Chapter 52
New Method of Analyzing NIRS Data from Prefrontal Cortex at Rest

Wakana Ishikawa, Masakaze Sato, Yukikatsu Fukuda, Takashi Matsumoto, Naohiro Takemura, Takeo Tsujii, and Kaoru Sakatani

Abstract The aim of this study was to develop a simple technique for objective assessment of mental stress levels by measuring hemoglobin concentration changes in the bilateral prefrontal cortex (PFC) at rest, employing two-channel near-infrared spectroscopy (NIRS). Each subject was instructed to think about nothing in particular for 3 min and then to complete the State-Trait Anxiety Inventory (STAI) test. Next, NIRS measurements were taken and the left/right asymmetry of PFC activity at rest was evaluated by calculating the proposed Laterality Index at Rest (LIR). There was a significant positive correlation between the LIR and STAI score in 39 subjects. The present method allowed evaluation of mental stress level from NIRS data in the PFC at rest.

52.1 Introduction

The incidence of stress-induced psychological and somatic diseases has been increasing rapidly in industrialized societies, and it is important to clarify the neurophysiological mechanisms of stress response in order to establish effective stress management methods. A simple, noninvasive method for assessment of stress response and for evaluation of the efficacy of relaxation methods is required for this purpose. We have previously used near-infrared spectroscopy (NIRS) for investigation of neurophysiological mechanisms of mental stress and to evaluate relaxation methods. We found that the prefrontal cortex (PFC) plays an important role in stress

W. Ishikawa (✉) • M. Sato • Y. Fukuda • T. Matsumoto
Department of Electrical Engineering and Bioscience, Waseda University, Tokyo, Japan
e-mail: ishikawa10@matsumoto.eb.waseda.ac.jp

N. Takemura • T. Tsujii • K. Sakatani
Department of Neurological Surgery, Division of Optical Brain Engineering,
Nihon University School of Medicine, Tokyo, Japan

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response; asymmetry of PFC activity measured by NIRS correlated with behavioral and somatic responses to mental stress [1–4]. In this study, we employed NIRS to evaluate the asymmetry of PFC activation during activity at rest without any task, using a newly developed parameter, Laterality Index at Rest (LIR). We also investigated the correlation between LIR and anxiety level evaluated with the State-Trait Anxiety Inventory (STAI) test.

52.2 Materials and Methods

52.2.1 Experimental Settings

The study population comprised 39 subjects (29 women; 10 men); 19 were 20–24 years old and 20 were 60–79 years old. Written informed consent was obtained from each subject on forms approved by the ethical committee of Nihon University School of Medicine. Each subject was seated in a comfortable chair in a dimmed room, and we measured oxy- and deoxy-Hb concentration changes in the bilateral PFC with a two-channel NIRS (PNIRS-10, Hamamatsu Photonics K.K., Japan). The NIRS probes were set symmetrically on the forehead; the positioning is similar to the midpoint between electrode positions Fp1/Fp3 (left) and Fp2/Fp4 (right) of the international 10–20 system. One trial consisted of the following steps. First, each subject completed the STAI questionnaire before NIRS measurements. Second, calibration of the equipment was performed. Third, the subject was told that the preparation period (1 min) would begin. Fourth, the subject was instructed to rest quietly for 3 min: rest period. This corresponds to the analysis period. Figure 52.1 schematically depicts the experimental protocol.

52.2.2 Data Analysis

In order to analyze left/right asymmetry of PFC activity at rest, we calculated the laterality scores. Consider

$$\Delta oxyR_{\min} = \min_{t \in analysis\ interval} \Delta oxyR_t \tag{52.1}$$

$$\Delta oxyL_{\min} = \min_{t \in analysis\ interval} \Delta oxyL_t \tag{52.2}$$

where $\Delta oxyR_t$ and $\Delta oxyL_t$ denote oxy-Hb concentration changes of the right and the left PFC. The quantities defined by Eqs. 52.1 and 52.2 are the variations with respect to their minimum values, so that they are always nonnegative. Based on these quantities, we defined the *Laterality Index at Rest* (*LIR*) as follows:

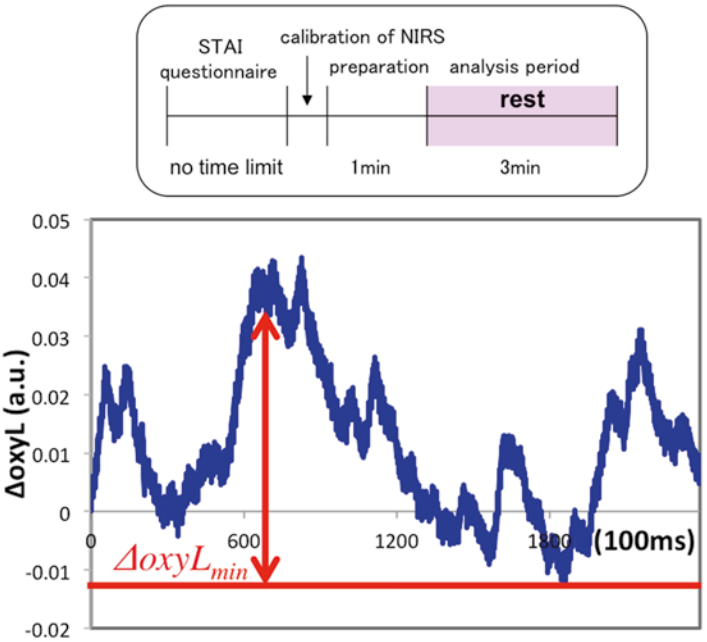

Fig. 52.1 The experimental protocol is illustrated in the *left panel*. Calibration refers to the fact that the hemoglobin concentration values are set to reference value so that measurement can start. The *panel* on the *right* shows typical traces of $\Delta oxyL_t$ and the minimum value of $\Delta oxyL_{min}$. As exemplified by the *red arrow*, the quantities defined by Eq. 52.2 are the variations with respect to the minimum value. The concept is the same for $\Delta oxyR_t$

$$LIR = \frac{\sum_{t \in analysis\ interval} \left(\left(\Delta oxyR_t - \Delta oxyR_{\min} \right) - \left(\Delta oxyL_t - \Delta oxyL_{\min} \right) \right)}{\sum_{t \in analysis\ interval} \left(\left(\Delta oxyR_t - \Delta oxyR_{\min} \right) + \left(\Delta oxyL_t - \Delta oxyL_{\min} \right) \right)} \tag{52.3}$$

The numerator of Eq. 52.3 consists of the difference between oxy-Hb concentration changes of the right and the left PFC summed over the analysis period (3 min). It is convenient if such index is normalized in such a way that the resulting numerical values are in $[-1, +1]$. The normalization constant is defined by the sum, instead of the difference, of oxy-Hb concentration changes of the right and the left PFC. It should be noted that if we had used $\Delta oxyR_t$ and $\Delta oxyL_t$ per se, instead of the variations from their minimum values, then the denominator could be zero or near zero where the target quantity diverges. It should also be noted that if the normalization constant becomes negative, then the index does not make much sense and makes it difficult to interpret the index. The quantities defined are schematically illustrated in Fig. 52.1. A positive LIR indicates that the right PFC is more active at rest than the left PFC, on average, while a negative LIR indicates that the left PFC is more active at rest than the right PFC, on average. We then analyzed the relation between LIR and STAI state scores.

52.3 Results

All subjects exhibited fluctuations of oxy-Hb in the bilateral PFC at rest. The amplitude varied among the subjects; Fig. 52.2 shows typical examples of $\Delta oxyR_t$ and $\Delta oxyL_t$ in subjects with high (60) and low (28) STAI scores. There was a significant positive correlation between exp (LIR) and STAI scores ($r=0.513$, $p=0.0008$). One reason for considering exp (LIR) instead of LIR is that we found that the correlation coefficient of STAI with exp (LIR) was larger than that with LIR. Generally, properties of a random variable change under coordinate changes. Fig. 52.3a shows the scatter

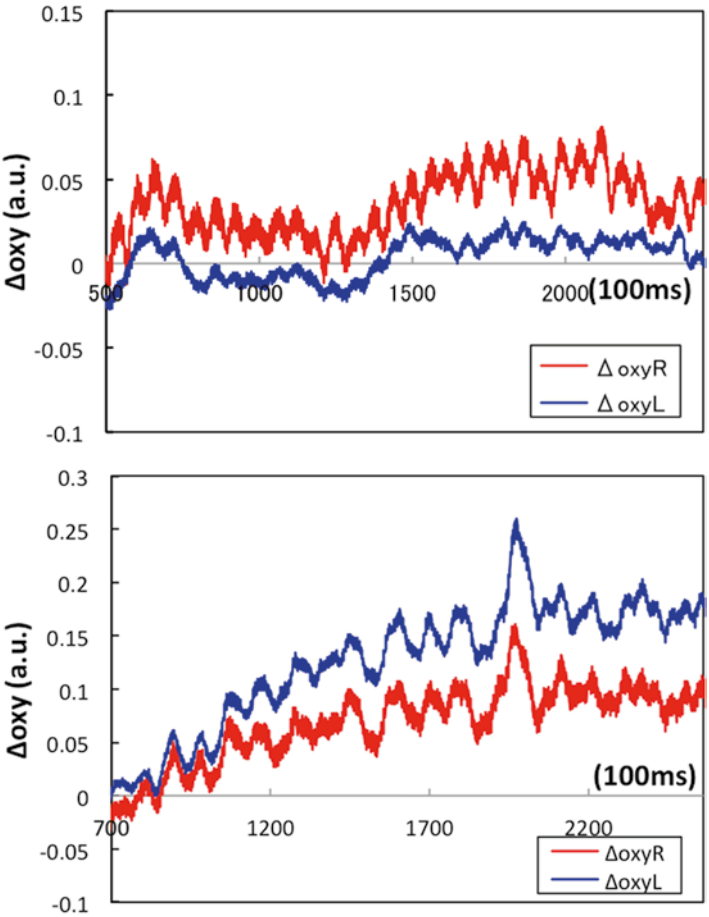

Fig. 52.2 The *left panel* shows typical examples of $\Delta oxyR_t$ and $\Delta oxyL_t$ in a subject with a high STAI score (60). The *right panel* shows typical examples of $\Delta oxyR_t$ and $\Delta oxyL_t$ in a subject with a low STAI score (28)

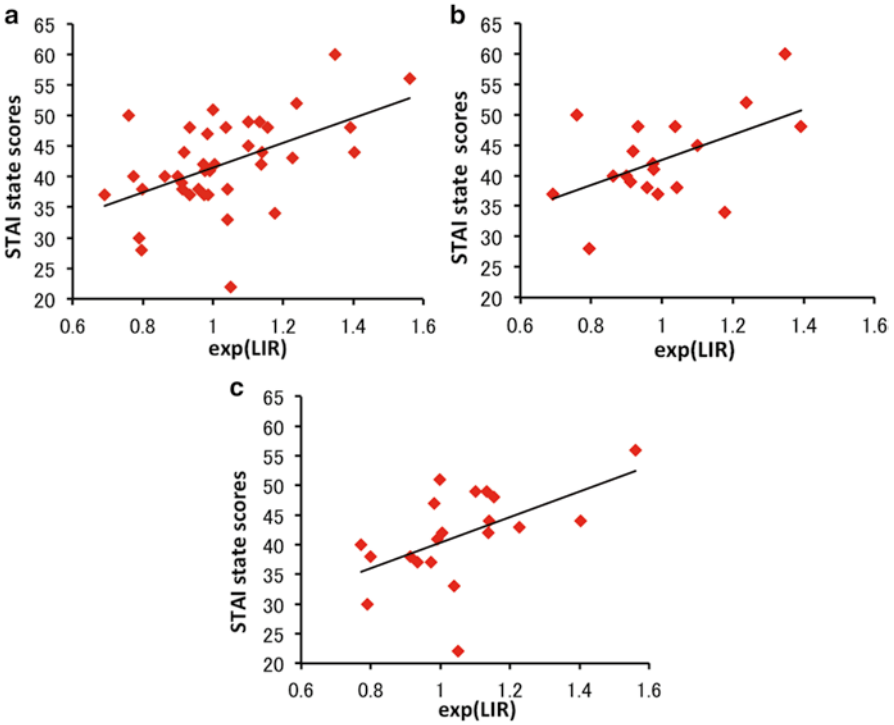

Fig. 52.3 (**a**) All STAI versus exp (LIR). Scatter plot of values of exp (LIR) against STAI test scores of all 39 subjects. Larger values of exp (LIR) indicate that the right PFC was more active at rest than the left PFC, corresponding to a higher anxiety level. (**b**) Scatter plot of exp (LIR) against STAI score for 19 young subjects. (**c**) Scatter plot of exp (LIR) against STAI score for 20 older subjects. Correlation lines are shown in *black*. Correlation coefficient of STAI with exp (LIR) was larger than that with LIR. Generally, the properties of a random variable change under coordinate changes

plot of exp (LIR) against STAI score for all 39 subjects. This indicates that the right PFC was more active at rest than the left PFC, corresponding to a higher anxiety level. In order to examine a possible effect of aging on the correlation between LIR and STAI, we analyzed the correlation in the young group ($n=19$, 20–24 years) and the older group ($n=20$, 60–79 years) separately. In the young group there was a significant positive correlation between the exp (LIR) and STAI state score ($r=0.525$, $p=0.021$) (Fig. 52.3b). In the older group we found a similar positive correlation between the exp (LIR) and STAI state scores ($r=0.536$, $p=0.015$) (Fig. 52.3c). This suggests that aging has no significant effect on the correlation. In the present project, at least, we have not found an index of interest for deoxy-Hb.

52.4 Discussion

Subjects with right-dominant oxy-Hb changes at rest, evaluated in terms of LIR, showed higher STAI scores, while those with left-dominant oxy-Hb changes at rest showed lower STAI scores. In NIRS activation studies, changes of oxy-Hb during activation imply evoked changes of regional cerebral blood flow (rCBF) in response to neuronal activation, since changes in oxy-Hb are correlated with changes in rCBF [5]. NIRS measurements during the resting condition have shown that a change in oxy-Hb occurred without a change in total Hb [6, 7]. In addition, simultaneous measurement of NIRS and electroencephalography (EEG) showed an increase of oxy-Hb when the EEG showed alpha 2 wave (10–13 Hz) and a decrease of oxy-Hb when the EEG showed alpha 1 wave (7–9 Hz) [7]. These observations indicate that changes in oxy-Hb at rest reflect changes of neuronal activity at rest. The left/right asymmetry of PFC activity is correlated with specific emotional responses to mental stress and personality traits [8–10]. It has been reported that positive and negative affective stimuli shift the asymmetry in PFC activity. For example, film-induced fear increases relative right-sided PFC activation [10], whereas induced positive affective stimuli elicit an opposite pattern of asymmetric activation [11]. In addition, asymmetry in PFC activity at rest is correlated with the emotional state [12]. Kemp et al. demonstrated that patients with major depressive disorder exhibited reduced left frontal activity in the resting state compared with normal controls [12]. These results suggest that asymmetry in PFC activity at the resting state can predict the emotional state. The PFC plays an important role in mediating somatic responses to stress via projections to the neuroendocrine and autonomic centers in the medial hypothalamus [13]. Interestingly, regulation of stress response is differentially mediated by the right and left PFC, which is similar to regulation of emotional responses. Here, NIRS data demonstrated that right-dominant PFC activity during stress tasks was associated with hyperactivity of the stress response system, while left-dominant PFC activity was associated with small stress responses [1–4]. However, further studies are needed to clarify the relation between the right/left asymmetry of PFC activity at rest and the stress response system. Finally, it should be noted that concentration changes in oxy-Hb measured by NIRS reflect blood flow changes in both intra- and extracerebral tissues including the skull and skin. Recent studies demonstrated that the scalp-related hemodynamic changes are locked into the functional activation tasks [14]. In addition, some of the oxy-Hb oscillation could be systemically driven. For example, systemic blood pressure fluctuations significantly altered NIRS recordings through expression in extracranial tissues and within the brain itself [15]. Further studies are necessary to clarify these effects on the present NIRS data.

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