Chapter 37
Relation Between Cognitive Function and Baseline Concentrations of Hemoglobin in Prefrontal Cortex of Elderly People Measured by Time-Resolved Near-Infrared Spectroscopy

Y. Murayama, Y. Sato, L. Hu, A. Brugnera, A. Compare, and Kaoru Sakatani

Abstract We evaluated relationship between cognitive function and cerebral blood oxygenation (CBO) of the prefrontal cortex (PFC) at rest in 113 adults (age 72.3 ± 12.0 years). We employed a two channel time-resolved near-infrared spectroscopy (TRS), which allows non-invasive measurements of baseline concentrations of oxyhemoglobin (oxy-Hb), deoxyhemoglobin (deoxy-Hb), total-hemoglobin (t-Hb) (μM) and oxygen saturation (SO_2, %) of the bilateral PFC without any tasks. We examined cognitive functions using the Mini-Mental State Examination (MMSE) (range from 0 to 30) and the Touch M which evaluates working memory function semi-automatically on a touchscreen (range from 0 to 100); the mean MMSE and Touch M scores of all subjects were 24.8 ± 4.6 (mean ± SD; range 11–30) and 41.3 ± 22.1 (range 1–100), respectively. Employing Pearson's correlation analysis, we evaluated correlation between the TRS parameters and cognitive function. We found a significant positive correlation between the MMSE scores and SO_2 ($r = 0.24$, $p < 0.02$). In addition, we observed significant positive correlations between Touch M scores and baseline concentrations of oxy-Hb ($r = 0.26$, $p < 0.02$), total-Hb ($r = 0.23$, $p < 0.05$), and SO_2 ($r = 0.23$, $p < 0.05$). TRS allowed us to evaluate the relation between CBO in the PFC at rest and cognitive function.

Keywords TRS • NIRS • Dementia • Alzheimer's disease • Cognitive function

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1 Introduction

As the world's population is rapidly aging, dementia has become an important public health problem. In order to prevent the onset and deterioration of cognitive function, it is important to develop techniques for objective assessment of cognitive function. Positron Emission Tomography (PET) and Magnetic Resonance Imaging (MRI) have been used for the diagnosis of dementia [1]; PET evaluates changes of cerebral blood flow and oxygen metabolism while MRI evaluates changes of volumes such as cortexes and hippocampus. These techniques, however, require large facilities and have high costs for examination and maintenance. A simple and less costly method to assess cognitive function is necessary for screening test of dementia.

Near infrared spectroscopy (NIRS) appears to be an attractive alternative method since it is compact and less costly than MRI or PET. NIRS, which employ continuous wave light, allows to measure relative changes of hemoglobin (Hb) concentration in cerebral blood vessels [2]. In contrast, time-resolved near infrared spectroscopy (TRS), which employs picosecond light pulses, permits quantitative measurements of Hb concentrations at rest [3]. TRS has been applied to monitoring of cognitive function in normal adults [4, 5] and cerebral blood flow in patients with cerebrovascular diseases [6].

In the present study, employing TRS, we evaluated relationship between cognitive function and Hb concentrations at rest of the prefrontal cortex (PFC) in middle and old-aged subjects.

2 Methods

2.1 Subjects

We studied 113 subjects (60 males, 53 females; age 72.3 ± 12.0 years (mean ± SD); range 45–91 years; 82 cases ≧65 years, 31 cases <65 years) who exhibited a variety of cognitive function between normal and dementia (see Sect. 2.2 Assessment of Cognitive Function). All subjects visited Southern Touhoku Kasuga Rehabilitation Hospital (Sukagawa city, Japan) due to various symptoms including forgetfulness. The subjects provided written informed consent as required by the Human Subjects Committee of the Rehabilitation Hospital; when the subject had difficult to understand the informed consent due to cognitive dysfunction, their family provided.

2.2 Assessment of Cognitive Function

Initially, we evaluated cognitive function of the subjects using the Mini Mental State Examination (MMSE), which is effective as a screening tool that can be used to systematically assess mental status [7]: no cognitive impairment = 24–30; mild

cognitive impairment = 18–23; severe cognitive impairment = 0–17. The mean MMSE scores were 24.8 ± 4.6 (range 11–30); 80 cases for normal, 23 cases for mild, 10 cases for sever cognitive impairment. In addition, we evaluated cognitive function using the Touch M (HUMAN Co. Ltd., Japan) which examines working memory function semi-automatically on a touchscreen [8]. The maximum scores of the Touch M is 100; the scores of 70–100, 40–69 and 0–39 indicate normal, mild impairment and impairment of working memory, respectively [8]. The mean Touch M scores were 41.3 ± 22.1 (range 1–100); 8 cases for normal, 37 cases for mild, 33 cases for sever cognitive impairment (total 78 cases).

2.3 TRS Measurement

We measured the baseline concentrations of Hb in the bilateral PFC at resting condition employing TRS (TRS-21, Hamamatsu Photonics K.K., Hamamatsu, Japan) [9], which was used in our previous studies [4–6]. Details of this system have been described by us previously [4–6]. Briefly, it consists of three pulsed laser diodes with different wavelengths (761, 791, and 836 nm) having a duration of 100 ps at a repetition frequency of 5 MHz, a photomultiplier tube, and a circuit for time-resolved measurement based on the time-correlated single photon counting method. The observed temporal profiles were fitted into the photon diffusion equation [3, 9] using the non-linear least-squares fitting method. The concentrations of oxy-Hb, deoxy-Hb, t-Hb (=oxy-Hb + deoxy-Hb) and SO_2 were calculated using the least-squares method. The concentrations of Hb were expressed in μM.

The TRS probes were set symmetrically on the forehead with a flexible fixation pad so that the midpoint between the emission and detection probes was 3 cm above the centers of the upper edges of the bilateral orbital sockets (Fig. 37.1a); this positioning is similar to the midpoint between electrode positions Fp1/Fp3 (left) and Fp2/Fp4 (right) of the international electroencephalographic 10–20 system. MRI confirmed that the emitter-detector was located over the dorsolateral and frontopolar areas of the bilateral PFC (Fig. 37.1b). The distance between the emitter and detector was set at 3 cm.

It was reported that the contribution ratio of the cerebral tissue to optical signals (i.e. ratio of partial optical pathlength to total optical pathlength) at the probe distances of 2, 3 and 4 cm as 33%, 55% and 69%, respectively [10]. Based on this result, we suggest the contribution rate of the PFC was about 55% in the present study.

2.4 Data Analysis

Employing Pearson's correlation analysis, we evaluated correlations between TRS parameters and cognitive function evaluated by the MMSE and Touch M scores. In addition, we compared TRS parameters between normal subjects (MMSE≧24) and subjects with cognitive impairment (MMSE≦23) using t-test.

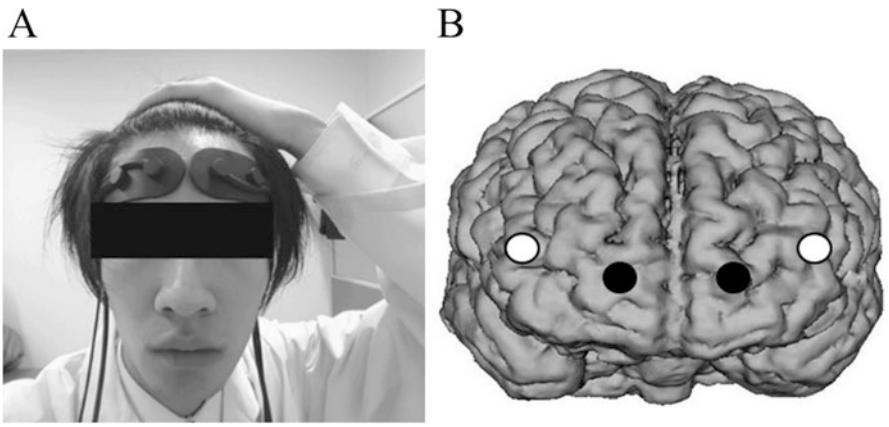

Fig. 37.1 (**a**), Location and (**b**), Position of the TRS probes (*The black dot* Emitter, *The white dot* Detector)

3 Results

There was a significant negative correlation between the age of the subjects and MMSE scores ($r = -0.43$, $p < 0.01$) (Fig. 37.2a) and Touch M scores ($r = -0.40$, $p < 0.01$) (Fig. 37.2b). In addition, there was a significant positive correlation between MMSE scores and Touch M scores ($r = 0.44$, $p < 0.01$) (Fig. 37.2c).

The SO_2 in the PFC measured by TRS varied between the subjects; however, there was a significant positive correlation between MMSE and SO_2 in the left PFC ($r = 0.24$, $p < 0.02$) and the right PFC ($r = 0.24$, $p < 0.02$) (Fig. 37.3).

There was a significant positive correlation between Touch M scores and SO_2 in the left PFC ($r = 0.25$, $p < 0.05$) and the right PFC ($r = 0.23$, $p < 0.05$) (Fig. 37.4a). In addition, Touch M scores showed a significant positive correlation with oxy-Hb concentrations at rest in the left PFC ($r = 0.27$, $p < 0.02$) and the right PFC ($r = 0.26$, $p < 0.02$) (Fig. 37.4b). In contrast, MMSE scores showed no correlation with oxy-Hb concentrations at rest.

Finally, we observed significant larger SO_2 in the bilateral PFC of normal subjects than those of impaired subjects (Table 37.1).

4 Discussion

The present study demonstrates that SO_2 in the bilateral PFC at rest showed a significant positive correlation with both the MMSE and Touch M scores. In addition, the baseline concentrations of oxy-Hb at rest also showed a significant positive correlation with Touch M scores. It should be emphasize that the correlation coefficient (r) was relatively low, but statistically significant. These results are consistent with our recent TRS study, which showed that elderly women with normal or

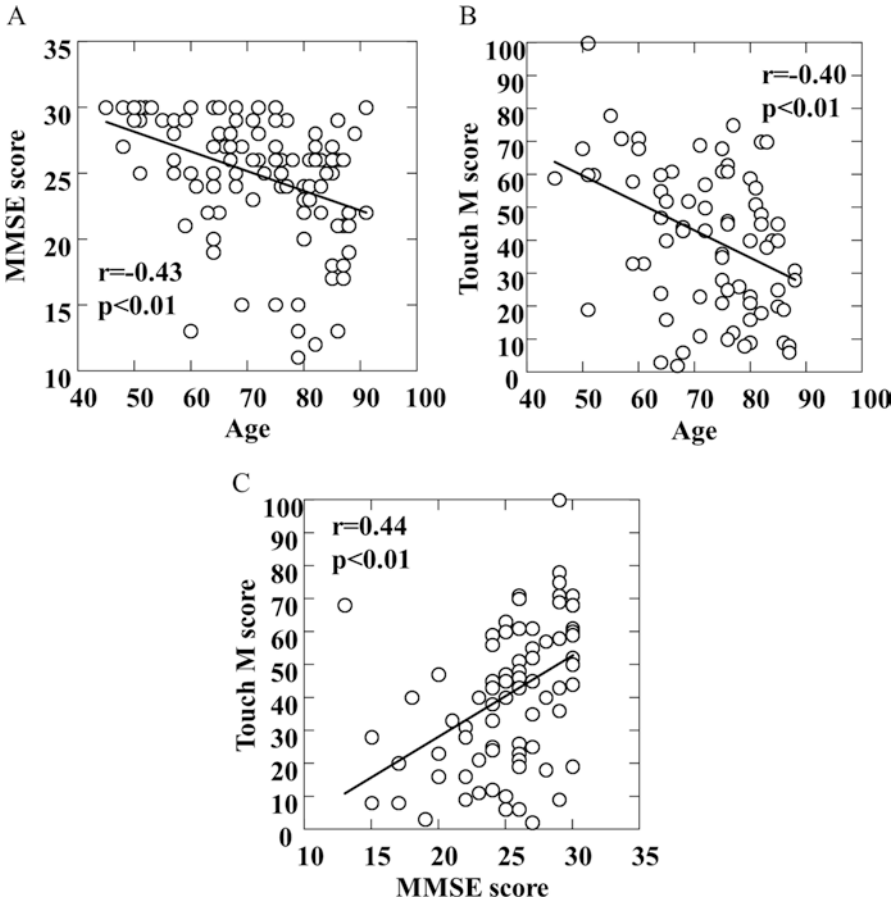

Fig. 37.2 Relationships between ages and cognitive function. (**a**) ages vs MMSE scores, (**b**) ages vs Touch M score, (**c**) MMSE scores vs Touch M score

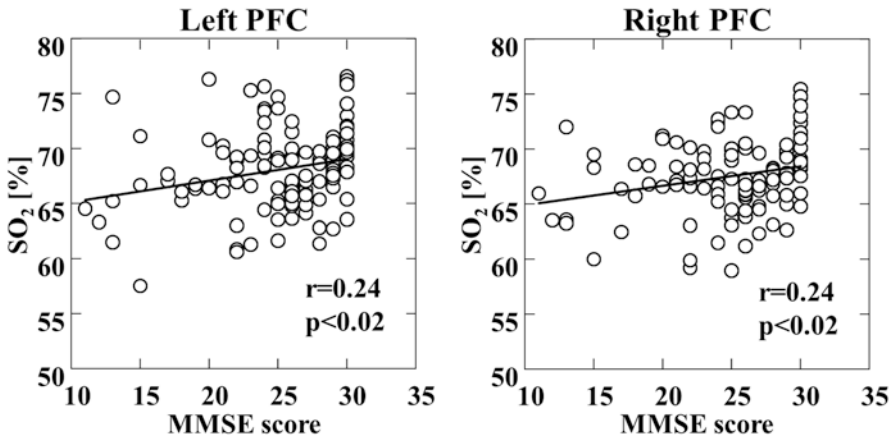

Fig. 37.3 Relationships between MMSE score and SO_2 in the left and right PFC

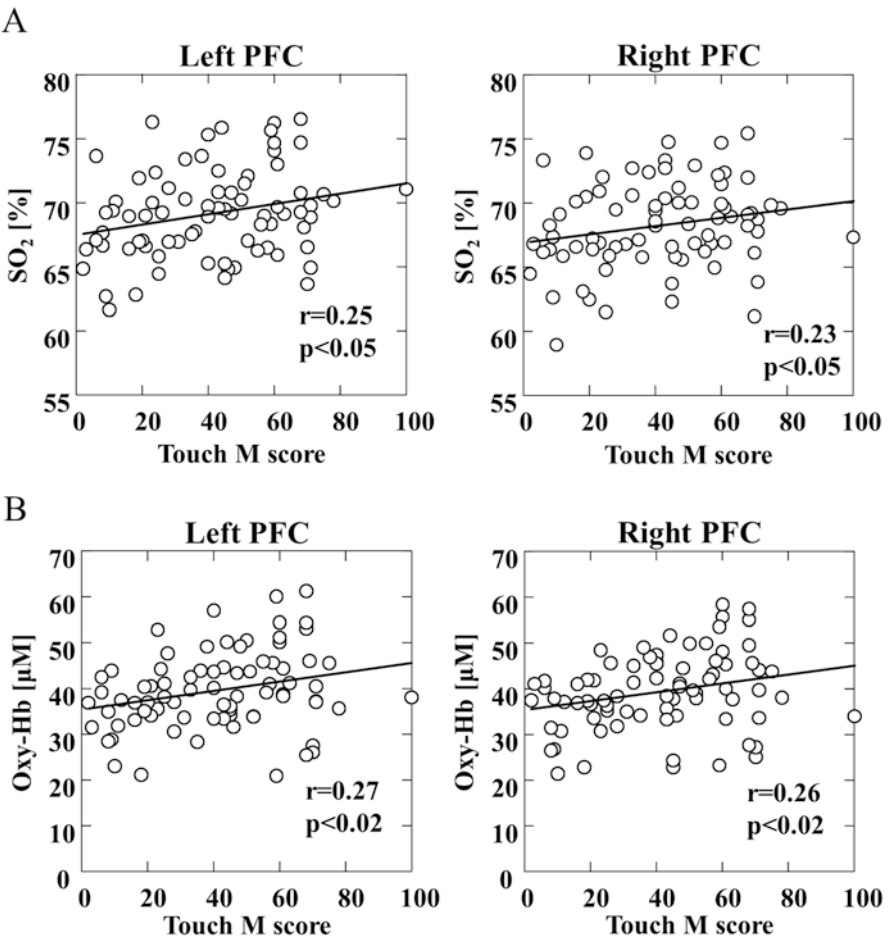

Fig. 37.4 Relationships between working memory function evaluated by Touch M and TRS parameters: (**a**) Touch M scores vs SO_2 in the left and right PFC. (**b**) Touch M scores vs oxy-Hb concentrations at rest in the left and right PFC

Table 37.1 Comparison of TRS parameters between normal subjects and subjects with impaired cognitive function

		Normal (MMSE ≥ 24)	Impaired (MMSE ≤ 23)	p value
Left	oxy-Hb	38.72	38.30	>0.1
	deoxy-Hb	18.15	18.90	>0.1
	total-Hb	56.86	57.20	>0.1
	SO_2	67.89	66.69	<0.05*
Right	oxy-Hb	38.70	37.05	>0.1
	deoxy-Hb	17.57	18.04	>0.1
	total-Hb	56.27	55.09	>0.1
	SO_2	68.50	66.91	<0.05*

* $p<0.05$

mild cognitive impairment (MMSE score 24.1 ± 3.8) exhibited higher baseline concentrations of oxy-Hb and t-Hb in the PFC than those with moderate cognitive impairment (MMSE score 10.3 ± 5.8) [5].

In order to elucidate the physiological basis of the relation between TRS measurements and cognitive function, the following observations should be considered. Simultaneous measurements of TRS and PET in normal adults demonstrated that SO_2 and t-Hb measured by TRS significantly increased, associated with an increase of regional cerebral blood flow (rCBF) and volume (rCBV) induced by acetazolamide [11]. In addition, dementia showed decreased rCBF or glucose metabolism in various brain regions including the frontal cortex, particularly in patients with frontal dysfunction, such as apathy [12, 13]. Based on these observations, we suggest that the concentrations of Hb in the PFC at rest measured by TRS correlate with the rCBF and rCBV in the PFC at rest, which reflect cognitive functions related with the PFC, such as working memory.

Finally, the advantages of TRS should be discussed. First, TRS allows us to measure Hb concentrations at rest; therefore, it allows us to assess cognitive function without any task. Second, TRS is compact and less expensive than PET and MRI. In addition, TRS has less stress on subjects at the time of measurement than PET and MRI. Further studies are necessary to apply TRS to screening test of cognitive dysfunction.

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