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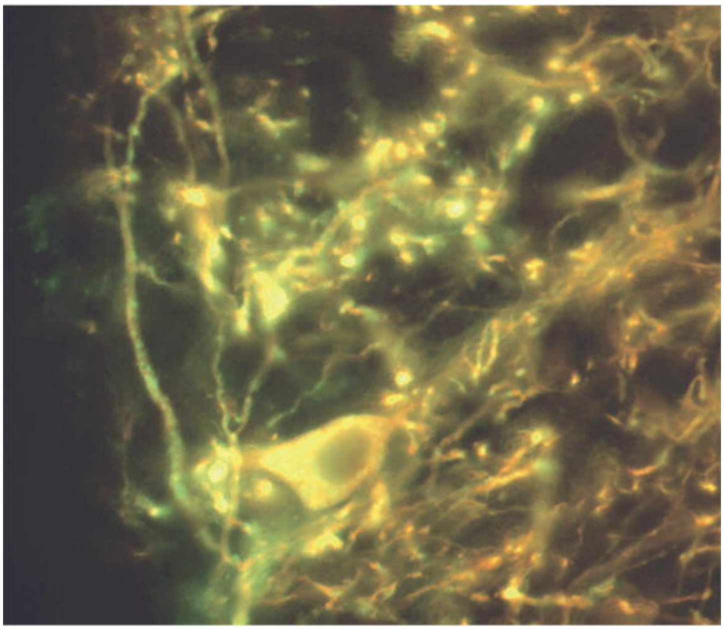

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Research Report

Relation between mental stress-induced prefrontal cortex activity and skin conditions: A near-infrared spectroscopy study

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ABSTRACT

Although psychological stress affects skin condition, the neurophysiological mechanism involved is unclear. In this study, we evaluated the relationship between skin condition and left/right asymmetry in prefrontal cortex (PFC) activity during mental stress tasks since recent studies have suggested that the right PFC dominates the regulation of the stress response system, including the hypothalamic–pituitary–adrenal (HPA) axis. Using near-infrared spectroscopy, we measured hemoglobin concentration changes in the bilateral PFC during a mental arithmetic task in normal adults and evaluated the laterality scores (i.e., [(right − left) / (right + left)]) of oxyhemoglobin concentration changes. Elicitation of stress was verified by the State-Trait Anxiety Inventory (STAI) and heart rate. The sebum levels and *Propionibacterium acnes* populations in the facial skin were measured before the task. The task significantly increased the STAI-II scores ($p = 0.00079$) and heart rate ($p = 0.0000049$). The oxyhemoglobin concentration increased in the bilateral PFC during the task, associated with a decrease in deoxyhemoglobin concentration. The laterality scores of oxyhemoglobin concentration changes were positively correlated with sebum levels ($r = +0.50$, $p = 0.026$) and *P. acnes* populations ($r = +0.49$, $p = 0.029$) in the facial skin before the task. There was a significant positive correlation between heart rate changes and the laterality scores of oxyhemoglobin concentration changes ($r = +0.54$, $p = 0.015$). These results demonstrate that the subjects with higher sebum levels and higher *P. acnes* populations in the facial skin have a right dominant PFC activity during a mental stress task and suggest that such subjects are sensitive to mental stress associated with hyperactivity of the stress response system, including the HPA axis system.

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Abbreviations: NIRS, near-infrared spectroscopy; HPA system, hypothalamic–pituitary–adrenal system; ANS, autonomic nervous system; PFC, prefrontal cortex; oxy-Hb, oxyhemoglobin; deoxy-Hb, deoxyhemoglobin; total-Hb, total hemoglobin; rCBF, Regional cerebral blood flow; *P. acnes*, *Propionibacterium acnes*; STAI, State-Trait Anxiety Inventory; LF, low frequency; HF, high frequency; LI, laterality index

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1. Introduction

The main components of the stress response system are the hypothalamic–pituitary–adrenal (HPA) system and the autonomic nervous system (ANS) of which the sympathetic medullary system plays a dominant role (Habib et al., 2001; Tsigos and Chrousos, 2002). Although activation of the stress response system improves the ability of an organism to maintain homeostasis, persistent activation of this system may lead to psychological or somatic diseases (Chiu et al., 2003; Chrousos and Gold, 1992; Stokes and Sternberg, 1939; Von Goozen et al., 2000). For example, acne vulgaris has long been known to develop under mental stress (Chiu et al., 2003; Stokes and Sternberg, 1939). It is thought that activation of the HPA axis during mental stress induces secretion of hormones such as corticotrophin-releasing hormone and adrenal steroid hormones, which cause sebaceous hyperplasia and can aggravate acne (Plewig and Kligman, 1975; Slominski et al., 2000; Zouboulis and Böhm, 2004). However, it is unclear why some persons develop acne and others do not following exposure to stresses.

The prefrontal cortex (PFC) plays an important role in mediating behavioral and somatic responses to stress via projections to the neuroendocrine and autonomic centers in the medial hypothalamus (Buijs and van Eden, 2000). 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 (Waldstein et al., 2000). Sullivan and Gratton observed that lesions to the right or bilateral PFC, but not the left PFC, decreased pre-stress corticosterone levels and the stress-induced corticosterone response in rats (Sullivan and Gratton, 1999). In addition, a recent functional MRI study revealed that right dominance of PFC activity during mental stress tasks correlated with changes in salivary-cortisol levels and heart rate (Wang et al., 2005). These findings suggest that subjects with right dominant PFC activity during mental stress may be sensitive to mental stress and tend to exhibit various stress-induced somatic disorders, including that of the skin.

In the present study, we analyzed the facial skin condition by quantifying the amount of sebum and the *Propionibacterium acnes* population and evaluated the relationships between the PFC activity during a mental arithmetic task and the facial skin condition before the task. We utilized near-infrared spectroscopy (NIRS) to evaluate PFC activity. NIRS is a noninvasive optical technique that can measure changes in the concentration of oxyhemoglobin (oxy-Hb) and deoxyhemoglobin (deoxy-Hb) in cortical vessels (Jöbsis, 1977). Changes in oxy-Hb concentration during tasks reflect neuronal activity as they correlate with evoked changes in regional cerebral blood flow (rCBF) (Hock et al., 1995; Hoshi and Tamura, 1993; Kameyama et al., 2006; Sakatani et al., 1998, 1999a,b; Tanida et al., 2004; Villringer and Chance, 1997). Unlike functional MRI, NIRS does not require a head constraint. As such, less environmental stress is caused by taking NIRS measurements. In a previous study, we demonstrated that right dominant PFC activity, as measured by NIRS, was associated with a greater increase of heart rate during the mental arithmetic task (Tanida et al., 2004), a finding consistent with reported studies which

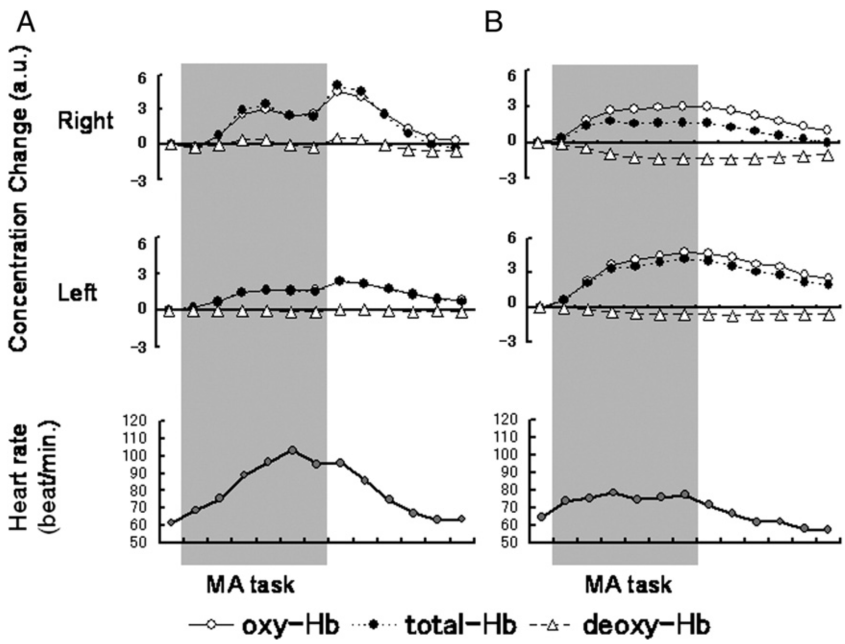

Fig. 1 – Typical examples of NIRS parameter changes in the right and left prefrontal cortex (PFC) and heart rate changes during mental arithmetic task in subjects showing large heart rate increases (A) and small heart rate increases (B). Note that the increases in oxy-Hb in the right PFC were greater than those in the left PFC (A), while the increases were greater in the left PFC than in the right PFC (B). The ordinate represents the change in concentration of oxy-Hb (open circle), deoxy-Hb (open triangle) and total-Hb (filled circle) in arbitrary units (a.u.). The gray area denotes the mental arithmetic (MA) task period (60 s).

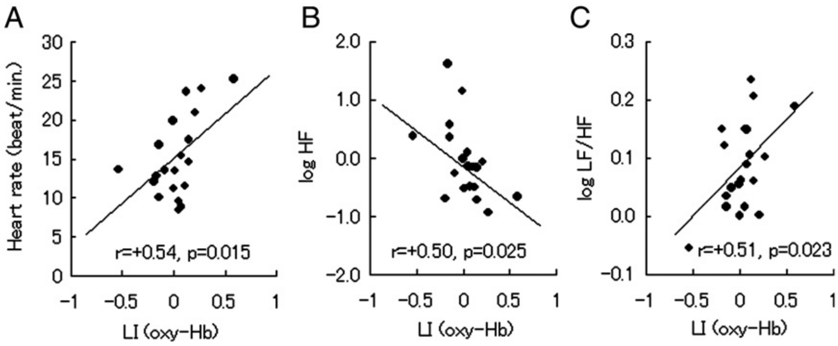

Fig. 2 – Relationship between left/right asymmetry of the PFC activity and ANS function. Graphs show the correlation between laterality index of changes in oxy-Hb concentration and changes in heart rate during a mental arithmetic task (A), log HF (B) and log LF/HF (C). There were significant positive correlations in heart rate changes (r=+0.52, p=0.020) and log LF/HF (r=+0.51, p=0.023) and negative correlation in log HF (r=−0.48, p=0.032). The abscissas represent the laterality index (LI) of changes in oxy-Hb.

employed other techniques (Waldstein et al., 2000; Wang et al., 2005).

2. Results

The mental arithmetic task significantly increased the STAI-II scores; the mean STAI-II scores before and after the task were 40.4±9.4 and 47.4±10.5, respectively (p=0.00079). In addition, heart rate significantly increased after the task; the mean heart rates before and after the task were 68.96±11.41 and 79.85±14.67 beats/min, respectively (p=0.0000049). These results suggest that the mental arithmetic task increased psychological stress levels in the subjects.

The task led to elevation of oxy-Hb and total-Hb concentrations and a decrease in deoxy-Hb concentration in the bilateral PFC of all subjects (Fig. 1) , indicating that activity was enhanced in this brain region. Right PFC dominant increases in oxy-Hb during the task were associated with large concurrent heart rate increases (Fig. 1A), while left PFC dominant increases in oxy-Hb were associated with small heart rate increases (Fig. 1B). Indeed, the LI of changes in oxy-Hb concentration positively correlated with changes in heart rate during the mental arithmetic task (r=+0.54, p=0.015) (Fig. 2A), consistent with our previous study (Tanida et al., 2004). In addition, there was a significant negative correlation between the LI of changes in oxy-Hb concentration and log HF (r=−0.50, p=0.025) and a positive correlation between the LI of changes in oxy-Hb concentration and log LF/HF (r=+0.51, p=0.023) (Figs. 2B, C).

There was a considerable amount of variation in sebum secretion and in the *P. acnes* population in the facial skin of subjects; the mean values for sebum secretion and *P. acnes* population were 198.4±128.6 μg/cm^2 and 4.3±0.75 cfu/cm^2, respectively. However, there was a significant positive correlation between the total sebum secretion and the *P. acnes* population (r=+0.64, p=0.0022). Regression analyses were used to investigate the relationship between left/right asymmetry in PFC activity during the task and the skin condition. There was a significant positive correlation between the LI of changes in oxy-Hb concentration and the level of sebaceous secretion (r=+050, p=0.026) and the P. *acnes* population (r=+0.49, p=0.029) (Fig. 3).

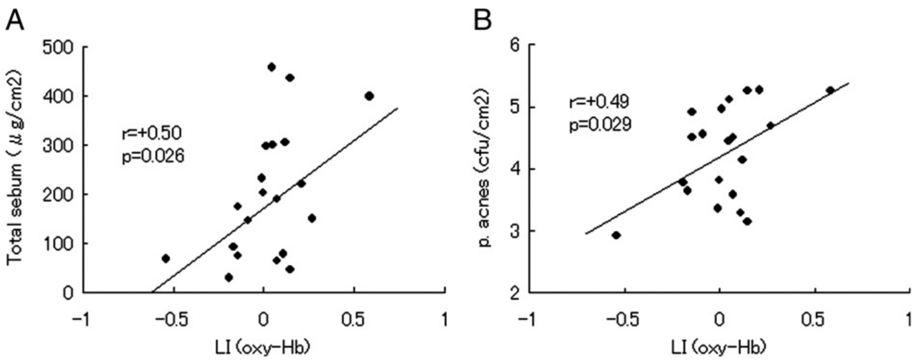

Fig. 3 – Relationship between left/right asymmetry of the PFC activity and skin condition. Graphs show the correlation between the laterality index of changes in oxy-Hb concentration during a mental arithmetic task and facial skin content of sebum (A) and the *P. acnes* population (B) before the task. Significant positive correlations were observed for the amount of sebaceous secretion (r=+0.50, p=0.026) and the *P. acnes* population (r=+0.49, p=0.029). The abscissas represent the laterality index (LI) of changes in oxy-Hb.

3. Discussion

In the present study, the mental arithmetic task caused an increase in oxy-Hb and total-Hb, associated with a decrease of deoxy-Hb, in the bilateral PFC of all subjects. These changes in NIRS parameters indicate neuronal activation in the PFC (Hock et al., 1995; Hoshi and Tamura, 1993; Kameyama et al., 2006; Sakatani et al., 1998, 1999a,b; Tanida et al., 2004; Villringer and Chance, 1997); the increase of oxy-Hb correlates with rCBF increases during neuronal activation, while the decrease of deoxy-Hb is caused by evoked rCBF rises which exceed increases in O_2 consumption during neuronal activity (Fox and Raichle, 1986). Neuroimaging studies have demonstrated that mental arithmetic tasks cause activation in the PFC and other brain regions such as the parietal cortex (Gruber et al., 2001; Kawashima et al., 2004; Menon et al., 2000). Gruber et al. found that both mental arithmetic and non-mathematical tasks activate the PFC and the parietal cortex and suggested that these regions support more general cognitive operations rather than specific modules for calculation (Gruber et al., 2001). Therefore, the PFC activity observed during the mental arithmetic task in the present study might reflect general cognitive operations such as attention and emotion. Furthermore, recent studies have demonstrated that mathematical processing, in particular the subtraction task employed here, may recruit the left frontal cortex and bilateral intraparietal sulcus (Houdé and Tzourio-Mazoyer, 2003). These results suggest that the right dominant PFC activity observed in the present study was not caused by mathematical processing.

We observed a significant correlation between left/right asymmetry of PFC activity during the mental arithmetic task and facial skin condition before the task; a right dominant PFC activity was associated with higher levels of sebum secretion and a larger *P. acnes* population. Elevation of facial skin sebum content and a larger *P. acnes* population may reflect an increase in HPA axis activity since activation of the HPA axis induces secretion of adrenal steroid hormones, such as glucocorticoids and adrenal androgens, which induce sebaceous hyperplasia and aggravate acne (Plewig and Kligman, 1975). In addition, human sebocytes express functional receptors for corticotrophin-releasing hormone which may modulate inflammatory cytokine production, lipogenesis and androgen metabolism in sebocytes (Slominski et al., 2000; Zouboulis and Böhm, 2004). Thus, we speculate that the subjects with right dominant PFC activity during mental stress might suffer from sustained activation of HPA axis under everyday stresses. This speculation is supported by the following studies demonstrating the anatomical and functional connections between the PFC and HPA axis. First, anatomical studies demonstrated the projections of the PFC neurons to the neuroendocrine center in the medial hypothalamus including the dorsomedial nucleus of the hypothalamus and sub-paraventricular nucleus (Buijs and van Eden, 2000). Secondly, a lesion study demonstrated that regulation of the dopamine response to mental stress is coupled to the right PFC (Sullivan and Gratton, 1999). Finally, a recent functional MRI study revealed that activation of the right PFC during mental stress tasks correlates with an increased salivary-cortisol level during the task (Wang et al., 2005).

Consistent with our previous NIRS study, right dominance of PFC activity during the mental arithmetic task was associated with an increase in heart rate (Tanida et al., 2004). In the present study an increase in heart rate during a mental arithmetic task was associated with a decrease in log HF and an increase in log LF/HF, indicating that the increase in heart rate was caused by an increase in sympathetic activity and a decrease in parasympathetic activity. Anatomical studies have demonstrated that direct projections from the PFC to the brain stem and spinal regions are involved in cardiovascular control (Verberne and Owens, 1998). The right-sided innervations of the vagus nerve and sympathetic fibers exert a greater influence on the sinoatrial node than the left-sided innervations. Thus, the right-sided innervations have a greater influence on heart rate. These observations indicate that activity in the right PFC modulates ANS function via neural networks between the PFC and the subcortical structures. It should be noted, however, that the laterality of the cerebrum in ANS regulation remains in dispute (Ahern et al., 2001; Waldstein et al., 2000; Wang et al., 2005; Wittling et al., 1998; Zamrini et al., 1990).

The right dominant PFC activity during the mental arithmetic task could be caused by not only hyperactivity of the right PFC but also hypoactivity of the left PFC. Although the present study did not include patients with mood disorders, it should be noted that depression is accompanied by hypoactivity of the left PFC (Bench et al., 1993), which is normalized after recovery from depression (Bench et al., 1995). In addition, transcranial magnetic stimulation of the left PFC improves mood in patients with medication-resistant major depression (George et al., 1995). These findings suggest that the chronic stress state in depression is accompanied with greater activity in the right PFC. It would be interesting to investigate whether right dominant PFC activity is a predictor of future depression.

Finally, potential limitations of the present study should be discussed. Firstly, NIRS does not allow the measurement of cerebral blood oxygenation changes in the whole brain, including deep brain structures. Thus, we have no measurement of brain activity, except for the PFC activity. In addition, we could not identify the precise location of the measurement area in the PFC due to the low spatial resolution of NIRS. Although the PFC plays an important role in stress responses (Buijs and van Eden, 2000; Sullivan and Gratton, 1999; Tanida et al., 2004; Wang et al., 2005), further studies are necessary to evaluate the precise activation areas in the whole brain that influence stress response including the skin condition. Secondly, we did not evaluate secretions of adrenal steroid hormones such as glucocorticoids and adrenal androgens which reflect the activity of the HPA axis. It remains necessary to clarify the relationships among brain activity, skin conditions (i.e., the levels of sebum secretion and *P. acnes* population) and the adrenal steroid hormones since the skin conditions could be affected by these hormones (Plewig and Kligman, 1975). Finally, all of the subjects in the present study were young female. Previously NIRS studies demonstrated that aging can affect PFC activity during cognitive tasks; oxy-Hb tends to decrease in the PFC of aged subjects during cognitive tasks (Hock et al., 1995; Sakatani et al., 1999b). In addition, neuroimaging studies have demonstrated gender differences in regional brain activity during different cognitive tasks (Hamann and Canli, 2004). Further investigation is needed to clarify the effects of aging and gender differences on the PFC activity during mental stress and the relation between asymmetry of the PFC activity and the stress responses.

In summary, the present study indicates that subjects with higher sebum levels and *P. acnes* populations in the facial skin showed a right dominant PFC activity during a mental stress task. In addition, these subjects exhibited greater heat rate increases during the task. These results support the hypothesis that the right PFC plays a key role in regulation of the HPA axis and the ANS in stress response and suggest that the subjects with right dominant PFC activity during a mental stress task might be sensitive to psychological stress associated with hyperactivity of the stress response system.

4. Experimental procedures

4.1. *Subjects*

We studied a total of 20 healthy young female subjects (mean age of 21.1±1.1 years). The subjects were highly educated college students and were all deemed right-handed according to the laterality quotient questionnaire of the Edinburgh Handedness Inventory. In order to avoid the influence of environmental stress, the subjects were seated in a comfortable chair, in an air-conditioned room with temperature and humidity maintained at approximately 22 °C and 40%, respectively. All subjects provided written informed consent as required by the Human Subjects Committee of the Shiseido Life Science Institute.

4.2. *Stress induction task and psychological studies*

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. 1022–13) as quickly as possible for 60 s. This mental arithmetic task has previously been used to investigate mental stress-induced PFC activity (Hoshi and Tamura, 1993; Shapiro et al., 2000; Tanida et al., 2004; Wang et al., 2005). In order to assess psychological stress levels, subjects were asked to fill in the State-Trait Anxiety Inventory (STAI) before and after task performance.

4.3. *NIRS measurements of PFC activity*

Cerebral blood oxygenation was measured in the bilateral PFC with a NIRS monitor which used spatially resolved reflectance spectroscopy (NIRO-300, Hamamatsu Photonics K.K., Hamamatsu, Japan). Details of this system have previously been described (Sakatani et al., 1999a; Suzuki et al., 1999). Briefly, near-infrared light from four laser diodes (775, 810, 850, and 910 nm) is directed to the head through a fiber-optic bundle, and the reflected light is transmitted to a multi-segment photodiode detector array. The NIRO-300 monitor simultaneously measures the concentration of oxy-Hb, deoxy-Hb, and total hemoglobin (total-Hb; oxy-Hb + deoxy-Hb). The hemoglobin concentrations were expressed as a change from baseline concentration (arbitrary units). The sampling time was 0.5 s.

The NIRS 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; the distance between the emitter and detector was set at 4 cm (Fig. 4A). This positioning is similar to the midpoint between electrode positions Fp1/Fp3 (left) and Fp2/F4 (right) of the international electroencephalographic 10-20 system. MRI confirmed that the emitter–detector was located over the dorsolateral and frontopolar areas of the PFC (Fig. 4B). Based on recent simulation studies on photon migration in the adult head (Okada and Delpy, 2003), we believe that the NIRS measured cerebral blood oxygenation changes at the surface of the cortical area of the PFC between the emitter and detector in the present study.

4.4. *Measurement and analysis of ANS function*

Heart rate was simultaneously monitored with PFC activity by placing a photo-electrical sensor (Tsuyama MGF KK, Tokyo, Japan) on the subject's right earlobe to measure pulse waves. Instantaneous heart rate was calculated every 10 s from a mean frequency value between 0.05 and 2 Hz by Fourier analysis. ANS function was evaluated by heart rate variability analysis; the low frequency (LF) amplitude (0.04–0.15 Hz) and the high frequency (HF) amplitude (0.15–0.4 Hz) were calculated by power spectral analysis over a 3 min-period at both the start of the task and after task performance.

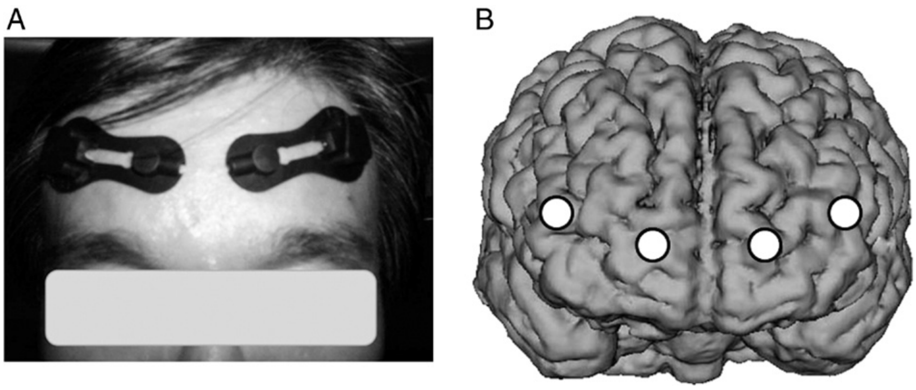

Fig. 4 – (A) Placement of NIRS probes on the bilateral forehead. (B) NIRS probes positions on MRI image. White circles indicate the emitters and detectors, which were located over the dorsolateral and frontopolar areas of the bilateral PFC.

4.5. Pre-stress measurements of facial skin sebum and *P. acnes*

Prior to commencing the mental arithmetic task we measured the level of sebaceous secretion and *P. acne* populations in the skin of the left and right cheeks. Sebum samples were collected by applying a piece of filter paper (2 cm^2) to the skin of the left and right cheeks, and total sebum secretions were measured by gas liquid chromatography (HP6890, Hewlett Packard, Palo Alto, USA; Column: F-LAB UA ± 1 [HT] 15W-0.5F 15m ± 500 µm¢ × 0.5 µm; injection temperature: 320 °C; detector temperature: 320 °C (FID); oven temperature: 40–320 °C (10 °C/min); carrier gas and flow rate: He, 1 µL/min; injection volume: 1 µL).

Facial skin microflora was collected using the stamp bottle method. The sponge part (diameter: 22 mm) attached to the cup of a stamp bottle containing sterile sampling liquid (1.01% Na_2HPO_4, 0.04% KH_2PO_4, 0.18% Triton X-100, pH 7.0) was held on the cheek for 30 s and rotated once while maintaining contact. The sponge part was then washed with 5 mL of the sampling liquid to collect the microflora resident on the cheek skin of subjects. The number of bacteria in the liquid was determined using a serial ten-fold dilution method and was converted into the number of bacteria per 1 cm^2 of skin. For bacterial analysis, aerobic bacteria were cultured on SCD Agar (Nissui, Tokyo, Japan) and anaerobes were cultured on GAM Agar Modified.

4.6. Data analysis

NIRS data were converted into a digitized format via the multi-purpose analyzing program BIMTAS II (Kissei Comtec Co. Ltd., Tokyo, Japan). Data were averaged every second, and baseline measurements were normalized to a 140-second segment for each trial. The cerebral blood oxygenation changes in the bilateral PFC were continuously monitored by NIRS during: (1) control conditions for 20 s; (2) the mental arithmetic task for 60 s; and (3) the recovery phase for 60 s. To analyze PFC activity in response to psychological stress, we calculated changes in oxy-Hb concentration during the mental arithmetic task as these correlate with rCBF changes during brain activation (Hock et al., 1995; Hoshi and Tamura, 1993; Kameyama et al., 2006; Sakatani et al., 1998, 1999a,b; Tanida et al., 2004; Villringer and Chance, 1997). The mean control values (measured during the first 10 s) were subtracted from the mean activation values (measured throughout task performance). In order to determine left/right asymmetry of PFC activity during the stress task, we calculated a laterality index (LI) for the oxy-Hb concentration changes ([right − left]/[right + left]); LI > 0 indicates greater activity of the right PFC, while LI < 0 indicates greater activity of the left PFC (Tanida et al., 2004). The sebum level and *P. acnes* population in the left and right cheeks were averaged in each subject. The relationships between PFC activity (LI of oxy-Hb), sebum level, *P. acnes* population, and heart rate changes were analyzed by Pearson's correlation coefficient.

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