

progressive gray matter reduction in the temporal lobe structures, which might be specific to overt schizophrenia within the schizophrenia spectrum.

Previous longitudinal studies using whole-brain voxel-based morphometric (VBM) analyses demonstrated progressive gray matter reduction predominantly in the left STG among temporal regions in first-episode schizophrenia (Mané et al., 2009; Whitford et al., 2006), which has been supported by several ROI studies showing approximately 2–6%/year reduction in this region during early phases of schizophrenia (Kasai et al., 2003a,b; Takahashi et al., 2010b). In accordance with these localized brain changes in schizophrenia, we found no cross-sectional and longitudinal gray matter changes in non-STG lateral temporal regions (middle and inferior temporal gyri) in our first-episode cohort. However, a cross-sectional MRI study by Onitsuka et al. (2004) reported gray matter reduction in these regions, which contribute to visual recognition and speech perception (Hickok and Poeppel, 2004) and are also related to auditory hallucination (Jardri et al., 2011), in male chronically medicated schizophrenia patients. The possibilities of non-STG gray matter changes later in the course of schizophrenia and potential medication effect on these regions seem worthy of further examination.

This study generally supports previous cross-sectional MRI findings of bilateral fusiform gyrus gray matter reduction in first-episode (Lee et al., 2002) and chronic (Onitsuka et al., 2003; Takahashi et al., 2006) schizophrenia. Our finding of marked ongoing gray matter reduction in the fusiform gyrus during first-episode schizophrenia is also consistent with an inverse correlation between the fusiform gyrus gray matter volume and initial untreated (Bangalore et al., 2009) or total (Premkumar et al., 2008) illness duration. No fusiform gray matter changes in previous longitudinal VBM studies might be partly attributable to methodological issues of these analyses such as problems of brain registration (Crum et al., 2003). Since our data of a significant correlation between a higher cumulative dose of antipsychotics and less severe gray matter reduction in the fusiform gyrus support the potential ameliorating effect of antipsychotics (Scherk and Falkai, 2006), different sample characteristics (e.g., medication status) might also partly explain these discrepancies. Although the pathological mechanisms underlying these progressive fusiform gray matter changes remain unknown, one postmortem study in the fusiform gyrus of schizophrenia reported reduced neuron density, enlarged minicolumn, and lack of minicolumn thinning that occurs during normal aging (Di Rosa et al., 2009), partly consistent with the hypothesis that anomalies of synaptic plasticity, abnormal brain maturation, and other factors may be relevant (Pantelis et al., 2005).

Despite the notion that dynamic brain changes during the early phases are likely to be related to clinical manifestations of schizophrenia (Takahashi et al., 2009), we did not find a significant relationship of the fusiform gyrus morphologic changes to clinical symptoms, which has been suggested by previous cross-sectional MRI studies (Ha et al., 2004; O'Daly et al., 2007; Nestor et al., 2007). This might be partly due to the small sample size of this study, as annual gray matter loss of the left posterior fusiform gyrus, which contains a core region of social cognition called the “fusiform face area” (Kanwisher et al., 1997), was non-significantly correlated with the severity of negative symptoms. It is also possible that fusiform gyrus abnormalities are more closely related to cognitive deficits, which were not comprehensively assessed in this study.

In this study, the reduction rate of the fusiform gyrus in first-episode schizophrenia (left,  $-2.6\%/year$ ; right,  $-2.3\%/year$ ) was comparable with that found in the STG (left,  $-2.8\%/year$ ; right,  $-1.5\%/year$ ) in the same group of subjects (Table 2). However, we found no direct association between the gray matter changes over time of these structures. Furthermore, whereas progressive changes of the STG were highly correlated with positive symptoms (Takahashi et al., 2010b), those of fusiform gyrus might be related to the severity of

negative symptoms. Interestingly, a cross-sectional MRI study found similar dissociable brain structure–function relationships; Nestor et al. (2007) reported that (1) reduced left STG volume was related to positive symptoms and executive deficits and that (2) reduced left fusiform gyrus was related to negative symptoms and facial memory deficits in the same subjects with chronic schizophrenia. Taken together, these findings suggest the regional specificity of the temporal lobe pathology in schizophrenia in showing that the STG and fusiform gyrus might have distinct contributions to different facets of the illness. Previous MRI studies of the STG suggested a period of intense gray matter reduction during early phases of schizophrenia (Takahashi et al., 2009, 2010a,b), but it remains unclear whether other brain regions have similar nonlinear pattern of progressive changes. Thus, further longitudinal follow-up of first-episode patients as well as additional patients with chronic disease would be required to examine the nature (including the regional specificity) of the progressive gray matter reduction in the course of schizophrenia.

For schizotypal subjects, to our knowledge, only two cross-sectional MRI studies have specifically delineated the fusiform gyrus; we previously reported gray matter reduction in its posterior region in a larger sample of ICD-10 schizotypal disorder patients (Takahashi et al., 2006), whereas another group reported normal fusiform gyrus volume in male subjects with SPD (Dickey et al., 2003). Despite the inconsistencies among the reports possibly due to differences in sample characteristics (e.g., community- or clinic-based, medication status, gender ratio) or imaging techniques, our findings support the notion that schizotypal patients partly share temporal abnormalities with schizophrenia patients, which presumably underlie the attenuated forms of schizophrenic features seen in these patients (Kurachi, 2003; Siever and Davis, 2004; Suzuki et al., 2005). Recent MRI studies using sophisticated Brodmann area (BA)-based analysis in unmedicated SPD (Goldstein et al., 2009; Hazlett et al., 2008) have generally supported our results of ICD-10 schizotypal disorder in showing that SPD patients have temporal gray matter reductions but frontal areas are relatively preserved in schizotypal subjects. In the present longitudinal comparison, only the schizophrenia patients showed progressive gray matter changes of the fusiform gyrus, suggesting that, in combination with lack of frontal changes (Hazlett et al., 2008; Suzuki et al., 2005), the absence of active pathological processes in the fusiform gyrus might be partly related to the sparing of schizotypal patients from the development of full-blown schizophrenia.

A few possible confounding factors in this study should be taken into account. First, this study was partly limited by the small sample size in terms of the study participants. We found no subregional effect in the fusiform findings despite the presumable differences in the functions of the anterior versus posterior portions (Kanwisher et al., 1997). We also failed to detect a significant relationship between the fusiform gyrus volume changes and clinical symptoms in first-episode schizophrenia. The limited statistical power due to small sample size might partly explain these unexpected results. On the other hand, given the small effect size of longitudinal fusiform changes in the schizotypal patients [Cohen's  $d = 0.25$  (left) and  $0.17$  (right)], merely a lack of statistical power could not fully explain disease specific fusiform reduction in schizophrenia [Cohen's  $d = 1.20$  (left) and  $1.23$  (right)]. Second, given the weak correlation between the left middle temporal gyrus volume and medication duration in the schizotypal subjects, the possibility exists that the medication effects have biased our results. However, the effect of medication alone could not explain our main finding of progressive fusiform changes specific to schizophrenia patients, who received larger amounts of antipsychotics than schizotypal patients, as correlation analyses suggested potential ameliorating effects of antipsychotics. The effect of medication on brain morphology has been controversial; a recent animal study suggests a toxic effect of antipsychotics on brain volumes

(Vernon et al., 2011), whereas previous *in vivo* data suggest both toxic (Ho et al., 2011) and protective (Lieberman et al., 2005; Molina et al., 2005) effects. As antipsychotic may act regionally rather than globally (Borgwardt et al., 2009) and typical and atypical antipsychotics are likely to have different effects (Dazzan et al., 2005) on the brain morphology, the association of detailed medication data (e.g., type, cumulative dose) and longitudinal changes in several brain regions should be further examined in a larger sample. Finally, although we focused on the temporal gray matter changes in this study, assessment of other key brain regions (e.g., prefrontal cortex) would be required to clarify the diagnostic and regional specificity of active brain changes early in the course of schizophrenia.

## 5. Conclusion

In combination with our previous findings of the temporal lobe structures in a larger cross-sectional sample (Takahashi et al., 2006) as well as longitudinal findings of the STG in the same group of subjects (Takahashi et al., 2010b), the present findings support the model that both schizophrenia and schizotypal patients partly share temporal lobe abnormalities as a morphologic substrate for the schizophrenia spectrum, with only schizophrenia patients exhibiting further ongoing pathological processes. These temporal lobe abnormalities are likely to be localized to specific regions (i.e., the STG and fusiform gyrus) and each temporal region might be differentially involved in the clinical manifestations of schizophrenia.

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# Frontal and right temporal activations correlate negatively with depression severity during verbal fluency task: A multi-channel near-infrared spectroscopy study

Q6 T. Noda<sup>a,b,\*</sup>, S. Yoshida<sup>a</sup>, T. Matsuda<sup>a</sup>, N. Okamoto<sup>a</sup>, K. Sakamoto<sup>a</sup>, S. Koseki<sup>c</sup>, Y. Numachi<sup>a</sup>, E. Matsushima<sup>b</sup>, H. Kunugi<sup>d</sup>, T. Higuchi<sup>e</sup>

<sup>a</sup> Department of Psychiatry, National Center of Neurology and Psychiatry Hospital, 4-1-1, Ogawahigashi, Kodaira, Tokyo 187-8551, Japan

<sup>b</sup> Section of Liaison Psychiatry & Palliative Medicine Division of Comprehensive Patient Care, Graduate School of Medical & Dental Sciences, Tokyo Medical & Dental University, 1-5-45, Yushima, Bunkyo, Tokyo 113-8519, Japan

<sup>c</sup> Department of School Education, Aichi University of Education, 1, Hirosawa, Igayacho, Kariya, Aichi 448-8542, Japan

<sup>d</sup> Department of Mental Disorder Research, National Institute of Neuroscience, National Center of Neurology and Psychiatry, 4-1-1, Ogawahigashi, Kodaira, Tokyo 187-8502, Japan

<sup>e</sup> National Center of Neurology and Psychiatry, 4-1-1, Ogawahigashi, Kodaira, Tokyo 187-8551, Japan

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## ABSTRACT

Multi-channel near-infrared spectroscopy (NIRS) is a noninvasive, on-the-spot, functional neuroimaging technique allowing detection of the spatiotemporal characteristics of brain activity. Previous NIRS studies indicated the oxy-hemoglobin (oxy-Hb) increase during a verbal fluency task (VFT) is attenuated in patients with major depressive disorder (MDD) as compared with healthy controls. However, the possible relationship between depression symptom severity and oxy-Hb change on NIRS has not yet been elucidated. To examine this relationship, we recruited 30 patients with MDD and 30 age-, gender- and intelligence quotient-matched controls. All underwent NIRS during VFT. As expected, the oxy-Hb increase during the task was significantly smaller in patients than in controls. After false discovery rate correction using 31 channels, the mean increase in oxy-Hb during the task showed a significant negative correlation with the total score of the Hamilton Rating Scale for Depression 21-item version (ch25:  $\rho = -.56$ ; FDR-corrected  $p: .001$ ). When each item of the HAM-D21 was examined individually, insomnia early in 9 channels ( $\rho = -.63$  to  $-.46$ ; FDR corrected  $p: .000-.014$ ), work and activity in 2 channels ( $\rho = -.61$  to  $-.57$ ; FDR corrected  $p: .001$  to  $.003$ ) and psychomotor retardation in 12 channels ( $\rho = -.70$  to  $-.44$ ; FDR corrected  $p: .000-.018$ ) showed significant negative correlations with the mean oxy-Hb increase in the right frontal temporal region. Although it is possible that our results were affected by medication, these data suggest reduced right frontal temporal activation on NIRS during VFT is related to the symptom severity of MDD.

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## Q5 1. Introduction

Major depressive disorder (MDD) is a severe and common psychiatric disorder with a lifetime prevalence of 6.7 per 100 (Waraich et al., 2004). Although depressive symptoms per se do not specifically appear in MDD but also in other psychiatric disorders including bipolar disorders, we do not have an objective diagnostic marker to obtain a clear-cut diagnosis for those patients. In Japan, a relatively new neuroimaging method, near-infrared spectroscopy

(NIRS) has been approved by the Ministry of Health, Labor and Welfare as a highly advanced medical technology to help distinguish between schizophrenia, depression and bipolar disorders in 2009. Verbal fluency task (VFT) is recommended as an activation task because of a relatively rich store of data. VFT is an easy task to examine the executive function and frequently used in neuroimaging studies (Alvarez and Emory, 2006) and is known to activate prefrontal cortex (PFC) in healthy subjects (Frith et al., 1991; Schlösser et al., 1998). Numerous neuropsychological studies suggest that patients with MDD show executive dysfunction (Gohier et al., 2009; Rose and Ebmeier, 2006; Fossati et al., 2003; Porter et al., 2003; Degl'Innocenti et al., 1998).

Multi-channel near-infrared spectroscopy (NIRS) is a noninvasive, on-the-spot, restraint-free functional neuroimaging technique allowing detection of the spatiotemporal characteristics of brain

\* Corresponding author. Department of Psychiatry, National Center of Neurology and Psychiatry Hospital, 4-1-1, Ogawahigashi, Kodaira, Tokyo 187-8551, Japan.

Tel.: +81 42 341 2711; fax: +81 42 346 1705.

E-mail address: [t-noda@ncnp.go.jp](mailto:t-noda@ncnp.go.jp) (T. Noda).

function near the brain surface using near-infrared light (Strangman et al., 2002a; Boas et al., 2004). NIRS has enabled bedside measurement of the concentrations of oxy-hemoglobin (oxy-Hb) and deoxy-hemoglobin (deoxy-Hb) changes with a high time resolution (.1 s). The concentrations of oxy-Hb and deoxy-Hb are assumed to reflect the regional cerebral blood volume (rCBV) changes, which was supported by the simultaneous NIRS and PET study (Villringer et al., 1997; Ohmae et al., 2006).

In fact, numerous studies have demonstrated that the oxy-Hb increase in the fronto-temporal regions during a VFT is significantly smaller in patients with MDD than in those with bipolar disorder or healthy controls (Pu et al., 2008; Kameyama et al., 2006; Suto et al., 2004; Matsuo et al., 2002). Moreover, NIRS studies using VFT have also demonstrated frontal lobe dysfunction in schizophrenia (Suto et al., 2004; Takizawa et al., 2008), and panic disorder (Nishimura et al., 2007). However, the relationship between depression symptom severity at the time of examination and oxy-Hb change on NIRS has not yet been clarified.

In neuroimaging studies using other methodologies, focusing on cortex level that NIRS reflects, positron emission tomography (PET) studies found that abnormal reductions of cerebral blood flow (CBF) and metabolism in patients with MDD in PFC (Kimbrell et al., 2002; Bench et al., 1995; Mayberg et al., 1994; Baxter et al., 1989). As for the relationship between executive function and CBF or metabolism, Elliott et al. (1997) showed activation in PFC was significantly attenuated relative to controls during the Tower of London planning task in PET study. In a functional magnetic resonance imaging (fMRI) study, depressed patients showed significant decreased prefrontal activation during VFT (Okada et al., 2003).

As for the relationship between depression symptom severity and frontal lobe function, Brody et al. (1999) found a positive correlation between change in Hamilton Rating Scale for Depression (HAM-D) scores and change in normalized inferior frontal gyrus (IFG) and ventrolateral PFC (VLPFC) metabolism, which indicates that IFG metabolism increased and VLPFC metabolism decreased as depression symptoms became better. Other initial studies also suggest that abnormal functions in dorsolateral PFC (DLPFC) are mood state dependent, attenuated during the depressed mood and reversing during symptom remission (Bench et al., 1995; Mayberg et al., 1994). In contrast, Drevets et al. (2002) showed the persistence of abnormal metabolic deficits using PET measures in the dorsomedial/dorsal anterolateral PFC in MDD during treatment. According to a review by Drevets (2000), a complex relationship exists between depression symptom severity and metabolic activity in the orbital cortex and VLPFC.

Findings obtained by more recent studies investigating cross-sectional relationship between depression symptom severity and brain function assessed by basal regional CBF and metabolism are also inconsistent. For example, Périco et al. (2005) reported that depression symptom severity was negatively correlated with regional CBF (rCBF) in the left amygdala, lentiform nucleus, and parahippocampal gyrus, and positively correlated with rCBF in the right postero-lateral parietal cortex, whereas Milak et al. (2005) showed only positive correlations in bilateral mesiotemporal cortex, parts of the ventral subgenual basal forebrain, and most of the thalamus, hypothalamus, ventral striatum, and midbrain. Accordingly more studies are warranted to clarify the relationship between depression severity and brain activity including frontal lobe function.

In the present study, considering the consistent finding of attenuated oxy-Hb changes during VFT in the fronto-temporal regions in depression, we hypothesized that oxy-Hb changes during VFT in NIRS could be objective indicators of depressive symptom severity. Thus, we used multi-channel NIRS to investigate the relationship between oxy-Hb changes and symptom severity in patients with MDD. Because NIRS can be measured easily and

noninvasively in a restraint-free environment over a short amount of time we expect that NIRS can be widely used to assess objectively depressive symptom severity as a clinical examination.

## 2. Materials and methods

### 2.1. Subjects

The subjects were 30 patients with MDD, and 30 healthy volunteers matched for age, gender and premorbid intelligence quotient (IQ). Premorbid IQ was estimated using the Japanese version of the National Adult Reading Test (Matsuoka et al., 2006). All subjects were right-handed according to the Edinburgh Inventory (Oldfield, 1971) and were native speakers of Japanese. All MDD subjects were outpatients of the National Center of Neurology and Psychiatry Hospital in Tokyo, Japan. They were diagnosed according to the Structured Clinical Interview for the Diagnostic Statistical Manual of Mental Disorders, 4th edition (DSM-IV) Axis I Disorders (SCID-I; First et al., 1995) by experienced psychiatrists. All patients were medicated with antidepressants. Twenty-seven out of 30 patients were prescribed with one or two antidepressants, 16 with SSRIs, 12 with tricyclics, 7 with milnacipran, 5 with tetracyclics, 2 with trazodone and 1 with mirtazapine. In addition, 20 patients were prescribed with anxiolytics, 16 with hypnotics, 7 with mood stabilizers and 9 with antipsychotics (Supplementary Table 1). Daily doses of all antidepressants were converted to an equivalent dose of imipramine (Inagaki and Inada, 2006) and anxiolytics/hypnotics to that of diazepam (Inagaki and Inada, 2006) for each patient. The controls were healthy volunteers recruited from the same geographical area through advertisements in free local magazines and our website announcement. They were interviewed using the SCID-I for MDD or SCID-NP for healthy volunteers and an unstructured interview for family history, and those individuals who had a current or past history of Axis I psychiatric disorder or a positive family history of Axis I psychiatric disorder within their first degree relatives were excluded. The exclusion criteria for both groups were previous head trauma, neurological illness, a history of electroconvulsive therapy, alcohol/substance abuse or addiction.

After the study procedures had been fully explained, written informed consent was obtained from every participant. This study was approved by the ethics committee of the National Center of Neurology and Psychiatry.

### 2.2. Clinical assessment

Depressive symptoms and the level of social functioning were evaluated by a single experienced psychiatrist using the GRID Hamilton Rating Scale for Depression 21-item version (GRID HAM-D21; Kalali et al., 2002) and Global Assessment of Functioning scores (GAF; American Psychiatric Association, 1994), respectively, without knowledge of the NIRS data on the same day that the NIRS measurements were conducted. Sleepiness was evaluated as the score on the Stanford Sleepiness Scale (SSS; Hoddes et al., 1973).

### 2.3. Activation task

The activation task was a letter version of VFT similar to that described by Takizawa et al. (2008). During the VFT, changes in oxy-Hb and deoxy-Hb were measured. The VFT consisted of a 30-sec pre-task baseline, a 60-sec VFT, and a 70-sec post-task baseline. The subjects were instructed to repeat the syllables /a/, /i/, /u/, /e/ and /o/ during the pre-task and post-task baseline periods. For the VFT, the subjects were instructed to generate as many words as possible.

One of the three initial syllables (A; 0–20 s /a/, /to/, or /na/, B; 20–40 s /i/, /ki/, or /se/, C; 40–60 s /o/, /ta/, or /ha/) was randomly

presented on the computer display placed in front of the subjects, every 20 s during the 60-sec task. The number of possible combinations of syllables is 27 ( $A;3 \times B;3 \times C;3 = 27$ ). We adopted 15 among the possible combinations. The number of correct words generated during the task was determined as a measure of task performance.

### 3. NIRS measurements

#### 3.1. NIRS device

We used a 52-channels NIRS (ETG-4000 Optical Topography System; Hitachi Medical Co., Tokyo, Japan) which measures relative changes in oxy-Hb and deoxy-Hb using two wavelengths (695 nm and 830 nm) of infrared light based on the modified Beer–Lambert law (Yamashita et al., 1996). With this system, these Hb values include a differential pathlength factor (DPF). In the NIRS system, “hemoglobin concentration change\*DPF” is calculated as a solution to the simultaneous equations based on the Beer–Lambert law, which cannot escape the effect of DPF. Although DPF varies among various brain regions Zhao et al., using a Monte Carlo simulation, reported the estimated DPF variation in the forehead region of adult humans was roughly homogeneous (Zhao et al., 2002).

The distance between a pair of source–detector probes was set at 3.0 cm and each area measured between a pair of source–detector probes was defined as a ‘channel’. The NIRS device is considered to measure ‘channels’ at a 2–3 cm depth from the scalp, that is, at the surface of the cerebral cortex (Hock et al., 1997; Okada and Delpy, 2003; Toronov et al., 2001).

#### 3.2. Probe positioning and measurement points

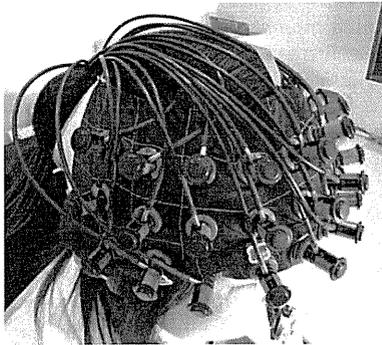
The NIRS probes were fixed with  $3 \times 11$  thermoplastic shells, with the lowest probes positioned along the Fp1–Fp2 line according to the international 10–20 system used in electroencephalography. The probes can measure Hb values from bilateral prefrontal and temporal surface regions. The measuring points were labeled ch1 to ch52 from right-posterior to left-anterior (Fig. 1). The correspondence between these NIRS channels and the measurement points on the cerebral cortex was confirmed by a multi-subject study of anatomical cranio-cerebral correlations (Okamoto et al., 2004) and presented on the basis of results obtained by the virtual registration method (Tsuzuki et al., 2007).

#### 3.3. Measurement parameters

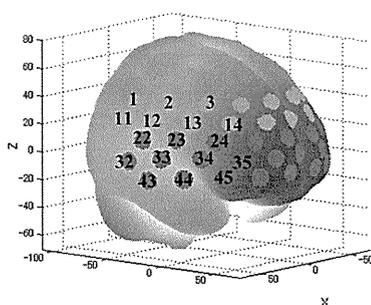
The rate of data sampling was .1 second (s). The obtained data were analyzed using integral mode; the pre-task baseline was determined as the mean over a 10 s period just prior to the task period, and the post-task baseline was determined as the mean over the last 5 s of the post-task period. Linear fitting was then applied to the data between these two baselines. The 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 automatic rejection of data with artifacts separately for each channel (Takizawa et al., 2008).

According to the aforementioned measurement parameters for integral mode, the waveforms of oxy-Hb, deoxy-Hb and total-Hb

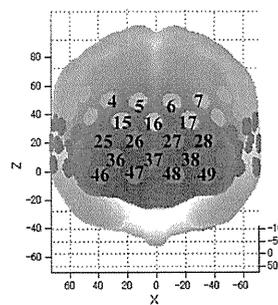
#### a Probe position



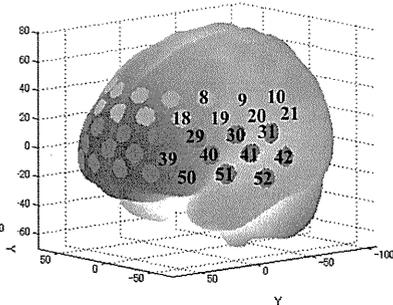
#### b Right temporal region



#### c Frontal region



#### d Left temporal region



**Fig. 1. Measurement points of 52 channels for near-infrared spectroscopy (NIRS)** (a) Probes with  $3 \times 11$  thermoplastic shells were placed over a subject's bilateral frontal regions. (b–d) The 52 measuring positions of the NIRS device are superimposed on the 3D-reconstructed cerebral surface, based on magnetic resonance imaging. The 52 measuring positions are labeled ch1 to ch52, from the right posterior to the left posterior. The dimensional figures b, c and d indicate the right temporal, frontal and left temporal brain regions, respectively. Because acquired NIRS data from the 21 channels in the upper two rows (pink channels) clearly contained artifacts presumably due to hair, as indicated by visual inspection of the waveforms, and signal to noise ratio seemed to be low, they were excluded from statistical analyses.

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changes were acquired from each subject in all 52 channels during VFT.

### 3.4. Measurement environment

The subjects sat on a comfortable chair in a silent and day-lit room. They were instructed to minimize motions such as head movements, strong biting and blinking during the NIRS measurement, to avoid artifacts.

Data clearly containing motion artifacts, based on both our observations and the NIRS recording, were excluded from further analyses.

## 4. Statistical analysis

Because acquired NIRS data from the 21 channels in the upper two rows clearly contained artifacts presumably due to hair, as indicated by visual inspection of the waveforms, and signal to noise ratio seemed to be low, they were excluded from statistical analyses.

The  $\chi^2$  test or Student's *t*-test was used to compare proportions and means, respectively, between the MDD and control groups.

As for the analysis of the NIRS data, we focused on oxy-Hb data, since oxy-Hb change (task period – pre- and post-task baseline period) is assumed to more directly reflect cognitive activation than deoxy-Hb change as shown by a stronger correlation with blood-oxygenation level-dependent signal measured by fMRI (Strangman et al., 2002b). The mean oxy-Hb changes were compared between the two groups (MDD and control) for each channel using Student's *t*-test. To examine the relationships between oxy-Hb changes and HAM-D21 total scores, HAM-D21 subscale scores, GAF, or other clinical variables, Spearman's rhos were calculated for MDD patients.

All statistical analyses were performed using SPSS for Windows, version 18.0.0 software (SPSS Japan, Tokyo, Japan). A value of  $p < .05$  (two-tailed) was considered to be statistically significant. We set the value of *q* specifying the maximum false discovery rate (FDR) at .05, such that the false positive rate was no more than 5% on average in treating the oxy-Hb data obtained from multiple channels (Singh and Dan, 2006).

## 5. Results

### 5.1. Demographic and clinical data of patients and controls

Table 1 summarizes demographic characteristics of the patients and controls. The two groups did not differ significantly in age, gender, handedness, estimated premorbid IQ or SSS.

**Table 1**  
Demographic and clinical data of patients with major depressive disorder and controls.

| Demographics                        | Patients with depression ( <i>n</i> = 30) | Healthy controls ( <i>n</i> = 30) | Group difference <i>p</i> -value |
|-------------------------------------|---|-----------------------------------|----------------------------------|
| Age (years)                         | 36.7 ± 11.6                               | 35.1 ± 9.4                        | .871                             |
| Gender (female/male)                | 16/14                                     | 16/14                             | 1.000                            |
| Edinburgh handedness inventory (%)  | 92.9 ± 9.7                                | 92.0 ± 11.5                       | .753                             |
| Age at onset (years)                | 30.9 ± 10.8                               | –                                 | –                                |
| Duration of illness (years)         | 5.8 ± 4.1                                 | –                                 | –                                |
| Duration of medication (years)      | 5.0 ± 3.6                                 | –                                 | –                                |
| GRID HAM-D21 total score            | 16.7 ± 4.8                                | –                                 | –                                |
| Estimated premorbid IQ              | 105.7 ± 9.5                               | 105.9 ± 8.3                       | .953                             |
| Sleepiness                          | 3.3 ± 1.1                                 | 2.9 ± .9                          | .104                             |
| GAF                                 | 57.6 ± 9.3                                | –                                 | –                                |
| Medication                          | –   | –                                 | –                                |
| Imipramine equivalent dose (mg/day) | 141.9 ± 127.6                             | –                                 | –                                |
| Diazepam equivalent dose (mg/day)   | 8.5 ± 11.6                                | –                                 | –                                |

The  $\chi^2$  test or *t*-test was used to compare these variables between patients and controls. GAF, Global Assessment of Functioning; GRID HAM-D21, GRID Hamilton Rating Scale for Depression 21 item; IQ, Intelligence Quotient.

### 5.2. Task performance

The number of words generated did not differ significantly among the 15 combinations employed (15 combinations:  $F[1, 45] = 1.1, p = .39$ ; three initial syllables:  $F[2, 90] = 1.2, p = .31$ ) in either group. The number of generated words during VFT did not differ significantly (patients:  $12.3 \pm 3.9$ ; controls  $13.9 \pm 4.3, t = 1.5, df = 58, p = .13$ ) between the MDD and control groups.

### 5.3. Group comparison

As shown in Supplementary figure 1, the MDD group had significantly smaller oxy-Hb increases than the control group in 22 channels (ch22–29, ch32–33, ch35–39 and ch44–50; FDR-corrected  $p: .000–.024$ ) during VFT.

### 5.4. Relationship with symptom severity at the time of examination

As shown in Fig. 2, there were significant negative correlations between mean oxy-Hb changes during the task and HAM-D21 total scores in one channel (ch25:  $\rho = -.56$ ; FDR-corrected  $p: .001$ ). Mean oxy-Hb changes during the task period showed significant negative correlations with three individual items of the HAM-D21 subscale scores (Fig. 3); insomnia early in 9 channels (ch23, ch25–27, ch36–37 and ch46–48:  $\rho = -.63$  to  $-.46$ ; FDR corrected  $p: .000–.014$ ), work and activity in 2 channels (ch44 and ch45:  $\rho = -.61$  to  $-.57$ ; FDR corrected  $p: .001$  to  $.003$ ), and psychomotor retardation in 12 channels (ch22–24, ch32, ch35–36, ch41, ch43–ch45, ch47 and ch51:  $\rho = -.70$  to  $-.44$ ; FDR corrected  $p: .000–.018$ ). Mean oxy-Hb changes showed no significant correlations with the remaining HAM-D21 subscale scores (i.e., depressed mood, guilt, insomnia middle, insomnia late, psychomotor agitation, anxiety psychic, anxiety somatic, loss of appetite, somatic symptoms general, sexual interest, hypochondriasis, loss of weight, insight, diurnal variation, and obsessional symptoms; ) (Fig. 4).

Furthermore, mean oxy-Hb changes showed no significant correlation with task performance during VFT or other clinical variables, such as age, duration of illness, and sleepiness (data not shown).

### 5.5. Relationships with medication

There were no significant correlations between the HAM-D21 total score and doses of antidepressants ( $\rho = -.23, p = .22$ ) or anxiolytics ( $\rho = .25, p = .18$ ). There were significant negative correlations between mean oxy-Hb changes during the task and doses of antidepressants in 6 channels (ch31, ch40–41, ch45, ch50–51:  $\rho = -.57$

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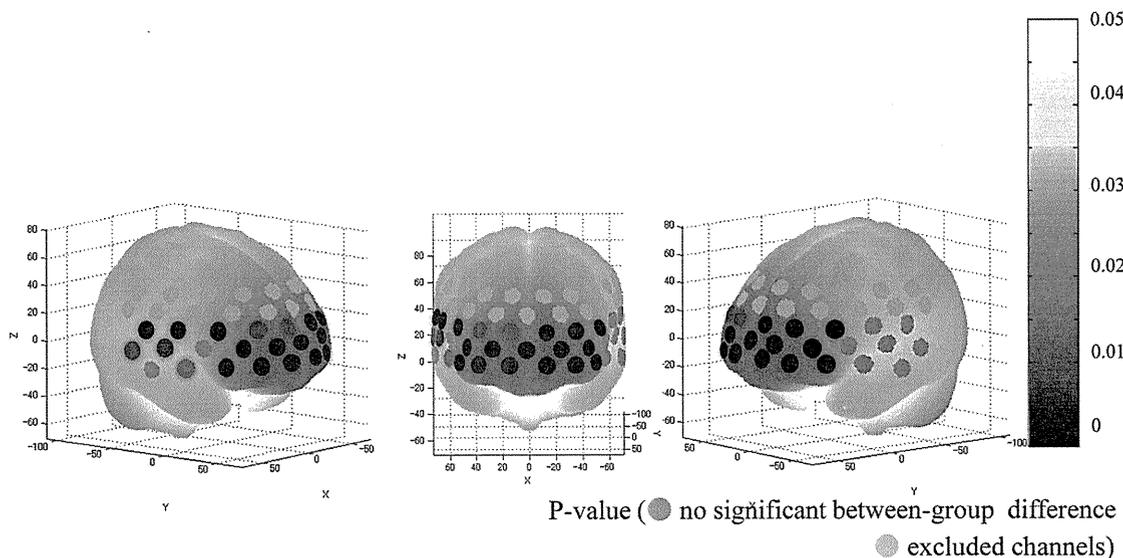


Fig. 2.  $p$ -value significance map of  $t$ -tests for oxy-Hb increases in patients with MDD compared with healthy controls during VFT using FDR correction. The warm colored circles represent significantly smaller oxy-Hb increases than in the control group at the channels indicated. There were 22 channels (ch22–29, ch32–33, ch35–39 and ch44–50; FDR-corrected  $p$ : .000–.024).

to  $-.48$ ; FDR-corrected  $p$ : .002 to .007). Mean oxy-Hb changes showed no significant correlations with doses of anxiolytics.

## 6. Discussion

### 6.1. Task performance

The number of words generated during the VFT did not differ significantly between patients and controls, which is consistent with the majority of previous studies (Matsuo et al., 2002; Fossati et al., 2003; Suto et al., 2004; Kameyama et al., 2006). Previous studies reported impairment on semantic fluency tasks in depression (Calev et al., 1989; Tarback and Paykel, 1995). However, on phonemic fluency task conflicting results patients showing normal or impairment performance in depression (Albus et al., 1996; Degl'Innocenti et al., 1998). Type of psychiatric disorder and task time setting may reflect the discrepancies (Fossati et al., 2003). In the present study, the time setting of VFT was three phonemes within 60 s, that is, 20 s for each phoneme, which differs from the standard VFT usually using 60 s for one phoneme. The time setting condition was designed as it is, so that the subjects were able to keep generating words regularly within the task period to avoid the effect of “not speaking”. It is possible that the time setting condition in the present study caused the lack of significant between group-difference in task performance.

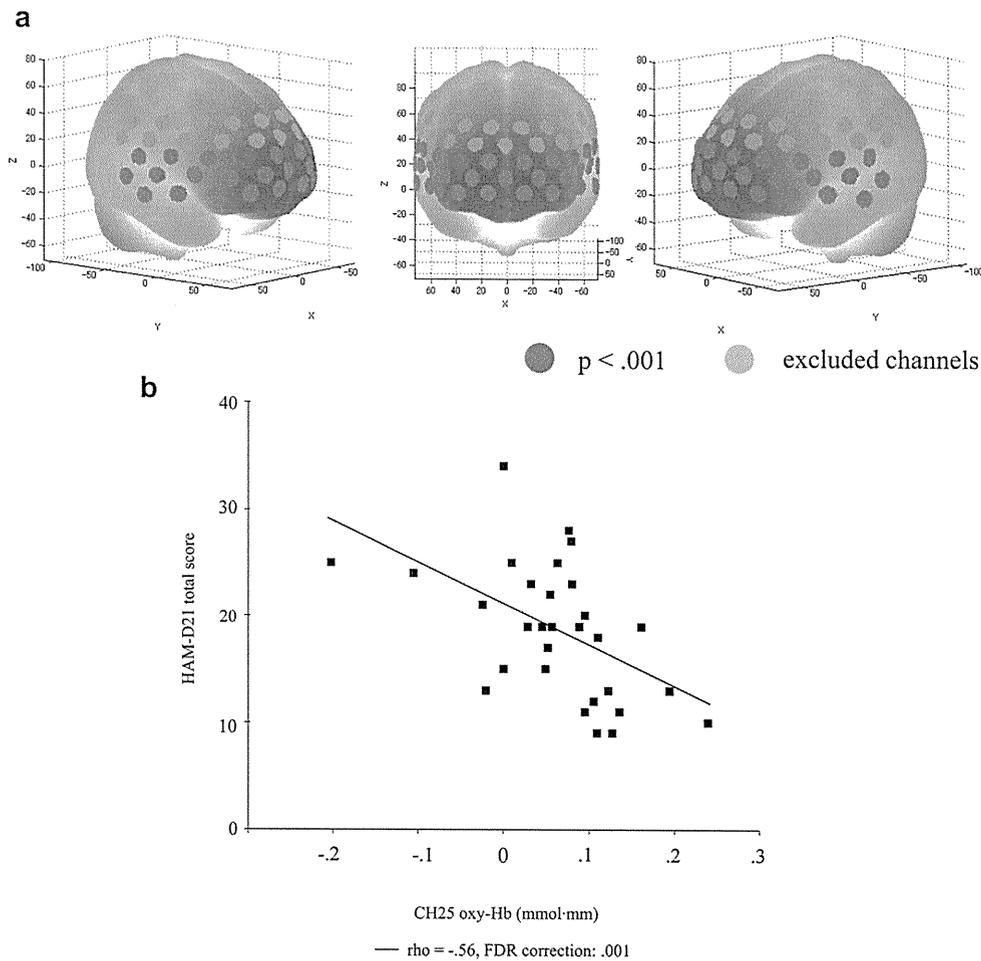
### 6.2. Between-group comparison of oxy-Hb activation

The present study showed oxy-Hb activation during VFT to be significantly smaller in the MDD group than in age-, gender- and IQ-matched healthy controls. This result is essentially consistent with those obtained using NIRS (Matsuo et al., 2002; Herrmann et al., 2004; Suto et al., 2004; Kameyama et al., 2006; Pu et al., 2008), single photon emission computed tomography (SPECT) (Mayberg et al., 1994) or functional magnetic resonance imaging (fMRI) (Okada et al., 2003).

### 6.3. Relationships with symptom severity at the time of examination

Mean oxy-Hb changes during the task period showed a significantly negative correlation with HAM-D21 total score at ch25. Ch25 is located approximately in the right DLPFC. The finding is in line with some initial studies (Bench et al., 1995; Mayberg et al., 1994) which suggest that abnormal functions in DLPFC are mood dependent. However, other more recent studies investigating cross-sectional relationship between depression psychopathology and brain function do not coincide with our result (Pérido et al., 2005; Milak et al., 2005). One of the reasons for the discrepancy may arise from the different methodologies; in the present study we adopted VFT for activation whereas the previous studies observed the basal activity with no activation task. Although speculative as it is, the activation of PFC by VFT may have led to the significant relationship between oxy-Hb changes and depression symptom severity in the right DLPFC.

More interestingly, mean oxy-Hb changes during the task period showed significant negative correlations with three individual HAM-D21 items in a wider area than they showed with HAM-D21 total scores; insomnia early in nine, work and activity in two and psychomotor retardation in twelve channels. The nine channels correlating with “insomnia early” were located approximately in the right pre-motor area, DLPFC and frontopolar and orbitofrontal areas. The two channels correlating with “work and activity” were located approximately in the right DLPFC and temporopolar area. The twelve channels correlating with “psychomotor retardation” were located broadly in the fronto-temporal areas with right hemispheric dominance. Although these findings should be treated with care given the exploratory nature of multiple analyses, it is noteworthy that at least some subscale scores of HAM-D21 appeared to show stronger relationship with oxy-Hb changes than HAM-D21 total scores. It has been pointed out that HAM-D17 and/or HAM-D21 are not necessarily unidimensional, and thus not adequate to assess depression severity (Bagby et al., 2004). Licht et al. (2005) showed that a set of the HAM-D containing six subscales constitute a unidimensional scale measuring severity of



**Fig. 3.** (a) The channels with a significant correlation between oxy-Hb changes and HAM-D21 total score after FDR correction. (b) Scatter graph showing the relationship between HAM-D21 total scores and oxy-Hb activation in CH25.

depression, whereas the remaining items covering neurovegetative symptoms showed a problematic response somewhat insensitive to depression severity. In fact, the multidimensionality was highlighted in the unstable factor structure, which was demonstrated by a failure to replicate a single unifying structure across studies (Bagby et al., 2004). The relatively strong relationship indicated between HAM-D21 subscale scores and oxy-Hb changes in divergent areas, compared to HAM-D21 total scores may be due to the multidimensional properties of HAM-D21. Graff-Guerrero et al. (2004) also demonstrated that each HAM-D subscale score showed a significant correlation with the basal CBF in variant areas, in some cases showing positive correlation and others negative.

#### 6.4. Relationships with medications

As all patients were taking antidepressants at the time of evaluation, the medication effect could not be ignored. Yet, there was no significant relationship between daily dose levels of antidepressants and the HAM-D21 total score. Although daily dose levels of antidepressants showed significant negative correlations with oxy-Hb changes in six channels, ch25, where a significant correlation between oxy-Hb changes and HAM-D21 total scores was observed, was not included in the six channels. Therefore, we suspect that the effect was small, if at all.

PET has been used to demonstrate that antidepressant medication normalizes both over-activity and under-activity in the frontal cortex (Kennedy et al., 2001, 2007; Mayberg et al., 2000; Goldapple et al., 2004). Unfortunately, our results could not clarify the relationship between medication and brain activation because our analysis was based on cross-sectional data. Although our data may reflect the more restraint-free, natural setting than those using fMRI or PET, further studies in drug-naïve patients are required to draw any conclusions as to the possible effects of medication on brain activation as measured by NIRS. Longitudinal studies investigating the relationship between the change in oxy-Hb data and symptom severity scores with a larger sample size are warranted to reach a conclusion on this matter.

The results of this study must be interpreted with caution due to certain limitations. First, because the analysis was based on cross-sectional data, causality cannot be determined. Longitudinal studies are needed to assess cause-and-effect relationships. Second, our sample size was not large, and is thus subject to type II error. Further studies with larger numbers of MDD patients are required. Finally, owing to the multidimensional properties of HAM-D21, assessment of depression symptom severity using HAM-D21 total scores may not be adequate, and thus, other scales such as Montgomery Asberg Depression Rating Scale (MADRS) or Beck Depression Inventory (BDI) should be tested in the future study.

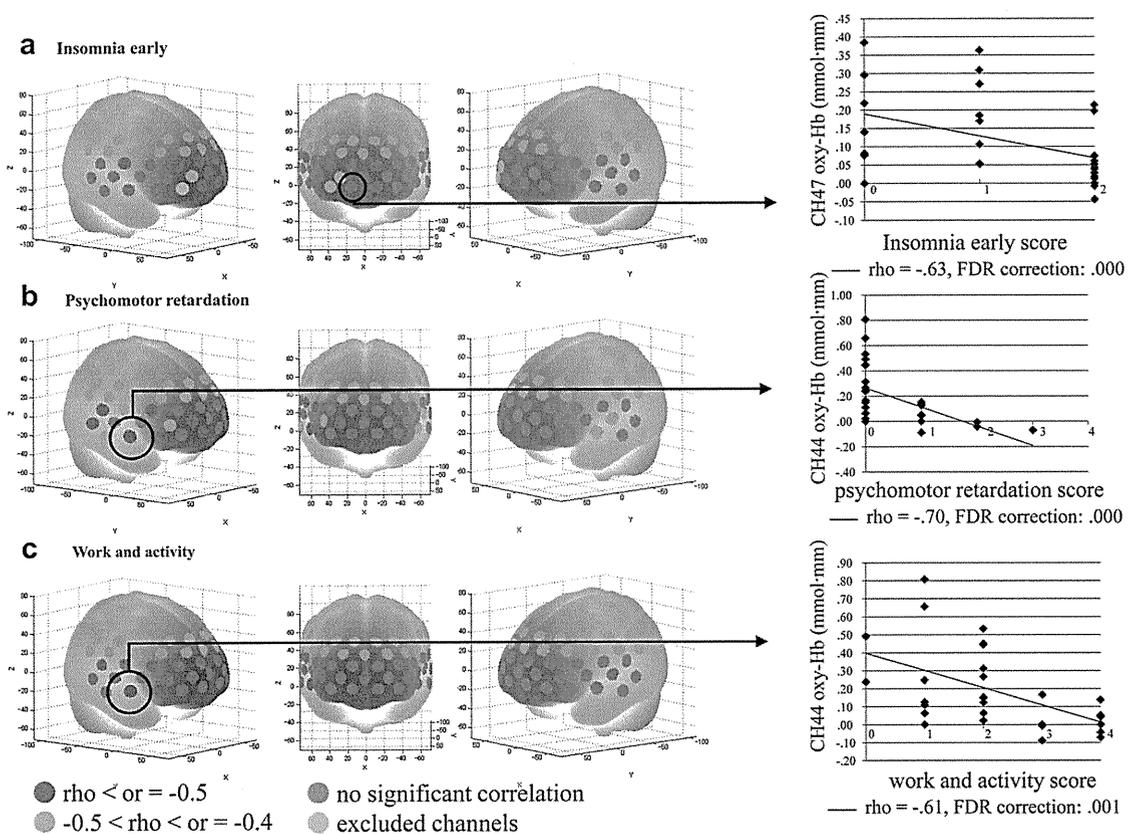


Fig. 4. rho-value map for the correlation between oxy-Hb activation in MDD patients and three individual HAM-D21 subscale scores after FDR correction. (a) insomnia early, (b) psychomotor retardation, and (c) work and activity.

## 7. Conclusion

In this study, we confirmed that the increase in oxy-Hb during a VFT task is significantly smaller in MDD than in age- and gender-matched healthy subjects. This difference could not be explained by a difference in task performance or premorbid IQ. The blunted increase in right DLPFC was associated with the symptom severity of MDD and therefore oxy-Hb changes during VFT in this region may be a state-dependent marker of depression.

## Role of the funding source

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## Contributors

T. Noda designed the study, wrote the protocol, assessment of depression severity, literature searches, statistically analyzed the data, and wrote the first draft of the manuscript. T. Matsuda was involved in patient recruitment and assessment of depression severity. H. Kunugi and S. Yoshida wrote the final version of the manuscript. All authors contributed to and have approved the final manuscript.

## 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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## Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jpsychires.2012.04.001.

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Regular Article

# Differential relationships between personality and brain function in monetary and goal-oriented subjective motivation: Multichannel near-infrared spectroscopy of healthy subjects

Toshimasa Sato, EdM, Masato Fukuda, MD, PhD,\* Masaki Kameyama, MD, PhD, Masashi Suda, MD, PhD, Toru Uehara, MD, PhD and Masahiko Mikuni, MD, PhD

Department of Psychiatry and Neuroscience, Gunma University Graduate School of Medicine, Gunma, Japan

**Aim:** To examine relationships between personality traits and cerebral cortex reactivity under different motivating conditions.

**Methods:** Relationships between personality traits assessed using the NEO Personality Inventory-Revised (NEO-PI-R) and cerebral cortex reactivity during a verbal fluency task monitored using multichannel near-infrared spectroscopy (NIRS) were examined under three different motivational conditions: control, monetary reward, and goal-oriented, in healthy young male volunteers.

**Results:** Significant correlations between cerebral cortex reactivity and personality traits were found in the frontopolar region: a positive correlation with agreeableness and a negative correlation with the neuroticism and conscientiousness scores of the NEO-PI-R under the three motivational conditions. Higher scores for agreeableness were more strongly associated with a greater increase in total hemoglobin concentration ([total-Hb]) under the goal-oriented and control conditions than under the monetary

reward condition. In addition, higher scores for neuroticism were more strongly associated with a greater increase in deoxygenated hemoglobin concentration ([deoxy-Hb]) under the monetary reward condition than the goal-oriented condition, and higher scores for conscientiousness were more strongly associated with a greater increase in [deoxy-Hb] under control conditions than under the goal-oriented condition.

**Conclusion:** Using multichannel NIRS, certain personality traits of the big-five model are related to frontopolar reactivity. These relationships vary depending on the motivational condition when brain functions are monitored: agreeableness, neuroticism, and conscientiousness are all related to frontopolar reactivity depending on the motivational condition.

**Key words:** brain activation, near-infrared spectroscopy, personality characteristic, subjective motivation.

PERSONALITY IS DEFINED as ingrained patterns of thought, feeling, and behavior characterizing an individual's unique lifestyle and model of

adaptation resulting from constitutional factors, development, and social experience. It has conventionally been conceptualized as consisting of several factors or dimensions. Representative examples of hypothesis-driven and empirically based major personality models are the Temperament and Character Inventory and the NEO Personality Inventory-Revised (NEO-PI-R), respectively.<sup>1,2</sup>

The brain substrates associated with the five dimensions of the NEO-PI-R have been studied in

\*Correspondence: Masato Fukuda, MD, PhD, Department of Psychiatry and Neuroscience, Gunma University Graduate School of Medicine, 3-39-22 Showa, Maebashi-shi, Gunma 371-8511, Japan. Email: fkdpsy@med.gunma-u.ac.jp  
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1 healthy subjects. The neuroticism score of the NEO-  
2 NEO-PI-R was negatively correlated with the ratio of the  
3 brain volume to the remainder of the intracranial  
4 volume on magnetic resonance imaging (MRI) and  
5 with insula metabolism on positron emission tomog-  
6 raphy (PET).<sup>3,4</sup> The extraversion score was positively  
7 correlated with orbitofrontal cortex metabolism on  
8 PET and with increased cerebral blood flow in the  
9 anterior cingulate gyrus, temporal lobes, and poste-  
10 rior thalamus on single-photon emission computed  
11 tomography (SPECT).<sup>4,5</sup> Significant correlations have  
12 also been observed in patients with psychiatric disor-  
13 ders: the depression score (one of the subscales of  
14 neuroticism) was correlated with MRI abnormalities  
15 in early-onset Alzheimer's disease,<sup>6</sup> the extraversion  
16 score was correlated with gray matter volume loss in  
17 the right posterior fusiform gyrus in patients with  
18 chronic schizophrenia,<sup>7</sup> and the agreeableness score  
19 was positively correlated with right orbitofrontal lobe  
20 volume and negatively correlated with left orbito-  
21 frontal lobe volume in frontotemporal dementia  
22 patients.<sup>8</sup>

23 Near-infrared spectroscopy (NIRS) is a recently  
24 available functional brain imaging technique in  
25 which cerebral blood volume (CBV) changes are  
26 monitored by measuring increases in oxygenated  
27 hemoglobin concentration ([oxy-Hb]) and decreases  
28 in deoxygenated hemoglobin concentration ([deoxy-  
29 Hb]). NIRS is particularly suitable for personality  
30 studies because it enables measurement in a natural  
31 setting, compared with other functional brain  
32 imaging techniques such as PET and functional  
33 MRI.<sup>9–11</sup> For example, NIRS enables examination of  
34 subjects in a sitting position, with their eyes open,  
35 and while speaking using a small apparatus by  
36 their bedside, with a fine time resolution.<sup>12</sup> Due to  
37 its technical advantages, NIRS addresses one of  
38 the main problems of functional neuroimaging  
39 personality studies: lack of a natural setting during  
40 neuroimaging.

41 Here, we examined differential relationships  
42 between personality traits assessed using the NEO-  
43 PI-R and frontal and temporal lobe activation during  
44 a verbal fluency task (VFT) using multichannel NIRS  
45 in healthy male subjects. Activation changes in brain  
46 functions were able to be monitored in a natural  
47 setting. In addition to the usual task-activated condi-  
48 tion, frontal lobe and temporal lobe activation was  
49 also examined under two motivationally modified  
50 versions of the task-activated condition: a monetary  
51 reward condition and a goal-oriented condition.

52 These conditions were used because human behav-  
53 iors are, in general, motivated by reward and social  
54 interaction, and because task-induced brain activa-  
55 tion is considered to be modified by the motivational  
56 state of the subject at the time of examination and  
57 hence to be differentially related to personality  
58 depending on the type of motivation.<sup>13</sup>

59 We hypothesized that the personality dimensions  
60 of the NEO-PI-R would be correlated with brain acti-  
61 vation, and that these relationships would vary  
62 between the monetary reward, goal-oriented, and  
63 control conditions.<sup>14,15</sup> All of the dimensions of the  
64 NEO-PI-R could be correlated with brain activation,  
65 because motivation is assumed to consist of various  
66 aspects of brain function. For example, personality  
67 dimensions reflecting interpersonal relationships  
68 such as extraversion and agreeableness could be  
69 positively correlated with brain function, especially  
70 under the goal-oriented condition, because subjects  
71 with high extraversion or agreeableness are assumed  
72 to be more motivated in a natural setting with an  
73 examiner. Personality dimensions reflecting interper-  
74 sonal relationships and emotional features such as  
75 openness and neuroticism could be positively and  
76 negatively correlated with brain function, respec-  
77 tively, particularly under the monetary reward and  
78 the goal-oriented conditions, because motivation is  
79 considered to be related to openness and to be  
80 decreased during high-tension situations such as an  
81 examination. In addition, personality dimensions  
82 reflecting an effort-related nature such as conscien-  
83 tiousness could be positively correlated with brain  
84 function, because motivation is closely correlated  
85 with effort.

## 86 METHODS

### 87 Subjects

88 Thirty-six healthy volunteers participated in this  
89 study. All of the subjects were male (mean age,  
90 23.6 ± 2.75 years; range, 19–29 years) and were  
91 scored as right-handed using the Edinburgh Handed-  
92 ness Inventory scale.<sup>16</sup> They were medics or medical  
93 department students with no history of any major  
94 psychiatric disorder, neurological disorder, substance  
95 abuse, head injury, or major physical illness, and they  
96 were not on any psychotropic medications at the time  
97 of the study. The subjects abstained from alcohol for  
98 at least 12 h prior to the NIRS measurements. This  
99 study was approved by the Institutional Review  
100 Board.

|    |   |  |    |
|----|---|--|----|
| 1  | Board of Gunma University Graduate School of                | conditions (six combinations) were completely          | 50 |
| 2  | Medicine. Written informed consent was obtained             | counterbalanced among the 36 (6 × 6) subjects.         | 51 |
| 3  | from all of the subjects prior to the study.                |  | 52 |
| 4  |   |  |    |
| 5  | <b>Assessment of personality characteristics</b>            | <b>Assessment of subjective changes induced by</b>     | 53 |
| 6  | The personality characteristics of the subjects were        | <b>motivational condition</b>                          | 54 |
| 7  | assessed using the Japanese version of the NEO-PI-R         | Subjective changes induced by the motivational con-    | 55 |
| 8  | (Tokyo Shinri, Tokyo, Japan). <sup>2</sup> The NEO-PI-R was | ditions were assessed immediately after each NIRS      | 56 |
| 9  | undertaken by all subjects after the NIRS measure-          | measurement condition using a questionnaire that       | 57 |
| 10 | ments using a standardized assessment protocol in           | the authors developed for this study. The question-    | 58 |
| 11 | which subjects completed a personality characteris-         | naire consisted of six items: motivation, effort, cen- | 59 |
| 12 | tics questionnaire.   | tration, tiredness, difficulty, and fatigue, and the   | 60 |
| 13 |   | subjects were required to score each item from 5       | 61 |
| 14 |   | (strongly agree) to 1 (strongly disagree).             | 62 |
| 15 | <b>Verbal fluency task and motivational</b>                 |  | 63 |
| 16 | <b>conditions</b>   |  | 64 |
| 17 | A modified letter version of a verbal fluency task was      | <b>NIRS measurements</b>                               | 65 |
| 18 | used as the activation task for measurement of CBV          | Changes in [oxy-Hb], [deoxy-Hb], and total hemo-       | 66 |
| 19 | changes. Subjects sat in a comfortable chair in a           | globin ([total-Hb]; the sum of [oxy-Hb] and [deoxy-    | 67 |
| 20 | bright room with their eyes open throughout the             | Hb]) were monitored using a 52-channel NIRS            | 68 |
| 21 | measurements. The verbal fluency task consisted of a        | machine based on the continuous wave method of         | 69 |
| 22 | 30-s pre-task baseline, a 60-s verbal fluency period, a     | measurement (ETG-4000; Hitachi Medical, Tokyo,         | 70 |
| 23 | 70-s post-task baseline, and 60-s relaxation period.        | Japan). The NIRS probe holders were placed on the      | 71 |
| 24 | Each subject underwent three consecutive sessions           | subject's frontal and temporal regions. Hemoglobin     | 72 |
| 25 | of the verbal fluency task with different motivational      | concentration changes were measured at 52 measure-     | 73 |
| 26 | conditions, with a rest of >5 min between sessions:         | ment points, with the lowest probe line positioned     | 74 |
| 27 | control, monetary reward, and goal-oriented condi-          | along the T3, F7, Fp1, Fp2, F8, and T4 lines in accor- | 75 |
| 28 | tions. We measured only one activation period per           | dance with the international 10/20 system used in      | 76 |
| 29 | motivational condition, because repeating the mea-          | electroencephalography. [Oxy-Hb] and [deoxy-Hb]        | 77 |
| 30 | surement dampens the effect of personality and              | were calculated based on absorption of near-infrared   | 78 |
| 31 | reward on brain activation. Under the control condi-        | light of two wavelengths (780 and 830 nm) emitted      | 79 |
| 32 | tion, the subjects were instructed to perform the           | from the emission probe and detected by the detec-     | 80 |
| 33 | verbal fluency task without any motivational condi-         | tion probe 3 cm away.                                  | 81 |
| 34 | tion, looking at a plus symbol on the CRT monitor in        | We chose the prefrontal cortex as the measured         | 82 |
| 35 | front of the subject. Under the monetary reward con-        | region because previous studies have reported that     | 83 |
| 36 | dition, the subjects were instructed before the session     | the prefrontal cortex was related to personality and   | 84 |
| 37 | that they would be paid 100 yen for each correct            | motivational conditions. <sup>4,17-19</sup>            | 85 |
| 38 | word generated. The subjects looked at a plus symbol        |  | 86 |
| 39 | on the CRT monitor during the session as under the          | <b>Statistical analysis</b>                            | 87 |
| 40 | control condition. Under the goal-oriented condi-           | <b>Task performance and subjective changes induced</b> | 88 |
| 41 | tion, the subjects were motivated to generate the           | <b>by the motivational conditions</b>                  | 89 |
| 42 | expected number of words by looking at the CRT              | Task performance and subjective changes induced        | 90 |
| 43 | monitor: on the CRT monitor, the number of words            | by the motivational conditions were analyzed using     | 91 |
| 44 | generated was overtly displayed as the number of            | one-way repeated-measures analysis of variance         | 92 |
| 45 | accumulated green rectangles, and the expected              | (ANOVA) and the Friedman test, respectively, with      | 93 |
| 46 | number of words was shown as a pink line above the          | 'condition' (the control, monetary reward, and         | 94 |
| 47 | accumulated rectangles. The subjects were instructed        | goal-directed conditions) as an independent factor,    | 95 |
| 48 | to continue the task even when they reached the goal        | followed by the post-hoc Wilcoxon test. Pearson's      |    |
| 49 | line. The order of the three syllable sets (six combi-      |  |    |
|    | nations) and the order of the three motivational            |  |    |

1 correlations of the NEO-PI-R scores with task perfor- 51  
2 mance were also examined. 52

3  
4 **NIRS data** 53

5 The channels for which the mean [total-Hb] during 54  
6 the task segment divided by the standard deviation of 55  
7 [total-Hb] during the pre-task segment was  $<5.0$  were 56  
8 excluded from further analysis, because such chan- 57  
9 nels tend to have low signal-to-noise ratios due to the 58  
10 limited near-infrared light detected. Based on this 59  
11 criterion, 29 channels (11, 14, 15, 18, 19, 24–29, 32, 60  
12 34–40, 42, and 44–52) were retained for further 61  
13 analysis. Channels were generally excluded if the 62  
14 signal was low under at least one reinforcement 63  
15 condition. 64

16 [Oxy-Hb] and [deoxy-Hb] measured during the 65  
17 task period were analyzed in three steps. First, chan- 66  
18 nels with significant [oxy-Hb] and/or [deoxy-Hb] 67  
19 changes were identified. The individually averaged 68  
20 [oxy-Hb] and [deoxy-Hb] waveforms were divided 69  
21 into the following three time segments: a pre-task 70  
22 segment for 10 s before the verbal fluency period; a 71  
23 task segment for 60 s during the task period; and a 72  
24 post-task segment for 60 s after the task period. The 73  
25 averages of [oxy-Hb], [deoxy-Hb], and [total-Hb] 74  
26 within these three time segments were calculated and 75  
27 analyzed using one-way repeated measures of ANOVA. 76  
28 The channels were considered to be activated by the 77  
29 verbal fluency task when the segment factor showed a 78  
30 significant effect ( $P < 0.05$ , ANOVA) and [Hb] during 79  
31 the pre-task and task segments was significantly 80  
32 different, as determined on a post-hoc *t*-test with 81  
33 Bonferroni correction, because these effects were 82  
34 considered to be independent at each channel. 83

35 Next, Pearson's correlations for [oxy-Hb], [deoxy- 84  
36 Hb], and [total-Hb] with task performance were con- 85  
37 ducted. Finally, the mean [oxy-Hb], [deoxy-Hb], and 86  
38 [total-Hb] during the task segments were analyzed 87  
39 using one-way repeated-measures analysis of covari- 88  
40 ance (ANCOVA) with 'condition' (control, monetary 89  
41 reward, and goal-directed conditions) as an indepen- 90  
42 dent factor and the five scores of the NEO-PI-R for 91  
43 'personality characteristics' (neuroticism, extraversion, 92  
44 openness, agreeableness, and conscientiousness) as 93  
45 covariates, followed by a post-hoc *t*-test. For 94  
46 channels showing statistically significant covariate 95  
47 effects of personality characteristics, the mean [oxy- 96  
48 Hb], [deoxy-Hb], and [total-Hb] during the task seg- 97  
49 ments were analyzed using correlation analysis with 98  
50 the five personality characteristics scores of the NEO-

PI-R under each condition. In addition, as a post-hoc 51  
test for interaction, for channels showing statistically 52  
significant interaction effects for the NEO-PI-R scores 53  
with 'condition' (the three conditions), the mean 54  
[oxy-Hb], [deoxy-Hb], and [total-Hb] during the task 55  
segments were analyzed using one-way repeated- 56  
measures ANCOVA with 'condition' (all pairs of 57  
conditions: control–monetary reward, control–goal 58  
oriented, and monetary reward–goal oriented) as an 59  
independent factor and the five scores of the NEO- 60  
PI-R for 'personality characteristics' as covariates. 61

62 In the second and third steps, channels with sig- 62  
nificant activation under all three conditions were 63  
used for analysis. Correlations and interactions were 64  
interpreted as statistically significant only if more 65  
than two neighboring channels had significance 66  
levels of  $P < 0.05$  to exclude the effects of multiple 67  
correlations; the probability that three spatially 68  
neighboring channels had a significance level of 69  
 $P < 0.05$  was less than 5% of all possible combina- 70  
tions of three channels among all of the channels 71  
with significant activation (maximum for [total-Hb]: 72  
 $n = 27$ ). 73

74  
75 **RESULTS** 76

77 **Comparison of the three conditions**

78 **NEO-PI-R scores and subjective changes induced**  
79 **by motivational condition and task performance**

80 The means and SDs for the NEO-PI-R scores were 81  
97.2  $\pm$  19.1 (neuroticism), 103.8  $\pm$  21.1 (extraver- 82  
sion), 116.9  $\pm$  15.0 (openness), 107.8  $\pm$  13.7 83  
(agreeableness), and 102.1  $\pm$  18.5 (conscientiousness). 84  
The means and SDs for task performance and the 85  
scores for the subjective changes induced by the moti- 86  
vational conditions were 19.9  $\pm$  5.9 (task perfor- 87  
mance), 3.6  $\pm$  0.8 (motivation), 3.2  $\pm$  0.9 (effort), 88  
3.5  $\pm$  0.9 (concentration), 2.5  $\pm$  1.1 (tiredness), 89  
3.3  $\pm$  0.6 (difficulty), and 2.2  $\pm$  1.0 (fatigue). Moti- 90  
vation was scored significantly higher under the 91  
monetary reward than under the control condition 92  
( $Z = -2.48$ ,  $P = 0.013$ ), and was not significantly dif- 93  
ferent between the goal-oriented condition and the 94  
control ( $Z = -1.63$ ,  $P = 0.103$ ) or monetary reward 95  
( $Z = -1.03$ ,  $P = 0.302$ ) conditions. Task performance, 96  
however, was not significantly different among the 97  
three conditions. The other scores were also not 98  
significantly different among the three conditions 99  
( $F = 0.093$ ,  $P = 0.911$ ).

NIRS data

The grand averaged waveforms for [oxy-Hb], [deoxy-Hb], and [total-Hb] during the verbal fluency task under the control, monetary reward, and goal-oriented conditions are shown in Figure 1. During the task period, [oxy-Hb] significantly increased in 27 channels (11, 14, 15, 18, 19, 24-29, 32, 34-40, and 44-51;  $F=9.0-30.2$ ,  $P<0.001$ ) under the control condition; in the same 27 channels (11, 14-15, 18, 19, 24-29, 32, 34-40, 44-51;  $F=13.6-49.6$ ,  $P<0.001$ ) under the monetary reward condition; and in these 27 channels (11, 14-15, 18, 19, 24-29, 32, 34-40, 44-52;  $F=10.4-35.4$ ,  $P<0.001$ ) under

the goal-oriented condition. During the task period, [deoxy-Hb] significantly decreased in 22 channels (24-29, 32, 34-40, 44-51;  $F=5.1-33.1$ ,  $P<0.039$ ) under the control condition; in 26 channels (14, 18, 24-29, 32, 34-40, 42, 44-51;  $F=4.0-58.9$ ,  $P<0.031$ ) under the monetary reward condition; and in 22 channels (24-29, 32, 34-40, 44-46, 48-52;  $F=5.3-42.5$ ,  $P<0.014$ ) under the goal-oriented condition. During the task period, [total-Hb] significantly increased in 27 channels (11, 14, 15, 18, 19, 24-29, 32, 34-40, 44-51;  $F=9.6-30.8$ ,  $P<0.001$ ) under the control condition; in 27 channels (11, 14, 15, 18, 19, 24-29, 32, 34-40, 44-52;  $F=8.6-33.7$ ,  $P<0.003$ ) under the monetary

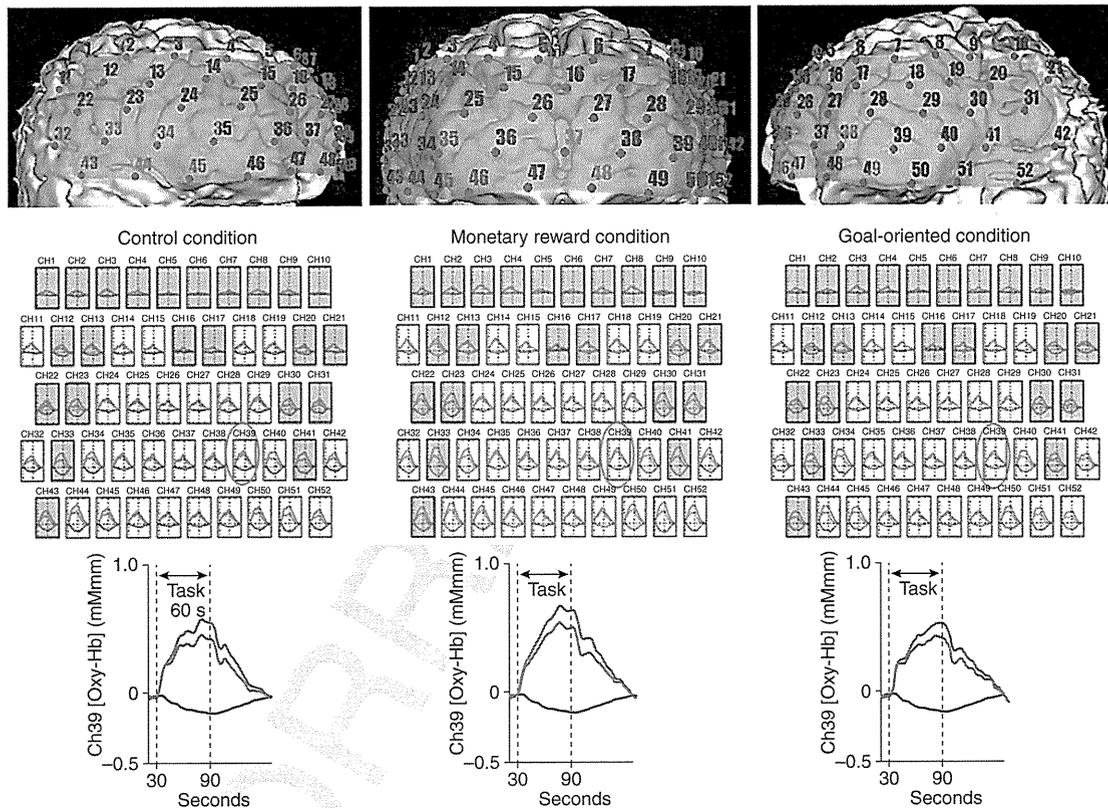


Figure 1. Grand averaged waveforms of hemoglobin concentration changes during the verbal fluency task under the control, monetary reward, and goal-oriented conditions. Grand averaged waveforms of (red) [oxy-Hb], (blue) [deoxy-Hb], and (green) [total-Hb] changes during the verbal fluency task (between the two vertical dotted lines) measured using frontal and temporal probes. (grey fill) Channels with low signal-to-noise ratios. An example of a grand averaged waveform is enlarged below. The upper figures show the measurement positions of the near-infrared spectroscopy machines, superimposed on a magnetic resonance image of a reconstructed cerebral cortex. Ch, channel number.

**Table 1.** Channels with significant correlations of [oxy-Hb], [deoxy-Hb], and [total-Hb] with task performance

| Condition       | [Oxy-Hb]  | [Deoxy-Hb]   | [Total Hb]   |
|-----------------|---|--|--|
| Control         | N (ch. 11, 24, 29, 34, 37, 39, 50: $R < 0.332, P < 0.048$ ) | $R > -0.237, P > 0.164$                                      | N (ch. 24, 29, 32, 34, 37, 39, 40, 50: $R < -0.337, P < 0.045$ ) |
| Monetary reward | $R < 0.274, P > 0.107$                                      | N (ch. 37: $R = -0.379, P = 0.022$ )                         | P (ch. 15: $R = 0.365, P = 0.029$ )                              |
| Goal-oriented   | $R > -0.314, P > 0.062$                                     | N (ch. 26, 27, 36, 37, 38, 48, 49: $R < -0.359, P < 0.032$ ) | $R > -0.317, P > 0.060$  |

Ch., channel no.; N, negative correlations; P, positive correlations. Bold, significant correlation ( $P < 0.05$ ).

reward condition; and in 28 channels (11, 14, 15, 18, 19, 24–29, 32, 34–40, 44–52;  $F = 9.9$ – $26.1, P < 0.001$ ) under the goal-oriented condition. One-way ANCOVA demonstrated no significant main effect of the independent variable ‘condition’: [oxy-Hb], [deoxy-Hb], and [total-Hb] changes during the task period were not significantly different among the three conditions ( $F < 3.86, P > 0.033$ ;  $F < 4.22, P > 0.025$ ; and  $F < 5.37, P > 0.010$ , respectively) in any channel.

## Correlation analysis

### Assessment of personality characteristics

None of the NEO-PI-R scores was significantly correlated with task performance under the control, monetary reward, or goal-oriented conditions ( $P > 0.073, P > 0.095$ , and  $P > 0.081$ , respectively).

### NIRS data

[Oxy-Hb] changes were negatively correlated in more than two neighboring channels with task performance under the control condition (ch. 29:  $r = -0.346, P = 0.039$ ; ch. 39:  $r = -0.338, P = 0.044$ ; ch. 50:  $r = -0.346, P = 0.039$ ), but not under the monetary reward condition ( $r < 0.274, P > 0.107$ ) or the goal-oriented condition ( $r > -0.314, P > 0.062$ ). [Deoxy-Hb] changes were significantly correlated in more than two neighboring channels with task performance under the goal-oriented condition (ch. 26:  $r = -0.359, P = 0.032$ ; ch. 27:  $r = -0.449, P = 0.006$ ; ch. 36:  $r = -0.426, P = 0.010$ ; ch. 37:  $r = -0.386, P = 0.020$ ; ch. 38:  $r = -0.456, P = 0.005$ ; ch. 48:  $r = -0.363, P = 0.029$ ; ch. 49:  $r = -0.367, P = 0.028$ ), but not under the control condition ( $r > -0.237, P > 0.164$ ) or the monetary reward condition ( $r > -0.379, P > 0.022$ ). [Total-Hb] changes were significantly correlated in more than two neighboring channels with task performance under the

control condition (ch. 29:  $r = -0.356, P = 0.033$ ; ch. 39:  $r = -0.350, P = 0.036$ ; ch. 40:  $r = -0.337, P = 0.045$ ; ch. 50:  $r = -0.371, P = 0.026$ ), but not under the monetary reward condition ( $r < 0.365, P > 0.029$ ) or the goal-oriented condition ( $r > -0.317, P > 0.060$ ). Table 1 lists channels showing significant correlations of [oxy-Hb], [deoxy-Hb], and [total-Hb] with task performance under three motivational conditions.

Covariate effects of personality characteristics in the ANCOVA were significant for [oxy-Hb] for neuroticism (ch. 18, 28, 29, 39;  $F > 4.39, P < 0.045$ ) and agreeableness (ch. 14, 15, 24–26, 35, 39, 40, 50, 51;  $F > 4.18, P < 0.050$ ), but were not significant for [deoxy-Hb] for any of the five dimensions. Covariate effects were significant for [total-Hb] for neuroticism (ch. 18, 28, 39;  $F > 4.50, P < 0.042$ ), agreeableness (ch. 14, 24–27, 29, 35, 37–40;  $F > 4.18, P < 0.050$ ), and conscientiousness (ch. 29, 40, 50;  $F > 4.28, P < 0.047$ ) in more than two neighboring channels. Table 2 lists channels having significant correlations of [oxy-Hb], [deoxy-Hb], and [total-Hb] with scores in NEO-PI-R, obtained as significant effects of ‘personality’ covariates in ANCOVA.

[Oxy-Hb] was positively correlated with agreeableness under the control condition ( $r > 0.353, P < 0.035$ ) and the goal-oriented condition ( $r > 0.344, P < 0.040$ ), and was negatively correlated with neuroticism under the monetary reward condition (ch. 28:  $r = -0.333, P = 0.047$ ) and the goal-oriented condition (ch. 28:  $r = -0.388, P = 0.019$ ; ch. 39:  $r = -0.329, P = 0.050$ ). [Total-Hb] was positively correlated with agreeableness scores under the control condition ( $r > 0.339, P < 0.043$ ) and the goal-oriented condition ( $r > 0.399, P < 0.016$ ), and was negatively correlated with neuroticism (ch. 18:  $r = -0.343, P = 0.041$ ; ch. 28:  $r = -0.343, P = 0.041$ ) and conscientiousness (ch. 40:  $r = -0.377, P = 0.023$ ) under the monetary reward condition. Figure 2 shows NIRS channels with significant correlations for

**Table 2.** Channels with significant correlations of [oxy-Hb], [deoxy-Hb], and [total-Hb] vs. NEO-PI-R score†

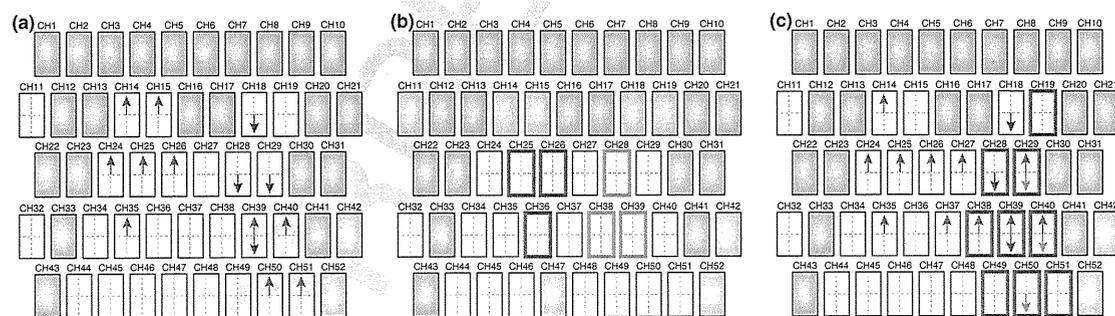
|                   | [Oxy-Hb]   | [Deoxy-Hb]                               | [Total Hb]   |
|-------------------|--|--|--|
| Neuroticism       | Ch. 18, 28, 29, 39, $F > 4.39$ ,<br>$P < 0.045$  | $F < 3.46$ , $P > 0.073$                 | Ch. 18, 28, 39, $F > 4.50$ ,<br>$P < 0.042$  |
| Extraversion      | Ch. 24, $F = 4.60$ , $P = 0.40$  | $F < 3.76$ , $P > 0.062$                 | $F < 3.64$ , $P > 0.066$   |
| Openness          | Ch. 25, 35, 39, $F > 4.59$ ,<br>$P < 0.040$  | Ch. 25, 45 51, $F > 6.43$<br>$P < 0.017$ | Ch. 35, 36, 39, $F > 4.45$ ,<br>$P < 0.043$  |
| Agreeableness     | Ch. 11, 14, 15, 24, 25, 26, 35,<br>37, 39, 40, 45, 50, 51,<br>$F > 4.27$ , $P < 0.048$ | Ch. 34, $F = 4.29$ , $P = 0.048$         | Ch. 11, 14, 24, 25, 26, 27, 29,<br>35, 37, 38, 39, 40, $F > 4.18$ ,<br>$P < 0.050$ |
| Conscientiousness | Ch. 40, 44, 50, $F > 4.18$ ,<br>$P < 0.050$  | Ch. 40, $F = 4.33$ , $P = 0.046$         | Ch. 29, 40, 44, 50, $F > 4.28$ ,<br>$P < 0.047$                                    |

†Obtained as significant effects of 'personality' covariates in ANCOVA. **Bold**, significant correlation ( $P < 0.05$ ).  $F$  and  $P$ -values are for the significant but the most weak correlation.  $P$  and  $F$ -values are the largest and smallest, respectively. Ch, channel number; NEO-PI-R, NEO Personality Inventory-Revised.

[Hb] with NEO-PI-R and significant interactions between NEO-PI-R and 'condition'.

Interaction effects between 'condition' and 'personality characteristic' were significant in more than two neighboring channels for [deoxy-Hb] for neuroticism (ch. 25, 26, 36;  $F > 3.45$ ,  $P < 0.038$ ) and conscientiousness (ch. 28, 38, 39;  $F > 3.35$ ,  $P < 0.042$ ), and for [total-Hb] for agreeableness (ch. 19, 27–29, 38–40, 49, 50;  $F > 3.43$ ,  $P < 0.039$ ). Post-hoc ANCOVA showed that higher scores for neuroticism were more strongly associated with a greater increase in [deoxy-Hb] under the monetary reward condition than under the goal-oriented condition

( $F > 6.367$ ,  $P < 0.017$ ), that higher scores for conscientiousness were more strongly associated with a greater increase in [deoxy-Hb] under the control condition than under the goal-oriented condition ( $F > 30.0$ ,  $P < 0.033$ ), and that higher scores for agreeableness were more strongly associated with a greater increase in [total-Hb] under the goal-oriented condition ( $F > 5.05$ ,  $P < 0.032$ ) and control condition ( $F > 4.31$ ,  $P < 0.047$ ) than under the monetary reward condition. Figure 3 shows relationship between agreeableness score and [total-Hb] under control, monetary reward, and goal-oriented conditions in ch. 39.



**Figure 2.** Near-infrared spectroscopy channels with significant correlations for (a) [oxy-Hb] (b) [deoxy-Hb], and (c) [total-Hb] with agreeableness (red arrows), neuroticism scores (blue arrows), and conscientiousness scores (yellow arrows) on the NEO Personality Inventory-Revised (upward for positive and downward for negative correlations), and those with significant (red outline) interactions between agreeableness and 'condition', (blue outline) interactions between neuroticism and 'condition', and (yellow outline) interactions between conscientiousness and 'condition' as determined on ANCOVA. (Light blue fill) Channels in which activations of [Hb] were not significant under any of the conditions. Ch., channel number.

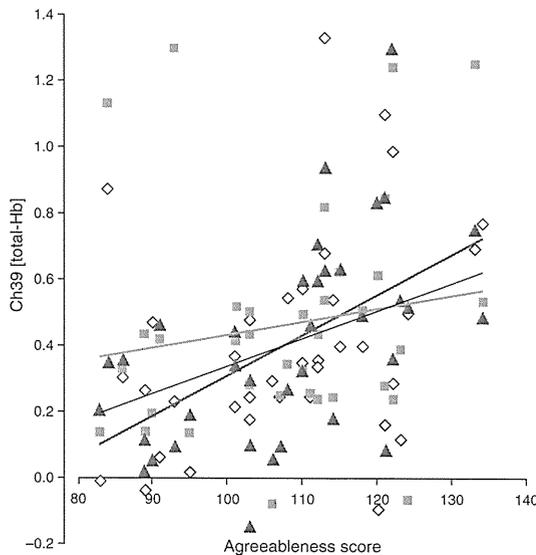


Figure 3. Relationship between agreeableness score and [total-Hb] under ( $\diamond$ ) control, ( $\blacksquare$ ) monetary reward, and ( $\blacktriangle$ ) goal-oriented conditions in ch. 39, in which their interactions were significant. Ch, channel number.

## DISCUSSION

In the present study we examined relationships between personality traits assessed using the NEO-PI-R and cerebral cortex reactivity during a verbal fluency task monitored using multichannel NIRS under three different motivational conditions: control, monetary reward, and goal-oriented, in healthy young male volunteers. The results indicate that (i) subjective motivation for the task was enhanced under the monetary reward condition, but without any improvement in task performance or cerebral cortex reactivity, that is, [oxy-Hb], [deoxy-Hb], and [total-Hb] changes during the task were not significantly different among the three conditions; (ii) cerebral cortex reactivity correlated negatively with task performance under the control condition for [oxy-Hb] and [total-Hb] and under the goal-oriented condition for [deoxy-Hb]; (iii) agreeableness was positively correlated with [oxy-Hb] and [total-Hb], neuroticism was negatively correlated with [oxy-Hb] and [total-Hb], and conscientiousness was negatively correlated with [total-Hb]; and (iv) agreeableness was more strongly associated with a greater increase in [total-Hb] under the goal-oriented

and control conditions than under the monetary reward condition, neuroticism was more strongly associated with a greater increase in [deoxy-Hb] under the monetary reward condition than under the goal-oriented condition, and conscientiousness was more strongly associated with a greater increase in [deoxy-Hb] under the control condition than under the goal-oriented condition.

These results suggest that (i) several of the personality traits in the big-five model are related to frontopolar reactivity; (ii) such relationships vary depending on the motivational condition when brain functions are monitored; and (iii) agreeableness, neuroticism, and conscientiousness are related to frontopolar reactivity depending on the motivational condition. The present subjects were psychologically motivated under the motivational condition, but not sufficiently to improve task performance. The advantage of the NIRS technique is that it can monitor brain functions as activation changes in a more natural setting than other neuroimaging methods. We hypothesized that personality dimensions reflecting interpersonal relationships such as extraversion and agreeableness might be positively correlated with brain functions, particularly under the goal-oriented condition, because subjects with high extraversion or agreeableness are assumed to be more motivated in a natural setting with an examiner. Agreeableness was found to be positively correlated with brain functions, particularly under the goal-oriented condition. We also hypothesized that personality dimensions reflecting interpersonal relationships and emotional features such as openness and neuroticism might be positively and negatively correlated with brain functions, respectively, particularly under the monetary reward and goal-oriented conditions, because motivation is considered to be related to openness and to be decreased in high-tension situations such as an examination. Neuroticism was found to be negatively correlated with brain functions, particularly under the monetary reward condition. Last, we hypothesized that personality dimensions reflecting an effort-related nature such as conscientiousness might be positively correlated with brain functions, because motivation is closely correlated with effort. Conscientiousness was found to be negatively correlated with brain functions, particularly under the control condition, contrary to our hypothesis.

These findings suggest that subjective motivation may differentially affect brain functions depending

on the motivation of the subjects. Such differential brain activation is, in addition, dependent on personality traits, based on the significant interactions between personality characteristics and motivational conditions for [total-Hb] and [deoxy-Hb]. Thus, subjective motivation was observed to be influenced by various factors such as brain function, motivational condition, and personality traits. These findings can be applied to motivational procedures in education and rehabilitation in medicine.

## Conclusions

Using multichannel NIRS, several of the personality traits in the big-five model were found to be related to frontopolar reactivity. These relationships vary depending on the motivational condition when brain functions are monitored; agreeableness, neuroticism, and conscientiousness are related to frontopolar reactivity depending on the motivational condition.

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