VIII. 2. Functional Neuroimaging of Autonomic Nervous Responses During Aroma-therapy Using [^{18}F]FDG PET

Duan X.[1], Tashiro M.[1], Wu D.[2], Yambe T.[3], Wang Q.[3], Sasaki T.[1], Kumagai K.[1], Luo Y.[3], Nitta S.[4], and Itoh M.[1]

[1]Cyclotron and Radioisotope Center, Tohoku University
[2]Division of Music Education, Miyagi University of Education
[3]Institute of Development, Aging and Cancer, Tohoku University
[4]Biomedical Engineering Research Organization, Tohoku University

Introduction

It is well known that olfactory stimulus has a powerful influence on mammalian behaviors and physiological functions, and the relationship between olfactory sensation and autonomic changes has been studied extensively. Various smells can induce autonomic changes compatible with autonomic relaxation[1,2] or excitation[3,4], as well as changes compatible with basic emotions[5]. Such autonomic changes following treatments with perfumed fragrances (aroma-therapy) can be detected by power spectral analysis (PSA) of heart rate variability (HRV). A few studies have demonstrated usefulness of HRV measurement for evaluation of autonomic changes induced by various odorants such as lavender[6,7]. It has been said that “lavender”, one of the most popular flower fragrances used in aroma-therapy, usually does not induce strong emotions but does comfortable feeling and relaxation. The effects of these fragrances on brain functions do not seem to be simple. It is expected that many brain regions, including sensory and limbic regions, are involved in olfaction. So far, positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) have been used to investigate regional brain activation due to various sensory and emotional stimuli. However, functional neuroanatomy of autonomic changes induced by aroma-therapy has not been studied well using PET. The aim of the present study is to investigate the effects of lavender fragrance on autonomic nervous functions in terms of HRV and to observe brain responses in terms of brain glucose metabolic changes measured by PET.

Methods

Ten healthy female volunteers, ranging 20 to 27 years old (mean age ± S.D.: 23±3.0 years old), were recruited for the present experiment after obtaining their written informed consent. The present study protocol was approved by the Ethics Committee of Tohoku University Graduate School of Medicine. Before starting the study, each subject was interviewed for her preferences to the lavender fragrance, and was also requested to rate her own stress using the Stress Response Scale (SRS-18). The subjects were requested to be seated on a comfortable chair with the eyes open in the PET operation room. Holter ECG recording in the NASA leads (FM-300, Fukuda Denshi, Tokyo, Japan) was performed for evaluation of the HRV. Respiratory rate was also monitored in order to ensure the absence of respiratory changes after lavender administration, but the data were lost because of technical problem. Then, the respiratory data were collected again from other 15 subjects (ranging 20 to 23 years old; mean age +/- S.D.: 21.0 +/- 1.0 years old).

To supply the lavender fragrance, a plaster prepared for aroma-therapy ("Lavender girl", Teikoku Pharmaceuticals, Tokyo, Japan) was attached on the subjects' right shoulder shortly before administration of [^{18}F]labeled fluorodeoxyglucose (FDG) injected through the right cubital vein (37 MBq). After 40-min-long uptake phase of FDG, all the electrodes and the lavender plaster were removed and soon PET scanning procedure was initiated using SET2400W scanne r (Shimadzu Inc., Kyoto, Japan). Subjects were requested to rate their own stress again using was also requested to rate her own stress using SRS-18 after PET scanning. PET brain images were analyzed to identify regional changes of glucose metabolic rate using Statistical Parametric Mapping (SPM2[10,11]). The threshold for the significance was set at $p< 0.001$ without corrections for multiple comparisons.

Analyzing HRV in the frequency domain is a valuable method to determine quantitatively the sympathetic and parasympathetic modulations of heart rate (HR)[8,9]]. Two main spectral components are most commonly distinguished in the HRV spectrum: low frequency (LF: 0.04 to 0.15 Hz) and high frequency (HF: 0.15 to 0.4 Hz) components, respectively[8,9)]. For further evaluation, normalized LF and HF (nLF and nHF, respectively) and low-high frequency ratio (LF/HF) were used.

Results

Representative data of HRV measurement taken from a subject are demonstrated in Fig. 1. R-R intervals tended to be longer later in the experiment compared to the initial resting condition. The R-R intervals were somewhat shorter in the lavender administration condition in comparison to the control. The fraction of HF was higher and the LF/HF ratio was lower in the lavender condition. nHF tended to increase and nLF tended to decrease in the first 10 min following lavender plaster administration, resulting in decreased LF/HF.

PET analysis revealed changes in cerebral metabolism between the conditions ($p < 0.001$). Administration of lavender administration was associated with activation in the orbitofrontal cortex, posterior cingulate cortex, brainstem (mainly pons), thalamus and cerebellum while deactivation was observed mainly in the pre/post-central gyrus and frontal eye field (Fig.1).

Discussion

So far, psychological and physiological effects of various odorants have been investigated, and it has been reported that lavender elicited mostly "relaxation" and "happiness"[12]. In the present study, spectral analysis of HRV indicated a significant increase in HF component and reduction in LF/HF ratios during the lavender use. The present results go in accordance with the previous study by Saeki and colleagues[6] where 10 healthy female subjects were studied. They demonstrated that lavender fragrance induced HRV changes associated with relaxation. Kuroda and colleagues[7] conducted a study using 12 subjects to find the similar results to those by Saeki et al.

It was expected that various olfactory regions, including the primary olfactory cortex and the most limbic regions, would be activated. A previous fMRI study demonstrated activation of these regions induced by olfactory stimulations[17]. A similar study was conducted using PET as well[18]. Another fMRI study demonstrated that the pleasant smell activated the medial part of orbitofrontal cortex and the unpleasant smell did the lateral part, respectively[19]. Metabolic reduction in the olfactory regions was reported in patients with disturbed olfaction[20].

Contrary to the authors' expectation, the present study did not find involvement of any primary olfactory regions but involvement of a few association regions such as the orbitofrontal cortex, thalamus and cerebellum. A possible explanation for this discrepancy may be the difference of time window because of methodological difference. FDG accumulation in the brain tissue is a rather slow process while olfaction is a relatively instantaneous phenomenon. Since the FDG PET method tends to average brain activities of longer time span (approximately 30 to 40 min), it does not detect brain responses which may last temporally. Therefore, it seems that an interpretation of the present results should be done based on the concept of "identifying brain regions influenced by environmental changes due to lavender fragrance lasting 40 minutes" that would make the interpretation easier.

Based on such a standpoint, lack of activation in the anterior cingulate gyrus in the present study would be reasonable because this region is regarded as one of the centers of sympathetic nervous activities that were possibly suppressed after lavender administration. Metabolic increase in the brainstem and posterior cingulate gyrus, though not usually included in the olfactory regions, seems to be associated with improved mental functions during relaxation rather than olfaction itself. The combined finding of a reduced sensorimotor activity and an improved arousal/cognitive function seem to be a good brain representation of "physical relaxation" and "improved mental functions" induced by lavender, as recognized as a calming or relaxing agent[21)].

In summary, the authors have demonstrated that lavender fragrance can promote relaxation by depressing sympathetic activity while augmenting parasympathetic activity in normal adults. Our findings suggest a possible use of lavender fragrance to treat patients with various types of autonomic dysfunctions.

References

1) Alaoui-Ismaili O., Vernet-Maury E., Dittmar A., et al., Chem Senses **22** (1997) 237.
2) Nagai M., Wada M., Usui N., et al., Neurosci. Lett. **289** (2000) 227.
3) Brauchli P., Ruegg P.B., Etzweiler F., et al., Chem. Senses **20** (1995) 505.
4) Alaoui-Ismaili O., Vernet-Maury E., Dittmar A., et al., Chem. Senses **22** (1997) 237.
5) Vernet-Maury E., Alaoui-Ismaili O., Dittmar A., et al., J. Auton. Nerv. Syst. **75** (1999) 176.
6) Saeki Y., Complement Ther Med. **8** (2000) 2.
7) Kuroda K., Inoue N., Ito Y., et al., Eur. J. Appl. Physiol. **95** (2005) 107.
8) Novak V., Saul J.P., Eckberg D.L., et al., Circulation **96** (1997) 1056.
9) La Rovere MT., Bigger JT Jr., Marcus FI., et al., Lancet **351** (1998) 478.
10) Friston K., Ashburner J., Frith C., et al., Human Brain Map. **2** (1995) 165.
11) Friston K.J., Holmes A., Poline J.B., et al., Neuroimage **4** (1996) 223.
12) Vernet-Maury E., Alaoui-Ismaili O., Dittmar A., et al., J. Auton. Nerv. Syst. **75** (1999) 176.
13) Pomeranz B., Macaulay R.J., Caudill M.A., et al., Am. J. Physiol. **248** (1985) 151.
14) Malliani A., Lombardi F., Pagani M., Br. Heart J. **71** (1994) 1.
15) Dunn C., Sleep J., Collett D., et al., J. Advanced Nursing **21** (1995) 34.
16) Stevensen C.J., Complementary Therapies in Med. **2** (1994) 27.
17) de Araujo I.E., Rolls E.T., Kringelbach M.L., et al., Eur. J. Neurosci. **18** (2003) 2059.
18) Qureshy A., Kawashima R., Imran M.B., et al., J. Neurophysmol. **84** (2000) 1656.
19) Rolls E.T., Kringelbach M.L., de Araujo I.E., Eur. J. Neurosci. **26** (2002) 695.
20) Levy L.M., Henkin R.I., Lin C.S., Finley A., J. Comput. Assist. Tomogr. **23** (1999) 767.
21) Buchbauer G., Jirovetz L., Jager W., et al., J. Biosciences **46** (1991) 1067.

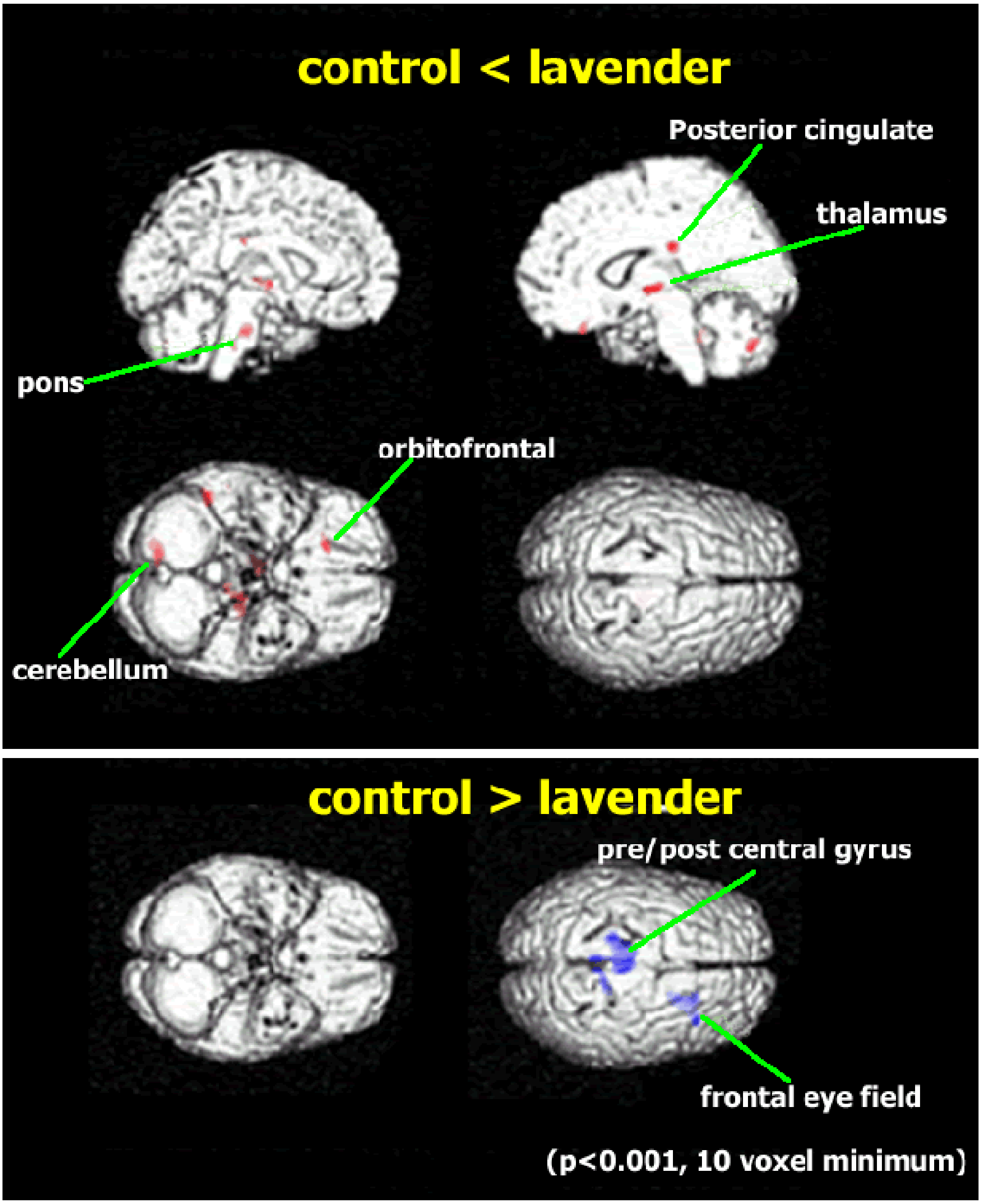

Figure 1. Results of voxel-by-voxel comparison of brain glucose metabolic images. Brain regions with metabolic increase due to lavender administration (control<lavender). And brain regions with metabolic reduction due to lavender administration (control>lavender). (p<0.001, 10 voxel minimum).