This study was approved by the institutional review board of Gunma University Hospital, and written informed consent was obtained from all the subjects and/or their family.

Electroconvulsive therapy

At least 2 days prior to the start of ECT, lithium and valproate were withdrawn while the administration of antidepressants was continued. Each patient was given ECT 1–3 times per week using a brief-pulse square wave ECT device (Thymatron DG_X, Somatics, LLC, Lake Bluff, IL, USA). All the patients received bilateral ECT by bifronto-temporal electrode placement. The half-age stimulation strategy (28) was used for the decision of the stimulus intensity of the first ECT. Seizure length was monitored by the cuff technique and a one-channel electroencephalograph (EEG) that was incorporated in the ECT device. The dose of stimulation was considered as effective when a generalized seizure with 20 s of motor manifestation or 25 s of EEG manifestation was evoked. We restimulated at a higher intensity (i.e. a 50% increase), in the case when the stimulation was not considered effective.

At each ECT session, atropine (0.01 mg/kg) was administered intravenously (i.v.) as premedication, and general anesthesia was induced using propofol (1 mg/kg, i.v.). After the loss of consciousness, succinylcholine chloride (1 mg/kg, i.v.) was administered. Patients were oxygenated (100% oxygen, positive pressure) from anesthetic induction until the resumption of spontaneous respiration.

The 21-item Hamilton Depression Rating Scale (HDRS) was used for the evaluation of the patient's symptoms. Patients were considered as fully remitted if they had ≥50% reduction in the HDRS score from pre-ECT treatments and an HDRS score ≤10.

DEX/CRH test

We modified the method of Holsboer et al. (29) as follows. A dose of 1.5 mg DEX (Banyu Pharmaceutical Corporation, Tokyo, Japan) was administered orally at 23:00 h. Around 13:30 h the following day, each patient lay in a supine position and a heparinized catheter was inserted into a forearm vein. At 14:00 h, the first blood sample was drawn through the intravenous catheter and immediately 100 µg of human CRH (Mitsubishi Pharma Corporation, Osaka, Japan) was administered intravenously. Blood samples were drawn again through the intravenous catheter at 14:15,

14:30, 15:00, and 16:00 h. Throughout the test, the patients were made to rest in a calm room.

Blood samples were immediately centrifuged and stored at −4°C. Serum cortisol concentration was measured using a radioimmunoassay kit (DiaSorin, Inc., Stillwater, MN, USA). The intra-assay coefficients of variation for cortisol were 5.0% and 3.5% at the mean concentrations of 10.0 and 28.5 µg/100 ml, respectively. The interassay coefficients of variation were 8.7 and 4.2 at the mean concentrations of 9.9 and 30.6 µg/100 ml, respectively. The detection range of this kit was 1.0–60 µg/100 ml.

The results were evaluated in accordance with the method of Holsboer et al. (29). 'BASAL' concentration was defined as the serum cortisol concentration collected at 14:00, 'PEAK' concentration was defined as the maximum serum cortisol concentration after CRH injection (between 14:15 and 16:00), and 'DELTA' concentration was defined as the difference between PEAK and BASAL concentrations. And the area under the time course curve (AUC) was calculated by trapezoidal integration. BASAL values reflect the suppressive effect of DEX administered the day before, whereas PEAK, DELTA and AUC values reflect the additional effects of the CRH injection. Furthermore, we evaluated the serum cortisol concentration on the basis of the standard cut-off value of DST (5 µg/100 ml) (30). Patients were expediently categorized as 'DST non-suppressors' when BASAL values exceeded 5 µg/100 ml and 'DEX/CRH non-suppressors' when PEAK values exceeded 5 µg/100 ml.

Each patient underwent the DEX/CRH test twice. The first DEX/CRH test was performed 2–12 days (mean 4.6, SD 3.7) before the first ECT and the second DEX/CRH test was performed 2–9 days (mean 4.9, SD 2.5) after the last ECT. Differences between the DEX/CRH test result of pre-ECT and that of post-ECT were assessed using Wilcoxon's signed rank test or Fishers's exact test in the case of dichotomous predictors.

^{18}F-FDG PET

The PET images were obtained using an SET 2400W instrument (Shimazu Corp., Kyoto, Japan) with a 59.5 cm transaxial field of view and a 20-cm axial field of view. This produced 63 image planes spaced 3.125 mm apart. The transaxial spatial resolution was 4.2 mm full-width half-maximum (FWHM) at the center of the field of view, and the axial resolution was 5.0 mm FWHM.

The subjects fasted for at least 8 h before PET. For PET studies, 4–5 MBq/kg of ^{18}F-fluorodeoxy-

glucose (^{18}F-FDG) was injected in an intravenous bolus at 11:00 h. After the injection, each subject remained in the resting state with their ears and eyes open for a 45-min uptake period. PET was performed for 8 min by the simultaneous trans-mission-emission method using a rotating external source (370 MBq ^{68}Ge/^{68}Ga at installation). Sub-sequently, attenuation-corrected transaxial images were reconstructed by ordered subset expectation maximization algorithm.

The patients underwent PET twice. The first PET was carried out before the first ECT (cases 1, 3, and 5 underwent the first PET 2–8 days before ECT) or in the early period of a course of ECT (cases 2, 4, and 6 underwent the first PET after their third ECT and case 7 after his fourth ECT). The second PET was conducted after about 1 month (mean, 32.7 days; SD, 9.7) after the last ECT. For the healthy volunteers, the same proce-dure of PET was performed once.

For the analysis of PET images, statistical parametric mapping was used (SPM 99, http://www.fil.ion.ucl.ac.uk/spm). For the spatial pre-processing of data, individual PET images were adjusted in accordance with the anterior commis-sure. Images were spatially normalized a standard space using the Montreal Neurological Institute (MNI) template. The normalized images were smoothed with an isotropic Gaussian kernel of 10 mm FWHM. Prior to voxel-based statistical analysis, the global cerebral metabolic rate for glucose was normalized to a fixed mean value (50 μmol/100 ml/min) by proportional scaling to remove the confounding effect of global activity. A two-sample t-test was performed between the patient group and the control group [patient group (first PET) vs. control group, patient group (second PET) vs. control group] and a paired t-test was carried out within patient group (first PET vs. second PET). Activities of brain regions that were

identified as having 100 or more contiguous voxels were defined as significant at a threshold of $P < 0.001$ (uncorrected for multiple comparisons). As the resulting t-values are known to approximate closely the standard Gaussian distribution (31), the values were described as Z-scores. For anatomical identification, the coordinates derived from the MNI template were transformed using the appro-priate algorithm (cf. http://www.mrc-cbu.cam.ac.uk/Imaging/Common/mnispace.shtml) to comply with the original grid of Talairach and Tournoux.

Results

The clinical course is shown in Table 1. All the patients were remitted sufficiently by ECT treat-ment. The mean HDRS scores were 29.3 before ECT and 4.3 after ECT. The number of ECT sessions was 6–20. All the patients were remitted until the second PET. They were still depressed at the time of the first PET, when the mean HDRS score was 25.3.

DEX/CRH test

The results of the DEX/CRH test of each patient are shown in Fig. 1. The serum cortisol response curve of pre-ECT was elevated compared with that of post-ECT. Before ECT, 28.6% of the patients (two of seven) were DST non-suppressors and all the patients (100%) were DEX/CRH non-suppres-sors. After ECT, the proportion of DST non-suppressors and DEX/CRH non-suppressors were 0% (0 of seven) and 28.6% (two of seven), respectively. The statistical analysis of DEX/CRH test results (Table 2) showed that BASAL, PEAK, DELTA and AUC values significantly decreased after ECT (Wilcoxon's test: Z between −1.992 and −2.197, $P < 0.05$). The rate of DEX/CRH non-suppressors also significantly decreased after ECT
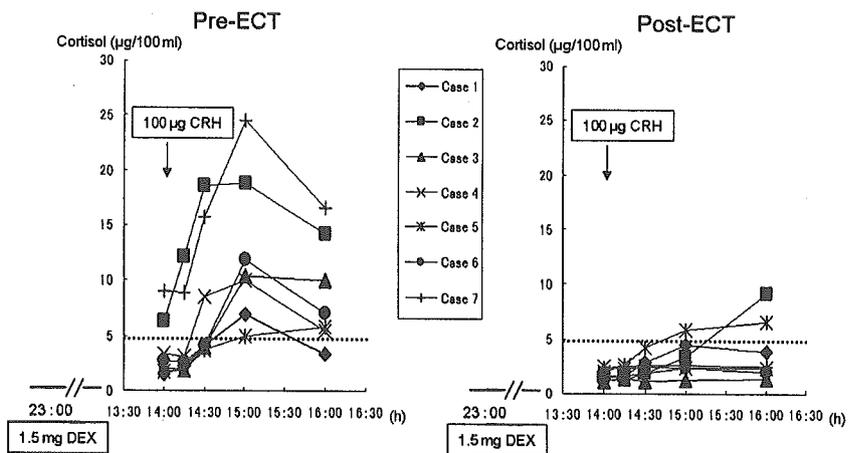

Fig. 1. Individual time course curve of serum cortisol concentration response to the DEX/CRH test.

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Table 2. Statistical analysis of DEX/CRH results

	Pre-ECT	Post-ECT	P
Wilcoxon's signed rank test			
Basal (μg/100 ml), mean (SD)	3.8 (2.8)	1.8 (0.5)	<0.05
Peak (μg/100 ml), mean (SD)	12.6 (6.7)	4.2 (2.8)	<0.05
Delta (μg/100 ml), mean (SD)	8.8 (4.0)	2.3 (2.9)	<0.05
AUC (μg/100 ml·min), mean (SD)	663.0 (334.2)	139.8 (165.6)	<0.05
Fisher's exact test			
Rate of DST non-suppressors, % (n)	28.6 (2/7)	0.0 (0/7)	n.s.
Rate of DEX/CRH non-suppressors, % (n)	100 (7/7)	28.6 (2/7)	<0.05

(Fisher's exact test $P = 0.021$). However, there was no difference in the rate of DST non-suppressors post-ECT when compared with pre-ECT (Fisher's exact test $P = 0.462$).

^{18}F-FDG PET

The result of SPM comparison between the patient group and the control group is shown in Table 3 and Fig. 2. In the first PET, the depressed patients presented a significant decrease in rCMRGlu in the bilateral orbitofrontal cortices (Brodmann's area 11), dorsolateral prefrontal cortices (right inferior frontal gyrus, Brodmann's area 46; left inferior frontal gyrus, Brodmann's area 45; right middle frontal gyrus, Brodmann's area 9; right superior frontal gyrus, Brodmann's area 10) and left caudate, and a significant increase in rCMRGlu in the left parietal lobe (Brodmann's area 7), and right paracentral gyrus (Brodmann's area 31) when compared with the control group. A significant hypometabolism in the bilateral orbitofrontal cortices, left inferior frontal gyrus (Brodmann's area 45), right superior frontal gyrus (Brodmann's area 10) and left caudate and a significant hypermetabolism in the left parietal lobe remained in the second PET. On the contrary, a significant hypometabolism in the right dorsolateral prefrontal cortices (Brodmann's area 9, 46) and a significant hypermetabolism in the right paracentral gyrus were absent in the second PET. A significant hypometabolism in some parts of prefrontal regions and a significant hypermetabolism in some parts of the parietal and occipital lobes were additionally observed in the second PET.

Only the three regions showed significant difference in the SPM comparison within the patient group. A significant decrease in rCMRGlu in the bilateral medial frontal cortices (Brodmann's area

Table 3. Summary of SPM comparison between patient group and control group. See Fig. 2

Brain region	Brodmann's area	Side	Depressed patients (first PET vs. control) Talairach coordinate x	y	z	Z-score	Remitted patients (second PET vs. control) Talairach coordinate x	y	z	Z-score
Hypometabolic area*										
Rectal/orbital gyrus	11	R	10	32	−23	4.03	10	30	−30	4.77
	11	L	−2	48	−21	3.83	−2	49	−21	4.14
	11	L	−6	38	−24	3.52	−6	38	−24	4.19
Inferior frontal gyrus	46	R	53	33	9	3.94				
	45	L	−48	22	14	3.91	−48	22	12	3.64
	10	L					−51	41	−2	3.67
Middle frontal gyrus	11	L					−34	43	−4	4.16
	9	R	40	29	37	3.48				
	10	R					44	55	5	4.87
	47	R					53	43	−4	4.18
Superior frontal gyrus	10	R	30	57	16	3.47	32	57	14	4.25
Medial frontal gyrus	10	R					4	59	21	4.30
Cingulate gyrus	24	R					8	−1	28	3.78
Caudate		R					14	20	3	3.89
		L	−12	12	10	3.58	−12	12	10	3.54
Hypermetabolic area*										
Parietal lobe, precuneus	7	L	−8	−33	46	4.92	−4	−50	47	4.87
	7	R					10	−77	44	4.63
	31	R					12	−69	24	4.46
Inferior parietal lobule	40	R					55	−50	49	4.06
Fusiform gyrus	19	R					22	−55	−9	4.30
	19	L					−30	−74	−13	3.95
Lingual gyrus	18	R					22	−76	−3	3.55
	18	L					−18	−74	−8	4.31
Paracentral gyrus	31	R	8	−19	45	4.40				

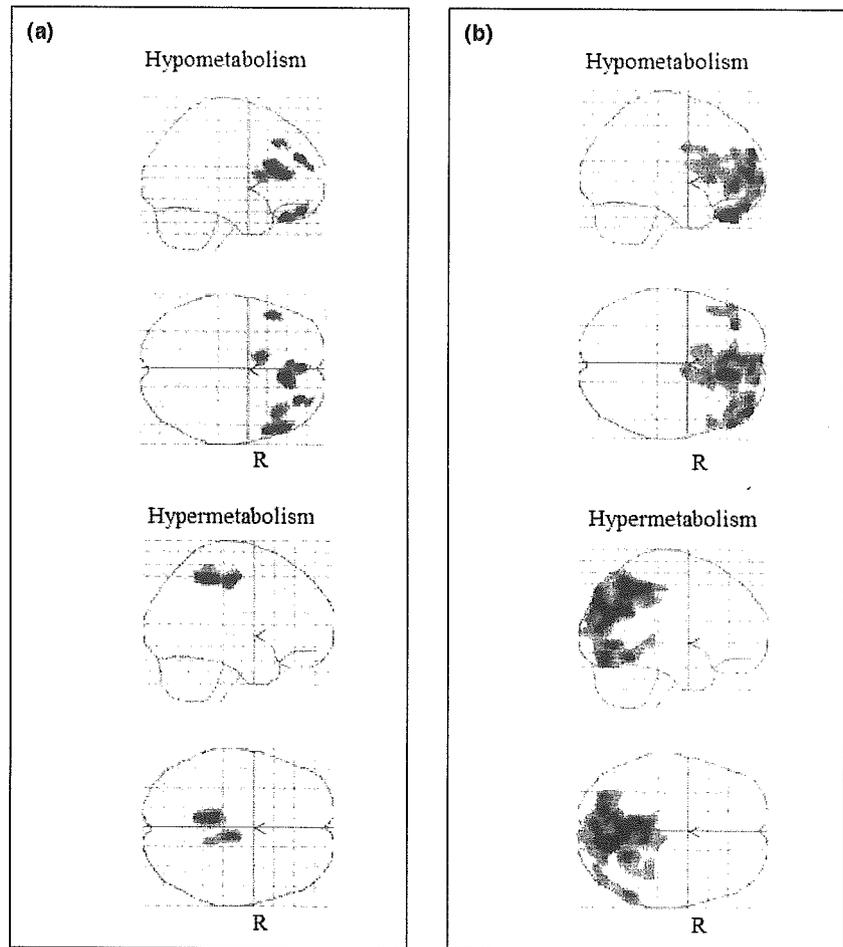*Significant in patient group compared with control group.

Fig. 2. Visualization of SPM comparison between patient group and control group. Significantly hypometabolic and hypermetabolic areas in depressed patients compared with control subjects (a) and in remitted patients compared with control subjects (b) (P < 0.001, uncorrected). 'R' indicates right side.

9, Talairach coordinate: 0, 54, 27, Z-score 4.31) and a significant increase in rCMRGlu in the left occipital lobe (Brodmann's area 18, Talairach coordinate: −24, −94, 21, Z-score 4.50) and left parietal lobe (Brodmann's area 7, Talairach coordinate: −26, −57, 54, Z-score 3.75) were found in the second PET compared with the first PET.

Discussion

In the present study, ECT was clinically effective for the depressed patients with medication treatment failures. After a course of ECT, cortisol response in the DEX/CRH test was normalized. However, cerebral glucose metabolism was not fully recovered.

Cortisol response in the DEX/CRH test diminished after the ECT, and such a change is similar to that after a successful treatment with antidepressant medications (17). After a successful course of ECT, BASAL, PEAK, DELTA, and AUC values significantly decreased, and the rate of 'DEX/CRH non-suppressors' also significantly decreased. These results may correspond to the normalization

of HPA function associated with symptomatic resolution induced by ECT. However, the significant change in HPA function was not detected by DST. Heuser et al. (15) have reported that the sensitivity of the DEX/CRH test for MDE (about 80%) greatly exceeds that of the standard DST (about 44%). In addition, so far it has been assumed that ethnicity affects DST results and that Japanese subjects have a particularly low sensitivity to the test (32). The result of this study is compatible with these reports. Furthermore, previous reports about the effect of ECT on DST results have indicated inconsistent results (11–14).

The normalization of the HPA axis function has been conceivable as one hypothesis about the mechanism of action of ECT. According to Fink and Ottosson (8) and Fink (9), the induced seizure causes the hypothalamus to elicit an immediate and large discharge of its hormone. In the ensuing cascade of hormonal effects, the pituitary gland discharges its products, and those, in turn, alter the discharge of cortisol from the adrenal glands. The first effects of stimulation are transitory, but by repeated stimulus, the normal feedback actions of the hormones of the HPA axis are again in place.

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The result of the present study might confirm the hypothesis by using more sensitive test of HPA function. In addition, The DEX/CRH test might be more useful in defining suitable cases for ECT in case of medication treatment failures.

Examinations by ^{18}F-FDG PET revealed that rCMRGlu in the ECT-treated patients was not fully recovered despite clinical remission. Most of abnormalities in PET images during MDE remained after a successful course of ECT while a slight recovery of rCMRGlu was observed in the right dorsolateral prefrontal cortices and right paracentral gyrus. In the patient group, changes in rCMRGlu after ECT treatments were subtle and not toward recovery. Hypometabolism in some parts of prefrontal regions and hypermetabolism in some parts of the parietal and occipital lobes were additionally observed after ECT treatments, although we cannot explain well the precise mechanism.

Our speculation is that ^{18}F-FDG PET hardly detected the state-dependent changes by ECT treatment and that the complete recovery of rCMRGlu followed long after the improvement of symptoms. Awata et al. (33) have reported that hypoperfusion in the frontal region in depressed patients is not reversed in 12 weeks after a successful ECT. However, Navarro et al. (34) have reported that anterior hypofrontality in depressed patients disappears in 12 months after ECT. The present finding indicates that the recovery of rCMRGlu may also not be observed completely 1 month after ECT. As another speculation, the remaining of abnormality of rCMRGlu might be associated with the relapse vulnerability following response to ECT. Sackeim et al. (35) showed that the pre-ECT medication failure was associated with a high relapse rate after ECT. To elucidate these speculations, it is necessary to conduct a follow-up FDG PET study.

Limitations of the present study include a small sample size, an open design and a concomitant pharmacotherapy. First, abnormalities in rCMRGlu in various brain regions should be interpreted with caution, taking into account the effects of sample size and medication. Secondly, we failed to perform the DEX/CRH test and ^{18}F-FDG PET simultaneously. Future studies should be conducted as to which brain areas (including hypothalamus) are associated with neuroendocrinological alterations caused by ECT.

In conclusion, depressed patients who failed trials of antidepressant medication showed a remission with ECT that was accompanied by resolution of HPA dysregulation. However, measures of cerebral brain metabolism did not resolve.

Follow-up studies will provide further insights into the clinical and pathophysiological relevance of this finding.

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Increased and Decreased Cortical Reactivities in Novelty Seeking and Persistence

A Multichannel Near-Infrared Spectroscopy Study in Healthy Subjects

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Abstract

Background: Near-infrared spectroscopy (NIRS) has enabled completely noninvasive measurements of regional cerebral blood volume (rCBV) changes in cortices. In the present study, we investigated the relationships between rCBV changes assessed with NIRS and two dimensions of personality, novelty seeking and persistence. *Methods:* Thirty right-handed healthy volunteers participated in the study. Their personality traits were assessed using the Temperament and Character Inventory (TCI), and changes in oxy- and deoxy-hemoglobin concentrations were monitored during 40 s unilateral finger tapping tasks over the subjects' bilateral temporal regions using a 24-channel NIRS machine. *Results:* The oxy-hemoglobin concentration increases were significantly correlated positively with novelty seeking scores and negatively with persistence scores in the TCI during the initial time segment of the left-finger tapping task. *Conclusion:* Increased and decreased brain activations demonstrated using multichannel NIRS were assumed to characterize the cortical reactivities underlying novelty seeking and persistence temperament, respectively.

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Introduction

Personality is defined as the ingrained patterns of thought, feeling, and behavior characterizing an individual's unique lifestyle and mode of adaptation, and resulting from constitutional factors, development, and social experience. It has traditionally been conceptualized as consisting of several factors or dimensions. One of the major models of personality was proposed by Cloninger et al. [1] on the basis of the hypothesis that personality consists of two components, biological and social, which are often called 'temperament' and 'character', respectively. Temperament is defined as biologically based, heritable, and stable throughout life, and character as socially acquired and refers to individual differences in voluntary goals and values [2]. Scores in four temperament dimensions and three character dimensions are defined using the Temperament and Character Inventory (TCI).

The neurobiological substrates of personality, especially those of temperament, have been studied from three points of views: psychological functions, neurochemical substances, and brain function characteristics responsible for each dimension of personality. For example, Cloninger [3] proposed four dimensions of temperament, that is, novelty seeking, harm avoidance, reward dependence, and persistence, and assumed behavioral activation, behavioral inhibition, behavioral dependence, and behavioral persistence systems as their psychological correlates,

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respectively. He also hypothesized three monoamine transmitters, namely, dopamine, serotonin, and noradrenaline, as the possible neurochemical substrates of the former three dimensions of temperament, respectively.

Brain function characteristics responsible for personality dimensions have been most proposed for the introversion-extraversion dimension, which is included in most major current models of personality as one of the fundamental dimensions. Introversion and extraversion were hypothesized to represent higher and lower cortical activities, respectively, especially in the frontal lobes, due to overactive and underactive reticulo-thalamo-cortical pathways [4] or to higher and lower activities in the behavioral inhibition system consisting of the ascending reticular activating system, the frontal lobe, septal regions, and hippocampus [5]. Recent advances in functional brain imaging methodologies have enabled the direct examination of these hypotheses in living human brains. Extraversion scores in the Five-Factor Inventory were negatively correlated with regional cerebral blood flow (rCBF) in the frontal lobes, although positively in the temporal lobes and limbic regions, in a [^{15}O]H$_2$O-PET study [6]. Extraversion-introversion scores in the Eysenck Personality Inventory were also negatively correlated with rCBF in all the brain regions in female subjects in a ^{133}Xe inhalation study [7]. The results were replicated in another study as lower rCBF in the temporal lobes in extraverts [8]. The results of these three studies support the hypothesis of higher and lower cortical activities in introversion and extraversion, respectively.

As for the temperament dimensions in the TCI, functional brain imaging studies demonstrated significant associations between brain activation and novelty seeking scores which form one facet of extraversion. Novelty seeking scores were positively correlated with glucose metabolism in the right middle frontal gyrus but were negatively correlated with glucose metabolism in the right middle temporal gyrus, left precentral gyrus, left parahippocampal gyrus and substantia nigra in a [^{18}F]-fluorodeoxyglucose (FDG) positron emission tomography (PET) study [9]. Novelty seeking scores were also positively correlated with rCBF in the right insula and left anterior cingulate in a single photon emission computed tomography (SPECT) study [10]. There has been only one study that examined the relationships between all the seven personality dimensions in the TCI and rCBF [11]. The SPECT study reported many significant relationships in male subjects: novelty seeking with activation in the left precentral and postcentral gyrus and deactivation in the temporal gyri,

occipital lobe, and precuneus; persistence with activation in the temporal , parietal, occipital, and limbic lobes and deactivation in the parietal, temporal, frontal lobes, the rolandic operculum, and insula; and self-directedness with activation in the left frontal lobe and deactivation in the precentral gyrus, frontal lobe, temporal lobe, and occipital lobe mainly on the right side. These results are in partial agreement with those examining the relationships between a few personality dimensions and rCBF or cerebral glucose metabolism.

The functional brain imaging results mentioned above suggest that brain function characteristics, particularly those in cortical activity levels, may serve as neurobiological substrates for the introversion-extraversion and the novelty seeking dimension in temperament. However, it should be cautioned that all the six studies measured rCBF or cerebral glucose metabolism while the subjects were in the resting state: that is, the obtained data corresponded to the state of the brain when no activation was demanded. Correlations of introversion-extraversion and novelty seeking scores with brain activities could be much higher if activational changes in rCBF or cerebral glucose metabolism are employed instead of those in the resting state because the introversion-extraversion and the novelty seeking dimensions refer to the personality characteristics particularly observed in response to environmental stimuli. Among four temperament dimensions in the TCI, novelty seeking and persistence scores are expected to exhibit close relationships with brain activation because they are assumed to represent activation and persistence of behavior; that is, novelty seeking as behavioral activation could correspond to enhanced reactivity of cerebral activities and persistence as behavioral persistence to their reduced reactivity.

The noninvasive and continuous monitoring of such activational changes of brain functions has become possible with the development of near-infrared spectroscopy (NIRS) technology. The successful trials of measuring brain functions in humans using an NIRS oxygen monitor were reported in 1993 by four research groups [12–15], and the spatiotemporal patterns of brain functional changes were demonstrated in 1995 by mapping the topograms of hemoglobin concentration changes using multichannel-NIRS machines [16]. The technological basis of NIRS was reviewed by Koizumi et al. [17], Strangman et al. [18], and Obrig and Villringer [19]. NIRS has a number of advantages: high time resolution, noninvasiveness [20], high tolerance for motion artifacts, portability, and low running cost. All these advantages of NIRS allow the measurement of a brain function along a detailed time

course while the brain is activated in a natural state. The brain substrates of emotion have been examined by NIRS [21].

Hemoglobin concentration measured using NIRS is interpreted to indicate regional cerebral blood volume (rCBV). Neural activity in the brain causes increases in oxygen consumption and glucose metabolism in the brain tissue, which are followed by an excessive increase in rCBF [22]. The excessive increase in rCBF results in an increase in oxygenated hemoglobin concentration ([oxy-Hb]) and a decrease in deoxygenated hemoglobin concentration ([deoxy-Hb]) during neural activation. An increase in [oxy-Hb] and a decrease in [deoxy-Hb] were demonstrated by NIRS to positively and negatively correlate with rCBF, respectively, in a $^{15}H_2O$ PET study [23].

In the present study, we monitored cortical reactivities as the [oxy-Hb] and [deoxy-Hb] changes using a multichannel NIRS machine during a finger tapping task in healthy subjects. We then examined the relationships between [oxy-Hb] and [deoxy-Hb] changes and personality features assessed using TCI. A simple motor task rather than a complex cognitive task was employed for brain activation in order to facilitate the interpretation of the obtained results from the viewpoint of behavior. Such a simple motor task is assumed to be more directly related to the behavioral activation system (novelty seeking dimension) and behavioral persistence system (persistence dimension) than to the other systems assessed by Cloninger's TCI, e.g. the behavioral inhibition system (harm avoidance dimension) and behavioral dependence system (reward dependence dimension): larger [Hb] changes reflect the excitability of neuronal activities and an hence enhanced reactivity of brain functions, and are expected in the subjects with high scores in novelty seeking (strong behavioral activations); smaller [Hb] changes reflect the unchangeability of neuronal activities and hence a reduced reactivity of brain functions and are expected in subjects with high scores in persistence (strong behavioral persistence). Task performances were also incorporated into the data analysis because [oxy-Hb] change magnitudes in NIRS were demonstrated to depend on task performances in healthy subjects in a multichannel NIRS study, with smaller [oxy-Hb] increases in high performers [24].

Our working hypotheses prior to this study were as follows: (1) significant positive correlations will be obtained between [oxy-Hb] and [deoxy-Hb] changes with novelty seeking scores and negative ones with persistence scores in the TCI, because these two dimensions are related to the reactivity of brain functions; (2) these correlations will

be stronger than those for the three dimensions of character in the TCI and even stronger than with the other two dimensions of temperament, because character dimensions are assumed to be less biologically based than temperament.

Methods

Subjects

Thirty healthy volunteers participated in this study (age: mean, 27.1 years [SD 3.0]; range, 22–33 years; 15 males and 15 females). None of these volunteers had a medical history of psychoneurological illness, chronic somatic illness, substance abuse or serious head injury, or were receiving any medications. All the subjects were right-handed and gave their written informed consent prior to the study. The present study was approved by the Institutional Research Board of Gunma University Graduate School of Medicine.

Activation Tasks

CBV was measured during a finger tapping task. The subjects were required to perform unilateral finger tapping as quickly and precisely as they could during the task periods. The subjects sat on a comfortable chair placing their arms on the armrest in a well-lighted room. The subjects were instructed to look ahead blankly, and to avoid any movements other than the finger tapping. They rehearsed the finger tapping before starting the measurement to ensure that they comprehended the task instructions.

The task consisted of three cycles of 40-second unilateral finger tapping and a subsequent 30-second rest. The rather long task period of 40 s was selected on the basis of our preliminary study that showed that the task periods of 20 and 30 s usually employed in most NIRS studies were not sufficiently long to reveal the temporal characteristics of hemoglobin concentration changes during the task.

The order of right- and left-finger tapping tasks was counterbalanced among the subjects. The subjects were allowed a 3-min rest between finger tapping tasks on each side. The finger tapping movements were recorded on video tapes to determine the number of finger tapping movements. The average numbers of finger tapping movements across three cycles were employed as finger tapping scores.

Measurement of Hemoglobin Concentrations

CBV was measured using a 24-channel NIRS machine (Hitachi ETG-100, optical topography system, Hitachi Medical Corp., Japan), which noninvasively measures [oxy-Hb] and [deoxy-Hb] in the cerebral cortex. The concentration of hemoglobin was measured using two wavelengths (780 and 830 nm) with a source-detector distance of 30 mm and a time resolution of 0.1 s. Near-infrared light was emitted from 1.5 mW continuous laser diodes, whose intensities were modulated within 1.0–4.9 kHz to prevent cross-talks between the channels and wavelengths.

Two sets of 12-channel probes of ETG-100 were placed bilaterally on the subject's temporal regions, with its center positioned at the midpoint between the vertex and the external ear hole. Each set of probes consisted of five source probes and four detector probes and measured the changes in [oxy-Hb] and [deoxy-Hb] at 12 measurement points in a 6 × 6 cm area (fig. 1). The correspondence of the
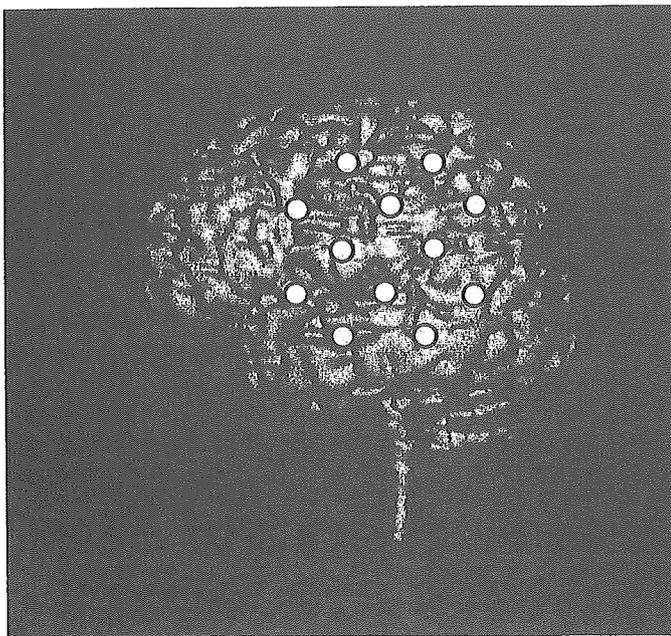
Fig. 1. The measuring positions of the NIRS apparatus in the present study (open circles) are superimposed on a magnetic resonance image of a three-dimensionally reconstructed cerebral cortex. Two sets of probes covering a 6 × 6 cm² area were placed bilaterally on the subject's temporal regions.

probe and channel positions to the cerebral cortex was examined by superimposing the measurement positions on a magnetic resonance image of a three-dimensionally reconstructed cerebral cortex of one of the subjects (fig. 1). The changes in total hemoglobin concentration were calculated as the sum of [oxy-Hb] and [deoxy-Hb]. The parameters for measurements were set as follows: pre-time, 10 s; relaxing time, 5 s; and post-time, 5 s in a parameter setting within ECT-100. The baselines for the measurements were corrected using a linear fitting method, connecting the pre- and the post-time baselines.

Assessment of Personality

The personality of the subjects was assessed using the TCI, immediately after the NIRS measurements. The TCI is a self-questionnaire consisting of 240 items developed by Cloninger et al. [1, 2, 25]. The TCI assumes that personality consists of four biological (temperament) and three social (character) dimensions. The four dimensions of temperament are novelty seeking, harm avoidance, reward dependence and persistence. The three dimensions of character are self-directedness, cooperativeness and self-transcendence.

Novelty seeking is defined as the tendency to actively respond to novel stimuli. Persistence is defined as the tendency to persevere despite frustration and fatigue. Self-directedness refers to the ability to control one's behavior to fit the situation in accordance with individually chosen goals and values. Cooperativeness accounts for individual differences in identification with and acceptance of other people.

Data Analysis

The obtained hemoglobin concentrations were analyzed in two steps: first, [oxy-Hb] and [deoxy-Hb] were processed to investigate the interindividual differences, and second, the relationships between hemoglobin concentration and personality were examined.

The [oxy-Hb] and [deoxy-Hb] from each subject were averaged across three cycles of the right- and left-finger tapping tasks for 24 channels, and were smoothed with a 5.0-second-moving average filter. The [oxy-Hb] and [deoxy-Hb] in the intraindividually averaged waveforms were then averaged for the following five time segments: (1) pre-task (10 s before task); (2) early-task (first third of task period); (3) middle-task (middle third of task); (4) late-task (last third of task), and (5) post-task (10 s after task). Channels with a low signal-to-noise ratio were excluded from further analyses, because of the paucity of near-infrared light detected, if the standard deviations of [oxy-Hb] and [deoxy-Hb] during the pre-task period exceeded 0.01 mM/mm. The channels with a significant activation of [oxy-Hb] and [deoxy-Hb] due to finger tapping were then selected for further analyses if [oxy-Hb] and [deoxy-Hb] changes across the four time segments (pre-task, early-task, middle-task, and late-task) were significant in the repeated analysis of variance (ANOVA).

For the above-selected channels, Spearman's correlation coefficients were calculated between the hemoglobin concentrations and TCI scores of the 30 subjects. Channels were selected for multiple regression analyses when at least one TCI score tended to correlate with hemoglobin concentration. For the selected channels, linear multiple regression analyses were performed to determine the relationships among the TCI scores, tapping scores and sex as independent variables, and mean increases in [oxy-Hb] and [deoxy-Hb] as the dependent variables. As confirmation analyses, hierarchical multiple-regression analyses were conducted. Independent variables were divided into temperament dimension scores (novelty seeking, harm avoidance, reward dependence and persistence scores), character dimension scores (self-directedness, cooperativeness and self-transcendence scores) and others (tapping scores and sex). The improvement of model fitness by the incorporation of each group was examined.

Results

For [oxy-Hb], channels with a sufficient signal-to-noise ratio and a sufficient activation during the task period were 18 and 19 channels during the left- (fig. 2) and right-finger tapping tasks (fig. 3), respectively. [oxy-Hb] increases during the left-finger tapping task tended to correlate with the scores of the TCI for three channels after Bonferroni's correction (p < 0.00079 = 0.1/18 channels/7 scores): novelty seeking scores positively correlated with [oxy-Hb] changes during the early- and middle-task segments in two channels in the left hemisphere (fig. 4: N1, rho = 0.59, p = 0.00053; N2, rho = 0.58, p = 0.00076), and persistence scores were negatively correlated with [oxy-Hb] changes during the early-task segment in one channel in the right hemisphere (fig. 4: P, rho = −0.64, p = 0.00013). No TCI scores tended to cor-
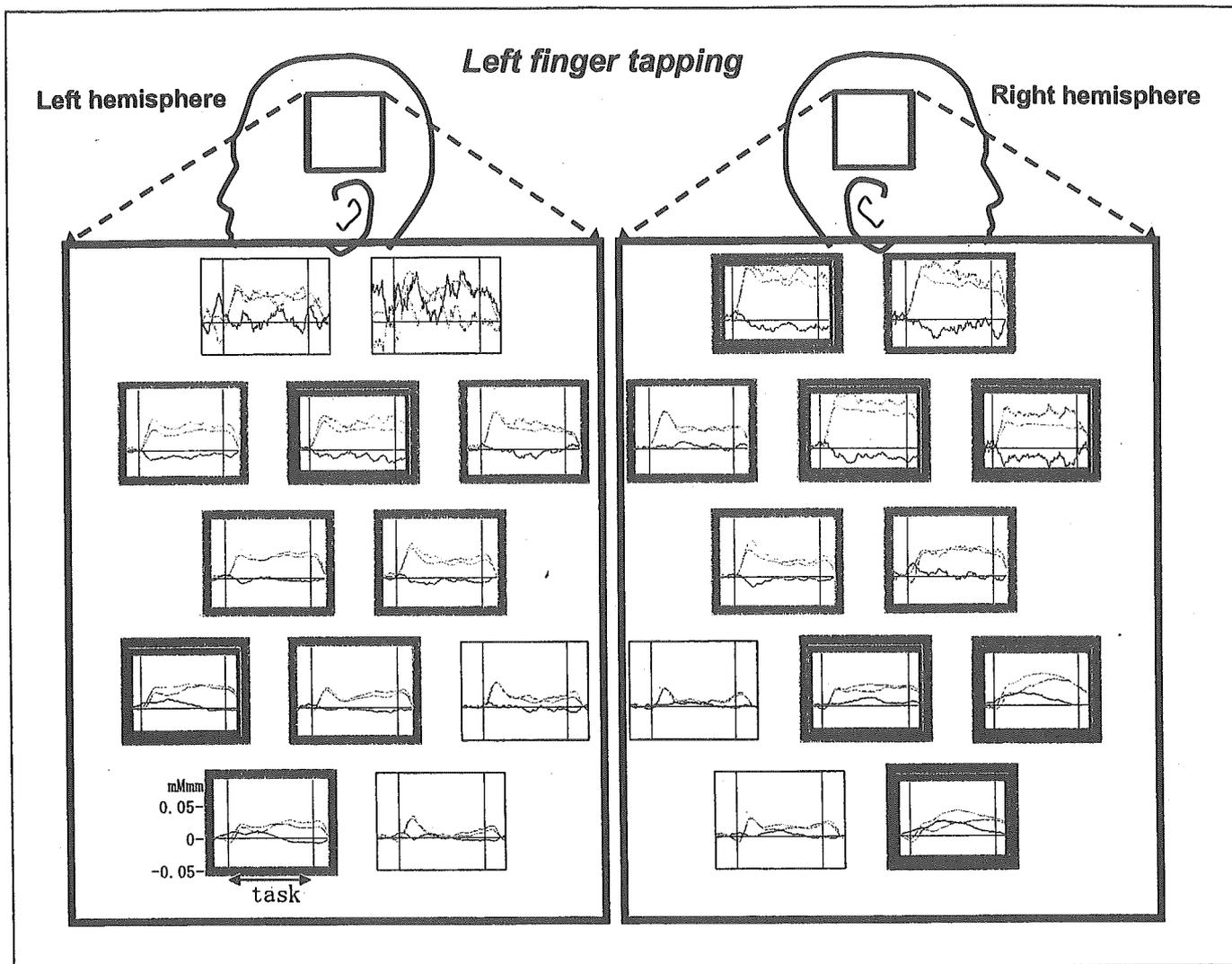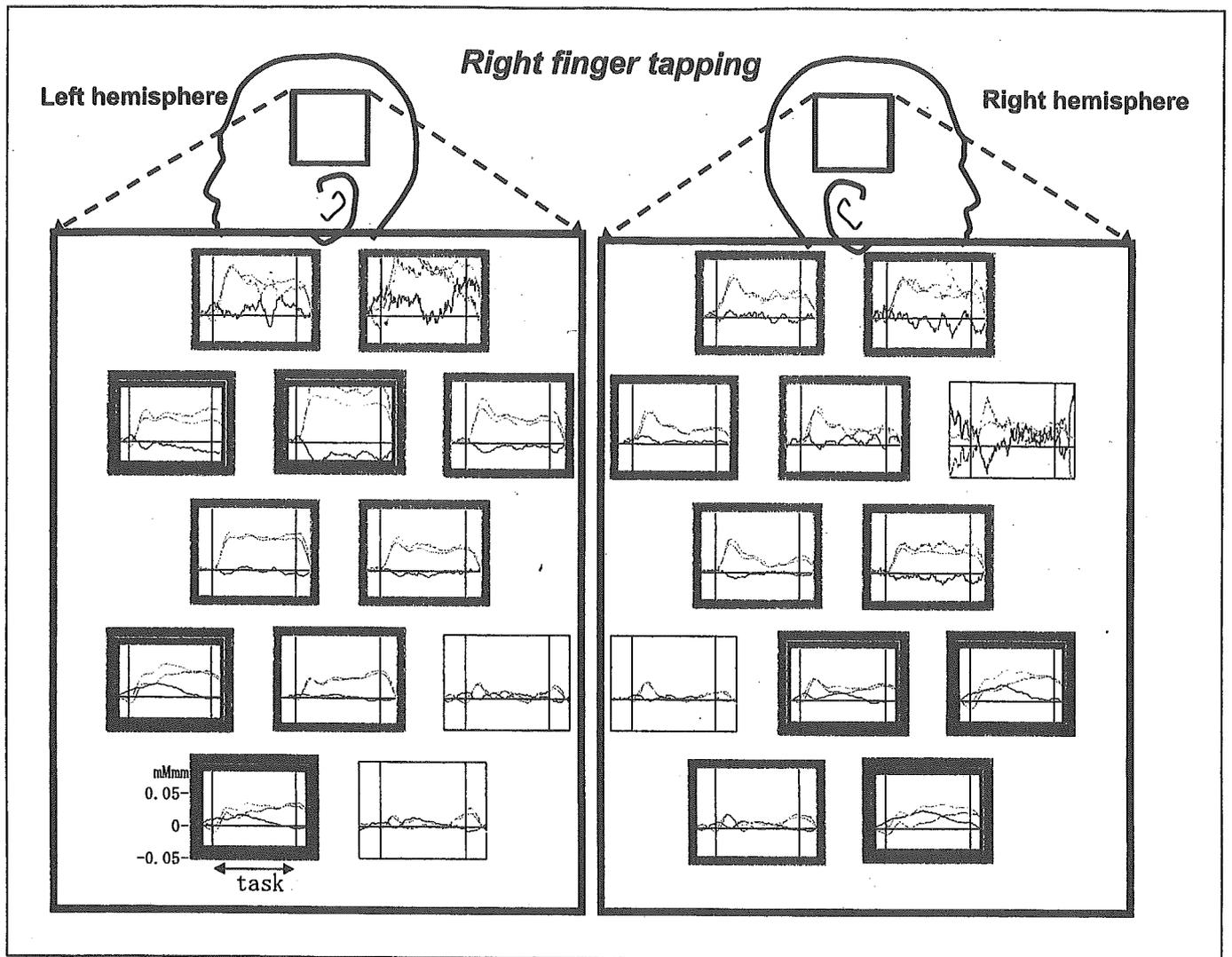
Fig. 2. Oxy-, deoxy-, and total-hemoglobin concentration changes in the left-finger tapping task are presented as grand average waveforms in 24 channels of the left (left) and the right temporal probes (right) in red, blue, and green lines, respectively. The channels with significant changes in [oxy-Hb] and [deoxy-Hb] are hemmed with red and blue squares, respectively. The channels with low signal-to-noise ratio are shaded in gray.

relate with [oxy-Hb] increases during the right-finger tapping task.

Linear multiple regression analyses were conducted for the three channels selected from the left-finger tapping task. For N1 and N2 channels, [oxy-Hb] increases during the early-task segment were well explained by the TCI scores and the tapping scores: significant variables were novelty seeking, persistence, self-directedness and tapping scores (table 1). For the P channel, [oxy-Hb] increases during the early-task segment were well explained by the TCI scores and the tapping scores: significant vari-

ables were novelty seeking scores (table 1). The model fitness of the hierarchical regression analysis significantly improved when temperament dimension scores were incorporated, whereas a small improvement was observed when character dimension scores were incorporated (table 2).

For [deoxy-Hb], eight channels had a sufficient signal-to-noise ratio and a sufficient activation in the task period both during the left- and right-finger tapping tasks. However, in all these channels, no TCI scores tended to correlate with [deoxy-Hb] increases.

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Right finger tapping

Left hemisphere — Right hemisphere

mMmm
0.05—
0—
−0.05—
task

3

Left finger tapping

Left hemisphere — Right hemisphere

L — R

N 1
N 2
P

4

Fig. 3. Oxy-, deoxy-, and total-hemoglobin concentration changes in the right-finger tapping task are presented as in figure 2.

Fig. 4. Three channels selected for multiple regression analyses are shown where [oxy-Hb] changes in the left-finger tapping task tended to correlate with the scores of novelty seeking (N1, N2) and persistence (P) in Spearman's correlation coefficients. The channels with significantly larger contralateral than ipsilateral hemoglobin concentration changes in the left and the right hemispheres are also shown as L and R, respectively.
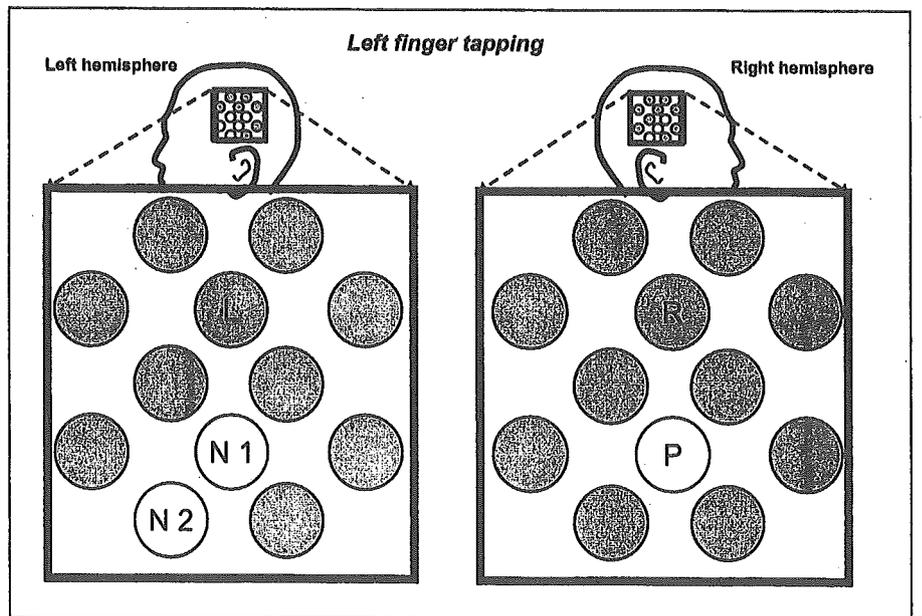
Table 1. Regressional coefficients (beta) of linear multiple regression analyses for the channels selected from the simple correlational analyses are summarized. [oxy-Hb] changes in the early-task segments in the left-finger tapping task were significantly explained by the TCI scores and tapping scores

Channel/time segment	N1/early R = 0.85*	N2/early R = 0.78*	p/early R = 0.77*
Temperament			
Novelty seeking	beta = 0.61*	beta = 0.57*	beta = 0.56*
Harm avoidance	0.31	0.27	0.13
Reward dependence	−0.01	0.12	−0.02
Persistence	−0.53*	−0.53*	−0.40
Character			
Self-directedness	0.53*	0.35	−0.09
Cooperativeness	0.01	−0.03	−0.15
Self-transcendence	−0.04	−0.10	−0.09
Sex	−0.11	−0.08	−0.34
Tapping score	−0.33*	−0.44*	−0.17

*p < 0.05.

Table 2. Model fitness of hierarchical regression analyses significantly improved when temperament dimension scores were incorporated into the regression for all selected channels, whereas a small improvement was observed in the case of incorporating character dimension scores

Channel/time segment	N1/early delta R² = 0.00	N2/early delta R² = 0.01	p/early delta R² = 0.04
Tapping score, sex			
+ Temperament	0.57*	0.53*	0.52*
+ Character	0.15	0.07	0.04
Tapping score, sex			
+ Character	0.10	0.03	0.11
+ Temperament	0.61*	0.57*	0.44*

*p < 0.05.

NIRS measuring positions in the present study are superimposed on a magnetic resonance image of a three-dimensionally reconstructed cerebral cortex of a representative subject to help in identifying the correspondence of the NIRS channels to the cerebral cortex area (fig. 1). The channels with significant correlations were situated mainly in the lower portion of the bilateral temporal probes, and corresponded not to the primary motor cortex but to the lower part of the cerebral cortex. Such brain structure correspondences were confirmed by determining the channel position of the presumed primary motor cortex: significantly larger contralateral than ipsilateral hemoglobin concentration changes were observed in the L channel (fig. 4) during the right-tapping task for [oxy-Hb] and in the R channel (fig. 4) during the left-tapping task for [oxy-Hb] and [deoxy-Hb].

Discussion

Relationship of Cortical Reactivity with Novelty Seeking and Persistence

In the present study, [oxy-Hb] changes monitored using a multichannel NIRS machine were significantly positively correlated with novelty seeking scores and negatively with persistence scores in the TCI, in the early-task segment during the left-finger tapping task on the lower channels of bilateral probes. The specificity of the correlations with novelty seeking and persistence compared with the remaining five personality dimension scores in the TCI was confirmed by multiple regression and hierarchical regression analyses. These results are in agreement with our working hypotheses described in the introduction section that (1) significant correlations with hemoglobin concentration changes would be obtained positively

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for novelty seeking scores and negatively for persistence scores in the TCI, and (2) these correlations would be stronger than for three dimensions of character and even for the other two dimensions of temperament. The unexpected results were that the significant correlations of cortical reactivity with novelty seeking and persistence scores were obtained (1) not in the channels corresponding to the primary motor cortex but in the channels situated lower than this region; (2) during the left but not during the right finger tapping task, and (3) for [oxy-Hb] but not for [deoxy-Hb] changes.

The results are in partial agreement with the previous studies described in the introduction in that strong correlations were observed between novelty seeking or extraversion and blood flow or glucose metabolism in various brain regions. The positive correlations in the present study are in line with positive correlations (9 in frontal lobe, 6, 10, in temporal lobe, 11 in the frontal and parietal lobes) but not with negative correlations (9 in temporal lobe, 6 in frontal lobe, 7 in the temporal lobe and 11 in the occipital lobe). The present study also differs from the previous three studies but is consistent with one study [11] in that significant correlations were also obtained for persistence scores. These discrepancies in the results may arise from the following three methodological differences between the previous studies and our present one. First, the measured objects were different: in previous PET, SPECT, and xenon studies, the basal level of blood flow or glucose metabolism was measured, whereas in the present NIRS study, the changes in [oxy-Hb] due to activation from the baseline were measured. In the NISR study, the obtained data corresponded to the reactivity of brain functions but not to activity levels in the resting state. Second, the states of the subjects during the measurements were different: the subjects were at rest in the PET, SPECT and xenon studies, whereas they were engaged in a task in the present NIRS study, that is, we evaluated the subjects in a more natural state. Third, the time resolutions were different: in the PET, SPECT and xenon studies, blood flow or metabolism averaged for comparatively long periods (10–20 min) was measured, whereas in the present study, rCBV changes in short periods (10–13 s) were examined. The significant positive contribution of self directedness scores to rCBV changes obtained in the N1 channel in the multiple regression analyses might have been obtained by chance, but is consistent with the association of self directedness with the left frontal activation in the previous study that examined the relationships between all the seven personality dimensions of the TCI and rCBF [11].

The interpretation of significant correlations of cortical reactivity with novelty seeking and persistence scores obtained in the present study can be enhanced by considering four factors of these correlations: the side of finger tapping, the channels of correlations, time segments, and correlation signs (positive/negative). First, the reason the correlations were obtained mainly during the left-finger tapping task, but not during the right-finger tapping task, was assumed to be related to the subjects' handedness: the left-finger tapping task was supposed to be a more sensitive task for elucidating the characteristics of brain activation because right-handed subjects require more effort for left-finger tapping task than for right-finger tapping task. Second, the significant correlations were obtained not in the channels corresponding to the primary motor cortex but in the channels situated lower than this region, probably corresponding to the peri-Sylvian region. The primary motor cortex is assumed to be activated directly in response to movements without interindividual differences, while the surrounding cortices are assumed to be activated according to a more general excitability with variations among subjects. Such interindividual differences in the general excitability of cortical neurons can be interpreted as corresponding to interindividual differences in novelty seeking and persistence. This is one of the possible explanations for the significant correlation of novelty seeking and persistence scores with [oxy-Hb] changes for the channels outside the motor cortex. Third, the most significant correlation of novelty seeking and persistence scores with [oxy-Hb] changes was obtained during the early period of the left-finger tapping task. The degree of brain activation can be assumed to be more dependent on the biological features of the brain soon after behavior starting, and to be gradually influenced by the subject's intentional factors in the later periods of the task. Such an assumption explains the significant correlations of the changes in [oxy-Hb] with novelty seeking and persistence scores in the early period of the task in the present study. Fourth, positive and negative correlations between the changes in [oxy-Hb] and novelty seeking and persistence scores, respectively, can be explained by the nature of each temperament dimension. The positive correlation between the changes in [oxy-Hb] and novelty seeking scores indicates that the novelty seeking tendency corresponds to the nature of behavioral activation, that is, the excitability of neuronal activities. The negative correlation between the changes in [oxy-Hb] and persistence scores was assumed to represent the nature of behavioral persistence, that is, the minimal changeability in neuronal activities corresponding to motor activation in the sub-

jects with high persistence scores. Finally, a lack of significant correlations for [deoxy-Hb] can be attributed to a lower signal-to-noise ratio in [deoxy-Hb] than in [oxy-Hb] as indicated by smaller numbers of channels with a significant activation of [deoxy-Hb] due to the finger tapping task (fig. 2, 3).

Limitations

There are three limitations of the present study: namely, that for the task employed, that associated with the features of NIRS methodology, and that associated with the NIRS apparatus used.

First, we employed a simple motor task for brain activation, the finger tapping task, instead of more complicated cognitive tasks. Although such a simple task might be helpful for elucidating the basic characteristics of brain activities, its lack of cognitive components prevented us from investigating the cognitive aspects of personality and confined us only to examining the behavioral output aspect of personality. Studies using more complicated tasks can clarify different aspects of brain activities for personality.

Second, regarding the limitation due to the methodology, the NIRS machine measures only activational changes but not the baseline hemoglobin concentration only in the cerebral cortex but not in deeper brain structures. There is a possibility that baseline rCBV at rest also correlates with novelty seeking and persistence scores and stronger correlations can be obtained for deeper brain structures such as the paralimbic regions, as demonstrated in previous studies. Hence, we cannot conclude whether or not the obtained significant correlations of [oxy-Hb] changes with novelty seeking and persistence scores is specific to the activational changes in cerebral functions nor to the cerebral cortex. Further studies using both NIRS and other methodologies, such as PET, SPECT, and functional magnetic resonance image, may lead to a more conclusive finding.

Third, as for the NIRS apparatus used in the present study, we could measure [oxy-Hb] changes only in the temporal channels. The future development of NIRS apparatus with more channels would enable measurements over broader areas, for example, simultaneous whole-head measurements, and thus help us identify brain regions with the strongest correlations with novelty seeking and persistence dimensions.

In conclusion, novelty seeking and persistence were demonstrated to positively and negatively correlate with the brain functional activation, respectively, during the initial time segment of the finger tapping task in a multi-

channel NIRS study, and the results were interpreted in terms of the excitability and unchangeability of brain functions. The present study examined brain reactivity only in the cerebral cortices, and it was not designed for elucidating all aspects of temperament but focused on novelty seeking and persistence. This was hence an exploratory study, and these findings should be interpreted only as associative and do not necessarily indicate causal relationships of novelty seeking and persistence with brain activities. However, these findings can help clarify the neurobiological substrates for novelty seeking and persistence in combination with the baseline measurement studies using other methodologies if the results are replicated in future studies.

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