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Lower prefrontal activity in adults with obsessive–compulsive disorder as measured by near-infrared spectroscopy

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ABSTRACT

Recent developments in near-infrared spectroscopy (NIRS) have enabled the non-invasive elucidation of the neurobiological underpinnings of psychiatric disorders. Functional neuroimaging studies in human patients have suggested that the frontal cortex and subcortical structures may play a role in the pathophysiology of obsessive–compulsive disorder (OCD). Here we used NIRS to investigate neurobiological function in 12 patients with OCD and 12 age- and sex-matched, healthy control subjects. The relative concentrations of oxyhemoglobin (oxy-Hb) were measured with prefrontal probes every 0.1 s, during performance of a Stroop color-word task, using 24-channel NIRS. Oxy-Hb changes in the prefrontal cortex of the OCD group were significantly smaller than those in the control group, especially in the left lateral prefrontal cortex. These results suggest that patients with OCD have reduced prefrontal hemodynamic responses as measured by NIRS.

1. Introduction

Obsessive–compulsive disorder (OCD) is one of the most common mental disorders in the general population, with a prevalence rate of 2% to 3% (Weissman et al., 1994). The main clinical manifestations in OCD patients are recurrent, intrusive, and distressing thoughts and/or repetitive behaviors, resulting in significantly impaired occupational and social functioning (Koran et al., 1996). However, while the clinical manifestations are well-characterized, the neurobiological mechanisms responsible for the disorder remain unknown.

It has been hypothesized that the cortico-striato-thalamic circuits play a key role in the pathophysiology of OCD (Menzies et al., 2008). Studies of OCD patients using positron emission tomography (PET) have identified abnormally high, functional activity in localized regions of the brain, including the orbitofrontal cortex, anterior cingulate cortex, and caudate nucleus (Baxter et al., 1987; Swedo et al., 1989a, 1989b). In addition, studies of OCD patients using single photon emission computed tomography (SPECT) indicate dysfunction of the orbitofrontal cortex and caudate nucleus (Busatto et al., 2000; Machlin et al., 1991). Whiteside et al. (2004) performed a meta-analysis of PET and SPECT findings and reported consistent abnormalities in the orbital gyrus and the head of the caudate nucleus in OCD patients. In another meta-analysis of functional magnetic resonance imaging (fMRI) findings in OCD patients, Menzies et al. (2008) found consistent abnormalities in the orbitofrontal cortex and striatum as well as other areas. Many studies have reported the dysfunction of the prefrontal cortex, it is possible that OCD patients have abnormal prefrontal hemodynamic responses.

Functional brain imaging methodologies such as PET, SPECT, and fMRI have the disadvantage of requiring large apparatuses, which prevents their use in a bedside setting for diagnostic and treatment purposes. Furthermore, these functional brain imaging methodologies do not offer high time resolutions. In contrast, multi-channel near-infrared spectroscopy (NIRS) systems have recently been developed to allow non-invasive and bedside functional mapping of the cerebral cortex, with high time resolution (Koizumi et al., 1999; Maki et al., 1995; Yamashita et al., 1996).

NIRS is a method that enables functional imaging of brain activity (Villringer and Chance, 1997). It measures changes in the concentration of oxy-hemoglobin (oxy-Hb) and deoxy-hemoglobin (deoxy-Hb), and changes in the redox state of cytochrome c oxidase by their different specific spectra in the near-infrared range between 700 and 1000 nm.

Abbreviations: OCD, obsessive–compulsive disorder; NIRS, near-infrared spectroscopy; Hb, hemoglobin; PET, positron emission tomography; SPECT, single photon emission computed tomography; fMRI, functional magnetic resonance imaging; ADHD, attention deficit hyperactivity disorder; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; SCID, Structured Clinical Interview for DSM-IV Axis I Disorders Patient Edition; SCID-NP, Structured Clinical Interview for DSM-IV Axis I Disorders Non-Patient Edition; FIQ, full-scale intelligence quotient; Y–BOCS, Yale–Brown Obsessive–Compulsive Scale; MOCI, Maudsley Obsessive–Compulsive Inventory; SCWC-1, Stroop color-word task number of correct answers for the first presentation; SCWC-2, Stroop color-word task number of correct answers for the second presentation; SCWC-3, Stroop color-word task number of correct answers for the third presentation.

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Because of neurovascular coupling (Gratton et al., 2001; Villringer and Dirnagl, 1995), brain activation leads to an increase in cerebral blood flow without a proportionate increase in oxygen consumption, and, consequently, to an increase in the concentration of oxy-Hb and a decrease in the concentration of deoxy-Hb (Villringer and Chance, 1997).

NIRS is a neuroimaging modality that is especially suitable for psychiatric patients for the following reasons (Matsuo et al., 2003). First, because NIRS is relatively insensitive to motion artifact, it can be used in experiments that might cause some motion in the subjects, such as those requiring the subject to produce a vocalization. Second, the subject can be examined in a natural sitting position, without any surrounding distractions. Third, the cost of this technique is much lower than other neuroimaging modalities, and implementing this procedure is relatively easy. Fourth, the high temporal resolution of NIRS is useful in characterizing the time course of prefrontal activity in psychiatric disorders (Kameyama et al., 2006; Suto et al., 2004). Accordingly, NIRS has been used to assess brain functions in many psychiatric disorders, including schizophrenia, bipolar disorder, depression, dementia, post-traumatic stress disorder, pervasive developmental disorders, and attention deficit hyperactivity disorder (ADHD) (Fallgatter et al., 1997; Kameyama et al., 2006; Kubota et al., 2005; Kuwabara et al., 2006; Matsuo et al., 2003; Negoro et al., 2010; Suto et al., 2004). In the context of OCD, Ota et al. (in press) examined reduced prefrontal hemodynamic responses in pediatric OCD children as measured by NIRS. Moreover, they determined cerebral hemodynamic changes in response to the Stroop color-word task in 12 OCD children and 12 healthy age- and sex-matched controls. They found that oxy-Hb changes in the control group were significantly larger than those in the OCD group in the prefrontal cortex, especially in the frontopolar cortex, during the Stroop color-word task.

To our knowledge, however, there are no reports of prefrontal hemodynamic responses in adult OCD patients as measured by NIRS. Previous studies have discussed whether the neural bases of adult OCD are similar to those of pediatric OCD (Kalra and Swedo, 2009; Maia et al., 2008). Previously published studies on OCD patients using SPECT have suggested that early-onset OCD cases show decreased regional cerebral blood flow in the right thalamus, left anterior cingulate cortex, and bilateral inferior prefrontal cortex, compared to late-onset subjects (Busatto et al., 2001). Few studies have provided evidence for pathophysiological distinct subtypes of OCD that vary in symptoms present in childhood versus those that emerged de novo, in adulthood (Busatto et al., 2001; Eichstedt and Arnold, 2001; Geller et al., 1998). Another resting state SPECT study suggested that the regions of dysfunction in pediatric OCD were largely consistent with those in adult OCD (Diler et al., 2004). Based on another study using NIRS in pediatric OCD patients, and previous studies using other neuroimaging techniques that showed dysfunction of the prefrontal cortex, we hypothesized that adult OCD patients have reduced prefrontal hemodynamic response as measured by NIRS, as well as pediatric OCD patients. Thus, in the present study, we used similar design that was used in pediatric OCD patients, i.e., we used multi-channel NIRS to examine the characteristics of prefrontal cerebral blood volume changes during the Stroop color-word task in adult OCD patients, and in age- and sex-matched control subjects.

2. Methods

2.1. Subjects

Twelve subjects (7 males and 5 females) aged 19–50 years and diagnosed with OCD, according to the DSM-IV-TR [American Psychiatric Association, 2000], were compared with 12 age-, sex-, and intelligence quotient (IQ)-matched healthy control subjects (7 males and 5 females) (Table 1).

The subjects with OCD were recruited from the outpatient units of the Department of Psychiatry at Nara Medical University. They underwent a standard clinical assessment comprising a psychiatric evaluation, a structured diagnostic interview (Structured Clinical Interview for DSM-IV Axis I Disorders Patient Edition; SCID), and a medical history evaluation under the supervision of an experienced psychiatrist. Two experienced psychiatrists confirmed the diagnosis of OCD in each patient. Of the subjects with OCD, none had comorbid major depressive disorder, schizophrenia, or bipolar disorder. One subject had comorbid social anxiety disorder. Patients who presented with a neurological disorder, a head injury, a serious medical condition, or a history of substance abuse/dependence were excluded. Intelligence was assessed using the Wechsler Adult Intelligence Scale — Third Edition by a trained psychologist, and patients whose full-scale IQ (FIQ) scores were below 70 were excluded. Two of the 12 OCD patients selected for the study were not medicated for the disorder (hereafter, drug naive), whereas the remaining 10 subjects were receiving medication for OCD symptoms (six, fluvoxamine; two, paroxetine; two, clomipramine). We then used factor analysis, developed by Leckman et al. (1997), to categorize the patients by symptom subtypes. The individual symptom subtypes included contamination and cleaning (33.3%, n = 4), obsessions and checking (41.7%, n = 5), symmetry and ordering (16.7%, n = 2), and hoarding (8.3%, n = 1).

Healthy control subjects were recruited through local print advertising, and 15 participants were recruited in this study. They also underwent a standard clinical assessment comprising of psychiatric evaluation, a structured diagnostic interview (Structured Clinical Interview for DSM-IV Axis I Disorders Non-Patient Edition; SCID-NP), and an evaluation of medical history by an experienced psychiatrist. Intelligence was assessed using the Wechsler Adult Intelligence Scale — Third Edition by a trained psychologist. Three participants were excluded as they did not meet the assessment criteria. Therefore, a total of 12 healthy subjects who did not have OCD and had no history or symptoms of psychiatric or neurological disorders were enrolled in the present study.

All subjects were right-handed and Japanese. Ethical approval for the present study was obtained through the Nara Medical University, and written informed consent was obtained from all subjects before the study.

2.2. Assessment of OCD symptoms

The Yale–Brown Obsessive–Compulsive Scale (Y–BOCS) (Nakajima et al., 1995) and the Maudsley Obsessive–Compulsive Inventory (MOCI) (Sánchez-Meca et al., 2011) were used to evaluate symptoms in the subjects with OCD.

The Y–BOCS is a well-accepted 10-item semi-structured clinician-rated instrument designed to assess the presence and severity of current OCD symptoms. The MOCI is a self-administered questionnaire with a true-false question format that was developed for evaluating the types

Table 1
Characteristics of the subjects.

	OCD mean(SD)	Control mean(SD)	p-value
Number[sex ratio: M:F]	12[7:5]	12[7:5]	1.00
Age (years)	32.1(10.0)	33.0(9.2)	0.81
Age of onset (years)	21.9(6.3)	NA	NA
Duration of illness (years)	11.8(8.1)	NA	NA
FIQ(WAIS-III)	92.0(19.5)	90.5(12.1)	0.83
Y–BOCS	24.5(3.5)	NA	NA
MOCI	16.7(4.4)	4.6(3.1)	<0.001
SCWC-1	44.0(11.2)	46.4(10.2)	0.58
SCWC-2	45.3(9.9)	48.0(12.3)	0.55
SCWC-3	49.0(11.8)	52.9(12.3)	0.43

Group differences tested with *t*-tests.
F, female; FIQ (WAIS-III), Full scale IQ score of the Wechsler Adult Intelligence Scale -Third Edition; M, male; MOCI, Maudsley Obsessional–Compulsive Inventory; NA, not applicable; OCD, Obsessive–compulsive disorder; SCWC-1, Stroop color-word task number of correct answers first time; SCWC-2, Stroop color-word task number of correct answers second time; SCWC-3, Stroop color-word task number of correct answers third time; Y–BOCS, Yale–Brown Obsessive–Compulsive Scale.

of obsessive–compulsive symptoms that are present (score = 1) or absent (score = 0) in the patient and for discriminating obsessive patients from other neurotic patients or healthy subjects. Whereas OCD subjects were assessed using the Y–BOCS and MOCI, control subjects were assessed using only the MOCI (Table 1) on the same day that they underwent NIRS.

2.3. The Stroop color-word task

In the present study, we reproduced the Stroop task according to a method described earlier (Goldman, 1975). The Stroop task consisted of two pages. The items on the first page included the color words RED, GREEN, and BLUE in black ink. The items on the second page included the words RED, GREEN, and BLUE printed in red, green, or blue ink, with the limitation that the word and ink could not match. On the two pages, the items were randomly distributed, except that no item within a column could follow itself.

Before administering the task, the examiners provided the subjects the following instructions: "These are tests of how quickly you can read the words on the first page, and say the colors of the words on the second page. After you have read the paper for 45 s, we will turn the page. Then you will read the turned paper again. And we will repeat this process with you."

We combined these two pages and made the Stroop color-word task simpler and easier. The entire sequence of the Stroop color-word task consisted of a 45-s task (p1), a 45-s task (p2) presented and was repeated three times , followed by the 45-s, p1 task. We designated the 45-s, p1 task as the baseline task. We counted the number of correct answers for each task and also evaluated the task performance. We named these counts the Stroop color-word task number of correct answers for the first presentation (SCWC-1), second presentation (SCWC-2), and third presentation (SCWC-3). The design – a word-reading task (baseline task) and an incongruent color-naming task (activation task) – was intended to be as easy as possible while meeting NIRS study requirements. A Stroop color-word task was simply used because activity in the inferior frontal gyrus is strongly related to Stroop interference (Laird et al., 2005), and the same task was used in a previous NIRS study of pediatric OCD subjects (Ota et al., in press), thus allowing a direct comparison of results between studies.

2.4. NIRS measurements

Oxy-Hb increases and deoxy-Hb decreases as measured by NIRS have been shown to reflect cortical activation. In animal studies, oxy-Hb has been shown to be the most sensitive indicator of regional cerebral blood flow, because the direction of change in deoxy-Hb is determined by the degree of change in venous blood oxygenation and volume (Hoshi et al., 2001). Therefore, we decided to focus on changes in oxy-Hb. In this study, oxy-Hb was measured with a 24-channel NIRS machine (Hitachi ETG-100, Hitachi Medical Corporation, Tokyo, Japan), by determining the absorption of two wavelengths of near-infrared light (760 and 840 nm). Oxy-Hb was calculated as previously described (Schweitzer et al., 2000). The inter-probe intervals of the machine were 3.0 cm, and it was determined that the machine measures points 2–3 cm beneath the scalp, which is the depth of the surface of the cerebral cortices (Toronov et al., 2001).

The subjects maintained a natural sitting position during the NIRS measurements. The NIRS probes were placed on the subject's prefrontal regions, and arranged to measure the relative concentrations of Hb changes at 24 measurement points in an 8×8 cm area. The lowest probes were positioned along the Fp1–Fp2 line, according to the international 10/20 system used in electroencephalography. The probe positions and measurement points on the cerebral cortex were confirmed by overlaying the probe positions on a three-dimensionally reconstructed MRI scan of the cerebral cortex of a representative subject in the control group (Fig. 1(A)). The absorption of near-infrared light was measured with a time resolution of 0.1 s. The data were analyzed using the "integral mode." The pre-task baseline was determined as the mean during the 10 s immediately preceding the task performance and the post-task baseline was determined as the mean during the 25 s immediately following completion of the task. Linear fitting was performed on the data between the two baselines. Moving average methods (moving average window, 5 s) were used to exclude short-term motion artifacts in the analyzed data.

We tried to minimize motion artifacts by closely monitoring subjects and by instructing them to avoid artifact-evoking body movements, such as neck movements, strong biting, and blinking. Particular attention was paid to blinking because it was identified as the most influential source of motion artifacts in a preliminary artifact-evoking study. Examiners who were blind to the diagnoses of the subjects evaluated the NIRS results.

2.5. Statistical analyses

Oxy-Hb changes were compared between each of the two groups with Student's *t*-tests, using the grand averages of waveforms every 0.1 s in each channel. This analysis enabled more detailed comparison of oxy-Hb changes along the time course of the task. Data analyses were conducted using MATLAB 6.5.2 (Mathworks, Natick, MA, USA) and Topo Signal Processing type-G version 2.05 (Hitachi Medical Corporation, Tokyo, Japan). OT-A4 version 1.63 K (Hitachi Medical Corporation, Tokyo, Japan) was used for the overlapping display of the grand average waveforms in both groups shown in Fig. 1(B). Since we performed 24 paired *t*-tests, the correction for multiple comparisons was made using Bonferroni correction. PASW Statistics 18.0 J for Windows (SPSS, Tokyo, Japan) was used for the statistical analyses.

3. Results

3.1. Demographic data

Demographic and clinical data are shown in Table 1. Age, sex and FIQ did not differ significantly among patients with OCD and healthy controls ($t = -0.23$, $df = 22$, $P = 0.81$/ $\chi^2 = 1$, $df = 1$, $P = 1.00$/ $t = 0.21$, $df = 22$, $P = 0.83$). The mean Y–BOCS score of OCD subjects was 24.5 (SD, 3.5; range, 19 to 31), the mean MOCI score of OCD subjects was 16.7 (SD, 4.4; range, 9 to 23), and the mean MOCI score of control subjects was 4.6 (SD, 3.1; range, 1 to 12). There were significant differences in the mean MOCI score between the two groups ($t = 7.60$, $df = 22$, $P < 0.001$). There were no significant differences in the SCWC-1, SCWC-2, and SCWC-3 scores between the two groups ($t = -0.55$, $df = 22$, $P = 0.58$/ $t = -0.59$, $df = 22$, $P = 0.55$/ $t = -0.79$, $df = 22$, $P = 0.43$).

3.2. Correlation between Stroop task performance and subject characteristics

Spearman's ρ correlations between the SCWC scores and the age, IQ, Y–BOCS scores, and MOCI scores can be seen in Table 2. In the OCD subjects, there was a positive correlation observed between the SCWC-1/ SCWC-3 scores and FIQ (Spearman's $r = 0.672/0.685$, $P < 0.05$). Negative correlation was observed between the SCWC-1/ SCWC-2 scores and Y–BOCS scores (Spearman's $r = -0.642/-0.586$, $P < 0.05$), and no correlations between the SCWC scores and MOCI scores was observed. In the control group, there were no significant correlations between the SCWC scores and age, FIQ, and MOCI scores. We also examined the correlation between the prefrontal hemodynamic responses and the SCWC scores. However, there was no significant correlation observed between the two values.

3.3. NIRS data from the subjects performing the Stroop color-word task

The grand average waveforms of oxy-Hb concentration changes during the Stroop color-word task in both groups can be seen in Fig. 1(B). Group differences were tested by multiple comparison test

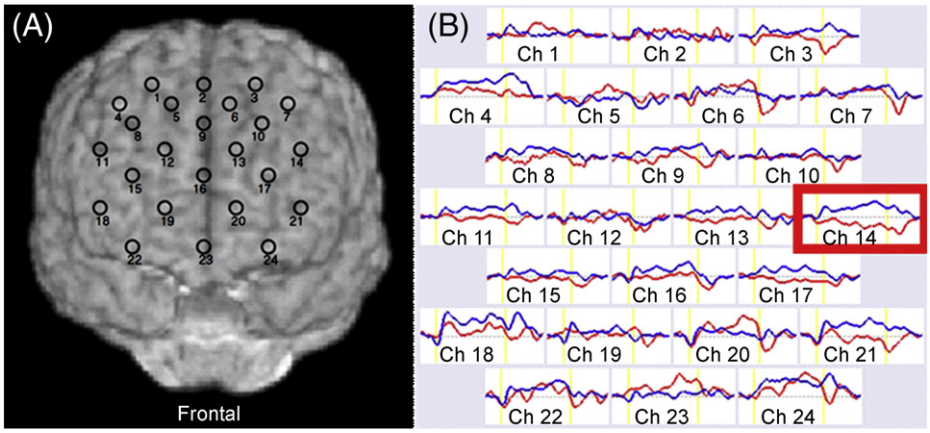

Fig. 1. (A) Cortical projection indicating the position of the 24 near-infrared spectroscopy (NIRS) measurement points (channels). The points were mapped onto anatomical frontal lobes using MRIcro software (MRIcro: developed by Dr. Chris Rorden, available at http://www.mricro.com). (B) Comparison of NIRS waveforms (changes in oxy-Hb concentration) between OCD and control groups during the Stroop color-word task for each of the 24 recording channels. Lines represent the grand averages of oxy-Hb waveforms recorded in the OCD (red lines), and control groups (blue lines). The vertical yellow lines indicate the start and end of Stroop task. Significant region is shown in red frame (Ch14). (Group differences were tested by multiple comparison test using Bonferroni correction. *P<0.002.).

using Bonferroni correction. The grand average waveforms of oxy-Hb concentration changes in the control group increased during the task period. On the other hand, those of the OCD group did not markedly change. Between the task period and the post-task period, the mean oxy-Hb difference in the OCD group was significantly smaller than that of the control group as measured at channel 14 ($t = -3.88$, $df = 19$, $P <$ Bonferroni-corrected $P = 0.002$). Topographic presentation of the t-value of oxy-Hb comparison between the control group and the OCD group during the Stroop color task can be seen in Fig. 2. The oxy-Hb changes in the control group were significantly greater than those in the OCD group during the task period in the prefrontal cortex.

4. Discussion

To our knowledge, this is the first NIRS study to examine prefrontal hemodynamic responses in adult subjects with OCD. In the prefrontal cortex, we found that oxy-Hb changes in OCD patients during the Stroop color-word task were significantly smaller than those in healthy control subjects. Therefore, the present study supported our hypothesis that prefrontal dysfunction is associated with adult OCD. This is consistent with findings from other imaging modalities, such as PET, SPECT, and fMRI, and with NIRS findings in pediatric OCD subjects.

In an fMRI study, Nakao et al. (2005a, 2005b) reported that OCD patients showed weaker activation than normal controls in the dorsolateral prefrontal cortex, anterior cingulate cortex, and caudate nucleus. In a PET study, Martinot et al. (1990) reported that absolute regional cerebral glucose metabolic rates in the lateral prefrontal cortex were significantly lower in OCD patients than in normal control subjects. In a SPECT study, Busatto et al. (2001) reported that late-onset OCD patients showed reduced regional cerebral blood flow in the orbitofrontal cortex. Ota et al. (in press) examined prefrontal hemodynamic responses in response to a Stroop color-word task in 12 OCD children and 12 healthy age- and sex-matched controls using NIRS. They found that oxy-Hb changes in the OCD group during the Stroop color-word task were significantly smaller than those in the control group, especially in the frontopolar cortex.

In the present study, we found that oxy-Hb changes in the prefrontal cortex of 12 OCD patients, during the Stroop color-word task, were significantly smaller than those in 12 healthy controls in, especially in the left lateral prefrontal cortex. Interestingly, prefrontal hemodynamic responses are smaller in adult OCD as well as pediatric OCD, but the region in which these attenuated prefrontal hemodynamic response occur are different between adults and pediatric subjects. The results of the present study may be related to differences in the neurobiology of adult and pediatric OCD (Kalra and Swedo, 2009).

Pediatric OCD more commonly occurs in boys than in girls, with a ratio of occurrence of 2–3:1 (Leonard et al., 1992). This ratio reverses in adult OCD, with a male-to-female ratio of 1:1.35 (Castle et al., 1995). In addition, pediatric subjects with OCD have a higher rate of comorbid ADHD and tic disorder (Swedo et al., 1989a, 1989b), a higher frequency of compulsions not preceded by obsessions (Geller et al., 1998), and a greater genetic contribution to the disease, as shown in mono- and dizygotic twin studies (Pauls et al., 1995). Studies of OCD patients using SPECT have suggested that early-onset OCD cases show decreased regional cerebral blood flow in the right thalamus, left anterior cingulate cortex, and bilateral inferior prefrontal cortex, relative to late-onset subjects (Busatto et al., 2001). Some studies have provided evidence for pathophysiologically distinct subtypes of OCD that vary in regard to the symptoms that present in childhood versus those that emerged de novo, in adulthood (Busatto et al., 2001; Eichstedt and Arnold, 2001; Geller et al., 1998). Therefore, there may be neurobiological differences between adult and pediatric OCD, providing one possible explanation for the different localization of prefrontal dysfunction between adult and pediatric OCD.

Alternatively, the results of the present study may be related to cortical development during childhood through adulthood. Flechsig (1901) elucidated the details of the myelination process in the cerebrum of humans, identifying 45 separate cortical areas and mapping the cerebral cortex using the myelination pattern. The first cortical region to myelinate is in the motor cortex, the second is the olfactory cortex, and the third is part of the somatosensory cortex. Next, myelination occurs in the frontopolar cortex, anterior cingulate cortex, inferior temporal cortex, and lastly, the dorsolateral cortex. Gogtay et al. (2004) reported that frontal-lobe maturation progressed in a back-to-front direction, beginning in the primary motor cortex (the precentral gyrus) and spreading anteriorly over the superior and inferior frontal gyri, with the prefrontal cortex developing last. Conversely, the frontal pole matured at

Table 2
Correlations between Stroop task and characteristics of the subjects.

	OCS			Control		
	SCWC-1	SCWC-2	SCWC-3	SCWC-1	SCWC-2	SCWC-3
Age	0.127	0.025	0.172	−0.211	0.046	0.384
FIQ(WAIS-III)	0.672*	0.575	0.685*	−0.011	−0.168	0.028
Y-BOCS	−0.642*	−0.586*	−0.422	NA	NA	NA
MOCI	−0.325	−0.368	−0.081	0.131	−0.067	−0.138

Group differences tested with Spearman's correlation test.
* $P < .05$.

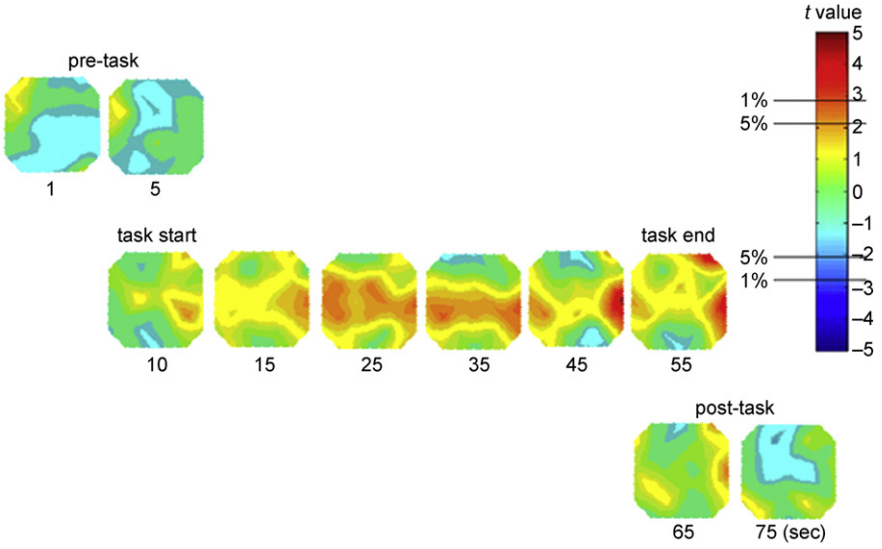

Fig. 2. Topographic presentation of the difference in t value (a measure of oxy-Hb concentration) between the control and the OCD groups during the Stroop color-word task. Individual maps of t values are presented in the order in which they were recorder. Numbers indicate the time (sec) from the start of NIRS recordings to and the recording period is separated (vertical groupings) into the pre-task baseline, Stroop task, and post-task baseline. The red, green, and blue areas in the topographs indicate positive, zero, and negative t values, with ± 2.9 and ± 2.1 for 1% and 5% statistical significance levels, respectively.

approximately the same stage of development as the primary motor cortex. Interestingly, the dorsolateral prefrontal cortex matures last. In the frontal cortex, Shaw et al. (2008) reported that the primary motor cortex attains peak cortical thickness relatively early, followed by the supplementary motor areas and most of the frontal pole. High-order cortical areas, such as the dorsolateral prefrontal cortex and cingulate cortex, reach peak thickness last.

Therefore, prefrontal dysfunction may arise in the frontopolar cortical that myelinates early and is fully developed in pediatric subjects with OCD. As the frontal-lobe matures, the area of prefrontal dysfunction gradually shifts to lateral areas near the dorsolateral prefrontal cortex. Subsequently, prefrontal dysfunction may arise in the lateral prefrontal cortex, as it myelinates later and is only fully developed in adults with OCD.

At channel 14, OCD patients had significantly smaller oxy-Hb changes than healthy controls in the present study. This channel is localized near the left lateral prefrontal region. Meanwhile, in the right lateral prefrontal region, OCD patients did not exhibit significantly smaller oxy-Hb changes than healthy controls.

In other functional and structural neuroimaging studies, dysfunctions and abnormalities in the left hemisphere have been reported. Using SPECT, Busatto et al. (2000) found reduced uptake of ethyl cysteinate dimer in the left dorsal anterior cingulate cortex of OCD patients relative to the control subjects. In a PET study, metabolic rates were significantly increased in the left orbital gyrus (Baxter et al, 1987). Kang et al. (2004) reported that left orbitofrontal volumes were significantly smaller in OCD patients. Nakamae et al. (2012) reported that OCD patients had statistically significant reductions in cortical thickness in a cluster that contained the left superior temporal gyrus and posterior insular cortex. Meanwhile, other studies reported dysfunctions and abnormalities in the right hemisphere or bilateral hemispheres (Alptekin et al., 2001; Busatto et al., 2000), but these results are comparatively inconsistent. In the present study, OCD patients had significantly smaller oxy-Hb changes than healthy controls, only in the left lateral prefrontal regions.

We used the Stroop color-word task as stimulation because the frontal gyrus has been described as one of the regions most strongly related to Stroop interference (Laird et al., 2005). Schroeter et al. (2002) examined hemodynamic responses during incongruent, congruent, and neutral trials of a Stroop task using NIRS in 14 adult healthy controls. They reported that hemodynamic responses in the lateral prefrontal cortex were stronger during incongruent tasks compared with congruent and neutral trials of the Stroop task bilaterally. Ehlis et al. (2005) investigated 10 healthy subjects by means of multi-channel NIRS during performance of congruent and incongruent trials of a Stroop color-word task. In that study, oxy-Hb and total-Hb changes indicated specific activation for interference trials in inferior-frontal areas of the left hemisphere. Negoro et al. (2010) examined brain activation in 20 children with ADHD and 20 healthy age- and sex-matched children during a Stroop color-word task using NIRS. In that study, oxy-Hb changes indicating specific activation in the inferior prefrontal cortex related to the SCWC were significantly lower in subject with ADHD than in the control group, and there were positive correlations between the SCWC and age. Ota et al. (in press) examined brain activation in 12 children with OCD and 12 healthy age- and sex-matched children during a Stroop color-word task using NIRS. In that study, they found oxy-Hb changes consistent with specific activation in the frontopolar cortex. However, there were no significant differences in the SCWC in the two groups. In both groups, there were positive correlations between the SCWC and age, and there were no correlations between the SCWC and FIQ. In the OCD group, there were no correlations between the SCWC and CY–BOCS scores.

In the present study, we found oxy-Hb changes that indicated specific activation in the left lateral prefrontal cortex. There were no significant differences in the SCWC of the two groups. In the OCD subjects, there were positive correlations between the SCWC and FIQ, negative correlations between the SCWC and Y–BOCS scores, and no correlations between the SCWC and age or MOCI scores. These data suggest that our Stroop color-word task may be useful for estimating the severity of obsessive–compulsive symptoms.

Potential limitations of the present study should also be considered. First, NIRS has disadvantages compared with other methodologies (Yamashita et al., 1996). Its main disadvantage is that it provides measurements of Hb concentration changes only as relative values, not as absolute values. We made a Stroop task that had a baseline task to overcome this problem. Furthermore, we measured Hb concentration changes from the activation task to the baseline task and performed the task three times to average potential sporadic changes and prevent the subjects from becoming tired. The grand average waveforms of oxy-Hb concentration changes in the OCD group do not show regional cerebral blood flow decrease during the activation task, but show differences in blood flow

between the baseline and activation tasks. Second, the spatial resolution for detecting hemodynamic responses from the scalp surface using NIRS is lower than those for fMRI, SPECT, and PET. However, it is certainly the case that reduced prefrontal hemodynamic responses in adults with OCD can be shown by NIRS. Third, the sample size was small. Future studies should include a larger sample size. Fourth, comorbid anxiety disorder was not excluded. Nevertheless, the subjects with OCD in the present study were free from current major depressive disorder. Fifth, 10 subjects were receiving medications in the present study. A previous study reported that OCD patients scanned previously were re-scanned during treatment with the tricyclic antidepressant clomipramine hydrochloride, comparisons of local cerebral glucose metabolic rates for both groups showed a relative decrease in regions of the orbital frontal cortex and the left caudate (Benkelfat et al., 1990). Previous studies on imaging have also showed the effects on brain function by antidepressant drugs. (Baxter et al., 1992; Nakao et al., 2005a, 2005b). Thus, the presence of antidepressant drugs may have influenced the present results.

Sixth, we used Stroop task which was reproduced according to the method described earlier (Goldman, 1975). Thus, the behavioral outcomes of the present study may be different from those using typical Stroop task.

5. Conclusion

To our knowledge, this is the first NIRS study to examine prefrontal hemodynamic responses in adults with OCD. We now know that prefrontal hemodynamic responses are lower in both adult and pediatric subjects with OCD, but the area of the reduced prefrontal hemodynamic responses are different between these populations. The multi-channel NIRS systems may be a very useful tool for assessing brain function, because multi-channel NIRS systems allow the implementation of non-invasive functional mapping of the cerebral cortex at the bedside and with much shorter measurement times (about 5 min) than other functional brain imaging methodologies.

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References

Alptekin K, Degirmenci B, Kivircik B, Durak H, Yemez B, Derebek E, et al. Tc-99m HMPAO brain perfusion SPECT in drug-free obsessive–compulsive patients without depression. Psychiatry Res 2001;107:51–6.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders, text revision (DSM-IV-TR). 4th ed. Washington, DC: American Psychiatric Association; 2000.

Baxter Jr LR, Phelps ME, Mazziotta JC, Guze BH, Schwartz JM, Selin CE. Local cerebral glucose metabolic rates in obsessive–compulsive disorder. A comparison with rates in unipolar depression and in normal controls. Arch Gen Psychiatry 1987;44(3):211–8.

Baxter Jr LR, Schwartz JM, Bergman KS, Szuba MP, Guze BH, Mazziotta JC, et al. Caudate glucose metabolic rate changes with both drug and behavior therapy for obsessive–compulsive disorder. Arch Gen Psychiatry 1992;49(9):681–9.

Benkelfat C, Nordahl TE, Semple WE, King AC, Murphy DL, Cohen RM. Local cerebral glucose metabolic rates in obsessive–compulsive disorder. Patients treated with clomipramine. Arch Gen Psychiatry 1990;47(9):840–8.

Busatto GF, Zamignani DR, Buchpiguel CA, Garrido GE, Glabus MF, Rocha ET, et al. A voxel-based investigation of regional cerebral blood flow abnormalities in obsessive–compulsive disorder using single photon emission computed tomography (SPECT). Psychiatry Res 2000;99(1):15–27.

Busatto GF, Buchpiguel CA, Zamignani DR, Garrido GE, Glabus MF, Rosario-Campos MC, et al. Regional cerebral blood flow abnormalities in early-onset obsessive–compulsive disorder: an exploratory SPECT study. J Am Acad Child Adolesc Psychiatry 2001;40(3):347–54.

Castle DJ, Deale A, Marks IM. Gender differences in obsessive compulsive disorder. Aust N Z J Psychiatry 1995;29(1):114–7.

Diler RS, Kibar M, Avci A. Pharmacotherapy and regional cerebral blood flow in children with obsessive compulsive disorder. Yonsei Med J 2004;45(1):90–9.

Ehlis AC, Herrman MJ, Wagener A, Fallgatter AJ. Multi-channel near-infrared spectroscopy detects specific inferior-frontal activation during incongruent Stroop trails. Biol Psychol 2005;69(3):315–31.

Eichstedt JA, Arnold SL. Childhood-onset obsessive–compulsive disorder: a tic-related subtype of OCD? Clin Psychol Rev 2001;21(1):137–57.

Fallgatter AJ, Roesler M, Sitzmann L, Heidrich A, Mueller TJ, Strik WK. Loss of functional hemispheric asymmetry in Alzheimer's dementia assessed with near-infrared spectroscopy. Brain Res Cogn Brain Res 1997;6(1):67–72.

Flechsig PE. Developmental (myelogenetic) localisation of the cerebral cortex in the human subject. Lancet 1901;158(4077):1027–30.

Geller E, Faerber EN, Legido A, Melvin JJ, Hunter JV, Wang Z, et al. Rasmussen encephalitis: complementary role of multitechnique neuroimaging. AJNR Am J Neuroradiol 1998;19(3):445–9.

Gogtay N, Giedd JN, Luck L, Hayashi KM, Greenstein D, Vaituzis AC, et al. Dynamic mapping of human cortical development during childhood through early adulthood. Proc Natl Acad Sci U S A 2004;101(21):8174–9.

Goldman CJ. A group version of the Stroop Color and Word Test. J Pers Assess 1975;39(4):386–8.

Gratton G, Goodman-Wood MR, Fabiani M. Comparison of neuronal and hemodynamic measures of the brain response to visual stimulation: an optical imaging study. Hum Brain Mapp 2001;13(1):13–25.

Hoshi Y, Kobayashi N, Tamura M. Interpretation of near-infrared spectroscopy signals: a study with a newly developed perfused rat brain model. J Appl Physiol 2001;90(5):1657–62.

Kalra SK, Swedo SE. Children with obsessive–compulsive disorder: are they just "little adults"? J Clin Invest 2009;119(4):737–46.

Kameyama M, Fukuda M, Yamagishi Y, Sato T, Uehara T, Ito M, et al. Frontal lobe function in bipolar disorder: a multichannel near-infrared spectroscopy study. Neuroimage 2006;29(1):172–84.

Kang DH, Kim JJ, Choi JS, Kim YI, Kim CW, Youn T, et al. Volumetric investigation of the frontal-subcortical circuitry in patients with obsessive–compulsive disorder. J Neuropsychiatry Clin Neurosci 2004;16(3):342–9.

Koizumi H, Yamashita Y, Maki A, Yamamoto T, Ito Y, Itagaki H, et al. Higher-order brain function analysis by trans-cranial dynamic near-infrared spectroscopy imaging. J Biomed Opt 1999;4:403–13.

Koran LM, Thienemann ML, Davenport R. Quality of life for patients with obsessive–compulsive disorder. Am J Psychiatry 1996;153:783–8.

Kubota Y, Toichi M, Shimizu M, Mason RA, Coconcea CM, Findling RL, et al. Prefrontal activation during verbal fluency tests in schizophrenia — a near-infrared spectroscopy (NIRS) study. Schizophr Res 2005;77(1):65–73.

Kuwabara H, Kasai K, Takizawa R, Kawakubo Y, Yamasue H, Rogers MA, et al. Decreased prefrontal activation during letter fluency task in adults with pervasive developmental disorders: a near-infrared spectroscopy study. Behav Brain Res 2006;172:272–7.

Laird AR, McMillan KM, Lancaster JL, Kochunov P, Turkeltaub PE, Pardo JV, et al. A comparison of label-based review and ALE meta-analysis in the Stroop task. Hum Brain Mapp 2005;25(1):6-21.

Leckman JF, Grice DE, Boardman J, Zhang H, Vitale A, Bondi C, et al. Symptoms of obsessive–compulsive disorder. Am J Psychiatry 1997;154(7):911–7.

Leonard HL, Lenane MC, Swedo SE, Rettew DC, Gershon ES, Rapoport JL. Tics and Tourette's disorder: a 2- to 7-year follow-up of 54 obsessive–compulsive children. Am J Psychiatry 1992;149(9):1244–51.

Machlin SR, Harris GJ, Pearlson GD, Hoehn-Saric R, Jeffery P, Camargo EE. Elevated medial-frontal cerebral blood flow in obsessive–compulsive patients: a SPECT study. Am J Psychiatry 1991;148(9):1240–2.

Maia TV, Cooney RE, Peterson BS. The neural bases of obsessive–compulsive disorder in children and adults. Dev Psychopathol 2008;20(4):1251–83.

Maki A, Yamashita Y, Ito Y, Watanabe E, Mayanagi Y, Koizumi H. Spatial and temporal analysis of human motor activity using noninvasive NIR topography. Med Phys 1995;22(12):1997–2005.

Martinot JL, Allilaire JF, Mazoyer BM, Hantouche E, Huret JD, Baron JC, et al. Obsessive–compulsive disorder: a clinical, neuropsychological and positron emission tomography study. Acta Psychiatr Scand 1990;82(3):233–42.

Matsuo K, Kato T, Taneichi K, Matsumoto A, Ohtani T, Hamamoto T, et al. Activation of the prefrontal cortex to trauma-related stimuli measured by near-infrared spectroscopy in posttraumatic stress disorder due to terrorism. Psychophysiology 2003;40(4):492–500.

Menzies L, Chamberlain SR, Laird AR, Thelen SM, Sahakian BJ, Bullmore ET. Integrating evidence from neuroimaging and neuropsychological studies of obsessive–compulsive disorder: the orbitofronto-striatal model revisited. Neurosci Biobehav Rev 2008;32(3):525–49.

Nakajima T, Nakamura M, Taga C, Yamagami S, Kiriike N, Nagata T, et al. Reliability and validity of the Japanese version of the Yale–Brown Obsessive–Compulsive Scale. Psychiatry Clin Neurosci 1995;49(2):121–6.

Nakamae T, Narumoto J, Sakai Y, Nishida S, Yamada K, Kubota M, et al. Reduced cortical thickness in non-medicated patients with obsessive–compulsive disorder. Prog Neuropsychopharmacol Biol Psychiatry 2012;37(1):90–5.

Nakao T, Nakagawa A, Yoshiura T, Nakatani E, Nabeyama M, Kawamoto M, et al. A functional MRI comparison of patients with obsessive–compulsive disorder and normal controls during a Chinese character Stroop task. Psychiatry Res 2005a;139(2):101–14.

Nakao T, Nakagawa A, Yoshiura T, Nakatani E, Nabeyama M, Yoshizato C, et al. Brain activation of patients with obsessive–compulsive disorder during neuropsychological and symptom provocation tasks before and after symptom improvement: a functional magnetic resonance imaging study. Biol Psychiatry 2005b;57(8):901–10.

Negoro H, Sawada M, Iida J, Ota T, Tanaka S, Kishimoto T. Prefrontal dysfunction in attention-deficit/hyperactivity disorder as measured by near-infrared spectroscopy. Child Psychiatry Hum Dev 2010;41(2):193–203.

Ota T, Iida J, Sawada M, Suehiro Y, Yamamuro K, Matsuura H, et al. Reduced prefrontal hemodynamic response in pediatric obsessive-compulsive disorder as measured by near-infrared spectroscopy. Child Psychiatry Hum Dev in press; 26.

Pauls DL, Alsobrook II JP, Goodman W, Rasmussen S, Leckman JF. A family study of obsessive–compulsive disorder. Am J Psychiatry 1995;152(1):76–84.

Sánchez-Meca J, López-Pina JA, López-López JA, Marín-Martínez F, Rosa-Alcázar AI, Gómez-Conesa A. The Maudsley Obsessive–Compulsive Inventory: a reliability generalization meta-analysis. Int J Clin Health Psychol 2011;11(3):473–93.

Schroeter ML, Zysset S, Kupka T, Kruggel F, Yves von Cramon D. Near-infrared spectroscopy can detect brain activity during a color-word matching Stroop task in an event-related design. Hum Brain Mapp 2002;17(1):61–71.

Schweitzer JB, Faber TL, Grafton ST, Tune LE, Hoffman JM, Kilts CD. Alterations in the functional anatomy of working memory in adult attention-deficit/hyperactivity disorder. Am J Psychiatry 2000;157(2):278–80.

Shaw P, Kabani NJ, Lerch JP, Eckstrand K, Lenroot R, Gogtay N, et al. Neurodevelopment trajectories of human cerebral cortex. J Neurosci 2008;28(14):3586–94.

Suto T, Fukuda M, Ito M, Uehara T, Mikuni M. Multichannel near-infrared spectroscopy in depression and schizophrenia: cognitive brain activation study. Biol Psychiatry 2004;55(5):501–11.

Swedo SE, Rapoport JL, Leonard H, Lenane M, Cheslow D. Obsessive–compulsive disorder in children and adolescents. Clinical phenomenology of 70 consecutive cases. Arch Gen Psychiatry 1989a;46(4):335–41.

Swedo SE, Schapiro MB, Grady CL, Cheslow DL, Leonard HL, Kumar A, et al. Cerebral glucose metabolism in childhood-onset obsessive–compulsive disorder. Arch Gen Psychiatry 1989b;46(6):518–23.

Toronov V, Webb A, Choi JH, Wolf M, Michalos A, Gratton E, et al. Investigation of human brain hemodynamics by simultaneous near-infrared spectroscopy and functional magnetic resonance imaging. Med Phys 2001;28(4):521–7.

Villringer A, Chance B. Non-invasive optical spectroscopy and imaging of human brain function. Trends Neurosci 1997;20(10):435–42.

Villringer A, Dirnagl U. Coupling of brain activity and cerebral blood flow: basis of functional neuroimaging. Cerebrovasc Brain Metab Rev 1995;7(3):240–76.

Weissman MM, Bland RC, Canino GJ, Greenwald S, Hwu HG, et al. The cross national epidemiology of obsessive compulsive disorder. The Cross National Collaborative Group. J Clin Psychiatry 1994;55:5-10. [Suppl.].

Whiteside SP, Port JD, Abramowitz JS. A meta-analysis of functional neuroimaging in obsessive–compulsive disorder. Psychiatry Res 2004;132(1):69–79.

Yamashita Y, Maki A, Koizumi H. Near-infrared topographic measurement system: imaging of absorbers localized in a scattering medium. Rev Sci Instrum 1996;67:730–2.