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Research Article

Odor Identification and Cognitive Function in Older Adults: Evidence from the Yakumo Study

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Abstract

This study examined the relationship between the olfactory function and the prefrontal function decline using longitudinal data. An individual linear regression coefficient (developmental decline slope) from 65 to 75 years of age for performance on the Digit Cancellation test (D-CAT), a personal function test, was calculated from the Yakumo study database (N=2,972; 36.8% males, 63.2% females), and the Odor Stick Identification Test was administered to healthy elderly people. The results showed that performance on odor identification was highly correlated with the longitudinal decline slope of attention performance, but not with that of logical memory performance. These results are consistent with the view that odor identification defects could be associated with aging-related decline in the prefrontal region, especially in elementary perceptual speed and executive function.

Introduction

Since an association between olfactory defects and cognitive decline was reported [1,2], many researchers have confirmed it, particularly for older individuals diagnosed with Alzheimer's and Parkinson's disease participants [3-6]. Odor familiarity and a preference have sometimes been seen as culture-dependent [7-9]. Jimbo et al. [10] assessed the olfactory abilities of Alzheimer's Disease (AD) patients and aged-matched Japanese control participants using the Odor Stick Identification Test for Japanese (OSIT-J), and they replicated earlier findings that the AD group had more serious olfactory defects than the controls did, irrespective of the stage of AD (the confidence level for statistically significant differences between mild AD and control groups was $p<0.05$; for mild AD and severe AD it was $p<0.001$, and for severe AD and control group it was $p<0.001$). Iwahara et al. [11] also reported a study in which they administered both the OSIT-J and the Nagoya University Cognitive Assessment Battery (NU-CAB) to healthy participants, and they too found certain associations between decrements in OSIT-J performance and cognitive functioning, not only among elderly but also among middle-aged participants. Therefore, the association between olfactory defects and age related cognitive decline appears universal and robust.

As for the underlying neural mechanisms that explain the association between olfactory defects and cognitive decline, Swan and Carmelli [4] proposed that impaired olfactory functioning relates mainly to verbal memory decline rather than impairments on measures of executive functioning after adjustment for baseline cognitive performance, age, education, sex, and history of smell-related difficulties. Just a brief note as for the corresponding neural regions of olfactory senses, fMRI and MEG studies showed that orbitofrontal cortex (especially right side) and insula is the responding brain region and executive function relates mainly to the orbitofrontal cortex, medial prefrontal cortex, striatum, nucleus accumbens [12-14]. Logical memory relates strongly to entorhinal cortex, amygdala and hippocampus.

They concluded that the predictive utility of impaired odor identification in older adults appears to be specific to a decline in the cognitive domain of verbal memory. On the other hand, Wilson et al. [15] also examined the association between the odor identification and the cognitive decline and they proposed a strong relationship between odor identification defects and declines in attention-executive functioning rather than in memory (confidence levels of significance in the perceptual speed was $p<0.001$ and semantic memory was $p<0.156$).

The purpose of this study was to determine which proposal is most accurate in regard to underlying neural mechanisms and functions. We utilized the Logical Memory Test to evaluate memory skills and the Digit Cancelation test (D-CAT) to evaluate attention-executive functioning, and we examined the relationship of these measures to the OSIT-J performance. As previous related studies employed different cognitive tasks, we have not certain prediction. However, our previous tentative examination showed more strong relation between olfactory deficit and declining of executive function rather than memory [11]. In their study, based upon the smell identification test,

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poor and normal odor groups of middle, younger old and older old were classified and compared their cognitive measure performances such as memory, and attention by an ANCOVA. The results suggested poor identification older old participants were inferior in not only memory but also attention measures however they showed poorer performances in attention-related measures (Stroop test) compared with memory measure.

To estimate cognitive functioning, we utilized the linear regression coefficient of these cognitive scores from longitudinal data spanning 11 years of aging (from age 65 to 75 years). Previous studies have showed that cognitive test performances largely decline linearly from around age of 50 and that the period after age 65 is in the most crucial for detecting links between odor identification defects and cognitive decline [6,16-18]. We hypothesized that if the Swan and Carmelli [4] proposal is valid, the correlation between odor identification performance and verbal memory tests would be higher than the correlation between odor identification performance and attention-executive tests, while. On the other hand, if the Wilson, et al. [15] proposal is valid, the relation of the odor identification test with memory and attention-executive test should be reversed.

In sum, the hypothesis of this study was that a decline of the olfactory ability relates attention-related function rather than memory function based upon our previous evidences. This suggests decline of prefrontal cortex function can be reflected by olfactory function. The purpose of this study was to develop a simple and low-cost test biomarker such as olfactory ability that intends to understand the development of neurodegenerative pathologies.

Method

Participants

Participants were community dwellers who voluntarily participated in the Yakumo Study and who were independent in activities of daily living. Just a brief not about the Yakumo Study. The Department of Preventive Medicine of the Nagoya University Medical School and the town of Yakumo jointly conducted the study since 1981 [19]. Investigations were conducted in the fields of epidemiology, internal medicine, orthopedics, neuropsychology, ophthalmology, otolaryngology and urology. Present study was undertaken as a part of the Neuropsychology Section and otolaryngology section. In the Yakumo study, community-dwelling participant's age over 40 joined voluntarily. Participants in the study were or had been engaged in a variety of jobs, not only in white collar, but also in agriculture, fishery and forestry.

Ethical approval was obtained from the Ethical Committee of Nagoya University Medical School for Yakumo Study (2011 # 643) and written informed consent for participation and data publication was obtained from each participant.

In addition, written informed consent for participation and data publication were obtained from each participant. The data analyzed here were from the period from 2011-13 collected by neuropsychology and otolaryngology teams. Participants had been engaged in a variety of jobs, not only white collar, but also agriculture, fishery and forestry. Therefore, this town can be regarded a representative sample of today's Japanese society.

From the larger database (N=277), we selected a convenience sample of 46 participants (25 women and 21 men) by the following criteria: (1) they were over 65 years old at the first measurement, (2) they participated in measurement of cognitive tests described below more than 4 times during the 11 year period (once per year) until the age of 75 years, (3) they were given the OSIT-J in 2013, and (4) they had shown no sign of mild cognitive dementia at the first measurement (participants were omitted if they earned a score below 23 on the Mini Mental State Examination or MMSE). The mean age at the first measurement was 65.43 years (SD=0.97) and the mean level of education was 10.8 years (SD=1.9). Their mean MMSE score was 28.2 (SD=1.9). As noted earlier, participants visited various section voluntarily, therefore, main reason relatively small size of number who was given OSIT-J test among all participants were due to consumed long time of otolaryngology section.

Procedures

Assessment of cognitive function

Participants in the neuropsychology section were given the Nagoya University Cognitive Assessment Battery (NU-CAB) that included the MMSE, Logical Memory Test, the verbal fluency test, the Stroop test, the D-CAT and the visuospatial test by a trained examiner.

Digit Cancellation Test data from the D-CAT1 were analyzed to address attention-executive functioning within the present study. In the D-CAT1, participants were requested to make a slash mark on the given single target digit (6) with a slash as fast and as accurately as possible within 60 seconds. The D-CAT1 assesses elementary perceptual speed and executive function. The D-CAT was developed for screening attention defects in Traumatic Brain Injury (TBI) patients and satisfactory reliability and validity data have been reported elsewhere [20,21].

The memory test we selected was the Japanese version of the Logical Memory Test within the Wechsler Memory Scale (WMSL: WMS-R, Japanese version translated by Sugishita [22]. For this task, the examiner read two short news stories consisting of 25 segments, and participants were then asked to recall the story immediately. Each segment of the story that was correctly recalled by the participant was assigned a score of 1 point; therefore, the total score ranged from 0 to 25 points.

Assessment of odor identification

The Odor Stick Identification Test (OSIT-J) was used to assess odor perception. This test possesses high reliability (r_s=0.795, p<0.0001) and validity (r_s=0.802, p<0.0001) [23]. The OSIT-J includes 12 different odorants to be identified. As odor perception is not necessarily culture-free, the Japanese version was employed [24,25]. The basic procedure resembles that of the San Diego Odor Identification Test [26]. The aromas used in the OSIT-J included curry, perfume, Japanese cypress, India ink, menthol, rose, wood, nattou/sweat socks, roasted garlic, condensed milk, gas for cooking, and Japanese mandarin aromas. Each fragrance was enclosed in microcapsules made of melamine resin. These microcapsules were mixed with an odorless solid cream and then shaped to look like a lipstick. During the inspection test, the examiner applied each odorant to a piece of paraffin paper. After application, the examiner handed the paper to the participant, who would then sniff the paper

Table 1: Correlation coefficients for measures.

	D-CAT1	Memory	OSIT-J
D-CAT1	1.000	0.0005	0.527
Memory		1.000	-0.096
OSIT-J			1.000

and identify the odor. Participants selected each answer from a set of cards, each of which listed the name of an odorant, including the correct answer. Each correct answer was scored as one point, with total performance ranging from 0 to 12 points.

Data analyses

Individually calculated linear regression coefficients of D-CAT1, Logical Memory, and OSIT-J, and t-tests were used. Normality tests for these data were conducted and the results recommend parameter statistics (Shapiro-Wilk scores were .995, .987, and .955, respectively and *P* scores were .999, .894, and .077, D-CAT1; Logical Memory, and OSIT-J, respectively and Kolmogorov-Smirnov scores were .041, .176, and .105, respectively and *P* scores were .200, .200, and .200, D-CAT1; Logical Memory, and OSIT-J, respectively),

Results

Because reliable regression coefficients require more than three points of measurement we examined cognitive decline in aging [27] by comparing multiple measurement points over an 11 year data collection span for our participants. The mean number of measuring points in our database was 6.9 (SD=1.9), establishing sufficient measurement points to yield highly reliable regression coefficients. Means and standard deviations (listed in parentheses) of linear regression coefficients for the D-CAT1, the Logical Memory Test, and performances on the OSIT-J were as follows; D-CAT1: -0.030 (0.043), memory: 0.145 (0.467), and OSIJ-J: 6.489 (3.057), respectively.

Table 1 shows the mutual correlation coefficients between measures. To examine our working hypothesis regarding whether the correlation coefficient between OSIJ-J and D-CAT1 was statistically different from the correlation coefficient between OSIJ-J and memory, the Hoelling formula was employed [28]. The result indicated that these two correlations were significantly different from each other ($t=3.421$, $df=42$, $p<0.01$). As seen in Table 1, the correlation between OSIT-J and D-CAT1 was high while the correlation between OSIT-J and memory was low.

Discussion

We examined in this study which of several proposals from prior research might best explain the underlying neural mechanisms and associated cognitive declines that seem to link with olfactory defects among elderly participants. As described earlier, Swan and Carmelli [4] proposed that impaired olfactory functioning relates mainly to verbal memory decline but not to decline of executive functioning. Wilson et al. [15] stressed the importance of executive dysfunction, although these perspectives are not necessarily mutually exclusive. As Swan and Carmelli [4] suggested, olfactory loss may be due to not only general illness but also to an alteration of central nervous system functioning that reflects progressively severe a neurologic illness. Underlying physiological dynamics may include that a byproduct of reduced levels of choline acetyltransferase in a number of brain regions including the olfactory tubercle and decreased metabolism in some classes of nasal tissue xenobiotics or dopaminergic insufficiencies in the olfactory tubercle represent pathological processes in metabolimbic brain areas including the olfactory tubercle and nucleus accumbens. Olfactory abilities could be related to functional cognitive decline even if triggered by normal aging processes that correlate with functional cognitive decline. Swan and Carmelli [4] stressed the role of memory while Wilson et al. [15] emphasized a relationship between odor identification deficits and declining perceptual speed and executive functioning.

Our findings showed that the similarity between the OSIT-J performance and the declining slope of the D-CAT1 was significantly higher than the correlation between the OSIT-J performance and the declining slope of memory performance. Thus, the Swan and Carmelli [4] proposal was not supported while the proposal by Wilson et al. [15] was supported.

These results suggest a similarity in both olfactory defects and D-CAT 1 after the age of 65 whereas the declining slope of memory differed. This means first that both D-CAT 1 and OSIT-J may assess similar prefrontal cortex function and second that the association between olfactory and memory facets, while important, is weaker than the association of olfactory and perceptual speed and executive functions. Neurocognitive measures that relate to prefrontal function such as the OSIT-J and D-CAT1 can detect cognitive aging earlier than those that relate to memory. Recent longitudinal brain imaging studies by Raz and colleagues have demonstrated the developmental changes in brain size reduce mainly through shrinkage of white matter [29,30]. They demonstrated that shrinkage of brain size appears earlier in the prefrontal area than in the other areas and there is a strong relationship between shrinkage of prefrontal lobe and executive function [31,32]. These findings seem to coincide with the findings in this study.

In our sample, compared to prefrontal function, verbal memory function was even after the age of 65 as both Park et al. [33] and Hedden et al. [34] have suggested. They demonstrated that a continuous regular decline occurs for processing-intensive tasks from 20 years onward but verbal knowledge increases across the life span. The verbal long-term memory task and free recall task in their study are quite similar to the memory test in this study. Our findings supported a proposed relationship between prefrontal cortex and odor function in relation to aging, though precise underlying neural mechanisms remain unclear. However, this study has a limitation. Present study showing the relative importance of attention-executive functioning correlates with odor identification was based upon community dowelling sample people. In other words, our studies examined for mostly normal aging, therefore, it is important that the present findings should be replicated with mild dementia sample because there is a possibility that verbal memory rather than attention-executive function might be more important in odor identification.

Therefore, further studies using different neuropsychological test such as the Stroop test and trail making test and replications in dementia population are needed.

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