Eur Arch Psychiatry Clin Neurosci (1994) 244:17–25

ORIGINAL PAPER

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Impaired interhemispheric integration in brain oxygenation and hemodynamics in schizophrenia

Received: 12 December 1993 / Accepted: 2 February 1994

Abstract We examined 38 patients with chronic schizophrenia to find and qualify disturbances in interhemispheric integration in brain oxygen metabolism and hemodynamics during a psychological task. A group of thirty-eight age- and sex-matched healthy volunteers were monitored as controls. Multi channel near-infrared (NIR) spectrophotometry was used to observe real-time alterations in cerebral oxygenation in areas of both hemispheres of the forebrain adjacent to the forehead during the mirror drawing task (MDT). In response to MDT normal volunteers showed distinct and well-integrated patterns of changes in oxygenated hemoglobin Hb, deoxygenated Hb, and blood volume total Hb. On the other hand, half the schizophrenics showed *dysregulated patterns* between hemispheres which never appeared in normal volunteers. Certain schizophrenic symptoms may be related to defective interhemispheric integration.

Key words Impaired interhemispheric integration
Brain oxygenation · Hemodynamics · Schizophrenia

Introduction

Some symptoms of schizophrenia have been presumed to occur as a result of defects in functional connections between different regions of the brain (Beamont and Diamont 1973; Dimond et al. 1980). Evidence suggestive of poor connections between the hemispheres in schizophrenia has been well supported by structural callosal pathology. Two postmortem studies reported an increased thickness of the corpus callosum in schizophrenic patients compared to psychiatric controls (Rosenthal and Bigelow 1972; Bigelow et al. 1983). Furthermore, a gender-related increase of callosal thickness (Nasrallah et al. 1986) and a significantly greater anterior corpus callosum in schizophrenia (Uematsu and Kaiya 1988) have been reported using in vivo magnetic resonance imaging MRI technology.

On corresponding functional differences based on the reported structural differences, many reports from the past decade have cited visual (Beamont and Diamond 1973; Eaton et al. 1979), auditory (Green 1978; Green and Kotenko 1980) and tactile stimuli (Carr 1980; Dimond et al. 1980), and samotosensory-evoked potentials (Gulmann et al. 1982) as evidence of defective callosal transfer in schizophrenia. Some of these studies have suggested an association between disorders of cerebral laterality and schizophrenia and some results have indicated dysfunction in a single hemisphere, whereas in other studies, abnormal patterns of functional organization or impaired interhemispheric integration have been indicated.

The search for the brain organization or laterality imbalance in schizophrenia has been accompanied by a ceaseless development in neuroimaging techniques for measuring brain function. Positron emission tomography (PET), for example, is the most powerful method for noninvasive measurement of glucose utilization, oxygen consumption, and cerebral blood flow (CBF) (Sheppard et al. 1983; Gur et al. 1987), and has a wealth of meaningful data. However, within a short time (several seconds or less) metabolism becomes linked to the CBF in a complex manner closely related to the behavioral state. The lack of methods for simultaneous measurement of metabolic rate and CBF has, however, inhibited more precise elucidation of the dynamic coupling between these two phenomena. Therefore, continuous and real-time monitoring techniques are required to evaluate the dynamic features of the cerebral metabolic changes which occur during behavioral-state transitions.

The near-infrared (NIR) spectrophotometric technique, which was first introduced by Jöbsis (1977), has been ap-

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plied to noninvasive measurement of the oxygenation state of tissue hemoglobin (Hb), especially in the brain, under physiologic and pathologic conditions (Brazy et al. 1985; Wyatt et al. 1986; Wray et al. 1988; Onoe et al. 1991; Tamura 1991; Okada et al. 1993). The technique of NIR spectrophotometry makes possible Real-time monitoring of the oxygenation state of circulating Hb and of blood volume total Hb in brain tissue, both of which may be indicative of the oxygen-consumption rate.

We applied a multichannel NIR spectrophotometric technique to evaluate interhemispheric integration in the brain metabolism and hemodynamics of schizophrenic patients during the mirror drawing task (MDT). The main objective of the study was to clarify whether there is a laterality imbalance or impaired interhemispheric integration in schizophrenia.

Subjects and methods

The study included 38 inpatients with schizophrenia (22 males, mean age 30.8 years, range 20–49 years; 16 females, mean age 30.6 years, range 21–46 years). All met DSM-III-R criteria for chronic schizophrenia (American Psychiatric Association 1987). Subclassifications were 5 catatonic, 13 disorganized, 15 undifferentiated, and 5 residual. Considering the standard deviation SD, mean age at onset was 18.9 years (SD, 3.6 years), average number of hospitalizations was 4.4 (SD, 5.3), and average duration of illness was 11.7 years (SD, 6.6 years). All patients were receiving antipsychotic medication at the time of testing. Patients with movement disorders, such as tardive dyskinesia, were not included in this study. Healthy volunteers were recruited as controls (22 males, mean age 28.9 years, range 20–45 years; 16 females, mean age 30.4 years, range 21–44 years). Volunteers with significant physical and/or psychiatric illness, alcohol or drug abuse, and/or a history of major psychiatric disorder among first-degree relatives were not included. A group of 12 patients with alcohol hallucinosis undergoing treatment with neuroleptics (all male, mean age 48.7 years, range 35–54 years) were also investigated. On examination they were well treated and showed no such symptoms as hallucinations or delusions. All of the patients and normal volunteers were right-handed. The study was approved by the Ethical Committee for Health Administration Center, Hokkaido University, and informed consent was obtained from all.

NIR spectrophotometric measurements

Changes in the oxygenation state of Hb were measured according to the method of Hazeki and Tamura (1988). Two portable computer-controlled NIR monitors (Research and Development, Shimadzu Corporation, Kyoto, Japan) were used to illuminate the hemispheres of the subjects and to monitor the reflected NIR light. The light sources were laser diodes (wave length = 780, 805, and 830 nm). Each monitor mixed the light beams from its three diodes and directed them through a single optical fiber to an illuminating optrode (6-mm diameter) placed on the forehead 75 mm from the center line of the forehead. Each optrode was attached with a double-sided adhesive ring. The optrodes and pickups were embedded in a black foam rubber cover to prevent interference from external light. Each pickup (10 mm^2) was placed 35 mm inward from the illuminating optrode (40 mm laterally from the central line of the forehead). The light detected by each pickup was conveyed through another fiber bundle to a photomultiplier tube operating in photon counting mode.

Tamura et al. (1989) have described this technique in detail and derived formulas for calculating the relative amounts of oxygenated Hb [HbO_2] and deoxygenated Hb [Hb] from in vitro and in vivo studies with human red-blood-cell suspension. The authors also demonstrated a good signal/noise ratio and reproducibility together with a significant response of the apparatus. Scattering of the NIR light by the tissue causes some uncertainty in the path length traveled by the photons, but the combination of laser diodes that fire picosecond bursts of light with a clock which can measure such short intervals allows this instrument to eliminate reflected photons that have traveled further than a specified distance (Oda et al. 1994; Wilson et al. 1992). Thus, the depth of the region observed in very sharply defined, and photons scattered from one hemisphere to the other are prevented from interfering with the other measurement. With an optrode-pickup spacing of 3.5 cm, the maximum depth of the region is 4 cm (Oda et al. 1993; Wilson et al. 1992). The relative changes in oxy-, deoxy- and total Hb were calculated according to the following equations.

$$\Delta[HbO_2] = -3.0\,\Delta OD_{805} + 3.0\,\Delta OD_{830}$$

$$\Delta[Hb] = 1.6\,\Delta OD_{780} - 2.8\,\Delta OD_{805} + 1.2\,\Delta OD_{830}$$

$$\Delta[\text{Total Hb}] = \Delta[HbO_2] + \Delta[Hb]$$

This method does not furnish a determination of the absolute volume of oxygenated or deoxygenated Hb. The results are instead expressed in terms of relative changes in these quantities as observed by changes in absorbance of NIR radiation. The variations in HbO_2 and Hb are added in order to estimate the variations in total Hb concentrations. In the absence of major changes in the hematocrit, changes in total Hb are indications of alterations in cerebral blood volume (CBV) within the region of interest (Wyatt et al. 1990; Brazy 1991). Alterations in CBV measured by NIR spectrophotometry are linearly related to those in CBF (Pryds et al. 1990).

The computer-controlled NIR monitor used was checked for laser safety before use in clinical studies. The lasers used were of class IIIB, which are not hazardous to the skin. The amount of energy absorbed by the tissue was several levels below American safety standards of 90 MW/cm^2 for long-term exposure (American National Standards for the Safe Use of Lasers 1976).

Mirror drawing task

A mirror-drawing apparatus (PSYMO-CF-503, Seiwa ME-Research Institute, Tokyo, Japan) was used for the psychologic tasks (Okada et al. 1983). The test figure is a five-point star, with a 7-mm-wide outline, 3.3 cm from tip to corner, on the floor of the apparatus. The star is reflected by a vertical mirror. Direct vision of the figure is masked by a horizontal shield.

The task is to trace the figure as quickly and accurately as possible with an electrical stylus while looking at the mirror reflection. The position and movement of the stylus are sensed electrically, and deviation from the path causes a buzzer to go off beneath the floor or the apparatus. The number of star segments traced and the frequency of the stylus leaving the path are automatically recorded on a digital counter. Pulse laser lights were continuously introduced into both lateral sides of the forebrain during the MDT (Okada et al. 1983) for 10 min, before the MDT (2 min), during the MDT with right hand (2 min), and after resting 2 min, during the MDT with left hand (2 min) and after the MDT (2 min). The subjects were seated and given short (approximately 20 s) instructions before each MDT on how to use the apparatus.

Calculations of total Hb response areas

Using a planimeter, total Hb response areas during the MDT were calculated as the areas circumscribed by total Hb response curves and the baseline.

Statistical treatment

Significance of differences was assessed by the χ^2 test (Tables 1 and 4), the median test using nonparametric one-way analysis

Table 1 Cerebral response pattern to mirror drawing tasks in normal volunteers schizophrenics and alcoholic forebrains using infrared spectrophotometry

Subjects	Dominant hemisphere response pattern		Bilateral response pattern		No response pattern		Dysregulated pattern		Total
	n	%	*n*	%	*n*	%	*n*	%	
Normal									
Male	13	59	8	36	1	5	0	0	22
Female	4	25	11	69	1	6	0	0	16
Total	17	45	19	50	2	5	0	0	38
Schizophrenics									
Male	0	0	9	41	3	14	10	45	22
Female	0	0	7	44	2	12	7	44	16
Total,	0	0	16	42	5	13	17	45	38
Alcoholics									
Male	2	17	9	75	1	8	0	0	12

Table 2 Differences of blood volume response areas between left and right hemispheres during mirror drawing tasks in normal volunteers and schizophrenics. Median, maximum (max), and minimum (min) values (mm^2) are shown. Statistical significances were assessed by median test with nonparametric one-way analysis (SAS). *Significances within subgroups*: Dominant (DO) vs bilateral (BI) in normals: with right hand (rh), $P < 0.0001$ ($\chi^2 = 18.23$, $df = 1$); with left hand (lh), $P < 0.0001$ ($\chi^2 = 24.38$, $df = 1$). BI vs dysregulated (DY) in schizophrenics: with rh, $P < 0.001$ ($\chi^2 = 10.66$, $df = 1$); with lh, $P < 0.04$ ($\chi^2 = 4.04$, $df = 1$). *Significances between subgroups*: BI in normals vs BI or DY in schizophrenics: with rh, $P < 0.24$ ($\chi^2 = 1.35$, $df = 1$) or $P < 0.0003$ ($\chi^2 = 13.01$, $df = 1$); with lh, $P < 0.75$ ($\chi^2 = 0.1$, $df = 1$) or $P < 0.003$ ($\chi^2 = 8.78$, $df = 1$). DO in normals vs BI or DY in schizophrenics: with rh, $P < 0.0001$ ($\chi^2 = 15.61$, $df = 1$) or $P < 0.18$ ($\chi^2 = 1.83$, $df = 1$); with lh, $P < 0.0001$ ($\chi^2 = 19.58$, $df = 1$) or $P < 0.02$ ($\chi^2 = 5.6$, $df = 1$). *df* degree of freedom

Subjects (*n*)	Δ Differences between left and right hemispheres					
	With right hand			With left hand		
	Median	max	min	Median	max	min
Normal						
Dominant (17)	110	390	40	100	340	20
Bilateral (19)	20	110	0	20	60	0
No response (2)	0	0	0	0	0	0
Schizophrenics						
Bilateral (16)	20	140	0	20	60	0
No response (5)	0	0	0	0	0	0
Dysregulated (17)	70	840	20	60	340	20

(SAS) (Table 2), general linear models (SAS, Type II, and NEC-PC), and Student's *t*-test (Table 3).

Results

Figure 1, A and B, shows the recordings from the left and right hemispheres, respectively, of the forebrain of a right-handed normal volunteer (24-year-old male). Total Hb increased more markedly in the supposedly dominant (left) hemisphere due to the MDT than in the nondominant (right) hemisphere. However, HbO_2 increased and Hb decreased simultaneously in a mirror-image fashion to accompany these changes in total Hb. Therefore, the changes of HbO_2 and Hb occurred almost symmetrically in both hemispheres. This type of response, in which total Hb increased markedly in the supposedly dominant hemisphere (according to handedness), was named the *dominant hemisphere response pattern.*

This type of response was counted in 13 of 22 males 59% and 4 of 16 females (25%) as shown in Table 1. Prompt responses of these variables to the MDT were usually observed in the beginning, but in some cases the subject reacted (tensed up?) to the instructions for performing the test, resulting in an early change in the physiological variables. Compared with the *bilateral response pattern*, which is described next, there were statistically significant differences in total Hb response areas between left and right hemisphere in the *dominant hemisphere response pattern* (Table 2).

Figure 1, C and D, shows recordings from the left and right hemispheres of the forebrain of another right-handed volunteer (27-year-old male). Total Hb increased symmetrically in both hemispheres due to the MDT. Increases of HbO_2 and decreases of Hb accompanied the changes of total Hb. Therefore, responses to the MDT of total Hb, HbO_2, and Hb were seem symmetrically in both hemispheres. This type was named the bilateral response pattern; it occurred in 8 of 22 males (36%) and 11 of 16 females (69%), as shown in Table 1.

In females more cases of the bilateral response pattern were observed than the dominant hemisphere response pattern, whereas in males the opposite was true (χ^2 test shows $P < 0.05$). One male and one female were classified as *no response pattern*, bacause absolutely no changes in the oxygenation state or hemodynamics were observed in either hemisphere during the MDT (Table 1).

Figure 2, A and B, shows the bilateral response pattern recorded from the left and right hemispheres, respectively, of the forebrain of a right-handed patient with schizophrenia (28 years old, male). Of 22 males and 16 females, 9 (41%) and 7 (44%), respectively, reacted in the bilateral

Table 3 Turn counts tracing star, frequency, and total time of error due to mirror drawing tasks in normal volunteers and schizophrenics. Values are mean ± SD: [a]Number of times star traced 2-min period. [b]Frequency of stylus leaving path. [c]Total time off path. Differences between bilateral response pattern in normals and each schizophrenic group: by general linear models (SAS, Type II, and NEC-PC) and Student's *t*-test at $^{*}P < 0.05$; $^{*2}P < 0.01$; $^{*3}P < 0.001$: Differences between bilateral and dysregulated groups in schizophrenics: $^{*4}P < 0.05$

Subjects (*n*)	With right hand			With left hand		
	Turn count[a] (*n*)	Error count[b] (*n*)	Error time[c] (s)	Turn count[a] (*n*)	Error count[b] (*n*)	Error time[c] (s)
Normal						
Dominant (17)	2.9 ± 2.3	58.2 ± 45.1	18.9 ± 12.7	4.4 ± 3.2	44.7 ± 32.0	16.2 ± 17.8
Bilateral (19)	3.4 ± 2.6	43.9 ± 28.5	14.9 ± 12.0	4.6 ± 2.1	40.5 ± 19.1	10.7 ± 6.2
No response (2)	3.5	18	7	4	23	7
Schizophrenics						
Bilateral (16)	1.1 ± 1.4^{*2}	68.4 ± 46.4	26.3 ± 22.0	2.0 ± 1.8^{*3}	67.6 ± 38.1	28.9 ± 19.7^{*2}
No response (5)	1.6 ± 1.0*	75.0 ± 38.3	25.8 ± 20.0	2.4 ± 1.0^{*2}	78.8 ± 44.8	26.0 ± 20.2
Dysregulated (17)	0.3 ± 0.6^{*3}	64.5 ± 34.9	31.0 ± 23.2*	0.8 ± 1.3$^{*3, *4}$	63.4 ± 31.3	42.8 ± 34.1^{*3}

Table 4 Type of neuroleptic treatment in different groups of cerebral response patterns

Subjects (*n*)	Phenothiazine derivatives		Butyrophenone derivatives		Both used	
	n	%	*n*	%	*n*	%
Schizophrenics						
Bilateral (16)	4	25	6	37.5	6	37.5
No response (5)	1	20	3	60	1	20
Dysregulated (17)	3	18	6	35	8	47
Alcoholics						
Bilateral (9)	4	44	5	56	0	0
No response (1)	0	0	0	0	1	100
Dominant (2)	1	50	1	50	0	0

response pattern (Table 1). Figure 2, C and D, shows a no response pattern (27 years old, female). Of 22 males and 16 females, 3 (14%) and 2 (12%), respectively, showed a no response pattern (Table 1).

A fourth pattern appeared in schizophrenics which was not observed in our sample of healthy subjects. We call this the *dysregulated pattern*, and it is characterized by a lack of any apparent coupling between the responses of the hemispheres or by disrupted integration. Figure 2 has two examples of the dysregulated pattern. Parts E and F show the results from one patient (34 years, female). When she began to draw the figure with her right hand, HbO_2, Hb, and total Hb increased in the left hemisphere; conversely, total Hb decreased in the right hemisphere. Such a decrease in total Hb never occurred in normal volunteers. Parts G and H show another dysregulated pattern (32 years, male). In this case, HbO_2 and total Hb decreased in the right hemisphere, whereas no responses of these variables were observed in the left hemisphere. In all, 10 of 22 males (45%) and 7 of 16 females (44%) showed the dysregulated pattern as indicated in Table 1. The recordings from the other 15 of the 17 schizophrenics found to show dysregulated patterns are displayed in Fig. 3.

It is difficult to characterize these data, except that one of the hemispheres always had a decrease in total Hb during the MDT. These responses are completely different in quality from the integrated patterns, i.e., the bilateral response pattern or dominant hemisphere response pattern, which were observed in normal volunteers. Differences in total Hb response areas between left and right hemispheres in the dysregulated pattern were statistically significant compared to those of the bilateral response pattern in schizophrenics (Table 2).

In the normal control group there were no significant differences between subjects showing the dominant hemisphere response pattern and the bilateral response pattern in turn count, error count, and error time in the MDT (Table 3). However, each group of schizophrenics traced the star in the MDT more slowly with longer error time than bilateral response pattern in normals (Table 3). Furthermore, the dysregulated group traced the star in the MDT more slowly than the bilateral group in schizophrenics. As is commonly observed in the MDT, schizophrenics were less skillful in tracing the pattern than controls, and here, the dysregulated group was less skillful than the bilateral group.

Mean age at determination, mean age at onset, average number of hospitalizations, and average duration of illness in three groups of schizophrenics were, respectively, as follows (± SD):

Bilateral ($n = 16$): 25.2 ± 10.3 years; 20.2 ± 4.3 years; 3.5 ± 2.2 years; 9.5 ± 4.8 years. No response ($n = 5$): 29.8 ± 4.7 years; 18.8 ± 2.5 years; 4.6 ± 3.9 years; 11.0 ± 6.9 years. Dysregulated ($n = 17$): 31.8 ± 7.6 years; 17.8 ± 2.7 years; 5.2 ± 7.3 years; 14.1 ± 7.2 years.

There were significant differences between bilateral and dysregulated subjects in their average duration of illness ($P < 0.05$ according to Student's *t*-test).

Of 38 patients, 13 (34.2%) were subclassified as disorganized type, and 15 of 38 patients (39.5%) were classified as undifferentiated type. There were no significant differences between the bilateral group and the dysregulated group in these subclassfications (*data not shown*).

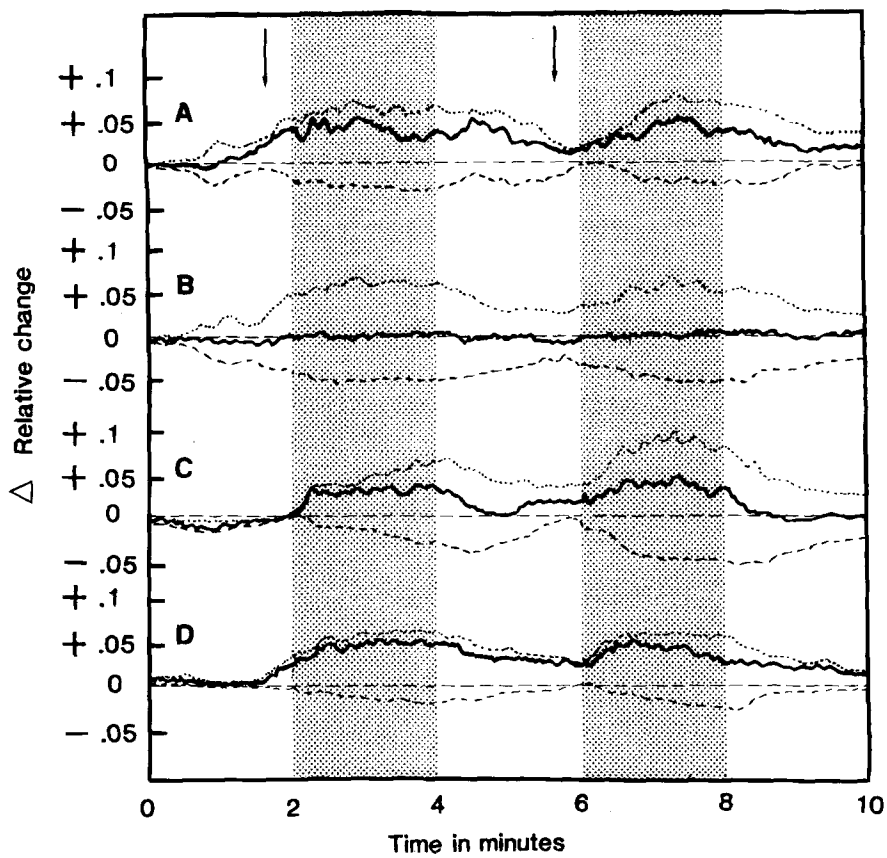

Fig. 1A–D Typical continuous recording patterns of changes in oxygenated Hb [HbO_2] (*dotted line*), deoxygenated Hb [Hb] (*broken line*) and blood volume (total Hb) (*solid line*) during the mirror drawing tasks (MDTs) in right-handed normal volunteers. The abscissa is clock time. The MDTs were performed during period shown with the *shaded areas* (first column with right hand; second with left hand). The ordinates show the relative changes of HbO_2, Hb, and total Hb from baseline states (0). *Vertical arrows* indicate time of the beginning of instructions on how to carry out the MDT. **A** typical recording from supposedly dominant (left) hemisphere of a volunteer of *dominant hemisphere response pattern* (24-year old male). **B** typical recording from non dominat (right) hemisphere of the same subject. **C** typical recording from dominant (left) hemisphere of a volunteer of *bilateral response pattern* (27-year-old male). **D** typical recording from nondominant (right) hemisphere of the same subject

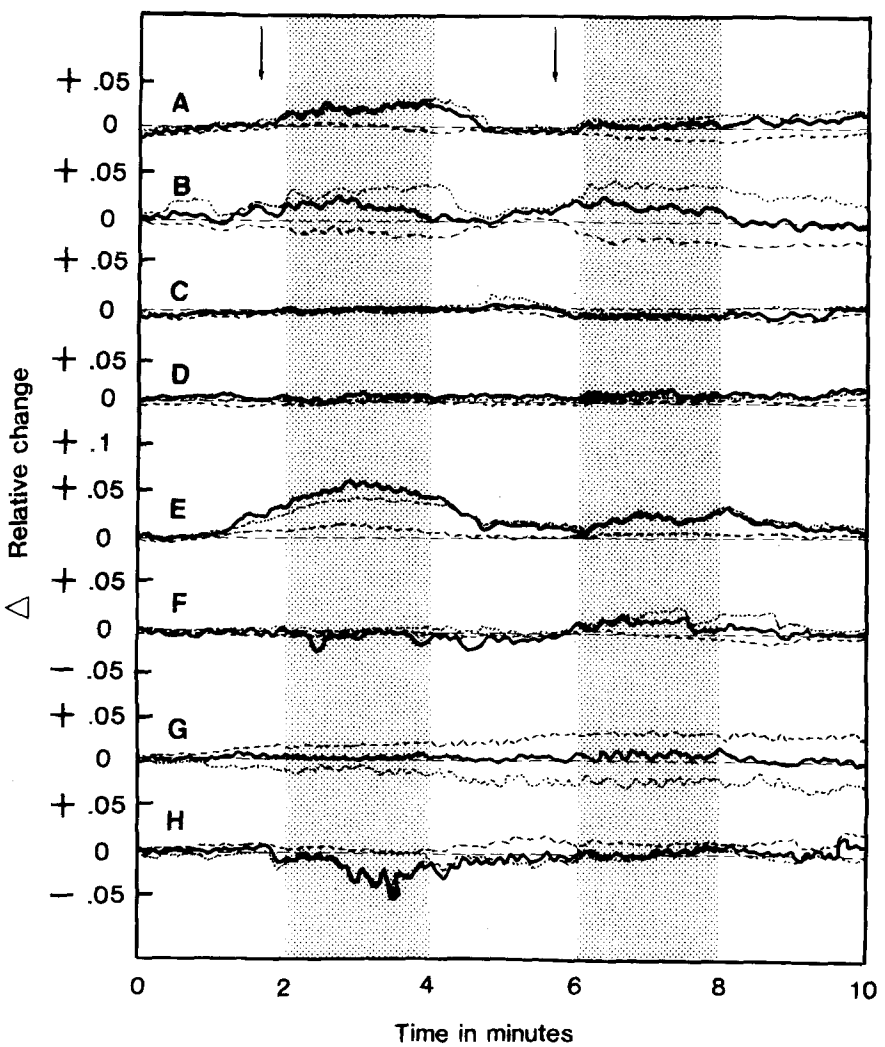

Fig. 2A–H Typical continuous patterns in right-handed schizophrenics. Details are described in legend for Fig. 1. **A** (left hemisphere) and **B** (right hemisphere) show a *bilateral response pattern* (28-year-old male). **C** (left) and **D** (right) show a *no response pattern* (27-year-old female). **E** (left) and **F** (right) show a *dysregulated pattern* (34-year-old female). **G** (left) and **H** (right) also show a *dysregulated pattern* (32-year-old male)

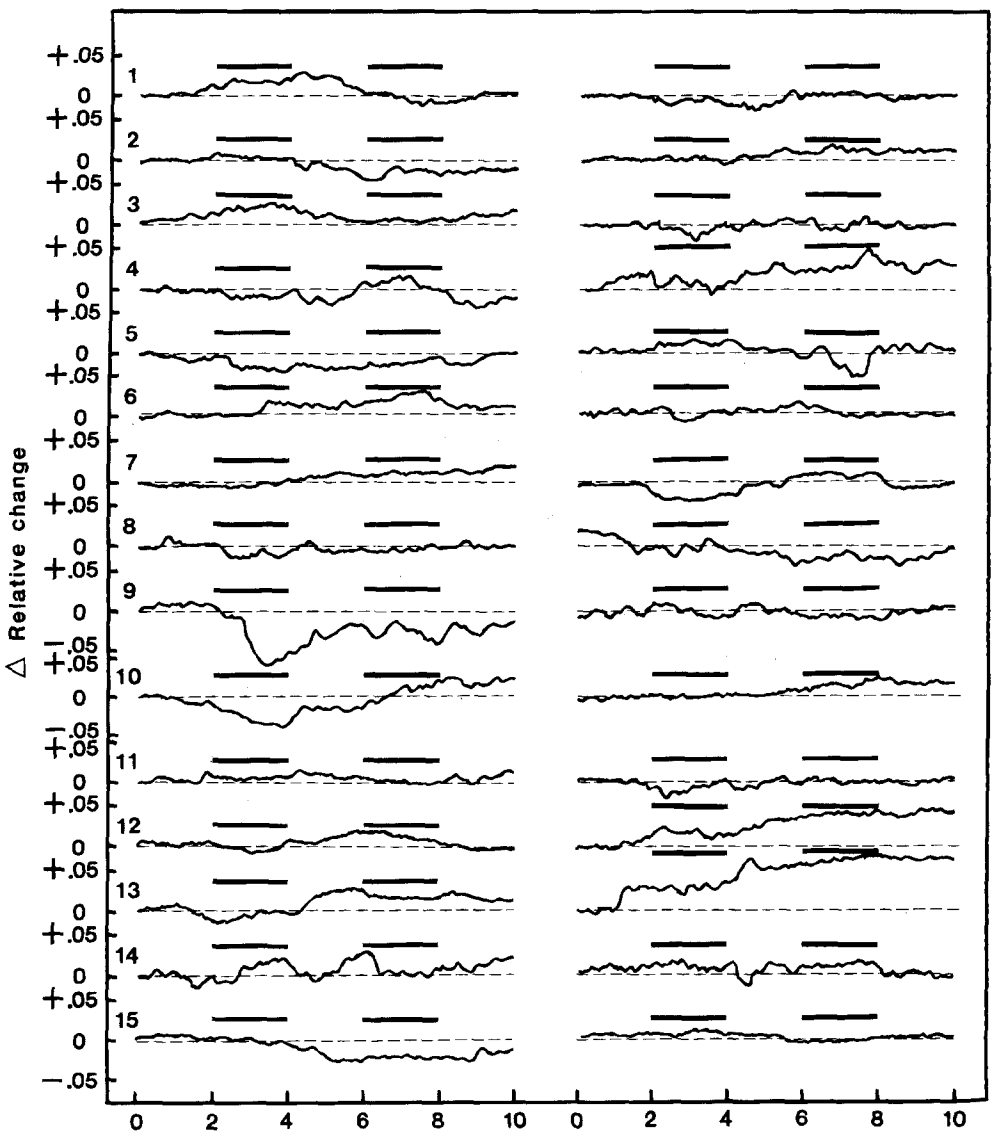

Fig. 3 Fifteen *dysregulated patterns* of changes in blood volume total Hb during the mirror drawing task MDT in right-handed schizophrenics. Numbers 1–9: males; 10–15 females. Left side is left hemisphere; right side is right hemisphere. The MDTs were performed during periods shown with *horizontal bars*

Discussion

The patients presented in this report were diagnosed as having chronic schizophrenia by DSM-III-R. Approximately three-quarters of patients were subclassified as disorganized or undifferentiated types. The essential features of these types were incoherence, marked loosening of associations or antisocial behavior, and, in addition, flat or grossly inappropriate affect with or without prominent delusions and hallucinations.

The term schizophrenia was coined by Eugen Bleuler (1911), who recognized that not all patients who had the "dementia praecox" proposed by Kraepelin (1927) actually deteriorated into a demented state. He chose the new name to refer to the "splitting of the mind" or "loosening of association" that occurs in these patients, and believed that all had some disturbance in their abilities to think clearly, to feel normal, and to act decisively. Since the time of Kraepelin and Bleuler, researchers have attempted to identify dysfunctions in schizophrenic patients. However, there has never been any direct pathophysiologic evidence concerning incoherence or loosening of association.

The MDT is a visuospatial drawing task that puts a unique demand on the brain. The subject must watch the star in the mirror very closely as he controls his hand. It is a task involving visual acuity and the intellect, as well as motor functions. It has also been used to induce psychologic stress regularly associated with physiologic responses, such as increase of muscle tension (Telford and Swenson 1942), elevation of blood pressure (Malmo and Shagass 1952), increase of electrodermal activities (Edelberg 1972), digital vasoconstriction (Kuwahara et al. 1965), and secretion of some hormones (Miyabo et al. 1976; Miyabo et al. 1977; Okada et al. 1983).

All of the patients with schizophrenia presented in this study were right-handed; therefore, age- and sex-matched right-handed healthy volunteers were selected. In normal volunteers bilaterally simultaneous increases of HbO_2 and

decreases of Hb in the forebrain occurred symmetrically in all cases except two. There were gender-related differences of hemodynamics between the hemispheres of the brain. Results of NIR implied that a large majority of women used both sides of the brain when concentrating on carrying out the MDT, because total Hb increased symmetrically in both hemispheres. Most men seem to have reacted by mainly using the dominant hemisphere, because total Hb increased more markedly in the supposedly dominant hemisphere. The gender differences were more marked in left-handers than in right-handers (Okada et al. 1993).

Hoshi and Tamura (1993 a) observed subjects solving arithmetic problems using the technique described here and asked them whether they had had a difficult time. Those who reported difficulties had shown significant increases in both HbO_2 and total Hb in the frontal region of the dominant hemisphere. Furthermore, they performed some functional brain mapping with this technique, i.e., using up to five channels in their optical monitoring system. They succeeded in detecting the region-specific changes in both the HbO_2 state and total Hb during various mental tasks, in addition to visual and auditory stimulation (Hoshi and Tamura 1993 b). They showed that the time course of increases in blood supply varied with each brain region, and that this and HbO_2 depended on the type of internal operations occurring during mental tasks. Their results clearly confirm our previous and present findings of hemispherically-integrated modulation of the oxygen delivery-oxygen utilization relationship during brain activation in normal volunteers when they are concerning on the MDT.

The most noteworthy characteristic of the NIR findings in schizophrenics was the complete lack of the dominant hemisphere response patterns, which occurred in 60% of normal male volunteers. In other words irregular patterns of blood flow in schizophrenics, even when they show some lateralization, have no resemblance to the well-modulated patterns that were so commonly observed in normal male volunteers. Conversely, almost half the schizophrenics showed the dysregulated patterns between hemispheres, a phenomenon which never appeared in normal volunteers. Schizophrenics showed lower abilities in the MDT than normals and the dysregulated group was even less "able" by that criterion than the bilateral group. Although there were no significant differences between the dysregulated and bilateral groups in the subclassification of the illness pattern, the former showed a longer average duration of illness than the latter. Therefore, it may be possible that the interhemispheric coordination of brain oxygenation and hemodynamics deteriorates as part of the process of the illness.

These results may reflect a fundamental disturbance of interhemispheric transfer in schizophrenia. The possibility that the effects were a result of the neuroleptics with which the subjects were medicated should be conclusively excluded by further experimentation. However, patients with alcohol hallucinosis who were undergoing treatment with neuroleptics did not display dysregulated patterns, which seems to warrant the conclusion that the dysregulated patterns observed in schizophrenics were not due to the effects of antipsychotic medications. Bartlett at al. (1991) reported that two neuroleptic treatments with different pharmacologic characteristics (thiothixene and haloperidol) had opposite effects on cerebral glucose utilization in chronic schizophrenic inpatients as determined by PET. However, in the present study, there were no significant differences between incidences of the bilateral response pattern and the dysregulated pattern in schizophrenics treated with phenothiazine derivatives, butyrophenone derivatives, or both, according to the χ^2 test.

Histories of the medications and patients' response patterns are shown in Table 4. Nearly half of the patients with alcohol hallucinosis were treated both with phenothiazine dervatives and butyrophenone derivatives. Therefore, the response patterns observed in this study seem to be independent of the different neuroleptic regimens.

Concerning laterality, neuropsychologic (Flor-Henry 1976), behavioral (Gur 1978), electrophysiologic (Shagass et al. 1983), and electroencephalographic (Etevenon et al. 1983) studies have suggested left-hemispheric dysfunction in schizophrenia. Asymmetries in brain tissues in schizophrenia have also been reported in neurochemical (Kerwin et al. 1988; Reynolds 1983; Reynolds et al. 1990; Okada et al. 1990; Okada et al. 1991) and morphometric (Brown et al. 1986; Crow et al. 1989) postmortem studies, and in findings on tissue density in a computed tomography (CT) scan of discordant monozygotic twins (Reveley et al. 1987). Furthermore, a number of regional cerebral blood flow (rCBF) studies and PET studies have demonstrated other asymmetries, although these results have been rather inconsistent (Mathew et al. 1988; Szechtman et al. 1988).

Gur et al. (1983, 1985) reported that more pronounced abnormalities in hemispheric activity are evident in schizophrenics when the measures are obtained during cognitive activation with the Xenon 133 technique for measuring rCBF. In a PET study with ^{11}C-glucose as the tracer, Wiesel et al. (1987) found left–right asymmetries in the temporal lobe and basal frontal cortex, with the metabolic rates of the patients being lower on the left side compared to the controls. Similar findings were also reported by Kling et al. (1986).

The pathologic process of schizophrenia may have some connection to – or even origin in – a failure of the brain to develop completely in the process which culminates in the "laterality" observed in normal subjects. The method using NIR spectrophotometry seems to hold great promise in the elucidation of defects in functional connections between different regions of the brain in schizophrenia. Such defects may explain the nature of schizophrenic symptoms, especially the incoherence or loosening of association, which is the most important fundamental symptom of schizophrenia.

Acknowledgements The authors are grateful to Dr. Naoki Kimura, Dr. Yasuo Kurokawa, Dr. Iori Oka, Dr. Hajime Narita, and their patients for their cooperation in this study. We also thank Mr. Tomomi Tamura of Research and Development, Shimadzu Corporation, for his kind help in NIR measurement, and Dr. Norio Takahashi for his expert statistical help. This work was supported in part by a Grant-in-Aid from the Ministry of Education, Science and Culture, Japan

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