Chapter 14
Optical Diagnosis of Mental Stress: Review

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1 Introduction

In recent years, the incidence of stress-induced psychological and somatic diseases has been increasing rapidly. Although activation of the stress system improves homeostasis, persistent activation of this system under everyday stress may lead to stress-induced diseases. It is, therefore, important to clarify the neurophysiological mechanism of stress response and to develop a simple, noninvasive method for assessment of stress response and for evaluation of the efficacy of relaxation methods for prevention of stress-induced diseases. We have used near-infrared spectroscopy (NIRS) for investigation of neurophysiological mechanisms of mental stress and relaxation methods [1–4]. We found that the prefrontal cortex (PFC) plays an important role in stress response and NIRS is useful for the diagnosis of mental stress. The present chapter reviews recent NIRS studies on stress and relaxation, including neuroimaging studies.

2 Role of the Prefrontal Cortex in Stress Response

The main components of the stress response system are the hypothalamic-pituitary-adrenal (HPA) system and the autonomic nervous system (ANS), within which the sympathetic medullary system plays a dominant role [5]. The PFC plays an important role in mediating behavioral and somatic responses to stress via projections to the

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centers of the HPA system and ANS in the medial hypothalamus [6]. Interestingly, a number of studies have demonstrated that the right PFC dominates the regulation of the HPA axis and ANS during mental stress. Electroencephalographic studies have shown that a greater right frontal activation is associated with increased heart rate during unpleasant emotional stimuli [7]. Sullivan and Gratton observed that lesions to the right or bilateral PFC, but not the left PFC, decrease prestress corticosterone levels and the stress-induced corticosterone response in rats [8]. In addition, a recent functional MRI study revealed that right dominance of PFC activity during mental stress tasks is correlated with changes in salivary cortisol level and heart rate [9]. These findings suggest that subjects with right dominant PFC activity during mental stress may be more sensitive to mental stress, and may be more prone to exhibit various stress-induced somatic disorders, including skin disorders.

3 Roles of PFC in Stress Response Evaluated by NIRS

NIRS is a noninvasive optical technique that can measure changes in the concentrations of oxyhemoglobin (oxy-Hb) and deoxyhemoglobin (deoxy-Hb) in cortical vessels [10]. Changes in oxy-Hb concentration during tasks reflect neuronal activity, as they correlate with evoked changes in regional cerebral blood flow (rCBF) [11–13]. Neuronal activation decreases deoxy-Hb, which causes an increase of the blood oxygen level-dependent (BOLD) signal in functional magnetic resonance imaging (f-MRI) [14]. NIRS thus provides more information about the evoked cerebral blood oxygenation changes than does the BOLD image, although the spatial resolution of NIRS is poor due to light scattering within the tissues. Unlike f-MRI, NIRS does not require head constraint, and therefore NIRS measurements may be less stressful for subjects.

We studied normal young right-handed females ($n=30$, mean age of 21.4 ± 1.4 years). We employed a mental arithmetic task as a psychological stressor. The subjects were asked to consecutively subtract a two-digit number from a four-digit number (e.g., $1{,}022-13$) as quickly as possible for 60 s. We measured cerebral blood oxygenation in the bilateral PFC with a NIRS monitor which uses spatially resolved reflectance spectroscopy (NIRO-300, Hamamatsu Photonics K.K., Hamamatsu, Japan). The center between the emitter and detector was identical to the Fp2 position of the international electroencephalographic 10–20 system used previously. MRI confirmed that the emitter–detector was placed over the PFC and the medial PFC.

We evaluated the asymmetry of PFC activity during the task by calculating the laterality index (LI) (i.e., [(right − left)/(right + left)]) of oxy-Hb changes. Positive values of LI indicate right-dominant PFC activity while negative values indicate left-dominant PFC activity. Then, we evaluated the relation between LI and heart rate changes during the task, as well as skin condition (i.e., level of sebum secretion, population of *Propionibacterium acnes*). Skin condition was evaluated because acne vulgaris is known to develop under mental stress. Activation of the HPA

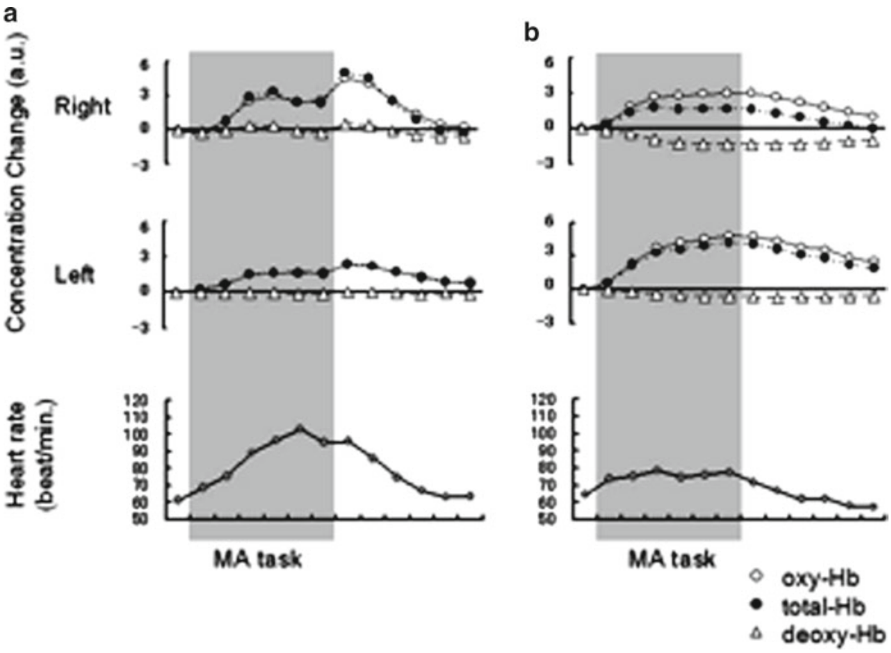

Fig. 14.1 Typical examples of changes in NIRS parameters and heart rate (HR) during mental arithmetic task in subjects with high HR increases (**a**) and low HR increases (**b**). The ordinate of NIRS parameters indicates the concentration changes of Oxy-Hb, Deoxy-Hb, and Total-Hb in arbitrary units. The ordinate of HR indicates number of beats per min. The *gray* area denotes the task period (60 s)

axis during mental stress induces secretion of corticotropin-releasing hormone and adrenal steroid hormones, which cause sebaceous hyperplasia and aggravate acne.

NIRS demonstrated that oxy-Hb increased in the bilateral PFC during the task, in association with a decrease of deoxy-Hb (Fig. 14.1). The task significantly increased heart rate ($p = 0.0000049$). We found that right PFC dominant increase in oxy-Hb during the task was associated with a large heart rate increase during the task (Fig. 14.1a), while left PFC dominant increase in oxy-Hb was associated with a small heart rate increase (Fig. 14.1b). The LI of oxy-Hb change was positively correlated with heart rate change ($r = +0.52$, $p = 0.020$) (Fig. 14.2a). In addition, there was a positive correlation between the LI of oxy-Hb change and sebum level ($r = +041$, $p = 0.0093$) (Fig. 14.2b) and *Propionibacterium acnes* population in the facial skin before the task ($r = +0.41$, $p = 0.0087$) (Fig. 14.2c).

These results indicate that subjects with a greater increase in heart rate and higher sebum level and *Propionibacterium acnes* population in the facial skin showed right dominant PFC activity during the mental stress task, and suggest that such subjects are more sensitive to mental stress associated with hyperactivity of the stress response system, including the HPA axis and ANS system.

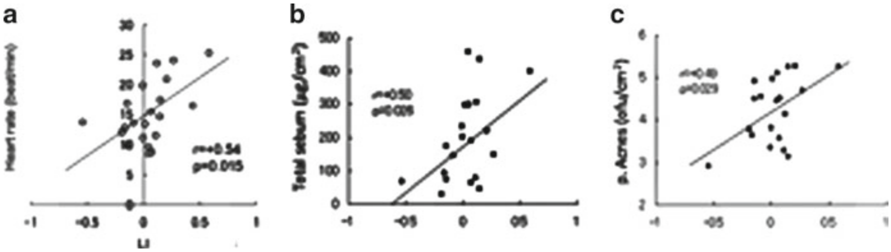

Fig. 14.2 (**a**) Relationship between the laterality index (LI) of oxy-Hb changes and heart rate (HR) changes during a mental arithmetic task. There was a significant positive correlation between LI and HR ($r = +0.54$, $p < 0.015$). (**b** and **c**) The correlation between the LI of oxy-Hb changes during the task and the facial skin content of sebum (**b**) and the *P. acnes* population (**c**) before the task. Significant positive correlations were observed for the amount of sebaceous secretion ($r = +050$, $p = 0.026$) and the *P. acnes* population ($r = +0.49$, $p = 0.029$)

4 Effects of Relaxation on PFC Activity and Stress Response

We evaluated the effects of fragrance on the subjects who exhibited right PFC dominant activity during the stress task and a high level of sebum secretion ($n = 12$) [3]. Fragrances have long been known to influence stress-induced psychosomatic disorders [15, 16]. We used a fragrance which was blended by a perfumer for this experiment. All subjects were asked to use the fragrance spray at least three times during the day and then to put the room fragrance at their bedside every night for 4 weeks. We compared the prestress level of sebum secretion before and after fragrance administration. In addition, we measured the PFC activity during the mental arithmetic task before and after fragrance administration, and compared the LI of oxy-Hb change (Fig. 14.3).

Administration of fragrance for 4 weeks significantly reduced the level of sebum ($p = 0.02$) in the fragrance group ($n = 6$). In addition, the LI-oxyHb decreased significantly from 0.11 ± 0.07 to -0.10 ± 0.18 ($p = 0.01$), indicating that the dominant side of the stress-induced PFC activity changed from the right to left side. In contrast, neither LI-oxyHb nor the level of sebum secretion changed significantly in the control group ($n = 6$). These results suggest that administration of fragrance reduced the level of sebum secretion by modulating the stress-induced PFC activity. That is, fragrance altered the dominant side of the stress-induced PFC activity from the right to the left side, and reduced the hyperactivity of the HPA system, which caused hypersecretion of sebum. The physiological mechanism of the effect of fragrance is not clear; however, one possibility is neuronal conditioning of PFC activity by olfactory stimulation, since the olfactory system connects to the PFC via the hypothalamus and limbic system. Indeed, the NIRS results demonstrated that olfactory stimulation causes an increase of oxy-Hb in the bilateral PFC. Therefore, repeated olfactory stimulation with fragrance could change the stress-induced PFC activity via the olfactory system.

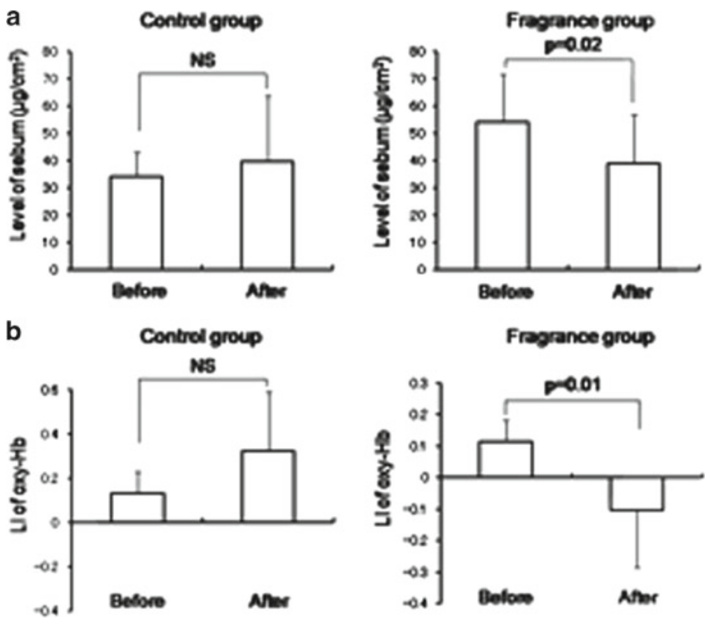

Fig. 14.3 Effects of fragrance administration on the prestress level of sebum secretion in the facial skin (**a**) and the laterality of PFC activity during a mental arithmetic task (**b**). The ordinates in (**a**) and (**b**) indicate the level of sebum secretion (μg/cm²) and the laterality index (LI) of oxy-Hb changes, respectively. The error bars indicate standard deviation. Fragrance administration significantly decreased the level of sebum secretion ($p=0.02$) and the LI of oxy-Hb ($p=0.01$)

5 Usefulness of Time-Resolved Spectroscopy for Stress Study

Conventional NIRS which employs continuous light does not allow measurement of Hb concentration at rest. In contrast, time-resolved spectroscopy, which employs picosecond pulses of light, can quantitatively evaluate Hb concentration at rest [17]. TRS has been employed for functional studies on normal adults [18–20] and for evaluation of the cerebral circulation in patients with cerebrovascular diseases [21, 22] and newborn infants [23].

Tsunetsugu et al. employed TRS to evaluate the effect of "forest therapy" on the PFC activity at rest [24]; forest therapy (i.e., forest-air bathing and walking) is popular in Japan. They compared the Hb concentration in the PFC at rest in a city environment and in a forest environment. The total Hb in the PFC in the forest environment was significantly smaller than that in the city environment. In addition, the salivary cortisol level in the forest environment was significantly smaller than that in the city environment. These results suggest that the city environment caused hyperactivity in the PFC, which was normalized by the forest environment.

6 Limitations of NIRS Measurements

Finally, potential limitations of NIRS should be discussed. NIRS measures the blood oxygenation changes within the illuminated area, which includes both intracranial and extracranial tissues. NIRS parameter changes may therefore be caused by changes in the blood flow of the scalp; however, we observed minimal changes in the skin blood flow during the task in a preliminary experiment. We therefore believe that the NIRS parameter changes predominantly reflect the blood oxygenation changes in the activated cortices. In addition, NIRS does not allow the measurement of cerebral blood oxygenation changes in the whole brain, including deep brain structures. Although the PFC plays an important role in stress responses, further studies are necessary to evaluate the precise activation areas within the brain that are related to the effect of fragrance and mental stress.

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