Cerebrovascular Response to Cognitive Tasks in Patients With Schizophrenia Measured by Near-Infrared Spectroscopy

by Akira Watanabe and Tadafumi Kato

Abstract

We assessed the cerebral hemoglobin oxygenation response in the left frontal area in 62 schizophrenia patients and 31 healthy subjects during a verbal fluency test (VF) and letter number span test (LN) measured by near-infrared spectroscopy (NIRS). Oxygenated hemoglobin (oxyHb) increased during VF and LN in both groups. Schizophrenia patients showed lower VF and LN performance and a smaller increase in oxyHb during VF than controls. A reduced oxyHb response during VF in schizophrenia patients was also observed even when their VF performance was matched with controls' performance. On the other hand, increase in oxyHb during LN in schizophrenia patients was comparable with that in controls. In addition, patients medicated with atypical antipsychotics showed a larger increase in oxyHb during VF and LN than those medicated with typical antipsychotics. The present study confirmed functional hypofrontality in schizophrenia patients reported by other modalities such as position emission tomography, single-photon emission tomography, and functional magnetic resonance imaging, the number of patients, between 10 and 20, was not large enough. These conventional imaging instruments have difficulties in measuring a large number of subjects using multiple tasks, because of radiation exposure, restriction of the place of measurement, or susceptibility of motion artifact.

NIRS is a new noninvasive optical method that can measure the change in oxyHb and deoxygenated hemoglobin (deoxyHb). In 1977, Jobsis (1977) successfully detected near-infrared light penetrating the human head and observed how the intensity of the detected light was influenced by respiration. Near-infrared lights admitted into the head from emitter probes are detected by the neighboring detector probes after repeatedly being scattered and partly absorbed. OxyHb and deoxyHb have different absorption spectra; therefore, concentrations of oxyHb and deoxyHb can be obtained by using the Lambert-Beer law formula (Koizumi et al. 1999; Madsen and Secher 1999). Because near-infrared light absorbed by the skull and skin is different among the subjects, absolute oxyHb and deoxyHb values cannot be obtained, but relative values compared with the values at the beginning of measurement can be obtained. However, several studies showed that NIRS could measure cerebral blood volume and cerebral oxygenation during cognitive tasks, repeatedly, conventionally, and

Keywords: Near-Infrared spectroscopy, verbal fluency test, letter number span test, working memory, hypofrontality, atypical antipsychotics.


Recently, functional hypofrontality—that is, reduced activation of the frontal lobe during cognitive tasks—has been one of the most consistent findings in neuroimaging studies of schizophrenia (Weinberger et al. 1986; Riehemann et al. 2001; Penades et al. 2002). However, its clinical significance has not been established, possibly because functional hypofrontality can be influenced by many clinical factors, such as psychological condition (Hawton et al. 1990; Spence et al. 1998; Erkwoh et al. 1999; Chen et al. 2000) and antipsychotic treatment (Bartlett et al. 1991; Honey et al. 1999; Miller et al. 2001). In addition, task performance was not controlled in most previous studies, which raised the question that these findings reflected only the reduced motivation in schizophrenia. To clarify the clinical significance of functional hypofrontality while controlling for these confounding factors, a large number of schizophrenia patients had to be examined. However, in most previous studies with positron emission tomography, single-photon emission tomography, and functional magnetic resonance imaging, the number of patients, between 10 and 20, was not large enough. These conventional imaging instruments have difficulties in measuring a large number of subjects using multiple tasks, because of radiation exposure, restriction of the place of measurement, or susceptibility of motion artifact.

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safely (Hoshi and Tamura 1993; Fallgatter et al. 1998; Fallgatter and Strik 1998).

In the present study, we hypothesized that functional hypofrontality is influenced by factors such as symptoms, effects of drugs, performance of task, and type of task. To verify these points, we measured the oxyHb and deoxyHb during the verbal fluency test (VF; Benton 1968) and letter number span test (LN; Gold et al. 1997) with one-channel NIRS in a large number of schizophrenia patients and assessed the relationship among the symptoms, antipsychotics, antiparkinsonian drugs, and performance of the task.

Methods

Subjects. We enrolled 62 (32 females and 30 males) schizophrenia patients and 31 (15 females and 16 males) healthy subjects, who had no general medical disease, substance abuse, or head injury. The age of patients and controls was 40.1 ± 12.3 (mean ± standard deviation [SD]) and 36.1 ± 11.6 years, respectively, and duration of education of patients and controls was 12.9 ± 2.0 and 13.6 ± 1.8 years, respectively. There were no significant differences between the two groups in age, gender, and duration of education. All were right-handed according to the results of the Annett’s scale (cutoff < 0.8) (Annett 1967). Patients were recruited from inpatients and outpatients of Kawaguchi Hospital and were diagnosed as having schizophrenia (34 paranoid, 16 disorganized, and 12 undifferentiated type) according to DSM-IV criteria (APA 1994). The psychotic symptoms were assessed by the Positive and Negative Syndrome Scale (PANSS) (Kay et al. 1987), and the positive, negative, and general psychopathology scales were 15.1 ± 7.1 (mean ± SD), 20.6 ± 8.4, and 35.4 ± 12.5, respectively. All patients were medicated with antipsychotics at the examination (29 atypical and 33 typical antipsychotics), and the dosage was 619 ± 479 mg/day (chlorpromazine equivalent; Inagaki et al. 1999). Forty-five of 62 patients were medicated with antiparkinsonian drugs, and the dosage was 2.8 ± 2.5 mg/day (biperiden equivalent; Inagaki et al. 1999). The duration of illness was 154 ± 132 months. All subjects gave written informed consent before participating in the present study. The present study was approved by the ethics committee of Kawaguchi Hospital.

VF. In VF, the subjects were asked to generate and speak as many words as possible beginning with a specified letter for 1 minute. VF required strategic retrieval and access to phonologic and orthographic information; therefore, it was reported to activate the frontal lobe (Elfgren and Risberg 1998). The number of words generated in 1 minute was used as the score for this task.

LN. In LN, the tester read a mixed series of alternating numbers and letters. The subjects were asked to answer first numbers in correct numerical order, and then the letters in correct alphabetical order. For example, the answer of the question “c5a2” is “25ac.” The test consisted of four trials at each string length, from two digits (one letter and one number, such as “e5”) to seven digits (three letters and four numbers, such as “d7a2e9”). When the subjects incorrectly answered all four trials in the same string length, the test was ended. LN required storage and processing of information; therefore, it was reported as the task of working memory (Gold et al. 1997). The number of correct answers was used as the score for this task.

NIRS. For NIRS measurement, a one-channel portable NIRS system, the HEO–200 instrument (Omron Ltd. Inc., Tokyo, Japan), was used. Chance et al. (1992) and Shiga et al. (1995) described the principle and formula of this instrument. The NIRS system measured the intensity of light detected at two wavelengths (760 nm and 850 nm) and calculated the change of optical density (optical density = −log [detected light intensity/emitted light intensity]), and then calculated the change of oxyHb and deoxyHb (ΔoxyHb = A*ΔOD760 [change of optical density at 760 nm] + B*ΔOD850 [change of optical density at 850 nm], ΔdeoxyHb = C*ΔOD760 + D*ΔOD850). The coefficients A, B, C, and D were assumed to be constant. Briefly, the subject’s forehead was cleaned with alcohol, and the probes were set so that the midpoint between the emission and detection probes was 3 cm above the center of the upper edge of the orbital socket with a flexible and adhesive fixation pad and an elastic band. This positioning was similar to the midpoint between the Fp1 and Fp3 positions according to the ten-twenty electrode system. The brain region measured by this positioning roughly corresponded to the dorsolateral prefrontal cortex. The distance between the probes was set at 4 cm, and the time resolution was 0.5 seconds. Two parameters, oxyHb and deoxyHb, were examined.

Statistical Analyses. At first, oxyHb and deoxyHb values during VF or LN were compensated by the averaged values of 0 to 15 seconds before VF or LN, respectively (i.e., the compensated values of oxyHb during VF = the values of oxyHb during VF – averaged oxyHb value of 0 to 15 seconds before VF). We adopted the variables for analysis as follows:

- VF pre[Hb (Hb = oxyHb or deoxyHb)] = 0 (baseline of VF)
- n/4[Hb] (n = 1, 2, 3, or 4) = [averaged Hb value in the nth quarter of VF]
- VF post[Hb] = [averaged Hb value 0 to 15 seconds after VF]
One-Channel NIRS of Cognitive Tasks in Schizophrenia


LN pre[\text{Hb}] = 0 \text{ (baseline of LN)}
\[ n \text{ digit}[\text{Hb}] (n = 2, 3, \text{ or } 4) = \text{[averaged Hb value in the LN } n \text{ digit]} \]
Because 22 of 62 (35%) patients could not reach five digits, we did not analyze the data of five digit, six digit, seven digit, and after LN. In addition, we excluded subjects (nine patients) who did not reach four digit, for LN analysis. To assess the differences between schizophrenia patients and controls, and patients medicated with atypical antipsychotics (atypical) and patients medicated with typical antipsychotics (typical), we analyzed the data by two-way (2 group [schizophrenia vs. control, or atypical vs. typical] \times 6 \text{ task} [VF pre, 1/4, 2/4, 3/4, 4/4, and VF post]) repeated measures analysis of variance (RMANOVA) in VF and two-way (2 group \times 4 \text{ task} [LN pre, two digit, three digit, and four digit]) RMANOVA in LN. When there was a significant main effect of task and significant interaction of group \times \text{task in RMANOVA}, we performed a \text{t} \text{ test between each variable to verify the differences between the groups as the post hoc test. We calculated Pearson’s correlation coefficients for the performance of VF and LN, the oxyHb or deoxyHb (3/4 [Hb], 4/4 [Hb], three digit [Hb], and four digit [Hb]), the PANSS score, the dosage of antipsychotics and antiparkinsonian drugs, duration of illness, education, and age. In addition, we performed a \text{t} \text{ test and } \chi^2 \text{ test to assess the differences in the profile (age, gender, education, VF score, and LN score). We considered } p < 0.05 \text{ as statistically significant for RMANOVA and } \text{t} \text{ test, and } p < 0.005 \text{ as statistically significant for Pearson’s correlation coefficients.}

Results

VF and LN Scores. The VF score of patients (7.4 ± 4.0) was significantly lower \((p < 0.001, \text{t} \text{ test})\) than that of controls (11.4 ± 4.3). The distribution of the answers across the task was not different between the two groups, although a statistical analysis could not be performed. In addition, the LN score of patients (9.1 ± 4.2) was significantly lower \((p < 0.001, \text{t} \text{ test})\) than that of controls (14.3 ± 2.0).

Statistical Analysis of VF Response. The change in oxyHb and deoxyHb during the tasks is shown in figure 1. In controls, oxyHb increased and deoxyHb decreased throughout the task. These values returned to the “pre” levels 15 to 30 seconds after the task (data not shown). On the other hand, the increase of oxyHb appeared to be stopped after 30 seconds in the schizophrenia group. The variables in each section are shown in figure 2. There was a significant main effect of task (oxyHb: F[5, 455] = 27.8, \( p < 0.001 \), deoxyHb: F[5, 455] = 37.4, \( p < 0.001 \)) and a significant interaction of group \times \text{task (oxyHb: F[5, 455] = 6.93, } p < 0.001 \), deoxyHb: F[5, 455] = 4.29, \( p < 0.001 \)) in oxyHb and deoxyHb (RMANOVA). There were significant differences between the two \((p < 0.05, \text{t} \text{ test})\) throughout VF for both oxyHb and deoxyHb, except for no significant difference in 2/4[deoxyHb]. This showed that oxyHb increased and deoxyHb decreased during VF in both groups, and that the increase in oxyHb and decrease in deoxyHb in schizophrenia patients was smaller than those in controls.

In the present study, the range of performance of schizophrenia patients and controls was 0 to 15, and 5 to 25, respectively. Therefore, we selected the subjects whose performance of VF was between 5 to 15 to match the VF score. Forty-five (25 females and 20 males) schizophrenia patients and 26 (15 females and 11 males) controls met the criterion. The mean age of patients and controls was 40.2 ± 13.2 and 36.9 ± 12.4 years, respectively. The mean VF score of patients and controls was 9.4 ± 3.2 and 10.1 ± 2.9, respectively. The time course of the oxyHb or deoxyHb in these subjects was similar to the curve shown in figure 2, in which the frontal activation leveled out after 30 seconds. There was no significant difference between the two groups in age, gender, or VF score. There was a significant main effect of task (F[5, 345] = 21.0, \( p < 0.001 \)) and a significant interaction of group \times \text{task (F[5, 345] = 2.92, } p < 0.05 \) in oxyHb (RMANOVA). On the other hand, there was a significant main effect of task (F[5, 345] = 31.6, \( p < 0.001 \)) and a similar trend of interaction of group \times \text{task (F[5, 345] = 1.89, } p < 0.1 \) in deoxyHb (RMANOVA). There were significant differences between the two in 1/4[oxyHb] \((p < 0.05, \text{t} \text{ test}), 4/4[oxyHb] (p < 0.05), \text{VF post}[oxyHb] (p < 0.05). These results argued against the hypothesis that hypofrontality is due to poor task performance.

Pattern Characterization. Although these statistical analyses appear to imply that a decreased response to VF is a common feature of schizophrenia patients, the raw data suggest that this is not true. While oxyHb increased during VF from the beginning to the end (“regular pattern,” figure 1-1) in general, some patients showed an “irregular pattern” (figure 1-2), characterized by lack of increase during VF, delayed increase, or start of decrease during VF. To examine these irregular pattern patients, the patients were classified into four groups based on whether they showed a significant increase in oxyHb at the first quarter or fourth quarter of VF compared with 0 to 15 seconds before VF, as shown in table 1. The frequency of the four patterns significantly differed between schizophrenia patients and controls (\( \chi^2 = 7.96, \ p < 0.05 \), \( \chi^2 \text{ test} \). Patients with the regular pattern showing an increase during VF from the beginning to the end (“regular pattern,” figure 1-1) in general, some patients showed an increase in oxyHb and decrease in deoxyHb compared with controls (group \times \text{task interaction; oxyHb: F}[5, 265]
Note.—deoxyHb = deoxygenated hemoglobin; LN = letter number span test; oxyHb = oxygenated hemoglobin; VF = verbal fluency test.

1 Ordinate represents tasks (VF and LN) and abscissa hemoglobin concentration (mM/mm). (A) Control (figure 1A, 25-year-old female) shows an increase in oxyHb and decrease in deoxyHb ("regular pattern") during VF and LN. (B) The schizophrenia patient (figure 1B, 27-year-old female) shows a decrease in oxyHb and increase in deoxyHb ("irregular pattern") during VF and LN.
Figure 2. Averaged values of oxyHb and deoxyHb

Figure 2. The averaged values of oxyHb and deoxyHb

Note.—ANOVA = analysis of variance; deoxyHb = deoxygenated hemoglobin; LN = letter number span test; ns = nonsignificant; oxyHb = oxygenated hemoglobin; VF = verbal fluency test.

1 Ordinate represents tasks (VF and LN), and abscissa averaged values of oxyHb and deoxyHb (mM mm). The values of oxyHb and deoxyHb during VF were analyzed by dividing the time course of the experiment into six periods, VF pre (0 to 15 seconds before VF), 1/4 (first quarter of VF), 2/4 (second quarter of VF), 3/4 (third quarter of VF), 4/4 (fourth quarter of VF), and VF post (0 to 15 sec after VF). LN was divided into four periods, LN pre (0 to 15 sec before LN), two digit, three digit, and four digit. The numbers of subjects who reached each digit are shown above the marker of LN. Schizophrenia patients showed a smaller increase in oxyHb and decrease in deoxyHb during VF than controls (group × task interaction; oxyHb: F[5, 455] = 6.93, p < 0.001, deoxyHb: F[5, 455] = 4.29, p < 0.001, two-way repeated measures ANOVA). On the other hand, patients showed an increase in oxyHb during LN similar to controls (group × task interaction: F[3, 246] = 0.981, ns) but patients showed a smaller decrease in deoxyHb than controls (group × task interaction: F[3, 246] = 3.47, p < 0.05).

*p < 0.05, **p < 0.01, ***p < 0.001 between patients and controls by t test

# Significant interaction (p < 0.05) of group × task by two-way repeated measures ANOVA

Table 1. Classification of change in oxyHb during VF

<table>
<thead>
<tr>
<th>Pattern</th>
<th>1/4 vs. pre</th>
<th>4/4 vs. pre</th>
<th>Controls (%)</th>
<th>Schizophrenia (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular pattern</td>
<td>Increase</td>
<td>Increase</td>
<td>21 (68)</td>
<td>24 (39)</td>
</tr>
<tr>
<td>Irregular pattern</td>
<td>Increase</td>
<td>No increase</td>
<td>0 (0)</td>
<td>4 (6)</td>
</tr>
<tr>
<td></td>
<td>No increase</td>
<td>Increase</td>
<td>2 (6)</td>
<td>5 (8)</td>
</tr>
<tr>
<td></td>
<td>No increase</td>
<td>No increase</td>
<td>8 (28)</td>
<td>29 (47)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>31</td>
<td>62</td>
</tr>
</tbody>
</table>

Note.—oxyHb = oxygenated hemoglobin; VF = verbal fluency test.

1 The frequency of the four patterns significantly differed between patients and controls (p < 0.05, χ² test). Increase: oxyHb value 0 to 15 seconds before VF was significantly smaller (p < 0.05, t test) than that in first quarter of VF or fourth quarter of VF.
Effects of Antipsychotics. To examine the effects of antipsychotics on the cerebral hemodynamics, the patients were divided into two groups, those medicated with atypical antipsychotics and those medicated with typical antipsychotics. However, in the present study, the age range of patients with atypical antipsychotics and those with typical antipsychotics was 18 to 57, and 30 to 60 years, respectively. Therefore, we selected the subjects who were older than 30 and compared NIRS variables between the groups. We compared the 23 (12 females and 11 males) patients medicated with atypical antipsychotics (atypical) and 29 (10 females and 19 males) patients medicated with typical antipsychotics (typical). There was no significant difference of chlorpromazine equivalent dosage of antipsychotics (Inageki et al. 1999) between the two groups (atypical: 551 ± 335, typical: 732 ± 114 mg/day). There were no significant differences between atypical and typical in age, gender, duration of education, duration of illness, PANSS score, the dosage of antipsychotics and antiparkinsonian drugs, duration of illness, education, and age. The LN score was correlated with positive (r = -0.390, p < 0.001), negative (r = -0.565, p < 0.001), general psychopathology scale (r = -0.464, p < 0.001), duration of illness (r = -0.382, p = 0.001), education (r = 0.432, p < 0.001), and age (r = -0.411, p < 0.001), respectively. There were no significant correlations between the VF score or the LN score and change in oxyHb or deoxyHb.

Discussion

In the present study, we found that (1) oxyHb increased during VF and LN in schizophrenia patients and controls; (2) the increase in oxyHb and decrease in deoxyHb during VF in schizophrenia patients were smaller than those in controls; (3) hypofrontality during VF, assessed by the smaller increase in oxyHb, was confirmed in schizophrenia patients matched for performance of VF; (4) patients medicated with atypical antipsychotics showed a larger increase in oxyHb and similar decrease in deoxyHb during VF and LN compared with those medicated with typical antipsychotics; (5) a larger number of patients showed an irregular pattern compared with controls; (6) patients with the regular pattern showed no hypofrontality and showed a higher VF performance than those with the irregular pattern; and (7) LN caused a similar increase in oxyHb and smaller
The finding that oxyHb increased and deoxyHb decreased during VF and LN in controls was in accordance with previous studies (Frith et al. 1991; Fallgatter et al. 1997; Elfgren and Risberg 1998; Audenaert et al. 2000; Haut et al. 2000). Several studies showed that schizophrenia patients showed lower performance and hypofrontality during VF (Frith et al. 1995; Scottish Schizophrenia Research Group 1998; Curtis et al. 1998, 1999). However, the results in patients whose performance of VF was matched with controls were controversial (Frith et al. 1995; Curtis et al. 1999). The present study showed that schizophrenia patients showed a significantly smaller increase in oxyHb and a trend of smaller decrease in deoxyHb than controls matched for VF score. The present study in a larger scale clarified that hypofrontality, assessed by the smaller increase in oxyHb, was seen in schizophrenia patients even when their performance matched controls, and it suggested that the previous controversy may have been caused by the diversity of cerebrovascular response in schizophrenia patients.

The finding that patients medicated with atypical antipsychotics showed a larger increase in oxyHb than those medicated with typical antipsychotics suggested the possibility that atypical antipsychotics improved the cerebrovascular response. However, other possibilities—that typical antipsychotics impaired the response, or that there was selection bias of the patients—cannot be excluded. The present findings were in agreement with previous
studies (Honey et al. 1999; Miller et al. 2001). In contrast, a decrease in deoxyHb in both groups showed a similar trend. The reason for this difference in the change between oxyHb and deoxyHb was unclear. In addition, lack of randomization of the two groups may have affected the present result. Further studies are needed to clarify the relationship between oxyHb and deoxyHb and the effects of antipsychotics on the cerebrovascular response.

Cerebral vasodilatation caused by cerebral neuronal activation far exceeds oxygen consumption (Fox and Raichle 1986). Therefore, cerebral neuronal activation usually causes an increase in oxyHb and decrease in deoxyHb. However, Hoshi et al. (1994) showed that some healthy subjects showed an irregular pattern—that is, a decrease in cerebral blood volume in the frontal lobe during problem solving and mental arithmetic using NIRS and positron emission tomography. Okada et al. (1994) also showed that 13 of 22 schizophrenia patients showed an irregular pattern (3 with no response and 10 with a decreased pattern) during the Mirror Drawing Task, while no controls showed this. In the present study, the frequency of the irregular pattern in patients (38/62, 61%) was higher than that in controls (10/31, 32%). In addition, the patients with a regular pattern showed an equivalent increase in oxyHb during VF to controls, and higher performance of VF than those with the irregular pattern. This suggested the validity of the subgrouping of patients into those with hypofrontality and those without hypofrontality. Further studies are needed to clarify the validity of the subgrouping.

The present study was limited because the region measured was at most 4 cm × 4 cm in the left frontal lobe and oxyHb and deoxyHb were relative values influenced by optical path length. Therefore, the possibility that we measured different regions between schizophrenia patients and controls and that optical path length was different between the two cannot be ruled out. In addition, we could not clarify the response in other regions that we did not measure in the present study.

The finding that patients showed an increase in oxyHb to the same extent as controls during LN suggested that hypofrontality may be task dependent, in accordance with the study of Curtis et al. (1998). This may suggest that cerebral vasodilatation induced by neuronal activation may be intact in schizophrenia patients. However, the decrease in deoxyHb in schizophrenia patients was significantly smaller than that in controls in LN, and LN activated the orbital prefrontal and dorsolateral prefrontal cortex, mainly in the right hemisphere (Haut et al. 2000). Therefore, the possibility that schizophrenia patients showed a smaller increase in oxyHb in other frontal regions during LN than controls cannot be ruled out. Further studies measuring the bilateral frontal lobe during LN are needed.

In the present study, we demonstrated that hypofrontality is explicit in schizophrenia patients. However, the neurobiological basis and pathophysiological significance of hypofrontality are controversial. Several studies showed that hypofrontality was found in antipsychotic-naive first episode schizophrenia (Andreasen et al. 1992), suggesting that it is a trait-dependent finding. On the other hand, hypofrontality was influenced by psychological condition (Hawton et al. 1990; Spence et al. 1998; Erkwoh et al. 1999; Chen et al. 2000), neuropsychological rehabilitation (Penades et al. 2002), and antipsychotic therapy (Bartlett et al. 1991; Honey et al. 1999; Miller et al. 2001), suggesting that it is a state marker. To resolve the question of whether hypofrontality is a state marker or a trait marker, many patients should be longitudinally followed up in their course of illness. Because NIRS could measure the cerebrovascular response repeatedly, conventionally, and safely, NIRS was useful in this effort.

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