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Activation of the Prefrontal Cortex During Verbal Fluency Tasks as Measured with 2-Channel Near-Infrared Spectroscopy in Children

Yoshimi TAMEKUCHI[1,2], Keiji HASHIMOTO[3], Manami HONDA[3,4], Kohei MIYAMURA[3], and Masahiro ABO[5]

[1]*Department of Otorhinolaryngology (Head and Neck Surgery), Tokyo Medical and Dental University, Graduate School of Medical and Dental Sciences, Cognitive and Behavioral Medicine Systems Neuroscience*
[2]*Department of Brain Pathophysiology, Kyoto University, Graduate School of Medicine, Human Brain Research Center*
[3]*Division of Rehabilitation Medicine and Developmental Evaluation Center, National Center for Child Health and Development*
[4]*Nico Children's Clinic*
[5]*Department of Rehabilitation Medicine, The Jikei University School of Medicine*

ABSTRACT

To investigate brain activation in the prefrontal cortex (PFC) during verbal fluency tasks (VFTs) consisting of 3 word-association tasks regarding fruits, vegetables, and vehicles, we examined changes in oxyhemoglobin volume in 8 apparently healthy right-handed children and 10 adult control subjects by means of 2-channel near-infrared spectroscopy. The average oxyhemoglobin volume in the left PFC during VFTs in the children (-0.011 ± 0.005) was significantly higher than in the adults (-0.017 ± 0.004 ; unpaired t-test, $p<0.01$). On the other hand, the average oxyhemoglobin volume in the right PFC during VFTs was significantly higher in adults (0.033 ± 0.052) than in children (-0.015 ± 0.012 ; unpaired t-test, $p<0.01$). These results suggest that higher activation during VFT in the left PFC in children and in the right PFC in adults reflect developmental plasticity for the ongoing organization of the neural network of the frontal lobe.

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Key words : children, near-infrared spectroscopy, frontal lobe function, verbal fluency task

INTRODUCTION

Near-infrared spectroscopy (NIRS) is a noninvasive optical method to determine changes in the concentrations of oxyhemoglobin and deoxyhemoglobin in the human cerebral cortex[1-6]. NIRS has been used to map primary motor and visual functions[7,8]. Cognitive research has also used NIRS. Fallgatter and Strik[9] have used NIRS and reading/picture observation to identify increases in oxyhemoglobin and decreases in deoxyhemoglobin in the left and right anterior prefrontal cortices (PFCs), but no differences were observed between the left and right PFCs. Watanabe et al.[10] observed increased levels of oxyhemoglobin in both the left and right inferior frontal gyri during a word-generation task, but found no decrease in deoxyhemoglobin. Recently, cerebral activation studies have been performed with xenon contrast-enhanced computed tomography (CT), single-photon emission CT, positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and transcranial Doppler ultrasonograpy[11-16]. However, because of restrictions imposed by space and motion, monitoring cerebral circulation during rehabilitation tasks with these methods is difficult. As a result, the kinds of task that can be performed during such monitoring are limited. We believe NIRS would be useful for monitoring cerebral activation during rehabilitation tasks because it does not present the

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為口よしみ，橋本　圭司，本田　真美，宮村　紘平，安保　雅博
Mailing address : Keiji HASHIMOTO, Division of Rehabilitation Medicine and Developmental Evaluation Center, National Center for Child Health and Development, 2-10-1 Okura, Setagaya-ku, Tokyo 157-8535, Japan.
E-mail : hashimoto-k@ncchd.go.jp

problems associated with conventional methods, such as fMRI and PET.

Explaining cognitive function with only CT or MRI of the head is often difficult[17-19]. With neuropsychological examinations, such as verbal fluency tasks (VFTs), frontal lobe dysfunction can sometimes be detected. In areas where function is reduced, blood flow and metabolism are probably also reduced. Consequently, objectively constructing an image of the affected regions by means of conventional single-photon emission CT is difficult. On the other hand, PET, fMRI, and diffusion tensor imaging might be useful for gaining an understanding of the affected areas[20]. However, these methods are available only at large institutions.

Compared with fMRI, NIRS provides greater freedom of use in various situations, such as situations resembling those in daily life. Thus, this method has the advantage that measurements can be performed during an entire testing session. Adelson et al.[21] have reported the use of NIRS in children after traumatic brain injury (TBI), and Hashimoto et al.[22] have used a multichannel NIRS system to examine frontal hemodynamics. However, a simple method is necessary for clinicians to measure frontal lobe function.

We have used 2-channel NIRS to easily demonstrate hemodynamics in the frontal part of the brain in patients with TBI as they performed the Wisconsin Card Sorting Test, Keio Version, and found that patients with TBI had lower total hemoglobin volume in the right PFC during this test than did control subjects[23].

The purpose of the present pilot study was to measure hemodynamics in the frontal part of the brain using 2-channel NIRS in apparently healthy children as they performed VFTs. We compared oxyhemoglobin volume in the prefrontal cortex (PFC) between these children and healthy adult control subjects.

SUBJECTS AND METHODS

Subjects

The subjects were 8 apparently healthy children (average age, 7.4±1.3 years ; 4 boys and 4 girls) and 10 apparently healthy adults who served as controls (average age, 39.2±4.2 years ; 6 women and 4 men). All participants were right-handed and had no history of acquired brain injury or cognitive dysfunction. Before the study, all subjects or their parents gave informed consent to participate in the research. This study was performed in accordance with the Ethics Committee of Nico Children's Clinic and the Japanese Union of Traumatic Brain Injury Rehabilitation and Advocacy. There was no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Experimental Procedure

The subjects performed VFTs lasting 1 minute. During each cycle, the subjects closed their eyes for 30 seconds, opened their eyes for the next 30 seconds, and then performed each task for 60 seconds. This set was performed 3 times with the block design (Fig. 1). The VFTs consisted of 3 word-association tasks for fruits, vegetables, and vehicles. We allowed the subjects to close their eyes to return brain activity to the original pre-VFT baseline. The procedure took place in a quiet room without windows. All procedures related to the experiment, including explanation of the study, obtaining informed consent, and fitting the NIRS system to the subjects, were completed within 6 minutes.

NIRS Imaging System

The NIRS measurements were performed with a 2-channel NIRS system (OMM-220, Shimazu Corp., Kyoto, Japan). The system consists of 4 fibers with 4 light sources and 4 detectors and allows simultaneous 2-channel recording. The system can detect cortical changes in oxyhemoglobin, deoxyhemoglobin, and total hemoglobin volume. To detect the function of the front part of the ce-

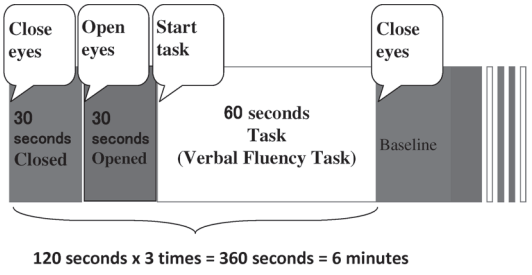


Fig. 1. Experimental protocol for NIRS
The participants performed VFTs lasting 1 minute each. During each cycle, the subjects closed their eyes for 30 seconds, opened their eyes for the next 30 seconds, and then performed each VFT for 60 seconds. This set was performed 3 times with the block design

rebrum, we placed the lower edge of the fiber holder 2 cm above the supraorbital margin to ensure that the fibers covered the front of the brain.

Measurement of Cerebral Blood Volume

If the hematocrit and perfusion pressure are stable, cerebral blood flow volume is related to focal oxyhemoglobin flow volume[22]. Therefore, a change in oxyhemoglobin volume can be an indicator of cerebral blood volume. The main purpose of this study was to evaluate hemodynamic changes in the frontal part of brain ; therefore, we used data on oxyhemoglobin volume for analysis. Because normative data for oxyhemoglobin volume are not available, we compared the oxyhemoglobin volume data of children with those of healthy adults. By comparing oxyhemoglobin volume during the performance of VFTs with the eyes open and oxyhemoglobin volume during the 30-second period before performance (baseline), we classified oxyhemoglobin volume into 3 groups as follows : 1) oxyhemoglobin volume increased during the task, 2) oxyhemoglobin volume decreased during the task, and 3) oxyhemoglobin volume did not change significantly.

Statistical Analysis

Oxyhemoglobin volume at the start of eye closing was set at 0 (baseline) and was recorded continuously thereafter. The oxyhemoglobin volume data recorded every 1.0 second for 3 cycles were divided into 2 independent groups as follows : (a) 90 data points while the eyes were open for 90 seconds, and (b) 180 data points for 180 seconds during the performance of 3 cycles of tasks. We compared the 2 groups by means of the unpaired *t*-test to divide channels into the 3 groups described above. We also compared the average oxyhemoglobin volume data during 3 cycles of the tasks between children and adults. The unpaired *t*-test was used to determine whether in oxyhemoglobin volume differed significantly between the 2 subject groups. Data were analyzed with the PASW Statistics 17.0 software program (SPSS Japan, Inc., Tokyo).

Results

When children performed VFTs, the oxyhemoglobin volume in the PFC decreased bilaterally in 1, increased on the left side in 3, decreased on the right side in 1, and did not change significantly on either side in 4. In adults, the oxyhemoglobin volume in the PFC increased bilaterally in 2, decreased bilaterally in 1, increased only on the right side in 2, decreased on the left side in 4, and did not change significantly on either side in 1.

Fig. 2 shows the mean hemodynamic changes in 3 cycles of closed eyes, open eyes, and the VFTs in the bilateral PFC in the 8 children and the 10 adults.

The mean changes in oxyhemoglobin volume in the 3 cycles of the block design in the 8 children and the 10 adults are shown in Table 1. In children the mean oxyhemoglobin volume in the PFC during VFTs was significantly greater on the left side (-0.011 ± 0.005) than on the right side (mean $\pm$ SD, -0.015 ± 0.012 ; unpaired *t*-test, $p < 0.01$). On the other hand, the mean oxyhemoglobin volume in the PFC during VFTs in adults was significantly greater on the right side (0.033 ± 0.052) than on the left side (-0.017 ± 0.004) (unpaired *t*-test, $p < 0.01$).

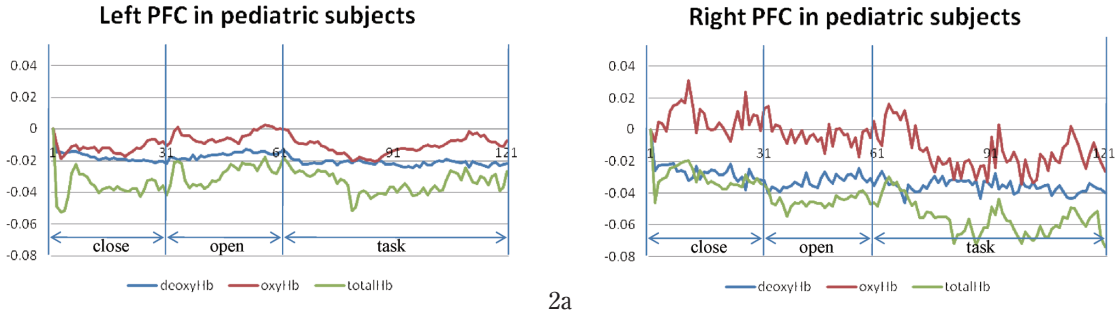
The mean oxyhemoglobin volume in the left PFC during VFTs was significantly higher in children (-0.011 ± 0.005) than in adults (-0.017 ± 0.004 ; unpaired *t*-test, $p < 0.01$). In contrast, mean oxyhemoglobin volume in the right PFC during VFTs was significantly higher in adults (0.033 ± 0.052) than in children (-0.015 ± 0.012 ; unpaired *t*-test, $p < 0.01$).

In this analysis, we found significantly higher activation during VFT in the left PFC in children and in the right PFC in adults.

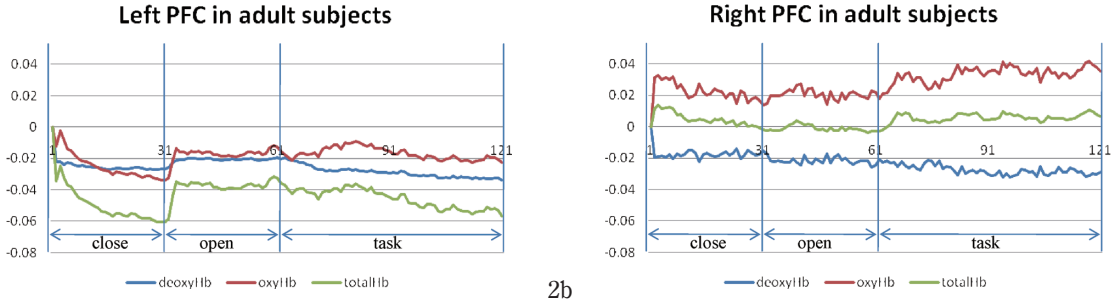
Discussion

NIRS is an optical technique with high temporal resolution and good spatial resolution that allows noninvasive measurement of tissue blood oxygenation. A challenge of using functional NIRS for cognitive neuroscience is to obtain data that can be systematically analyzed and are universally interpretable and, thus, may answer important scientific questions about the functional organization and neural systems underlying human higher cognition[24]. The present work is focused on assessing and correlating brain activation, connectivity, and cortical lateralization of the frontal cortex in response to language-based stimuli using NIRS.

Chaudhary et al.[25] observed increases in oxygenated hemoglobin during VFTs in the frontal cortex of 15 healthy right-handed adults. Bilateral activation and symmetrical



2a



2b

Fig. 2. Mean hemodynamic changes in the bilateral PFC in 3 cycles of VFTs in 8 children (a) and 10 adults (b)

Table 1.

		Child		Adult		
		mean	SD	mean	SD	
Right hemisphere	open	−0.003	0.006	0.021	0.003	
	task	−0.015	0.012	0.033	0.052	**
Left hemisphere	open	−0.004	0.004	−0.017	0.004	
	task	−0.011	0.005	−0.017	0.004	**

Significant difference : ** $P<0.01$

connectivity were observed in the PFC, independent of the stimuli presented. In addition, left cortical dominance and asymmetrical connectivity were observed in the anterior frontal cortex during VFTs. This result differed from our findings in both children and adults : we found asymmetrical activation in oxyhemoglobin volume in the PFC and predominant activation on the right side. These differences may be due to differences between their method and ours. We recorded prestimulus baseline data with eyes closed and eyes open for 30 seconds each 3 times using the block design. Chaudhary et al., however, recorded the baseline with random jaw movement and under resting conditions. We must consider the possibility that the time intervals for the eyes to be open and closed were not sufficient to stabilize the cerebral hemodynamic response ; thus, a baseline obtained with eyes open might not have been appropriate. More research using the block design with a longer period for the baseline and an appropriate baseline task is required.

Kuwabara et al.[26] used NIRS to examine 10 adults with pervasive developmental disorders (PDD) and 10 age- and sex-matched healthy subjects while they performed a letter fluency task. Although the number of words generated during the letter fluency task did not differ significantly between the groups, the analysis of covariance including IQ as a confounding covariate showed a bilateral reduction in oxyhemoglobin concentration in patients with PDD compared with healthy subjects. Moreover, the reduction in

the oxyhemoglobin concentration in the right PFC was significantly correlated with verbal communication deficits in patients with PDD. Kuwabara et al. concluded that these results might be useful for applying NIRS to child psychiatry.

Moriguchi et al.[27] monitored developmental changes in behavioral performance and examined prefrontal activation by means of NIRS. They found that children showed better behavioral performance and significantly stronger inferior prefrontal activation at 4 years of age than at 3 years of age. Children who performed better at tasks at 4 years of age showed significant activation of the right inferior prefrontal regions at that age and significant activation of the bilateral inferior prefrontal regions at 3 years of age. Children who showed poorer performance at 4 years of age exhibited no significant inferior prefrontal activation at that age but showed significant left inferior prefrontal activation at 3 years of age. Moriguchi et al. oncluded that these results indicate the importance of the longitudinal method to address the link between cognitive development and neural development.

Gaillard et al.[28] have used fMRI to identify age-dependent activation patterns of verbal fluency. Children and adults showed activation in similar areas, predominantly the left inferior frontal cortex (Broca's area) and the left middle frontal gyrus (dorsolateral PFC). Children had, on average, a 60% greater extent of activation than did adults, with a trend for greater a magnitude of activation. Thus, fMRI using verbal fluency paradigms can be used to determine language dominance in the anterior brain in children. The greater activation found in children may reflect developmental plasticity for the ongoing organization of neural networks, which underlie language capacity.

In the present study, we found significantly higher activation during VFTs in the left PFC in children and in the right PFC in adults. In children, activation was greater, especially in the left PFC, but activation in the right PFC was lower than in adults. When we defined the 0 point for oxyhemoglobin volume as the start of the first eye-closing phase, we can consider that the average oxyhemoglobin volume in the left PFC during VFTs in children was significantly higher than in adults. Predominant activation of the left PFC was greater in children than in adults, suggesting that 2-channel NIRS reflects developmental plasticity for the ongoing organization neural network of frontal lobe function.

This result supports the findings of Gaillard's study[28] described above. The significant higher activation during VFT in the left PFC in children and in the right PFC in adults might have occurred because of the plasticity of neural development in both hemispheres in children. Because VFTs require verbal function, the predominant activation in the left frontal area might also be due to a relationship with language function.

We often use neuropsychological tests when diagnosing developmental disabilities in children. By using a measurement such as the 2-channel NIRS technique reported here, we could diagnose certain types of frontal lobe dysfunction, such as verbal fluency, and objectively measure hemodynamic changes in the frontal lobe. In the present study, we found that healthy children had significantly higher oxyhemoglobin volume in the left PFC than did adults. This result suggests we can detect the developmental plasticity of frontal lobe activation in children in whom neuropsychological dysfunction has not been diagnosed with neuropsychological testing. In the future, greater use of simple 2-channel NIRS systems for examining neuropsychological function can be expected for children with certain developmental disabilities.

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