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Prefrontal activation predicts social functioning improvement after initial treatment in late-onset depression

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ABSTRACT

The activation of oxygenated hemoglobin (oxy-Hb) has been shown to be lacking in the prefrontal cortex (PFC) of patients with late-onset depression (LOD), in verbal fluency task (VFT)-related near-infrared spectroscopy (NIRS). In our previous studies, we have emphasized the connection between the lack of activation in the frontopolar cortex and social functioning disorder in patients with LOD. In this study, we investigated whether the responsiveness to medical treatment of untreated patients with LOD, particularly social functioning improvements, could be predicted by NIRS findings at the initial examination. The subjects were 29 patients with LOD who were diagnosed with major depression at 65 years or older at the initial examination (mean age ± standard deviation, 72.4 ± 5.71 years). We measured the changes in hemoglobin concentration in the prefrontal and temporal cortex regions during a VFT by using 52-channel NIRS. In addition, depression status and social functioning were evaluated with the Hamilton Depression Rating Scale and the Social Adaptation Self-evaluation Scale, respectively, at the initial examination and 8 weeks after the treatment. A negative correlation was found between the NIRS activation in the right ventrolateral PFC region before treatment and the improvement in social functioning. These results suggested that the social functioning improvements were greater in LOD with initially lower NIRS activation in the right ventrolateral PFC region. NIRS is a simple technique that can be used before treatment to evaluate the social functioning levels of patients with LOD, and predict social functioning improvement after treatment.

1. Introduction

As the aging of populations continues in society, there has been a growing interest in psychiatric disorders in the elderly (WHO, 2008). Depression, which is a disease with a high prevalence, is common in the elderly in the general population (Blazer, 1989; NIH consensus conference 1992). In recent years, increased knowledge of the disease and the increased use of pharmacotherapy with new-generation antidepressants such as selective serotonin reuptake inhibitors and selective serotonin noradrenaline reuptake inhibitors have resulted in improved treatment effects in patients with depression. However, social functioning disorder remains despite improvements in the depression symptoms (Hirschfeld et al., 2002). It has been suggested that improvements in social functioning are important for patients with depression to be able to adapt to society. Thus, social functioning is being taken into consideration in the treatment of patients with depression. Social functioning is instrumental to the quality of life, and it requires complex operations of various executive functions that include monitoring, reasoning, organizing, selecting, and planning. Depression and schizophrenia cause severe impairments in social functioning (WHO, 2004). Social functioning has received widespread attention as one of the most important outcomes in psychiatric disorders and has been related to cognitive functioning and the underlying brain activity.

The dysfunction of the prefrontal cortex (PFC) in patients with depression has been reported in previous studies that used neuropsychological tests (Beats et al., 1996; Degl'Innocenti et al., 1998; Moritz et al., 2002). This PFC dysfunction in patients with depression has been increasingly clarified by functional brain imaging

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studies (Baker et al., 1997; Baxter et al., 1989; Drevets et al., 1997; Nobler et al., 2002; Okada et al., 2003, 2009). To date, it has been widely reported that cerebral blood flow and glucose metabolism are decreased in the dorsolateral prefrontal cortex and increased in the ventrolateral and ventromedial prefrontal cortex in patients with depression (Drevets, 2000). The medial prefrontal cortex has dense reciprocal connections with the amygdala and is presumed to inhibit the abnormally increased amygdala activity in patients with depression (Etkin et al., 2011). The medial prefrontal hyperactivity may indicate the need for stronger control in patients with depression compared to healthy controls. By contrast, lateral prefrontal area has primarily been associated with cognitive functions. However, recent studies suggest that the cognitive control functions may also pertain to emotion. Specifically, functional imaging studies demonstrate the recruitment of the lateral prefrontal area during the regulation of negative emotion through reappraisal/suppression strategies (Eippert et al., 2007; Levesque et al., 2003; Ochsner et al., 2002, 2004; Phan et al., 2005). Thus, a defect in the regulation of negative affect due to lateral prefrontal dysfunction is indeed a plausible mechanism for causing depression.

Multichannel near-infrared spectroscopy (NIRS), a functional neuroimaging technology widely used in recent years, can measure the hemodynamics over the surface of the cortices of the bilateral frontotemporal regions (Heinzel et al., 2013; Strangman et al., 2002a). This technique enables the detection of spatiotemporal characteristics of brain function by measuring the concentrations of oxy-hemoglobin (oxy-Hb) and deoxy-hemoglobin (deoxy-Hb), which are assumed to reflect the regional cerebral blood volume as demonstrated by good correlations with functional MRI (fMRI) signals (Sato et al., 2013). NIRS has several advantages over existing imaging techniques, such as positron emission tomography (PET), Single photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI), because it is noninvasive, without using any radioactive substances, and is easy to administer, tolerates small movements, is inexpensive, and provides excellent time resolution (Ferrari and Quaresima, 2012). Meanwhile, it also contains disadvantages such as its poor spatial resolution, and the fact that it could not measure the deeper layer of the brain. Indeed, NIRS has been used to assess brain functions in many psychiatric disorders (Kameyama et al., 2006; Matsuo et al., 2003; Pu et al., 2008; Takizawa et al., 2014). In addition, NIRS was approved for application in clinical practice by the Ministry of Health, Labor, and Welfare of Japan in April 2009 as a clinical evaluation method for the differential diagnosis assistance of depression symptoms in psychiatric treatment in Japan. NIRS, which is a simple and noninvasive technique that can analyze the temporal course of brain function changes over a short period and in a natural position, allows for a relatively convenient examination that can be conducted in the outpatient clinic. In particular, it is a functional brain imaging examination that poses relatively little burden on elderly patients.

There have been several reports on the use of NIRS in patients with late-onset depression (LOD). A consistently reduced oxy-Hb activation in the PFC (hypoactivation) has been observed in patients with LOD according to NIRS findings in a study using a verbal fluency task (VFT) with the initial sounds of words, which is most commonly employed (Matsuo et al., 2000, 2005; Pu et al., 2008). However, there have only been a few reports on the connection between therapeutic responses in patients with LOD and NIRS findings. An objective diagnostic method for the prediction of depression treatment responses has yet to be established in other studies of neurological functional imaging as well.

There are still some debates as to what clinical aspects the NIRS signal actually reflects. One study by Noda et al. (2012) has demonstrated a significant negative correlation between NIRS signal activations in the frontal and right temporal regions and depression severity. However, in our previous study, we found a stronger cross-sectional correlation between NIRS signal activations in the PFC during the verbal fluency task and social functioning rather than the depressive symptom severity (Pu et al., 2008). In the present study, we performed pretreatment NIRS measurements in untreated patients with LOD and investigated the relationship between the treatment response of these patients, particularly the degree of improvement in social functioning, and the pretreatment NIRS findings. We hypothesized that pretreatment activity in the PFC is related to both pretreatment and degree of improvement in social functioning in patients with LOD.

2. Materials and methods

2.1. Participants (Table 1)

The subjects were 29 patients [7 males, 22 females, mean ± standard deviation (SD) age: 72.4 ± 5.71 years] who were diagnosed with major depressive disorder based on the DSM-IV (American Psychological Association, 1994) using the Mini-International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al., 1998). None of the patients had clinical evidence of other central nervous system disorders based on medical history and examination. They visited the outpatients ward of Tottori University Hospital for the first time between September 2006 to July 2010 with an initial onset episode at an age of 65 years or older. The control group comprised of 29 healthy adults [7 males, 22 females, mean ± standard deviation (SD) age: 71.6 ± 5.57 years] matching the patients in terms of age and sex, with no history of neuropsychiatric diseases. The NIRS data of 7 out of 29 patients had been reported in our previous study (Pu et al., 2008) but not about their relationship with treatment response. All the patients with LOD were in a depressed mood state (Hamilton Depression Rating Scale [Hamilton Depression Rating Scale (HAM-D) score ≥15; 17 items; mean ± SD HAM-D score: 20.6 ± 5.22]. All the participants were right-handed with criteria of more than 80% by the Edinburgh

Table 1
Demographic and clinical variables of the participants.

Demographics	Patients (n = 29) (mean ± SD)	Healthy controls (n = 29) (mean ± SD)	t	df	Group difference
Age, years	72.4 ± 5.7	71.6 ± 5.6	−0.605	56	0.548
Gender, women/men	22/7	22/7	$X^2 = 0$	1	1.000
Handedness (%)	97.9 ± 6.2	97.9 ± 6.4	−0.042	56	0.925
Education, years	10.6 ± 1.9	11.6 ± 2.0	2	56	0.071
Estimated premorbid IQ	97.1 ± 12.4	92.6 ± 28.1	−0.782	56	0.437
Duration of illness, years	4.7 ± 5.6	–	–	–	–
Nuber of words generated	10.7 ± 3.9	12.2 ± 3.2	1.621	56	0.111
MMSE	27.5 ± 1.9	27.4 ± 2.4	−0.189	56	0.851
HAMD	20.6 ± 5.2	–	–	–	–
SASS	28.7 ± 9.8	41.0 ± 6.3	7.680	56	<0.001

Abbreviations: IQ, Intelligence Quotient; MMSE, Mini-Mental State Examination; HAMD, Hamilton Rating Scale for Depression; SASS, Social Adaptation Self-Evaluation Scale.

Inventory Index (Oldfield, 1971). All subjects gave their consent in a written form after receiving comprehensive information on the study protocol. The study was approved by the ethics committee of Tottori University Faculty of Medicine.

2.2. Assessments

Treatment with antidepressants was started for all patients, and symptom evaluations were conducted before and 8 weeks after the treatment (2 time points). Antidepressant choice was based on the judgment of the attending physician in the outpatient ward, and the dosage was increased to reach sufficient quantity within 4 weeks in all cases. The breakdown of the antidepressants used was paroxetine (10–40 mg) for 15 patients and milnacipran (50–150 mg) for 14 patients. Prior to NIRS measurement, all the subjects were assessed using Mini-Mental State Examination (MMSE) for their cognitive function and undertook self-assessments of social functioning: the Social Adaptation Self-evaluation Scale (SASS) (Bosc et al., 1997; Goto et al., 2005) scale was used. In addition, the patients were assessed for depression severity using the HAMD (Hamilton, 1960) by two trained psychiatrists (TY, KK).

2.3. NIRS measurements

2.3.1. Activation task

The task procedure in the present study was similar to that of Takizawa et al. (2008). Hb changes were measured during the VFT (letter version). The VFT was chosen, because it has been often used for cognitive activation in NIRS studies, and previous reports showed measurable prefrontal activation during the letter fluency task in healthy subjects (Herrmann et al., 2003, 2006; Kameyama et al., 2004; Pu et al., 2014). Each subject sat on a comfortable chair and was instructed to minimize movement such as head movements, strong biting and eye blinking during the NIRS measurements, so as to avoid artifacts.

The 160-s block-design VFT contains 3 different time periods: a 30-s pre-task period, a 60-s task period, and a70-s post-task period (Fig. 1). For the pre- and post-task baseline periods, the subjects were instructed to consecutively repeat the five Japanese vowels ("a", "i", "u", "e", "o") aloud. As readout from NIRS, the contrast between the verbal fluency condition and the vocalization condition was used to increase specificity for the verbal fluency. During the task period, they were instructed to generate as many Japanese words beginning with a designated syllable as possible. The three sets of initial syllables (A; /to/,/se/,/o/, B; /a/,/ki/,/ha/, C; /na/,/i/,/ta/) were presented in counterbalanced order among the subjects and each syllable changed every 20 s during the 60-s task. The total number of correct words generated during the VFT was adopted as a measure of task performance.

2.3.2. NIRS methodology

The 52-channel NIRS (ETG-4000, Hitachi Medical Co.) measures relative changes in oxy-Hb and deoxy-Hb using 2 wavelengths (695 and 830 nm) of infrared light based on the modified Beer–Lambert law (Yamashita et al., 1996). In this system, these Hb values include a differential pathlength factor (DPF). In addition, Zhao et al. (2002), using a Monte Carlo simulation, reported that the estimated DPF variation in the forehead region of adult humans was regarded as roughly homogenous. The distance between pairs of source-detector probes was set at 3 cm, and each measuring area between pairs of source-detector probes was defined as a "channel" (ch). The NIRS measures points at a depth of 2–3 cm below the scalp. This corresponds to the surface of the cerebral cortex (Okada and Delpy, 2003; Toronov et al., 2001). The probes of the NIRS were placed on the frontotemporal region of the participant, with the midcolumn of the probe located over Fpz, and the lowest probes were located along the T3-Fp1-Fpz-Fp2-T4 line in accordance with the international 10/20 system for electroencephalography. The arrangement of the probes enabled the measurement of Hb values from both prefrontal and temporal cortical surface regions (Fig. 2). The correspondence between the NIRS channels and the measurement points on the cerebral cortex was confirmed by a multi-subject study of anatomical craniocerebral correlation (Okamoto et al., 2004). The spatial information of each channel was estimated by using functions from the Functional Brain Science Laboratory at Jichi Medical University in Japan (http://www.jichi.ac.jp/brainlab/virtual_reg.html) (Tsuzuki et al., 2007).

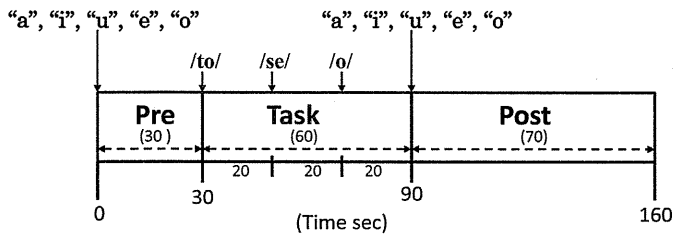

Fig. 1. The task design of verbal fluency test (VFT).

The data sampling rate was 10 Hz. The obtained data were analyzed using the integral mode: the pre-task baseline was determined as the mean over a 10-s period immediately before the task period; and the post-task baseline was determined as the mean over the last 5 s of the post-task period. Linear fitting was applied to the data between these 2 baselines to reduce the effect of linear trend artifact. A moving average method using a window width of 5 s was applied to remove any short-term motion artifacts. Because we could not remove all artifacts in this way, we applied semi-automatic rejection of data with artifacts separately for each channel (Pu et al., 2012; Takizawa et al., 2008). (Number of channels, 33–52 [mean, 49.8; SD, 4.7]).

For the analysis of the hemodynamic response data, Hb variables for each channel were averaged for the both time segments (pre-task baseline and task period). We focused on oxy-Hb concentrations during the 60-s task period, since the oxy-Hb change (task period − pre-task baseline period) was assumed to more directly reflect cognitive activation than the deoxy-Hb change, as previously shown by animal studies and correlations with fMRI blood oxygenation level-dependent signals (Hoshi et al., 2001; Strangman et al., 2002b).

2.4. Statistical analysis

Statistical analyses were performed using SPSS Statistics 19.0 software (Tokyo, Japan).

First, we compared the patients group with healthy controls in terms of demographic data, MMSE and SASS scores using Student's t-tests and a chi-square test whenever appropriate. Next, we compared the NIRS activation (oxy-Hb) during the VFT between groups using a Student's t-test for each channel. In the case of multiple between-group comparison analyses for NIRS data, FDR correction was adopted to correct for the multiplicity of the analyses. Moreover, the relationship between pretreatment NIRS activation in each channel and the SASS score was analyzed using Pearson's product moment correlation analysis to confirm the cross-sectional relationship between the NIRS activation and the SASS score. We also tested the relationship between the pretreatment SASS score and the degree of improvement in the SASS score using Pearson's product moment correlation analysis in order to

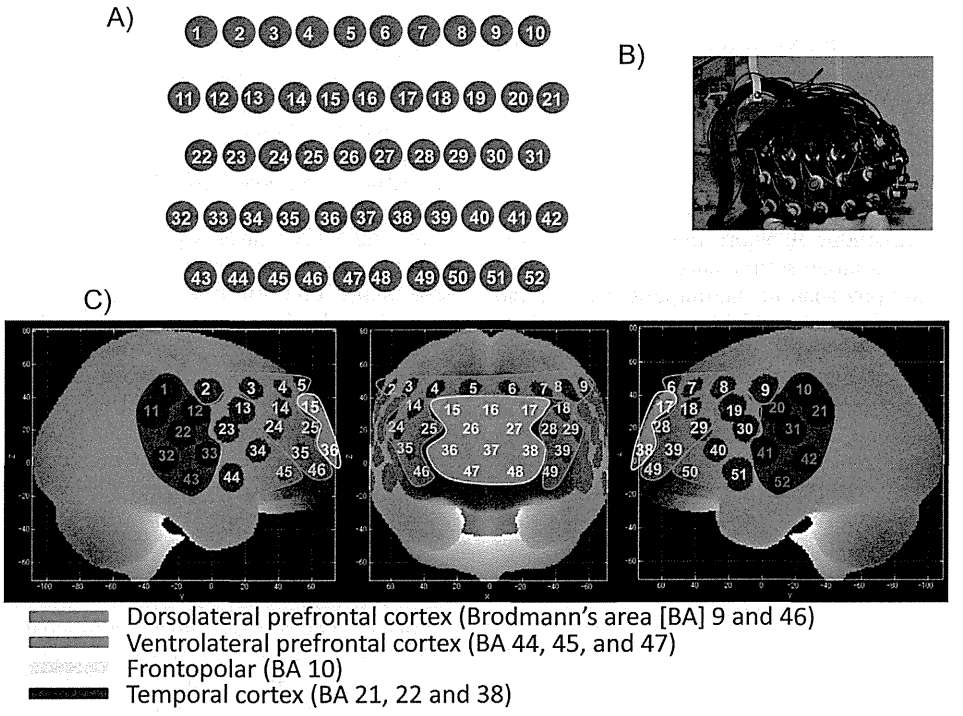

Fig. 2. Probe setting and measurement points for 52-channel near-infrared spectroscopy (NIRS). (A) The 52 measuring areas are labeled ch1–ch52 from the right posterior to the left anterior. (B–C) The probes with 3 × 11 thermoplastic shells were placed over a subject's bilateral prefrontal and superior temporal cortical surface regions. The channel numbers are indicated above the estimated cortical regions.

see whether the pretreatment SASS score may affect the degree of improvement.

Depression symptoms (HAM-D data) and social functioning (SASS data) pre- and post-8 weeks of after the treatment in the patients were compared with paired t-tests. With the objective of analyzing the relationship between pretreatment NIRS activation and clinical characteristics improvements due to treatment, particularly, the improvement in depression symptoms and social functioning, Pearson's correlation coefficient was calculated for each channel between the NIRS activation and the treatment-induced degree of improvement that was indicated by the SASS score. Moreover, in case there was a significant cross-sectional correlation between pretreatment NIRS activation and the SASS score, we performed additional partial correlation analyses between the degree of improvement in the SASS score and pretreatment NIRS activation data using the pretreatment SASS score as a control variable. A p value <0.05 was considered to be statistically significant. The multiplicity of the correlation analyses including NIRS data from 52 channels was not corrected, and therefore the results should be taken as exploratory.

3. Results

3.1. Between-group comparison

There was no significant difference between the groups in age, sex, educated years and MMSE scores, but the SASS score was significantly lower in the patients than the controls (Table 1).

The patients were associated with a significantly smaller NIRS activation than the controls at 33 channels (ch12, ch14, ch15, ch17, ch18, ch20, ch21, ch23 to ch29, ch31 to ch36, ch38 to ch46, ch49 to ch52; FDR-corrected p: 0.001–0.032), distributed predominantly in the ventrolateral and dorsolateral PFC, frontopolar, and temporal regions (Fig. 3).

3.2. Cross-sectional relationship between NIRS activation and the SASS score

The pretreatment NIRS activation in the area approximately located in the frontopolar and dorsolateral PFC was significantly correlated with the pretreatment SASS score (ch1, ch6, ch9, ch10, ch19 to ch21, ch25 to ch27, ch29, ch31, ch34, ch36, ch39, ch41, ch42, ch44, ch46, ch49, ch51, and ch52; R = 0.37 to 0.58; p = 0.001–0.048) (Fig. 5A).

3.3. Changes of depression symptoms and social functioning

A significant improvement in the HAM-D scores was observed between the two time points (pretreatment: 20.6 ± 5.22, post-treatment: 9.4 ± 7.37; t = 9.687, df = 28, p < 0.001). A significant improvement was also seen in the SASS scores (pretreatment: 28.7 ± 5.84, posttreatment: 35.5 ± 8.87, t = −4.716, df = 28, p < 0.001) (Fig. 4). There was no significant correlation between the pretreatment SASS score and the degree of improvement in the SASS score (R = −0.173, p = 0.369).

3.4. Relationship between pretreatment NIRS activation and the degree of improvement in depression symptoms and social functioning

Significant negative correlations between the degree of improvement in the SASS score after treatment and the pretreatment NIRS activation were observed in 8 channels (ch11, ch13, ch23, ch26, ch30, ch34, ch42, and ch44, R = −0.39 to −0.55; p = 0.0045–0.036) located approximately in the right ventrolateral PFC region (Fig. 5C). The pretreatment NIRS activation in any channel was not correlated with the degree of improvement in the HAM-D score after treatment (R = −0.24 to 0.31, n.s.).

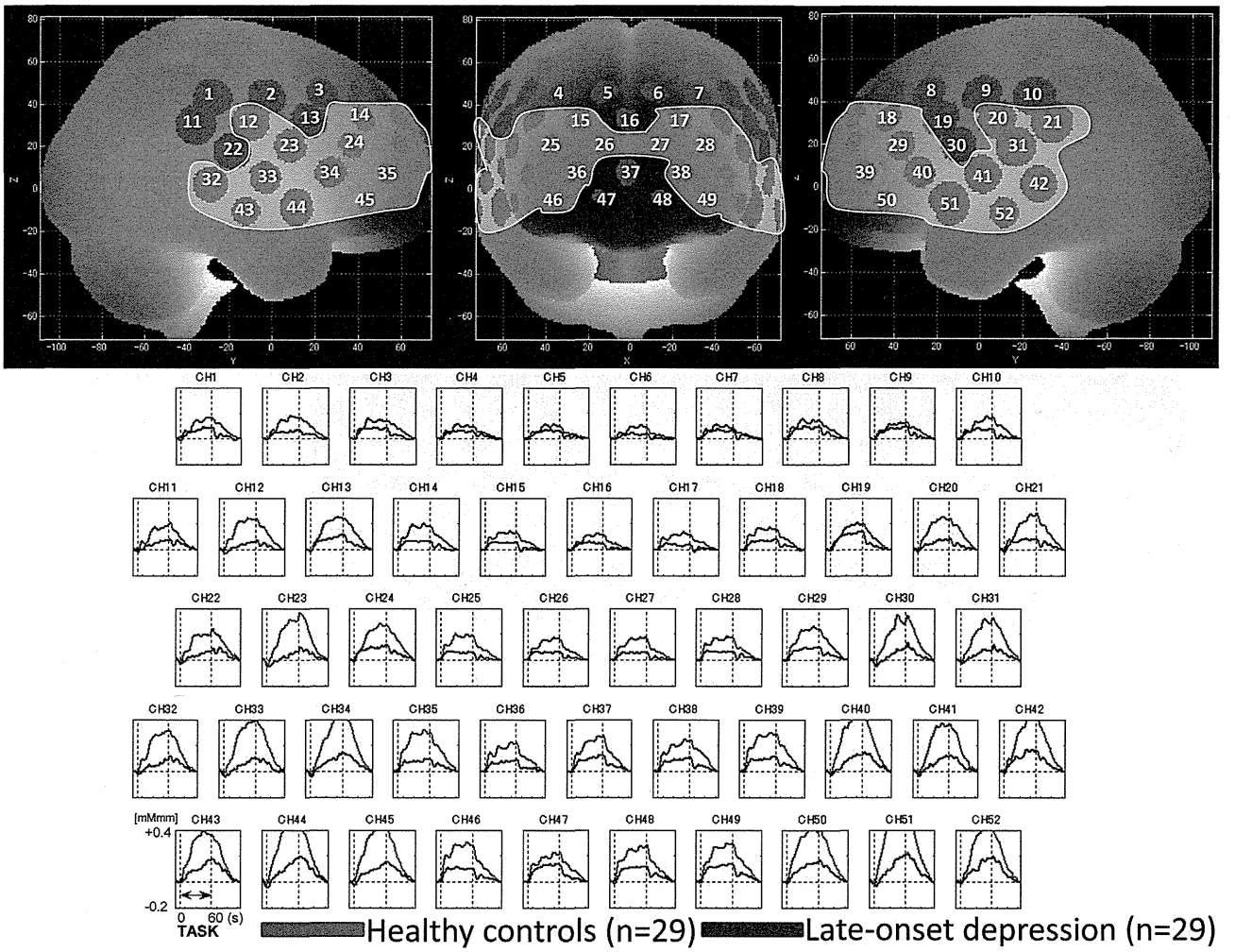

Fig. 3. Above: Brain area in yellow corresponds to the NIRS channels with significantly lower levels of activation in the LOD group than in the control group (FDR-corrected $p < 0.05$). The locations of NIRS channels were probabilistically estimated and anatomically labeled in the standard brain space in accordance with Tsuzuki et al. (2007). Below: Grand averaged waveforms of oxy-hemoglobin (oxy-Hb) during VFT (between two dotted vertical lines in each graph) in 52 channels over frontal and temporal regions measured by NIRS. Red and blue lines represent LOD and control groups, respectively.

As significant cross-sectional correlation analyses revealed significant relationship between the pretreatment SASS score and NIRS activation data in multiple channels located in the PFC, additional partial correlation analyses was conducted using the pretreatment SASS score in order to eliminate the effect of variance of pretreatment SASS score from the relationship between the degree of improvement in the SASS score and pretreatment NIRS activation data. Although the correlation between the pretreatment SASS score and the degree of improvement in the SASS score was not significant, a negative correlation coefficient ($R = -0.173$) suggest that it may have enhanced the negative relationship between the pretreatment NIRS activation and the degree of improvement in the SASS score to some extent. As a result, correlations between degree of improvement in the SASS score and pretreatment NIRS activation data remained significant in 6 channels mainly located in the right ventrolateral PFC (ch13, ch23, ch30, ch34, ch42, and ch44; $R = -0.43$ to -0.54; $p = 0.007$ to 0.024) (Fig. 5C).

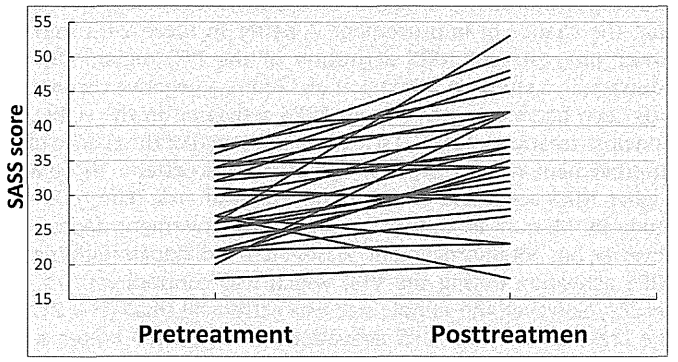

Fig. 4. SASS before and after treatment in patients with LOD.

4. Discussion

In this study, the pretreatment NIRS activation in the area approximately located in the frontopolar and dorsolateral PFC were positively correlated with the pretreatment SASS score; this is similar to our previous finding (Pu et al., 2008), whereas the pretreatment NIRS activation in the area approximately located in the right ventrolateral PFC was negatively correlated with the degree of improvement in the SASS score after 8 weeks of treatment. Our findings suggest the pretreatment NIRS activation not only

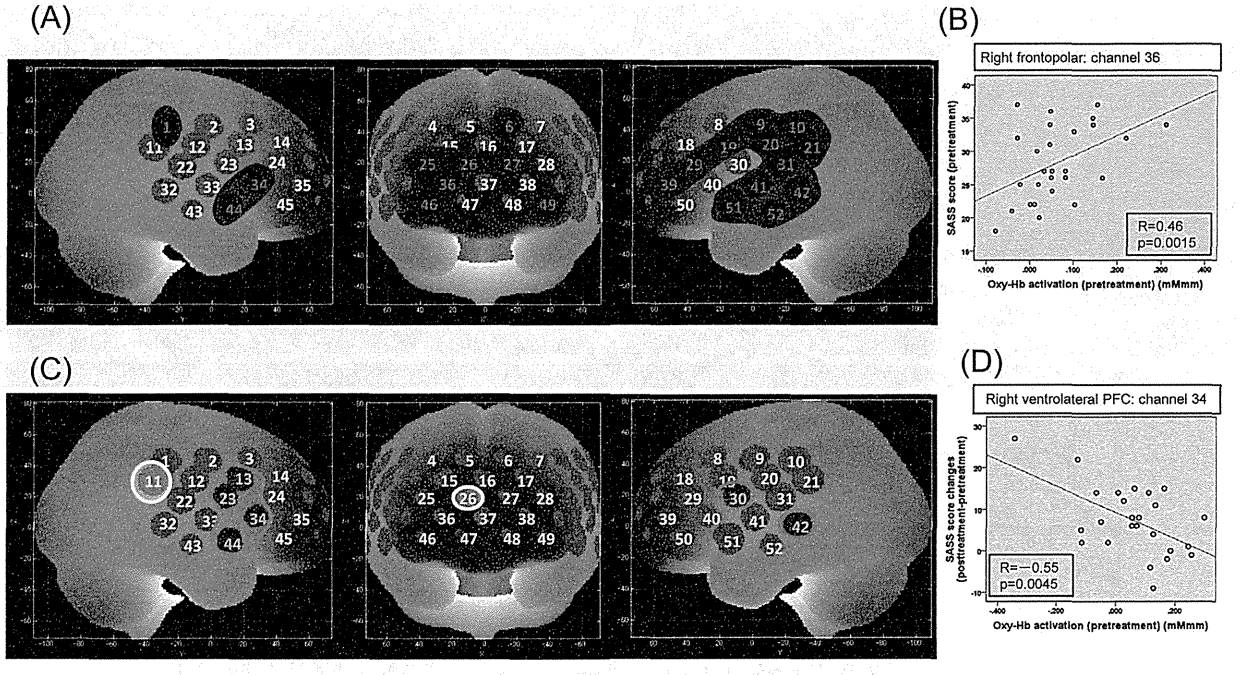

Fig. 5. Relationship between pretreatment NIRS activation and pretreatment SASS score, degree of improvement in the SASS score (posttreatment-pretreatment) in patients with LOD. (A) The brain areas indicated in blue correspond to the NIRS channels that exhibited a significant correlation (Pearson's product moment correlation; $p < 0.05$) between pretreatment NIRS activation and pretreatment SASS score. (B) Scatter diagram at channel 36 (right frontopolar; Pearson's product moment correlation; $R = 0.46$ and $p = 0.0015$). (C) The brain areas indicated in yellow and green correspond to the NIRS channels that exhibited a significant correlation (Pearson's product moment correlation; $p < 0.05$) between pretreatment NIRS activation and degree of improvement in the SASS score (posttreatment-pretreatment). Of these 8 (yellow and green) nominally significant correlations, 6 (green) were still (nominally) significant after correction for baseline SASS values. (D) Scatter diagram at channel 34 (right ventrolateral PFC; Pearson's product moment correlation; $r = -0.55$ and $p = 0.0045$). The locations of NIRS channels were estimated probabilistically and labeled anatomically in the standard brain space in accordance with Tsuzuki et al. (2007).

correlated with social functioning in untreated patients with LOD, but also predicted the treatment response. However, the relationship was somewhat reverse; increased NIRS activation in the PFC was related to higher social functioning but predicted decreased improvement in social functioning after 8 weeks of treatment.

In agreement with our previous study (Pu et al., 2008), we found a cross-sectional relationship between brain activity in the frontopolar, dorsolateral PFC and social functioning. Social functioning requires complex operations of executive function that include monitoring, reasoning, organizing, selecting, and planning. Burgess et al. (2000) noted that the frontopolar region is involved in high-level executive control and, thus, is likely to be a vital component of social functioning. Moreover, the dorsolateral PFC has primarily been associated with cognitive or executive functions, such as the maintenance and manipulation of items, working memory, intention formation, goal-directed action, abstract reasoning, and attentional control (Miller and Cohen, 2001). Considering these observations, it may be reasonable to postulate that the hemodynamic response observed in these areas during the VFT in the present study was associated with social functioning level.

The area where the pretreatment NIRS activation showed negative correlation with the improvement in social functioning was mainly the right ventrolateral PFC, which did not overlap so much with the area that showed cross-sectional positive relationship with the SASS score. It has been suggested that the cerebral blood flow and metabolism in the ventrolateral PFC at rest are abnormally increased in unmedicated patients with depression (Baxter et al., 1987; Biver et al., 1994; Cohen et al., 1992; Drevets et al., 1992). However, a complex relationship exists between depression severity and physiologic activity in the ventrolateral PFC. Although physiologic activity in the area is elevated in the depressed phase, the activity correlates inversely with depression severity (Drevets et al., 1992). Also, physiologic activity in the area is increased in outpatient, treatment-responsive patients but not in more severely ill or treatment-refractory patients with depression. The patients that gained better response by the treatment in the present study showed lower pretreatment NIRS activation in the ventrolateral PFC, which may have been due to the relatively higher pre-task baseline activation causing the "ceiling effect" than those who showed poor treatment response.

There have been only few studies that investigated whether NIRS methodology may be useful for predicting the treatment response in patients with depression. Eschweiler et al. (2000) have reported that pretreatment NIRS is useful for predicting the effects of depression treatment (improvement in depression status), although they did not predict the degree of social functioning improvement. They found a negative correlation between the improvements in depression symptoms by magnetic stimulation and pretreatment NIRS activation in the left PFC region during a mirror-drawing task, which is similar to the results of our study, indicating that the chance of improvement is better in those with initially lower pretreatment NIRS activation in the PFC region. On the contrary, in a study by Mimura et al. (2005), a negative correlation was seen between pretreatment NIRS activation in the right PFC and post-treatment HAM-D scores, suggesting that the chance of an improvement in the depression symptoms was better in those with higher NIRS activation in the right temporal area (ch43). In the study by Mimura et al. (2005), better post-treatment depression severity, but not improvement, was seen in individuals with higher NIRS activation during the VFT, which was contradictory to our results. However, the sample size was extremely small ($n = 7$) and the brain area of the NIRS activation that predicted better post-treatment depression severity in the study was different from the area indicated in the present study, and also they did not use the

degree of improvement as the treatment outcome. Another possible reason may be the difference in the treatment subjects between their study (young-and middle-age-onset depression) and ours (LOD); it is possible that the implications of the pretreatment NIRS findings differ in different age groups. When analyzing the NIRS data of depression, it may be important to consider differences in the age groups, including those with young- and middle-age-onset depression and those with LOD because the pathophysiology of the illness may differ depending on the age groups. According to Alexopoulos (1989), there are differences in various aspects, such as genetic causes, organic abnormalities in the brain, treatment resistance, and persistence, depending on the initial onset age of the patients, even if they all suffer from LOD. Because differences in etiology, pathology, symptoms, and prognosis have been reported to be caused by differences in the initial onset age, it is also important to conduct analyses by carefully taking the age of initial onset into consideration.

The above two studies focused on severity of depression symptoms as the treatment outcome. In the present study, we adopted the social functioning level as one of the outcomes and found that the pretreatment NIRS activation was related to improvement in social functioning but not in depression severity. In real-world clinical settings, treatment of patients with depression not only focuses on improving depression symptoms but also considers improving and recovering social functioning. Social functioning is defined as the ability to fulfill a role in a relationship with a partner and family and to engage in work and social activities among mutual interactions of the environment and the individual. It has been suggested that depression severity and levels of social functioning are not always closely associated. According to Bosc (2000) and Keller et al. (2000), depression symptoms do not necessarily coincide with social functioning when one is recovering from depression, and, according to Hirschfeld et al. (2002), the social functioning disorder remains despite the improvements in the depression symptoms, suggesting that the recovery periods for the depression symptoms and social functioning are different. Kennedy et al. (2007) suggests that residual symptomatology of depression after remission, as well as sustained neurocognitive deficits, may lead to enduring social functioning disorder. According to our previous study, we assumed that pretreatment activity in the PFC associated with verbal fluency task is related to both pretreatment and degree of improvement in social functioning but not depression severity in patients with LOD. We should await further studies using multivariate analysis including independent variables such as depression severity, cognitive function and social functioning to reach a conclusion about the relationship between these factors and NIRS activation. In any way, taking into consideration the capital importance of social functioning improvements in depression treatment, not only the improvement of depression status but also the improvement and recovery of social functioning should be considered more in evaluating the responsiveness of depression treatment.

Finally, there were a number of limitations in the present study. First, the second evaluation was conducted 8 weeks after the initiation of treatment; this was probably too short a period for evaluating the response to treatment, especially in terms of social functioning. In the future, it is important to analyze the long-term treatment response at 3 months, 6 months, and 1 year after the initiation of treatment. Second, NIRS data was measured only at the initial examination of the untreated patients and not at the post-treatment time point. In the future, we plan on conducting long-term longitudinal analyses of NIRS data at 3 months, 6 months, and 1 year after the start of treatment and analyzing whether the depression-related hypoactivation that is observed at the initial examination is improved in a state-dependent manner. Third, the effects of multiple tests were not taken into account in the correlation analyses, and thus, the findings are at best explorative. Future studies with a larger sample size should be undertaken taking into consideration this matter.

The present study indicated a correlation between the degree of improvement in social functioning due to 8 weeks of treatment and pretreatment NIRS activation in the right ventrolateral PFC region. The pretreatment NIRS activation not only correlated with social functioning in untreated patients with LOD, but also predicted the treatment response in social functioning. Although NIRS is not without several disadvantages, it is an active brain function imaging technique that can be performed quickly and noninvasively in the outpatient ward. Thus, it is considered to have a high clinical utility, especially for elderly patients.

5. Conclusion

We investigated whether the response to medical treatment of untreated patients with LOD, particularly social functioning improvements, could be predicted by NIRS findings in the initial examination. We found that pretreatment NIRS activation in the right ventrolateral PFC was associated with the improvements in social functioning. NIRS is a relatively simple method that may be used before treatment to evaluate the social functioning levels of patients with LOD, and may predict social functioning improvement after treatment.

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Contributors

1. Conception and design, or acquisition of data, analysis and interpretation of data (Shenghong Pu, Kazuyuki Nakagome, Takeshi Yamada, Katsutoshi Yokoyama, Hiroshi Matsumura, Izumi Nagata, Koichi Kaneko).
2. Drafting the article or revising it critically for important intellectual content (Shenghong Pu, Kazuyuki Nakagome, Takeshi Yamada, Katsutoshi Yokoyama, Hiroshi Matsumura, Izumi Nagata, Koichi Kaneko).
3. Final approval of the version to be published (Shenghong Pu, Kazuyuki Nakagome, Takeshi Yamada, Katsutoshi Yokoyama, Hiroshi Matsumura, Izumi Nagata, Koichi Kaneko).

Conflict of interest

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

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Research report

Association between social functioning and prefrontal hemodynamic responses in elderly adults

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HIGHLIGHTS

- Prefrontal hemodynamic responses and social functioning in elderly adults was studied.
- Hemodynamic responses measured by near-infrared spectroscopy during verbal fluency task.
- Social functioning assessed using social adaptation self-evaluation scale (SASS).
- Prefrontal cortical activation is associated with the SASS total score.
- NIRS might prove to be a useful biological marker for social functioning in elderly adults.

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ABSTRACT

Social functioning has received widespread attention as one of the most important outcomes in psychiatric disorders and has been related to cognitive functioning and the underlying brain activity. Cognitive decline, however, appears not only in the psychiatric population but also in aged individuals. In our previous study, we demonstrated a significant relationship between social functioning and prefrontal cortex (PFC) activity in patients with depression. However, it has not been shown whether the above relationship could be extended to healthy populations. The purpose of the present study was to investigate a possible association between social functioning and prefrontal hemodynamic responses in healthy elderly adults by using a non-invasive and low-constraint functional neuroimaging technique, near-infrared spectroscopy (NIRS). Study subjects included 55 healthy, elderly volunteers. We measured hemodynamic responses over prefrontal cortical (PFC) areas during the verbal fluency task by using multi-channel NIRS and analyzed the relationship between task-associated hemodynamic responses and social functioning as measured by the social adaptation self-evaluation scale (SASS). A significant positive relationship was observed between the SASS total score and PFC activation. Our findings suggest that PFC activation is associated with social functioning in healthy elderly adults. Furthermore, hemodynamic responses assessed using non-invasive NIRS could be a useful biological marker of these characteristics.

1. Introduction

Cognitive function in elderly adults is an important area of study not only in Japan but also world-wide as the average lifespan continues to increase because of improvements in technology and modern medicine. While early work primarily focused on the pathological changes in cognitive function associated with systemic medical disease (e.g., cardiovascular disease) or neurological disease (e.g., Alzheimer's disease), recent studies have begun to focus on the cognitive changes that occur as a part of healthy aging.

It is well established that cognitive functions, such as selective attention, memory, and executive function, decline with age [1,2]. Today, larger numbers of individuals are reaching ages where functional decline is more common [3]. As the proportion of individuals over the age of 60 grows, it is of utmost socioeconomic importance to promote their functional independence and increase their quality of life. Seniors consistently cite cognitive health as important for quality of life [4], and cognition is widely recognized by researchers

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as an important contributor to late life functioning [5–7]. Without sufficient cognitive skills, it becomes difficult to meet social and financial duties that are part of daily life. Major individual differences in rate and onset of decline are observed [8,9], but even minor cognitive deficits can severely impact the ability of elderly adults to cope with the demands of daily living. One major aspect of cognition relevant to social functioning is executive function, which has been defined as the ability to deviate from a stereotyped behavior locked to environmental stimuli. Executive function is typically associated with the prefrontal cortex (PFC), a region involved in other high-level cognitive functions, such as working memory and language processing. Considering the significance of social functioning in healthy elderly adults, it may be worthwhile to elucidate the relationship between PFC neural activity and social functioning in this group.

Here, we examined hemodynamic responses in frontotemporal regions during engagement in an executive task in healthy elderly adults by using the non-invasive neuroimaging method of multi-channel near-infrared spectroscopy (NIRS). Near-infrared light penetrates into tissues and is absorbed by hemoglobin, and the degree of absorption is dependent on the oxygenation state of the tissue [10]. It is well established that oxygen consumption, regional cerebral blood response, and oxygenated hemoglobin supply are increased in highly activated neural regions [11,12]. NIRS allows the measurement of oxygenated ([oxy-Hb]) and deoxygenated hemoglobin ([deoxy-Hb]) concentrations in micro-blood vessels, which are correlated with changes in regional cerebral blood volume (rCBV) [13–15]. Recent research supports the utility of NIRS as an early detection method for dementia [16,17]. In contrast to other neuroimaging methodologies, such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), NIRS can be easily, rapidly, and non-invasively performed in a restraint-free environment, making it especially suitable for psychiatric patients. NIRS has been used to assess brain functions in elderly adults [18–21] and in patients with various psychiatric disorders, including schizophrenia, depression, and bipolar disorder [22–24].

One of the most useful tools for assessing social functioning is the social adaptation self-evaluation scale (SASS). This 21-item scale was developed by Bosc et al. [25] to evaluate patients' social motivation and behavior in depression; the reliability and validity of the Japanese version of the SASS were subsequently confirmed [26]. Each item is scored from 0 to 3, corresponding to minimal and maximal social adjustment, with a total score range of 0 to 60. The subjects are asked to instantly provide their opinion about the question. Previous studies used principal component analysis to demonstrate that 21 SASS items could be summarized into three factors: interpersonal relations, interest and motivation, and self-perception (Table 1) [26]. Many mood disorder patients with symptoms in remission fail to successfully reintegrate into society, presumably because of their residual social functioning deficit, which is relevant to their cognitive capacity. Extending the view to nonclinical populations, cognitive dysfunction in healthy elderly adults may also affect social functioning capacity and social adaptation. We have demonstrated the association of reduced prefrontal [oxy-Hb] activation induced by a verbal fluency task (VFT) with functional impairment assessed by SASS in patients with geriatric depression by using 52-channel NIRS [20]; however, medication is a possible mediator of this association. If similar findings are obtained for generally healthy, unmedicated elderly adults, those would support the universal relevance of the prefrontal hemodynamic responses to social functioning.

The purpose of the present study was to investigate an association between social functioning and PFC hemodynamic responses in healthy elderly adults by using NIRS. We hypothesized that PFC hemodynamic responses associated with executive function should correlate with social functioning in healthy elderly adults, as we previously demonstrated in patients with geriatric depression [20].

Table 1
The items included in each factor obtained by principal component analysis of the Japanese version of the social adaptation self-evaluation scale (SASS).

First factor: interpersonal relations
10. External relationship quality
9. Relationship seeking behavior
8. Gregariousness
12. Social attractiveness
7. Family relationship quality
11. External relationship appreciation
6. Family seeking behavior
13. Social compliance
Second factor: interest and motivation
16. Intellectual interest
3. Work enjoyment
1. Job interest or 2. Home work interest
4. Interest in hobbies
15. Social inquisitiveness
14. Community involvement
21. Control of surroundings
5. Quality of spare time
Third factor: self-perception
18. Rejection sensitivity
17. Comminication difficulties
19. Vainess
20. Difficulties in coping with resources

2. Material and methods

2.1. Subjects (Table 2)

A total of 55 healthy elderly volunteers (26 males and 29 females) aged between 60 and 81 years (mean ± SD, 70.1 ± 5.4) participated in this study. All the participants were recruited between April 2007 and March 2009 on the basis of consecutive referrals. All participants were right-handed with the criterion of more than 80% by the Edinburgh Inventory Index [27] and were native Japanese speakers.

Two experienced psychiatrists screened participants and excluded those with psychiatric symptoms above the threshold level. Our exclusion criteria were as follows: history of neurological or psychiatric disease; use of psychoactive medications; substance misuse; and serious medical conditions, including history of heart disease, diabetes, or untreated hypertension. Participants whose hypertension was controlled by prescription medication were admitted into the study. All participants were screened for dementia by using the Mini Mental State Examination (MMSE) [28,29], and any individual scoring below 24 was excluded.

All subjects provided written consent after receiving comprehensive information about the protocol. The study was approved by the ethics committee of Tottori University Faculty of Medicine.

2.2. Self-report measures

Prior to scanning, all the participants completed two self-assessments: the Beck Depression Inventory (BDI) for depression severity and the SASS for social functioning.

2.3. Activation task

The task procedure in the present study was similar to that described by Takizawa et al. [30]. The cognitive activation task included a 30-s pre-task baseline, a 60-s VFT, and a 70-s post-task baseline. For the pre- and post-task baseline periods, the subjects were instructed to consecutively repeat the five Japanese vowels

("a," "i," "u," "e," and "o") aloud. The subtraction method (task minus the average of the pre- and post-task baseline) was used to minimize the vocalization effects during VFT. During the task period, they were instructed to generate as many Japanese words beginning with a designated syllable as possible. The three sets of initial syllables (A: /to/, /se/, /o/; B: /a/, /ki/, /ha/; C: /na/, /i/, /ta/) were presented in counterbalanced order among the subjects, and each syllable changed every 20 s during the 60-s task. The total number of correct words generated during the VFT was adopted as a measure of task performance.

2.4. NIRS machine

Hb changes were measured with a 52-channel NIRS machine (ETG-4000; Hitachi Medical Co., Tokyo, Japan). Each patient sat in a comfortable chair and was instructed to minimize head movement, jaw clenching, and eye blinking during the NIRS measurement to reduce artifacts. The NIRS machine measures relative changes in [oxy-Hb] and [deoxy-Hb] by using two wavelengths of infrared light (695 and 830 nm) based on the modified Beer–Lambert law [31]. In this system, these Hb values include a differential path-length factor (DPF). Zhao et al. [32] used a Monte Carlo simulation and reported that the estimated DPF variation in the forehead region of adult humans was homogeneous. Therefore, the distance between pairs of source-detector probes was set at 3 cm, and each measurement area between pairs of source-detector probes was defined as a "channel" (ch). The machine measures points at a depth of 2 to 3 cm below the scalp, which corresponds to the cortical surface [33,34]. The probes of the NIRS machine were placed on the frontotemporal region of each participant, with the midcolumn of the probe located over Fpz, and the lowest probes placed along the T3-Fp1-Fpz-Fp2-T4 line in accordance with the international 10/20 system for electroencephalography. This arrangement enabled the measurement of Hb values from both prefrontal and superior temporal cortical surface regions. The correspondence between the NIRS channels and the measurement points on the cerebral cortex was confirmed by a multi-subject study of anatomical craniocerebral correlation [35] and was presented according to the results of the virtual registration method [36].

The rate of data sampling was 0.1 s, and the obtained data were analyzed using the integral mode: the pre-task baseline was determined as the mean over the 10-s period immediately before the task period, and the post-task baseline was the mean over the last 5 s of the post-task period. Linear fitting was applied to the data recorded between both baselines. A moving average method, using a 5-s window width, was applied to remove short-term motion artifacts. Because we could not remove all artifacts in this way, we applied automatic rejection of data with artifacts separately for each channel [22,37].

For the analysis of the hemodynamic response data, Hb variables for each channel were averaged for the both time segments (pre-task baseline and task period). We focused on [oxy-Hb] concentrations during the 60-s task period, since the oxy-Hb change (task period – pre-task baseline period) was assumed to more directly reflect cognitive activation than the deoxy-Hb change, as previously shown by animal studies and correlations with fMRI blood oxygenation level-dependent signals [12,38]. However, the [deoxy-Hb] analyses are also presented.

2.5. Data analyses

All statistical analyses were performed using SPSS Statistics 19.0 (Tokyo, Japan).

The mean [Hb] changes for the pre-task baseline period and that for the task period were compared in each channel by using Student's paired *t*-tests to confirm the statistically significant increase associated with the VFT. Because we performed 52 paired two-tailed *t*-tests, we applied a correction for multiple comparisons using a false discovery rate (FDR); we set the value of q specifying the maximum FDR to 0.05, so that there were no more than 5% false positives on average [39].

Pearson's product moment correlation coefficients were calculated to determine if there were relationships between the mean [Hb] changes during the task period and SASS scores for each NIRS channel. We again adopted an FDR-based procedure for the multiple testing correction in correlational analyses for 52 channels and focused on those channels where r values reached a significance level of $P < 0.05$ (FDR-corrected). For primary analysis, we examined the relationship between task-related [Hb] changes and SASS total scores. As secondary analyses, we also examined the relationship between task-related [Hb] changes and three SASS factor scores: interpersonal relations, interest and motivation, and self-perception (Table 1) [26]. Moreover, to detect any confounding factors, we also investigated the relationships between [Hb] changes and task performances of VFT, BDI, MMSE; age; and education level.

Table 2
Participant characteristics.

Demographics	healthy older adults ($n = 55$) mean (SD)
Age (years)	70.1 (5.4)
Gender (females/males)	29/26
Right-handedness (%)	96.8 (7.4)
Education (years)	11.4 (1.9)
MMSE	27.4 (2.4)
BDI	5.7 (4.7)
SASS total	39.4 (7.2)
Interpersonal relationships	16.6 (4.0)
Interest and motivation	15.9 (3.2)
Self-perception	6.9 (1.3)
Number of words generated	12.0 (4.3)

3. Results

Table 2 shows the participants' demographic data and task performance.

3.1. Test for significance in [Hb] change during activation period relative to baseline

The grand-averaged waveforms of [oxy-Hb], [deoxy-Hb], and [total-Hb] during VFT in healthy elderly adults are shown in Fig. 1.

We found a significant [oxy-Hb] increase during VFT performance in 47 channels (ch2 to 5, 8, 10, 12 to 52; FDR-corrected P vales: 0.001 to 0.045) and a significant [deoxy-Hb] decrease during the VFT in 42 channels (ch2, 8 to 11, 13, 14, and 18 to 52; FDR-corrected P: 0.001 to 0.040), which confirmed cognitive activation during the VFT.

3.2. Correlation analyses

The mean [oxy-Hb] changes showed a significant positive correlation with total SASS score in 22 channels (ch3, 6, 7, 14, 15, 17 to 19, 25 to 29, 35 to 37, 39, and 46 to 50; R: 0.33 to 0.48; FDR-corrected P: 0.001 to 0.021), with the highest correlations located approximately in the frontopolar, left ventrolateral, and bilateral dorsolateral PFC regions (Figs. 2a and 3).

Moreover, the mean [oxy-Hb] change positively correlated with the following two SASS factor scores: interpersonal relationship (19 channels: ch17, 18, 25, 26, 28, 29, 35 to 37, 39, 40, and 44 to

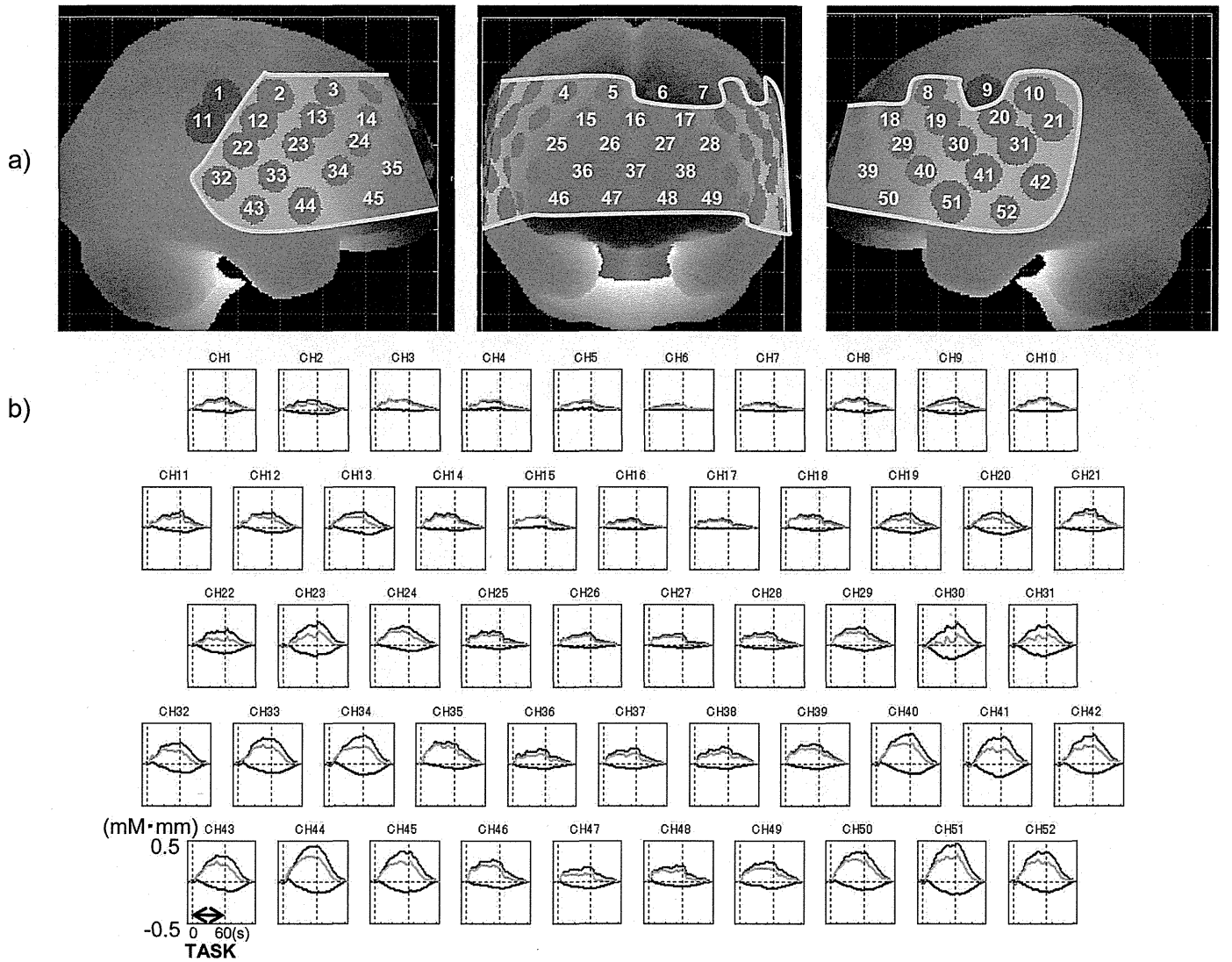

Fig. 1. (a) The yellow regions correspond to the NIRS channels, which showed significant increases in mean [oxy-Hb] during the task period compared with the pre-task baseline (FDR-corrected $P < 0.05$). (b) Grand average waveforms in healthy elderly adults ($n = 55$). [Oxy-Hb], [deoxy-Hb], and [total-Hb] concentration changes during the 60-s verbal fluency task (between two dotted vertical lines in each graph) are presented as grand average waveforms for all 52 channels as red, blue, and green lines, respectively. NIRS channel locations were probabilistically estimated and anatomically labeled in the standard brain space in accordance with Tsuzuki et al. [36].

51; R: 0.33 to 0.51; FDR-corrected P: 0.001 to 0.018), located predominantly in the frontopolar and ventrolateral PFC (Figs. 2b and 3); and interest and motivation (13 channels: ch6, 14, 17, 25 to 28, 37, 39, and 46 to 49; R: 0.35 to 0.49; FDR-corrected P: 0.001 to 0.011), located predominantly in the frontopolar and dorsolateral PFC (Figs. 2c and 3); however, the hemodynamic response did not show any significant relationship with self-perception factor scores.

There was no significant correlation between mean [oxy-Hb] change (in any channel) and task performance during VFT (R: −0.29 to 0.06, ns), BDI (R: −0.40 to −0.01, ns), MMSE (R: −0.11 to 0.22, ns), age (R: −0.29 to 0.26, ns), or education level (R: −0.15 to 0.20, ns).

The mean [deoxy-Hb] changes in any channel were not significantly correlated with the SASS total scores (R: −0.32 to 0.29, ns), interpersonal relationship (R: −0.29 to 0.21, ns), interest and motivation (R: −0.31 to 0.31, ns), self-perception (R: −0.38 to 0.18, ns) factor scores, task performance during VFT (R: −0.21 to 0.33; ns), BDI (R: −0.20 to 0.30, ns), MMSE (R: −0.32 to 0.15, ns), age (R: −0.26 to 0.31, ns), or education level (R: −0.10 to 0.29, ns).

4. Discussion

Using 52-channel NIRS, we observed considerable hemodynamic responses over prefrontal and superior temporal areas during the VFT in healthy elderly adults. Furthermore, the task-associated [oxy-Hb] increase showed a significant positive correlation with the average total SASS score, and this relationship was strongest with regard to PFC activation. More specifically, a significant positive relationship was observed between SASS interpersonal relationship factor scores and frontopolar and ventrolateral PFC activation, and between SASS interest and motivation factor scores and frontopolar and dorsolateral PFC activation. Our findings suggest that PFC activation is associated with social functioning in healthy elderly adults. The frontal hypothesis of cognitive aging assumes that the cerebral cortex deteriorates disproportionately and that aging affects the frontal lobe first [40]. Neurobiological data [41] tend to support this hypothesis; age-related deterioration of the brain have been shown to occur earliest in the PFC [42], which is involved in memory, attention, executive function and emotion, as well as other complex cognitive

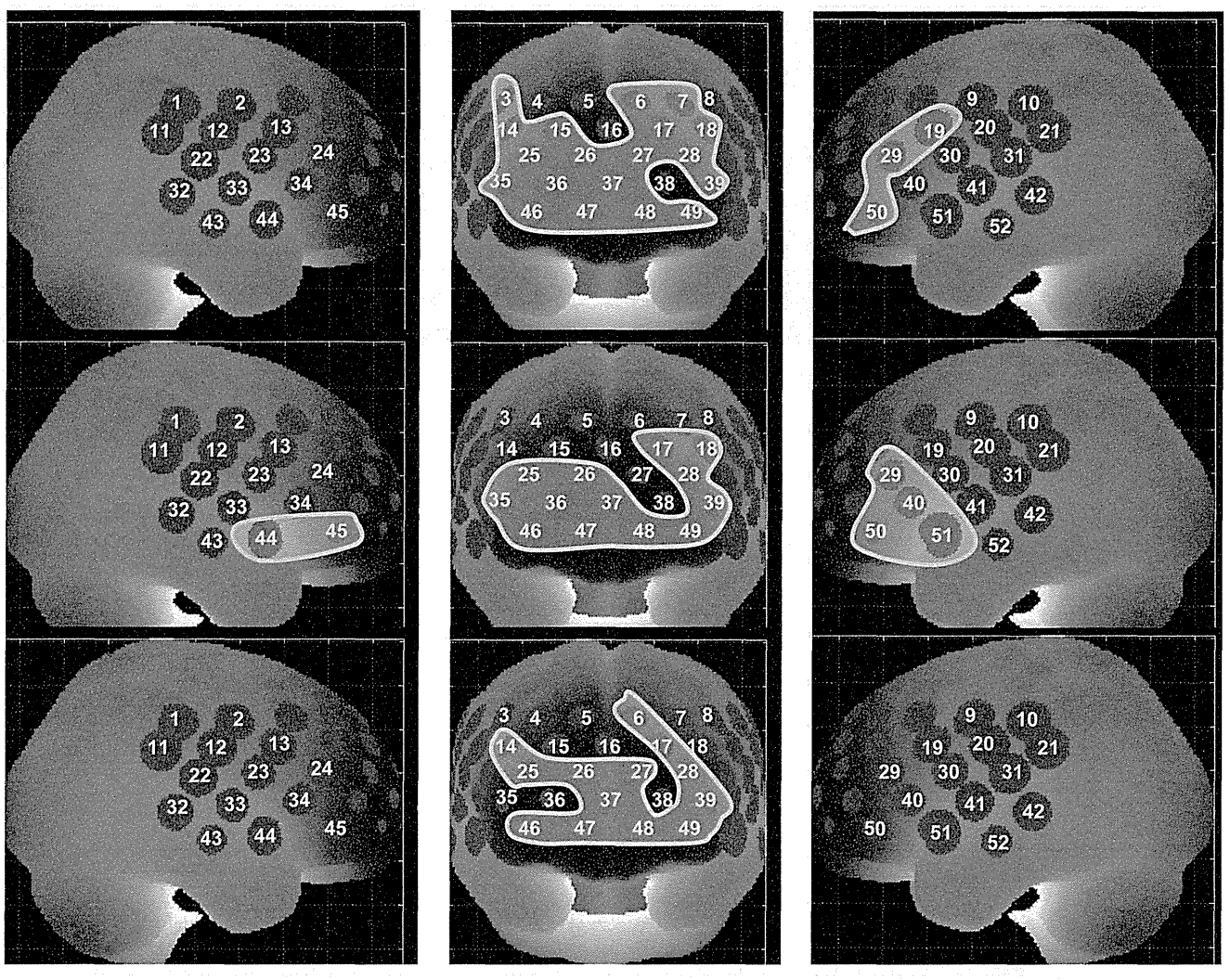

Fig. 2. The relationship between [oxy-Hb] and SASS scores in healthy elderly adults. Yellow brain areas correspond to NIRS channels that showed a significant positive correlation (Pearson's product moment correlation, FDR-corrected $P < 0.05$) between [oxy-Hb] and total SASS (a), interpersonal relationship (b), and interest and motivation (c) scores.

functions [40,43,44]. In addition, older age has been associated with lower blood flow and metabolism at rest, particularly in frontal cortex [45]. In the present study, we identified specific PFC regions associated with functional level in healthy elderly adults.

The PFC is cytoarchitectonically subdivided into several regions: dorsolateral (BA 9/46), ventrolateral (BA 44/45/47), and frontopolar (BA 10) [46,47]. However, these regions have not been successfully mapped to specific cognitive functions. The frontopolar cortex is the most anterior part of the frontal lobe, which is one of the least well-understood regions of the human brain. It has been suggested to have enlarged and become specialized during hominid evolution [48], and is assumed to provide a higher level of control to coordinate ventro- and dorsolateral functions to maximize task performance [47,49]. One important feature of the frontopolar cortex is that the number of dendritic spines per cell and the total spine density are higher than in other PFC regions [50]. This indicates that the functional properties of the frontopolar cortex are more likely to be involved in integration.

A close association between NIRS response and social functioning has been shown for some psychiatric diseases. Takizawa et al. [30] showed reduced PFC [oxy-Hb] activation during VFT in schizophrenia patients by using NIRS and the inverse relationship between hemodynamic responses and social functioning using global assessment of functioning scores. We similarly demonstrated an association of reduced [oxy-Hb] activation in the PFC regions during VFT with functional impairment assessed by SASS total scores in late-onset major depressive disorder patients [20]. Social functioning requires complex operations of executive function that include monitoring, reasoning, organizing, selecting, and planning. Burgess et al. [51] noted that the frontopolar region is involved in high-level executive control and, thus, is likely to be a vital component of social functioning. Considering these observations together, it may be reasonable to postulate that the hemodynamic response observed in the frontopolar regions during the VFT in the present study was associated with social functioning level. The functional properties of the frontopolar cortex are particularly important from a clinical point of view in that they may provide some hint as to how social functioning can be improved in elderly adults.

Furthermore, a significant positive relationship was observed between SASS interpersonal relationship factor scores and frontopolar and ventrolateral PFC activation, and between SASS interest and motivation factor scores and frontopolar and dorsolateral PFC activation. The dorsolateral PFC appears to manipulate information, whereas the ventrolateral PFC appears to store and retrieve information from short-term stores [42,52–54]. Moreover, the dorsolateral PFC and lateral frontopolar cortex are involved in integrating emotion and cognition [43] and motivation and cognition

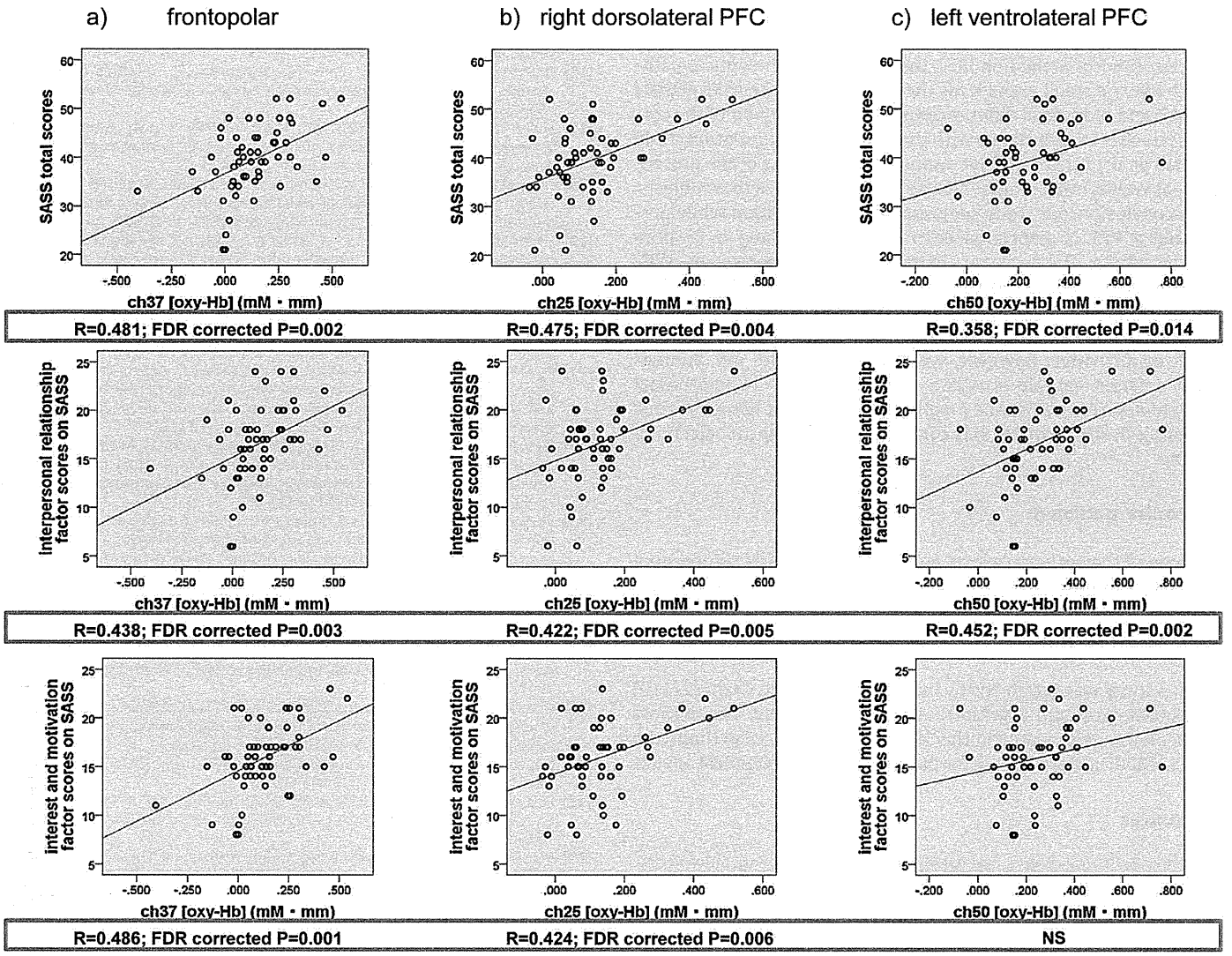

Fig. 3. Scatter diagrams showing the relationship between SASS scores and mean [oxy-Hb] changes in channels 37 (frontopolar) (a), 25 (right dorsolateral PFC) (b), and 50 (left ventrolateral PFC) (c).

[55,56]. Accordingly, it seems reasonable to consider that [oxy-Hb] activation in the dorsolateral PFC is relevant to the interest and motivation factor, and in the ventrolateral PFC, it is relevant to the interpersonal relationship factor in social functioning.

In the present study, instead of using fMRI, we used NIRS to measure neuronal activation at the surface of the prefrontal and temporal cortices. One of the primary advantages of using NIRS is that the technique can be performed under less body constraint than other imaging modalities such as fMRI, which requires the subject to maintain an unusual body posture with restricted head movement; thus, NIRS is useful for studying brain activity under more "natural" conditions, especially suitable for elderly adults [20,21,57–60]. Furthermore, NIRS can measure brain activity in the frontpolar region with high signal-to-noise ratio, whereas fMRI has potential problems for data quality of areas located under the frontal sinus [61].

Although NIRS has advantages compared to fMRI as above, it is also associated with a limitation in measurement depth and poor spatial resolution. In the present study, we could not investigate other areas than PFC, such as hippocampus and/or posterior regions of the brain, which are known to be related to memory and visuo-spatial processing. Moreover, intermingling effect of extracranial hemodynamic changes such as skin blood flow in the measurement data has raised a question as to what extent NIRS signals reflect hemodynamic changes in the brain. For example, Takahashi et al. [62] suggested that the majority of the hemodynamic changes measured by NIRS in the forehead reflected the skin blood flow during a verbal fluency task. This finding indicated that extracranial hemodynamic changes such as skin blood flow are a considerable source of the task-related signals in the forehead and may be present in a wide range of cognitive tasks. However, the impact of the extracranial artifacts, including their significance and generality, has not been clarified. On the other hand, recent studies using simultaneous NIRS-fMRI measurements investigating PFC showed a significant correlation between NIRS and BOLD signals, although with a wide regional and inter-individual variability [38,63]. More recently, Sato et al. [64] demonstrated that temporal changes in the NIRS signals in the activated area were significantly correlated with the BOLD signals in the gray matter rather than the extracranial BOLD signals or skin blood flow measured with a laser Doppler flowmeter. Moreover, the amplitudes of the task-related responses of the NIRS signals were significantly correlated with the BOLD signals in the gray matter *across participants*. The finding is important. As the amplitude of the NIRS signals includes the differential pathlength factor (DPF), which is assumed to be variable among different individuals, some researchers consider that direct comparison of the

amplitude between individuals is somewhat problematic. However, according to their finding as well as a similar finding obtained for sensorimotor activation [65], the variation in the optical pathlength may be small enough for the amplitude of the NIRS signals to represent individual differences in functional activity of the cortices, which is in accordance with the Monte Carlo simulation study by Zhao et al. [32]. It may give support to the results of the present study as well as other studies analyzing NIRS signals across subjects.

In conclusion, our study suggests that PFC activation while performing a VFT is associated with social functioning in healthy elderly adults; furthermore, hemodynamic responses to WFT assessed using non-invasive NIRS could be a useful biological marker of social functioning in aged populations, more specifically in terms of interpersonal relationship, and interest and motivation. To be confirmative, however, we need to replicate our findings using a larger sample size and also implement a longitudinal study to assure whether the longitudinal change of hemodynamic responses in an individual may correspond to change in social functioning.

Disclosure statement

None of the authors reports any financial interests or potential conflicts of interest.

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Serotonin and dopamine receptors in motivational and cognitive disturbances of schizophrenia

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Negative symptoms (e.g., decreased spontaneity, social withdrawal, blunt affect) and disturbances of cognitive function (e.g., several types of memory, attention, processing speed, executive function, fluency) provide a major determinant of long-term outcome in patients with schizophrenia. Specifically, motivation deficits, a type of negative symptoms, have been attracting interest as (1) a moderator of cognitive performance in schizophrenia and related disorders, and (2) a modulating factor of cognitive enhancers/remediation. These considerations suggest the need to clarify neurobiological substrates regulating motivation. Genetic studies indicate a role for the monoamine systems in motivation and key cognitive domains. For example, polymorphism of genes encoding catecholamine-O-methyltransferase, an enzyme catabolizing dopamine (DA), affects performance on tests of working memory and executive function in a phenotype (schizophrenia vs. healthy controls)-dependent fashion. On the other hand, motivation to maximize rewards has been shown to be influenced by other genes encoding DA-related substrates, such as DARPP-32 and DA-D_2 receptors. Serotonin (5-HT) receptors may also play a significant role in cognitive and motivational disabilities in psychoses and mood disorders. For example, mutant mice over-expressing D_2 receptors in the striatum, an animal model of schizophrenia, exhibit both decreased willingness to work for reward and up-regulation of 5-HT_{2C} receptors. Taken together, genetic predisposition related to 5-HT receptors may mediate the diversity of incentive motivation that is impaired in patients receiving biological and/or psychosocial treatments. Thus, research into genetic and neurobiological measures of motivation, in association with 5-HT receptors, is likely to facilitate intervention into patients seeking better social consequences.

Keywords: serotonin, 5-HT receptors, motivation, cognition, schizophrenia, dopamine, negative symptoms, psychosis

INTRODUCTION

Disturbances of mental processes, including cognitive function (e.g., several types of memory, attention, processing speed, and executive function, fluency) and motivation characterize many of the psychiatric illnesses, such as schizophrenia, mood disorders, and substance abuse (Simpson et al., 2011; Choi et al., 2014; Sumiyoshi, in press). Recently, the development of biological (e.g., pharmacotherapy and brain stimulation) and psychosocial (e.g., cognitive rehabilitation) interventions is targeting social function/adaptation as an important outcome measure (Harvey et al., 2011; Leifker et al., 2011). In this context, negative symptoms (decreased spontaneity, social withdrawal, and blunt affect) and cognitive impairment provide a major determinant of long-term outcome. Specifically, motivation deficits have been attracting interest as a moderator of (1) cognitive performance in patients with schizophrenia and related disorders, and (2) beneficial influence of cognitive enhancers/remediation (Fervaha et al., 2014; Strauss et al., 2014). These considerations suggest the need to clarify neurobiological substrates regulating motivation for improving quality of life in a rational and effective manner.

We herein present a theory/hypothesis that the research into genetic and neurobiological measures of motivation, linked to serotonin (5-HT) receptors, would facilitate treatment of patients with schizophrenia or other psychiatric illnesses.

MOTIVATIONAL DISTURBANCES IN SCHIZOPHRENIA

Schizophrenia is characterized by a range of symptoms, e.g., positive symptoms (delusions, hallucinations, thought disorders), negative symptoms, mood symptoms, and cognitive impairment. Specifically, there is a suggestion that negative symptoms can be separated into two domains; (1) a motivational dimension, consisting of avolition, anhedonia, and asociality, and (2) a diminished expressivity dimension, consisting of restricted affect and alogia (Strauss et al., 2014). There is a general consensus that motivational disturbances may overlap some (e.g., anhedonia), but not all (e.g., blunt affect, alogia) aspects of negative symptoms. The former dimension has been considered to be of greater importance in terms of functional outcome, quality of life, and recovery from the disease (Strauss et al., 2014). Whether other aspects of symptomatology of schizophrenia (e.g., mood

symptoms) may substantially affect motivation in patients or vulnerable people remains to be determined (Schlosser et al., 2014).

DOPAMINE (DA) SYSTEMS GOVERNING MOTIVATION AND COGNITION

The neural basis for intrinsic motivation has been an issue of extensive research. For example, activity of the anterior striatum and prefrontal cortex (PFC), measured by the functional MRI, has been shown to be associated with intrinsic motivation (Murayama et al., 2010). This line of anatomical evidence is consistent with genetic studies indicating a role for the monoamine systems in cognition and motivation, as discussed below.

The Val158Met polymorphism of the genes encoding catecholamine-O-methyltransferase (COMT), an enzyme catabolizing DA, affects performance on tests of working memory and executive function in a phenotype (schizophrenia vs. healthy controls)-dependent fashion (Egan et al., 2001). Thus, individuals with the val/val carriers in *COMT* show greater efficacy of the enzyme, leading to decreased DA levels in the PFC. The enzyme has also been suggested to mediate uncertainty-based exploration that is linked to DA levels in the PFC. For example, individuals with at least one met-allele show enhanced exploration compared to those with val/val genotype (Frank et al., 2007).

On the other hand, motivation to maximize rewards has been shown to be influenced by other DA-related genes expressed in the striatum/nucleus accumbens (NAc). Specifically, reward learning and negative reward avoidance are affected by genotypes of a polymorphism (rs907094. A/G) of the gene encoding DARPP-32 (a protein required for synaptic plasticity and reward learning mediated by DA-D_1 receptors) and the D_2 receptor (related to avoidance of negative outcomes), respectively (Frank et al., 2007; Klein et al., 2007). Thus, individuals with T/T genotype show greater expression of mRNA for the DARPP-32 gene, leading to greater performance to maximize rewards compared to C-allele carriers (reviewed in Frank et al., 2009). Similarly, T/T carriers of genes encoding D_2 receptors are associated with greater density of these receptors in the striatum and greater likelihood to maximize rewards (Hirvonen et al., 2004; Frank et al., 2007). A recent study (Simpson et al., 2013) reported that overexpression of D_3 receptors, a member of the D_2 receptor family, in the striatum selectively impaired incentive motivation, as measured by an operant task.

The mechanisms by which DA receptors govern motivation and cognitive functions may involve timing perception. For example, genetically-engineered mice overexpressing D2 receptors in the striatum have been shown to elicit impaired working memory, behavioral flexibility and sensorimotor gating, i.e., behavioral abnormalities reminiscent of schizophrenia (Kellendonk et al., 2006). These model animals also demonstrate reduced motivation, as well as alteration of interval timing organization, as measured by the operant timing task (Drew et al., 2007). Further studies indicate that the impaired timing in these mutant mice mediates the ability of decreased motivation to worsen cognitive functions, including working memory and attention (Ward et al., 2009). These lines of evidence suggest a strategy for the intervention into motivational disturbances, in terms of biological and/or tailor-made treatments.

Figure 1 summarizes a concept about how genes encoding these DA-related substrates contribute to cognitive and motivational behaviors.

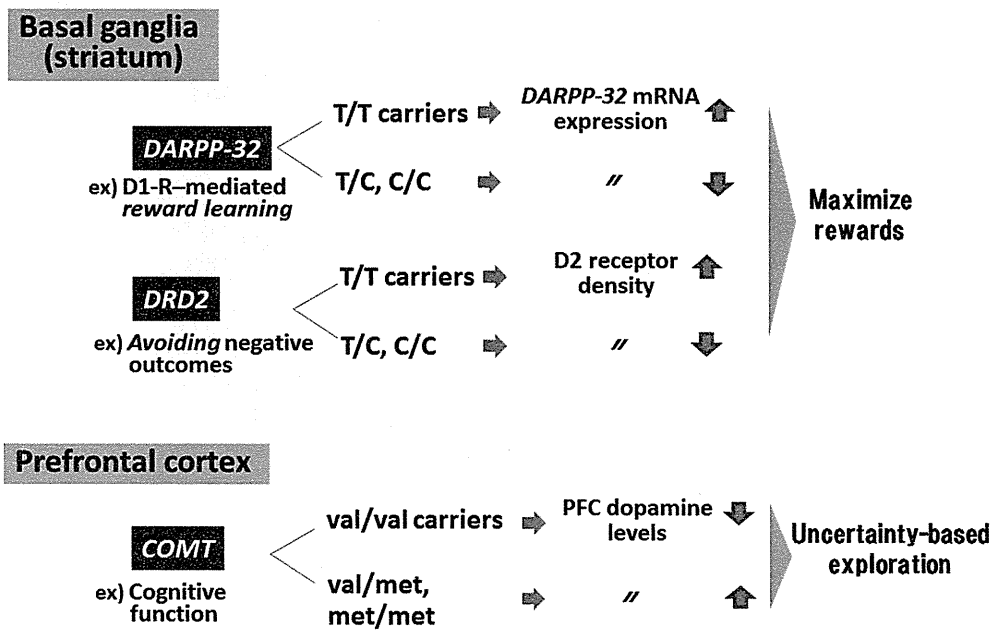

FIGURE 1 | Genes in the dopaminergic motivational system. Polymorphisms of genes encoding *DARPP-32* and dopamine (DA)-D_2 receptors *(DRD2)* affect behaviors to maximize rewards, while the polymorphism in *COMT* are associated with uncertainty-based exploration. Information in the Figure was extracted from Frank et al. (2009).