Geriatrics Gerontology International

DOI: 10.1111/ggi.14287

ORIGINAL ARTICLE

EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

Effect of intensive olfactory training for cognitive function in patients with dementia

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Received: 29 May 2021
Revised: 6 September 2021
Accepted: 14 September 2021

Aim: Recent evidence has revealed an association between neurodegenerative disorders and olfactory dysfunction. However, whether olfactory training can improve cognitive impairment in patients with dementia requires further study. The present study aimed to resolve this by developing an intensive olfactory training (IOT) protocol and assessing its impact on each of the cognitive domains in patients with dementia.

Methods: Patients were prospectively recruited between June 2020 and September 2020. Baseline evaluations included demographic data, olfactory function test, depression scale and detailed cognitive function tests. Thirty-four patients in the experimental group underwent IOT twice a day with a 40-odor set for 15 days, while 31 individuals in the control group received conservative management. Follow-up evaluations using the depression scale and detailed cognitive function tests were performed after IOT.

Results: Baseline characteristics were not different between the two groups. The IOT group showed significant improvements in depression, attention, memory and language functions, but not global cognition, frontal executive, or visuospatial functions compared with the control group.

Conclusion: This study shows the ability of IOT to alleviate depression and improve some cognitive functions in patients with dementia. These results suggest that IOT may be an effective non-pharmacological approach for improving the symptoms of dementia. Geriatr Gerontol Int 2022; 22: 5–11.

Keywords: cognition, dementia, neurodegenerative disease, olfactory training, smell.

Introduction

Neurodegenerative diseases are caused by the loss of function or degradation of nerve cells and are characterized by dysfunction of cognitive, sensory and perceptual systems, as well as the loss of motor control and autonomic nervous system function. The loss of independence in daily living and dependence on treatment have adverse effects on prognosis. These challenges make care for the elderly with neurodegenerative diseases more burdensome and more complex than the care for those without neurodegenerative diseases, including Alzheimer's disease (AD). Means to preserve cognitive function and minimize behavioral disorders in patients with dementia are being actively pursued.

Olfaction is known to have a strong stimulating power because it is projected directly to the cortex without passing through the thalamic nuclei. The human olfactory nervous system is composed of complex circuits in which primary and secondary cortical regions are interconnected and transmit information to the hippocampus, which is responsible for memory, and is involved in attention, conditioning and spatial perception.[1] However, the pool of basal stem cells of the epithelium, which are used to replenish dying olfactory neurons, decreases with age.[2] The activity of central olfaction-related brain structures (piriform cortex, amygdala, the entorhinal cortex and parts of the cerebellum) is also reduced,[3] and olfactory dysfunction more commonly appears in patients with neurological disorders.[4] In the elderly aged ≥65, 10% have olfactory deficits,[5] whereas 85% of patients with AD[6] and approximately 90% of patients with Parkinson's disease (PD)[7] experience olfactory deficits. This evidence highlights the association between neurodegenerative diseases and olfactory dysfunction.

The olfactory nerve is uniquely capable of regeneration,[8] thus emerging studies are evaluating the effects of olfactory training in the elderly or patients with neurodegenerative diseases who experience decreased olfactory function. Functional magnetic resonance imaging revealed regenerated connectivity in olfactory function in patients who had undergone olfactory training.[9] Furthermore, previous studies have shown that olfactory training in patients with olfactory dysfunction partially restored olfaction.[10,11] However, the effect of olfactory training on cognitive function has not been well-established. While some studies report

that olfactory training improves cognitive function,[12–15] others have reported no such effects.[16–18] Previous studies on olfactory training have performed a limited number of cognitive functional tests and have not confirmed the effect of olfactory training, which affects various cognitive functions.

In this study, we examined which domain of cognitive function in patients with dementia can be improved by olfactory training. For this purpose, we developed an intensive olfactory training (IOT) protocol and extensively investigated its effects on cognitive domains in patients with dementia. This study aims to evaluate the precise effects of IOT on each of the five cognitive domains in patients with dementia in an attempt to identify new approaches with which to improve cognition.

Methods

Study design and participants

This study is a prospective, randomized controlled, pilot study to explore the effects of an IOT program on cognition in patients with dementia. The patients included in this study were individuals with dementia aged ≥65 in three nursing facilities in Cheongju City, South Korea. All participants were able to communicate and were capable of performing olfactory training and cognitive function tests. Dementia was diagnosed in local clinics or hospitals by psychiatrists or neurologists. Exclusion criteria were as follows: (i) those with nasal- and sinus-related diseases such as respiratory infection, active rhinitis, and chronic sinusitis that might affect the olfactory function test or training; (ii) those who or whose guardians could not understand the purpose and process of the study; (iii) any patient with severe dementia that had a Mini-Mental State Examination (MMSE) score less than 10 points.

All procedures were performed in accordance with the ethical standards of the institution and/or the national research committee as well as with the 1964 Helsinki Declaration and its subsequent amendments. This study was carried out with approval from the Institutional Review Board (IRB) of Namseoul University (IRB no. 1041479-HR-202005-006) from June to September 2020. Written informed consent was obtained from all patients, legally authorized representatives or both.

Clinical assessment

Baseline evaluation

The demographic data of the participants were collected. Olfactory function was evaluated using the odor identification with the YSK olfactory function (YOF) test (RHICO Medical Co., Seoul, Korea).[19] The YOF test consists of threshold, discrimination and odor identification domains. However, in the preliminary evaluation for olfactory function using the YOF test, we found that many older people with dementia had difficulty in performing

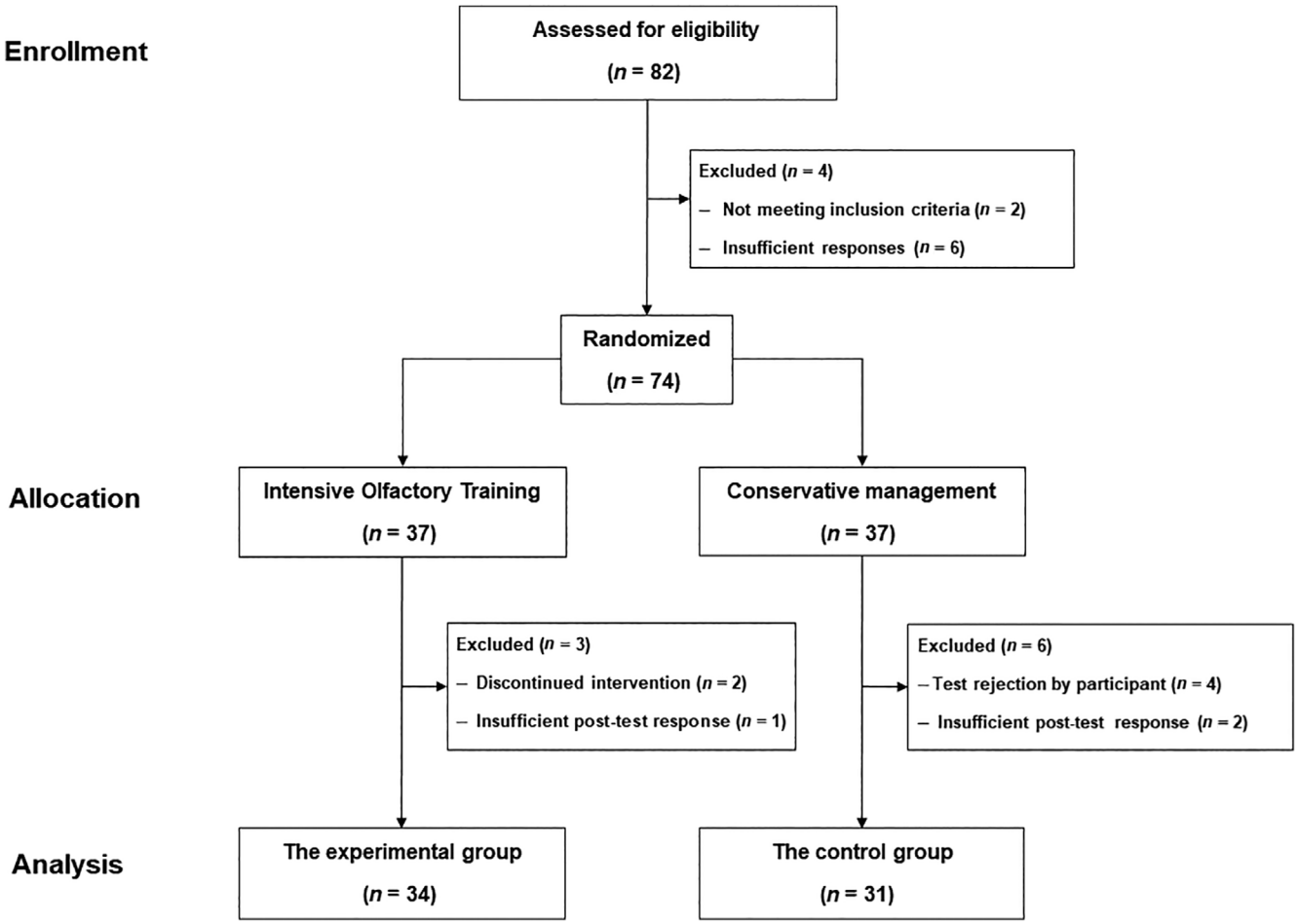

Figure 1 Flow chart of the study.

Table 1 Demographics and clinical features between the experimental and control groups

Variable	Exp. ($n = 34$)	Con. ($n = 31$)	*P*-value
Sex (male)	8 (23.5)	9 (29.0)	0.778†
Age, years	85 (65–97)	85 (65–100)	0.843
Dementia duration, years	6.97 (2–15)	6.87 (2–15)	0.941
Education, years			0.769
0–3	16 (47.1)	12 (38.7)	
4–9	13 (38.2)	13 (41.9)	
≥10	5 (14.7)	6 (19.4)	
YOF	6 (2–10)	6 (0–9)	0.299
SGDS-K	10 (1–15)	8 (1–14)	0.057
K-IADL	2.18 (0.82–3.00)	2.09 (0.90–3.00)	0.674
Common comorbidity			
DM	11 (32.3)	10 (32.2)	1.000†
HTN	17 (50)	13 (41.9)	0.620†
Musculoskeletal problem	5 (14.7)	5 (16.1)	1.000†

Data are presented as median (minimum–maximum) or *n* (%). Mann–Whitney *U*-test for continuous variables.

Cont., control group; DM, diabetes mellitus; Exp., experimental group; HTN, hypertension; K-IADL, Korean-Instrumental Activities of Daily Living; SGDS-K, Korean Version of Short Form Geriatric Depression Scale; YOF, YSK olfactory function test.

†Fisher's exact for categorial variables.

threshold and discrimination tests. Therefore, this study only tested for odor identification with the YOF test. This decision was supported by a previous study showing that odor identification is useful in predicting dementia risk.[20] The Korean Version of the Consortium to Establish a Registry for Alzheimer's disease Assessment Packet (CERAD-K)[21] was used for neuropsychological tests. The CERAD-K consists of nine subscales: (i) Verbal Fluency Test (VFT) for semantic memory; (ii) modified Korean version of the Boston Naming Test (K-BNT) for language function; (iii) MMSE in the Korean version of the CERAD assessment packet (MMSE-KC) for global cognitive function; (iv) Word List Memory Test (WLMT) for attention or working memory; (v) Constructional Praxis Test (CPT) for visuospatial function; (vi) Word List Recall Test (WLRT) for verbal memory encoding; (vii) Word List Recognition Test (WLRcT) for verbal memory retrieval; (viii) Constructional Recall Test (CRT) for visual memory; and (ix) trail making test for frontal executive function. However, during the preliminary evaluation, a significant number of patients with dementia did not complete the trail making test within the specified time or did not understand the procedure, thus the trail making test was replaced by the Stroop color and word test (SCWT) in this study. In addition, the Korean-Instrumental Activities of Daily Living[22] was evaluated in all subjects with dementia. Depression was evaluated using the Short Geriatric Depression Scale-Korean version (SGDS-K).[23]

Table 2 Baseline evaluation of cognitive function test between both groups

Variable	Exp. ($n = 34$)	Con. ($n = 31$)	*P*-value
MMSE-KC	17 (12–25)	17 (10–23)	0.895
VFT	6 (3–15)	6 (2–12)	0.756
K-BNT	6 (1–11)	7 (2–11)	0.534
WLMT	8 (1–13)	9 (2–18)	0.212
CPT	6.5 (2–11)	7 (2–9)	0.304
WLRT	1 (0–6)	1 (0–7)	0.715
WLRcT	2 (0–10)	3 (0–10)	0.323
CRT	2 (0–5)	2 (0–5)	0.771
SCWT	11.5 (0–23)	9 (0–25)	0.617

Data are presented as median (minimum–maximum).

Cont., control group; CPT, Constructional Praxis Test; CRT, Constructional Recall Test; Exp., experimental group; K-BNT, modified Korean version of the Boston Naming test; MMSE-KC, Mini-Mental State Examination in the Korean version of the CERAD assessment packet; SCWT, Stroop Color and Word Test; VFT, Verbal Fluency Test; WLMT, Word List Memory Test; WLRT, Word List Recall Test; WLRcT, Word List Recognition Test.

Table 3 Comparison of differences in olfactory, depression and cognitive function tests between the baseline and follow-up evaluations in both groups

Variable	Difference between baseline and the follow-up scores		*P*-value
	Exp. ($n = 34$)	Cont. ($n = 31$)	
YOF	−4.5 (−10 to 2)	2 (−1 to 5)	<0.001
SGDS-K	4.5 (−2 to 10)	−2 (−5 to 1)	<0.001
MMSE-KC	1 (−3 to 8)	1 (−2 to 3)	0.272
VFT	1 (−1 to 6)	0 (−6 to 4)	0.001
K-BNT	1 (0–6)	0 (−2 to 1)	0.001
WLMT	2 (−2 to 8)	−1 (−9 to 3)	<0.001
CPT	0 (−3 to 4)	0 (−2 to 5)	0.305
WLRT	1 (−1 to 3)	0 (−3 to 3)	0.031
WLRcT	2 (−3 to 8)	−1 (−4 to 2)	<0.001
CRT	0 (−1 to 5)	0 (−3 to 3)	0.234
SCWT	0 (−10 to 8)	0 (−6 to 10)	0.597

Data are presented as median (minimum–maximum).

Cont., control group; CPT, Constructional Praxis Test; CRT, Constructional Recall Test; Exp., experimental group; K-BNT, modified Korean version of the Boston Naming test; MMSE-KC, Mini-Mental State Examination in the Korean version of the CERAD assessment packet; SCWT, Stroop Color and Word Test; SGDS-K, Korean Version of Short Form Geriatric Depression Scale; VFT, Verbal Fluency Test; WLMT, Word List Memory Test; WLRT, Word List Recall Test; WLRcT, Word List Recognition Test; YOF, YSK olfactory function test.

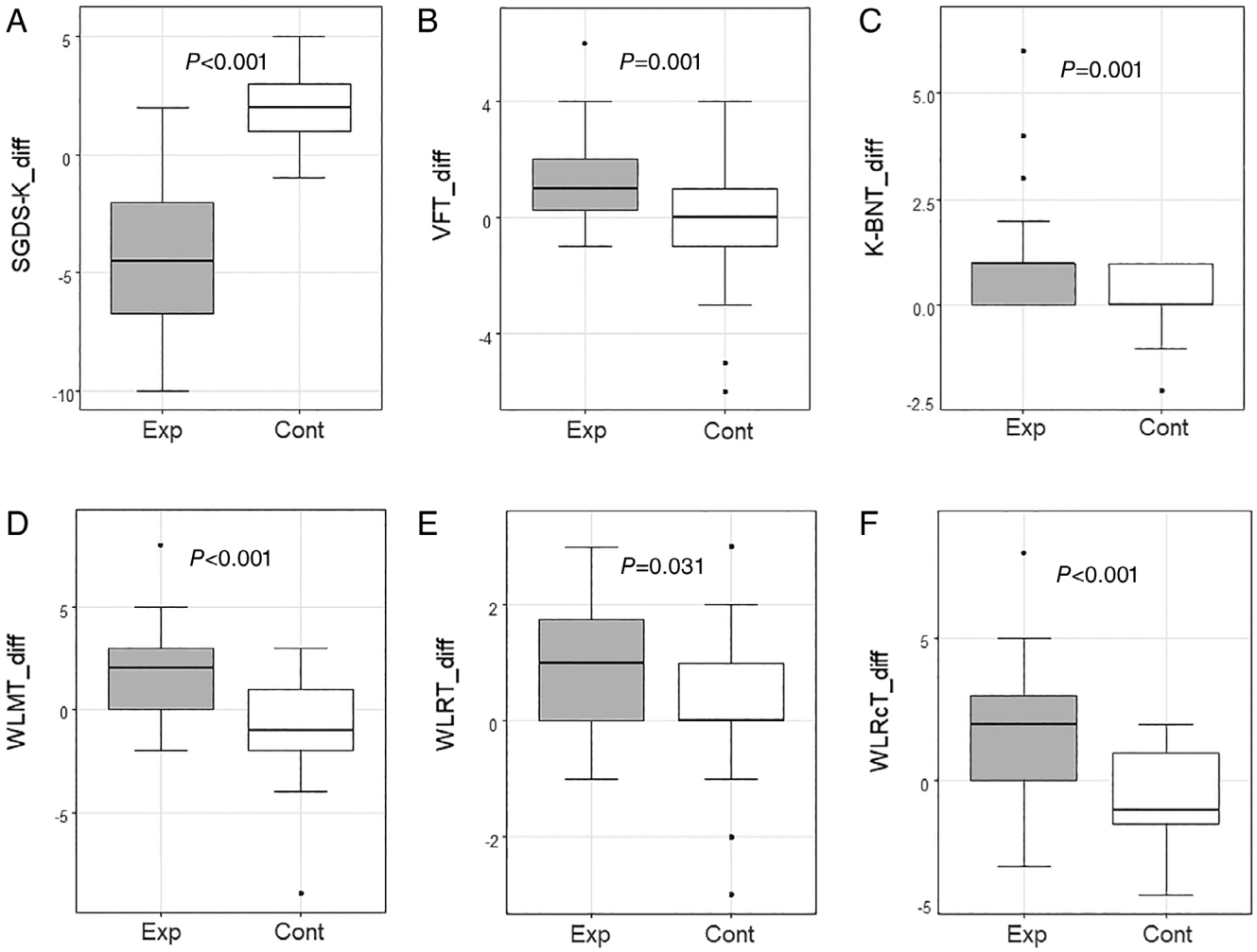

Figure 2 Comparison of differences in depression and cognitive function tests between experimental group and control group. Compared with the control group, the IOT group showed significant decreases in (a) SGDS-K ($P < 0.001$), (b) VFT ($P = 0.001$), (c) K-BNT ($P = 0.001$), (d) WLMT ($P < 0.001$), (e) WLRT ($P = 0.031$) and (f) WLRcT ($P < 0.001$). Cont, control group; CPT, WLRT, Word List Recall Test; Diff, difference; Exp, experimental group; K-BNT, modified Korean version of the Boston Naming test; SGDS-K, Korean Version of Short Form Geriatric Depression Scale; VFT, Verbal Fluency Test; WLMT, Word List Memory Test; WLRcT, Word List Recognition Test.

Intensive olfactory training protocol

Participants were randomly assigned into two groups. The IOT was added to conservative management in the experimental group, while only conservative management was performed in the control group. The experimental group was provided with a separate IOT twice a day for 15 days (in total, 30 sessions), and failure to participate six or more times (20%) was set as the criterion for dropout.

Through the literature review[9,10,16,24] and consultation with a professional aromatherapist, we developed and applied several prototypes of IOT to patients with dementia. During preliminary evaluations, we modified the methods of IOT and confirmed the IOT protocol after thorough discussion. Based on our experiences from these preliminary evaluations, we asked patients with dementia to smell 40 aroma oils in a predefined numerical order determined by the patients' responses during the preliminary assessments (Table S1). For each odor, a 0.5 cm sponge was placed on the bottom of a 20-mL flexible container, and we applied two drops of aroma on to the sponge to maintain a low concentration of each odor. During the training, we opened the lid of the container and placed the container 2–3 cm away from the noses of participants. We pressed the body of the container once to allow the participants to smell the odor for 5 s. The process was repeated for the remaining odors, with several seconds rest between odors. The training took an average of 15 min/per session for each individual in total.

Follow-up evaluation

Follow-up evaluations for SGDS-K, YOF, VFT, K-BNT, MMSE-KC, WLMT, CPT, WLRT, WLRcT, CRT and SCWT were performed the day after the completion of the IOT for the experimental group. The control group also conducted the same tests 16 days after the conservative management.

Statistical analysis

Statistical analyses were performed with SPSS (version 23.0; IBM Corp., Armonk, NY, USA). As the collected data showed a non-parametric distribution, Fisher's exact for categorical variables and the Mann–Whitney *U*-test for continuous variables were performed to evaluate the difference between experimental and

control groups. The Wilcoxon tests were performed for the difference between the pre- and post-tests. The results were statistically significant at $P < 0.05$.

Results

Clinical features at baseline evaluation between the experimental and control groups

Of the 82 participants, six were excluded because they did not complete cognitive and olfactory tests and two were excluded due to a history of head injury and stroke. We assigned number tags to a total of 74 participants and randomly assigned 37 participants to the experimental group and 37 participants to the control group. Two participants in the experimental group who were unable to receive the experimental treatment six times or more and four who expressed their intention to refuse olfactory and cognitive tests were excluded, resulting in a total of 68 participants were included in the follow-up testing. As one participant in the experimental group and two in the control group could not complete the tests, the data of 65 participants were included in the data analysis (Fig. 1).

Participants were finally analyzed in the IOT group ($n = 34$) and the control group ($n = 31$). The two groups showed no significant differences in demographics and clinical features, including YOF, SGDS-K, Korean-Instrumental Activities of Daily Living and common comorbidities (diabetes mellitus, hypertension, musculoskeletal problems) (Table 1). Moreover, cognitive function tests at baseline revealed no significant difference in any parameters between the two groups (Table 2).

Effects of intensive olfactory training in patients with dementia

Changes in olfactory function, depression and cognitive function tests between the experimental group and the control group are shown in Table 3, and the significant results are presented in Fig. 2. Compared with the control group, the experimental group exhibited significant improvements in the scores for: SGDS-K ($P < 0.001$; Fig. 2a); VFT ($P = 0.001$; Fig. 2b); K-BNT ($P = 0.001$; Fig. 2c); WLMT ($P < 0.001$; Fig. 2d); WLRT ($P = 0.031$; Fig. 2e); and WLRcT ($P < 0.001$; Fig. 2f). Whereas changes in MMSE-KC ($P = 0.272$), CPT ($P = 0.305$), CRT ($P = 0.234$) and SCWT ($P = 0.597$) were not significantly different between the groups.

Discussion

This study aimed to describe the effects of IOT on cognitive function in patients with dementia. We found that IOT reduced depression and improved some cognitive functions. Existing olfactory training methods have used a small number of aromatic oils ranging from one to four different odors.[10,16,18,25–27] However, we developed and applied an IOT with 40 odors to stimulate various olfactory bulbs in patients with dementia to achieve a more enriched odor stimulation. In addition, five domains of cognitive function were investigated using the CERAD-K, with the trail making test replaced with SCWT as described above. The CERAD is widely used for dementia research as it is a relatively simple screening test with the advantage of examining all five domains of cognitive function. Collectively, to the best of our knowledge, this study is the first to investigate all cognitive domains in the evaluation of the effects of IOT in patients with dementia using a large number of stimulating odors.

As material for olfactory training, most studies use EAO.[10,16,18,25] EAO is an aromatic substance, extracted from flowers, fruits, stems, leaves and roots of plants, which has not been artificially synthesized. EAO is widely used potentially to promote health or well-being through massage or inhalation. The application method of EAO for olfactory stimulation varies from study to study. Methods of application include dropping essential oil on the collar or underwear, attaching an aroma patch,[16,18] using Sniffin' sticks,[17] odor diffusion in a common area of the hospital,[26] and placing the bottle near the nose to identify the intensity of odor.[13] We developed an olfactory training kit consisting of 40 flexible bottles, each with two drops of EAO on a sponge located at the bottom of the bottle. The kit was designed to come out with a low concentration of odor by pressing the flexible bottle. This method is based on the blind smell theory,[28,29] which has the advantage of being able to detect sub-threshold odors in the brain even in the absence of conscious perception, making it possible to apply olfactory training for a longer period.

Odor affects human emotion by acting on the amygdala, hippocampus and insula through the olfactory bulb. The therapeutic effects of olfactory training in mood disorders, including depression, have been investigated. A previous study showed that olfactory stimulation might improve behavioral and psychological symptoms of dementia, including hallucinations, agitation/aggression, irritability/lability and aberrant mortal activity in patients with AD or vascular dementia.[16] A recent study showed that olfactory training could not only improve olfactory dysfunction and subjective well-being in the elderly, but also reduce depressive symptoms.[10] Similarly, we observed that IOT significantly improved olfactory dysfunction and depression in patients with dementia. This study showed that IOT significantly ameliorated cognitive deficits including memory impairment in patients with dementia. Our findings on the effects of IOT on olfactory dysfunction, depression and cognitive deficits (Table 3) suggest that olfactory training may improve cognitive impairment directly by reducing cognitive deficits or indirectly by alleviating depression. Therefore, it is reasonable to infer that olfactory function is interconnected in the pathophysiological processes of depression and/or cognitive circuits. However, the precise mechanism(s) between olfactory training and enhanced cognitive functions remains to be further elucidated. In animal experiments, the anxiolytic and antidepressant effects of IOT have been observed, in addition to antioxidant activity in the amygdala, and reduced tau phosphorylation.[30] Therefore, we hypothesize that IOT may be effective in treating depression in patients with dementia through antioxidant activity and reduction of tau phosphorylation. More research is needed to address this issue in detail.

A few studies have evaluated cognitive function following olfactory stimulation in patients with neurodegenerative diseases. Previous studies employing olfactory training using lavender oil showed no improvement in MMSE in the elderly or patients with dementia.[16,18] Likewise, in a study evaluating a 16-odor IOT in individuals with PD, MMSE was not improved.[17] In contrast, a previous study evaluating a four-odor olfactory training protocol observed significant improvements in the Montreal Cognitive Assessment and the Controlled Oral Word Association Test.[10] Furthermore, olfactory stimulation in patients with AD has been known to improve memory.[13–15] The varying results observed in the previous studies may be attributed to differences in the number of odors applied, training method and training period. In addition, most previous

studies used a simple rating scale to examine global cognitive function, making it difficult to identify the effects of IOT on different cognitive domains in detail.

In this study, we showed that IOT in patients with dementia ameliorated cognitive deficits in attention, memory and language functions, but not in global cognition, frontal executive, and visuospatial functions. However, this does not mean that IOT is unable to influence some of the cognitive functions, as we used a relatively short-term training period of 15 days. Indeed, a long-term IOT study of 3 months was initially planned but was reduced to 15 days because of the COVID-19 pandemic. Given the short duration of IOT, we could conclude that attention, memory, and language functions might be improved more quickly by IOT than the other cognitive functions. Further studies will be necessary to confirm the long-term IOT effects on improving various cognitive functions.

This study has several limitations. First, the IOT was conducted for a short period of 15 days, as described previously. This time frame is not sufficient to draw conclusions about all cognitive functions examined in this study. Second, it was difficult to rule out the possibility of a placebo effect as just one more activity was added to the control group. Third, our patients with dementia might be heterogeneous, although AD is the most common type of dementia. We could not obtain the detailed information, including dementia subtype in our participants. Accordingly, in this pilot study, we aimed to focus on the effect of IOT in patients with dementia. Fourth, this study excluded patients with dementia who could not discriminate between smells as well as those patients with severe stages of dementia considering poor compliance. Therefore, our findings cannot be generalized to those populations. Finally, while the short-term effect of IOT was identified, it remains to be investigated whether these effects would be maintained in the long-term. Future long-term studies with a large sample size are needed to confirm our findings.

In conclusion, this study shows that IOT can improve depression, attention, memory and language functions in patients with dementia. IOT may be considered as a non-pharmaceutical treatment option for patients with dementia.

Disclosure statement

The authors declare no conflict of interest.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information may be found in the online version of this article at the publisher's website:

Table S1 Forty odors used for olfactory training in the study

How to cite this article: Cha H, Kim S, Kim H, Kim G, Kwon K-Y. Effect of intensive olfactory training for cognitive function in patients with dementia. Geriatr. Gerontol. Int. 2022;22:5–11. https://doi.org/10.1111/ggi.14287