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Research report

Continuous inhalation of essential oil increases gray matter volume

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ABSTRACT

Research into the health benefits of scents is on the rise. However, little is known about the effects of continuous inhalation, such as wearing scents on clothing, on brain structure. Therefore, in this study, an intervention study was conducted on a total of 50 healthy female people, 28 in the intervention group and 22 in the control group, asking them to wear a designated rose scent on their clothes for a month. The effect of continuous inhalation of essential oil on the gray matter of the brain was measured by calculating changes in brain images of participants taken before and after the intervention using Magnetic Resonance Imaging (MRI). The results showed that the intervention increased the gray matter volume (GMV) of the whole brain and posterior cingulate cortex (PCC) subregion. On the other hand, the GMV of the amygdala and orbitofrontal cortex (OFC) did not change. This study is the first to show that continuous scent inhalation changes brain structure.

1. Introduction

Aromatherapy is one of the traditional remedies that uses essential oils extracted from plants based on their scent effects and is currently used in many fields. Aromatherapy is based on the theory that inhaling or absorbing essential oils causes changes within the limbic system, the part of the brain associated with memory and emotion (Seyyed-Rasooli et al., 2016). Aromatherapy stimulates physiological responses in the nervous, endocrine, or immune systems and can affect heart rate, blood pressure, breathing, brain wave activity, and the release of various hormones throughout the body (Seyyed-Rasooli et al., 2016). The limbic system comprises subcortical (amygdala, hippocampus) and cortical structures (parahippocampal cortex, cingulate cortex, etc.) and plays a central role in emotional regulation and memory (Rolls, 2019; Soudry et al., 2011). Numerous functional magnetic resonance imaging (fMRI) studies conducted in healthy, normal people have shown that olfactory stimuli activate primary and secondary olfactory cortical areas (e.g., Wang et al., 2005). However, the pattern of activation is inconsistent as it is influenced by various experimental factors such as task instructions and stimulus quality (Van Regemorter et al., 2022).

The smell can be broadly divided into two aspects: intensity and pleasantness. Among these, intensity has been observed to be related to activity in the primary olfactory cortex including the amygdala (Anderson et al., 2003). Pleasure, on the other hand, is associated with the secondary olfactory cortex (Bérard et al., 2021) including the orbitofrontal cortex (OFC), which is involved in odor identification and olfactory memorization receiving direct input from the olfactory tract (Zald and Pardo, 1997; Zald et al., 2002; Zatorre et al., 1992; Small et al., 1997). In addition to the amygdala and OFC, the posterior cingulate cortex (PCC) shows interesting trends. PCC is involved in memory-odor associations, odor memory retrieval, and semantic memory processes (Maddock et al., 2001; Binder et al., 2009; Bird et al., 2015). Previous studies have shown that patients with olfactory dysfunction (OD) who are more demanding on olfactory memory tasks have greater PCC responses to olfactory stimuli compared to subjects with normal olfactory sense (Pellegrino et al., 2016; Pellegrino et al., 2021). Furthermore, the PCC is activated in response not only to pleasant scents (e.g. lavender scent. Duan et al., 2007; Jung et al., 2004) but also to unpleasant scents (Billot et al., 2017). This is unlike the OFC, which is activated mostly in response to pleasant scents (O'doherty et al., 2000; Grabenhorst et al., 2007), and the amygdala, which is activated in response to strong or unfamiliar scents (Anderson et al., 2003; Jung et al., 2006). Fig. 1 shows

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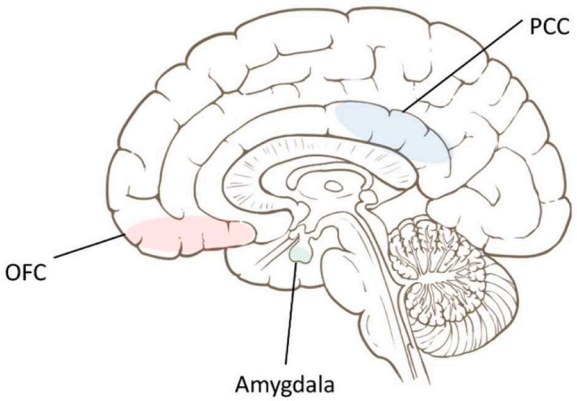

Fig. 1. Human brain. OFC: orbitofrontal cortex. PCC: posterior cingulate cortex.

the locations of these three regions on an illustration of a whole brain.

Based on the above previous studies, this study will investigate the effects of daily inhalation of rose scent on GMV in women's brains. Regarding GMV in the brain, in addition to the whole brain, from the perspective of the region of interest (ROI), we assessed the GMV of the amygdala, OFC, and PCC. The reasons for limiting the target audience to women are that women are generally more sensitive to odors than men (Doty and Cameron, 2009), respond more emotionally to odors (Chen and Dalton, 2005), and are more susceptible to emotional conditioning with odors (Bell et al., 1992; Dalton, 1999; Herz, 2016; Kirk-Smith et al., 1983). Therefore, many studies examining odor-evoked memory have focused exclusively on women (eg, Herz et al., 2004; Toffolo et al., 2012). On the other hand, since many men do not have the habit of wearing scents, it is expected that they are more likely than women to feel uncomfortable with the intervention. Therefore, we decided to exclude men from the study to reduce the possibility that their inclusion would uncontrollably affect the study results.

2. Materials and methods

2.1. Participants

From September to October 2018, with the support of a private staffing agency, 51 healthy women were recruited to Kyoto as research participants. They were compensated by a staffing agency. After that, they were randomly divided into the following two groups by a double-blind method: 29 participants in the intervention group (aged 41–69 years, mean [M] ± standard deviation [SD]: 50.9 ± 7.6 years) and 22 participants in the control group (aged 41–65 years, M ± SD: 51.2 ± 6.7 years). To account for the possibility that some participants would drop out, a larger number of participants were recruited than the theoretically required number of 17 participants in each group calculated with G*Power 3.1.9.7 with effect size f = 0.25; α error probability = 0.05; power = 0.8. More participants were assigned to the intervention group in anticipation of the possibility that many participants would find the scent unpleasant and drop out. In terms of results, although there were no dropouts, one participant in the intervention group was excluded from the analysis due to an inability to successfully perform post-intervention brain imaging. As a result, 28 subjects in the intervention group (aged 41–69 years, M ± SD: 51.2 ± 6.7 years) and 22 subjects in the control group (aged 41–65 years, M ± SD: 51.2 ± 7.5 years), a total of 50 healthy women (aged 41–69 years, M ± SD: 51.2 ± 7.1 years) were included in the study. Considering that this study (1) measures the brain structure, (2) uses scent, and (3) targets healthy subjects, the exclusion criteria were as follows: (1) going to a hospital for psychosomatic medicine, psychiatry, gynecology, or otolaryngology; (2) having a mental and nervous system disease, gynecological disease, otolaryngological disease, serious physical disease (malignant tumor, heart failure, liver disorder, renal disorder, endocrine disease, diabetes, nutritional disorder, alcoholism); (3) taking central nervous system drugs, hormone drugs, etc.; (4) smoking; (5) being pregnant or breast-feeding; (6) disliking the scent of rose essential oil; (7) having a history of allergies to commercially available fragrances and cosmetics. This study was approved by the Ethics Committee of Kyoto University (approval number 27-P-13) and was conducted following the guidelines and regulations of the institute. All participants provided written informed consent before participation and maintained anonymity.

2.2. Procedure

Participants were asked to wear the designated scent on their clothes every day for a month. That is, (1) the intervention group, 1–3 drops of rose essential oil (0.5%) per time, (2) the control group, 1–3 drops of water per time, twice a day dropped on the aroma seal and were required to wear it on their clothes. Essential oils were diluted with dipropylene glycol (DPG). DPG is a polyhydric alcohol that combines PG (propylene glycol) and is a safer and less irritating ingredient than PG. To investigate the effects of continuous inhalation of essential oil, DPG was selected in this study because it has high water retention, antibacterial properties, and is effective in increasing the shelf life of products (Japan Cosmetic Association, 2021), and has been confirmed to be safe for the human body, including the skin (Cosmetic Ingredient Review Expert Panel, 1984). Participants were asked not to change their lifestyle significantly during the experiment. Participants gathered at Kyoto University before and after the one-month intervention, and brain images were taken using an MRI machine using the method described below.

2.3. MRI data acquisition

All magnetic resonance imaging (MRI) data were obtained using a 3-T Siemens scanner (Verio, Siemens Medical Solutions, Erlangen, Germany or MAGNETOM Prisma, Siemens, Munich, Germany) with a 32-channel head array coil. A high-resolution structural image was acquired using a three-dimensional (3D) T1-weighted magnetization-prepared, rapid-acquisition gradient echo pulse sequence. The parameters were as follows: repetition time (TR), 1900 ms; echo time (TE), 2.52 ms; inversion time (TI), 900 ms; flip angle, 9°; matrix size, 256 × 256; field of view (FOV), 256 mm; and slice thickness, 1 mm. DTI data were collected by spin-echo echo-planar imaging (SE-EPI) using generalized auto-calibrating partially parallel acquisitions (GRAPPA). The image slices were parallel to the orbitomeatal (OM) line. The parameters were as follows: TR = 14,100 ms; TE = 81 ms; flip angle = 90°; matrix size = 114 × 114; FOV = 224 mm; slice thickness = 2 mm. The baseline image (b = 0 s/mm^2) and 30 different diffusion directions were obtained with a b-value of 1000 s / mm^2.

2.4. GM-BHQ

T1-weighted images were pre-processed and analyzed using Statistical Parametric Mapping 12 (SPM12; Wellcome Trust Center for Neuroimaging, London, United Kingdom) running on MATLAB R2015b (Mathworks Inc., Sherborn, MA, United States). Each MPRAGE image was divided into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) images. The segmented GM images were spatially normalized using a diffeomorphic anatomical registration through an exponentiated lie algebra (DARTEL) algorithm (Ashburner, 2007). A modulation step was also incorporated into the pre-processing model to reflect the regional volume and preserve the total GM volume before the warp. As a final preprocessing step, all normalized, segmented, and modulated images were smoothed with an 8 mm full width at half-maximum (FWHM) Gaussian kernel. Intracranial volume (ICV) was calculated by summing the GM, WM, and CSF images for each subject.

Proportional GM images were generated by dividing the smoothed GM image by ICV to control for differences in whole-brain volume between participants. These proportional GM images were used to generate the mean and standard deviation (SD) images of all participants. Next, we calculated the GM brain healthcare quotient (BHQ), which is like the intelligence quotient (IQ). The mean was defined as BHQ 100, and SD was defined as 15 BHQ points. By this definition, about 68% of the population is between BHQ 85 and BHQ 115, and 95% of the population is between BHQ 70 and BHQ 130. Individual GM quotient images were calculated using the following formula: $100 + 15 \times$ (individual proportional GM–mean)/SD. Next, automatic anatomical labeling (AAL) atlas73 was used to extract regional GM quotients and averages across regions to create participant-specific GM-BHQs. For more details, see Nemoto et al. (2017) and Kokubun et al. (2023). In addition to GM-BHQ, which is representative of the whole brain, we also used the amygdala, OFC, and PCC subregions of GM-BHQ from the perspective of the region of interest (ROI).

2.5. Statistical analysis

Repeated measures ANOVA assessed the following changes due to intervention: whole brain, amygdala, OFC, and PCC GM-BHQ. All statistical analyses were performed using IBM SPSS Statistics Version 28 (IBM Corp., Armonk, NY, USA).

3. Results

Table 1 shows the results of an independent samples t-test. It is shown that there was no statistical mean difference between the two groups for age ($t = 0.006$, $p = 0.995$), BMI ($t = 0.103$, $p = 0.918$), whole-brain ($t = 0.307$, $p = 0.760$), amygdala ($t = 0.259$, $p = 0.796$), OFC ($t = 0.590$, $p = 0.558$), and PCC ($t = 0.585$, $p = 0.561$) GM-BHQ. Therefore, in the observed variables, we could confirm that the distribution of study participants was roughly homogeneous.

Table 2 shows the changes after the intervention. First, according to the analysis of covariance (ANCOVA) test, which controlled for changes before and after the intervention using baseline values, there were significant differences at the 5% level for both whole-brain ($F = 5.562$, $p = 0.023$) and PCC ($F = 6.863$, $p = 0.012$) GM-BHQ. There was also a significant difference in the post-hoc paired-samples t-test between pre and post-intervention groups at the 1% and 5% levels for whole-brain ($t = 3.248$, $p = 0.003$, $d = 0.623$) and PCC ($t = 2.661$, $p = 0.013$, $d = 0.494$) GM-BHQ, respectively. On the other hand, amygdala ($F = 0.058$, $p = 0.811$) and OFC ($F = 3.070$, $p = 0.086$) GM-BHQ did not show significant changes in the ANCOVA test. Furthermore, the results of multiple comparisons using the Benjamini & Hochberg method showed that the changes in whole-brain and PCC GM-BHQ were still statistically significant. Fig. 2 shows changes in the means for the four variables.

4. Discussion

Research into the health benefits of scents is on the rise (Ebrahimi et al., 2022; Fukada et al., 2012; Atsumi and Tonosaki, 2007; Watanabe et al., 2015; Kawai et al., 2020; Choi et al., 2014). The efficacy of scent has also been confirmed in brain research (Wang et al., 2005; Van Regemorter et al., 2022). However, most of these studies have examined the effects of temporary odor stimulation on brain responses. Therefore, in this study, we investigated the changes that occur in brain structure when a person is continuously exposed to scent stimuli for a month. Rose essential oil was used to scent the intervention group, and plain water was used to scent the control group. A total of 50 people, 28 in the intervention group and 22 in the control group were asked to wear the designated scent on their clothes for a month. The results showed that daily inhalation of rose essential oil increased the GMV of the whole brain and its PCC subregion measured by GM-BHQ. On the contrary, the amygdala and OFC GM-BHQ did not show any significant changes. These results remained unchanged even after multiple comparisons using the Benjamini & Hochberg (BH) method.

The PCC is involved in memory-odor associations, odor memory retrieval, and semantic memory processes (Maddock et al., 2001; Binder et al., 2009; Bird et al., 2015). Previous studies have shown that patients with olfactory dysfunction (OD) have weaker activation in regions directly related to olfactory function, including the amygdala (Yunpeng et al., 2021; Pellegrino et al., 2021), and stronger activation in regions indirectly related to olfactory function, including the PCC, in response to olfactory stimuli compared to people with normal sense of smell (Pellegrino et al., 2016; Pellegrino et al., 2021). Stronger activation in the PCC of OD patients may indicate more demanding olfactory memory processing (Van Regemorter et al., 2022). Therefore, it can be considered that, under conditions of sustained odor exposure, as in our experiments, the PCC, which processes odor memories, was more activated than the amygdala, which is responsible for sensing odors.

Another possibility is that the subjects who kept sniffing the rose essential oil found it unpleasant and were regulating their emotions. A previous study has shown that negative odor-induced emotions result in activation of the PCC, while regulation of odor-induced emotions results in mild lower activation of the amygdala (Billot et al., 2017). Meanwhile, an fMRI study reported that activation in regions of the OFC was reduced by the odor of food eaten to the point of satiety, with a similar tendency in some subjects in the amygdala (O'doherty et al., 2000). Relatedly, studies using jasmine and mixtures suggest that the medial OFC is activated in response to pleasant scents alone (Grabenhorst et al., 2007). Another study confirms from electrophysiological recordings that the amygdala typically responds to unfamiliar and hedonic neutral odor stimuli (Jung et al., 2006). From these, in our current research, we cannot deny the possibility that by continuous inhalation of rose essential oil, the brain perceives it as unpleasant, which may activate PCC and simultaneously prevent the activation of the OFC and amygdala. However, it is difficult to reach this conclusion based on changes in brain volume, and it is only one possibility.

The result of this study that continuous inhalation of rose essential oil increases the GM of PCC has implications for the practice of dementia prevention. Previous studies have shown that Alzheimer's disease (AD) patients have decreased GMV in PCC (Shimoda et al., 2015; He et al., 2007; Liu et al., 2008). A meta-analysis of structural neuroimaging

Table 1
Comparison of baseline intervention group and control group.

	Control		Intervention			
	Mean	SD	Mean	SD	*t*	*p*
Age (years old)	51.230	6.740	51.210	7.465	0.006	0.995
BMI (kg/m^2)	21.445	2.768	21.354	3.378	0.103	0.918
Whole brain	100.061	7.167	100.634	6.036	0.307	0.760
Amygdala	100.679	11.450	101.536	11.690	0.259	0.796
OFC	99.068	10.412	100.637	8.411	0.590	0.558
PCC	96.388	12.628	98.337	10.911	0.585	0.561

$n = 22$ for control and $n = 28$ for intervention; * $p < 0.05$; OFC: orbitofrontal cortex. PCC: posterior cingulate cortex.

Table 2
Changes before and after the intervention.

	Control		Intervention				
	Mean	SD	Mean	SD	*F*	*p*	partial η^2
Whole brain	-0.071	1.063	0.558	0.909	5.562	0.023*	0.106
Amygdala	0.015	3.415	0.182	3.437	0.058	0.811	0.001
OFC	-0.141	1.076	0.476	1.367	3.070	0.086	0.061
PCC	-0.330	1.399	0.725	1.441	6.863	0.012*	0.127

n = 22 for control and n = 28 for intervention; The test was based on the ANCOVA method, which controlled for changes before and after the intervention using baseline values; * $p < 0.05$ after multiple comparisons using the Benjamini & Hochberg (BH) method; OFC: orbitofrontal cortex. PCC: posterior cingulate cortex.

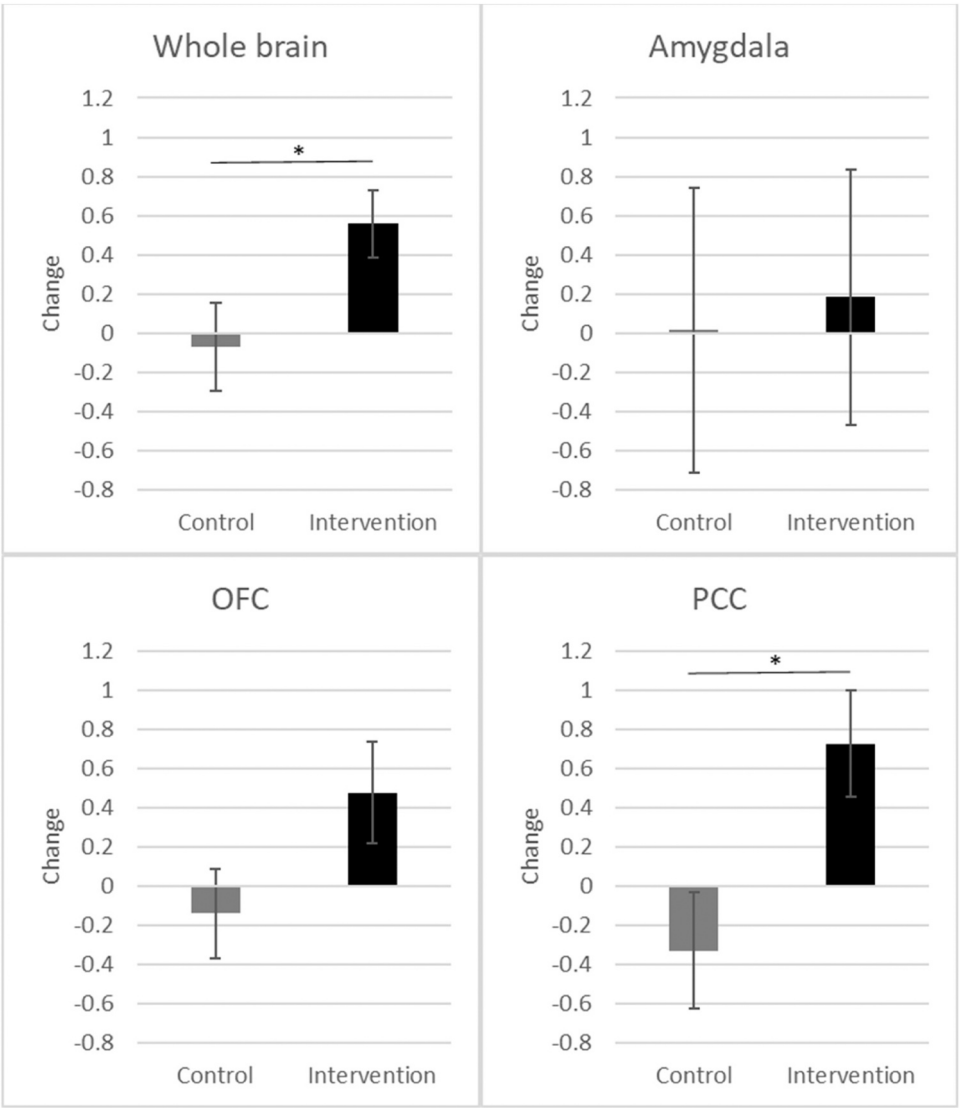

Fig. 2. Changes before and after the intervention. The vertical axis is the change before and after the intervention. Error bars are standard errors of the mean. OFC: orbitofrontal cortex. PCC: posterior cingulate cortex. See Table 2 for other information.

studies also identified GM atrophy in PCC as an antecedent biomarker predicting progression to AD (Whitwell et al., 2008; Gili et al., 2011; Shiino et al., 2006; Karas et al., 2007). Therefore, the result of the current study suggests that continuous inhalation of rose essential oil may prevent brain atrophy and prevent dementia. In this study, not only PCC but also whole brain GM increased. Given that the brain works in concert rather than just some of its structures, simply showing that specific scents cause changes in some brain structures is not enough to say that the effect of the intervention was sufficient (Koob et al., 2013; Frigerio et al., 2021). Therefore, considering previous research that showed that whole-brain GM predicts dementia risk more accurately than specific brain regions (Edmonds et al., 2016; Watanabe et al., 2021), continuous inhalation of rose essential oil for a month is thought to be beneficial from a whole-brain perspective.

4.1. Limitation

This study has three limitations. The first is the composition of the participants, that is, the participants in this study were only women. Relatedly, the study did not ask about the participants' lifestyle,

exercise, diet, education, career, etc. These confounding factors may have influenced the brain and brain volume. Therefore, future studies should test for reproducibility when men are included and these confounding factors are controlled. The second concerns the intervention method. Although this study used a double-blind method, it is not that method in the original sense. This is because the participants in the experiment could easily guess that the liquid was just water from the smell they wore. Therefore, the reproducibility of the present research results should be verified by using liquids with some scent safe for the human body. Relatedly, this study used rose scent and no other scents. Therefore, while the results of this study indicate that rose is effective, they do not indicate that other scents are not effective. Future studies should test the results of this study by adding groups with scents other than the rose. The third issue concerns compliance with intervention conditions. Participants were not monitored to see if they were wearing scent correctly. Therefore, variations in participants' adherence may have influenced the experimental results. Future research should monitor participants by requiring reports with photos etc. Alternatively, the following ideas may provide good hints for understanding participants' adherence to the intervention: asking the participants to smell the scent that will be applied to them listening to their opinions before participating in the study; measuring their emotions/mood when smelling the scent; and asking whether the person has followed the instructions throughout the period. Although these were not done in the current study, future studies should consider adopting such methods.

5. Conclusion

It has been confirmed that aromatherapy has effects on various parts of the body, including the brain. However, to the authors' knowledge, there have been no studies to date that have investigated the effects of simple interventions such as adding fragrance to clothes on the brain. In this study, continuous inhalation of essential oil was shown to increase the GMV of the healthy female whole brain and its PCC subregion.

Ethical approval

The studies involving human participants were reviewed and approved by the Ethics Committees of Kyoto University (approval number 27-P-13).

Authors' contributions

K.K. did a formal analysis and wrote the original draft; Y.Y. and K.N. did conceptualization; Y.Y. did data curation, funding acquisition, investigation, administration, and supervision; K.N. did methodology development, writing review, and editing. All authors reviewed the final manuscript.

Informed consent

The patients/participants provided their written informed consent to participate in this study.

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CRediT authorship contribution statement

Kokubun Keisuke: Formal analysis, Writing – original draft, Writing – review & editing. **Yamakawa Yoshinori:** Conceptualization, Data curation, Funding acquisition, Investigation, Project administration, Supervision, Writing – review & editing. **Nemoto Kiyotaka:** Conceptualization, Methodology, Writing – review & editing.

Declaration of Competing Interest

There is no conflict of interest.

Data availability

Data will be made available on request.

References

Anderson, A.K., Christoff, K., Stappen, I., Panitz, D., Ghahremani, D.G., Glover, G., et al., 2003. Dissociated neural representations of intensity and valence in human olfaction. Nat. Neurosci. 6 (2), 196–202. https://doi.org/10.1038/nn1001.

Ashburner, J., 2007. A fast diffeomorphic image registration algorithm. NeuroImage 38, 95–113. https://doi.org/10.1016/j.neuroimage.2007.07.007.

Atsumi, T., Tonosaki, K., 2007. Smelling lavender and rosemary increases free radical scavenging activity and decreases cortisol level in saliva. Psychiatry Res. 150 (1), 89–96. https://doi.org/10.1016/j.psychres.2005.12.012.

Bell, I.R., Miller, C.S., Schwartz, G.E., 1992. An olfactory-limbic model of multiple chemical sensitivity syndrome: possible relationships to kindling and affective spectrum disorders. Biol. Psychiatry 32 (3), 218–242. https://doi.org/10.1016/0006-3223(92)90105-9.

Bérard, N., Landis, B.N., Legrand, L., Tyrand, R., Grouiller, F., Vulliémoz, S., et al., 2021. Electrical stimulation of the medial orbitofrontal cortex in humans elicits pleasant olfactory perceptions. Epilepsy Behav. 114, 107559 https://doi.org/10.1016/j.yebeh.2020.107559.

Billot, P.E., Andrieu, P., Biondi, A., Vieillard, S., Moulin, T., Millot, J.L., 2017. Cerebral bases of emotion regulation toward odours: a first approach. Behav. Brain Res. 317, 37–45. https://doi.org/10.1016/j.bbr.2016.09.027.

Binder, J.R., Desai, R.H., Graves, W.W., Conant, L.L., 2009. Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. Cereb. Cortex 19 (12), 2767–2796. https://doi.org/10.1093/cercor/bhp055.

Bird, C.M., Keidel, J.L., Ing, L.P., Horner, A.J., Burgess, N., 2015. Consolidation of complex events via reinstatement in posterior cingulate cortex. J. Neurosci. 35 (43), 14426–14434. https://doi.org/10.1523/JNEUROSCI.1774-15.2015.

Chen, D., Dalton, P., 2005. The effect of emotion and personality on olfactory perception. Chem. Senses 30 (4), 345–351. https://doi.org/10.1093/chemse/bji029.

Choi, S.Y., Kang, P., Lee, H.S., Seol, G.H., 2014. Effects of inhalation of essential oil of Citrus aurantium L. var. amara on menopausal symptoms, stress, and estrogen in postmenopausal women: a randomized controlled trial. Evid. -Based Complement. Altern. Med. 2014, 796518 https://doi.org/10.1155/2014/796518.

Cosmetic Ingredient Review Expert Panel, 1984. Final report of the safety assessment of butylene glycol, hexylene glycol, ethoxydiglycol, and dipropylene glycol. Int. J. Toxicol. 4 (5) https://doi.org/10.3109/10915818509078692.

Dalton, P., 1999. Cognitive influences on health symptoms from acute chemical exposure. Health Psychol. 18 (6), 579–590. https://doi.org/10.1037/0278-6133.18.6.579.

Doty, R.L., Cameron, E.L., 2009. Sex differences and reproductive hormone influences on human odor perception. Physiol. Behav. 97 (2), 213–228. https://doi.org/10.1016/j.physbeh.2009.02.032.

Duan, X., Tashiro, M., Wu, D.I., Yambe, T., Wang, Q., Sasaki, T., Itoh, M., 2007. Autonomic nervous function and localization of cerebral activity during lavender aromatic immersion. Technol. Health Care 15 (2), 69–78. https://doi.org/10.3233/THC-2007-15201.

Ebrahimi, H., Mardani, A., Basirinezhad, M.H., Hamidzadeh, A., Eskandari, F., 2022. The effects of Lavender and Chamomile essential oil inhalation aromatherapy on depression, anxiety and stress in older community-dwelling people: a randomized controlled trial. Explore 18 (3), 272–278. https://doi.org/10.1016/j.explore.2020.12.012.

Edmonds, E.C., Eppig, J., Bondi, M.W., Leyden, K.M., Goodwin, B., Delano-Wood, L., Alzheimer's Disease Neuroimaging Initiative, 2016. Heterogeneous cortical atrophy patterns in MCI not captured by conventional diagnostic criteria. Neurology 87 (20), 2108–2116. https://doi.org/10.1212/WNL.0000000000003326.

Frigerio, A., Ballerini, L., Valdes Hernandez, M., 2021. Structural, functional, and metabolic brain differences as a function of gender identity or sexual orientation: a systematic review of the human neuroimaging literature. Arch. Sex. Behav. 50 (8), 3329–3352. https://doi.org/10.1007/s10508-021-02005-9.

Fukada, M., Kano, E., Miyoshi, M., Komaki, R., Watanabe, T., 2012. Effect of "rose essential oil" inhalation on stress-induced skin-barrier disruption in rats and humans. Chem. Senses 37 (4), 347–356. https://doi.org/10.1093/chemse/bjr108.

Gili, T., Cercignani, M., Serra, L., Perri, R., Giove, F., Maraviglia, B., Bozzali, M., 2011. Regional brain atrophy and functional disconnection across Alzheimer's disease evolution. J. Neurol., Neurosurg. Psychiatry 82 (1), 58–66. https://doi.org/10.1136/jnnp.2009.199935.

Grabenhorst, F., Rolls, E.T., Margot, C., Da Silva, M.A., Velazco, M.I., 2007. How pleasant and unpleasant stimuli combine in different brain regions: odor mixtures. J. Neurosci. 27 (49), 13532–13540. https://doi.org/10.1523/JNEUROSCI.3337-07.2007.

He, Y., Wang, L., Zang, Y., Tian, L., Zhang, X., Li, K., Jiang, T., 2007. Regional coherence changes in the early stages of Alzheimer's disease: a combined structural and resting-state functional MRI study. Neuroimage 35 (2), 488–500. https://doi.org/10.1016/j.neuroimage.2006.11.042.

Herz, R.S., 2016. The role of odor-evoked memory in psychological and physiological health. Brain Sci. 6 (3), 22. https://doi.org/10.3390/brainsci6030022.

Herz, R.S., Eliassen, J., Beland, S., Souza, T., 2004. Neuroimaging evidence for the emotional potency of odor-evoked memory. Neuropsychologia 42 (3), 371–378. https://doi.org/10.1016/j.neuropsychologia.2003.08.009.

Japan Cosmetic Association (2021). List of videos that help you understand cosmetics : DPG. April 8, 2021. Available at: ⟨https://japan-ca.jp/column/1109.html⟩ (Accessed on 19 December 2023).

Jung, J., Hudry, J., Ryvlin, P., Royet, J.P., Bertrand, O., Lachaux, J.P., 2006. Functional significance of olfactory-induced oscillations in the human amygdala. Cereb. Cortex 16 (1), 1–8. https://doi.org/10.1093/cercor/bhi090.

Jung, K.Y., Kim, J.M., Lee, I.K., Kim, J.H., Joo, E.Y., Hong, S.B., et al., 2004. Cortical representation to odorant stimulation: statistical non-parametric mapping of low resolution electro magnetic tomography (LORETA). J. Korean Neurol. Assoc. 334–339.

Karas, G., Scheltens, P., Rombouts, S., Van Schijndel, R., Klein, M., Jones, B., et al., 2007. Precuneus atrophy in early-onset Alzheimer's disease: a morphometric structural MRI study. Neuroradiology 49, 967–976. https://doi.org/10.1007/s00234-007-0269-2.

Kawai, E., Takeda, R., Ota, A., Morita, E., Imai, D., Suzuki, Y., Okazaki, K., 2020. Increase in diastolic blood pressure induced by fragrance inhalation of grapefruit essential oil is positively correlated with muscle sympathetic nerve activity. J. Physiol. Sci. 70 (1), 1–11. https://doi.org/10.1186/s12576-020-00733-6.

Kirk-Smith, M.D., Van Toller, C., Dodd, G.H., 1983. Unconscious odour conditioning in human subjects. Biol. Psychol. 17 (2-3), 221–231. https://doi.org/10.1016/0301-0511(83)90020-0.

Kokubun, K., Yamakawa, Y., Nemoto, K., 2023. The link between the brain volume derived index and the determinants of social performance. Curr. Psychol. 42 (15), 12309–12321. https://doi.org/10.1007/s12144-021-02544-3.

Koob, G.F., Everitt, B.J., Robbins, T.W., 2013. Reward, motivation, and addiction. Fundamental Neuroscience. Academic Press, pp. 871–898.

Liu, Y., Wang, K., Chunshui, Y.U., He, Y., Zhou, Y., Liang, M., et al., 2008. Regional homogeneity, functional connectivity and imaging markers of Alzheimer's disease: a review of resting-state fMRI studies. Neuropsychologia 46 (6), 1648–1656. https://doi.org/10.1016/j.neuropsychologia.2008.01.027.

Maddock, R.J., Garrett, A.S., Buonocore, M.H., 2001. Remembering familiar people: the posterior cingulate cortex and autobiographical memory retrieval. Neuroscience 104 (3), 667–676. https://doi.org/10.1016/S0306-4522(01)00108-7.

Nemoto, K., Oka, H., Fukuda, H., Yamakawa, Y., 2017. MRI-based Brain Healthcare Quotients: a bridge between neural and behavioral analyses for keeping the brain healthy. PLoS One 12 (10), e0187137. https://doi.org/10.1371/journal.pone.0187137.

O'doherty, J., Rolls, E.T., Francis, S., Bowtell, R., McGlone, F., Kobal, G., et al., 2000. Sensory-specific satiety-related olfactory activation of the human orbitofrontal cortex. Neuroreport 11 (4), 893–897.

Pellegrino, R., Haehner, A., Bojanowski, V., Hummel, C., Gerber, J., Hummel, T., 2016. Olfactory function in patients with hyposmia compared to healthy subjects-An fMRI study. Rhinology 54 (4), 374–381. https://doi.org/10.4193/rhino16.098.

Pellegrino, R., Farruggia, M.C., Small, D.M., Veldhuizen, M.G., 2021. Post-traumatic olfactory loss and brain response beyond olfactory cortex. Sci. Rep. 11 (1), 4043. https://doi.org/10.1038/s41598-021-83621-2.

Rolls, E.T., 2019. The cingulate cortex and limbic systems for action, emotion, and memory. Handb. Clin. Neurol. 166, 23–37. https://doi.org/10.1016/B978-0-444-64196-0.00002-9.

Seyyed-Rasooli, A., Salehi, F., Mohammadpoorasl, A., Goljaryan, S., Seyyedi, Z., Thomson, B., 2016. Comparing the effects of aromatherapy massage and inhalation aromatherapy on anxiety and pain in burn patients: A single-blind randomized clinical trial. Burns 42 (8), 1774–1780. https://doi.org/10.1016/j.burns.2016.06.014.

Shiino, A., Watanabe, T., Maeda, K., Kotani, E., Akiguchi, I., Matsuda, M., 2006. Four subgroups of Alzheimer's disease based on patterns of atrophy using VBM and a unique pattern for early onset disease. Neuroimage 33 (1), 17–26. https://doi.org/10.1016/j.neuroimage.2006.06.010.

Shimoda, K., Kimura, M., Yokota, M., Okubo, Y., 2015. Comparison of regional gray matter volume abnormalities in Alzheimer' s disease and late life depression with hippocampal atrophy using VSRAD analysis: a voxel-based morphometry study. Psychiatry Res. Neuroimaging 232 (1), 71–75. https://doi.org/10.1016/j.pscychresns.2015.01.018.

Small, D.M., Jones-Gotman, M., Zatorre, R.J., Petrides, M., Evans, A.C., 1997. Flavor processing: more than the sum of its parts. Neuroreport 8 (18), 3913–3917.

Soudry, Y., Lemogne, C., Malinvaud, D., Consoli, S.M., Bonfils, P., 2011. Olfactory system and emotion: common substrates. Eur. Ann. Otorhinolaryngol., Head. Neck Dis. 128 (1), 18–23. https://doi.org/10.1016/j.anorl.2010.09.007.

Toffolo, M.B., Smeets, M.A., van den Hout, M.A., 2012. Proust revisited: odours as triggers of aversive memories. Cogn. Emot. 26 (1), 83–92. https://doi.org/10.1080/02699931.2011.555475.

Van Regemorter, V., Rombaux, P., Dricot, L., Kupers, R., Grégoire, A., Hox, V., Huart, C., 2022. Functional imaging in olfactory disorders. Curr. Otorhinolaryngol. Rep. 10 (4), 421–426. https://doi.org/10.1007/s40136-022-00433-2.

Wang, J., Eslinger, P.J., Smith, M.B., Yang, Q.X., 2005. Functional magnetic resonance imaging study of human olfaction and normal aging. J. Gerontol. Ser. A Biol. Sci. Med. Sci. 60 (4), 510–514. https://doi.org/10.1093/gerona/60.4.510.

Watanabe, E., Kuchta, K., Kimura, M., Rauwald, H.W., Kamei, T., Imanishi, J., 2015. Effects of bergamot (Citrus bergamia (Risso) Wright & Arn.) essential oil aromatherapy on mood states, parasympathetic nervous system activity, and salivary cortisol levels in 41 healthy females. Complement. Med. Res. 22 (1), 43–49. https://doi.org/10.1159/000380989.

Watanabe, K., Kakeda, S., Nemoto, K., Onoda, K., Yamaguchi, S., Kobayashi, S., Yamakawa, Y., 2021. Grey-matter brain healthcare quotient and cognitive function: a large cohort study of an MRI brain screening system in Japan. Cortex 145, 97–104. https://doi.org/10.1016/j.cortex.2021.09.009.

Whitwell, J.L., Shiung, M.M., Przybelski, S.A., Weigand, S.D., Knopman, D.S., Boeve, B.F., Jack, C.R., 2008. MRI patterns of atrophy associated with progression to AD in amnestic mild cognitive impairment. Neurology 70 (7), 512–520. https://doi.org/10.1212/01.wnl.0000280575.77437.a2.

Yunpeng, Z., Han, P., Joshi, A., Hummel, T., 2021. Individual variability of olfactory fMRI in normosmia and olfactory dysfunction. Eur. Arch. Oto Rhino Laryngol. 278, 379–387. https://doi.org/10.1007/s00405-020-06233-y.

Zald, D.H., Pardo, J.V., 1997. Emotion, olfaction, and the human amygdala: amygdala activation during aversive olfactory stimulation. Proc. Natl. Acad. Sci. 94 (8), 4119–4124. https://doi.org/10.1073/pnas.94.8.4119.

Zald, D.H., Mattson, D.L., Pardo, J.V., 2002. Brain activity in ventromedial prefrontal cortex correlates with individual differences in negative affect. Proc. Natl. Acad. Sci. 99 (4), 2450–2454. https://doi.org/10.1073/pnas.042457199.

Zatorre, R.J., Jones-Gotman, M., Evans, A.C., Meyer, E., 1992. Functional localization and lateralization of human olfactory cortex. Nature 360 (6402), 339–340. https://doi.org/10.1038/360339a0.