Reduced Frontal Functional Asymmetry in Schizophrenia During a Cued Continuous Performance Test Assessed With Near-Infrared Spectroscopy

by Andreas J. Fallgatter and Werner K. Strik

Abstract

Near-infrared spectroscopy (NIRS) allows noninvasive, in vivo measurement of changes in the concentrations of oxygenated hemoglobin ($O_2$Hb) and deoxygenated hemoglobin (HHb) in brain tissue based on their distinctive optical properties. A previous NIRS investigation on healthy subjects (Fallgatter and Strik 1997) found indications of right frontal activation during a Continuous Performance Test (CPT) that are consistent with results from positron emission tomography (PET) and event-related potentials studies. The indications consisted of right frontal blood oxygenation changes, consistent with a hemodynamic response, along with a significant left frontal increase in HHb. The current study investigated whether this characteristic lateralized frontal NIRS activation pattern was present in a group of nine schizophrenia patients during the execution of a CPT. In contrast to the previous study, no overall or hemispheric activation effects were found in the schizophrenia subjects. Direct comparison of the results of the two studies confirmed group differences, with a lack of lateralized activation in schizophrenia patients. Furthermore, a trend of higher left/right HHb ratios at rest and during activation was found in patients with schizophrenia. The finding is interpreted as a sign of reduced specific lateralized frontal reactivity, possibly based on a left hemisphere functional deficit.


Abnormal structural or functional hemisphere asymmetries in schizophrenia disorders have been assessed in different research areas and are important for the understanding of the pathophysiological mechanisms underlying the disorder (Flor-Henry 1983). Left temporal structural or cytoarchitectural deficits are described in postmortem studies (Jakob and Beckmann 1986; Crow et al. 1989; Falkai et al. 1992) and are further supported by magnetic resonance imaging (MRI) studies (Rossi et al. 1990; McCarley et al. 1993).

A PET study found hemisphere asymmetries in metabolism in schizophrenia patients at rest, with relative $11$-C glucose uptake in left temporal and basal frontal areas lower than that in controls (Wiesel et al. 1987). This finding was not related to the duration of the neuroleptic treatment. In never-medicated schizophrenia patients, a loss of the physiological right-greater-than-left asymmetry of the metabolic rate in thalamic areas was found, with relative $[^{18}\text{F}]-\text{fluorodeoxyglucose}$ uptake reduced in the right thalamic area (Buchsbaum et al. 1996).

Because the structural abnormalities frequently found in the cerebrum of schizophrenia patients are not sufficiently specific or sensitive, cognitive activation paradigms to investigate the functional aspects of schizophrenia have gained particular interest. Electrophysiological investigations show pathological asymmetries of the acoustically evoked P300 in schizophrenia, with right hemisphere lateralization of the peak of the brain’s electrical field (Morstyn et al. 1983; Roemer and Shagass 1990; McCarley et al. 1993; Strik et al. 1993, 1994a, 1994b). These findings correlate with performance in a language-related neuropsychological test that is sensitive to left temporal functional deficits (verbal pairs test, Heidrich and Strik 1997) and further support the loss or even reversal of physiological functional brain asymmetries in schizophrenia disorders. In a study with functional magnetic resonance imaging (fMRI) during word production, reduced left frontal and greater left temporal activation was found in schizophrenia patients compared with controls (Yurgelun-Todd et al. 1996). Additionally, performance of the Wisconsin Card Sorting Test resulted in a right lateralized frontal activation in healthy subjects.
assessed with fMRI that was not present in schizophrenia patients (Volz et al. 1997). In a PET study, a loss of physiological activation of the right frontal hemisphere has been described in schizophrenia patients performing a degraded form of the CPT (Buchsbaum et al. 1990). The studies indicate that different cognitive functions are associated with different regional activation patterns.

NIRS, a new noninvasive optical method, allows the photometrical in vivo assessment of changes in the concentration of oxy- and deoxyhemoglobin in brain tissue (Jöbsis 1977). The method has been shown to be sensitive enough to measure the physiological blood oxygenation changes during cognitive activation in healthy subjects (Hoshi and Tamura 1993; Fallgatter et al. 1998; Fallgatter and Strik 1998). Consistent with the above-mentioned PET study (Buchsbaum et al. 1990), an asymmetric right frontal activation during performance of a CPT was found in an NIRS investigation in healthy subjects (Fallgatter and Strik 1997). Subjects showed an initial increase of HHb and a parallel decrease of O₂Hb only in right frontal regions, and an inverse trend after some seconds, which lasted until the end of the task. This pattern was interpreted as a sign of increased oxygen consumption, with initial O₂ decrease, and a compensatory hemodynamic overshoot (Fox and Raichle 1986). However, hemispheric activation differences were significant only for HHb concentrations, with left-sided values higher than right-sided values.

In psychiatry, NIRS has been applied for the investigation of patients with Alzheimer’s dementia. A bifrontal activation pattern (a reduction of HHb along with an increase of O₂Hb) was found in patients with dementia during the verbal fluency test (VFT), while controls showed a more specific activation confined to left frontal regions (Fallgatter et al. 1997b). In parietal areas, on the other hand, indications for a reduced hemodynamic response were found during the VFT in patients with dementia (Hock et al. 1996).

The CPT is suitable for isolated cognitive activation of frontal brain regions during neurophysiological measurements because only a minimal behavioral response (button press) and no eye movements are required. Several more attention-demanding variations of the classical CPT (Rosvold et al. 1956) with shorter interstimulus intervals and presentation times, degradation of the stimuli, and implementation of a NoGo condition (Go-NoGo task) have been developed (Nuechterlein et al. 1986; Earle-Boyer et al. 1991; Cornblatt and Keilp 1994). Schizophrenia patients and their siblings have increased reaction times and higher error rates than controls. The latter were shown to be correlated with negative symptoms (Cornblatt and Keilp 1994; van den Bosch et al. 1996; Finkelstein et al. 1997).

The aim of the current study is to investigate the oxygenation changes in schizophrenia patients during performance of a CPT by means of the NIRS technique. The study is the continuation of a previous investigation on healthy subjects showing a right-lateralized activation pattern with left hemisphere HHb increase (Fallgatter and Strik 1997). Based on the results of the PET study of Buchsbaum et al. (1990), it was expected that this lateralized activation would be absent in schizophrenia subjects.

### Method

**Subjects.** Ten schizophrenia inpatients (4 females, 6 males) diagnosed according to the DSM—IV criteria were investigated with NIRS during the CPT (American Psychiatric Association 1994). All of them were investigated in stable clinical condition prior to discharge. One female patient was excluded from further analysis due to left-handedness. Subdiagnoses of the remaining 9 patients were disorganized (n = 3; 295.10), catatonic (n = 3; 295.20), and paranoid (n = 3; 295.30); schizophrenia was diagnosed according to DSM—IV criteria by the independent judgment of two senior psychiatrists based on a clinical interview. Patients had a mean age of 34.7 ± 13.1 years and were on neuroleptic treatment (mean chlorpromazine equivalent dose 501 ± 361 mg/day). Three patients took additional benzodiazepine medication. Psychopathology and neuroleptic treatment were unchanged in all patients for a minimum of 2 weeks. After complete description of the study, written informed consent was obtained.

The control group consisted of 10 healthy subjects (5 women, 5 men) who had performed the CPT during an NIRS registration with identical methodological settings. The results of this control group have been published elsewhere (Fallgatter and Strik 1997). Controls were of comparable mean age (30.0 ± 2.1 years, t = 0.33, not significant [ns]). All of them were right-handed and medication-free, and none had a personal or family history of neurological or psychiatric disorder. In a clinical interview, absence of schizophrenia symptoms and other relevant psychopathological features was confirmed in all control subjects.

**NIRS Technique.** Principles and validation of the NIRS methodology have been published elsewhere (Jöbsis 1977; Delpy et al. 1988; Chance 1991; Hoshi and Tamura 1993; Fallgatter and Strik 1997, 1998; Fallgatter et al. 1997, 1998). Two identical Critikon 2020 Cerebral Redox Monitors (Johnson and Johnson Medical Ltd.), each with a flexible electro-optic cable and a sensor with an emitter-detector spacing of 45 mm, were used. This NIRS system works with two detectors, employs an algorithm based on
quantified absorption spectra (Wray et al. 1988), includes an optical path length factor of 6.5 and matched detector-coupling efficiencies, and has compensation for background absorbers (Lewis and Stoddart 1994).

Each patient was investigated in a dimly lit and sound-attenuated room while sitting in a comfortable chair. Both sensors were carefully fixed with a flexible fixation pad and with an elastic light-attenuating band that was at an identical position on every patient, located symmetrically between electrode positions Fp1/F3 and Fp2/F4 of the International 10/20 system for electroencephalogram (EEG) electrode positions (Jasper 1958).

CPT. After a baseline period with eyes closed and without any instruction, subjects were asked to execute a modified O-X version of the CPT (Brandeis et al. 1995; Fallgatter et al. 1997a), which was displayed on a monitor 120 cm from the subject’s eyes. This CPT version consisted of 12 different letters that were presented for 200 ms each between the two vertical fixation lines in the center of the screen. The interstimulus interval was 1,650 ms. Subjects were instructed to press the mouse button with the index finger of their right hand as fast as possible every time the letter O was followed directly by the letter X. Thus the letter O (primer) was a signal to prepare a motor response (i.e., a mouse button press), whereas X served as target when directly following an O, prompting the subject to answer with a mouse button press (Go condition). The 10 letters A, B, C, D, E, F, G, H, J, and L were either signals to avoid the prepared motor response when they directly followed an O (NoGo condition) or meaningless distractors when presented after any letter other than O. Following this mental activation, a poststimulus segment was recorded with closed eyes.

Data Analysis. Data acquisition was performed by the NIRS system with an analog-to-digital rate of 1 Hz. Data were stored on hard disk and transcribed into ASCII format off line. The lengths of the three recording segments for the schizophrenia subjects were 10–34 seconds for the prestimulus baseline (controls 28–51 seconds), 141–146 seconds for the task (controls 139–143 seconds), and 28–49 seconds for the poststimulus baseline (controls 138–146 seconds). To enable group comparisons, the length of all recording segments of both schizophrenia patients and controls were normalized to the respective minima, resulting in a duration of 10 seconds for the prestimulus baseline, 139 seconds for the task, and 14 seconds for the poststimulus baseline. These time intervals are adequate for the measurements of the cerebral hemodynamic response, which occurs within 3 seconds of rise and fall time (Bandettini et al. 1992). Since the absolute quantification of HHb and O$_2$Hb concentrations is ambiguous, a baseline correction with the respective prestimulus average values was performed for every individual measurement. These baseline-corrected values are referred to as relative values. Subsequently, the individual average concentrations of HHb and O$_2$Hb were calculated for the segments: prestimulus baseline (−10 to −1 seconds), activation (0–138 seconds), and poststimulus baseline (138–152 seconds) separately for the left and for the right hemispheres.

Statistics. Based on the results from the control group study, in which left-lateralized HHb increases were significant but no significant changes in O$_2$Hb were found (Fallgatter and Strik 1997), confirmatory statistics were performed on the schizophrenia patients only for HHb with a 2 × 3 repeated measures analysis of variance (ANOVA; 2 hemispheres × 3 segments). Furthermore, a 2 × 3 ANOVA (2 groups × 3 segments) of the normalized (log$_e$) left/right raw HHb ratios was computed as a direct exploratory test for group differences in relative hemisphere activation. The same procedure was followed for the exploratory analyses of the O$_2$Hb measurements. All reported $p$ values are two-tailed.

**Results**

CPT Performance. The error rate was low. On 22 decisions, schizophrenia subjects made an average of 0.57 (range 0–2) errors of omission (misses) and 3.57 (range 1–7) errors of commission (false alarms). Reaction times for correct responses were 465.3 ± 97.9 ms. No significant differences were found in comparison with the healthy controls as to rate of omission errors (0.60, range 0–2; $t = 0.06$), commission errors (1.40, range 1–3; $t = 1.57$), and reaction times (376.7 ± 59.1 ms; $t = 1.77$; Fallgatter and Strik 1997).

NIRS Results. The means and standard deviations of all raw values of HHb and O$_2$Hb in the three segments for controls and schizophrenia subjects are reported in table 1. The grand average HHb and O$_2$Hb values of left- and right-sided measurements after baseline correction are displayed in figure 1 for schizophrenia patients and controls.

This typical right hemisphere activation pattern with an initial increase of HHb and a parallel decrease of O$_2$Hb found in the previous study (Fallgatter and Strik 1997) was not present in schizophrenia patients (figure 1). In a confirmatory analysis on relative HHb concentration, no activation or hemispheric effects were revealed (2 × 3 ANOVA; main effect hemispheres [df = 1,8] F = 0.67, ns; segments [df = 2,16] F = 0.03, ns; interaction hemispheres × segments [df = 2,16] F = 0.49, ns).

The same was true for an exploratory analysis on relative O$_2$Hb concentration (2 × 3 ANOVA; main effect
Table 1. Means and standard deviations of left and right hemisphere raw values of the parameters HHb and O$_2$Hb for controls and schizophrenia subjects

<table>
<thead>
<tr>
<th></th>
<th>Mean (± SD), μmol/l</th>
<th>Segment 1</th>
<th>Segment 2</th>
<th>Segment 3</th>
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<tr>
<td></td>
<td></td>
<td>Segment 1</td>
<td>Segment 2</td>
<td>Segment 3</td>
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<tr>
<td>HHb</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>C left</td>
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<td>32.53 (6.17)</td>
<td>32.35 (6.24)</td>
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<tr>
<td>S left</td>
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<td>34.26 (8.11)</td>
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<td></td>
</tr>
<tr>
<td>C right</td>
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<td>29.65 (4.30)</td>
<td>29.63 (4.35)</td>
<td></td>
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<tr>
<td>O$_2$Hb</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>C left</td>
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<td>75.75 (11.24)</td>
<td>75.38 (11.16)</td>
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<tr>
<td>S left</td>
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<td>64.31 (16.14)</td>
<td>64.58 (16.49)</td>
<td>64.34 (16.29)</td>
<td></td>
</tr>
</tbody>
</table>

Note.—C = healthy controls; HHb = deoxygenated hemoglobin; O$_2$Hb = oxygenated hemoglobin; S = patients with schizophrenia; SD = standard deviation; segment 1 = prestimulus baseline; segment 2 = task; segment 3 = poststimulus baseline.

Figure 1. Baseline-corrected trajectories (31 point-smooth) of HHb and O$_2$Hb for the left and right hemispheres in healthy controls and patients with schizophrenia

Note.—C = healthy controls; S = patients with schizophrenia.

* Thin lines show HHb. Bold lines show O$_2$Hb (no significant changes). Activation with the Continuous Performance Test occurs between the dotted lines.

Hemispheres [df = 1, 8] F = 0.28, ns; segments [df = 2, 16] F = 0.39, ns; interaction hemispheres × segments [df = 2, 16] F = 0.39, ns).

The direct comparison of the left/right ratios of raw HHb differed as a trend between groups ([df = 1, 17] F = 3.43, p < 0.10), and significantly for the factor segments ([df = 2, 34] F = 3.96, p < 0.05) and for the interaction groups × segments ([df = 2, 34] F = 3.36, p < 0.05). The trend of a group difference was due to a higher overall left/right ratio in schizophrenia subjects than in controls, while the segment and interaction effects were due to a left-lateralized HHb increase during the task in controls but not in subjects with schizophrenia (figure 2). The respective normalized left/right ratios of O$_2$Hb did not differ between groups and segments (2 × 2 ANOVA for factor groups [df = 1, 17] F = 1.55, ns; for factor seg-
Reduced Frontal Functional Asymmetry

Figure 2. Normalized left/right ratios of raw HHb concentrations during prestimulus baseline, task, and poststimulus baseline (segments 1–3) for schizophrenia patients and healthy controls. 

Discussion

Based on the results of a previous study in healthy controls (Fallgatter and Strik 1997), hemisphere differences in concentration changes of HHb during performance of a CPT were investigated in DSM-IV schizophrenia subjects. In both groups, mean HHb concentrations were higher in the left than in the right hemisphere at rest and during activation; there was a trend for this asymmetry to be more pronounced in schizophrenia subjects than in controls (figure 2). No final conclusions can be drawn as to the meaning of increased HHb levels without changes of O2Hb in brain tissue; however, in light of typical activation patterns consisting of HHb decrease and O2Hb increase (Fox and Raichle 1986), this may be interpreted as an expression of a low activation level with reduced metabolic turnover. This pattern is consistent with a PET study showing reduced left frontal 11-C glucose uptake in schizophrenia patients (Wiesel et al. 1987).

The asymmetry in hemispheric HHb concentration increased significantly during activation in controls but not in schizophrenia patients (figure 2). This increase, along with the HHb and O2Hb response pattern (Fox and Raichle 1986) and results from electrophysiological (Strik et al. 1998) and PET studies (Buchsbaum et al. 1990), was interpreted as a sign of right frontal activation in controls (Fallgatter and Strik 1997). The absence of this lateralized activation in schizophrenia subjects cannot be attributed to a worse performance since omission and commission errors did not differ. Therefore, it appears to be due to a different functional response to the activation conditions of the CPT, which require sustained attention and choice reaction including inhibitory motor control. In principle, the results are consistent with the study of Buchsbaum et al. (1990), who found a loss of hemisphere asymmetry in schizophrenia during the CPT, but also described reduced metabolic rates in both frontal lobes. Quantification of the metabolic hypofrontality is more ambiguous with NIRS than with PET due to the interactions between oxygen consumption and the compensating blood flow changes. However, the results of our study can be parsimoniously interpreted as an expression of a reduced frontal reactivity on the basis of a left-lateralized hypofunction.

The behavioral results apparently are in contrast with studies reporting a reduced performance by schizophrenia subjects in the CPT. This difference is explained by the application of a very easy CPT version with long presentation times (200 ms) and increased interstimulus intervals (1,650 ms) along with a short overall duration (139 seconds). A possible influence of medication on our results cannot be ruled out, however, as control subjects, obviously, were medication-free.

In a group of patients with Alzheimer’s dementia, loss of a physiological asymmetry was found during a verbal fluency test (Fallgatter et al. 1997a). The verbal fluency task elicited specifically left frontal blood oxygenation changes in healthy subjects. This finding is consistent with the hemispheric location of speech-related brain regions, whereas right frontal activation during the CPT has been related to the inhibitory (NoGo) subset of the task (Strik et al. 1998). A direct comparison between the findings in dementia and schizophrenia patients is not possible due to the different tasks. However, dementia patients appear to activate bifrontally. This finding was interpreted as an increased but less efficient effort by dementia patients with additional recruitment of contralateral regions, while schizophrenia patients display signs of reduced reactivity during the CPT.

The NIRS method appears suitable to assess meaningful functional cerebral alterations in psychiatric disorders. The signal-to-noise ratio and the spatial resolution of NIRS are still low, but this limitation is counterbalanced by its easy, noninvasive, low-cost application. Further methodological developments, measurements in different brain regions, and comparisons between different methods will clarify the usefulness of NIRS for future research and clinical practice.
References


The Authors

Andreas J. Fallgatter, M.D., is Privat-Dozent, University of Wuerzburg, Wuerzburg, Germany. Werner K. Strik, Ph.D., M.D., is Professor, University of Bern, Bern, Switzerland.
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Fax: 301-571-0769
E-mail: wilsonk@stanleyresearch.org

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