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A quantitative near-infrared spectroscopy study: A decrease in cerebral hemoglobin oxygenation in Alzheimer's disease and mild cognitive impairment

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Abstract

A newly developed quantitative near-infrared spectroscopy (NIRS) system was used to measure changes in cortical hemoglobin oxygenation during the Verbal Fluency Task in 32 healthy controls, 15 subjects with mild cognitive impairment (MCI), and 15 patients with Alzheimer's disease (AD). The amplitude of changes in the waveform, which was quantitatively calculated by a signal processing method, was significantly lower in the frontal, and the bilateral parietal areas in the AD group, whereas that in the MCI group was significantly lower only in the right parietal area. The NIRS system may be a potential tool for the primary screening of AD.

Keywords: Near-infrared spectroscopy; Alzheimer's disease; Mild cognitive impairment; Hemoglobin oxygenation; Quantitative method; Primary screening

1. Introduction

Brain imaging [computed tomography and magnetic resonance imaging (MRI)] and cognitive tests are usually used for the diagnosis of Alzheimer's disease (AD) (Poulin & Zakzanis, 2002). Positron emission tomography (PET) and single photon emission tomography (SPECT) are more powerful, and their diagnostic sensitivity and specificity are 70–90% (Dougall et al., 2004; Patwardhan et al., 2004; Staffen et al., 2005). PET with an amyloid-imaging tracer (Klunk et al., 2004) and functional MRI (Mandzia et al., 2002; Remy et al., 2004) are also promising. However, these devices are expensive for routine clinical use. Multichannel near-infrared spectroscopy (NIRS) is an alternative. NIRS is an optical method that allows non-invasive in vivo measurement of concentration in oxygenated and deoxygenated hemoglobins (Hbs) in cortical areas (Yamashita et al., 1996). Although the possible usefulness of NIRS has been reported for the evaluation of AD and other mental illnesses (Fallgatter et al., 1997; Hock et al., 1997; Suto et al., 2004), one of the disadvantages is that the changes in Hb concentration are not measurable as absolute values, restricting its clinical use. Therefore, we used a new multi-channel NIRS machine with a short activation method, and obtained clinically useful quantitative data from subjects with AD or mild cognitive impairment (MCI).

2. Materials and method

2.1. Subjects

For the control group, 32 healthy, medication-free, right-handed subjects with no history of neuropsychiatric illness were recruited after signing a written informed consent form following an explanation of the present study.

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Table 1
Clinical data

	Control	MCI	AD
No. of subjects	32	15	15
Age [mean (*SD*)]	57.3 (6.4)	63.0 (6.4)	59.2 (3.9)
Female:male	16:16	8:7	10:5
MMSE score [mean (*SD*)]	29.1 (0.8)	26.3 (1.6)	15.1 (7.0)
No. of words in VFT [mean (*SD*)]	15.7 (4.7)	15.5 (5.4)	7.5 (4.6)

Then, 15 right-handed probable AD patients according to the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association (NINCDS–ADRDA) criteria (McKhann et al., 1984) and 15 right-handed amnestic MCI cases according to the criteria of Petersen et al. (2001) were examined after signing a written informed consent form by themselves. The spouses of four AD patients with a low Mini Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) score (<10) signed alternatively. The clinical data are shown in Table 1. The three groups were matched in terms of age, sex ratio, and education. This study was approved by the ethical review committee of the Juntendo University School of Medicine.

2.2. NIRS

Changes in hemoglobin concentration during the task were measured using the whole head type NIRS system (ETG-7000, Hitachi Medical, Tokyo, Japan). Each probe of the NIRS system had 24 channels in an area of 9×9 cm (Maki et al., 1995), and four probes were placed on the subject's frontal (24 channels), bilateral parietal (24 channels each), and occipital (12 channels) areas (Fig. 1). The lowest line of the frontal probe was located on the Fp_1–Fp_2 line according to the international 10/20 electrode system (The EEG Society, 1958). The center of the parietal probe was located at P_3/P_4, and the occipital probe was on the O_1–O_2 line. The correspondence of the probe positions was confirmed by superimposition of the probes on a representative three-dimensionally constructed MRI of a healthy volunteer.

The amplitude of changes in the oxygenated hemoglobin (oxy-Hb) waveform in each area during the task was expressed as the activation index (A-Index). The index was calculated by the signal processing of (i) excluding the motion artifacts, (ii) averaging the data (Maki et al., 1995), (iii) principal component analysis(PCA) (Jolliffe, 1986; Watanabe et al., 2004) of the averaged [oxy-Hb] data in a probe to obtain the representative time-course, and (iv) fitting the representative time-course calculated by PCA to a hemodynamic activation model using the simplex method (Nelder & Mead, 1965; Fig. 2).

First, the trial data including the motion artifacts were excluded from our analysis by finding the abrupt [oxy-Hb] change, which was empirically defined as more than 0.5 mM mm change in 0.2 s.

Second, [oxy-Hb] were averaged in each channel with the linear fitting and a 0.5 Hz low pass filter was performed to decrease the noise from the heartbeat (about 1 Hz). The negative [oxy-Hb] changes during the task were excluded from the analysis in this step because the PCA was not able to distinguish the negative [oxy-Hb] change waveform from the positive [oxy-Hb] change waveform of the same amplitude (Table 2).

Third, the representative time-course $\sqrt{\lambda/n} \cdot m_{\mathrm{oxy}}(t)$ in each area was calculated by PCA on the averaged [oxy-Hb] data of each probe, where $\lambda\,\mathrm{mM}^2\,\mathrm{mm}^2$ denotes the largest eigen value in PCA, $m_{\mathrm{oxy}}(t)$ denotes the normalized time-course of the first component in PCA, t denotes the time between the beginning time of the pre-stimulation period and the end time of the post-stimulation period, and n denotes the number of channels of each probe.

Fourth, the A-Index in each area was determined by fitting the representative time-course to the simple hemodynamic model using the simplex method (Fig. 2). The model described the typical [oxy-Hb] change divided into the pre-activation period, the activation period, and the post-activation period. The model consisted of the parameters $t_1,t_2,\ldots,t_6,y_1,y_2,y_3$ and an expression $f(t)$, where the beginning time of the stimulation period was defined as 0 s, t_1 (=−10 s) denoted the beginning time of the pre-stimulation period, t_2 denoted the beginning time of the activation period, t_3 denoted the beginning time of the plateau period, t_4 denoted the end time of the of the plateau period, t_5 denoted the beginning time of the post-activation period, t_6 (=34 s) denoted the end time of post-stimulation period, and y_1,y_2,y_3 mM mm denoted the [oxy-Hb] value during the pre-activation period, the plateau period, and the post-activation period, respectively, and the expression was as below.

$$f(t) = \begin{cases} y_1 & (t_1 \leqslant t \leqslant t_2) \\ (y_1 - y_2) \times (t - t_2)/(t_2 - t_3) + y_1 & (t_2 \leqslant t \leqslant t_3) \\ sy_2 & (t_3 \leqslant t \leqslant t_4) \\ (y_2 - y_3) \times (t - t_4)/(t_4 - t_5) + y_2 & (t_4 \leqslant t \leqslant t_5) \\ y_3 & (t_5 \leqslant t \leqslant t_6). \end{cases}$$

The adequate parameters for $t_2,\ldots,t_5,y_1,y_2,y_3$ were found by performing the simplex method and the minimizing function $\sum_{t=t_1}^{t_6}\left(m_{\mathrm{oxy}}(t) - f(t)\right)^2$. (The expression $f(t)$ was treated as the dispersed value every 0.1 s.) The initial value of the parameter for the fitting calculation was set from the representative time-course data $\sqrt{\lambda/n} \cdot m_{\mathrm{oxy}}(t)$ in each area as described below:

t_2, beginning time of the stimulation period;
t_3, 1/4 of the length of the stimulation period after the beginning time of the stimulation period;
t_4, 1/5 of the length of the relaxation period after the beginning time of the relaxation period;
t_5, 4/5 of the length of the relaxation period after the beginning time of the relaxation period;