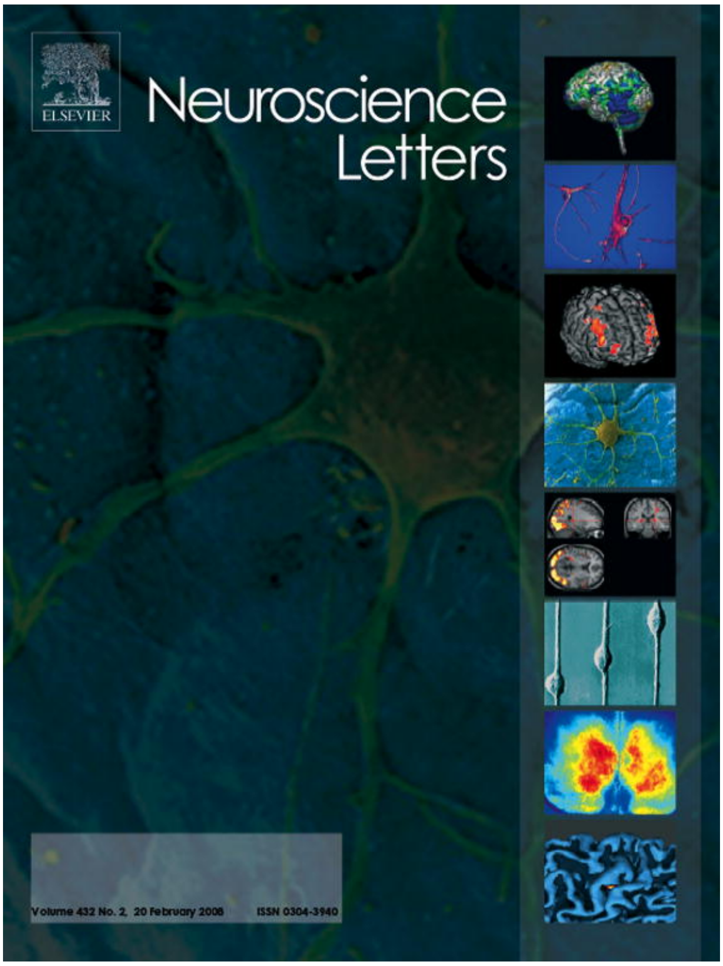
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Effects of fragrance administration on stress-induced prefrontal cortex activity and sebum secretion in the facial skin

Masahiro Tanida [a], Masako Katsuyama [a], Kaoru Sakatani [b,*]

[a] *Bioengineering Research Laboratories, Shiseido Life Science Research Center, Yokohama, Japan*
[b] *Department of Neurological Surgery, Division of Optical Brain Engineering, Nihon University School of Medicine, 30-1, Oyaguchi-Kamimachi, Itabashi-ku, Tokyo 173-8610, Japan*

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Abstract

Although fragrances have long been known to influence stress-induced psychosomatic disorders, the neurophysiological mechanism remains unclear. We evaluated the effect of fragrance on the relation between the level of sebum secretion in the facial skin and the stress-induced prefrontal cortex (PFC) activity, which regulates the activity of the hypothalamic–pituitary–adrenal axis. Employing near infrared spectroscopy, we measured hemoglobin concentration changes in the bilateral PFC during a mental arithmetic task in normal adults ($n = 31$), and evaluated asymmetry of the PFC activity in terms of the laterality index (i.e., [(right − left)/(right + left)]) of oxyhemoglobin concentration changes (LI-oxyHb). We measured the level of sebum secretion in the facial skin before the task performance. There was a significant positive correlation between the LI-oxyHb and the level of sebum secretion ($r = +0.44$, $p = 0.01$). We selected the subjects who exhibited high levels of sebum secretion and right-dominant PFC activity for the study on the fragrance effect ($n = 12$). Administration of fragrance for four 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 levels 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. The PFC may be involved in the neurophysiological mechanism of fragrance effects on systemic response to mental stress.

Keywords: Acne vulgaris; Adrenal steroid hormone; Hypothalamic–pituitary–adrenal system; Mental stress; NIRS; Prefrontal cortex

Fragrances have long been known to have various psychological and physical effects. Rovesti and Colombo observed that exposure to fragrances such as mint, lavender, or jasmine improved the symptoms of anxious or depressive states in humans [23]. Several animal studies have revealed that olfactory stimulation with fragrances improves stress-induced immune suppression [28] and suppresses the skin inflammatory reaction induced by immobilization stress in mice [15]. In addition, a recent study on humans has demonstrated that smelling of lavender and rosemary decreases salivary cortisol levels [2]. These results indicate that fragrances can improve various stress-induced psychosomatic disorders; however, the neurophysiological mechanisms of their effects remain unclear.

Acne vulgaris has long been known to develop under mental stress [30,5]. Mental stress activates the hypothalamic–pituitary–adrenal (HPA) axis and induces secretion of hormones such as corticotrophin-releasing hormone and adrenal steroid hormones [11,35], which cause sebaceous hyperplasia and aggravation of acne [20,29,39]. Recent studies have demonstrated that the activity of the HPA axis is regulated by the prefrontal cortex (PFC), particularly the right PFC [4,31,38]. A functional MRI study revealed that right PFC activity during mental stress tasks correlated with changes in salivary-cortisol levels [38]. Recently, employing near infrared spectroscopy (NIRS), we evaluated the relationship between skin condition and left/right asymmetry in the PFC activity during mental stress tasks [34]. We found that the subjects who exhibit right-dominant PFC activity during mental stress tasks have higher levels of sebum secretion in the facial skin, suggesting that such subjects are sensitive to mental stress associated with hyperactivity of the HPA axis. In the present study, on the

* Corresponding author. Tel.: +81 3 3972 8111x2481; fax: +81 3 3554 0425.
E-mail address: sakatani@med.nihon-u.ac.jp (K. Sakatani).

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basis of these findings, we hypothesized that administration of fragrance may alter left/right asymmetry in PFC activity during mental stress tasks, resulting in amelioration of hypersecretion of sebum in the facial skin, which is caused by activation of the HPA system [20].

We studied a total of 31 healthy young female subjects (mean age of 22.2 ± 2.3 years). Firstly, we selected the subjects who showed right-dominant PFC activity during mental stress tasks and high levels of sebum secretion in the facial skin. Then, the subjects were asked to draw lots to be classified into the control and fragrance groups. We compared the left/right asymmetry of PFC activity and the levels of sebum secretion in the subjects with fragrance treatment (fragrance group) and without treatment (control group). 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 n accordance with the requirements of the Human Subjects Committee of the Shiseido Life Science Institute.

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 [38,34,14,27,33]. Elicitation of stress was verified by the State-Trait Anxiety Inventory (STAI) and measurements of heart rate. Heart rate was monitored simultaneously with PFC activity, by placing a photo-electrical sensor (Tsuyama MGF KK, Tokyo, Japan) on the subject's right earlobe to measure pulse waves.

We measured hemoglobin concentration changes in the bilateral PFC employing NIRS (NIRO-300, Hamamatsu Photonics K.K., Hamamatsu, Japan). Details of this system have previously been described [24,32]. Briefly, near-infrared light from four laser diodes (775, 810, 850, and 910 nm) is directed to the head through a fibre-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. MRI confirmed that the emitter-detector was located over the dorsolateral and frontopolar areas of the PFC [34].

In order to evaluate the possible effect of skin blood flow changes during the mental arithmetic task, we measured changes in the facial skin temperature using a thermograph (TH71, NEC San-ei Instruments, Tokyo) prior to the present study ($n = 8$). The task caused minimal changes in the skin temperature (within ±0.2 °C; data not shown), suggesting that skin blood flow changes during the task would not have greatly influenced the NIRS parameter changes.

Prior to commencing the mental arithmetic task, we measured the level of sebaceous secretion in the facial skin. For measurements of the levels of sebum secretion, we used the Sebumeter (SM810, Courage + Khazaka, Köln, Germany) in all subjects; the levels of sebum secretion was measured in the left and right cheeks, and averaged in each subject. In the study on the effect of fragrance on the facial skin sebum, we measured the sebum before and four weeks after fragrance administration.

A fragrance with a floral green tone was adopted. To estimate the subject's preference for the fragrance, they were asked to evaluate the fragrances using a visual analogue scale from −100 (i.e. "not pleasant at all") to +100 (i.e. "very pleasant"). The mean preference value for the subjects in this experiment was +47.3 ± 28.5 ($n = 6$); all of them expressed positive ("pleasant") scores for the fragrance they used. A fragrance spray (5% ethanol solution) and a room fragrance (filter paper soaked in 50% odorless paraffin solution) were prepared containing the above-mentioned scent. All subjects were asked to use the spray at least 3 times during the day and then to put the room fragrance at their bedside every night for 4 weeks.

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 s 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 since these correlate with rCBF changes during activation [34,14,33,24,13,17,25,26,36]. 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 [34,33]. We used Mann–Whitney's U test for the comparisons of changes in STAI-II score and heart rate before and during the task, and Student's t test for the comparison of pre-stress levels of sebum secretion between right (i.e. LI > 0) and left (i.e. LI < 0) dominant PFC activity groups. To evaluate the effects of fragrances on the PFC activity during the task, we compared the LI of oxy-Hb concentration changes before and after fragrance administration in the right-dominant group employing paired t test. In addition, we compared the pre-stress levels of sebum secretion before and after fragrance administration employing Wilcoxon's rank test.

The mental arithmetic task significantly increased the STAI-II scores and heart rate in all subjects; the changes in STAI-II scores and heart rate were 7.26 ($p = 3.33\text{E}{-5}$) and 11.70 ($p = 3.56\text{E}{-11}$), respectively. NIRS demonstrated that the task

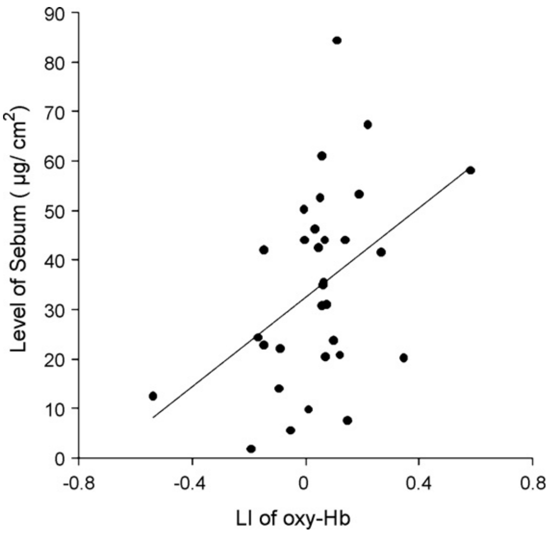

Fig. 1. Relationship between left/right asymmetry of PFC activity and the pre-stress level of sebum secretion in the facial skin. The abscissa represents the laterality index (LI) of changes in oxy-Hb, while the ordinate indicates the level of sebum secretion (μg/cm^2). There was a significant positive correlation between the LI of oxy-Hb and the level of sebum secretion ($r = +0.44$, $p = 0.01$).

led to elevation of oxy-Hb and total-Hb associated with a decrease in deoxy-Hb in the bilateral PFC. Regression analyses were used to investigate the relationship between left/right asymmetry in PFC activity during the task and the level of sebum secretion. There was a significant positive correlation between the LI of oxy-Hb and the level of sebum secretion ($r = +0.44$, $p = 0.01$) (Fig. 1), which is consistent with our previous study [33].

We selected 12 subjects who exhibited right PFC dominant activity (LI of oxy-Hb > 0.035) with high levels of sebum secretion (>20.3 μg/cm^2) for evaluation of the effect of fragrance. These subjects were classified into control ($n = 6$) and fragrance ($n = 6$) groups; there were no significant differences in levels of sebum secretion or LI of oxy-Hb between the two groups before fragrance administration ($p > 0.05$). After administration of fragrances for four weeks, the pre-stress level of sebum secretion was significantly reduced from 54.1 ± 17.5 μg/cm^2 to 39.0 ± 17.8 μg/cm^2 ($p = 0.02$) (Fig. 2A). In addition, the LI of oxy-Hb significantly decreased from 0.11 ± 0.07 to -0.10 ± 0.18 after fragrance administration ($p = 0.01$), indicating that right-dominant PFC activity was changed to left-dominant PFC activity (Fig. 2B). In contrast, both of the pre-stress level of sebum secretion and the LI of oxy-Hb remained unchanged in the control group. Finally, fragrance administration decreased the task-induced changes in STAI-II score from 7.8 ± 9.4 to 0.7 ± 8.3 and heart rate from 7.7 ± 4.7 beat/min to 4.4 ± 5.7 beat/min, although the differences were insignificant ($p > 0.05$).

This is the first demonstration that the PFC plays an important role in the effect of fragrances on the systemic response to mental stress. We found that administration of fragrance altered the dominant side of the stress-induced PFC activity from the right to the left side, and reduced the level of sebum secretion in subjects

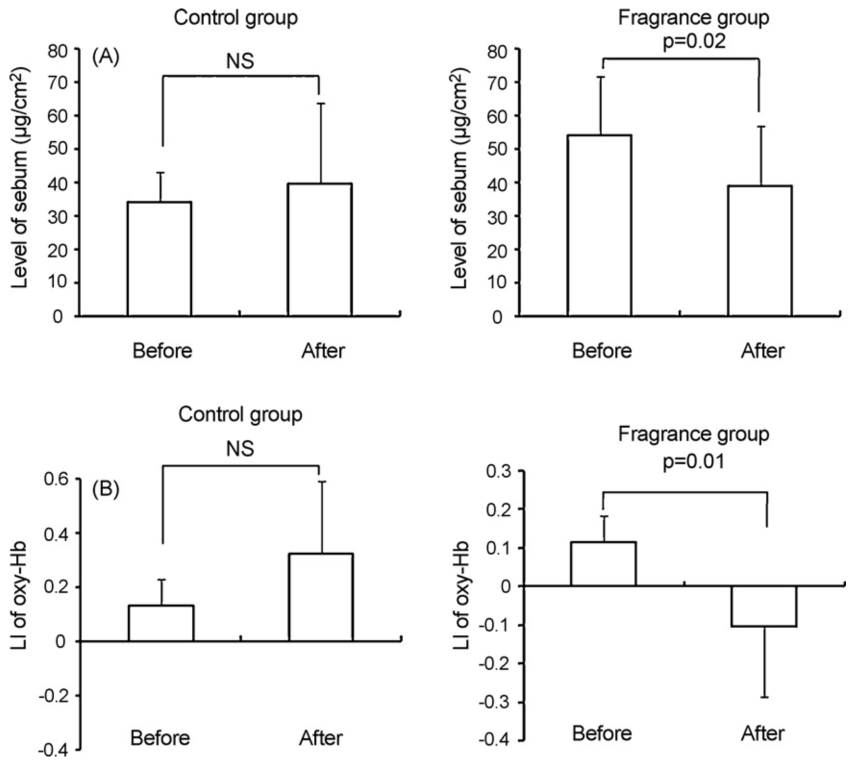

Fig. 2. Effects of fragrance administration on the pre-stress level of sebum secretion in the facial skin (A) and the laterality of PFC activity during a mental arithmetic task (B). The ordinates in A and B indicate the level of sebum secretion (μg/cm^2) and the laterality index (LI) of oxy-Hb changes, 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 ($p = 0.01$).

who exhibited right-dominant PFC activity and hypersecretion of sebum before the administration.

Recent studies have demonstrated that the right PFC regulates the activity of the HPA axis [4,31,38,34]. Activation of the HPA axis causes an increase of adrenal steroid hormones such as glucocorticoids and adrenal androgens, which induce sebaceous hyperplasia and secretion of sebum [20]. In addition, corticotrophin-releasing hormone could induce lipogenesis and androgen metabolism in sebocytes by activating the receptors for corticotrophin-releasing hormone in sebocytes [29,39]. These results suggest that administration of fragrance reduced the level of sebum secretion by modulating the stress-induced PFC activity.

The physiological mechanism of the modulation of the stress-induced PFC activity by fragrance administration is not established; however, the following two possible mechanisms should be considered. First, neuronal conditioning of PFC activity by olfactory stimulation may occur. Anatomical studies have established the neural network from the olfactory bulb to the frontal lobe; the olfactory bulb connects to the thalamus, hypothalamus, and limbic system, which provide secondary connections to the frontal lobe [21]. Fulbright et al., employing fMRI, observed that odors elicit activation in the frontal lobe [10]. In addition, recent NIRS studies have demonstrated that olfactory stimulations cause increases of oxy-Hb in the bilateral frontal cortices, indicating activation in these brain regions [16,18]. These results suggest that persistent olfactory stimulations with fragrance could cause changes in the stress-induced PFC activity via the network between the PFC and the olfactory system.

Another possible mechanism is an influence of steroid hormones such as glucocorticoids on the proliferation of neural cells. It is well established that glucocorticoids inhibit the proliferation of progenitor cells in the hippocampal dentate gyrus of adult mammals. In addition, it was demonstrated that glucocorticoids could inhibit the proliferation of oligodendrocyte precursors in the white and gray matter regions of adult rat forebrain [1]. Therefore, changes in the level of circulating glucocorticoids could influence the proliferation of oligodendrocyte precursors in the frontal lobe, which might alter the frontal lobe function. Indeed, a recent study on humans has demonstrated that odorant inhalation decreases salivary cortisol levels [2].

Fragrances have relaxant effects in humans; for example, they improve the symptoms of anxious or depressive states [23], and reduce heart rate by modulating the autonomic nervous system [8]. In the present study, fragrances tended to reduce the STAI-II score changes and heart rate changes induced by a mental arithmetic task. The relaxant effects of fragrances were associated with changes in the dominant side of PFC activity from the right to the left side. Recent neuroimaging studies have demonstrated that negative affective stimuli generally activate the right PFC, while left PFC activation is associated with positive emotions [6,9]. In addition, right dominance of PFC activity during the mental arithmetic task was associated with an increase in heart rate [34,33]. These observations suggest that fragrances affect the stress responses of emotions and the autonomic nervous system by modulating the PFC activity.

A number of studies have demonstrated that fragrances improve stress-induced immune suppression [28,19]. In patients with depression, fragrances normalized neuroendocrine hormone levels and immune function [19]. In addition, fragrances could reverse the immune suppression induced by high pressure stress in mice [28]. It should be noted that PFC activity is known to modulate the immune system [3]. Animal studies have demonstrated that asymmetric disruptions of PFC function via unilateral lesions differentially affect immune function, causing enhancement or suppression depending on the side of the lesion [37]. Rosenkranz et al. have demonstrated that higher levels of right-prefrontal activation predict a poorer immune response in human [22]. In addition, Davidson et al. evaluated the effect of mindfulness meditation on the PFC activity and immune function, and revealed that the meditators exhibited increases in left-sided PFC activation and enhancement of immune function compared with the nonmeditators [7]. These results suggest that the PFC plays a role in the effects of fragrances on stress-induced immune suppression as well as emotional responses to stress.

A number of limitations of the current study are worthy of mention. Firstly, this was a pilot study designed to evaluate the possibility that fragrances might influence the relation between stress-induced PFC activity and the systemic response to mental stress. For this reason, the study group was small, which may have contributed to the fact that we did not observe statistically significant differences in the task-induced changes of heart rate and STAI-II scores before and after administration of fragrance. Secondly, all of the subjects in the present study were young females; however, aging and gender-difference could affect activity of the brain, including the PFC, induced by cognitive tasks [13,26,12]. Further studies are necessary to evaluate the fragrance effects on aged and male subjects. Thirdly, we did not evaluate adrenal steroid hormones, which reflect the activity of the HPA axis. It remains necessary to clarify the relationships among stress-induced PFC activity, skin condition, and adrenal steroid hormones. 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 important roles in stress responses [4,31,38,34,33], further studies are necessary to evaluate the precise activation areas in the whole brain that are related to the effect of fragrance and mental stress.

In summary, the present results indicate that administration of fragrance reduced the level of sebum secretion in association with changes in the stress-induced PFC activity. The PFC may play an important role in the neurophysiological mechanism of fragrance effects on systemic response to mental stress.

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