ASDs from the HC group, and the ADHD from the HC group.

First, we used stepwise analysis for all channels that showed a significant difference ($P < 0.05$) between the ASDs and ADHD group, the ASDs and HC group, or the ADHD and HC group to select the channels to be used in Fisher's linear discriminant analysis. A stepwise analysis was performed in a forward direction using P values for entry ($P = 0.05$) and removal ($P = 0.10$).

Second, we classified each participant according to these values using Fisher's linear discriminant analysis. We cross validated the classification method using a leave-one-out procedure 40–42 times, to account for each participant. We determined the predictive power of the classification procedure by calculating specificity and sensitivity, as well as average sensitivity and specificity values and mean classification accuracy.

2.4.4. Additional analyses

We evaluated whether [deoxy-Hb] changes had tendencies similar to the [oxy-Hb] changes among the 3 groups, although, overall, we focused on [oxy-Hb] changes. We also addressed prefrontal [oxy-Hb] changes in ASDs adults with ADHD symptoms, who are difficult to differentiate clinically from ADHD adults. We defined a subgroup of ASDs adults who exceeded the ASRS cutoff (>3) ($n = 10$). A different activation between participants with a diagnosis of ASDs who also had ADHD symptoms and the ADHD group would represent an ASDs-specific brain dysfunction. The 3 diagnostic groups (the ASDs subgroup with ADHD symptoms, the entire ADHD group, and the entire HC group) were then compared using the statistical procedures described above. Furthermore, we compared [oxy-Hb] changes between male and female subjects in each group, because a previous NIRS study demonstrated that [oxy-Hb] changes were affected by sex (Kameyama et al., 2004). In addition, we performed a correlation analysis to examine the relationship between [oxy-Hb] changes and clinical conditions and demographic data, such as age, symptom severity, and task performance.

3. Results

3.1. Clinical characteristics and behavioral results

All patients with ADHD and 10 patients with ASDs exceeded the cutoff of the ASRS (Table 1). The ASRS scores of all HC subjects were below the cutoff value. The mean WURS scores of the patients exceeded the threshold (>46), suggesting a difficulty in distinguishing these 2 disorders based on retrospective inhibitory-reporting assessments in their childhood. The ASDs group had significantly higher AQ scores than did the other groups. No statistically significant differences were observed among the 3 groups in any of the task-performance indices.

3.2. NIRS data results

3.2.1. SST

The typical grand-averaged waveforms for [oxy-Hb] in the left VLPFC (ch50) in the HC, ASDs, and ADHD groups are shown in Fig. 3. During the SST period, we found significant main effects of the group in 29 channels (ch1–3, 10–13, 18, 20, 22, 24, 28, 29, 31, 32, 35–39, 41, 42, and 45–51; F [df = 2, 53–58] = 3.911–15.448; FDR-corrected $P \leq 0.001$–0.026).

The [oxy-Hb] changes in the ASDs group were significantly smaller than those in the ADHD group in 2 channels corresponding to the left VLPFC (ch50 and 51; post-hoc $P = 0.030$–0.034) (Figs. 3 and 4, see Inline Supplementary Table S1). Tukey's HSD test indicated that [oxy-Hb] changes in the ASDs group were significantly smaller than those in the HC group in 28 channels corresponding to the bilateral DLPFC, left VLPFC, left premotor area (PMA), left presupplementary motor area (SMA), and frontal pole (ch2, 3, 10–13, 18, 20, 22, 24, 28, 29, 31,

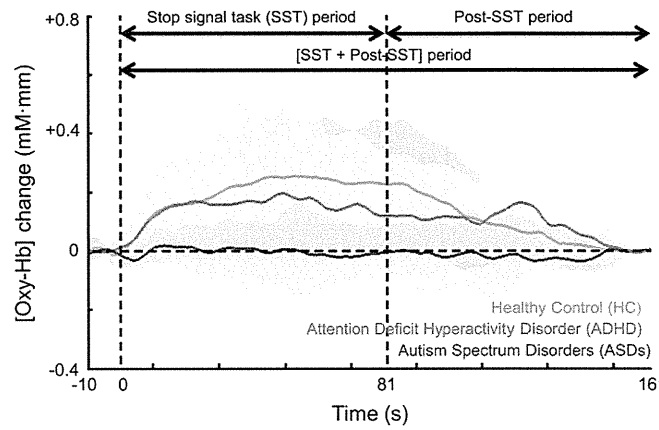

Fig. 3. Time courses of the hemodynamic responses in the left ventrolateral prefrontal cortex (ch50) for the 3 diagnostic groups. The [oxy-Hb] changes for the healthy control (HC) group (black, $n = 21$), attention deficit hyperactivity disorder (ADHD) group (pink, $n = 19$), and autism spectrum disorders (ASDs) group (blue, $n = 21$) during the activation stop signal task (SST) and post-SST conditions are presented as grand-averaged waveforms in ch50. The shaded color indicates the standard deviation.

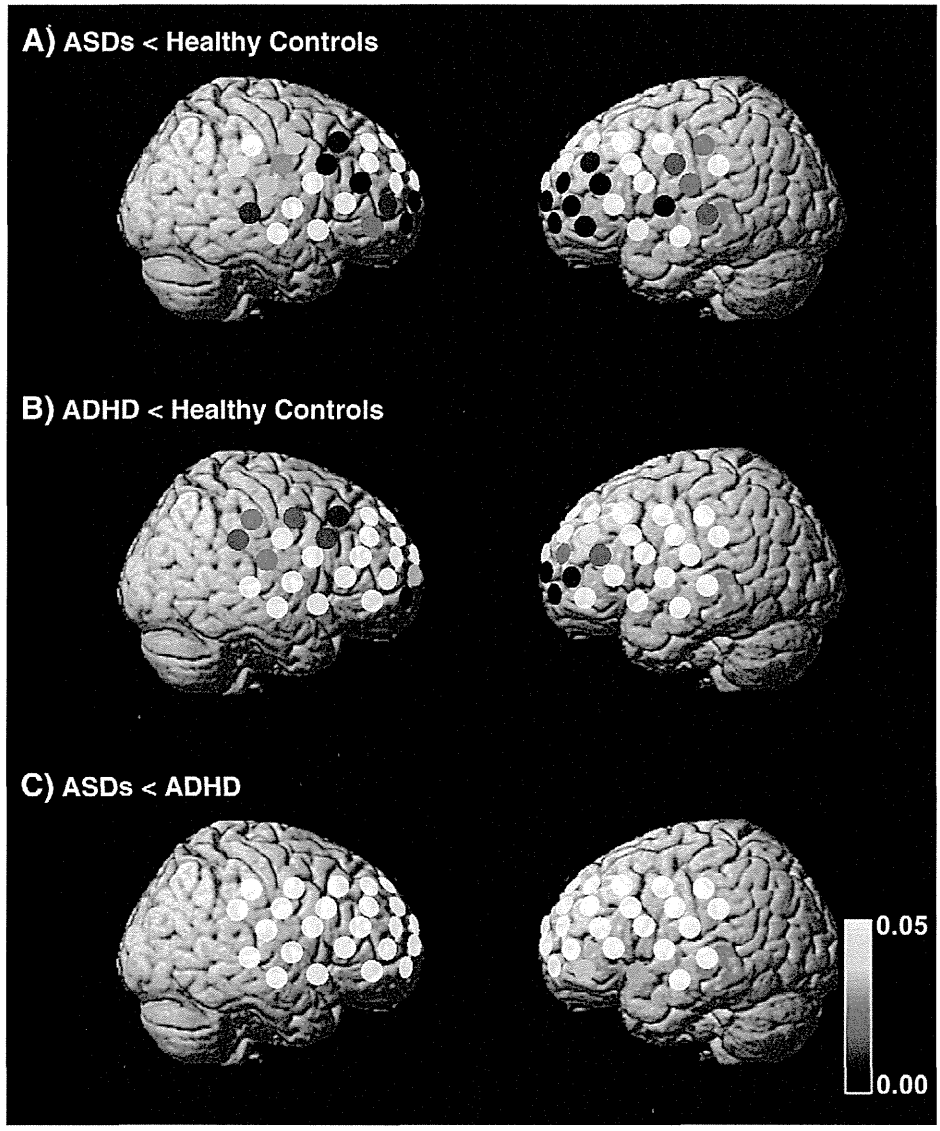

Fig. 4. Differences in [oxy-Hb] changes during the SST between the HC and ADHD groups (A), between the HC and ASDs groups (B), and between the ASDs and ADHD groups (C) (A: post-hoc $P \leq 0.001$–0.046; B: post-hoc $P = 0.001$–0.047: and C: post-hoc $P = 0.030$–0.034). The colored bar represents the P value.

32, 35–39, 41, 42, and 45–51; post-hoc $P \leq 0.001$–0.046) (Figs. 3 and 4, see Inline Supplementary Table S1). [oxy-Hb] changes in the ADHD group were significantly smaller than those in the HC group in 17 channels corresponding to the frontal pole, the bilateral DLPFC, the right PMA, and the right pre-SMA (ch1–3, 11–13, 18, 22, 28, 29, 36, 38, 39, and 46–49; post-hoc $P = 0.001$–0.047) (Fig. 4, see Inline Supplementary Table S1).

Inline Supplementary Table S1 can be found online at http://dx.doi.org/10.1016/j.nicl.2013.10.002.

During the [SST + post-SST] period, there was a main effect of the group in 31 channels (ch2, 3, 8–10, 12, 13, 18, 20, 24, 26–31, 35–39, 41, 42, and 45–52; F [df = 2, 53–58] = 4.291–12.721; FDR-corrected $P \leq 0.001$–0.019).

The [oxy-Hb] increases observed in the ADHD group were significantly larger than those recorded in the ASDs group in 5 channels corresponding to the left VLPFC and frontal pole (ch24, 30, 41, 50, and 51; post-hoc $P = 0.003$–0.046) (Figs. 3 and 5, Supplementary Table A. 2). The number of channels that exhibited significantly different NIRS signals between the ASDs and ADHD groups were larger for the [SST + post SST] analysis than that for the SST analysis, which was mainly driven by a post-SST reascending in [oxy-Hb] in the ADHD group (Fig. 3). The post-hoc Tukey's HSD test revealed that the [oxy-Hb] increases observed during the [SST + post-SST] period in the ASDs group were significantly smaller than those in the HC group in 31 channels corresponding to the bilateral DLPFC, bilateral VLPFC, bilateral PMA, bilateral pre-SMA, and frontal pole (ch2, 3, 8–10, 12, 13, 18, 20, 24, 26–31, 35–39, 41, 42, and 45–52; post-hoc $P \leq 0.001$–0.033) (Figs. 3 and 5, see Inline Supplementary Table S2). The [oxy-Hb] increases observed in the ADHD group were significantly smaller than those in the HC group in 11 channels corresponding to the frontal pole, bilateral DLPFC, right PMA, and right pre-SMA (ch3, 13, 27, 28, 35, 38, 39, and 46–49; post-hoc $P = 0.005$–0.046) (Fig. 5, see Inline Supplementary Table S2).

Inline Supplementary Table S2 can be found online at http://dx.doi.org/10.1016/j.nicl.2013.10.002.

3.2.2. VFT

During the VFT period, we found no significant main effects of the group. There were no significant differences in [oxy-Hb] changes between the ASDs and ADHD groups during the VFT. During the [VFT + post-VFT] period, we found significant main effects of the group in 2 channels (ch13 and 34; F [df = 2, 51–55] = 7.277–8.056; FDR-corrected $P = 0.001$–0.002).

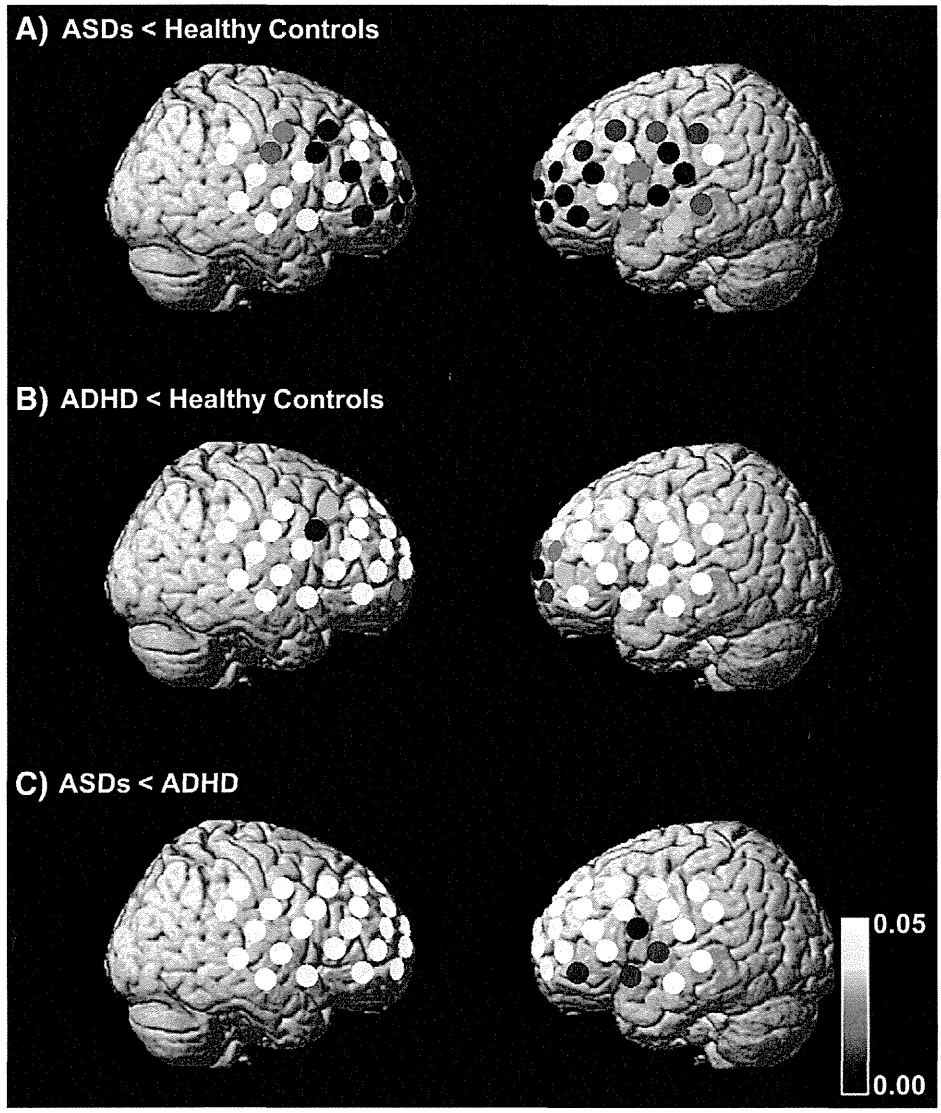

Fig. 5. Differences in [oxy-Hb] changes during the [SST + post-SST] period between the HC and ADHD groups (A), between the HC and ASDs groups (B), and between the ASDs and ADHD groups (C) (A: post-hoc $P \leq 0.001$–0.033; B: post-hoc $P = 0.005$–0.046; and C: post-hoc $P = 0.003$–0.046). The colored bar represents the P value.

There were no significant differences for any channels between the ASDs and ADHD groups during the [VFT + post-VFT] period. Post-hoc Tukey's HSD tests showed that the [oxy-Hb] changes in the ASDs group were significantly smaller than those in the HC group in 2 channels corresponding to the left VLPFC and DLPFC (ch13 and 34; post-hoc $P = 0.002$–0.003) during the [VFT + post-VFT] period. The [oxy-Hb] changes in the ADHD group were significantly smaller than those recorded in the HC group in 2 channels corresponding to the left VLPFC and DLPFC (ch13 and 34; post-hoc $P = 0.004$–0.019) during the [VFT + post-VFT] period.

3.3. Classification and cross-validation

3.3.1. Discrimination between the ASDs and ADHD groups

ANOVA revealed the presence of significant differences between patients with ASDs and those with ADHD in the left VLPFC. Individual brain responses were characterized by expression values in 2 channels with significant differences in the mean [oxy-Hb] during the SST period between ASDs and ADHD adults (ch50 and 51). The stepwise analysis selected 1 channel (ch50: left VLPFC) using the mean [oxy-Hb] during the SST period ($P = 0.02$). The leave-one-out classification algorithm using the mean [oxy-Hb] during the SST period had an accuracy of 72.9% (sensitivity, 85.7%; specificity, 57.9%).

Individual brain responses were characterized by expression values in 5 channels with significant differences in the mean [oxy-Hb] during the [SST + post-SST] period between adults with ASDs and those with ADHD (ch24, 30, 41, 50, and 51). The stepwise regression analysis selected 1 channel (ch30: left VLPFC) using the mean [oxy-Hb] during the [SST + post-SST] period ($P = 0.002$). The algorithm that used the mean [oxy-Hb] during the [SST + post-SST] period had high accuracy (81.4%; sensitivity, 90.0%; specificity, 70.6%).

3.3.2. Discrimination of the ASDs from the HC group

ANOVA revealed the presence of significant differences between patients with ASDs and HC individuals in the broad prefrontal area. Individual brain responses were characterized by expression values in 34 channels that were significantly different regarding the mean [oxy-Hb] during the SST period between patients with ASDs and healthy adults (ch2, 3, 7–13, 17, 18, 20, 22, 24, 28, 29, 31, 32, 35–39, 41, 42, and 45–52). The stepwise regression analysis selected 1 channel (ch39: left VLPFC) using the mean [oxy-Hb] during the SST period ($P < 0.001$). The leave-one-out classification algorithm had an accuracy of 81.1%

(sensitivity, 90.5%; specificity, 71.4%) using the mean [oxy-Hb] during the SST period.

Individual brain responses were characterized by expression values in 36 channels that showed significant differences in the mean [oxy-Hb] during the [SST + post-SST] period between patients with ASDs and healthy adults (ch2, 3, 7–10, 12, 13, 18–20, 24–32, 35–39, 41, 42, and 45–52). The stepwise regression analysis selected 2 channels (ch47 and 50: frontal pole and left VLPFC) using the mean [oxy-Hb] during the [SST + post-SST] period ($P < 0.001$). The algorithm that used the mean [oxy-Hb] during the [SST + post-SST] period had high accuracy (89%; sensitivity, 90.0%; specificity, 80.0%).

3.3.3. Discrimination of the ADHD from the HC group

ANOVA revealed the presence of significant differences between patients with ADHD and HC individuals in the right pre-SMA, right PMA, and bilateral DLPFC. Individual brain responses were characterized by expression values in 17 channels with significant differences in the mean [oxy-Hb] during the SST period between patients with ADHD and healthy adults (ch1–3, 11–13, 18, 22, 28, 29, 36, 38, 39, and 46–49). The stepwise regression analysis selected 1 channel (ch11: right pre-SMA and right PMA) using the mean [oxy-Hb] during the SST period. The leave-one-out classification algorithm using the mean [oxy-Hb] during the SST period had a mean accuracy of 78.8% (sensitivity, 84.2%; specificity, 76.2%).

Individual brain responses were characterized by expression values in 11 channels with significant differences in the mean [oxy-Hb] during the [SST + post-SST] period between patients with ADHD and healthy adults (ch3, 13, 27, 28, 35, 38, 39, and 46–49).

The stepwise regression analysis selected 1 channel (ch13: right pre-SMA and right PMA) using the mean [oxy-Hb] during the [SST+post-SST] period ($P = 0.006$). The algorithm that used the mean [oxy-Hb] during the [SST + post-SST] period had a mean accuracy of 72.5% (sensitivity, 72.2%; specificity, 71.4%).

3.3.4. Additional analyses

There were no significant main effects in the results obtained for [deoxy-Hb] during the task or the [task + post-task] period, for either the SST or VFT tasks (see inline Supplementary material A. 2). In addition, the secondary group comparison (the ASDs subgroup with ADHD symptoms, the entire ADHD group, and the entire HC group) yielded statistical conclusions regarding clinical characteristics, behavioral results, and NIRS data results that were similar to those of the original group comparisons (see Inline Supplementary Table S3 and Supplementary material A. 3). There were no significant differences in NIRS data between male and female subjects during the task or the [task + post-task] period. Finally, for both the SST and VFT, there were no significant correlations between [oxy-Hb] changes during the task or the [task + post-task] period and clinical symptoms or task performance for either the ASDs or the ADHD group.

Inline Supplementary Table S3 can be found online at http://dx.doi.org/10.1016/j.nicl.2013.10.002.

4. Discussion

To our knowledge, this is the first study showing differences in prefrontal activation associated with inhibitory control between adults with ASDs and those with ADHD. We found more profound abnormalities in the PFC during inhibitory control in drug-naïve individuals with ASDs than in drug-naïve individuals with ADHD, despite similar performance levels. Although the ASDs group showed underactivation in the left VLPFC compared to the HC group, the ADHD group did not exhibit a significant decrease in VLPFC activation compared to the HC group. Significant differences between the ASDs and ADHD groups were found during the SST, even in comparisons between the ASDs subgroup with ADHD symptoms and the ADHD group. These differences in activation were localized to the left VLPFC. In contrast, there were no significant differences in [oxy-Hb] increases during the VFT between the ASDs and ADHD groups. The use of NIRS, a portable neuroimaging device, represented a strong advantage of our study. Therefore, our findings may be a step toward the development of a clinically useful biomarker for the differential diagnosis of the 2 commonest neurodevelopmental disorders, which has been difficult when based on clinical and neuropsychological measures.

4.1. Activation of [Oxy-Hb] in the left VLPFC

This study found significantly reduced activation in the left VLPFC in drug-naïve adults with ASDs compared to drug-naïve adults with ADHD (Figs. 4 and 5), which is consistent with the previously reported structural abnormalities in the left VLPFC of patients with ASDs, including reduced gray matter density (Yamasaki et al., 2010; Abell et al., 1999). The right dominant abnormalities observed in the ADHD group were consistent with the results of previous structural (Makris et al., 2007; Overmeyer et al., 2001) and fMRI studies performed during go/no-go (Casey et al., 2007) and stop tasks (Rubia et al., 1999; Hart et al., 2013). Our findings are also consistent with the results of fMRI studies showing dysfunction in this region during facial imitation (Dapretto et al., 2006; Bookheimer et al., 2008). Action mirroring is assumed to underlie the imitation of an observed action, social understanding, and communication with other people, and the mirroring system is a function of the VLPFC (Dapretto et al., 2006).

The reduced [oxy-Hb] increase observed in the left VLPFC of the ASDs group was inconsistent with the results of previous studies showing increased activation (Schmitz et al., 2006) or similar activation (Xiao et al., 2012) in this region for the ASDs group compared to that for the HC group during a go/no-go task. Thus, the SST load, as an inhibition task, may be higher than that of the go/no-go task (Rubia et al., 2001).

Furthermore, our previous study using NIRS during a go/no-go task found that activation under the no-go condition was lower than that under the go condition in the HC group (Nishimura et al., 2011), unlike the results of the present study. Therefore, the pattern of activation observed in the PFC during the SST may be different from that observed in a go/no-go task. The present results for the SST showed that the ASDs group might have a greater abnormality in the left VLPFC than the ADHD group. This result is consistent with the findings of a neuropsychological study reporting that children with ASDs had a more profound disability in inhibitory control than did children with ADHD (Corbett et al., 2009). An fMRI study performed in children showed that the DLPFC was significantly less activated in boys with ADHD than in those with ASDs during a sustained attention task (Christakou et al., 2012), which is in contrast with the activation pattern observed here. This might be because the task used in that study did not involve inhibitory controls.

The meaning of the [oxy-Hb] reascending observed in the left VLPFC in the ADHD group during the post-SST period remains unclear. However, patients with schizophrenia also showed a similarly robust [oxy-Hb] reascending during the post-task period of the VFT in previous NIRS studies (Suto et al., 2004; Takizawa et al., 2008). These results may be explained by a common dysfunction of the monoamine system in ADHD and schizophrenia, as the repertoire of ADHD-related genes resembles that of schizophrenia-related genes (Williams et al., 2010b; Burbach, 2010). In the present study, NIRS signal analyses that included the post-SST period distinguished the ASDs and ADHD groups better (Fig. 5). The classification accuracy observed between the ASDs and ADHD groups using [oxy-Hb] changes during the [SST + post-SST] period was also higher than the accuracy obtained using [oxy-Hb] changes only during the SST period. The high time resolution of NIRS enables detailed measurements of time-course changes, thus providing important insights into differences in inhibitory control during the SST between patients with ASDs and those with ADHD.

4.2. Differences between the HC and patient groups

Our results support the hypothesis that the ASDs group has lower activation in a broad prefrontal area (Figs. 4 and 5) relative to the HC group. The classification accuracy obtained using [oxy-Hb] changes between the ASDs and HC groups during both the SST and the [SST + post-SST] period was highest in the channels for the left VLPFC. These results are consistent with those of previous studies (Yamasaki et al., 2010; Abell et al., 1999). A previous fMRI study showed that compared to healthy adults, adults with ASDs had significantly lower task-related activation in the DLPFC during a spatial working memory task (Luna et al., 2002; Ohnishi et al., 2000; Smith et al., 2004; Rinehart et al., 2002). Further, compared to healthy children, children with autism also showed reduced activation in the right DLPFC and VLPFC during a novelty detection task (Gomot et al., 2006).

The fMRI study revealed that pre-SMA and PMA would show functional interconnectivity via the basal ganglia circuitry to mediate response execution or inhibition, whereas the VLPFC would influence the basal ganglia circuitry via connectivity with pre-SMA (Duann et al., 2009). The DLPFC, with its direct connections to the basal ganglia (Alexander et al., 1986), is part of a distributed neural network supporting the selection and suppression of motor responses (Garavan et al., 2002). The fMRI study on ASDs children showed that when using a go/no-go task, there was a significant negative correlation between age and 2 right VLPFC correlation pairs: right VLPFC–bilateral pre-SMA and right VLPFC–right caudate (Lee et al., 2009). Our study detected a dysfunction in the neural basis of inhibition in adults with ASDs in areas including the bilateral VLPFC, DLPFC, Pre-SMA, and PMA, when compared to healthy controls using the NIRS, although it was difficult to detect a dysfunction of the basal ganglia.

As hypothesized, compared to the HC group, the ADHD group showed underactivation of the right SMA, pre-SMA, and bilateral DLPFC during the SST. The classification accuracy obtained using [oxy-Hb] changes between the ADHD and the HC group during both the SST and the [SST + post-SST] period was highest in the channels for the right pre-SMA and right PMA. These results are consistent with those of previous studies on drug-naïve adult patients with ADHD (Cubillo et al., 2010; Rubia et al., 2011), which used fMRI to show reduced activation in the right PFC during the SST. We also found that the ADHD group had lesser activation than the HC group in the left DLPFC, which has been directly implicated in attention switching in normal adults (Smith et al., 2004). A recent meta-analysis showed that patients with ADHD have consistent functional abnormalities in 2 distinct domain-dissociated right hemispheric fronto-basal ganglia networks, the VLPFC, supplementary motor area, and anterior cingulate cortex for inhibition and the DLPFC, parietal, and cerebellar areas for attention (Hart et al., 2013). Regarding cortical surface areas that NIRS could measure, these results are consistent with our current study and a recent NIRS study of adults with ADHD, which used the SST to show reduced bilateral activation of the inferior frontal cortex in these individuals compared to healthy adults (Schecklmann et al., 2013).

Our observation of decreased frontal activation during the SST was in contrast to previous studies showing no abnormality of activation in patients with ADHD during a go/no-go task (Dibbets et al., 2009; Kooistra et al., 2010). This inconsistency may be related to task differences and MPH treatment history. Most of the patients included in those 2 previous studies (Dibbets et al., 2009; Kooistra et al., 2010) had been chronically medicated with MPH, and there is evidence of long-term effects of MPH on brain structure (Shaw et al., 2009) and brain function (Konrad et al., 2007).

4.3. Limitations

This study had several limitations. First, trying to differentiate two behaviorally defined psychiatric disorders by using biological markers may not be the final goal for the psychiatry, since the current diagnostic system is solely based on the categorization by behavior. Rather, future psychiatry should pursue comprehensive recapturing of the association between various dimensions of behavior and their biological basis. The importance of identified biomarkers in the current study should be interpreted in this context. For example, neuroimaging biomarkers may be more useful in making decision on the use of a certain pharmacological intervention for an individual patient, compared with the behaviorally categorized diagnosis per se, which should be clarified in future studies. Second, only 6 patients underwent structured interviews using the ADI-R, ADOS, and CAADID. Although we included other participants in this study only when at least 2 of the 3 trained child psychiatrists had seen patients and given consistent diagnoses, the inter-rater reliability for their evaluating psychiatrists was not established. Third, our study focused on adult subjects; thus, it is unclear whether our results can be extended to children with ASDs and ADHD. Fourth, the application of our results in clinical practice requires the replication of the findings in an independent sample. Fifth, the number of patients included in the subsample (patients having ASDs with ADHD symptoms: 10 participants) was smaller than the optimal sample size for neuroimaging (Carter et al., 2008). However, we found a significant difference in prefrontal activation between patients having ASDs with ADHD symptoms and those having ADHD. Although we also analyzed the correlation between [oxy-Hb] changes during the task or the [task + post-task] period and ASRS scores in addition to the analysis of this subsample using cut off score of ASRS, there were no significant correlations for either the ASDs or the ADHD group. Finally, because subjects were matched for IQ in each group and since IQ scores were relatively high, participants in our study may not be representative of all general patients. It is necessary that our data be replicated in a larger sample of participants.

4.4. Conclusions

In conclusion, the present study provides evidence of functional differences in activation in the left VLPFC between drug-naïve patients with ASDs and those with ADHD. Thus, the signal time course in the left VLPFC may be a diagnostic marker for distinguishing ADHD from ASDs. NIRS may be a candidate for an auxiliary diagnostic tool that is useful for both clinicians and patients.

Competing interests

Dr. Kiyoto Kasai reports the following financial relationship. The University of Tokyo and the Research and Developmental Center, Hitachi Medical Corporation, have had an official contract for a collaborative study on the clinical applications of near-infrared spectroscopy in psychiatric disorders, which has been approved by the Research Promotion Office, University of Tokyo Hospital. For the present study, the Hitachi Medical Corporation provided a project grant (JPY 300,000/year). Drs. Ayaka Ishii-Takahashi, Ryu Takizawa, Yuki Kawakubo, Hitoshi Kuwabara, and Kiyoto Kasai at the University of Tokyo and Shingo Kawasaki at the Hitachi Medical Corporation developed the "stimulus presentation device and stimulus task presentation method for optional measurement apparatus" described (patent no. 2008-146721, Japan; patent no. 12996190, United States of America; patent no. 09758336.3, European Union; and patent no. 20090120823.5, the People's Republic of China). The University of Tokyo transferred this patent to the Hitachi Medical Corporation, and the Hitachi Medical Corporation paid a transfer fee (JPY 100,000) to the University of Tokyo. The other authors report no conflicts of interest.

Role of the funding source

This study was supported in part by Grants-in-Aid for Scientific Research (innovative areas nos. 23118001 & 23118004 [Adolescent Mind & Self-Regulation] to KK; no. 23791309 to RT) and for the "Development

of Biomarker Candidates for Social Behavior" study carried out under the Strategic Research Program for Brain Sciences (to KK) by the MEXT. This study was also supported in part by Health and Labor Sciences Research Grants for Comprehensive Research on Disability Health and Welfare (H23-seishin-Ippan-002 to RT&YN&AI), the Japan Society for the Promotion of Science, KAKENHI (Grant-in-Aid for Young Scientists (B) no. 2479201 to AI)), an Intramural Research Grant for Neurological and Psychiatric Disorders of NCNP (no. 23-10 to RT&YN), and by the Japan Research Foundation for Clinical Pharmacology (to RT).

Author contributions

Ishii-Takahashi, M.D., Ph.D., had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Ishii-Takahashi, M.D., Ph.D., Kawakubo, Ph.D., Kasai, M.D., Ph.D. Acquisition of data: Ishii-Takahashi, M.D., Ph.D., Kawakubo, Ph.D., Kuwabara, M.D., Ph.D., Okuhata, Ph.D., Hamada, Med. Analysis and interpretation of data: Ishii-Takahashi, M.D., Ph.D., Hamada, Bed, Nishimura, Ph.D., Takizawa, M.D., Ph.D., Kawasaki, MS. Drafting of the manuscript: Ishii-Takahashi, M.D., Ph.D. Critical revision of the manuscript for important intellectual content: Nishimura, Ph.D. Takizawa, M.D., Ph.D., Matsubayashi, Ph.D., Yamasue, M.D., Ph.D., Kasai, M.D., Ph.D. Statistical analysis: Ishii-Takahashi, M.D., Ph.D., Nishimura, Ph.D., Takizawa, M.D., Ph.D., Kawasaki, MS. Obtained funding: Ishii-Takahashi, M.D., Ph.D., Takizawa, M.D., Ph.D., Nishimura, Ph.D., Kawakubo, Ph.D., Kasai, M.D., Ph.D. Administrative, technical, or material support: Kawasaki, MS. Study supervision: Kano, M.D., Ph.D., Kasai, M.D., Ph.D., Igarashi M.D., Ph.D. All contributors have approved the final version of the manuscript.

Acknowledgments

The authors would like to thank all the participants in this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.nicl.2013.10.002.

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Journal of Affective Disorders ∎ (∎∎∎∎) ∎∎∎–∎∎∎

Contents lists available at SciVerse ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Preliminary communication

The relationship between positive and negative automatic thought and activity in the prefrontal and temporal cortices: A multi-channel near-infrared spectroscopy (NIRS) study ☆

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ARTICLE INFO

Article history:
Received 1 May 2013
Accepted 24 May 2013

Keywords:
Major depressive disorder
Near-infrared spectroscopy
Automatic thought
State of mind model

ABSTRACT

Background: Recently, neurobiological studies of the cognitive model of depression have become vastly more important, and a growing number of such studies are being reported. However, the relationship between the proportion of positive and negative automatic thought and activity in the prefrontal and temporal cortices has not yet been explored. We examined the relationship between brain activity and the proportion of positive and negative automatic thought in patients with major depressive disorder (MDD), using multi-channel near-infrared spectroscopy (NIRS).

Methods: We recruited 75 individuals with MDD (36 females; mean age=39.23 ± 12.49). They completed the Hamilton Rating Scale for Depression, Automatic Thoughts Questionnaire-Revised, Japanese version of the National Adult Reading Test, and the State-Trait Anxiety Inventory. Brain activation was measured by 52-channel NIRS.

Results: We found that activation in the vicinity of the right superior temporal gyrus is related to a deviation to negative of the proportion of positive and negative thoughts in individuals with MDD. Left dorsolateral prefrontal cortex activity was higher in the group with comparatively frequent positive thought.

Limitations: Our participants were patients taking antidepressant medication, which is known to influence brain activity. Second, the poor spatial resolution of NIRS increases the difficulty of identifying the measurement position.

Conclusions: We found that activation of the prefrontal and temporal cortices is related to the proportion of automatic thoughts in the cognitive model of depression.

1. Introduction

Major depressive disorder (MDD) is one of the most common mental disorders, with a lifetime risk of approximately 9% for males and 17% for females (Hasin et al., 2005). MDD is diagnosed when a persistent and unreactive depressive mood and/or the absence of positive affect are accompanied by a range of symptoms, the number and combination of which needed to make a diagnosis are operationally defined (American Psychiatric Association, 2000). The effectiveness of treating MDD with cognitive behavioral therapy (CBT) has

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http://dx.doi.org/10.1016/j.jad.2013.05.067

been substantiated by a growing number of clinical intervention studies (e.g., Cuijpers et al., 2008; Dobson, 1989). For example, CBT was found to significantly reduce depressive symptoms in a meta-analysis of randomized controlled trials (Beltman et al., 2010).

One possible factor in CBT's effectiveness in treating depression is that MDD is characterized by enhanced negative information processing (e.g., Beck, 1976; Teasdale, 1985). Depressive patients have frequent negative automatic thoughts about themselves, their future, and the world (Beck, 1967); these automatic thoughts induce depressive mood states in the cognitive model of depression. Hollon and Kendall (1980) found that patients with MDD showed significantly greater numbers of negative automatic thoughts than non-MDD patients. Therefore, for CBT to be effective in treating depressive symptoms, it is important that automatic thoughts become more functional and positive (e.g., Furlong and Oei, 2002).

Recently, the effects of negative and positive cognition in MDD have been investigated. Ingram and Wisnicki (1988) found an inverse relationship between the frequency of positive thoughts and the level of dysphoria. In addition, Kendall (1983) suggested that an examination of both the positive and negative dimensions of cognition might contribute to a greater understanding of the psychopathology of MDD.

The state of mind (SOM) model was proposed as a model incorporating both positive and negative dimensions (Schwartz and Garamoni, 1986). The primary focus of the SOM model is the proportion of positive and negative thoughts, although overall frequency of thoughts has potential significance as well (Schwartz and Garamoni, 1989). The SOM model suggests that adaptive psychological functioning is characterized by an optimal proportion of positive and negative cognition (Schwartz and Garamoni, 1986). This model posits five states of mind: positive dialog, internal dialog of conflict, negative dialog, positive monologue, and negative monologue. They are defined by the SOM ratio (the ratio of positive cognitions to sum of positive and negative cognitions: *Positive cognitions/(positive cognition+negative cognition)*). Positive dialog is the internal dialog between positive and negative cognition (defined by an SOM ratio of $.62 \pm .06$), hypothesized as optimal for coping with stress. The internal dialog of conflict, defined by an SOM ratio of $.50 \pm .06$, is associated with mild levels of psychopathology. Negative dialog (defined by an SOM ratio of $.38 \pm .06$) is associated with moderate psychopathology. Positive monologue consists of all positive cognition and is defined by an SOM ratio of .69 or more, while negative monologue (all negative cognition) is defined by an SOM ratio of .31 or less; this is an indicator of extreme psychopathology (Schwartz and Garamoni, 1986). SOM ratios of patients with major depression were found to be approximately .35, therefore qualifying as negative dialog (Garamoni et al., 1991; Schwartz et al., 2002).

Some neuroimaging studies have suggested a deterioration in cognitive function in MDD (Disner et al., 2011; Noda et al., 2012). Disner et al. (2011) showed that the neurobiological mechanisms that putatively underlie cognitive biases in depression seem to be influenced by neurobiological processes and a diminishing of the top-down system. According to Disner et al. (2011), the neurobiological process is best attributed to a bottom-up pathway that begins in the amygdala and proceeds through the subgenual and anterior cingulate cortex, striatum, nucleus accumbens, and hippocampus to the prefrontal cortex (PFC). In fact, the attenuation in cognitive control seems to be region-specific, for example, the dorsolateral prefrontal cortex (DLPFC) for rumination and cognitive bias and the ventral lateral prefrontal cortex (VLPFC) for biased attention; this curbs the top-down relationship with the pertinent subcortical regions (Disner et al., 2011). Thus, executive functions such as cognitive control are thought to be important in emotion regulation, including the regulation of negative automatic thoughts in MDD.

Many neuroimaging studies of MDD use the verbal fluency task (VFT) to examine executive function (Matsuo et al., 2002; Okada et al., 2003). The VFT is a simple task frequently used in neuroimaging studies that is known to activate the PFC in healthy subjects (Alvarez and Emory, 2006; Frith et al., 1991; Schlösser et al., 1998). Previous studies have suggested that patients with MDD have a reduced response in the left PFC during the VFT (Okada et al., 2003). In addition, the VFT is useful in evaluating semantic memory functions inspired by specific verbal stimuli (Sumiyoshi et al., 2005) and in examining the statements made during the task (McGurk and Meltzer, 2000). Thus, the VFT could be used as a cognitive task to examine the information processing of automatic thoughts triggered by external environmental stimuli.

The VFT is often used in near-infrared spectroscopy (NIRS) studies of MDD. NIRS is a non-invasive optical technique that monitors hemodynamic changes related to cortical neural activity by measuring the concentrations of oxygenated hemoglobin (oxy-Hb) and deoxygenated hemoglobin (deoxy-Hb) in capillary blood vessels (Villringer and Dirnafl, 1995). Recent research suggested that reduced right frontal and temporal cortex activation visible by NIRS during the VFT is related to the severity of symptoms of MDD (Noda et al., 2012). Additionally, VFT can show significant differences between healthy controls and patients with MDD or bipolar disorder by the increases in oxy-Hb in the front-temporal regions (Kameyama et al., 2006; Matsuo et al., 2002; Pu et al., 2008; Suto et al., 2004). NIRS is frequently used with the VFT to examine the PFC (Suda et al., 2010). Because measurement via NIRS is conducted with the subject in a seated, natural posture, this is a low-invasive method that places few burdens on subjects. Therefore, NIRS is considered suitable for examining patients with psychiatric disorders such as MDD.

In the present study, given that cognitive function is important to emotion regulation in MDD, we hypothesized that a high SOM ratio (high positive automatic thought) in patients with MDD would activate the PFC, related to cognitive control, based on the findings of Disner et al. (2011). Thus, we examine the relationship between the ratio of positive and negative automatic thoughts and activity in the prefrontal and temporal cortices based on oxy-Hb changes as shown by multi-channel NIRS.

2. Methods

2.1. Participants

Seventy-five participants (36 females, 39 males; mean age$=$ 39.23 ± 12.49) were recruited from among in- and out-patients receiving treatment for MDD at the National Center of Neurology and Psychiatry in Japan. Participants had been diagnosed with MDD by experienced psychiatrists following the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (SCID: First et al., 1996; American Psychiatric Association, 2000). Participants were excluded based on remission status as defined by a score of 7 points or less on the Hamilton Rating Scale for Depression (HAMD; Hamilton, 1960). All participants were right-handed (as measured by the Edinburgh Handedness Inventory, Oldfield, 1971) native Japanese speakers with no history of head injury. This study was approved by the ethics committee of the National Center Hospital of Neurology and Psychiatry, and research was conducted in accordance with the Helsinki Declaration (as revised, 1989). Written informed consent was obtained from all participants after a complete explanation of the study.

2.2. Assessment of clinical symptoms and automatic thought

After NIRS scanning, all participants completed an assessment and clinical evaluation that utilized the following structured interview and questionnaires.

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2.2.1. Hamilton rating scale for depression (17-item version, HAMD)

The HAMD (Hamilton, 1960) was administered by experienced psychiatrists to assess the severity of participants' depressive symptoms. The HAMD separates the frequency of the depressive symptom from its intensity in most items, refines several problematic anchors, and integrates both a structured interview guide and consensus-derived conventions for all items.

2.2.2. Automatic thoughts questionnaire-revised (ATQ-R)

The ATQ-R (Kendall et al., 1989) measures the frequency of cognitive self-statements associated with depressed mood. The Japanese version of the ATQ-R (Kodama et al., 1994) includes 28 items on negative automatic thoughts (NAT) and 10 items on positive automatic thoughts (PAT). All items are scored on a 5-point Likert scale, with 1=*not at all* and 5=*all the time*. The validity and reliability of the Japanese version of the ATQ-R was demonstrated by Kodama et al. (1994).

2.2.3. The Japanese version of the national adult reading test (JART)

The National Adult Reading Test (NART, Nelson and Willison, 1991) was used to calculate an estimate of participants' verbal IQ. The Japanese version of the national adult reading test (JART) was developed by Matsuoka and Kim (2006). The JART is a widely accepted tool that has been found to have good reliability and validity (Matsuoka and Kim, 2006).

2.2.4. State-trait anxiety inventory (STAI)

The STAI (Spielberger, 1983) is a widely used self-report scale for the assessment of state and trait anxiety in research and clinical practice. The Japanese version of the STAI (Nakazato and Mizuguchi, 1982) includes 20 items on state anxiety (STAI-S) and 20 items on trait anxiety (STAI-T). All items are scored on a 4-point Likert scale, with 1=*not at all* and 4=*all the time*. Validity and reliability of the Japanese version of the STAI has been proven by Nakazato and Mizuguchi (1982).

2.3. NIRS Measurement

2.3.1. NIRS system

Brain activity was measured by near-infrared spectroscopy (NIRS). In this study, the NIRS measurements were performed using a 52-channel ETG-4000 Optical Topography System (Hitachi Medical Corporation, Tokyo, Japan). This machine uses two set wavelengths of near-infrared light (695 and 830 nm) to recognize form differences in the absorption spectrum, enabling the measurement of oxy-Hb and deoxy-Hb (Maki et al., 1995). The 17 emitter probes and 16 detector probes were plugged into a holder and arranged into a 3×11 array. The distance between the pair of emission and detector probes was 3.0 cm; the measuring area between each pair of detector probes was defined as a "channel" (ch).

Probes were placed on participants' frontal region. The lowest probes were positioned along the Fp1–Fp2 line in accordance with the international 10–20 system used in electroencephalography.

2.3.2. Activation task

Changes in hemoglobin concentration were measured during the VFT (Takizawa et al., 2008). The cognitive activation task was structured to include a 30-s pre-task period, a 60-s task period, and a 70-s post-task period. For the pre- and post-task baseline periods, participants were instructed to consecutively repeat five Japanese vowels (*a, i, u, e, o*) aloud. During the task periods, they were asked to generate as many Japanese words as possible that began with a designated syllable. The initial syllables were presented in counterbalanced order among the participants, with each syllable changing every 20 s (0–20 s:/to/,/na/,/a/; 20–40 s:/se/,/i/,/ki/; 40–60 s:/o/,/ta/,/ha/) during the 60-s task period. Participants' task performance was measured by the number of words generated during each 60-s task period.

2.3.3. Measurement parameters of NIRS data

The obtained data were analyzed using the integral mode. The pre-task baseline was established as the mean oxy-Hb level over the 10-s period immediately preceding the task period; the post-task baseline was defined as the mean over 5–50 s following the task period; the liner fitting between the pre- and the post-task baselines was applied to the data between the these two baseline measurements. We examined oxy-Hb in this study because the detection of oxy-Hb is generally reported to be the highest in sensitivity and reliability when using light (Tamura, 2002). Therefore, we calculated the average increase in oxy-Hb from baseline levels for each channel during the task period.

2.3.4. Measurement environment

Each participant was seated in a comfortable chair and instructed to remain still in order to prevent movement artifacts—specifically, no head movements, no strong biting, and no unnecessary eyebrow movement during the NIRS measurements. Data clearly containing motion artifacts, based on both our observations and the NIRS recording, were excluded from further analyses.

2.4. Statistical analysis

First, we calculated the proportion of positive and negative automatic thoughts according to the SOM model (Schwartz and Garamoni, 1986): *positive thought/(positive thought+negative thought)*. For our analysis, we considered the difference in the number of items, the score per item was used about a positive and negative each; higher scores indicate a greater number of positive automatic thoughts (PAT). Participants were classified into two groups depending on whether they scored ≥.5 SD above or below the mean of the SOM ratio: the High Positive group ($n=28$) and Low Positive group ($n=23$). The middle group (SOM ratio=$.34 \pm .11$; $n=24$) was excluded from our analysis.

We then conducted χ^2 tests for sex and age, and two-sample *t*-tests for education (year), verbal IQ, HAMD, and task performance to examine the differences in demographic data and clinical symptoms between the High Positive and Low Positive groups to identify factors affecting brain activity. We used paired *t*-tests to compare average change in oxy-Hb levels (task period – pre-task baseline period). We also compared the number of words generated during the VFT.

A one-way analysis of covariance (ANCOVA) was then performed, with participants' groups as the independent variable and the during-task oxy-Hb changes as the dependent variable; variables significantly different between groups were included as covariates. Finally, we performed a correlation analysis to investigate the relationship between brain activity on channels that differed significantly in the groups and the task performance and clinical index excluding depressive symptoms. All statistical analysis was performed using PASW for Windows (Release 18.0.3; SPSS Japan Inc., Tokyo, Japan).

3. Results

3.1. Participants' automatic thoughts and severity of depression

Mean scores and correlations of the NAT, PAT, SOM ratio, and HAMD in all participants are shown in Table 1. Mean scores of the SOM ratio across all subjects showed a value defined as *negative dialog*. We also observed a moderate negative correlation between SOM ratio and depression severity ($r=-.48$, $p<.001$).

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3.2. Increased activation from the baseline

In all participants, the average of oxy-Hb changes significantly increased in 50 channels between the baseline (pre-task period) and the task period (ch2–4, ch7, ch8, ch11–52, $p < .05$; ch1, ch9, ch10, $p < .10$) (Fig. 1).

3.3. Group characteristics

Demographic data and ATQ-R, HAMD, and STAI scores for each group of participants are shown in Table 2. There were no significant differences in sex, years of education, and verbal IQ, but significant differences were found in HAMD scores between the two groups ($t(49)=3.87$, $p<.01$: unbiased Hedges' $g=-1.07$, 95% CI [−1.66 to .48].): the Low Positive group was significantly higher than the High Positive group. In addition, we found a significant difference in age ($t(49)=3.15$, $p<.01$: unbiased Hedges' $g=.87$, 95% CI [.27–1.45]), revealing that participants in the High Positive group were significantly older than those in the Low Positive group.

3.4. Task performance

The number of words generated during the VFT did not differ significantly between the High Positive and Low Positive groups, $t(49)=1.59$, $p=.12$: unbiased Hedges' $g=.44$, 95% CI [−.12–1.00].

3.5. Differences in NIRS data by the proportion of positive and negative automatic thoughts

As shown in Figs. 2–4, the average of oxy-Hb change in the High Positive group was smaller than that in the Low Positive group at

Table 1
Descriptive statistics and correlations of automatic thoughts, SOM ratio and depression severity ($n=75$).

		Mean	[95% CI]	*SD*	1	2	3	4	5
1	ATQ-R total	94.35	[93.03 95.68]	32.91	–	−.55**	.98**	−.90**	.45**
2	PAT	19.88	[19.31 20.44]	5.97		–	−.40**	.83**	−.39**
3	NAT	113.80	[112.51 115.08]	30.87			–	−.83**	.43**
4	SOM ratio	.34	[.26 .41]	.11				–	−.48**
5	HAMD	17.12	[15.97 18.27]	6.15					–

Note: ATQ-R=Automatic Thoughts Questionnaire-Revised; PAT=Positive automatic thought; NAT=Negative automatic thought; SOM ratio=PAT/(PAT+NAT); HAMD=GRID-Hamilton Depression Rating Scale.

** $p<.01$.

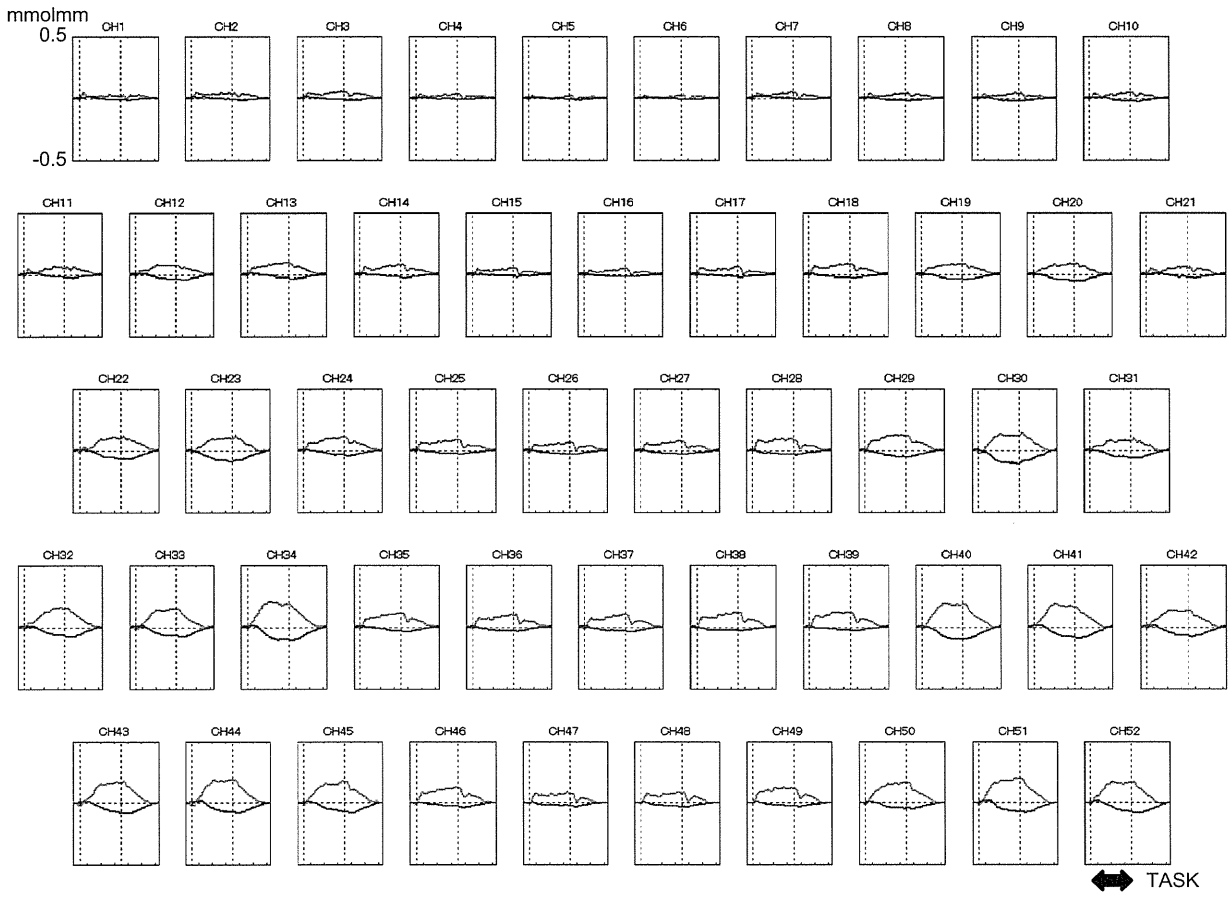

Fig. 1. The study sample ($N=51$) average of oxy-Hb (red line) and deoxy-Hb (blue line) during the 60-s Verbal Fluency Task (between the two dotted vertical lines in each graph) in 52 channels over the frontal and temporal regions as measured by NIRS. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

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Table 2
Characteristics of the participant's groups.

	High positive (n=23)		Low positive (n=28)		χ^2/t-Value	Unbiased Hedge's g [95% CI]
	Mean	SD	Mean	SD	df (49)	
Sex (M:F)	11:12		11:17		.38 *n.s.*	
Age	44.57	13.56	34.14	10.03	3.15**	.87 [.27 1.45]
Education (year)	14.13	2.65	13.96	1.95	.26 *n.s.*	.07 [−.48 .63]
Verbal IQ	103.46	11.66	102.93	9.91	.21 *n.s.*	.05 [−.50 .60]
HAMD	14.30	5.05	20.64	6.38	3.87**	−1.07 [−1.66 −.48]
Task performance	13.09	4.83	11.29	3.22	1.59 *n.s.*	.44 [−.12 1.00]

Note: HAMD=GRID-Hamilton Depression Rating Scale 17-item version; GAF=Global Assessment of functioning.
** $p<.01$.

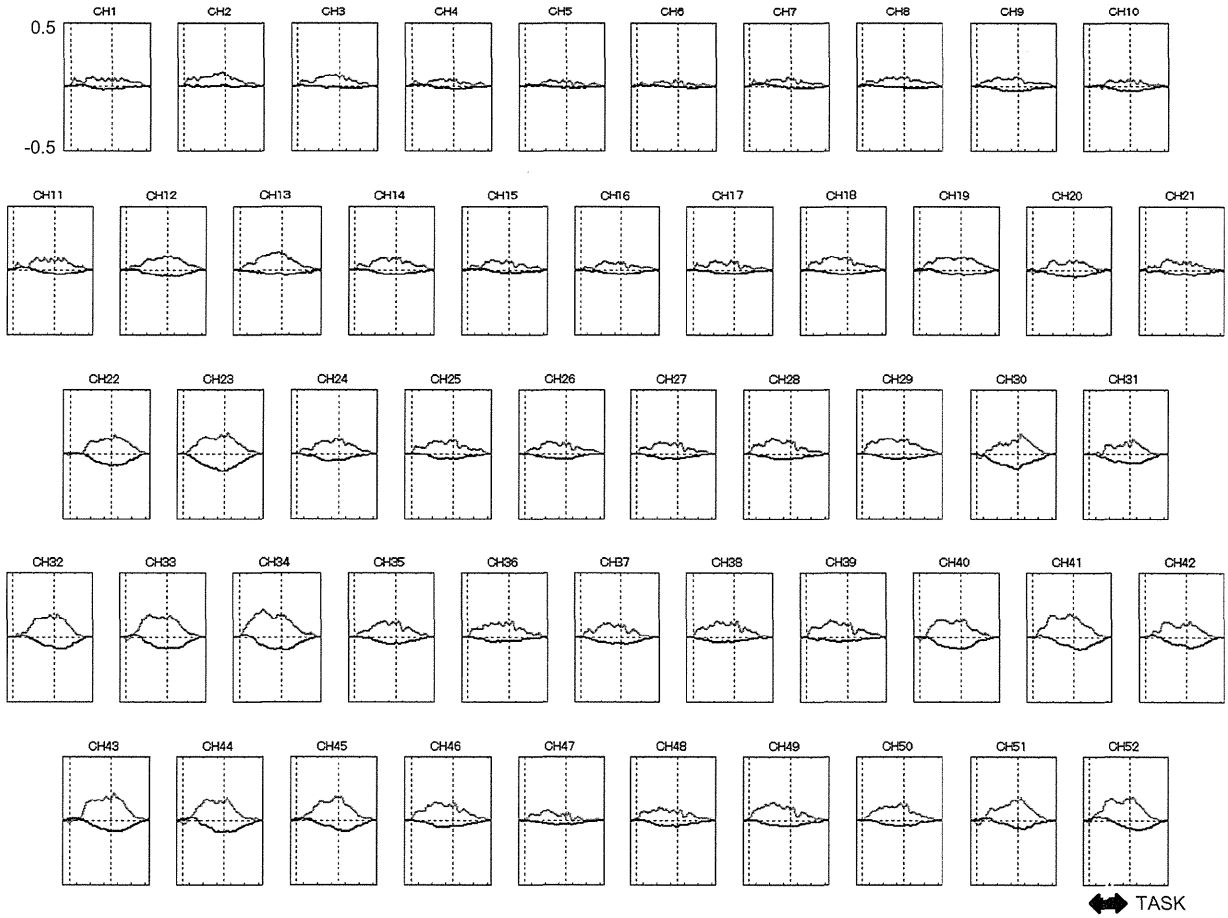

Fig. 2. The High Positive group (n=23) average of oxy-Hb (red line) and deoxy-Hb (blue line) during the 60-s Verbal Fluency Task. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

ch10 (F(1, 47)=2.98, $p<.10$: $\eta^2=.060$), ch11 (F(1, 47)=5.69, $p<.05$: $\eta^2=.114$), ch22 (F(1, 47)=4.09, $p<.05$: $\eta^2=.091$), and ch33 (F(1, 47)=3.28, $p<.10$: $\eta^2=.072$). In contrast, the average oxy-Hb change in the High Positive group was higher than that of the Low Positive group at ch28 (F(1, 47)=7.57, $p<.01$: $\eta^2=.139$). There were no significant differences among the other 48 channels.

3.6. Relationships Between brain activity in channels showing significant group differences, task performance, and clinical measurement

As shown in Tables 3 and 4, significant correlations were found between significantly different channels and the factors that may influence this difference. In the High Positive group, ch10, ch28, and ch33 showed significant positive and negative correlations with VFT performance (ch10: $r=-.58$, $p<.01$; ch28: $r=.47$, $p<.05$; ch33: $r=.48$, $p<.05$). However, in the Low Positive group, ch11 was significantly negatively correlated with STAI-S ($r=-.49$, $p<.05$).

4. Discussion

The purpose of this study was to examine differences in brain activity relevant to executive function according to the proportion of positive and negative automatic thoughts in patients with MDD, using NIRS. We classified participants into two groups based on their proportion of positive and negative automatic thoughts, and then compared brain activation in each channel between the two

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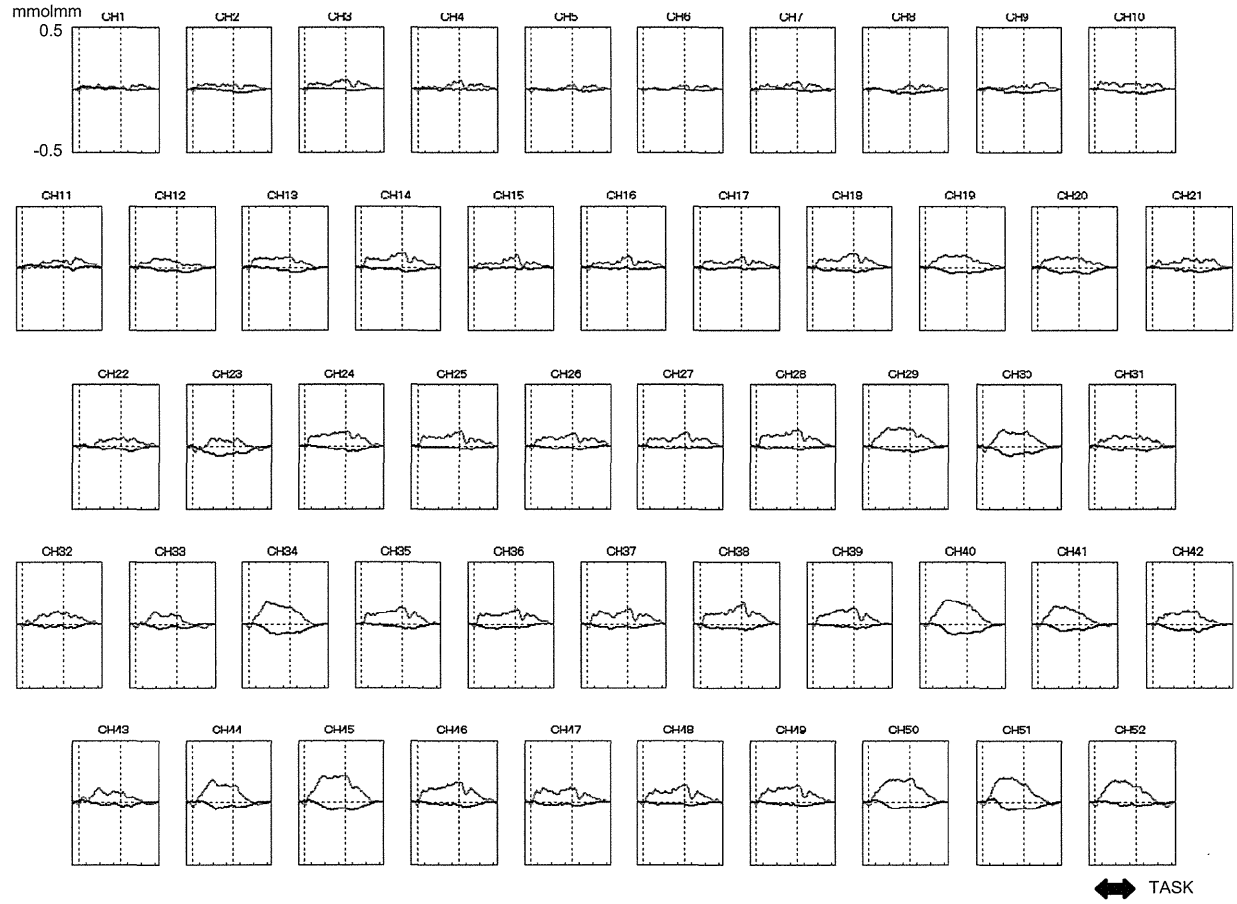

Fig. 3. The Low Positive group ($n=28$) average of oxy-Hb (red line) and deoxy-Hb (blue line) during the 60-s Verbal Fluency Task. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

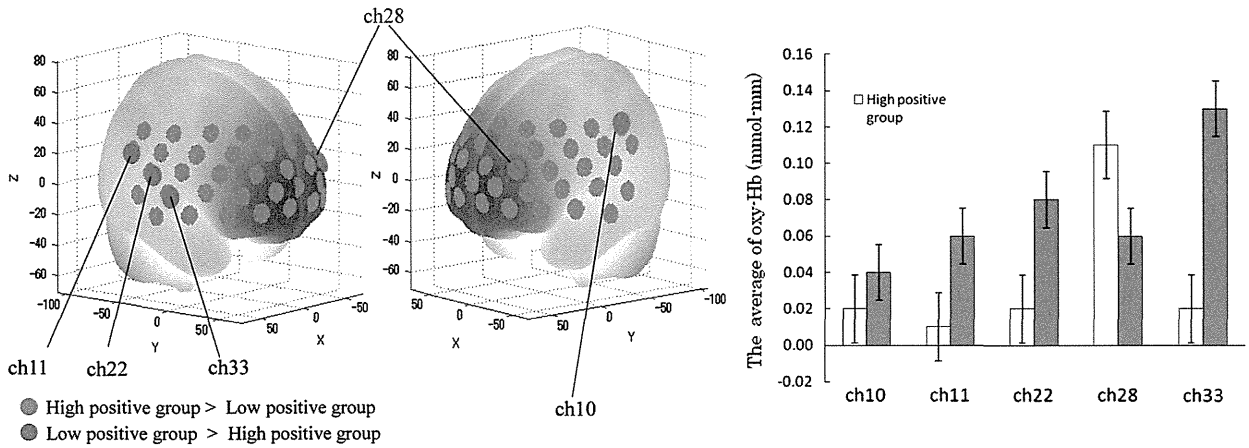

Fig. 4. Channels that differences were found in the average of [oxy-Hb] changes between the groups.

groups. In this study, participants with a high frequency of positive automatic thoughts showed lower activation in the right superior temporal gyrus (STG) than did those with a low frequency of positive automatic thoughts, whereas participants with a high frequency of positive automatic thoughts showed higher activation in the left dorsolateral prefrontal cortex (DLPFC) than those with a low frequency of positive automatic thoughts.

We found that activation in the vicinity of the right superior temporal gyrus (STG; ch11, 33: by Tsuzuki et al., 2007) is related to a deviation to negative in the proportion of positive and negative automatic thoughts in MDD. The right STG is known to be associated with negative emotional processing. Our findings are consistent with those of a meta-analysis of functional neuroimaging studies in MDD patients that found increased right STG activity in MDD patients compared to healthy controls during the presence of a negative emotional stimulus (Fitzgerald et al., 2008). This suggests that hyperactivity in the right STG is associated not only with the negative emotion itself but also with the imbalance in the proportion of negative automatic thought to all automatic thought.

In our study, however, participants with a high frequency of positive automatic thoughts showed higher activity in the left DLPFC than did those with a low frequency of positive automatic thoughts. The DLPFC is involved in cognitive abilities characterized

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Table 3
Correlations between significantly different channels and STAI-S, STAI-T, and VFT performance in High positive group ($n=23$).

	ch10	ch11	ch22	ch28	ch33
STAI-S	.06	−.03	.14	.17	.29
STAI-T	−.03	−.16	.05	.25	.08
VFT performance	−.58***	.14	.40†	.47*	.48*

Note: STAI-S=State Anxiety Inventory; STAI-T=Trait Anxiety Inventory; GAF=Global Assessment of Functioning ; VFT=Verbal Fluency Task

*** $p<.01$,
* $p<.05$,
† $p<.10$.

Table 4
Correlations between significantly different channels and STAI-S, STAI-T, and VFT performance in Low positive group ($n=28$).

	ch10	ch11	ch22	ch28	ch33
STAI-S	.05	−.49*	−.31	.08	−.15
STAI-T	.23	.08	.27	−.07	.19
VFT performance	.10	.36†	.11	−.14	−.08

Note: STAI-S=State Anxiety Inventory; STAI-T=Trait Anxiety Inventory; GAF=Global Assessment of Functioning ; VFT=Verbal Fluency Task.

* $p<.05$,
† $p<.10$.

as executive functions (e.g., working memory and attention capacity) that help maintain goals and predict the future consequences of behavior. A large number of studies have shown impaired executive function and other functional abnormalities in the DLPFC of patients with MDD (Snyder, 2012); for example, Elliott et al. (1997) found decreased activation in the DLPFC in patients with MDD. In addition, Henry and Crawford (2005) showed that patients with MDD were significantly impaired on all verbal fluency measures, using the VFT as a multifaceted executive function task. Thus, impaired executive function in MDD patients is well established in the literature. According to Davidson (1995), the left hemisphere is dominant for processing positive/approach emotions. This study also showed that individuals who experienced more positive than negative thought showed more activation in the left DLPFC. It has further been reported that hypoactivity in the left DLPFC is associated with rumination (Ray et al., 2005); it is reasonable to propose that individuals who experience more negative than positive automatic thought may be more likely to ruminate (Wells, 2008). Hypoactivity in the DLPFC is correlated with altered patterns of rostral anterior cingulate cortex (ACC) activity, which is thought to contribute to rumination by facilitating the inhibition of positive information and impeding the inhibition of negative information (Elliott et al., 2002). The presence of either decreased inhibition for negative emotion or increased inhibition for positive emotion predicts greater severity of depressive symptoms (Eugene et al., 2010). Together, these findings support ours regarding variations in activity in the left DLPFC as we observed between participant groups in this study.

Our study revealed the relationship between automatic thoughts and prefrontal and temporal cortex activity in MDD. Porto et al. (2009) hypothesized that CBT can improve the brain functionally. Specifically, if individuals' depressive symptoms are improved after CBT, their automatic thoughts will become more functional (Maag and Swearer, 2005; Matsunaga et al., 2010). Moreover, we can prove this functional improvement with NIRS: the averages of oxy-Hb in ch10, ch11, ch22, ch28, and ch33 show the change in the proportion of automatic thoughts. In the future, we will be able to verify the effectiveness of CBT with NIRS; this possibility has been anticipated in recent studies (Mayberg et al., 2005).

Nevertheless, the current study has a few limitations. First, the sample comprised patients with MDD under medical treatment; most patients were taking medication at the time of measurement. Factors such as antidepressant medication and the duration of the disorder can affect brain activity, thereby confounding our results. Second, NIRS has poor spatial resolution, which complicates the identification of the measurement position when using NIRS alone. We compensated for this by positioning a probe as demonstrated in previous studies (e.g., Kameyama et al., 2004), but cannot discount this fundamental limitation of the method. We expect that the development of new measurement technology will eliminate this issue in the future.

In this study, we revealed that activity in the prefrontal and temporal cortices is related to the proportion of automatic thoughts in the cognitive model of depression. Our findings suggest the possibility of considering the dysfunction of a top-down system to a cerebral emotions region as a biological base of the cognitive model of depression. Findings such as these can contribute to promote a more accurate understanding of depression.

Role of funding source

This work was supported by MEXT KIBANKEISEI (2010) from the Ministry of Education, Culture, Sports, Science, and Technology of Japan, Health and Labor Sciences Research Grants (Comprehensive Research on Disability, Health, and Welfare), an Intramural Research Grant for Neurological and Psychiatric Disorders of NCNP (no. 23-10), and Health and Labor Sciences Research Grants for Comprehensive Research on Disability, Health and Welfare (H22-seishin-ippan-001 and H23-seishin-ippan-002).

Conflict of interest

All the authors declare that they have no conflicts of interest with respect to this study or its publication.

Acknowledgments

The authors thank all the participants in this study.

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Please cite this article as: Koseki, S., et al., The relationship between positive and negative automatic thought and activity in the prefrontal and temporal cortices: A.... Journal of Affective Disorders (2013), http://dx.doi.org/10.1016/j.jad.2013.05.067