

**ORIGINAL****Multi-channel near-infrared spectroscopy reveals reduced prefrontal activation in schizophrenia patients during performance of the kana Stroop task**

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**Abstract :** The purpose of the present study was to investigate the activity of frontal lobe of patients with schizophrenia during performance of two Japanese versions of the Stroop task (kana and kanji) by measuring changes in the concentration of oxygenated hemoglobin (oxyHb) with near-infrared spectroscopy (NIRS). Fourteen schizophrenia patients and 14 age- and gender-matched healthy control subjects participated in the study after giving consent. The relative changes of concentrations of oxyHb were measured by NIRS during performance of the Stroop task. Significant Stroop effects, as measured by the number of correct responses, were observed with both the kana and the kanji versions. Analysis of NIRS data revealed that the schizophrenia patients showed reduced activation in the prefrontal cortex compared to healthy controls during performance of the kana Stroop task, and that both schizophrenia patients and healthy controls showed lack of activity in the prefrontal cortex during performance of the kanji Stroop task. The results of the present study suggest the possibility that the kana Stroop task cause a greater Stroop effect than the kanji Stroop task, and schizophrenia patients show decreased prefrontal vascular reactivity associated with the inhibition required during the performance of the kana Stroop task. *J. Med. Invest.* 59 : 45-52, February, 2012

**Keywords :** *near-infrared spectroscopy (NIRS), schizophrenia, Stroop task, hypofrontality, oxygenated hemoglobin (oxyHb)*

**INTRODUCTION**

Both hypofrontality and hyperfrontality have been reported in functional imaging studies of schizophrenia patients. These studies have used positron emission tomography (PET), single-photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI) approaches.

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Hypofrontality has frequently been observed in schizophrenia patients during performance of attention and working memory tasks. Findings across studies have been inconsistent however, with some studies reporting reduced prefrontal cortex activation (1-4). and others reporting unaltered or increased frontal activation (5-8). These discrepancies may be attributable to methodological differences in factors such as medication, task design, task performance and task requirements.

The Stroop task (9) is a useful test of selective attention and inhibition, and involves frontally mediated cognitive processes such as response inhibition, interference resolution, and behavioral conflict

resolution. Functional neuroimaging studies have found several areas of the frontal cortex that appear to be specifically activated during performance of the Stroop task.

The Stroop test has been used to compare the frontal activation patterns of schizophrenia patients with those of healthy subjects (3, 4, 8, 10-13). PET studies using the Stroop task have shown lower activities in the left paracingulate (10), left middle frontal gyri (11) or anterior cingulate region (3, 13) in schizophrenia patients. Studies with fMRI using the Stroop task have reported decreased or increased activation in various brain areas in schizophrenia patients compared with controls (4, 8). Another fMRI study reported that the schizophrenia patients showed both decreased conflict- and error-related activity in the anterior cingulate cortex (12). The Stroop phenomenon is potentially interesting in Japanese linguistics because there exist differences in the way phonogram kana and ideogram kanji are processed. Relatively little work has been done with the Stroop task in Japanese, though prior research has shown that there are differences in Stroop effects between kana and kanji. The previous study has reported that behavioral reaction time was longer in the kanji Stroop task than the kana Stroop task (14). It is necessary to study both kana and kanji of the Stroop task in the neuroimaging studies, too.

Near-infrared spectroscopy (NIRS) is an optical

imaging technique which allows non-invasive measurement of changes in the concentration of oxygenated (oxyHb) and deoxygenated (deoxyHb) hemoglobin in brain tissue (15). NIRS is therefore useful in assessing the brain function of healthy adults (16) and patients with psychiatric disorders, and has been used in several neuroimaging studies of schizophrenia patients (16-20).

In the present study, we used NIRS to examine differences between healthy subjects and schizophrenia patients during performance of the Stroop task. Two different writing systems are used in Japan. Japanese kana is a syllabic writing system in which each symbol represents a syllable, thus allowing direct phonetic reading, whereas Japanese kanji is a logographic writing system. A kana version and a kanji version of the Stroop task were used in the present study.

## METHODS

### Subjects

Fourteen patients with a DSM-IV-TR diagnosis of schizophrenia (age  $29.8 \pm 5.7$  years, mean  $\pm$  SD ; 3 males, 11 females), and 14 age- and sex-matched healthy control subjects (age  $29.7 \pm 6.5$  years, mean  $\pm$  SD ; 3 males, 11 females) were included (Table 1). The patients were outpatients or inpatients of the Department of Psychiatry of Tokushima

Table 1. The  $2 \times 2 \times 4$  repeated ANOVA for changes in oxyHb concentration during performance of the kana Stroop task and the kanji Stroop task.

Change in oxyHb concentration (mmol  $\times$  mm)

Task	Schizophrenia Patients				Control Subjects				
	Area1	Area2	Area3	Area4	Area1	Area2	Area3	Area4	
kana	congruent	0.11 $\pm$ 0.09	0.12 $\pm$ 0.06	0.12 $\pm$ 0.08	0.14 $\pm$ 0.09	0.14 $\pm$ 0.10	0.16 $\pm$ 0.13	0.16 $\pm$ 0.14	0.15 $\pm$ 0.12
	incongruent	0.15 $\pm$ 0.13	0.13 $\pm$ 0.06	0.14 $\pm$ 0.09	0.16 $\pm$ 0.13	0.33 $\pm$ 0.21	0.23 $\pm$ 0.13	0.33 $\pm$ 0.20	0.23 $\pm$ 0.16
Main effect		Interaction							
diagnosis	task	area	diagnosis $\times$ task	diagnosis $\times$ area	task $\times$ area	diagnosis $\times$ task $\times$ area			
$F=5.24^*$	$F=12.2^{**}$	$F=1.54$	$F=5.86^*$	$F=3.06^*$	$F=6.54^{**}$	$F=4.05^*$			
Task	Schizophrenia Patients				Control Subjects				
	Area1	Area2	Area3	Area4	Area1	Area2	Area3	Area4	
kanji	congruent	0.12 $\pm$ 0.07	0.14 $\pm$ 0.04	0.11 $\pm$ 0.06	0.14 $\pm$ 0.07	0.13 $\pm$ 0.12	0.16 $\pm$ 0.15	0.16 $\pm$ 0.15	0.15 $\pm$ 0.10
	incongruent	0.11 $\pm$ 0.07	0.12 $\pm$ 0.07	0.12 $\pm$ 0.06	0.14 $\pm$ 0.12	0.14 $\pm$ 0.10	0.15 $\pm$ 0.11	0.15 $\pm$ 0.12	0.14 $\pm$ 0.09
Main effect		Interaction							
diagnosis	task	area	diagnosis $\times$ task	diagnosis $\times$ area	task $\times$ area	diagnosis $\times$ task $\times$ area			
$F=0.66$	$F=0.14$	$F=1.05$	$F=0.003$	$F=0.98$	$F=1.0$	$F=1.12$			

\*\* $P < .01$ , \* $P < .05$  ANOVA and Bonferroni's post-hoc PLSD

University Hospital. All subjects were right-handed, as assessed by the Edinburgh Handedness Inventory (21). The control subjects had no history of psychiatric or neurological disorder. All subjects completed the JART, which is a Japanese version of the NART (National Adult Reading Test), a widely used measure of premorbid IQ in English-speaking patients with dementia (22).

Schizophrenia symptoms were evaluated using the Positive and Negative Syndrome Scale (PANSS) (23). The patients had a mean total PANSS score of  $46.4 \pm 7.9$  (PANSS sub-scores : positive  $10.9 \pm 3.1$  ; negative  $11.5 \pm 2.5$  ; global  $24.0 \pm 4.8$ ). All patients were being treated with typical (n=2) or atypical antipsychotic medication (n=9) or a combination of both (n=3) (mean chlorpromazine equivalent dose : 220 mg/day, range 100-400 mg/day) (24).

Written informed consent was obtained from all participants prior to study entry, and the study was approved by the Ethics Committee of Tokushima University Hospital.

#### *Stroop task and procedure*

The cognitive paradigm used in the present study was the Stroop task. The task was presented in a block design that consisted of rest periods and four test conditions (congruent and incongruent conditions in kana script, and then congruent and incongruent conditions in kanji script). The performance of each of the four task conditions was separated by a rest period. In the rest periods, subjects were instructed to look at a dot on the computer screen. The duration of each of the four task conditions and each rest period was 30 seconds. NIRS measurement was performed during the rest periods and all four task conditions. The task was presented in a block design, in which each block was separated by a rest period. Namely, the task consisted of the following sequence : rest, kana congruent condition, rest, kana incongruent condition, rest, kanji congruent condition, rest, and kanji incongruent condition. During the Stroop task, subjects were asked to read as many words as possible on a computer screen displaying 100 words. In the Stroop task, subjects were randomly presented with the words 'red', 'green', 'yellow,' and 'blue' which were written in kana or kanji script and printed in red, green, yellow, or blue ink. In the congruent condition, word meaning was congruent with the color of the ink and subjects were instructed to read out the word. In the incongruent condition, the four words were printed in an incongruent color (e.g. the word

'blue' was printed in yellow ink). Subjects were instructed to name, as quickly as possible, the color of the ink in which the words were printed. The investigator recorded the number of correct and incorrect verbal responses.

#### *Near-Infrared Spectroscopy*

NIRS measurement was performed using ETG4000, NIRS system with 24 optodes (Hitachi Medical Corporation, Tokyo, Japan), using two wavelengths of near-infrared light (695 and 830 nm). The absorption of light was measured, and changes in oxyHb and deoxyHb concentrations were calculated according to the Beer-Lambert law using the difference in absorption between the two wavelengths. The distance between the emission and the detector was 3.0 cm, and the machine took measurements at points located 2-3 cm beneath the scalp, i.e. on the surface of the cerebral cortices. The NIRS probes were placed symmetrically and bilaterally over the frontal region. Two plastic shells, to which 9 optodes were attached, were placed symmetrically with one shell on the left forehead and one shell on the right forehead. The probes measured the relative changes in oxyHb and deoxyHb concentrations at 12 measurement points within a  $6 \times 6$ -cm area of the left and right hemispheres, respectively. The lowest probes were positioned along the Fp1-Fp2 line in accordance with the International 10/20 Electrode Placement System for electroencephalography. The distance from the midline to the most medial and the most lateral probes was 1.5 cm and 7.5 cm, respectively.

#### *Data analysis and statistics*

The number of correct responses for each of the four task conditions was recorded for all subjects. Between-group non paired sample t-tests were performed for each of the four task conditions. Changes in oxy Hb concentration, which is the most sensitive indicator of changes in rCBF (25), were recorded from pre-task baseline. The peak change in oxyHb concentration in each task condition was recorded for each subject. Four areas were defined to allow investigation of the individual effects of the task parameters within different regions of NIRS measurement (Area 1 with channels 1,2,3,4,6, and 8 ; Area 2 with channels 5,7,9,10,11,and 12 ; Area 3 with channels 13,14,16,17,19, and 22 ; and Area 4 with channels 15,18,20,21,23,and 24) according to the method of Ehlis *et al.* (16) (Figure 1). The average of the peak change in oxyHb concentration in

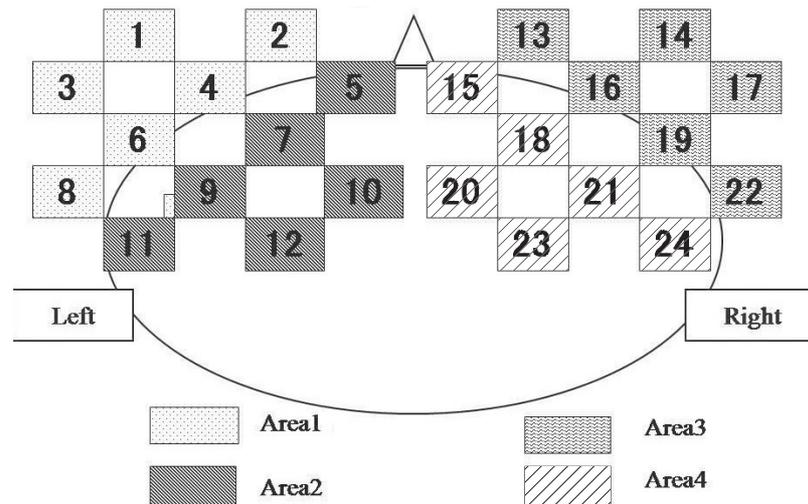


Figure 1. The optodes over the bilateral frontal region measured the relative changes in oxy Hb and deoxyHb concentrations at 12 measurement points within a 6 × 6-cm area of the left and right hemispheres.

each area (Area1, Area2, Area3 and Area4) was calculated in each subject. Data concerning changes in OxyHb concentrations were analyzed with three way analysis of variance (ANOVA). The following variables were used: (i) “diagnosis” (control and schizophrenia), (ii) “task condition” (kana congruent and kana incongruent, or kanji congruent and kanji incongruent), and (iii) “area” (Areas 1, 2, 3, and 4). The Huynh-Feldt procedure was used to correct the degrees of freedom where necessary. Student’s t-test was used to compare behavioral and demographic data (age, education, JART, task performance). For the schizophrenia patient group, Spearman’s correlation coefficients were calculated to determine the relationship between changes in oxyHb concentration and the dose of antipsychotic medication, task performance, and PANSS score.

## RESULTS

There was no significant difference between groups in the number of years of education (controls:  $14.6 \pm 2.4$ ; patients:  $14.4 \pm 1.9$ ;  $t=0.261$ ,  $df=26$ ,  $p>0.05$ ). However, a significant difference in the JART scores was observed between the two groups (controls:  $103.6 \pm 6.9$ ; patients:  $95.9 \pm 9.6$ ;  $t=2.419$ ,  $df=26$ ,  $p<0.05$ ).

### Stroop performance

There was no significant difference between groups in the performance of the kana congruent task (control:  $64.14 \pm 15.0$ ; patients:  $63.0 \pm 9.2$ ;  $t=0.228$ ,  $df=26$ ,  $p>0.05$ ), the kana incongruent task

(control:  $36.79 \pm 8.5$ ; patients:  $31.43 \pm 8.0$ ;  $t=1.718$ ,  $df=26$ ,  $p>0.05$ ), or the kanji congruent task (control:  $50.93 \pm 11.6$ ; patients:  $48.29 \pm 7.2$ ;  $t=0.725$ ,  $df=26$ ,  $p>0.05$ ). In the kanji incongruent condition, however, controls gave more correct responses than the schizophrenia patients (control:  $37.71 \pm 5.7$ ; patients:  $32.21 \pm 6.8$ ;  $t=2.326$ ,  $df=26$ ,  $p<0.05$ ). For both the control group and the schizophrenia patient group, within-subject comparisons using paired t-tests showed that the Stroop effect was significant in the kana condition (controls:  $t=7.117$ ,  $df=13$ ,  $p<0.01$ ; patients:  $t=9.77$ ,  $df=13$ ,  $p<0.01$ ), as indicated by a lower number of correct responses in the incongruent condition (controls:  $36.8 \pm 8.5$ ; patients:  $31.4 \pm 8.0$ ) than in the congruent condition (controls:  $64.1 \pm 15.0$ ; patients:  $63.1 \pm 9.2$ ). A significant Stroop effect was also observed in the kanji Stroop task (controls:  $t=5.404$ ,  $df=13$ ,  $p<0.01$ ; patients:  $t=8.075$ ,  $df=13$ ,  $p<0.01$ ), as indicated by a lower number of correct response in the incongruent condition (controls:  $37.8 \pm 5.7$ ; patients:  $32.2 \pm 6.8$ ) than in the congruent condition (controls:  $50.9 \pm 11.6$ ; patients:  $48.3 \pm 7.2$ ).

### NIRS data

No significant correlation was found between the JART score and the change in oxyHb concentration during any of the four task conditions for controls or schizophrenia patients (Spearman correlation, kana congruent:  $p=0.25$ ; kana incongruent:  $p=0.13$ ; kanji congruent:  $p=0.84$ ; kanji incongruent:  $p=0.41$ ). No significant correlation was found between the change in oxyHb concentration during any of the four task conditions and task performance

(Spearman correlation, kana congruent :  $p=0.26$  ; kana incongruent :  $p=0.28$  ; kanji congruent :  $p=0.95$  ; kanji incongruent :  $p=0.68$ ).

For the kana Stroop task, the  $2 \times 2 \times 4$  repeated ANOVA for changes in oxyHb concentration revealed a significant main effect for the variable ‘diagnosis’ ( $F=5.243, df=1, p<0.05$ ) and the variable ‘task’ ( $F=12.228, df=1, p<0.05$ ). (Table 1, Figure 2). No significant main effect was found for the variable ‘area’ ( $F=1.544, df=3, p>0.05$ ). The post-hoc analysis using Bonferroni’s connection revealed that Schizophrenia patients showed a significantly less pronounced increase in oxyHb concentration than controls ( $F=25.349, df=1, p<0.01$ ). With respect to the ‘task’ there are significant differences between oxyHb concentrations in the kana congruent and in the kana incongruent condition. (kana congruent < kana incongruent,  $F=20.329, df=1, p<0.01$ ). The interactions ‘task  $\times$  diagnosis’ ( $F=5.855, df=1, p<0.01$ ), ‘area  $\times$  diagnosis’ ( $F=3.063, df=3, p<0.05$ ), ‘task  $\times$  area’ ( $F=6.541, df=3, p<0.01$ ), and ‘task  $\times$  area  $\times$  diagnosis’ ( $F=4.046, df=3, p<0.05$ ) were significant. The post-hoc analysis revealed that schizophrenia patients showed a significantly smaller increase in oxyHb concentration than the controls during the kana incongruent condition ( $F=33.249, df=1, p<0.01$ ). The post-hoc analysis revealed that schizophrenia patients controls showed a significantly smaller increase in area1,2 and 3 than controls (area1 ;  $F=9.505, df=1, p<0.01$ , area2 ;  $F=$

4.518,  $df=1, p<0.05$ , area3 ;  $F=12.799, df=1, p<0.01$ ), but there were no significant differences between controls and schizophrenia patients in area4 ( $F=1.648, df=1, p>0.05$ ).

For the kanji Stroop task, the  $2 \times 2 \times 4$  repeated ANOVA for changes in oxyHb concentration revealed no significant main effect for the variable ‘diagnosis’ ( $F=0.658, df=1, p>0.05$ ) (Table 1). No significant main effect was found for the variable ‘task’ ( $F=0.143, df=1, p>0.05$ ) or ‘area’ ( $F=1.048, df=2.356, p>0.05$ ). The interactions ‘task  $\times$  diagnosis’ ( $F=0.003, df=1, p>0.05$ ), ‘area  $\times$  diagnosis’ ( $F=0.975, df=2.356, p>0.05$ ), ‘task  $\times$  area’ ( $F=0.996, df=3, p>0.05$ ), and ‘task  $\times$  area  $\times$  diagnosis’ ( $F=1.116, df=3, p>0.05$ ) were not significant.

In the schizophrenia patient group, no significant correlation was found between the change in oxyHb concentration and the dose of antipsychotic medication under any of the four task conditions (Spearman correlation, kana congruent :  $r=-0.101, p>0.05$  ; kana incongruent :  $r=0.779, p>0.05$  ; kanji congruent :  $r=0.316, p>0.05$  ; kanji incongruent :  $r=0.348, p>0.05$ ). No significant correlation was found between the PANSS score and the change in oxyHb concentration under any of the four task conditions for schizophrenia patients (Spearman correlation, kana congruent :  $r=-0.307, p>0.05$  ; kana incongruent :  $r=-0.231, p>0.05$  ; kanji congruent :  $r=-0.312, p>0.05$  ; kanji incongruent :  $r=-0.511, p>0.05$ ).

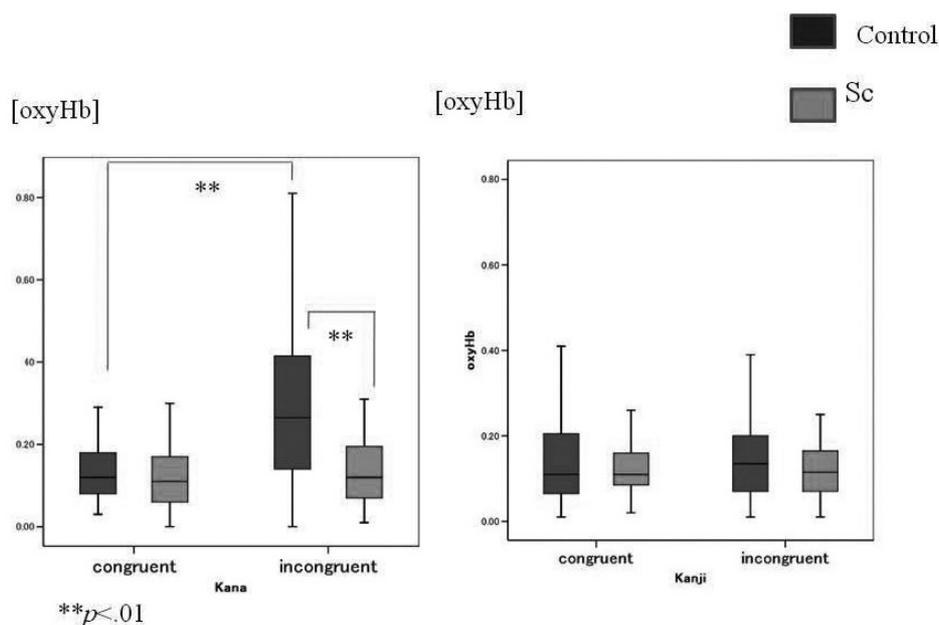


Figure 2. Left : the kana Stroop task. Right : the kanji Stroop task. Schizophrenia patients showed reduced activation in the prefrontal cortex compared to healthy controls during performance of the kana version of the Stroop task, but not during performance of the kanji version of the Stroop task.

## DISCUSSION

Regarding performance, there was no significant difference between schizophrenia patients and controls in the performance of the kana congruent, the kana incongruent, or kanji congruent tasks. Under the kanji incongruent condition, the controls gave more correct responses than the schizophrenia patients. This result is compatible with those of previous studies (26, 27), where a kanji Stroop task employing a mixture of congruent and incongruent tasks was used.

We examined activation patterns in the prefrontal cortex during performance of a kana and a kanji version of the Stroop task. Ehlis *et al.* used the Stroop task in a NIRS study of the left frontal area, and demonstrated specific activation of left inferior-frontal regions in response to the Stroop interference condition (16). In the present study, increased activation was observed in the bilateral frontal cortex of healthy control subjects during performance of the kana Stroop task.

We also found that schizophrenia patients showed reduced activation in the prefrontal cortex compared with age- and sex-matched healthy controls during performance of the kana Stroop task. It has been suggested that differences in task performance may be a confounding factor in studies of schizophrenia. Several studies have reported that schizophrenia patients perform poorly in the alphabet or kanji Stroop task in comparison to healthy controls (4, 21, 28). In the present study, we observed no significant differences between healthy subjects and schizophrenia patients in performance of the kana Stroop task, probably because the patients were mild cases with relatively high levels of intelligence who were receiving maintenance treatment. Our results suggest that there were significant differences between the bilateral frontal lobes of the schizophrenia patients and those of the controls, even though no differences in task performance were observed.

Pervious neuroimaging studies have reported that schizophrenia patients show altered brain activation during performance of the Stroop task (3, 4, 13). Using a [<sup>15</sup>O] H<sub>2</sub>O positron emission tomography (PET) approach, Carter *et al.* demonstrated failure of activation of the anterior cingulate gyrus in schizophrenia patients during a single-trial Stroop task (13). In a PET study, Yücel *et al.* found that activation occurred in both the limbic and the paralimbic anterior cingulate regions in healthy subjects during performance of the Stroop task, but that activation

only occurred in the paralimbic region in schizophrenia patients (3). A fMRI study by Weiss *et al.* reported reduced activation in the dorsolateral prefrontal, the anterior cingulate, and the parietal regions in schizophrenia patients compared to healthy controls during performance of a modified Stroop task (4). The results of the present NIRS study are consistent with those of the fMRI study of Weiss *et al.* NIRS studies that have used alternative attention and executive tasks have reported hypofrontality in schizophrenia patients (18, 20). The present results are also consistent with other NIRS studies using a different task. Ehlis *et al.* studied the left frontal area with NIRS and found significantly reduced activation in schizophrenia patients compared with healthy controls during performance of two verbal fluency tasks (18). Likewise, using 52-channel NIRS, Takizawa *et al.* demonstrated that schizophrenia patients had a slower and less pronounced increase in the bilateral prefrontal activation than healthy controls during performance of a verbal fluency task (20). We found a significant difference in OxyHb concentrations between schizophrenia patients and controls during performance of only kana but not kanji Stroop task. No differences in oxyHb concentration between control and patients during the performance of the kanji Stroop task are consistent with previous studies that used the kanji Stroop task (26, 27). The greater reduction of the number of correct answer in kana than kanji Stroop task suggests that the kana Stroop task may require more inhibition not to read kana letters. Schizophrenia patients may have decreased prefrontal vascular reactivity associated with the inhibition required during the performance of the kana Stroop task.

The results of the present study should be interpreted with caution. The sample size was small and there were an unequal number of male and female subjects. Since men and women may have a different lateralization pattern, further studies are needed to examine differences of lateralization pattern between female and male subjects. The decreased activation observed during the kana Stroop task in schizophrenia patients in the present study was therefore unlikely to have been due to a hyperperfusion state at pre-task baseline. It is also possible that antipsychotic medication may have had an influence on our findings, although no significant correlation was found between the mean of the peak change in oxyHb concentration and antipsychotic dosages during any of the four Stroop task conditions. In the present study, a significant

difference in the JART scores was also observed between the two groups. It is also possible that the differences in intelligence estimated by JART may have influenced our findings, although no significant correlation was found between the mean of the peak change in oxyHb concentration and the JART score.

In contrast to the kana Stroop test, no increase in activation occurred during performance of the kanji incongruent task compared with the kanji congruent task in either controls or schizophrenia patients. Yamada *et al.* have established that the kanji script has a much stronger connection to semantics than to phonology (29), and thus less interference occurs with use of the kanji Stroop task than with the kana version. It is possible that activation of increased blood flow is not necessary for performance of the kanji incongruent Stroop task.

In summary, the change in oxyHb concentration during performance of the Stroop task was significantly less in schizophrenia patients than in healthy control subjects. The results of the present study suggest the existence of prefrontal dysfunction in patients with schizophrenia.

## CONFLICT OF INTEREST

None of the authors have any conflicts of interest to declare.

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