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 (780nm and 830nm) with a source-detector distance of 30mm and a time resolution of 0.1s. Near-infrared light was emitted from 1.5mW continuous laser diodes, whose intensities were modulated within 1.0 to 4.9kHz 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 6x6cm area (Fig. 1). The correspondence of the 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, 10s; relaxing time, 5s; and post-time, 5s 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-s-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 (10s 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 (10s 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 0.01mMmm. 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 correlate 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 variables 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.

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 correlated positively 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 were 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 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, 11 in the temporal and occipital lobes]. 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 (10-20min) was measured, whereas in the present study, rCBV changes in short periods (10-13s) were examined. The significant positive contribution of self directedness scores to rCBV changes obtained in the N1 channel in the multiple regression analyses might be 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 in 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 subjects 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 and 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 multichannel 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.

Acknowledgments

This research was supported in part by a Grant-in-Aid for Scientific Research (C) from the Japanese Ministry of Education, Culture, Sports, Science and Technology and a Health and Labour

Sciences Research Grant for Research on Psychiatric and Neurological Diseases and Mental Health (MF) and a Health and Labour Sciences Research Grants for Special Research from the Japanese Ministry of Health, Labour and Welfare (MM). The authors gratefully thank Drs. Itsuro Ida, Masaki Kameyama, Yutaka Yamagishi of the Department of Psychiatry and Human Behavior, Gunma University Graduate School of Medicine and two medical students, Mr. Ryu Takizawa and Ms. Ayako Kawakami in the university for their collaborations. The authors also gratefully acknowledge the assistance of Mr. Suguru Hattori in statistical analysis and helpful comments on the manuscript revision by Dr. Akihiko Oshima.

REFERENCES

[1] Cloninger CR, Svrakic DM, Przyback TR: A psychobiological model of temperament and character. Arch Gen Psychiatry 1993; 50: 975-990.

[2] Cloninger CR, Svrakic DM: Integrative psychobiological approach to psychiatric assessment and treatment. Psychiatry 1997; 60: 120-141.

[3] Cloninger CR: Temperament and personality. Curr Opin Psychiatry 1994; 4:266-273.

[4] Eysenck HJ: A Model for Personality. New York, Springer-Verlag, 1981.

[5] Gray JA. A critique of Eysenck's theory of personality. In: A Model for Personality, ed by Eysenck HJ, New York, Springer-Verlag, 1981; 246-276.

[6] Johnson DL, Wiebe JS, Gold SM, Andreasen NC, Hichwa RD, Watkins GL, Boles Ponto LL: Cerebral blood flow and personality: a positron emission tomography study. Am J Psychiatry 1999; 156: 52-257.

[7] Mathew RJ, Weinman ML, Barr DL: Personality and regional cerebral blood flow. Br J Psychiatry 1984; 144: 529-532.

[8] Stenberg G, Risberg J, Warkentis S, Rosen I: Regional patterns of cortical blood flow distinguish extraverts from introverts. Personality and Individual Differences 1990; 11:663-673.

[9] Youn T, Lyoo IK, Kim JJ, Park HJ, Ha KS, Lee DS, Abrams KY, Lee MC, Kwon JS: Relationship between personality trait and regional cerebral glucose metabolism assessed with positron emission tomography. Biol Psychology 2002; 60: 109-120.

[10] Sugiura M, Kawashima R, Nakagawa M, Okada K, Sato T, Goto R,: Correlation between human personality and neural activity in cerebral cortex. Neuroimage 2000; 11: 541-546.

[11] Turner RM, Hudson IL, Butler PH, Joyce PR: Brain function and personality in normal males: a SPECT study using statistical parametric mapping. NeuroImage 2003; 19:1145-1162.

[12] Chance B, Zhuang Z, Unah C, Alter C, Lipton L: Cognition-activated low-frequency modulation of light absorption in human brain. Proc Natl Acad Sci USA 1993; 90: 3770-3774.

[13] Hoshi Y, Tamura M: Detection of dynamic changes in cerebra; oxygenation coupled to neuronal function during mental work in man. Neurosci Lett 1993; 150: 5-8.

[14] Kato T, Kamei A, Takahashi S, Ozaki T: Human visual cortical function during photic stimulation monitoring by means of near-infrared spectroscopy. J Cereb Blood Flow Metab 1993; 13: 516-520.

[15] Villringer A, Planck J, Hock C, Schleinkofer L, Dirnagl U: Near infrared spectroscopy (NIRS): a

new tool to study hemodynamic changes during activation of brain function in human adults. Neurosci Lett 1993; 154: 101-104.

[16] Maki A, Yamashita Y, Ito Y, Watanabe E, Mayanagi Y, Koizumi H: Spatial and temporal analysis of human motor activity using noninvasive NIR topography. Med Phy 1995; 22: 1997-2005.

[17] Koizumi H, Yamashita Y, Maki A, Yamamoto T, Ito Y, Itagaki H, Kennan R: Higher-order brain function analysis by trans-cranial dynamic near-infrared spectroscopy imaging. J Biomed Opt 1999; 4: 403-413.

[18] Strangman G, Boas DA, Sutton JP: Non-invasive neuroimaging using near-infrared light. Biol Psychiatry 2002; 52: 679-693.

[19] Obrig H, Villringer A: Beyond the visible - imaging the human brain with light. J Cereb Blood Flow Metab 2003; 23: 1-18.

[20] Ito Y, Kennan RP, Watanabe E, Koizumi H: Assessment of heating effects in skin during continuous wave near infrared spectroscopy. J Biomed Opt 2000; 5: 383-390.

[21] Herrman MJ, Ehlis A-C, Fallgatter AJ: Prefrontal activation through task requirements of emotional induction measured with NIRS. Biol Psychol 2003;64:255-263.

[22] Fox PT, Raichle ME, Mintun MA, Dence C: Nonoxidative glucose consumption during focal physiological neural activity. Science 1988; 241: 462-464.

[23] Hock C, Villringer K, Müller-Spahn F, Wenzel R, Heekeren H, Schuh-Hofer S, Hofmann M, Minoshima S, Schwaiger M, Dirnagl U, Villringer A: Decrease in parietal cerebral hemoglobin oxygenation during performance of a verbal fluency task in patients with Alzheimer's disease monitored by means of near-infrared spectroscopy (NIRS) - correlation with simultaneous rCBF-PET measurements. Brain Res 1997; 755: 293-303.

[24] Kameyama M, Fukuda M, Uehara T, Mikuni M: Sex and age dependencies of cerebral blood volume changes during cognitive activation: a multichannel near-infrared spectroscopy study. NeuroImage 2004; 22:1715-1721.

[25] Stallings MC, Hewitt JK, Cloninger CR, Heath AC, Eaves LJ: Genetic and environmental structure of the tridimensional personality questionnaire: three or four temperament dimensions? J Pers Soc Psychol 1996; 70: 127-40.

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	N2 / early	P / early
		R=.85*	R=.78*	R=.77*
Temperament	Novelty Seeking	beta=.61*	beta=.57*	beta=.56*
	Harm Avoidance	.31	.27	.13
	Reward	-.01	.12	-.02
	Dependence	-.53*	-.53*	-.40
	Persistence			
Character	Self-directedness	.53*	.35	-.09
	Cooperativeness	.01	-.03	-.15
	Self-transcendence	-.04	-.10	-.09
	Sex	-.11	-.08	-.34
	Tapping score	-.33*	-.44*	-.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	N2 / early	P / early
Tapping score, Sex	delta	delta	delta
+Temperament	R^2=.00	R^2=.01	R^2=.04
+Character	.57*	.53*	.52*
	.15	.07	.04
Tapping score, Sex	delta	delta	delta
+Character	R^2=.00	R^2=.01	R^2=.04
+Temperament	.10	.03	.11
	.61*	.57*	.44*

*: $p<0.05$

Legends for figures

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 6x6cm^2 area were placed bilaterally on subject's temporal regions.

Fig. 2

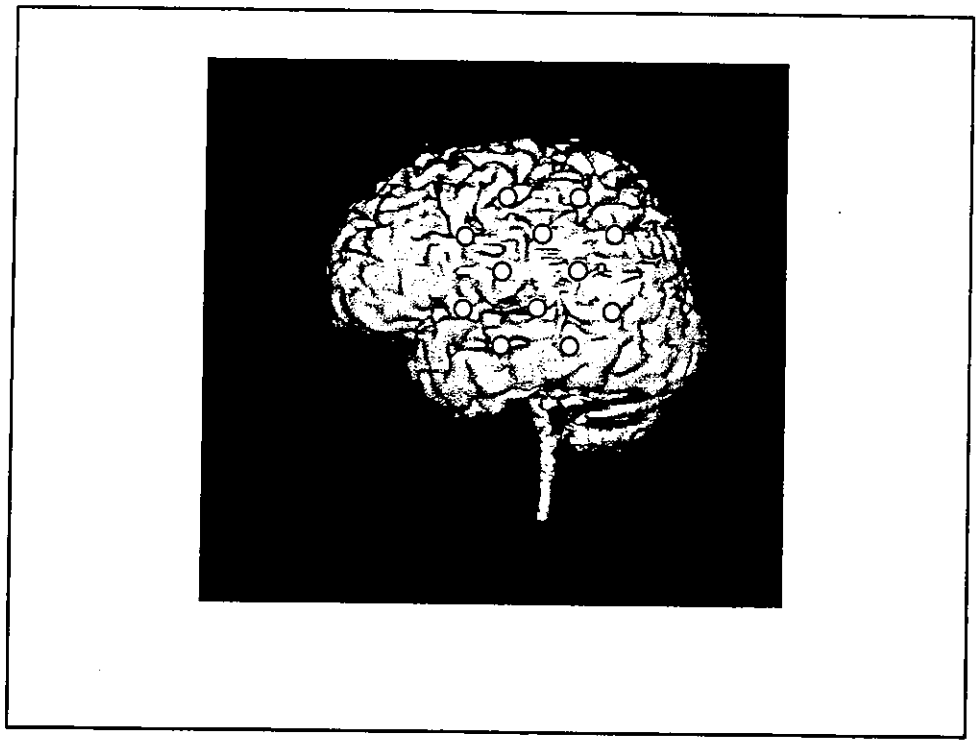
Oxy-, deoxy-, and total-hemoglobin concentration changes in the left-finger tapping task are presented as grand average waveforms in 24 channels of the left (left) and the right temporal probes (right) in red, blue, and green lines, respectively. The channels with significant changes in [oxy-Hb] and [deoxy-Hb] are hemmed with red and blue squares, respectively. The channels with low signal-to-noise ratio are shaded with gray.

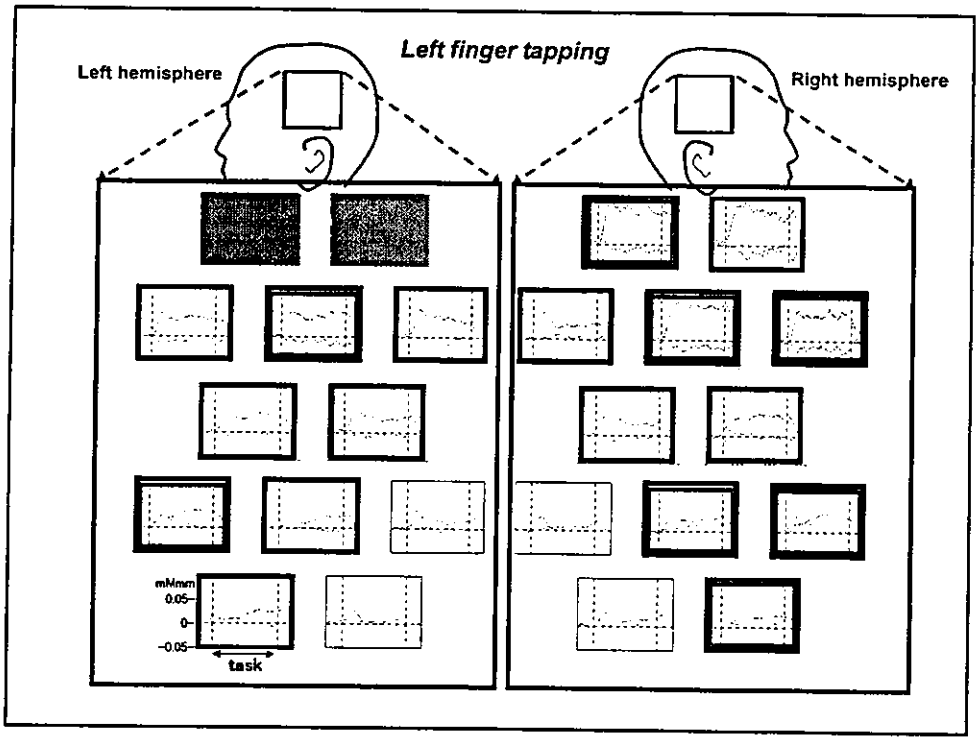
Fig. 3

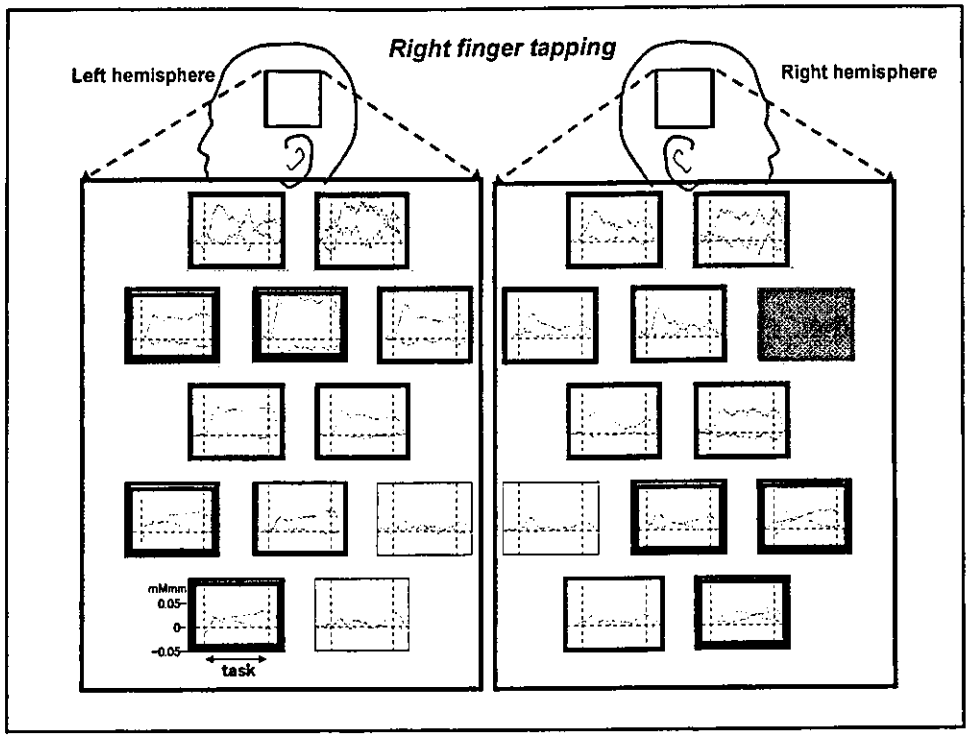
Oxy-, deoxy-, and total-hemoglobin concentration changes in the right-finger tapping task are presented as in Fig.2.

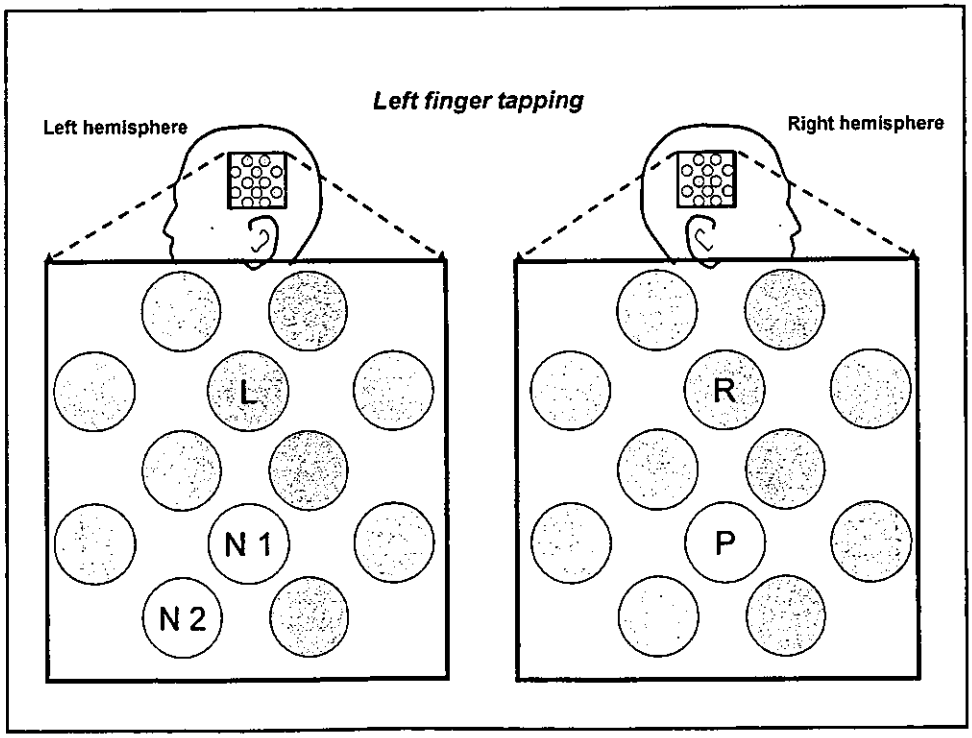
Fig. 4

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.




Left finger tapping
Left hemisphere
Right hemisphere
mM/mm
0.05
0
-0.05
task


Right finger tapping
Left hemisphere
Right hemisphere
mMmm
0.05
0
-0.05
task


Left finger tapping
Left hemisphere
Right hemisphere
L
N 1
N 2
R
P

Multichannel Near-Infrared Spectroscopy in Depression and Schizophrenia: Cognitive Brain Activation Study

Tomohiro Suto, Masato Fukuda, Makoto Ito, Toru Uehara, and Masahiko Mikuni

Background: *Recent developments in near-infrared spectroscopy (NIRS) have enabled the noninvasive clarification of brain functions in psychiatric disorders with measurement of hemoglobin concentrations as cerebral blood volume.*
Methods: *Ten patients with depression, 13 patients with schizophrenia, and 16 age- and gender-matched healthy control subjects participated in the study after giving consent. The relative concentrations of oxyhemoglobin [oxyHb] were measured with frontal and temporal probes every .1 sec during word fluency and unilateral finger tapping tasks, with two 24-channel NIRS machines.*
Results: *The [oxyHb] increase patterns during the word fluency task varied among the three groups, although their task performances were similar: the depression group was characterized by a smaller [oxyHb] increase during the first half of the task period and the schizophrenic group by a small trough of [oxyHb] at the start of the task period and [oxyHb] re-increase in the posttask period. [OxyHb] increases during the finger-tapping task were rather larger in the patient groups than in the control group.*
Conclusions: *The characteristic time courses of [oxyHb] changes in the frontal lobe were elucidated for depression and schizophrenia. Near-infrared spectroscopy, with its noninvasiveness and high time resolution, can be a useful tool for research and clinical purposes in psychiatry.*

Key Words: Near-infrared spectroscopy, cerebral blood volume, depression, schizophrenia, word fluency test, diagnosis

Neuroimaging studies have revealed structural and functional brain abnormalities in psychiatric disorders. Schizophrenia was reported to be characterized by volume reductions of several structures in frontal and temporal lobes, as reviewed by Shenton et al (2001). Schizophrenia was also found to show two types of abnormal brain function (Weinberger et al 2001) in many functional neuroimaging studies using positron emission tomography (PET), single-photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI): "hypofrontality" (i.e., decreased activation in glucose metabolism and regional cerebral blood flow [rCBF]) in the frontal lobes in most of the so-called frontal tasks (reviewed by Andreasen et al 1998), and "hyperfrontality" (i.e., increased activation in glucose metabolism and rCBF) if task performances in schizophrenic patients were matched with those in healthy controls (summarized by Weinberger et al 2001). Mood disorders are also characterized by structural and functional brain abnormalities. They include volumetric reduction in the subgenual prefrontal cortex (Drevets et al 1997), decreased rCBF and glucose metabolism in the dorsolateral prefrontal cortex, and increased rCBF and glucose metabolism in the orbital and medial prefrontal cortices, compared with those observed in healthy subjects (Brody et al 2001; Drevets 2000; Liotti and Mayberg 2001).

Functional brain imaging methodologies, such as PET, SPECT, and fMRI have the disadvantage of requiring large apparatuses. This prevents their use in a bedside setting for diagnostic and treatment purposes. Recently, the development of near-infrared spectroscopy (NIRS) has enabled noninvasive and bedside measurements of regional cerebral blood volume (rCBV) in terms of the relative concentrations of oxyhemoglobin [oxyHb] and deoxyhemoglobin [deoxyHb], with a high time resolution. Near-infrared spectroscopy is based on the principle that near-infrared light is preferentially absorbed by [oxyHb] and [deoxyHb] and not so much by other body tissues. Near-infrared light emitted from the skin travels into the body, is reflected and absorbed by body tissues, and reappears on the skin. The absorption of near-infrared light thus reflects Hb concentrations in the tissue beneath emission and detection probe pairs. Measurements with two or more wavelengths of near-infrared light enable the determination of [oxyHb] and [deoxyHb] changes, because their absorptions vary along its wavelength. The successful monitoring of brain functions in humans with NIRS was first reported in four studies (Chance et al 1993; Hoshi and Tamura 1993; Kato et al 1993; Villringer et al 1993), and multichannel NIRS machines were developed in the late 1990s (Maki et al 1995; Tamura et al 1997).

The [oxyHb] increase and [deoxyHb] decrease in NIRS have been shown to reflect cortical activation by simultaneous measurements with other methodologies. For example, high correlations were obtained between [oxyHb] increase and rCBF change in a $^{15}H_2O$ PET study (Hock et al 1997) and between [deoxyHb] decrease (Kleinschmidt et al 1996, Mehagnoul-Schipper et al 2002, Toronov et al 2001) or [oxyHb] changes (Strangman et al 2002b) and cerebral blood oxygenation increase in MRI studies.

Near-infrared spectroscopy has advantages and disadvantages over other methodologies. The advantages of NIRS are 1) near-infrared light is completely noninvasive, hence repeated measurements are possible; 2) Hb data obtained have a time resolution on the order of .1 sec, which is superior to those of other imaging methodologies for cerebral blood flow and metabolism but is inferior to those of event-related potentials and magnetoencephalography, which directly measure electrical activity of neurons with a time resolution on the order of milliseconds; 3) subjects are under natural conditions during examination so that they can perform the task; and 4) apparatuses are small and portable. The disadvantages of NIRS are that it enables

From the Department of Psychiatry and Human Behavior, Gunma University Graduate School of Medicine, Gunma, Japan.
Address reprint requests to Masato Fukuda, M.D., Ph.D., Gunma University Graduate School of Medicine, Department of Psychiatry and Human Behavior, 3-39-22 Showa, Maebashi, Gunma 371-8511, Japan.
Received May 30, 2003; revised September 16, 2003; accepted September 17, 2003.

0006-3223/04/$30.00
doi:10.1016/j.biopsych.2003.09.008

BIOL PSYCHIATRY 2004;55:501–511

Table 1. Characteristics of the Subjects

Major Depressive Disorder

Case No.	Age	Sex	I/O	Course	PS	MS	HAMD	Medication (mg/day)	WFT
DP1	24	M	I	SE	Absence	Presence	6	Mianserin 20, paroxetine 40, carbamazepine 400	14
DP2	30	M	O	RE	Absence	Presence	2	Amitriptyline 100	15
DP3	51	M	O	SE	Absence	Presence	2	Amitriptyline 25, lithium 800, bromocriptine 7.5	16
DP4	52	M	O	RE	Presence	Absence	0	Clomipramine 10, trazodone 25	23
DP5	54	M	O	SE	Absence	Absence	12	Trazodone 50, paroxetine 40	9
DP6	55	M	I	RE	Presence	Presence	8	Maprotiline 100, milnacipran 150	22
DP7	57	M	O	SE	Absence	Absence	1	Mianserin 20	5
DP8	59	M	O	SE	Absence	Presence	17	Milnacipran 45	17
DP9	60	M	O	RE	Absence	Presence	19	Mianserin 30, fluvoxamine 150, levomepromazine 10, carbamazepine 200, L-thyroxine .05	16
DP10	37	F	O	RE	Absence	Presence	18	Clomipramine 125, levomepromazine 10	9
Mean	47.9	M9/F1	I2/O8	SE5/RE5	Presence 2/ Absence 8	Presence 7/ Absence 3	7.5		14.6
SD	12.8						6.7		5.7

Schizophrenia

					PANSS[b]				
Case No.	Age	Sex	I/O	Subtype	+	−	+/−	Medication (mg/day)	WFT
SC1	23	M	O	P	10	24	34	Risperidone 2	16
SC2	26	M	O	R	9	10	2	Chlorpromazine 50, haloperidol 3	19
SC3	28	M	O	R	15	14	29	Levomepromazine 10, risperidone 6	19
SC4	28	M	O	P	11	10	28	Chlorpromazine 100, nemonapride 40, olanzapine 5	19
SC5	28	M	O	P	21	26	43	Risperidone 8	10
SC6	37	M	O	R	9	18	16	Chlorpromazine 50, bromperidol 27, olanzapine 10	17
SC7	40	M	O	P	15	15	23	Chlorpromazine 25, levomepromazine 50, risperidone 2	9
SC8	50	M	O	R	18	23	41	Chlorpromazine 150, bromperidol 6, risperidone 9	17
SC9	57	M	O	R	9	11	26	Chlorpromazine 175, haloperidol 3	16
SC10	29	F	O	R	9	14	22	Risperidone 2	16
SC11	42	F	O	P	12	12	22	Quetiapine 50	10
SC12	49	F	O	P	14	12	13	Haloperidol 4.5, zotepine 300	13
SC13	56	F	O	P	12	10	16	Levomepromazine 5, bromperidol 15, perospiron 32	15
Mean	37.9	M9/F4	I0/O13	P7/D0/C0/ U0/R6	12.6	14.5	26		15.1
SD	12				3.8	5.9	8.5		3.5

Control Subjects (n = 16)

	Age	Sex	WFT
Mean	42.9	M12/F4	16.8
SD	4.6		3.6

I/O, inpatient/outpatient; SE, single episode; RE, recurrent episode; PS, psychotic symptoms; MS, melancholic symptoms; HAMD, Hamilton Rating Scale for Depression; WFT, word fluency task; M, male; F, female; P, paranoid; R, residual types; D, disorganized; C, catatonic; U, undifferentiated; PANSS, Positive and Negative Syndrome Scale; +, positive; −, negative; +/−, general.

measurement of Hb concentration changes 1) only as relative values, not as absolute values; 2) only in the cortex immediately beneath the probes but not in deeper brain structures; 3) with a high time resolution but with a poor spatial resolution; and 4) not only in the brain but also in more surface structures, such as the skin and skull.

Considering the advantages and disadvantages described above, NIRS is assumed to be particularly useful in assessing the dynamic aspects of cortical activation in rather broad areas. Based on these characteristics of NIRS, NIRS studies have been carried out for motor and cognitive activations in healthy and psychiatric subjects, as reviewed by Koizumi et al (1999), Obrig and Villringer (2003), and Strangman et al (2002a). We have found that the time courses of [oxyHb] changes during a motor task varied depending on the measuring channel and that interindividual differences in the amplitude of [oxyHb] increase determined with multichannel NIRS machines correlated with subject personality (Ito et al, unpublished data).

Most NIRS studies demonstrated activation-related [oxyHb] and [totalHb] (sum of [oxyHb] and [deoxyHb]) increases during language tasks (Hock et al 1997; Matsuo et al 2000, 2002; Sakai et al 2000; Sato et al 1999; Watanabe et al 1998; Yamamoto et al 1999) and cognitive tasks (Fallgatter and Strik 1997, 1998; Hock et al 1995; Hoshi et al 2000; Tamura et al 1997), as well as during motor tasks (Colier et al 1999; Hirth et al 1997; Maki et al 1995; Obrig et al 1996). Fallgatter et al (1998) reported, however, that

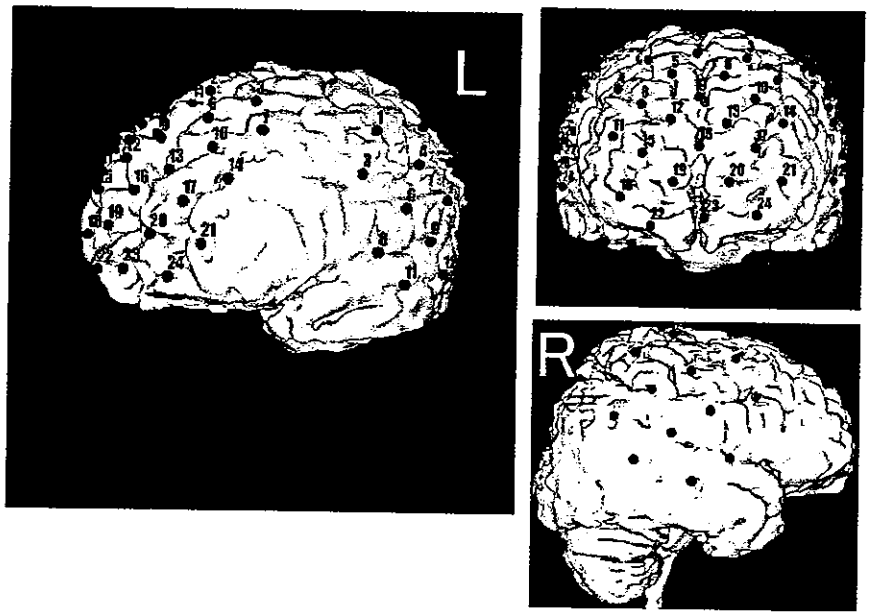


Figure 1. Cortical projection at near-infrared spectroscopy (NIRS) measurement positions. The measurement positions of the NIRS machines are superimposed on a magnetic resonance image of a reconstructed cerebral cortex of a representative subject.

[deoxyHb] increases and [oxyHb] decreases during a reading-aloud task. Thus, [deoxyHb] changes are less consistent, in that both increases and decreases in [deoxyHb] have been reported.

Near-infrared spectroscopy has only recently been applied to the examination of psychiatric patients as well as healthy subjects, and some NIRS studies of depression, schizophrenia, and other psychiatric disorders have recently been reported. Regarding depression, hemispheric asymmetry and reduced hemodynamic response during cognitive activation have been suggested. Okada et al (1996) found altered hemispheric differences in [totalHb] changes in the frontal region of depressive patients during a mirror drawing task. Matsuo et al (2000, 2002) found, with some inconsistencies, in patients with major depressive disorder and bipolar disorder that both the extent of [oxyHb] increase during a word fluency task and that of [oxyHb] decrease during hyperventilation tend to be reduced. Such reduced [oxyHb] increases in depression were reported to predict good therapeutic efficiency of repetitive transcranial magnetic stimulation (Eschweiler et al 2000).

As for schizophrenia, characteristic Hb changes were indicated in some NIRS studies. Okada et al (1994) found dysregulated hemispheric differences in [oxyHb] and [deoxyHb] during a mirror drawing task. Fallgatter and Strik (2000) also found that hemispheric asymmetry of [deoxyHb] during the Continuous Performance Test is reduced in schizophrenic patients as compared with healthy subjects. Other psychiatric and neurologic applications of NIRS include the study of Alzheimer's dementia (Hock et al 1997) and the determination of the language-dominant hemisphere before neurosurgical operation in epileptic patients (Watanabe et al 1998).

All the NIRS studies on psychiatric patients cited above suffer from the paucity of channels for measurements: the NIRS machine used is composed of one to a few channels. Considering the observation that Hb changes monitored from above the skull vary markedly depending on the measuring point, simultaneous measurements from multiple channels during activation are desirable for the assessment of specific findings in psychiatric populations.

In the present study, we used multichannel NIRS machines to examine the temporal and topographical characteristics of rCBV changes during cognitive activation in patients with major depressive disorder, patients with schizophrenia, and gender- and age-matched control subjects. Our aim was to assess brain dysfunctions in psychiatric disorders along the time course; that is, in addition to the frontal lobe dysfunction findings as revealed by PET, SPECT, and fMRI studies expressed as mean decreases in cerebral blood flow and metabolism rate across the task period employed, patients with depression and schizophrenia would show characteristic time courses of rCBV changes across the task period. We also hypothesized that such a brain dysfunction is task-demand-specific; thus, we used motor activation as a control task for cognitive activation.

Methods and Materials

Subjects

The subjects were 10 patients with major depressive disorders, 13 patients with schizophrenia, and 16 healthy control subjects. All patients were inpatients or outpatients of the Department of Neuropsychiatry, Gunma University Hospital in Gunma, Japan. They were diagnosed according to DSM-IV criteria (American Psychiatric Association 1994). Table 1 summarizes the demographic characteristics, psychopathology, courses of the illnesses, and medication dosages of the subjects.

All the patients were 23–60 years old, and were taking psychotropic drugs at the time of examination. Their psychopathology was assessed with the 24-Item Hamilton Rating Scale for Depression (Hamilton 1960) for major depressive disorders and the Positive and Negative Syndrome Scale (Kay et al 1998) for schizophrenia. The patients generally had mild symptomatology or were in remission, and at most they were taking moderate doses of psychotropic drugs.

The healthy control subjects included 12 men and four women (mean age 42.9 years, SD 4.6, range 36–52). They had no history of schizophrenia, mood disorders, epilepsy, or other psychiatric disorders. Based on the checklist filled out by these healthy subjects, we excluded those who were taking any medications or had a history of a major physical illness, neurologic disorder, substance abuse, alcohol abuse, or head trauma.

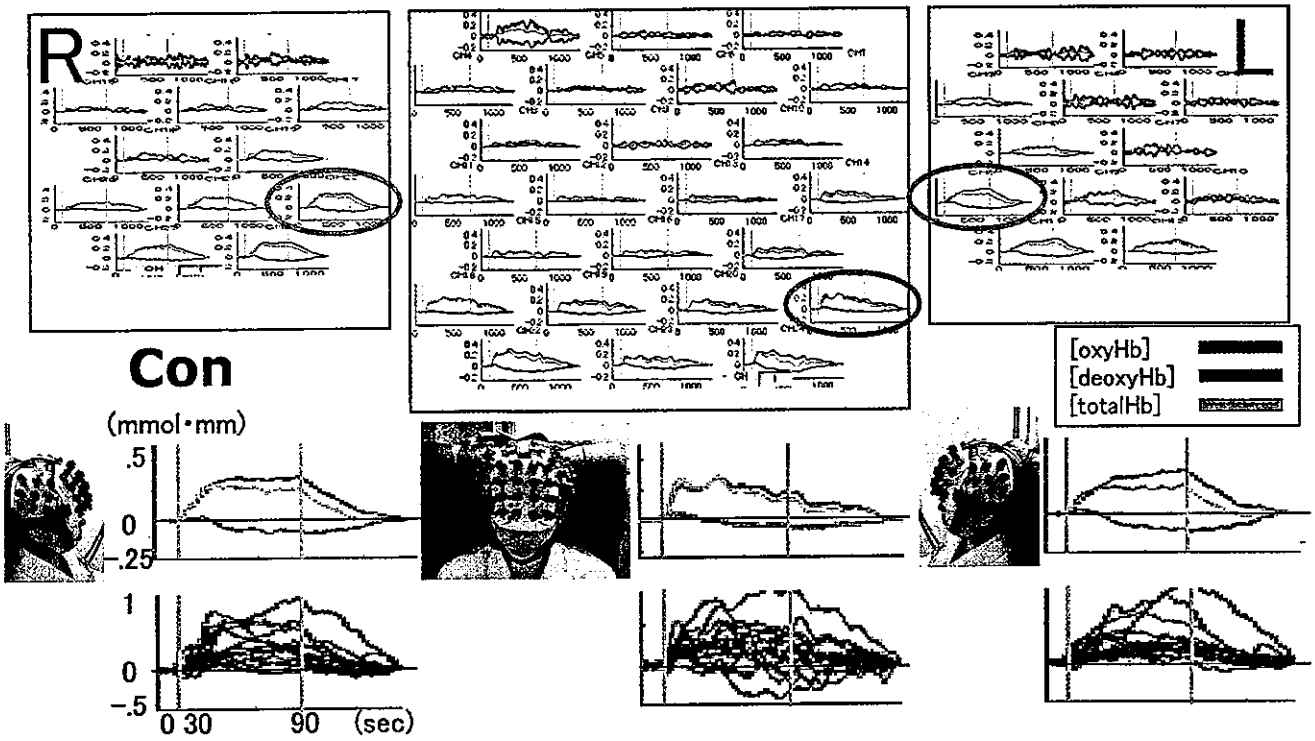


Figure 2. Grand average waveforms of hemoglobin concentration changes during cognitive activation in the control (Con) group. Grand average waveforms of oxyhemoglobin ([oxyHb]; red line), deoxyhemoglobin ([deoxyHb]; blue line), and total hemoglobin [totalHb]; green line) changes during cognitive activation (between two vertical light-blue lines) in the frontal channels (center), and the left (right) and right temporal channels (left) in the control group. Three sets of grand average waveforms and superimposed individual waveforms of [oxyHb] changes in representative channels (circled in orange) are enlarged below.

The gender ratio and age did not significantly differ among the groups.

All the subjects were right-handed, as based on their Edinburgh scores (Oldfield 1970; mean 95.6, SD 7.9, range 76.5–100). This study was approved by the institutional review board of Gunma University Graduate School of Medicine, and written informed consent was obtained from all the subjects before the study.

Activation Tasks

Hemoglobin concentration changes were measured during cognitive and motor activations. The subjects each sat on a comfortable chair in a daylight room with their eyes open throughout the measurements. The cognitive activation consisted of a 30-sec pretask baseline, a 60-sec word fluency task, and a 60-sec posttask baseline. In the word fluency task, the subjects were instructed to generate as many words whose initial syllable was /a/, /ka/, or /sa/ as they could. The three initial syllables changed in turn every 20 sec during the 60-sec task, to reduce the time during which the subjects were silent. The number of words generated during the word fluency task was determined as a measure of task performance. The subjects were instructed to repeat the syllables /a/, /i/, /u/, /e/, and /o/ during the pretask and posttask baseline periods.

The motor activation consisted of a 30-sec pretask rest, a 40-sec right-finger-tapping task, and a 30-sec posttask rest. The subjects were instructed to tap their four fingers with their thumb in turn as quickly and accurately as they could. They practiced right-finger tapping after receiving instructions, and it was confirmed that they could perform the task correctly.

In both the cognitive and motor activations, the subjects were instructed with an auditory cue at the start and end of the task or baseline period and at the task category change. Between any cognitive and motor activations and the next activation, the subjects had a recess of at least 3 min.

NIRS Measurements

In this study, [oxyHb], [deoxyHb], and [totalHb] were measured with two 24-channel NIRS machines (Hitachi ETG-100; Hitachi Medical Corporation, Tokyo, Japan) at two wavelengths of near-infrared light (760 and 840 nm), the absorption of which was measured, and [oxyHb] and [deoxyHb] were calculated as described by Maki et al (1995). [TotalHb] was calculated as the sum of [oxyHb] and [deoxyHb]. The interprobe distance of the machine was 3.0 cm, and it was determined that the machine measures points 2 to 3 cm beneath the scalp, that is, the surface of the cerebral cortices (Hock et al 1997; Toronov et al 2001).

The probes of the NIRS machines were placed on a subject's frontal and bilateral temporal regions. The probes on the subject's frontal region measured the relative concentrations of Hb changes at 24 measurement points in an 8 × 8 cm area, with the lowest probes positioned along the Fp_1–Fp_2 line, according to the international 10/20 system used in electroencephalography. Each set of probes on the subject's bilateral temporal region measured the relative concentrations of Hb changes at 12 measurement points in a 6 × 6 cm area, with the central probe

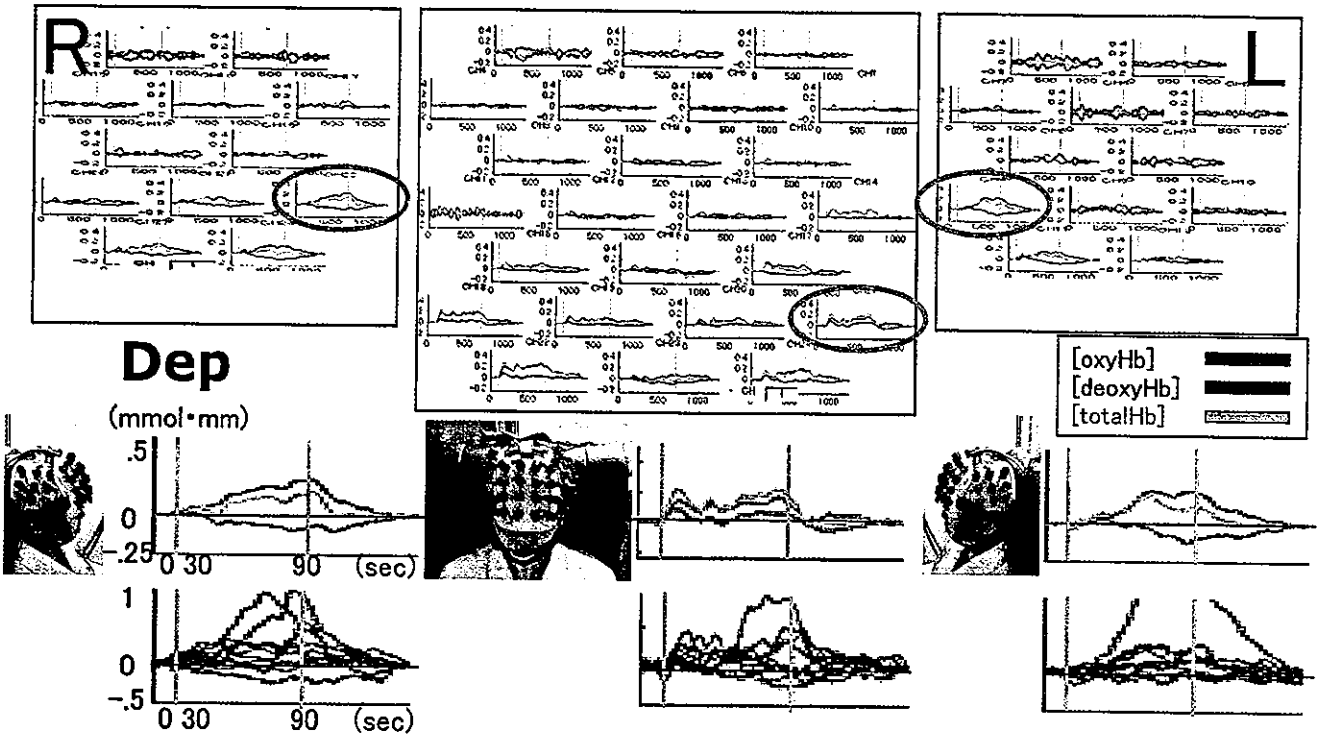


Figure 3. Grand average waveforms of hemoglobin concentration changes during cognitive activation in the depression (Dep) group. Grand average waveforms of oxyhemoglobin ([oxyHb]; red line), deoxyhemoglobin ([deoxyHb]; blue line), and total hemoglobin [totalHb]; green line) changes during cognitive activation (between two vertical light-blue lines) in the frontal channels (center), and the left (right) and right temporal channels (left) in the control group. Three sets of grand average waveforms and superimposed individual waveforms of [oxyHb] changes in representative channels (circled in orange) are enlarged below.

positioned at the midpoint between the vertex and the external ear hole. The correspondence of the probe positions and the measurement points on the cerebral cortex were confirmed by superimposition of the probe positions on a magnetic resonance image of a three-dimensionally reconstructed cerebral cortex of a representative subject in the healthy control group (Figure 1).

The absorption of near-infrared light was measured with a time resolution of .1 sec. The obtained data were analyzed with the "integral mode": the pretask baseline was determined as the mean across 10 sec just before the task period, the posttask baseline was determined as the mean across 5 sec 50 sec (cognitive activation) or 5 across 5 sec 5 sec (motor activation) after the task period, and linear fitting was performed on the data between two baselines. Moving average methods were used to exclude short-term motion artifacts in the analyzed data (moving average window: 5 sec).

According to the above-mentioned measurement parameters for the integral mode, the waveforms of [oxyHb], [deoxyHb], and [totalHb] changes were acquired from all the subjects in all 48 channels during the cognitive and motor activations. We tried to exclude motion artifacts by closely monitoring artifact-evoking body movements, such as neck movements, strong biting, and blinking (identified as most influential in the preliminary artifact-evoking study), and by instructing the subjects to avoid these movements during the NIRS measurements. Moreover, data that clearly contained motion artifacts, determined based both on our observation and on the NIRS recording, were excluded from further analyses.

The grand average waveforms of three types of Hb concentration changes and superimposed individual waveforms of [oxyHb] changes were obtained in all the subjects, based on individual subjects' waveforms in all 48 channels. These grand average waveforms of [oxyHb] changes in all 48 channels were also imaged as topographs of [oxyHb] changes with the linear compensation method.

[OxyHb] data in the three groups were compared in two ways. First, as is usually done in block design experiments, [oxyHb] data were averaged across three task segments (pretask, task, and posttask), analyzed with two-way analysis of variance (ANOVA) with "diagnosis" (control, depression, and schizophrenia) and "task segments" (pretask, task, and posttask) as independent variables in all 48 channels, and compared by post hoc Scheffe multiple comparison. Second, [oxyHb] changes were compared between each of the two patient groups and the control group with Student t tests using the grand average waveforms every .1 sec in each channel. This analysis enabled more detailed comparison of [oxyHb] changes along the time course of the task. Significance level corrections for multiple comparisons were not carried out in this analysis.

Results

Cognitive Activation

The number of words generated during the word fluency task showed no statistically significant differences among the three groups (depression group: mean 14.6, SD 5.7; schizophrenia

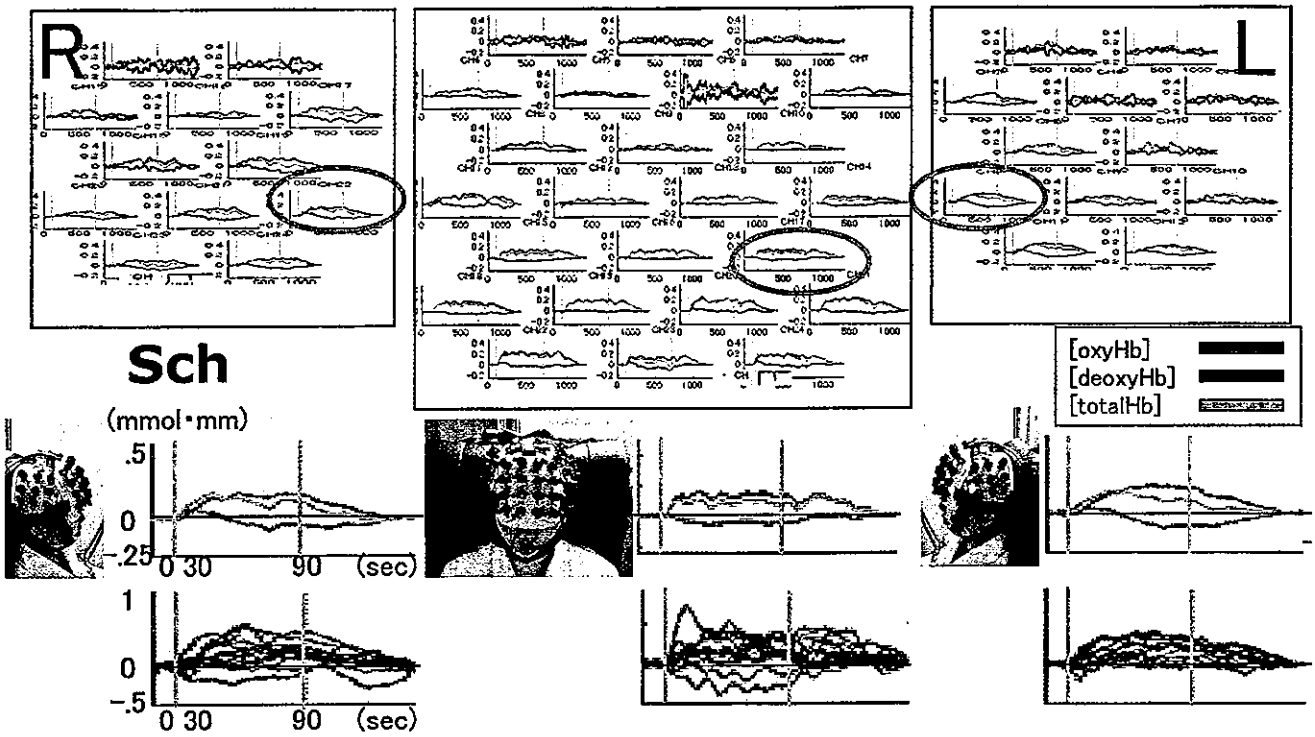


Figure 4. Grand average waveforms of hemoglobin concentration changes during cognitive activation in the schizophrenia (Sch) group. Grand average waveforms of oxyhemoglobin ([oxyHb]; red line), deoxyhemoglobin ([deoxyHb]; blue line), and total hemoglobin [totalHb]; green line) changes during cognitive activation (between two vertical light-blue lines) in the frontal channels (center), and the left (right) and right temporal channels (left) in the control group. Three sets of grand average waveforms and superimposed individual waveforms of [oxyHb] changes in representative channels (circled in orange) are enlarged below.

group: mean 15.1, SD 3.5; control group: mean 16.8, SD 3.6; comparison among the three groups: $F = 1.04$, $p = .36$; one-way ANOVA).

Figures 2–4 show the grand average waveforms of [oxyHb], [deoxyHb], and [totalHb] during the cognitive activation in the control, depression, and schizophrenia groups, respectively. The three sets of waveforms of Hb changes enlarged below were those in the representative channels in which the difference in [oxyHb] changes between the patients and control subjects was most statistically significant. The superimposed individual waveforms of [oxyHb] changes shown at the bottom of the figures confirmed that the grand average waveforms essentially represent most individual data in each group. Figure 5 shows the topographs of [oxyHb] changes for the three groups during the cognitive activation. As shown in the grand average waveforms, Hb concentrations could not be measured

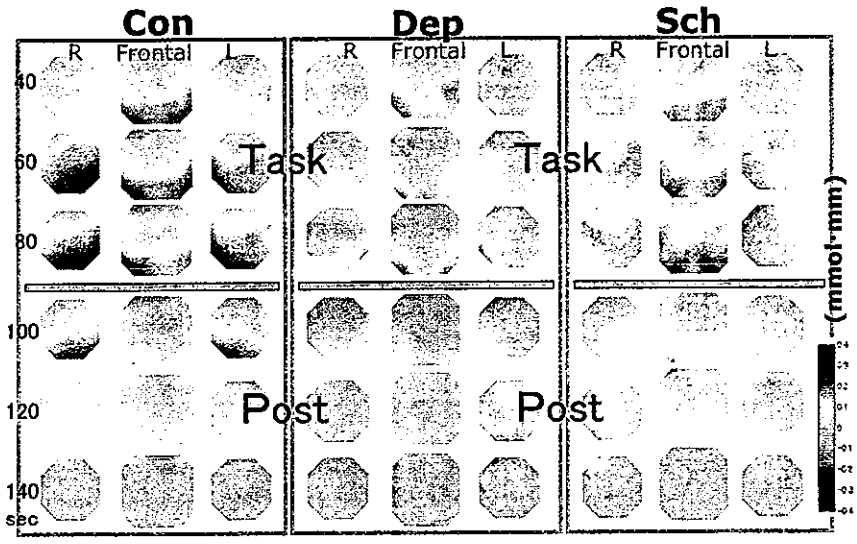


Figure 5. Topographic presentation of oxyhemoglobin [oxyHb] changes during cognitive activation in the three groups. The [oxyHb] changes in the control (Con, left), depression (Dep, center), and schizophrenia groups (Sch, right) are presented as topographic maps along the time course of the task (from top to bottom). Each set of topographic maps is composed of three maps corresponding to the results in the frontal and bilateral temporal channels. The time from the start of the task is presented in seconds on the left. The red, green, and blue areas in the topographs indicate increase, no change, and decrease in [oxyHb], respectively.

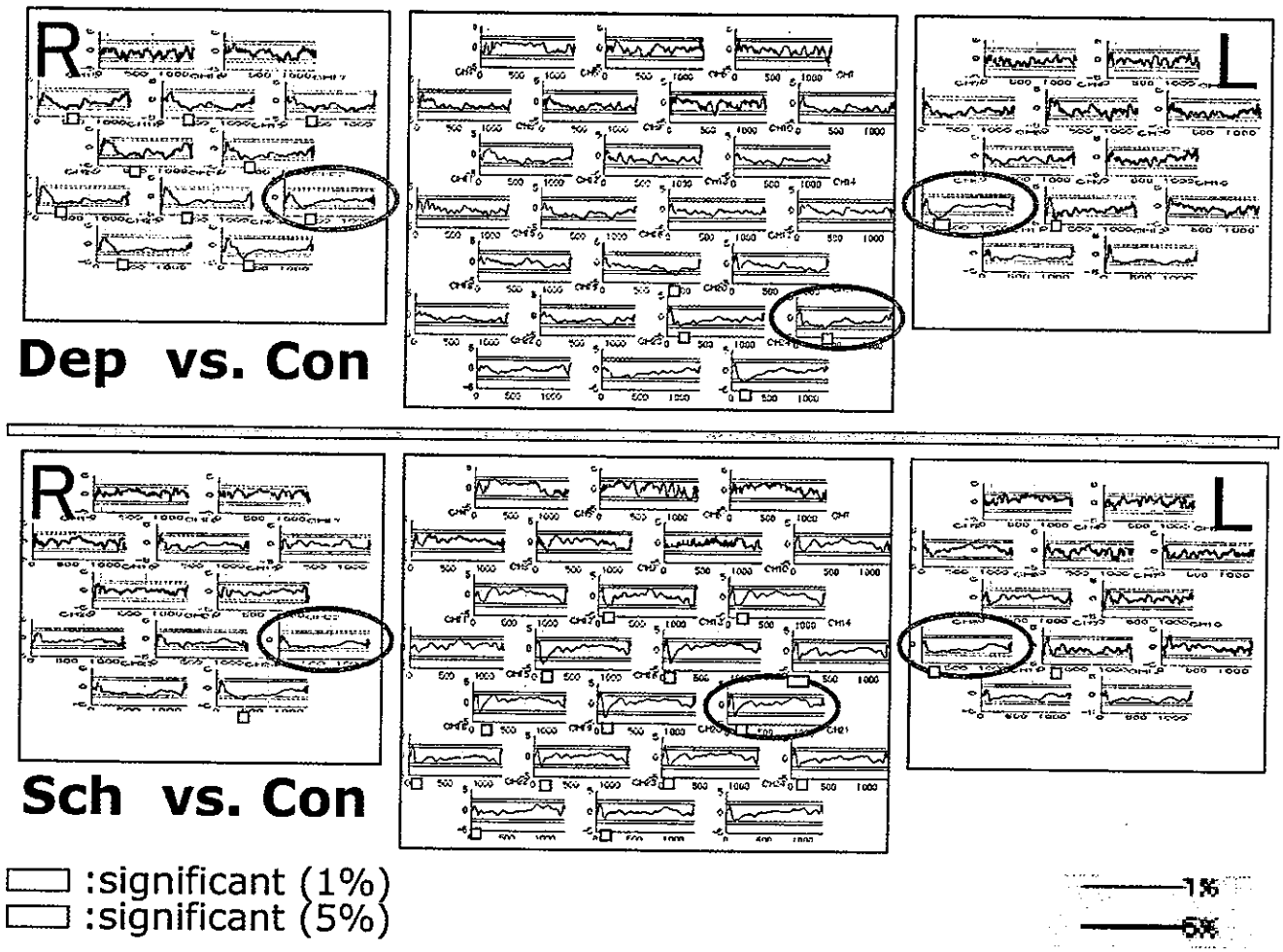


Figure 6. *t* value graphs showing oxyhemoglobin [oxyHb] comparison between the patient and control groups during cognitive activation. *t* values of [oxyHb] comparison between the depression and control groups (Dep vs. Con, top), and between the schizophrenic and control groups (Sch vs. Con, bottom) in 48 channels as presented as in Figure 2. Blue and red lines in each *t* graph correspond to 5% and 1% statistical significance levels, respectively, and the times with significant differences in each graph are marked light yellow and yellow.

with a sufficient signal/noise ratio in the upper frontal and temporal channels.

In the control group (Figure 2), clear [oxyHb] increases were observed during the task period, and the time-course patterns of the changes differed depending on the measuring channel. In the frontal channels, [oxyHb] rapidly increased immediately after the start of the task period, was maintained at the activated level during the task period, and decreased gradually after the task was finished. In the temporal channels, [oxyHb] continued to increase across the task period, peaked at the end of the task period, and decreased gradually in the posttask period. Such [oxyHb] increases during the task period were clearly observed in the lower frontal and anterior lower temporal channels (Figure 5).

In the depression group (Figure 3), [oxyHb] increases during the task period were smaller than those in the control group for both the frontal and temporal channels across the task period. The [oxyHb] topographs show that the increases were observed in the lower frontal and anterior lower temporal channels, as in the control group (Figure 5).

In the schizophrenia group (Figure 4), [oxyHb] showed a sustained moderate increase during the task period and began to decrease immediately after the end of the task period, but then re-increased during the posttask period, particularly in the left frontal channels. The [oxyHb] changes were prominent in almost the same regions as those in the control and depression groups (Figure 5). Additionally, detailed examination of the grand average waveforms shown in Figure 4 revealed a small trough of [oxyHb] immediately after the start of the task period in the frontal channels, which was not evident in the control and depression groups.

The two-way ANOVA revealed a significant main effect of "task segments" in 31 of 48 channels, and post hoc comparison confirmed that [oxyHb] increases during the task period were larger than those in the pretask period. The main effect of "diagnosis" was significant in only eight of 48 channels, and post hoc comparison clarified that [oxyHb] increases in the depression group were smaller than those in the control group in two channels and in the schizophrenic group in two other channels. All the interactions of "task segments" and "diagnosis" were nonsignificant.

The results of the *t* test for the between-group comparison of

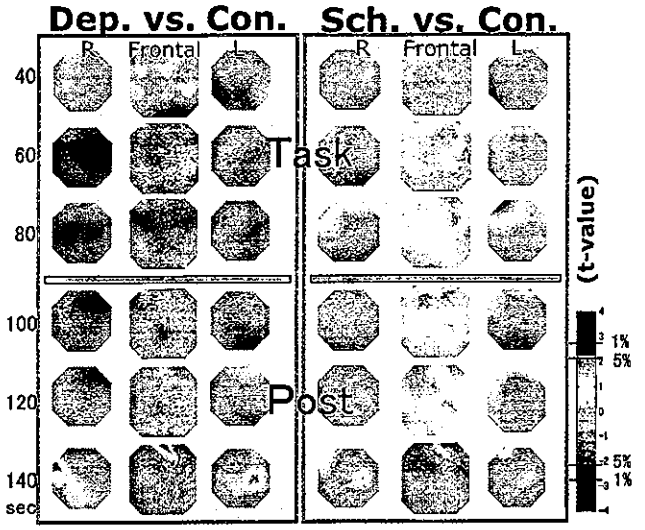


Figure 7. Topographic presentation of *t* value of oxyhemoglobin [oxyHb] comparison between the patient and control groups during cognitive activation. *t* values of [oxyHb] for the depression and control groups (Dep. vs. Con., left) and the schizophrenia and control groups (Sch. vs. Con., right) are presented as topographic maps along the time course of the task (from top to bottom). Each set of topographic maps is composed of three maps corresponding to the results in the frontal and bilateral temporal channels. The time from the start of the task is presented in seconds on the left. The red, green, and blue areas in the topographs indicate positive, zero, and negative *t* values, with 2.1 and 2.8 for 5% and 1% statistical significance levels, respectively.

[oxyHb] changes during the cognitive activation are shown in Figure 6. Parts of the results are shown in Figure 7 in the form of topographs. [OxyHb] increases in the depression group were significantly smaller than those in the control group during the first half of the task period in the left lower frontal ($p < .05$) and bilateral lower anterior temporal channels ($p < .01$).

In the schizophrenia group, [oxyHb] increases were smaller immediately after the start of the task period in the lower frontal channels ($p < .01$) and during the first half of the task period in the bilateral lower anterior temporal channels ($p < .05$), but rather larger for the posttask period in one left frontal channel ($p < .05$) than those in the control group.

Motor Activation

The grand average waveforms of [oxyHb], [deoxyHb], and [totalHb] changes during the finger-tapping task are shown in Figure 8. [OxyHb] increases during the finger tapping task in the depression group were significantly larger than those in the control group during the latter half of the task period in the left frontal channels ($p < .01$, data not shown), and those in the schizophrenic group were not significantly larger than those in the control group. Thus, [oxyHb] increases in the patient groups were or tended to be larger than those in the control group during the finger-tapping task and were smaller during the word fluency task.

Discussion

In this study using multichannel NIRS machines, the temporal and topographic characteristics of rCBV changes in the depressive and schizophrenic patients were compared with those in healthy controls during cognitive and motor activations. [OxyHb] increases during the task period were evident in most NIRS channels during both activations in all three groups. The time course of [oxyHb] increases, however, differed among the three groups with the same performance in the word fluency task: compared with the control group, the major depression group was characterized by a smaller [oxyHb] increase during the first half of the task period in the frontal and temporal channels, and the schizophrenic group by a small trough of [oxyHb] at the start of the task period, by a smaller [oxyHb] increase during the first half of the task period in the temporal channels, and by an [oxyHb] re-increase in the posttask period in one frontal channel. The differences in [oxyHb] increase between the patient and control groups observed in the word fluency task were assumed to be task-specific, because [oxyHb] increases in the patient groups were rather larger than those in the control group during the finger-tapping task.

Three points should be noted regarding the task parameters used in this study. First, the task period was longer in the present study. Most previous NIRS studies using finger-tapping and word fluency tasks used shorter task periods (i.e, 10–30 sec [Colier et al 1999; Maki et al 1995; Obrig et al 1996; Watanabe et al 1998]), although some previous studies used a 60-sec task period (Hirth et al 1997; Hock et al 1997; Matsuo et al 2000, 2002). We adopted longer task periods (40 sec for the finger-tapping task and 60 sec for the word fluency task) to enable a more detailed examination of the time course of rCBV changes. Second, we adopted a modified version of the word fluency task: the beginning syllables of the words to be generated were changed every 20 sec for the 60-sec task period. The reason for the use of this modified version was to avoid a silent period in the task. Some of the subjects, particularly the psychiatric patients, who experienced difficulty in generating words, tended to stop thinking and to become silent during the task period, which resulted in the loss of cerebral activation. Therefore, the syllables assigned to the words were changed after a shorter period to make the task easier. These changes resulted in the lack of significant difference in performance among the three groups. Third, the subjects were required to repeat syllables during the baseline periods in the word fluency task, instead of remaining silent as in other studies. The observed [oxyHb] changes during the task period, therefore, indicate the differences between simple utterance and word fluency tasks. This procedure enables the differentiation between the utterance process and the word-generating effort.

The [oxyHb] increases observed during the task period of the word fluency task and confirmed by ANOVA are assumed to reflect the rCBV increases due to the task-related cortical activation, hence demonstrating that cerebral activation due to cognitive activation is successfully detected by NIRS. The [oxyHb] increase differences between either the patient groups and the control groups were significant in only four channels when [oxyHb] changes were averaged across each time segment; however, when [oxyHb] increases were compared along the time course of the task, as shown in the *t* test results, many more channels showed significant differences, mainly in the lower frontal and anterior lower temporal channels, where the signal/noise ratio was higher. Moreover, the time courses of such significance were also assessed every .1 sec.

[OxyHb] increases in the patients with major depressive disorders were smaller than those in the control subjects during the word fluency task, even though the task performance was not significantly different between the two groups. Significant group differences in cognitive activation were observed in the lower left frontal and bilateral anterior lower temporal channels,

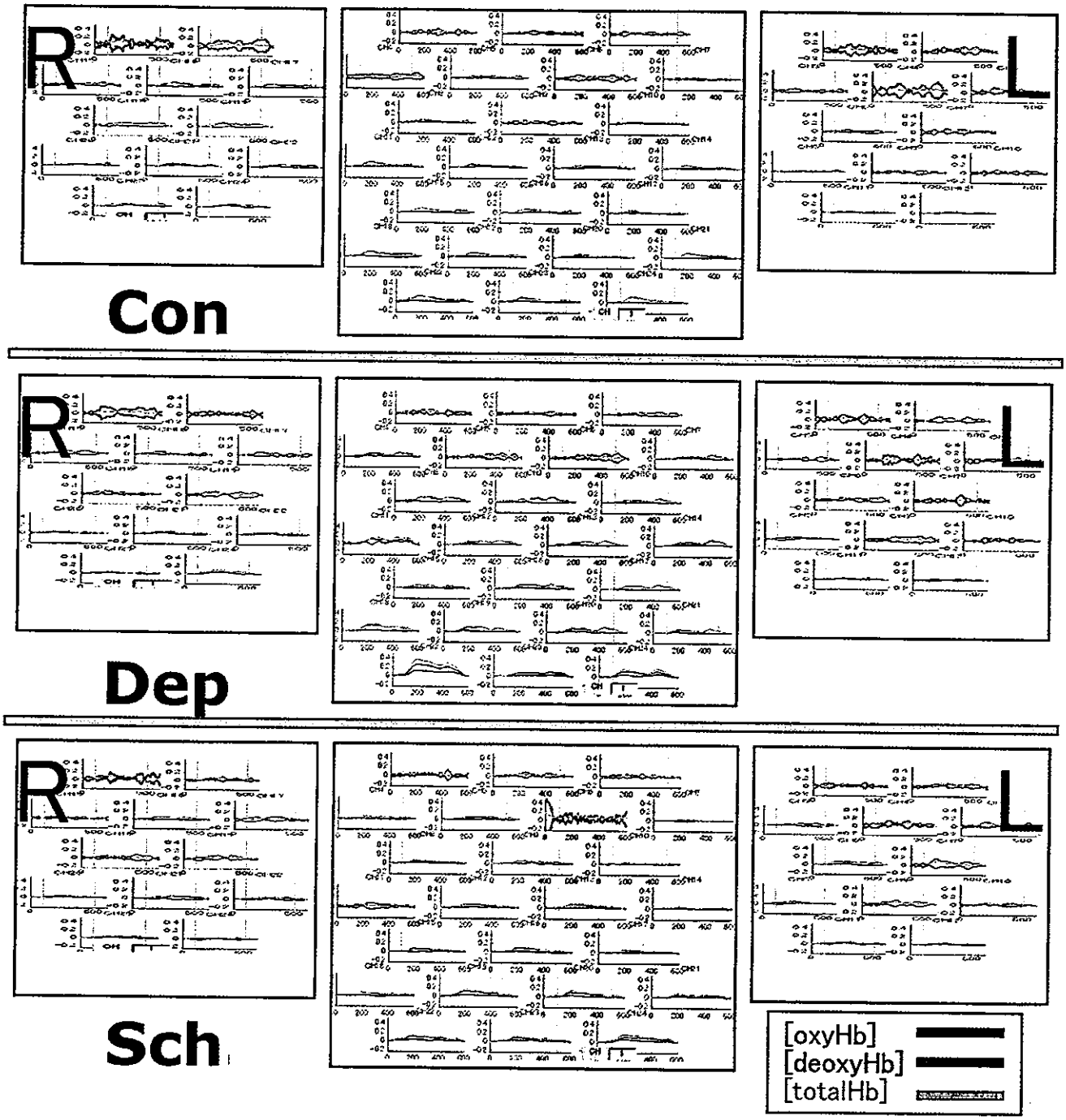


Figure 8. Grand average waveforms of hemoglobin concentration changes during motor activation in the three groups. Grand average waveforms of oxyhemoglobin ([oxyHb]; red line), deoxyhemoglobin ([deoxyHb]; blue line), and total hemoglobin ([totalHb]; green line) during motor activation (between two vertical light blue lines) in the control (Con, upper), depression (Dep, middle), and schizophrenia groups (Sch, lower).

which are assumed to almost correspond to the left lower dorsolateral prefrontal area and the bilateral perisylvian area, respectively. Decreased [oxyHb] activation in depression is consistent with decreased rCBF and metabolism in the dorsolateral prefrontal cortex in the resting state observed in functional neuroimaging studies using other methodologies, such as PET, SPECT, and fMRI, as reviewed by Drevets (2000). The decreased rCBV activation during the cognitive task period in this study indicates that the cerebral cortex of depressive patients cannot gain a sufficient increase in blood supply to overcompensate for the consumed oxygen as in the case with healthy control subjects. The repeated loss of overcompensation for blood supply could result in a shortage of reserved energy in the cerebral cortex and in its clinical presentation as depression.