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Frontal brain activation during the Wisconsin Card Sorting Test assessed with two-channel near-infrared spectroscopy

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Abstract Near-infrared spectroscopy (NIRS) is a new non-invasive optical technique suitable to assess the concentration changes of oxygenated (O_2HB) and deoxygenated (HHB) hemoglobin in brain tissue. Previous NIRS studies showed distinct patterns of blood oxygenation changes during different cognitive tasks. In particular, bilateral frontal hypo-oxygenation was found during reading, right frontal hyper-oxygenation during the Continuous Performance Test, and left frontal hyper-oxygenation during the Verbal Fluency Test. The Wisconsin Card Sorting Test (WCST) is a neuropsychological test which is presumed to activate prevalently the frontal lobes. This was demonstrated by lesion studies and functional imaging (single photon emission computed tomography and positron emission tomography). In the present study, a two-channel NIRS system was applied to investigate frontal brain areas of ten healthy subjects during performance of the WCST. A significant bilateral increase of O_2HB in frontal brain regions without hemispheric differences was found during the WCST compared with a baseline at rest. This result indicates an enhanced perfusion of the frontal lobes consistent with local activation. The findings add further evidence that the NIRS technique is sensitive enough to detect physiological blood oxygenation changes. Furthermore, a comparison with previous studies revealed an activation pattern distinct from those observed during other cognitive tasks. It is concluded that the results reflect local responses to specific task demands of the WCST.

Key words NIRS · WCST · Mental activation · Laterality

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Introduction

Near-infrared spectroscopy (NIRS) is a non-invasive optical technique which allows measurement of light absorbance in living tissues. It is based on the different absorption spectra of oxyhemoglobin (O_2HB) and deoxyhemoglobin (HHB). According to Lambert-Beer's law, the concentration changes of these chromophores can be calculated from the amount of light absorption at their specific wavelengths. In the context of brain metabolism, in vivo measurements of O_2HB and HHB concentrations changes are possible and of enormous interest because they provide an indication of the oxygen consumption due to neuronal activity, and of the resulting perfusion overshoot.

Since its first description by Jöbsis in 1977, the NIRS technique has been successfully applied for the examination of cerebral metabolism in states of global cerebral hypoperfusion in children (Brazy et al. 1985; Von Siebenthal et al. 1992; Wyatt 1994) and in adults (Germon et al. 1994; Kirkpatrick et al. 1995; Williams et al. 1994). These investigations showed that the NIRS technique was able to detect reliably the massive reductions of cerebral oxygenation during cerebral ischemia.

Recent evidence indicates that the method is sensitive enough to detect the small oxygenation changes during physiological brain activation. One-channel studies have shown that the O_2HB concentration changes during mental tasks, such as calculation or picture observation, can be detected in the left frontal lobes of healthy subjects (Hock et al. 1995; Hoshi et al. 1993, 1994; Villringer et al. 1993). Our group has shown that there were distinctive activation patterns between different neuropsychological tasks. A right frontal brain activation during the continuous performance test was demonstrated with a two-channel NIRS registration in healthy subjects (Fallgatter and Strik 1997) consistent with neurophysiological (Strik et al. 1998) and positron emission tomography (PET) studies (Buchsbaum et al. 1990). A further investigation showed a completely different pattern of activation associated with

a reading task consisting of bilateral prefrontal hypo-oxygenation. This result was interpreted as a sign of relative hypoperfusion due to an activation of language-related temporal areas (Fallgatter et al. 1998). An investigation with an active language-generation task (verbal fluency test), on the other hand, showed an oxygenation overshoot in left frontal areas in normal adults, and a loss of this response lateralization with a pattern of bilateral hyperoxygenation in patients with Alzheimer's dementia. The HHB and O_2HB concentration changes followed the rhythm of the subsets of the task with a delay of a few seconds (Fallgatter et al. 1997), which matches well the reaction times of the metabolic response (Bandettini et al. 1992).

Among the various neuropsychological tests developed to investigate frontal lobe functions, the Wisconsin Card Sorting Test (WCST) has gained particular attention (Goldberg and Podell 1995). Originally, it was developed to test the abstract reasoning abilities, and the ability to modify cognitive strategies according to environmental influences, in normal adult populations (Berg 1948; Grant and Berg 1948). The WCST was later reported to be specifically sensitive to frontal brain lesions in epileptic patients (Milner 1963, 1964), but also to other types of brain lesions (Drewe 1974). Although in some of the more recent studies the test failed to clearly discriminate between frontal and non-frontal brain lesions (Anderson et al. 1991; Grafman et al. 1990; Reitan and Wolfson 1994), it is still considered as a standard measure for frontal lobe function (Cronin-Golomb 1990), and as an idoneous method for frontal lobe activation in functional brain imaging studies.

In fact, single photon emission computed tomography (SPECT; Berman et al. 1986, 1990; Kawasaki et al. 1993; Marenco et al. 1993; Parellada et al. 1993; Rezai et al. 1993; Weinberger et al. 1986, 1988, 1992) and PET (Berman et al. 1995) studies have shown that activation of prefrontal cortical areas, in particular the dorsolateral prefrontal regions, are critical for the adequate performance of the WCST. Although indications for a lateralized activation were found, the question of whether the task activates the frontal lobes asymmetrically remained unanswered due to inconsistent results.

The present study was conducted to investigate whether NIRS is sensitive enough to assess the metabolic changes in the frontal lobes during performance of the WCST, and whether contingent functional lateralizations of the frontal lobes could be detected during the test.

Methods

A total of ten healthy subjects (five females and five males) without experience in the Wisconsin Card Sorting Test and with a mean age of 30.0 years (age range 27–33 years) were investigated. All of them were right-handed and medication free, and none of them had a personal or family history of alcohol- or substance abuse or any other neuropsychiatric illness.

The detailed principles of the NIRS technique are described elsewhere (Chance 1991; Delpy et al. 1988; Germon et al. 1994; Jöbis 1977; Kirkpatrick et al. 1995; Fallgatter and Strik 1997; Fallgatter et al. 1997, 1998). Two identical CritikonTM 2020 Cerebral Redox Monitors were used. The system includes two detectors and an algorithm based on quantified absorption spectra (Wray et al. 1988); the optical pathlength factor was 6.5 and compensation for background absorbers was implemented (Johnson and Johnson 1996). Each system consisted of a user interface connected to an external PC with a 486 processor, a flexible electro-optical cable and an adult head sensor with an emitter-detector spacing of 45 mm. Sequential pulses of monochromatic light at the wavelengths of 776.5, 819.0, 871.4 and 908.7 nm were emitted. A reflective proximity mechanism close to the emission window stopped the light transmission whenever the sensor was off the subject.

After cleaning of the subject's forehead with alcohol, both sensors were carefully applied on the skin by means of a flexible fixation pad. In addition, the sensors were fixed to the subjects with an elastic, light-absorbing band. The sensors were attached in identical positions in every subject, symmetrically at both fronto-temporal regions close to the hairline between the EEG electrode positions Fp1/F3 and Fp2/F4 of the International 10/20 system (Jasper 1958). From these sensor positions, chromophore concentration changes in the underlying cortical and subcortical brain tissue can be detected. Although the exact size of the brain volume penetrated by the method is not known, it is assumed that the spatial resolution of NIRS is poor measuring summary chromophore concentrations from a tissue up to several centimeters below the sensor.

The investigation took place in a sound-attenuated, dimly lit room, while the subjects sat on a comfortable chair with their chin resting on a stuffed support to avoid head movements. No further physiological recordings, such as heart rate, blood pressure, and thorax excursion measurements, were performed during the test. At a distance of 120 cm on eye level, a computerized version of the WCST (Cardsort program, Neurosoft) was displayed, consisting of a maximum of 128 cards and a minimum of 60 cards when six categories were completed without any mistake. A short demonstration of the handling of the computer mouse and an example of the acoustic feedback for the correctness of the cardsorting process was provided for every subject. According to the instructions of the Wisconsin Card Sorting Test Manual (Heaton et al. 1993), subjects were only told to match each of the appearing cards to one of the four key cards and to consider the feedback given by the computer. The total time of investigation including preparation (30 min) and stabilization of the system (15 min) was approximately 1 h.

After recording of a prestimulus baseline with eyes closed without specific instruction, the subjects had to execute the computerized form of the WCST. During baseline and task, data acquisition was performed by the NIRS systems with a rate of 1 Hz. Data were stored on hard disk. After transcription of the raw data into ASCII format, the length of the prestimulus baseline and task recordings of every subject were normalized to 25 and 216 s. respectively. These time intervals are considered to be largely sufficient to stabilize the cerebral hemodynamic response which has been shown to occur within 3 s rise and fall time (Bandettini et al. 1992). For quantification, the average values of HHB and O_2HB for prestimulus baseline (–25 to –1 s) and WCST activation (0–216 s) were computed separately for the left and right hemisphere. A baseline correction with the respective prestimulus value was performed for every measurement. In the following, these baseline-corrected values are referred to as the relative concentrations. 2 × 2 ANOVAs for repeated measurements [hemispheres (left vs right) × segments (activation vs baseline)] were computed for the parameters HHB and O_2HB (relative concentrations).

Results

Every subject completed all six WCST categories comprising 60 correct answers. The average time needed for the complete WCST was 285.8 s (216–475 s), the total error rate 18.7 (8–44). An age-matched normative sample

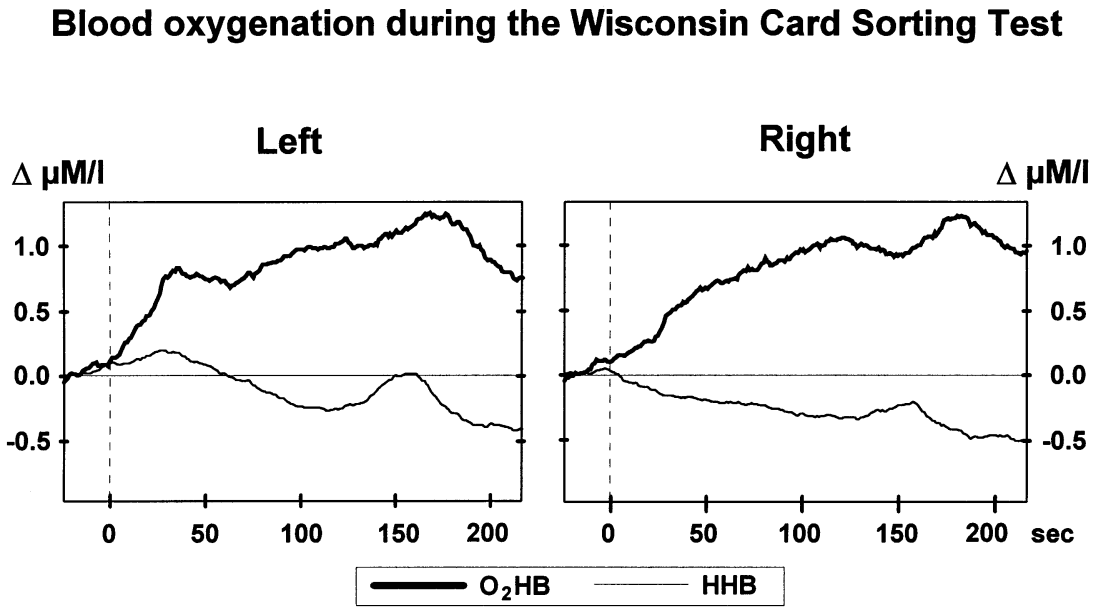

Fig. 1 Average trajectories of the relative concentrations (absolute values – baseline) of oxyhemoglobin (O_2HB) and deoxyhemoglobin (HHB) in ΔµM/l brain tissue, measured over left- and right-hemispheric frontal brain areas. A 25-point smoothing was applied only for this illustration which results in a slight blurring of the activation effects' onset back into the baseline period. Performance of the WCST started at 0 s which is indicated by the *dotted vertical lines*

Table 1 Relative chromophore concentrations during the WCST (activation – baseline) in µM/l ± SD for the left and right hemispheric frontal recording areas

	Left	Right
HHB	–0.13 ± 1.01	–0.29 ± 0.84
O_2HB	0.87 ± 1.14	0.83 ± 0.71

Table 2 *F*-values (*df* = 1,9) of 2 × 2 ANOVAs on O_2HB and HHB. Factors are: left vs right hemisphere (hemisphere) and baseline vs activation (segment)

	O_2HB	HHB
Hemisphere	0.01	0.68
Segment	11.26**	0.59
Hemisphere × segment	0.01	0.68

**$p < 0.01$

completed 5.62 ± 1.08 categories and had a total error rate of 16.16 ± 13.31 (Heaton et al. 1993).

The prestimulus baseline raw values were significantly higher for the left vs right hemisphere for O_2HB (75.3 ± 11.7 vs 68.8 ± 6.4 µM/l, $t = 2.63$, $p < 0.05$) and, as a trend, for HHB (32.6 ± 6.7 vs 29.9 ± 4.1 µM/l, $t = 1.87$, $p < 0.1$). As there are many unresolved problems concerning the measurement of absolute quantities of O_2HB and HHB, we did not rely on these values but on the baseline-corrected relative concentrations.

To control for the stability of the baseline measurements over time, the chromophore concentrations at rest before the WCST were compared with a baseline rest recorded 20 min before. Paired *t*-tests revealed no significant differences indicating a sufficient stability of the baseline measurements over time (HHB left hemisphere $t = 1.56$, n.s.; HHB right hemisphere $t = 0.27$, n.s.; O_2HB left hemisphere $t = 1.44$, n.s.; O_2HB right hemisphere $t = 0.34$, n.s.). The grand average values of left- and right-sided measurements after baseline correction are displayed for O_2HB and for HHB in Fig. 1. The relative left and right hemispheric concentrations, averaged over the activation period, are reported as means and standard deviations in Table 1. The relative concentration of O_2HB in the left and right frontal lobes increased during the performance of the WCST (0–216 s; Fig. 1). This relative increase of O_2HB was significant compared with baseline in a 2 × 2 ANOVA; no statistical differences were found between left- and right-sided measurements (Table 2). The average relative HHB concentration curves showed a slight decrease during the performance of the paradigm, with similar trajectories for left- and right-sided measurements (Fig. 1). This was not confirmed, however, by a 2 × 2 ANOVA, neither as a hemispheric nor as an activation effect (Table 2).

Discussion

The relative O_2HB concentration in frontal brain tissue increased significantly and bilaterally during the performance of the WCST compared with a resting condition. This result can be interpreted as an expression of increased cerebral perfusion as a consequence of an activated brain metabolism during the task. Simultaneously, HHB showed a progressive reduction. Although not significant, this latter effect is consistent with an enhanced HHB draining, secondary to hyperperfusion. The result appears to be specific for the specific demands of the

WCST and not due to the general effects of attention, perception, and motor response. In fact, the activation pattern clearly differs from the bilateral frontal hypo-oxygenation during a reading task, from the lateralized left frontal signs of hyperperfusion during the Verbal Fluence Test, and also from the right lateralized frontal activation during the Continuous Performance Test (see Introduction; Fallgatter et al. 1997, 1998; Fallgatter and Strik 1997).

The finding of an increased frontal brain metabolism during the WCST compared with rest in healthy subjects is in line with preceding neuroimaging studies (Berman et al. 1986; Kawasaki et al. 1993; Marenco et al. 1993; Parellada et al. 1993; Rezai et al. 1993; Weinberger et al. 1986, 1988, 1992; Berman et al. 1995). In these investigations, the main activation during the task was consistently localized in dorsolateral prefrontal areas. However, several physiological studies indicated an additional activation of non-frontal brain regions (Berman and Weinberger 1990; Berman et al. 1995; Marenco et al. 1993). Since, for technical reasons, the applied NIRS technique was restricted to anterior frontal regions, the present study does not add information as to the specificity of this frontal brain activation, however.

The question of lateralized cortical activation during the WCST has not been resolved consistently by SPECT and PET. The first studies did not report any side differences of the prefrontal activation (Berman et al. 1986; Weinberger et al. 1986, 1988). In more recent studies, however, a prevalence of left-sided prefrontal activation was described (Berman and Weinberger 1990; Berman et al. 1995; Kawasaki et al. 1993; Rezai et al. 1993; Weinberger et al. 1992). Marenco et al. (1993), on the other hand, found a right-sided anterior dorsolateral prefrontal activation using a simple matching-to-sample task as a control condition. The lack of hemispheric effects in the present study could be obviously explained by a lack of sensitivity of the NIRS method for subtle lateralization effects. However, hemispheric activation differences were detected with the same method during the Continuous Performance Test and during the Verbal Pairs Test (Fallgatter and Strik 1997; Fallgatter et al. 1997b). The present results indicate, therefore, that any hemispheric differences evoked by the WCST might be less pronounced than in the previously mentioned tests.

In conclusion, the present investigation supports the results from SPECT and PET studies, showing an enhanced frontal lobe perfusion during performance of the WCST. No further information was added concerning the regional specificity of the changes, and the question of any activation asymmetries could not be convincingly resolved. However, the study adds further evidence that the NIRS technique is sensitive enough to detect blood oxygenation changes elicited by physiological brain activity, and to identify distinctive patterns for neuropsychological tests with different cognitive demands. Present limitations of the method include a low signal-to-noise ratio which does not permit the reported statistical effects to be reliably confirmed in single recordings. An improvement of the technique to reduce the noise and to improve the spatial resolution is necessary before this non-invasive, easy-to-handle, and low-cost method can be successfully used for monitoring of functional brain metabolism in neuropsychology and psychiatry.

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