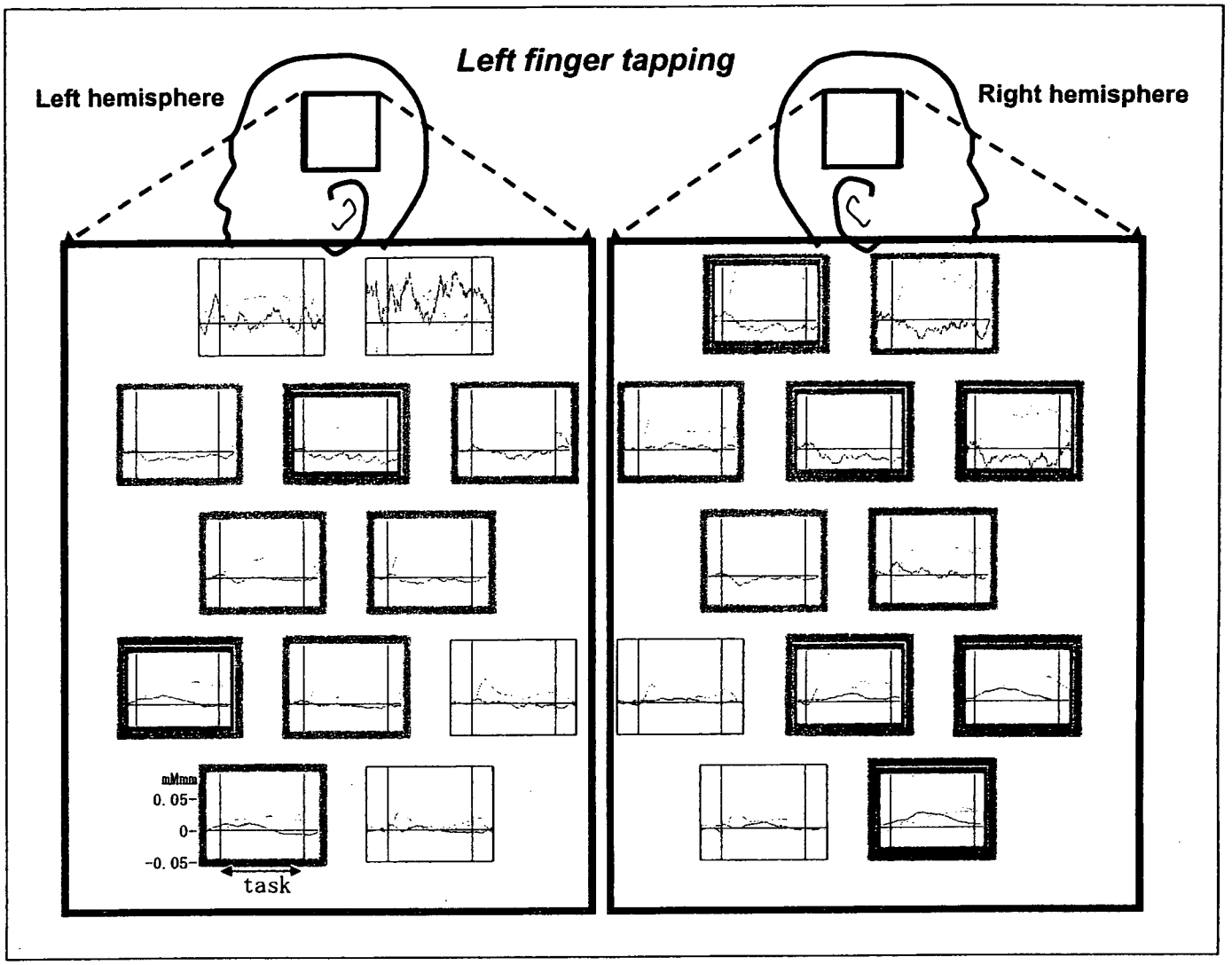
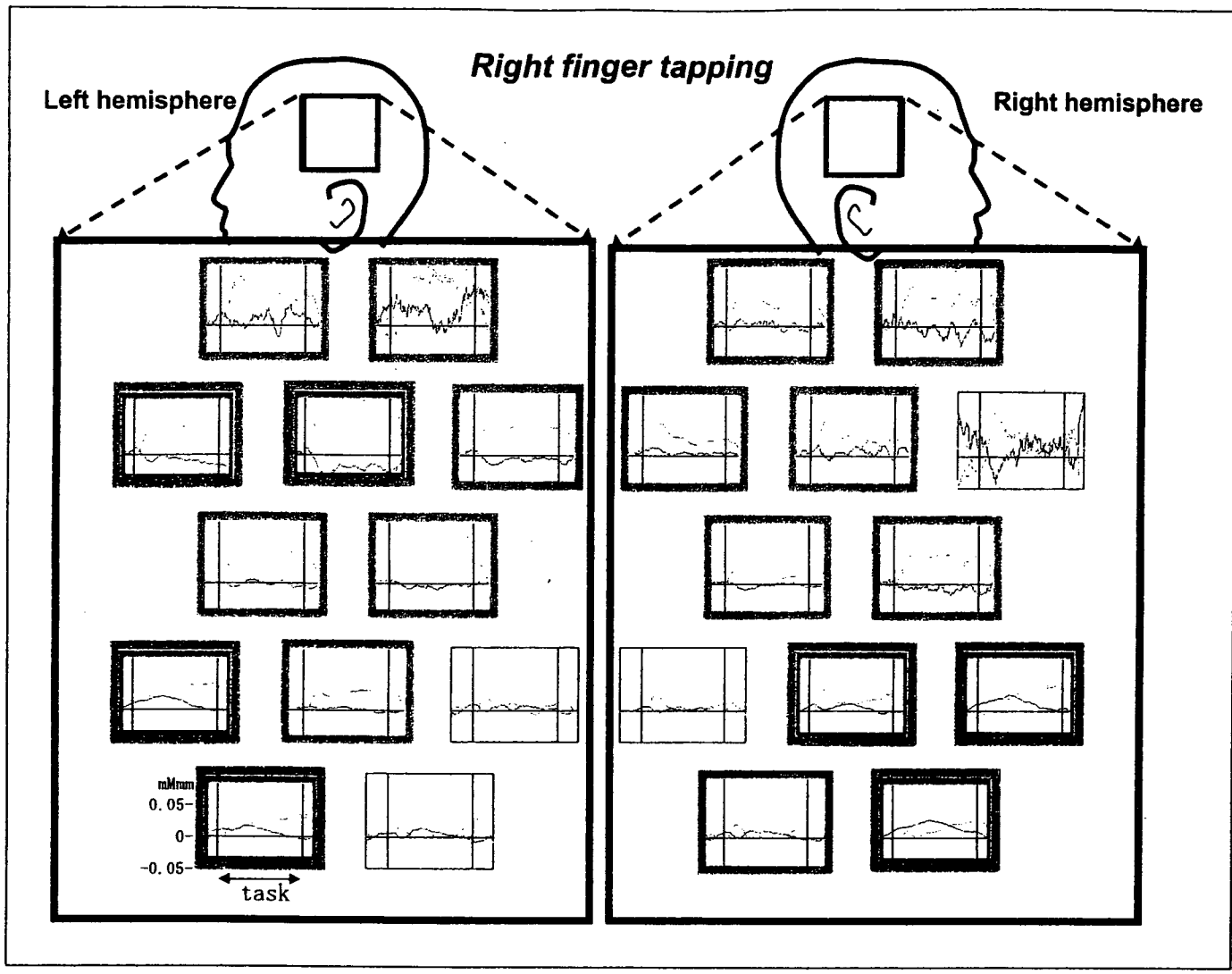


Fig. 2. Oxy-, deoxy-, and total-hemoglobin concentration changes in the left-finger tapping task are presented as grand average waveforms in 24 channels of the left (left) and the right temporal probes (right) in red, blue, and green lines, respectively. The channels with significant changes in [oxy-Hb] 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 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.



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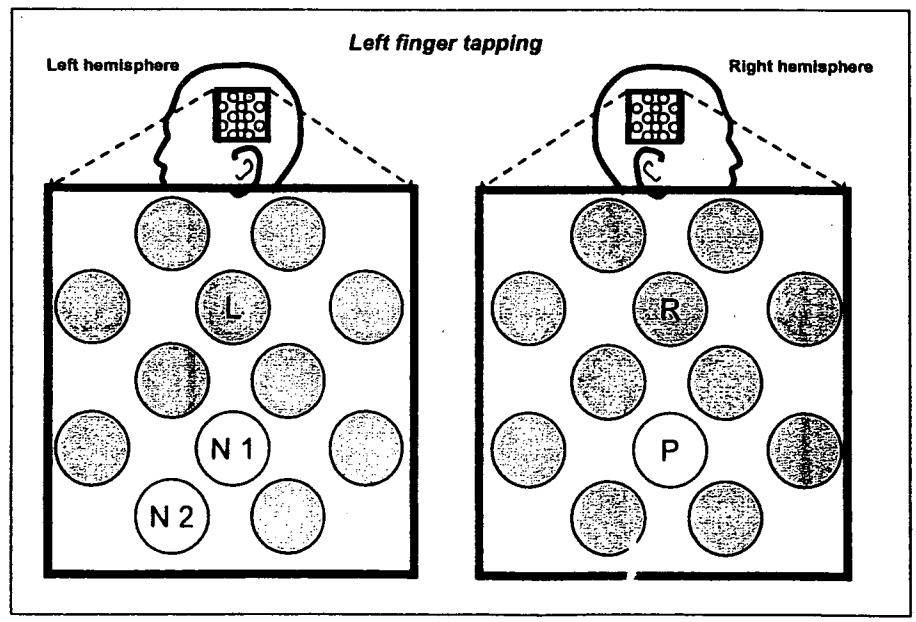

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Fig. 3. Oxy-, deoxy-, and total-hemoglobin concentration changes in the right-finger tapping task are presented as in figure 2.

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 $R^2 = 0.00$	N2/early delta $R^2 = 0.01$	p/early delta $R^2 = 0.04$
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

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.

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 (M.F.) and a Health and Labour Sciences Research Grants for Special Research from the Japanese Ministry of Health, Labour and Welfare (M.M.). 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.

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NeuroImage 29 (2006) 172 – 184

Frontal lobe function in bipolar disorder: A multichannel near-infrared spectroscopy study

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Received 3 March 2005; revised 12 July 2005; accepted 13 July 2005
Available online 25 August 2005

Frontal lobe dysfunction has been implicated as one of the pathophysiological bases of bipolar disorder. Detailed time courses of brain activation in the bipolar disorder group were investigated using multichannel near-infrared spectroscopy (NIRS), a recently developed functional neuroimaging technology with a high time resolution, and were compared with those in the major depression and healthy control groups. Seventeen patients with bipolar disorder, 11 equally depressed patients with major depression, and 17 healthy controls participated in the study. Changes in oxy hemoglobin concentration ([oxy-Hb]) during cognitive and motor tasks were monitored using frontal and temporal probes of two sets of 24-channel NIRS machines. [oxy-Hb] increases in the bipolar disorder group were smaller than those in the healthy control group during the early period of a verbal fluency task, larger than those in the major depression and healthy control groups during the late period of this task, and were smaller than those in the major depression group during a finger-tapping task. Depressive symptoms and antidepressant dosages did not correlate with [oxy-Hb] changes in the two patient groups. Bipolar disorder and major depression were characterized by preserved but delayed and reduced frontal lobe activations, respectively, in the present high-time-resolution study by multichannel NIRS.

Keywords: Near-infrared spectroscopy; Cerebral blood volume: Bipolar disorder; Major depression; Verbal fluency task; Diagnosis

Introduction

Bipolar disorder and major depressive disorder (major depression) are two of the principal disorders among mood disorders. Although their etiology and pathophysiology have not yet been completely elucidated, a number of structural and functional neuroimaging studies suggest the importance of the frontal lobe. For example, a reduction in the volume of cerebral regions (Beyer and Krishnan, 2002; Fossati et al., 2004; Sheline, 2003; Strakowski et al., 2002), particularly the gray matter and glial cell density (Davidson et al., 2002) in the frontal lobe, has been reported in structural neuroimaging studies. In functional neuroimaging studies using positron emission tomography (PET), single-photon emission computed tomography (SPECT), or functional magnetic resonance imaging (fMRI), abnormal changes in cerebral glucose metabolism and cerebral blood flow have been demonstrated, particularly in the prefrontal cortex (Drevets, 2000; Stoll et al., 2000; Videbech, 2000), and they were often reported to be associated with cognitive dysfunctions in some studies (Sweeney et al., 2000; Veiel, 1997).

In many of the functional neuroimaging studies demonstrating abnormal prefrontal functions, mixed patients with bipolar disorder and major depression were examined; that is, different diagnostic groups (e.g., bipolar disorder and major depression) with various mood states (e.g., depressed and manic) were often classified into one patient group (Strakowski et al., 2000). Differences in abnormalities in frontal lobe functions between patients with bipolar disorder and those with major depression have been suggested in recent studies, in which depressed patients with bipolar disorder and those with major depression were examined separately. Decreased prefrontal activity (hypofrontality) both at rest and during an activation task has been consistently demonstrated in depressed patients with major depression in a number of PET, SPECT, and fMRI studies (Brody et al., 2001; Drevets, 2000; Liotti and Mayberg, 2001; Malhi et al., 2004b; Rogers et al., 2004).

On the other hand, in depressed patients with bipolar disorder, the reported changes in the frontal lobe function during an activation task are so far inconsistent (Strakowski et al., 2000, 2004) although changes at rest are consistent in showing decreased activity (Blumberg et al., 2002): increased activity (visuospatial working memory task, Chang et al., 2004), decreased activity

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Available online on ScienceDirect (www.sciencedirect.com).

1053-8119/$ - see front matter
doi:10.1016/j.neuroimage.2005.07.025

(Stroop task, Blumberg et al., 2003; auditory discrimination continuous performance task, Ketter et al., 2001; positive affect induction, Malhi et al., 2004a; emotional recognition, Yurgelun-Todd et al., 2000), and unchanged frontal lobe functions (semantic decision task, Curtis et al., 2001) compared to healthy controls have been reported, even within the same task, that is the verbal fluency task (increased activity, Curtis et al., 2001; decreased activity, Matsuo et al., 2002, 2004; unchanged function, Dye et al., 1999).

As far as the authors surveyed, only two research groups have directly contrasted the frontal lobe functions between depressed patients with bipolar disorder and those with major depression, but these studies showed inconsistent results. In near-infrared spectroscopy (NIRS) studies, Matsuo et al. found reduced [oxy-Hb] increases in the prefrontal region during a verbal fluency task in both the bipolar disorder and major depression groups compared with the healthy control groups, and found no significant differences between the bipolar disorder and major depression groups (Matsuo et al., 2000, 2002, 2004, 2005). However, in fMRI study, Lawrence et al. (2004) found larger prefrontal activations in response to emotional stimuli in the bipolar disorder group than in the major depression group. The reasons for the differences in the results of these research groups have not been clarified.

NIRS is a recently developed noninvasive functional neuroimaging technique. NIRS can detect regional cerebral blood volume (rCBV) changes in terms of changes in oxy hemoglobin concentration ([oxy-Hb]) and deoxy hemoglobin concentration ([deoxy-Hb]). The principle of NIRS is based on the modified Lambert–Beer law, and NIRS monitors the absorption of near-infrared light by oxy and deoxy hemoglobin using two different wavelengths. Both the [oxy-Hb] increase and [deoxy-Hb] decrease detected by NIRS have been shown to reflect cortical activation by simultaneous measurements using other methodologies (Hock et al., 1997; Kleinschmidt et al., 1996; Mehagnoul-Schipper et al., 2002; Toronov et al., 2001). The correlations with cerebral blood flow have been shown to be stronger for [oxy-Hb] than for [deoxy-Hb] (Malonek et al., 1997; Strangman et al., 2002b). In an animal study using a perfused brain rat model, [oxy-Hb] was also demonstrated to be the most sensitive marker of CBF changes among [oxy-Hb], [deoxy-Hb], and [total-Hb] (Hoshi et al., 2001).

NIRS has some advantages and disadvantage over other functional neuroimaging methodologies such as PET, SPECT, and fMRI. The three advantages of NIRS are (1) the complete noninvasiveness of the measurement enabling repeated measurements, (2) the high time resolution of 0.1 s enabling a detailed clarification of temporal changes in rCBV, and (3) the portability and compactness of its apparatus enabling measurements under natural conditions with subjects sitting on a comfortable chair. The disadvantages of NIRS are that it measures hemoglobin concentrations (1) only as relative changes, 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 low spatial resolution, and (4) not only in the brain but also in other 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.

NIRS has been demonstrated to enable the detection of brain activations during cognitive tasks in healthy controls (reviewed by Hoshi, 2003; Obrig and Villringer, 2003; Strangman et al., 2002a). For mood disorders, several NIRS studies have been conducted. Okada et al. (1996) reported no dominant hemispheric changes in [total-Hb] in the prefrontal area of patients with major depression during a mirror drawing task. In addition to Matsuo et al. (2000, 2002, 2005) as described above, both Suto et al. (2004) and Herrmann et al. (2004) reported reduced frontal activation during a verbal fluency task in patients with major depression. Eschweiler et al. (2000) found that reduced [oxy-Hb] increases predict a good therapeutic efficacy of repetitive transcranial magnetic stimulation in patients with major depression.

In the present study, we evaluated the spatial and temporal characteristics of rCBV changes during cognitive activation in patients with bipolar disorder by multichannel NIRS, and compared them with those in patients with major depression. The verbal fluency task was employed as cognitive activation and the finger-tapping task as cognitively undemanding control activation. The inconsistency in frontal lobe activation in bipolar disorder has not been clarified in any functional neuroimaging methodologies as described above, and there have been no studies that assessed the temporal characteristics of cerebral activation in mood disorders except a NIRS study in our laboratory (Suto et al., 2004). The objectives of the present study are (1) to clarify the characteristics of brain activations in patients with bipolar disorder along the task time course with the aid of the high time resolution of NIRS and (2) to compare them with those in healthy controls as well as patients with major depression of similar psychopathology. We hypothesized that (1) the characteristics of the frontal lobe function are expressed more clearly in cognitive activation than in control motor activation, (2) cognitive activations in bipolar disorder are consistent in some time segments and inconsistent in other time segments with those in major depression, and (3) such differences in activations along the time course can explain, at least in part, the inconsistent results in cognitive activation regarding bipolar disorder.

Materials and methods

Subjects

Seventeen patients with bipolar disorder, 11 patients with major depression, and 17 healthy controls participated in the present study (Table 1). The patients with bipolar disorder and those with major depression were recruited among the outpatients and inpatients at Gunma University Hospital, and were diagnosed according to the criteria in the *Diagnostic and Statistical Manual of Mental Disorders, 4th ed.* (American Psychiatric Association 1994).

The patients with bipolar disorder included 11 males and 6 females (age: mean, 40.9 years; SD, 13.3; range, 20–62), and 4 patients with bipolar I disorder and 13 patients with bipolar II disorder. At the time of the study, all the subjects were euthymic to subdepressive as indicated by their scores in the 24-item Hamilton Rating Scale for Depression (HRSD, Hamilton, 1960; mean, 9.4; SD, 6.5; range, 1–22), and were on medication with mood stabilizers and/or antidepressants.

The patients with major depression, including 9 males and 2 females (age: mean, 44.8 years; SD, 13.1; range, 24–59), were euthymic to subdepressive at the time of the study (HRSD score: mean, 10.4; SD, 9.5; range, 0–26) with the same severity as the patients with bipolar disorder ($t = -0.32$, $P = 0.76$), and were on

Table 1
Characteristics of subjects

Case	Age	Sex	Subtype	HRSD	Performance	Total imipramine equivalent dose mg/day	Medication (imipramine equivalent dose) mg/day
Bipolar disorder (n = 17)							
1	39	M	II	12	8	243.8	Clomipramine 75 (93.8), paroxetine 40 (150), lithium 800, levomepromazine 15
2	27	F	I	10	11	0	Lithium 600, risperidone 2
3	33	M	II	11	11	125	Maprotiline 50 (50), milnacipran 75 (75), lithium 400, bromocriptine 5
4	43	F	II	11	17	325	Amitriptiline 150 (150), amoxapine 100 (100), maprotiline 75 (75), lithium 600, bromocriptine20
5	57	F	II	10	21	60	Milnacipran 60 (60), lithium 600
6	38	M	II	3	18	240	Imipramine 60 (60), maprotiline 150 (150), milnacipran 30 (30), sodium valproate 400
7	49	M	II	19	21	0	Chlorpromazine 50, lithium 400, sodium valproate 800
8	33	M	II	1	19	0	Lithium 600
9	48	M	II	10	17	200	Imipramine 125 (125), paroxetine 20 (75), lithium 1000
10	28	M	II	17	10	287.5	Clomipramine 200 (250), trazodone 75 (37.5), lithium 600, risperidone 1
11	62	M	II	17	20	125	Paroxetine 30 (112.5), trazodone 25 (12.5)
12	57	M	I	3	14	162.5	Milnacipran 150 (150), trazodone 25 (12.5), lithium 800
13	20	F	II	5	13	12.5	Sulpiride 25 (12.5), lithium 200, sodium valproate 400
14	50	M	I	4	14	0	Lithium 1200
15	28	M	II	22	17	100	Dosulepin 50 (50), mianserin 10 (25), sulpiride 50 (25), levomepromazine 10
16	25	F	I	3	8	0	Lithium 400, sodium valproate 400
17	59	F	II	2	11	0	Carbamazepine 400, lithium 600
Mean	40.9	M11/F6	I4/II13	9.4	14.7	110.7	
SD	13.3			6.5	4.4	114.2	
Major depression (n = 11)							
1	54	M		12	9	175	Paroxetine 40 (150), trazodone 50 (25)
2	51	M		2	16	25	Amitriptyline 25 (25), lithium 800, bromocriptine 7.5
3	52	M		0	23	25	Clomipramine 10 (12.5), trazodone 25 (12.5)
4	24	M		6	14	200	Mianserin 20 (50), paroxetine 40 (150), carbamazepine 400
5	57	M		1	5	50	Mianserin 20 (50)
6	30	M		2	15	100	Amitriptyline 100 (100)
7	59	M		17	17	45	Milnacipran 45 (45)
8	37	F		8	9	156.3	Clomipramine 125 (156.3), levomepromazine 10
9	55	M		26	14	50	Dosulepin 50 (50)
10	26	F		14	11	125	Milnacipran 100 (100), sulpiride 50 (25)
11	48	M		26	23	75	Clomipramine 50 (62.5), trazodone 25 (12.5)
Mean	44.8	M9/F2		10.4	14.2	93.3	
SD	13.1			9.5	5.6	62.3	
Healthy controls (n = 17)							
Mean	42.8	M13/F4			16.5		
SD	4.5				3.6		

M, male; F, female; I, bipolar I disorder; II, bipolar II disorder; HRSD, 24-item Hamilton Rating Scale for Depression.

medication with antidepressants. Eight of the 11 patients were also included in our previous study (Suto et al., 2004): two patients in the study were excluded from the present one because more strict criteria for artifact rejection of body movements in NIRS measurements were employed in the present study, and three new patients were added.

The healthy controls included 13 males and 4 females (age: mean, 42.8 years; SD, 4.5; range, 36–52). They had no history of any major psychiatric disorders, neurological disorders, substance abuses, head injuries, or major physical illnesses, and were not on any psychotropic medications at the time of the study. Sixteen of the 17 healthy controls were also included in our previous study (Suto et al., 2004).

The mean ages and sex ratios were not significantly different among the three groups ($F = 0.44$, $P = 0.65$; chi square = 1.14, $P = 0.57$). All the subjects were right-handed as indicated by their Edinburgh scores (Oldfield, 1970; mean, 95.1; SD, 12.0; range, 33.3–100). The present 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 prior to the study.

Activation tasks

Hemoglobin concentration changes were measured during cognitive and motor activations. The subjects sat on a comfortable

chair in a daylight room with their eyes open throughout the measurements. The cognitive activation consisted of a 30-s pretask baseline, a 60-s verbal fluency task, and a 60-s post-task baseline. During the verbal fluency task, the subjects were instructed to generate as many words whose initial syllable was either /a/, /ka/, or /sa/ as they could. The three initial syllables were employed in this order and changed every 20 s during the 60-s task to reduce the time during which the subjects remained silent. The number of words generated during the verbal 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 post-task baseline periods as a Japanese phrase for "A, B, C" in English.

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

NIRS measurements

NIRS machine

In this study, changes in [oxy-Hb], [deoxy-Hb], and [total-Hb] were measured using two 24-channel NIRS machines (Hitachi ETG-100) at two wavelenghts of near-infrared light (780 and 830 nm) whose absorption was measured, and [oxy-Hb] and [deoxy-Hb] were calculated. [total-Hb] was calculated as the sum of [oxy-Hb] and [deoxy-Hb]. The distance between the pair of emission and detector probes was 3.0 cm, and it was considered that the machines measure points at 2–3 cm depth from the scalp, that is, the surface of cerebral cortices (Hock et al., 1997; Toronov et al., 2001).

Probe positions and measurement points

The probes of the NIRS machines were placed on the subject's frontal and bilateral temporal regions. The frontal probes measured the hemoglobin concentration changes at 24 measurement points in a 9×9 cm^2 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 bilateral temporal probes measured the hemoglobin concentration changes at 12 measurement points in a 6×6 cm^2 area, with the central probe positioned at the midpoint between the vertex and the external ear hole. These measurement points were labeled F1–F24, L1–L12, and R1–R12 for the frontal, left temporal, and right temporal channels, respectively, from top to bottom.

The correspondence of the probe positions and the measurement points on the cerebral cortex was confirmed by superimposing the probe positions on a magnetic resonance image of a three-dimensionally reconstructed cerebral cortex of a representative subject in the healthy control group (Figs. 1–3), and the correspondence was also supported by a multisubject study of anatomical cranio-cerebral correlation (Okamoto et al., 2004).

Measurement parameters

The absorption of near-infrared light was measured with a time resolution of 0.1 s. The obtained data were analyzed using the "integral mode": the pretask baseline was determined as the mean

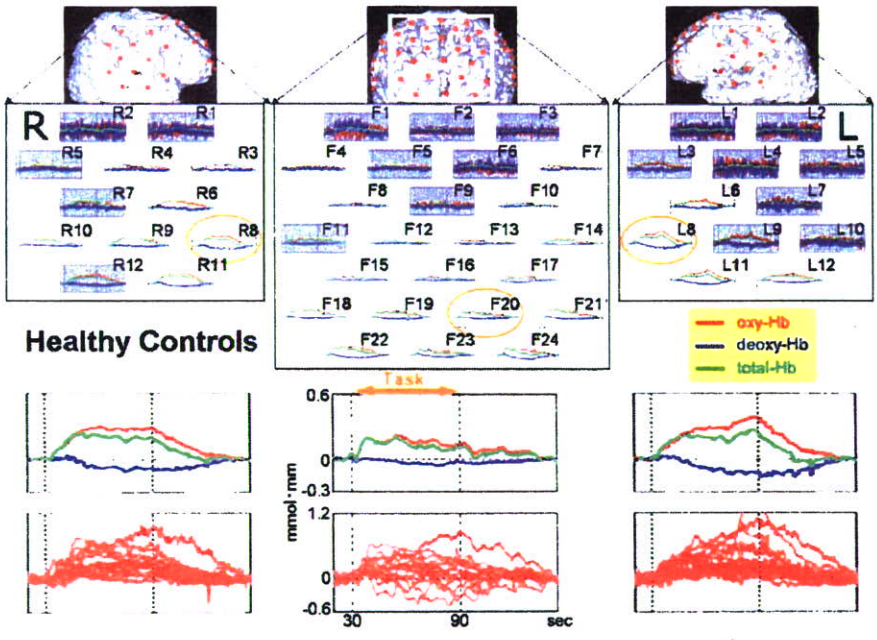

Fig. 1. Grand averaged waveforms of hemoglobin concentration changes during cognitive activation in the healthy control group. Grand averaged waveforms of [oxy-Hb] (red line), [deoxy-Hb] (blue line), and [total-Hb] (green line) changes during cognitive activation (between two vertical dotted lines) measured by the frontal (center) probe and the left (right) and right temporal (left) probes in the healthy control group. The channels with low signal-to-noise ratios were presented with gray meshing. Three sets of the grand averaged waveforms and superimposed individual waveforms of [oxy-Hb] changes in representative channels (circled in orange) are enlarged below. The upper figures show the measurement positions of the NIRS machines, which were superimposed on a magnetic resonance image of a reconstructed cerebral cortex of a representative subject.

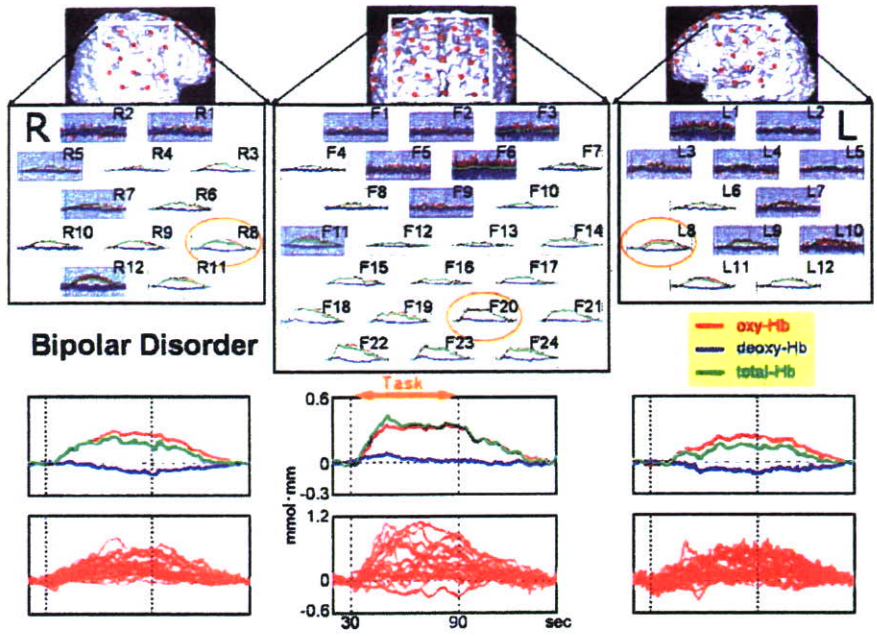

Fig. 2. Grand averaged waveforms of hemoglobin concentration changes during cognitive activation in the bipolar disorder group. Grand averaged waveforms of [oxy-Hb] (red line), [deoxy-Hb] (blue line), and [total-Hb] (green line) changes during cognitive activation (between two vertical dotted lines) measured by the frontal (center) probe and the left (right) and right temporal (left) probes in the bipolar disorder group. The channels with low signal-to-noise ratios were presented with gray meshing. Three sets of the grand averaged waveforms and superimposed individual waveforms of [oxy-Hb] changes in representative channels (circled in orange) are enlarged below. The upper figures show the measurement positions of the NIRS machines, which were superimposed on a magnetic resonance image of a reconstructed cerebral cortex of a representative subject.

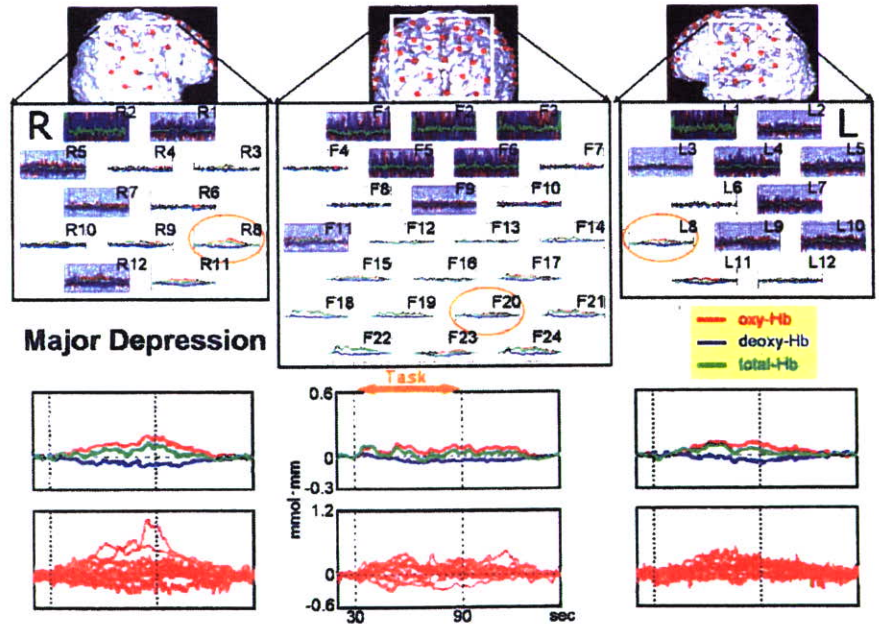

Fig. 3. Grand averaged waveforms of hemoglobin concentration changes during cognitive activation in the major depression group. Grand averaged waveforms of [oxy-Hb] (red line), [deoxy-Hb] (blue line), and [total-Hb] (green line) changes during cognitive activation (between two vertical dotted lines) measured by the frontal (center) probe and the left (right) and right temporal (left) probes in the major depression group. The channels with low signal-to-noise ratios were presented with gray meshing. Three sets of the grand averaged waveforms and superimposed individual waveforms of [oxy-Hb] changes in representative channels (circled in orange) are enlarged below. The upper figures show the measurement positions of the NIRS machines, which were superimposed on a magnetic resonance image of a reconstructed cerebral cortex of a representative subject.

across last 10 s of the 30-s pretask period, the post-task baseline was determined as the mean across last 5 s of the 50 and 5-s post-task periods for the cognitive and motor activations according to Suto et al. (2004) and Ito et al. (2005), respectively, and linear fitting was applied to the data between these two baselines. The moving average methods were used to exclude short-term motion artifacts in the analyzed data (moving average window: 1 s).

Data analysis

The waveforms of [oxy-Hb], [deoxy-Hb], and [total-Hb] changes were acquired from all the subjects in all 48 channels during the cognitive and motor activations. NIRS data that clearly contained motion artifacts determined by close observations of the subjects were excluded from further analyses.

The grand averaged waveforms of three types of hemoglobin concentration changes and superimposed individual waveforms of [oxy-Hb] changes were obtained for all the subjects on the basis of individual subjects' waveforms in all 48 channels. These grand averaged waveforms of [oxy-Hb] changes in all 48 channels were also imaged as topographs of [oxy-Hb] changes by the linear compensation method:

[oxy-Hb] data in the channels with low signal-to-noise (S/N) ratios were excluded from further statistical analyses when their standard deviations during the pretask period exceeded 0.040 in any subject group: seven frontal (F1–3, F5, F6, F9, and F11), eight left temporal (L1–5, L7, L9, and L10), and five right temporal (R1, R2, R5, R7, and R12) channels. The S/N ratios of [oxy-Hb] data in these channels positioned over hair-covered areas tended to be low due to the paucity of near-infrared light detected.

[oxy-Hb] data in the three groups were compared in two ways. First, as usually employed in block design experiments, the [oxy-Hb] data were averaged across three task segments (pretask, task, and post-task), analyzed using three-way repeated-measures analysis of variance (ANOVA) with "diagnosis" (healthy controls, patients with bipolar disorder, and patients with major depression), "task segments" (pretask, task, and post-task), and "channels" (28 channels) as independent variables, and compared using post hoc one-way ANOVA. Second, [oxy-Hb] changes were compared between two of the three groups by Welch's t test using the grand averaged waveforms every 0.1 s in each channel. This analysis enabled a more detailed comparison of [oxy-Hb] changes along the time course of the task. The differences were interpreted as meaningful if 30 and 20 consecutive comparison points reached a significance level of 5% among 600 and 400 points during the task periods in the verbal fluency and finger-tapping tasks, respectively, to avoid multiple comparison errors.

The relationships of the [oxy-Hb] changes with the clinical symptoms, medications, and task performances were investigated in the bipolar disorder and major depression groups. For the bipolar disorder group, correlations of the [oxy-Hb] changes during the task period with the HRSD scores, imipramine equivalents of antidepressant dosages (Inagaki et al., 1999, with some modification), lithium dosages, and number of words generated were examined. In addition, multiple regression analyses were performed with the [oxy-Hb] changes as a dependent variable, and the HRSD scores, antidepressant dosages, lithium dosages, number of words generated, and age of the subjects as independent variables for the verbal fluency task, and the HRSD score, antidepressant dosages, lithium dosages, age of the subjects as independent variables for the finger-tapping task. For the major depression group, the same analyses were performed, except that lithium dosages were eliminated from the correlation and multiple regression analyses because only one patient with major depression was treated with lithium. The [deoxy-Hb] data were also analyzed in the same way as the [oxy-Hb] data.

Results

Cognitive activation

The numbers of words generated during the verbal fluency task were not significantly different among the three groups (healthy control: mean, 16.5; SD, 3.6; bipolar disorder: mean, 14.7; SD, 4.4; major depression: mean, 14.2; SD, 5.6; one-way ANOVA $F = 1.15$, $P = 0.33$). The grand averaged waveforms of [oxy-Hb], [deoxy-Hb], and [total-Hb] during the verbal fluency task in the healthy control, bipolar disorder, and major depression groups are shown in Figs. 1–3, respectively. The three sets of waveforms of hemoglobin concentrations enlarged below the figures were from the representative channels, and the superimposed individual waveforms of the [oxy-Hb] changes are shown at the bottom of the figures. The [oxy-Hb] changes during the verbal fluency task can be displayed as the topographs for the three groups, as shown in Fig. 4.

As for [oxy-Hb], the three-way repeated-measures ANOVA revealed a significant main effect of "time segments" ($F = 493.3$, $P < 0.001$) and "channels" ($F = 5.2$, $P < 0.001$); the results of the post hoc one-way repeated-measures ANOVA, in which the pretask and task periods were compared, demonstrated significant [oxy-Hb] increases during the task period: in 16 frontal (F4, F7, F8, F10, and F13–24) channels and two left (L8 and L11) and four right temporal (R8–11) channels in the healthy control group; in 16 frontal (F4, F7, F8, F10, and F13–24) channels and four left (L6, L8, L11, and L12) and six right temporal (R3, R6, and R8–11) channels in the bipolar disorder group; and in six frontal (F14, F17, F18, F19, F21, and F22) channels and one left temporal (L8) channel in the major depression group. The main effect of "diagnosis" was also significant ($F = 46.4$, $P < 0.001$), and the post hoc one-way ANOVA clarified that the [oxy-Hb] increases during the task period in the major depression group were smaller than those in the bipolar disorder (F20 and F23) and healthy control (L8) groups. The interactions of "time segments" and "diagnosis" ($F = 34.3$, $P < 0.001$), and "time segments" and "channels" ($F = 4.2$, $P < 0.001$) were significant, but the interactions of "diagnosis" and "channels" ($F = 0.6$, $P = 0.987$), and "time segments", "diagnosis", and "channels" ($F = 0.6$, $P = 0.994$) were not significant. These significant effects were similarly observed when the [oxy-Hb] changes during the task period were divided into three time segments of 20 s (the early, middle, and late task segments).

The results of the t test for the between-group comparison of the [oxy-Hb] changes during the cognitive activation are shown in Fig. 5, and some of these results are shown in Fig. 6 in the form of topographs. Compared with those in the healthy control group, the [oxy-Hb] increases in the bipolar disorder group were significantly smaller during the early task period in six lower frontal (F13, F16, F18, F20, F21, and F24) channels and two left lower anterior temporal (L8 and L12) channels, but were significantly larger during the late task period in four frontal (F14, F15, F20, and F23) channels. When compared with those in the major depression group, the [oxy-Hb] increases in the bipolar disorder group were

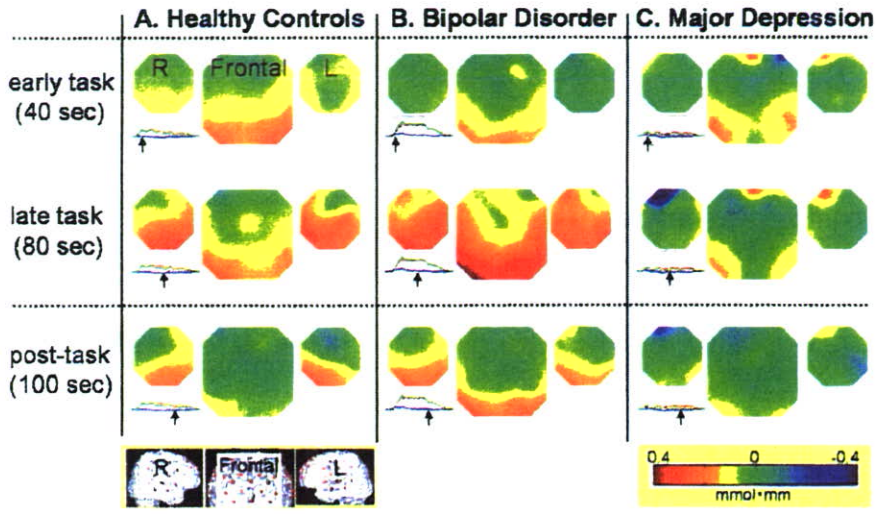

Fig. 4. Topographical presentation of [oxy-Hb] changes in the three groups during cognitive activation. The [oxy-Hb] changes in the healthy control (A, left), bipolar disorder (B, center), and major depression (C, right) groups are presented as topographical maps along the time course of the task (from top to bottom). Each set of topographical maps is composed of three maps corresponding to the frontal and bilateral temporal probes. The times from the task start are presented in seconds on the left side and are indicated by arrows on the representative grand averaged waveforms of hemoglobin concentration in each group, and the red, green, and blue areas in the topographs indicate an increase, no change, and a decrease in [oxy-Hb], respectively. Topographical maps do not exclude data of channels with low signal-to-noise ratios for general view of the activation.

significantly larger during the late task period in 14 frontal (F4, F7, F8, F10, F12, F14, and F16–23) channels and four left (L6, L8, L11, and L12) and four right anterior temporal (R3, R6, R9, and R11) channels, and were significantly smaller during the early task period in one frontal (F18) channel. Additionally, the [oxy-Hb] increases in the major depression group were significantly smaller than those in the healthy control group in eight frontal (F4, F10, F12, F13, F16, F20, F23, and F24) channels and four left (L6, L8, L11, and L12) and four right lower anterior temporal (R6, R8, R9, and R11) channels mainly during the early task period.

In the healthy control group (Fig. 1), [oxy-Hb] rapidly increased immediately after the start of the task period, remained activated during the task period, and then decreased gradually after the end of the task. Such [oxy-Hb] increases during the task period were clearly observed in the lower frontal channels. In the bipolar disorder group (Fig. 2), [oxy-Hb] gradually increased after the start of the task period, reached its peak with a comparable magnitude to but with a longer latency than that in the healthy control group, and then decreased gradually in the post-task period, mainly in the lower frontal and bilateral anterior temporal channels. In the major depression group (Fig. 3), rapid but small increases in [oxy-Hb] were observed after the start of the task period, but the subsequent [oxy-Hb] increases during the task period were smaller.

As for [deoxy-Hb], the three-way repeated-measures ANOVA revealed a significant main effect of "time segments" ($F = 85.1$, $P < 0.001$) and "channels" ($F = 2.8$, $P < 0.001$); the results of the post hoc one-way repeated-measures ANOVA, which the pretask and task periods were compared, demonstrated significant [deoxy-Hb] changes during the task period: decreases in four frontal (F14, F17, F22, and F24) channels and three left (L8, L11, and L12) and two right temporal (R8 and R11) channels in the healthy control group; decreases in one frontal (F14) channel and one left temporal (L8) channel and increases in one right temporal (R4) channel in the bipolar disorder group; and decreases in three frontal (F15, F17, and F20) channels in the major depression group. The main effect of "diagnosis" was also significant ($F = 6.7$, $P = 0.001$), and the post hoc one-way ANOVA clarified that the degrees of [deoxy-Hb] decreases during the task period in the bipolar disorder group were smaller than those in the healthy control group (F17 and F20). The interactions of "time segments" and "diagnosis" ($F = 9.3$, $P < 0.001$), and "time segments" and "channels" ($F = 2.2$, $P < 0.001$) were significant, but the interactions of "diagnosis" and "channels" ($F = 0.9$, $P = 0.669$), and "time segments", "diagnosis", and "channels" ($F = 0.9$, $P = 0.710$) were not significant.

Motor activation

The grand averaged waveforms of [oxy-Hb], [deoxy-Hb], and [total-Hb] changes during the finger-tapping task are shown in Fig. 7. As for [oxy-Hb], the three-way repeated-measures ANOVA revealed a significant main effect of "time segments" ($F = 493.3$, $P < 0.001$) and "channels" ($F = 5.2$, $P < 0.001$); the results of the post hoc one-way repeated-measures ANOVA, in which the pretask and task periods were compared, demonstrated significant [oxy-Hb] increases during the task period: in 13 frontal (F8, F12 16, and F18–24) channels and seven right temporal (R3, R4, R6, and R8–11) channels in the healthy control group: in seven frontal (F13, F15, F16, F20, and F22–24) channels and one left (L6) and three right temporal (R3, R4, and R6) channels in the bipolar disorder group; and in 13 frontal (F4, F7, F12–14, F16–20, and F22–24) channels and one left (L6) and three right temporal (R3, R6, and R9) channels in the major depression group. The main effect of "diagnosis" was significant ($F = 46.4$, $P < 0.001$), and the post hoc one-way ANOVA clarified that the [oxy-Hb] increases during the task period in the bipolar disorder group were smaller than those in the healthy control (R11) and major depression (R9) groups. The interaction of "task segments" and "diagnosis" was significant in one right temporal (R11) channel. The t test results were consistent with the results of ANOVA mentioned above.

As for [deoxy-Hb], the three-way repeated-measures ANOVA revealed a significant main effect of "time segments" ($F = 19.7$, $P < 0.001$) and "channels" ($F = 1.5$, $P = 0.048$). The results of

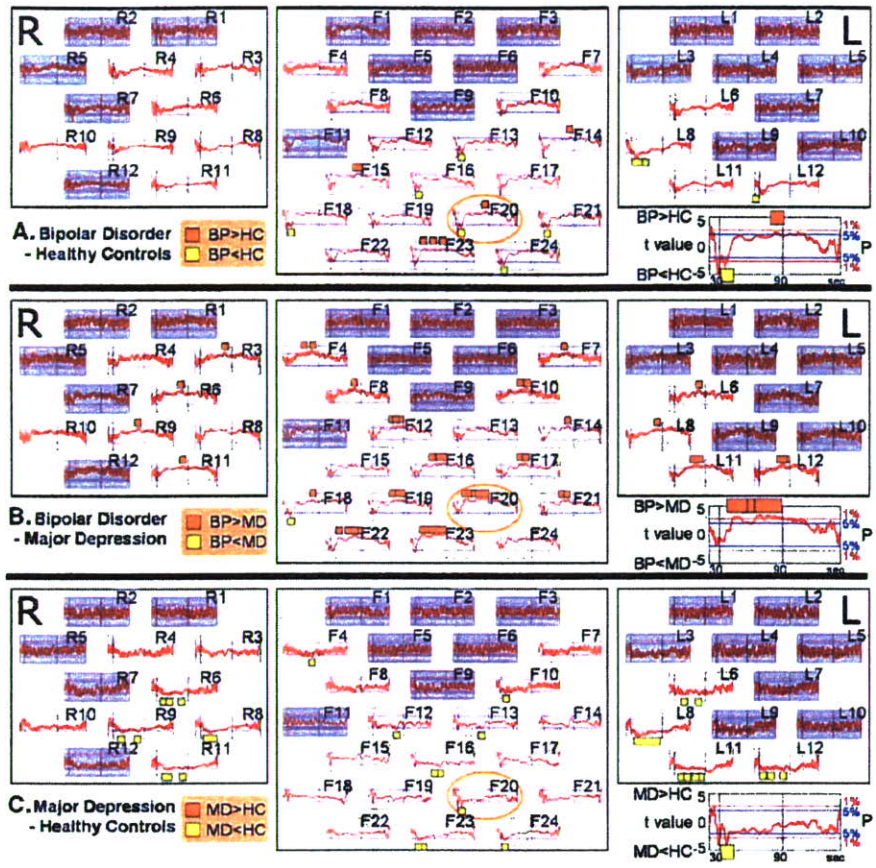

Fig. 5. *t* value graphs of [oxy-Hb] comparison between the groups during cognitive activation. BP, bipolar disorder group; MD, major depression group; HC, healthy control group. The *t* values of [oxy Hb] comparison between the bipolar disorder and healthy control groups (A, upper), between the bipolar disorder and major depression groups (B, middle), and between the major depression and healthy control groups (C, bottom) in 48 channels are presented, as shown in Fig. 1. The channels with low signal-to-noise ratios were presented with gray meshing. Three graphs (circled in orange) are enlarged below as typical representatives. The blue and red lines in each *t* graph correspond to the statistical significance levels of 5% and 1%, respectively, and the times with significant differences in each graph are marked orange (yellow) when the [oxy-Hb] changes in the bipolar disorder group were larger (smaller) than those in the healthy control groups in panel A, when the [oxy-Hb] changes in the bipolar disorder group were larger (smaller) than those in the major depression group in panel B, and when the [oxy-Hb] changes in the major depression group were larger (smaller) than those in the healthy control group in panel C.

the post hoc one-way repeated-measures ANOVA, which the pretask and the task periods were compared, demonstrated significant [deoxy-Hb] changes during the task period: increases in one frontal (F23) channel and one right temporal (R8) channel in the bipolar disorder group, and increases in one left (L12) and one right temporal (R11) channels and decreases in one right temporal (R3) channel in the major depression group. The interaction of "time segments" and "channels" (F = 1.6, P = 0.009) was also significant. The main effect of "diagnosis" (F = 2.0, P = 0.130) and the interactions of "time segments" and "diagnosis" (F = 1.4, P = 0.233), "diagnosis" and "channels" (F = 0.8, P = 0.774), and "time segments", "diagnosis", and "channels" (F = 0.9, P = 0.768) were not significant.

Correlation with clinical symptoms and medications

As for the verbal fluency task, the [oxy-Hb] changes were not significantly correlated with the HRSD scores and antidepressant dosages in all the channels in both the bipolar disorder and major depression groups, and were not significantly correlated with the task performance in all the channels in all the three groups even when significance level corrections for multiple correlations were not employed. The [oxy-Hb] changes were significantly correlated with the lithium dosages in two right temporal channels (R9, Spearman's rho = 0.50, P = 0.043; R11, *rho* = 0.56, P = 0.019) in the bipolar disorder group when significance level corrections were not employed. However, no significant correlations were obtained in the multiple regression analyses including the HRSD scores, antidepressant dosages, lithium dosages, number of words generated, and age of the subjects in both the bipolar disorder and major depression groups.

The [deoxy-Hb] changes were significantly correlated with the HRSD scores in one frontal channel (F20, rho = −0.50, P = 0.041) and one right temporal channel (R11, rho = −0.52, P = 0.031), and with the lithium dosages in one right temporal channel (R3, rho = 0.49, P = 0.045), but were not significantly correlated with the antidepressant dosages and task performance in the bipolar disorder group when significance level corrections were not employed. However, no significant correlations were obtained in the multiple regression analyses in the bipolar disorder group. The [deoxy-Hb] changes were significantly correlated with the antidepressant dosages in four frontal channels (F7, rho = 0.64, P –

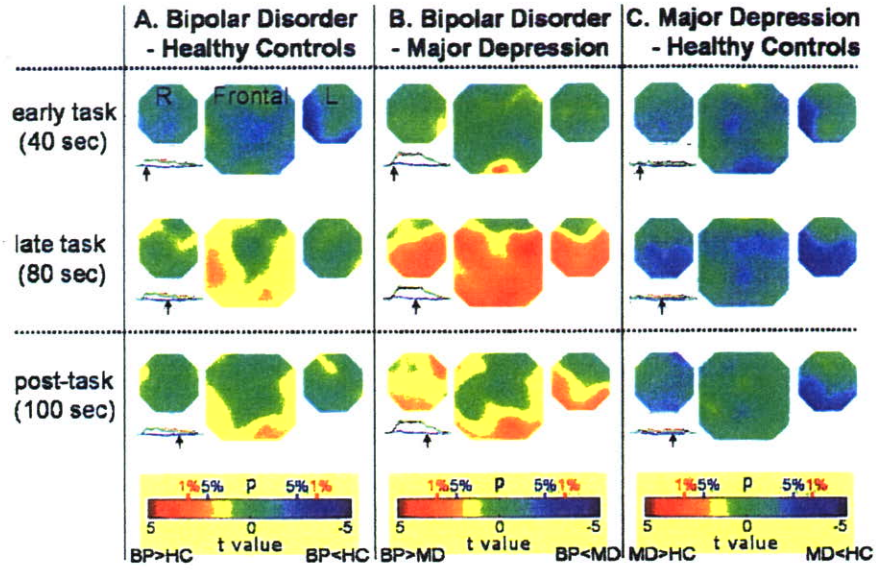

Fig. 6. Topographical presentation of t value of [oxy-Hb] comparison between the groups during cognitive activation. BP, bipolar disorder group; MD, major depression group; HC, healthy control group. The t values of [oxy-Hb] for the bipolar disorder and healthy control groups (A, left), the bipolar disorder and major depression groups (B, center), and the major depression and healthy control groups (C, right) are presented as topographical maps along the time course of the task (from top to bottom). Each set of topographical maps is composed of three maps corresponding to the frontal and bilateral temporal probes. The times from the task start are presented in seconds on the left side and are indicated by arrows on the representative grand averaged waveforms of hemoglobin concentration in each group. The red, green, and blue areas in the topographs indicate positive, zero, and negative t values, with 2.0 and 2.7 for the statistical significance levels of 5% and 1%, respectively, in panel A, and with 2.1 and 2.8 for the statistical significance levels of 5% and 1%, respectively, in panels B and C. Topographical maps do not exclude data of channels with low signal-to-noise ratios for general view of the activation.

0.033; F18, rho = 0.62, $P = 0.043$; F21, rho = 0.60, $P = 0.049$; F24, rho = 0.83, $P = 0.002$) and with the task performance in one frontal channel (F22, rho = −0.61, $P = 0.047$), but were not significantly correlated with the HRSD scores in the major depression group when significance level corrections were not employed. The significant correlations were obtained in the multiple regression analyses in one frontal channel (F24, $R = 0.87$, $P = 0.043$): the significant variable was the antidepressant dosages (beta = −0.83, $P = 0.036$) in the major depression group.

As for the finger-tapping task, the significant correlations in [oxy-Hb] were obtained in the multiple regression analyses in one right temporal channel (R10, $R = 0.73$, $P = 0.041$): the significant variables were the lithium dosages (beta = −0.48, $P = 0.046$) and age (beta = 0.61, $P = 0.012$) in the bipolar disorder group. The significant correlations in [deoxy-Hb] were obtained in the multiple regression analyses in one right temporal channel (R11, $R = 0.78$, $P = 0.016$): the significant variables were the HRSD scores (beta = 0.49, $P = 0.031$), antidepressant dosages (beta = −0.47, $P = 0.028$), and age (beta = −0.57, $P = 0.010$) in the bipolar disorder group. However, no significant correlations were obtained in both [oxy-] and [deoxy-Hb] in the multiple regression analyses in the major depression group.

Discussion

Summary of obtained results

In the present study, the rCBV changes during the cognitive and motor tasks in the bipolar disorder group were compared with those in the healthy control and major depression groups. rCBV increases were successfully demonstrated by NIRS during both the cognitive and motor activations in all the three groups. Their time courses were different among the three groups: the [oxy-Hb] increases in the bipolar disorder group were smaller in the early task period but larger in the late task period than those in the healthy control group, and were comparable to those in the early task period but larger than those in the late task period in the major depression group. The differences in the time courses of the [oxy-Hb] changes were found specifically during the verbal fluency task but not during the finger-tapping task. These [oxy-Hb] changes during the verbal fluency task reflected the cognitive activation in the frontal lobe and the finger-tapping task cognitively undemanding activation. On the other hand, the number of channels with significant changes of [deoxy-Hb] during the task period was smaller than that with significant changes of [oxy-Hb] in any group, probably due to the lower S/N ratios in [deoxy-Hb] than in [oxy-Hb]. Cognitive activation was accompanied consistently by increases in [oxy-Hb] but inconsistently by decreases or increases in [deoxy-Hb]. The discrepancy in the changes in [oxy-Hb] and [deoxy-Hb] corresponds to the findings of Ehlis et al. (2005) that decreases in [deoxy-Hb] during cerebral activation are not as consistently observed increases in [oxy-Hb], and that the changes in [deoxy-Hb] are to be interpreted carefully.

Three points should be noted regarding the task parameters used in this study. First, the task period was relatively long in the present study. Most previous NIRS studies used a short task period for the finger-tapping and verbal fluency tasks (i.e., 10–30 s Colier et al., 1999; Maki et al., 1995; Obrig et al., 1996; Watanabe et al., 1998); on the other hand, some studies used a 60-s task period (Hirth et al., 1997; Hock et al., 1997; Kameyama et al., 2004; Matsuo et al., 2000, 2002, 2004, 2005; Suto et al., 2004). We adopted longer task periods (40 s for the finger-tapping task and 60 s for the verbal fluency task) to examine in detail the time course of

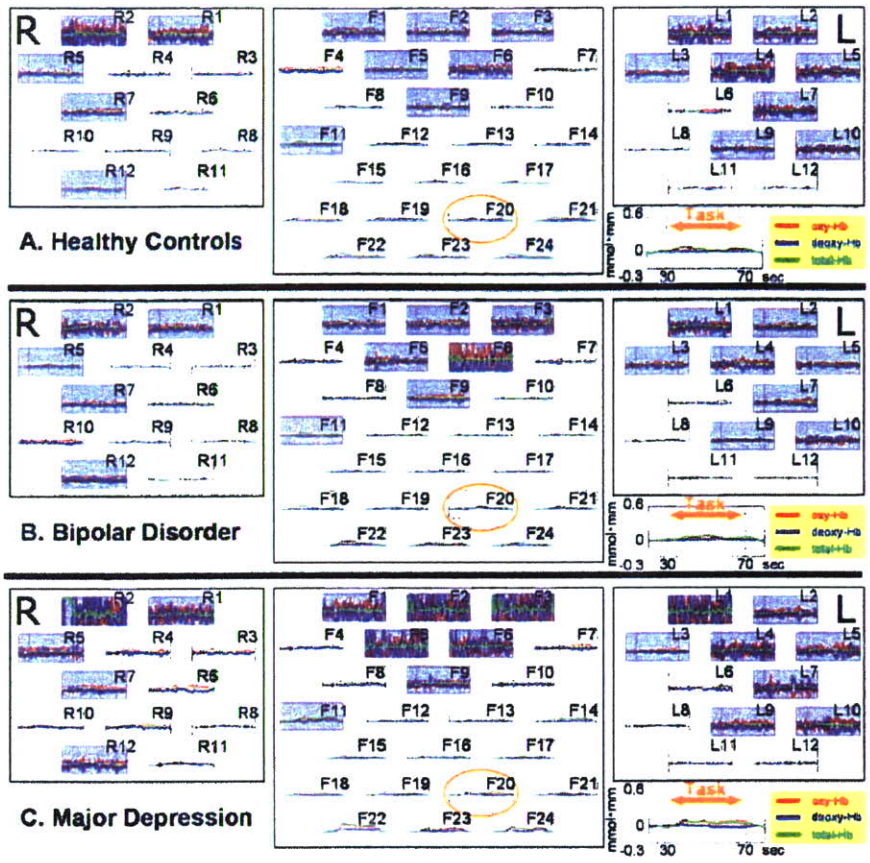

Fig. 7. Grand averaged waveforms of hemoglobin concentration changes during motor activation in the three groups. Grand averaged waveforms of [oxy-Hb] (red line), [deoxy-Hb] (blue line), and [total-Hb] (green line) during motor activation (between two vertical dotted lines) measured by the frontal (center) probe and the left (right) and right temporal (left) probes in the healthy control group (A, upper), bipolar disorder (B, middle), and major depression (C, bottom) groups. The channels with low signal-to-noise ratios were presented with gray meshing. The grand averaged waveform hemoglobin concentration changes in the representative channels (circled in orange) are enlarged below.

cerebral activation. Second, a modified version of the verbal fluency task was adopted: the syllables assigned were changed every 20-s during the 60-s task period in the verbal fluency task to decrease the time during which the subjects were silent. This task procedure not only contributed to the minimization of poor cerebral activation caused by the subjects' silence, but also made the task easier, particularly for clinical patients. The modification could result in no significant differences in task performance among the groups. Third, word repetition was performed in the pretask baseline period instead of keeping silent as in many other studies. This procedure enabled the exclusion of the effect of simple utterance from cerebral activation in word generation.

[oxy-Hb] changes

The discrepancies in the results of previous studies of the bipolar disorder described in the Introduction could be due to the differences in their task designs employed: the duration of the task (30–60 s), number of task repetitions (1–10 times), and baseline conditions before and after the task period (rest vs. word repetition). Among these three factors, the baseline condition could be the most critical because frontal lobe hyperactivity was observed when the subjects were required to perform some simple tasks during the baseline periods (Curtis et al., 2001; Chang et al., 2004), while frontal lobe hypoactivity was observed when the subjects were resting without performing any task during the baseline periods (Matsuo et al., 2002, 2004; Yurgelun-Todd et al., 2000). The larger [oxy-Hb] increases observed in the bipolar disorder group in the present study are consistent with this baseline condition hypothesis. The mechanisms underlying frontal lobe hyperactivity due to the simple task during the baseline periods could be that a simple task during the pretask period could (1) accelerate the following activation or (2) reduce the frontal activity level by relaxing the patients with bipolar disorder much more than the healthy controls.

Another factor of the task design that can influence the frontal activation in bipolar disorder is the initial syllable designation in the verbal fluency task. In the present study, the initial syllables were changed every 20 s during the 60-s task to decrease the time during which the subjects remained silent, while in Matsuo's (2002) study, the initial syllables were unchanged throughout the 60-s task period, resulting in a smaller number of generated words (means: 11.2, 9.2, and 12.4 for the healthy control, bipolar disorder, and major depression groups, respectively) than that in the present study (means: 16.5, 14.7, and 14.2, respectively). Better performances in the present study, particularly in the later task period, may result in a larger activation in the bipolar disorder group. This interpretation is supported by the differences in the

time course of [oxy-Hb] changes between the bipolar disorder and healthy control groups: the results of t test, in which the two groups were compared every 0.1 seconds, revealed significant differences in [oxy-Hb] increases mainly in the later task period.

The baseline condition and initial syllable designation mentioned above can explain the results in the bipolar disorder group but not those in the major depression group. The frontal lobe hypoactivity in the major depression group has been consistently demonstrated irrespective of the baseline condition of the task employed and was also demonstrated in the present study even with task performances comparable to those in the healthy control and bipolar disorder groups. The differences in [oxy-Hb] increases between the bipolar disorder and major depression groups, therefore, could be interpreted to reflect the differences in frontal lobe function between these two groups: the frontal lobe function is potentially preserved in terms of its reactivity, but it is difficult to be activated in the bipolar disorder group and shows markedly reduced reactivity in the major depression group. The decreased reactivity in the major depression group was consistent with the results of previous studies (reviewed by Drevets, 2000; Malhi et al., 2004b; Rogers et al., 2004). The difference in frontal lobe reactivity between the bipolar disorder and major depression groups can be employed for differential diagnosis between bipolar disorder and major depression in clinical settings in the future.

Correlations with clinical symptoms and medications

Clinical symptoms, antidepressant medications, and age were generally not related to the altered frontal lobe activation in both the bipolar disorder and major depression groups in the present study. Lithium medication was correlated only in a temporal channel in the bipolar disorder group. The findings regarding clinical symptoms are consistent with the results of some previous activation studies that found no correlation between frontal lobe activation and clinical symptoms (major depression, Okada et al., 1996; bipolar disorder, Yurgelun-Todd et al., 2000), but they are inconsistent with the results of a study that found significant correlations (major depression, Fu et al., 2004). Future studies are warranted to clarify the influences of clinical symptoms and medications on frontal lobe activation by examining the same patient population longitudinally, because these correlations in the present study were examined across many subjects.

Limitation of the study

There are three points that should be improved in the present study. The first point is the limited cerebral regions that could be measured using NIRS probes. A considerable nonmeasured area existed between the areas covered by the frontal and temporal probes due to their arrangement on the skull, which prevented the examination of the lower posterior frontal cortex. In addition, 20 of the 48 channels in the upper frontal and upper posterior temporal probes had to be excluded from detailed analyses because of their low S/N ratios, which prevented the examination of some parts of the upper frontal, parietal, and temporal cortices. The second point is the subjects' characteristics. The sample sizes were small, the sex ratios were somewhat skewed, and the patients' symptoms were rather mild. The mild symptomatology may contribute to the absence of significant correlations between clinical symptoms and frontal lobe activation. The third point is that all the patients were on medications at the time of the examination. Although there were no significant correlations between the antidepressant or lithium dosages and frontal lobe activation in the present study, the possibility remains: a part of the observed findings could result from the effects of the psychotropic drugs the patients were taking, for example, the anticholinergic effects of the antidepressant drugs or the influences of different lithium dosages between the bipolar disorder and major depression groups. Further studies are required to improve these three points.

In conclusion, bipolar disorder and major depression were characterized by preserved but delayed and reduced frontal lobe activation patterns, respectively, in the present study by multichannel NIRS with a high time resolution. NIRS with its noninvasiveness and high time resolution could be a useful research tool for examining in detail the time courses of brain activation in mood disorders, as well as a clinically useful tool for the differential diagnosis of patients with bipolar disorder and those with major depression in the near future.

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 (MF), a Health and Labor Sciences Research Grant for Research on Psychiatric and Neurological Diseases and Mental Health (MF), and a Health and Labor Sciences Research Grant for Special Research from the Japanese Ministry of Health, Labor and Welfare (MM).

We thank Dr. Itsuro Ida, Dr. Akihiko Oshima, and Mr. Suguru Hattori of the Department of Psychiatry and Human Behavior, Gunma University Graduate School of Medicine, for collaboration.

The preliminary results of this study were presented in the 59th Annual Meeting of the Society of Biological Psychiatry on April 29–May 1, 2004 in New York, U.S.A.

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THE JOURNAL OF
CHILD PSYCHOLOGY AND PSYCHIATRY
ACAMH
Journal of Child Psychology and Psychiatry 49:1 (2008), pp 79–87 doi:10.1111/j.1469-7610.2007.01817.x

Trauma exposure and posttraumatic stress disorder in delinquent female adolescents

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Background: Although juveniles within the justice system have high psychiatric morbidity, few comprehensive investigations have shown posttraumatic stress disorder (PTSD) in female delinquents. Here, we aim to describe the nature and extent of PTSD and trauma exposure and to clarify the relationships among comorbidity and psychosocial factors in juvenile female offenders. **Method:** Sixty-four girls were randomly interviewed using structured tools. Self-report measures were used to assess depression, eating behaviour, impulsivity and parental attitude. **Results:** The PTSD prevalence was 33%, and 77% of the female juvenile offenders had been exposed to trauma. The offenders with PTSD showed a significantly high psychiatric comorbidity. Depression and adverse parenting were associated with PTSD development, and abnormal eating was also correlated with PTSD symptoms. Marked differences in the frequency and intensity of PTSD evaluation depending on the type of comorbidity and trauma were observed. **Conclusions:** Incarcerated young females in Japan have serious trauma-related problems, and the degree of depression is a strong predictor of PTSD development and symptoms. This study highlights the importance of adequate diagnosis and treatment of PTSD in delinquent female adolescents. **Keywords:** Trauma, female, delinquency, comorbidity, depression, eating disorder, posttraumatic stress disorder. **Abbreviations:** CAPS: Clinician-Administered PTSD Scale for DSM-IV; MINI-kid: Mini-International Neuropsychiatric Interview for Children and Adolescents; DSD: DSM Scale for Depression; BIS-11: Barratt Impulsiveness Scale 11th version; EAT-26: Eating Attitudes Test-26; PBI: Parental Bonding Instrument; IES-R: Impact of Event Scale-Revised.

Juvenile female offenders have high rates of trauma exposure. For instance, Cauffman, Feldman, Waterman, and Steiner (1998) showed that most incarcerated females are exposed to multiple types of trauma. Recent studies have revealed that witnessing a violent crime and being confronted with traumatic news are the most frequently reported sources of trauma in female juvenile offenders (Dixon, Howie, & Starling, 2005). In particular, a high lifetime PTSD incidence (67%) has been observed among young women in custody (Cauffman et al., 1998) compared with the general population's incidence range of 1–14% (American Psychiatric Association, 1994). It has been documented that chronic exposure to violence results in the numbing of feelings or substance use and increased risk-taking behaviours, including violent activities, in an attempt to cope with or adapt to the feeling of being unsafe (Crimmins et al., 2000). Additionally, Giaconia et al. (1995) found that those with any history of PTSD symptomatology (14.5%) were more likely than those without to have behavioural or emotional problems, interpersonal problems, academic failure, suicidal behaviour, and health problems. Based on the previous studies (Ruchkin, Schwab-Stone, Koposov, Vermeiren, & Steiner, 2002; Dixon et al., 2005), there is evidence that juvenile offenders with PTSD experience higher rates of comorbid psychiatric disorders than those without PTSD. In particular, evidence suggests that young female offenders with PTSD have more comorbidity than those without PTSD, with depression, substance abuse/dependence, psychoses and eating disorders occurring significantly and more frequently. Reasonably, it could be speculated that there is a mutual relevancy among juvenile offences including illicit drug use or delinquency, trauma exposures including adverse parenting, and psychological behavioural problems including mood liability, abnormal eating behaviours, or impulsivity.

In Japan, although there has been extensive research on the frequency of PTSD in incarcerated juvenile delinquents (Yoshinaga, Kadomoto, Otani, Sasaki, & Kato, 2004), there is little comprehensive and structured research on PTSD development, including several psychosocial measurements in female juvenile delinquents. The aims of this study are (1) to describe the nature and extent of trauma exposure and PTSD, (2) to clarify the point prevalence of PTSD, (3) to examine the relationship between psychiatric comorbidity and PTSD (traumatic exposure), (4) to analyse the associations between PTSD diagnosis and socio-demographic factors, depressive symptoms, impulsivity, abnormal eating behaviour and parenting attitude, (5) to determine the risks and factors that can be used to predict PTSD development, and whether PTSD

Conflict of interest statement: No conflicts declared.

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