Alzheimer's, Dementia & Cognitive Neurology

Research Article

ISSN: 2399-9624

Olfactory function evaluation in a 1102 community-dwelling 20-90-year old Japanese population in relation with age, sex and mental decline

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Abstract

Purpose: Decline of olfactory function has been linked to aging of the brain and also to risk of developing dementia and other neurodegenerative diseases according to several Western studies of community-dwelling populations. The aim of this study was to understand the usefulness of a smell identification test to identify early signs of mental decline in relation with age, sex, and education in a community-dwelling population in Japan.

Material and methods: The participants comprised of 1102 volunteers aged 20-90 (437 male and 665 female) who entered the Hirosaki University observational longitudinal study that first started in 2005. Each participant self-evaluated their olfactory abilities and later on were subject to modified Pocket Smell Test (mPST) odor identification test developed in collaboration with Sensonics Inc. followed by the Mini Mental State Examination (MMSE) to evaluate mental fitness. Multiple statistical analyses were performed to determine the usefulness of the simplified 4-odor (grape, onion, rose and soap) to understand non-invasively possible deterioration of brain function in relation with self-estimation of olfactory function, subjects age, sex, education and MMSE.

Results: The results revealed similarities between self-estimation of olfactory sensory capabilities and mPST odor identification test (82.2% accuracy). A clear relationship between aging, sex, education and olfactory system impairment was also observed. In addition, the polyserial correlation coefficient was 0.3313, suggesting the association between olfactory impairment and decline of mental fitness. Thus, mPST appears useful to detect an early decline of mental fitness in Japanese general population.

Introduction

The loss of smell has been reported in a number of studies and is associated with aging [1,2], gender [3] and various health ailments including neurodegenerative diseases such as Alzheimer's disease (AD) [2,4-6]. It has been reported that olfactory dysfunction is one of the earliest sign of neurodegeneration in AD [7]. The impairment of olfactory function was thoroughly investigated in the National Health and Nutrition Examination Survey (NHANES) in US using the Pocket Smell Test™ (PST) as the olfactory function identification test [8]. The NHANES confirmed the relationship between age, gender, race, education, general health, physical activity, smoking, drinking, and the loss of olfactory function. To date, no similar large analysis (>1000 participants) of Japanese nationals has been conducted.

The Iwaki study is an annual health promotion study in Japan over 20 years of age that started in 2005 and aimed to prevent lifestyle-related diseases including AD and prolong lifespan [9,10]. The olfactory function test was introduced for the first time in 2016 into the study protocol with the approval from the ethical committee in Hirosaki University. Due to time limitations, only 4-item PST was used instead of the 12-item Brief Smell Identification Test (B-SIT) and 40-item University of Pennsylvania Smell Identification Test (UPSIT) which were well-established olfactory function tests used to detect early AD with higher accuracy and sensitivity than that of 4-item PST [11].

The purpose of our study is therefore to evaluate the usefulness of a smell identification test to detect early mental fitness decline using the Mini Mental State Examination (MMSE) in Japanese population.

Materials and methods

Preparation of modified PST

Olfactory function in Iwaki Project was assessed using the 4-item PST, version B, with modification necessary for a Japanese population such as changing optional answers to reflect cultural differences in addition to translating the language from English to Japanese. The modified Pocket Smell Test (mPST) was prepared by and purchased from Sensonics Inc. (Haddon Heights, NJ, USA). The appearance of the test is shown in Figure 1.

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Key words: *olfactory function, aging, MMSE, mental decline, smell identification test*

Received: August 06, 2017; **Accepted:** August 28, 2017; **Published:** August 31, 2017

Participants

This study was conducted between May to June 2016. A total of 1148 healthy volunteers aged 20 years and above participated in the Iwaki Project. Subjects with unavailable mPST and MMSE results were excluded from our study. As a result, 1102 participants (437 male and 665 female) were included. The data collection for this study was approved by the Ethics Committee of the Hirosaki University School of Medicine and all participants provided written informed consent before the study. Demographic and clinical data as well as life-style information were obtained from self-questionnaires and interviews.

Assessment of olfactory identification function

All participants reported the self-awareness of their olfactory function in daily-living activity as normosmia or hyposmia, then received the mPST, a 4-item (soap, grape, onion, rose), four-choice, scratch-and-sniff, forced choice olfactory identification test, to measure their olfactory identification function with slight modifications to the NHANES 2011-2014 Chemosensory protocol [12,13]. The perfect score for the test is set to 4. Since olfactory dysfunction was defined as less than 5 in NHANES using 2 of 4-item PST (version A + B, totally 8 odorants), we defined 2 as the threshold between normosmia and hyposmia in this study using the mPST [12].

Assessment of mental fitness

All participants received the MMSE to measure their mental fitness. The test developed originally in the mid 70's evaluates various parameters that include the assessments of orientation to place and time, short-term memory, episodic long-term memory, subtraction, ability to construct a sentence and oral language ability [14-17]. According to the Alzheimer's Society, MMSE is the most commonly used test for complaints of problems with memory or other mental abilities and the test can be used by clinicians to help diagnose dementia [18]. The perfect score for the test is set to 30. The definition of the mental fitness decline is less than 28.

Statistical analysis

To analyze the age-related changes in odor identification abilities, participants were divided into 10-year subgroups. The data from mPST and MMSE were presented as mean, standard deviation and 95% confidence intervals. The univariate, and age, sex and education-adjusted multivariate logistic regression analyses were performed by R software version 3.3.2 from the R project.

Results

Participants characteristics and test results

Details of study participants are shown in Table 1. Age of participants ranged from 20 to 90 years old and included 437 males and 665 females. All participants were at the time of the study healthy and provided information via questionnaire that included illness history, past and current medication prior to testing.

Comparison of self-reported and mPST-based smell dysfunction

Prior to performing the mPST and MMSE, participants were asked to self-describe the quality of their smell ability in daily life. A relationship between self-reported olfactory dysfunction and mPST-based olfactory dysfunction defined as less than 2 good answers during mPST administration was observed. A comparison between self-reported olfactory abilities and mPST shows a similarity between those two with an accuracy of 82.2%. The number and percentage of subjects with unawareness of smell loss are 143 and 13.0%, respectively.

Comparison of the smell and cognitive functions in subjects grouped by age

The mean value of mPST and MMSE score results with the standard deviation in each age subgroup is shown in Table 1. Moreover, loess smoothed curves were prepared with the area of 95% confidence interval (Figure 2 a, b). For participants under 50 years old, the mPST score value from 3.60 to 3.71 was determined as the average range. The score gradually decreased to 3 and 2 at 69 and 87 years old respectively, as estimated from the loess smoothed curve (Figure 2a). A similar analysis was conducted to find a relationship with MMSE performance (Figure 2b). Years just prior to 60 years old (~5 years) were found to be the age range turning point where a decline of mental fitness from the average value (MMSE 29.7 to 29.8) seen in younger group (less than 60 years old) was observed. The data also indicated a gender difference with male seeing an earlier decline in olfactory functions compared to females according to age (Table 1).

The odds ratios (OR) and 95% confidence intervals of measured olfactory dysfunction, which was defined as less than 2, were calculated and are shown in Table 3. Data indicates that the OR in mPST score decline and MMSE decline are similar in both univariate and age-sex-education-adjusted model. In addition, the polyserial correlation coefficients between olfactory impairment and decline of mental fitness were calculated as 0.3650, 0.2967 and 0.3313 in male, female and all-comers, respectively.

Discussion

This is the first report about olfactory function evaluation in Iwaki Project. Our study looked at the relationship between the olfactory identification function and age in a cohort composed of 1102 individuals of the Japanese general population. The results in this cross-sectional observation study in Iwaki Project show that the mean score in 4-item mPST in each age category, including younger age, is

Table 1: Characteristics of the subjects in each age range categories

Age (years)	Sample size			Self-reported smell loss						mPST score						MMSE score						Amount of education (years)					
	All	Male		All		Male		Female		All		Male		Female		All		Male		Female		All		Male		Female	
	n	n	%	n	%	n	%	n	%	mean	sd	mean	sd	mean	sd	mean	sd	mean	sd	mean	sd	mean	sd	mean	sd	mean	sd
20-29	60	24	40.0	3	5.0	3	12.5	0	-	3.60	0.81	3.33	1.01	3.78	0.59	29.7	0.9	29.5	1.3	29.8	0.4	13.4	1.5	13.1	1.7	13.6	1.4
30-39	178	83	46.6	7	3.9	4	4.8	3	3.2	3.79	0.47	3.72	0.55	3.84	0.39	29.8	0.5	29.7	0.5	29.8	0.5	13.0	1.5	12.9	1.5	13.1	1.6
40-49	188	77	41.0	3	1.6	0	-	3	2.7	3.71	0.53	3.68	0.55	3.74	0.52	29.7	0.7	29.6	0.9	29.8	0.4	12.9	1.5	12.7	1.5	13.0	1.6
50-59	208	82	39.4	17	8.2	12	14.6	5	4.0	3.65	0.62	3.50	0.74	3.75	0.50	29.7	0.7	29.7	0.5	29.6	0.8	12.7	1.5	12.4	1.7	12.8	1.3
60-69	285	109	38.2	28	9.8	14	12.8	14	8.0	3.16	1.00	2.81	1.17	3.39	0.81	29.1	1.4	28.9	1.7	29.3	1.2	11.9	1.8	12.3	2.0	11.7	1.7
70-79	146	48	32.9	20	13.7	8	16.7	12	12.2	2.65	1.15	2.54	1.22	2.70	1.12	28.3	2.0	28.1	2.2	28.4	1.8	10.6	2.0	10.9	2.1	10.5	1.9
80+	37	14	37.8	3	8.1	0	-	3	13.0	2.22	1.36	1.64	1.34	2.57	1.27	27.6	2.3	26.8	2.9	28.1	1.8	10.2	2.3	10.5	3.1	10.1	1.8
Total	1102	437	39.7	81	7.4	41	9.4	40	6.0	3.37	0.9	3.23	1.00	3.47	0.8	29.3	1.3	29.2	1.5	29.4	1.2	12.2	1.9	12.3	1.9	12.2	1.9

Table 2. Comparison of smell function evaluations between self-reported method and mPST.

		mPST ≦ 2 Hyposmia	mPST ≧ 3 Normosmia
Self-reported	Hyposmia	28	53
	Normosmia	143	878

Table 3. Odds ratios (OR) and 95% confidential intervals (CI) of olfactory dysfunction (mPST≦2) and mental decline (MMSE≦28)

Age (years)	**mPST score**						**MMSE score**					
	Univariate model			Age, sex and education- adjusted model			Univariate model			Age, sex and education- adjusted model		
	OR	95% CI	p-value**	OR	95% CI	p-value**	OR	95% CI	p-value**	OR	95% CI	p-value**
20-39*	1.00			1.00			1.00			1.00		
40-49	0.62	0.21 - 1.85	0.395	0.64	0.21 - 1.92	0.428	1.28	0.47 - 3.47	0.631	1.23	0.45 - 3.35	0.687
50-59	1.65	0.71 - 3.79	0.242	1.73	0.75 - 4.01	0.200	1.45	0.56 - 3.75	0.441	1.33	0.51 - 3.45	0.560
60-69	6.60	3.31 - 13.19	< 0.001	7.22	3.56 - 14.61	< 0.001	6.87	3.20 - 14.76	< 0.001	5.31	2.44 - 11.57	< 0.001
70-79	15.46	7.57 - 31.59	< 0.001	18.13	8.45 - 38.91	< 0.001	25.76	11.86 - 55.99	< 0.001	15.15	6.70 - 34.28	< 0.001
80+	24.07	9.75 - 59.41	< 0.001	27.33	10.46 - 71.40	< 0.001	33.82	13.00 - 88.03	< 0.001	18.24	6.66 - 49.94	< 0.001
Male sex (vs. female)	1.87	1.35 - 2.60	< 0.001	2.57	1.77 - 3.72	< 0.001	1.11	0.80 - 1.55	0.542	1.52	1.03 - 2.23	0.035
Education (year)	0.76	0.70 - 0.84	< 0.001	0.98	0.89 - 1.09	0.734	0.59	0.53 - 0.65	< 0.001	0.76	0.69 - 0.85	< 0.001

*; The younger age subgroups were combined.
**; p-value was calculated by Wald's test.

Figure 1. The 4-item smell identification test (mPST). Four "Scratch and Sniff" cards were used by participants to correctly identify each test odorants (brown color) among 4 choices written in Japanese (English translation shown in blue).

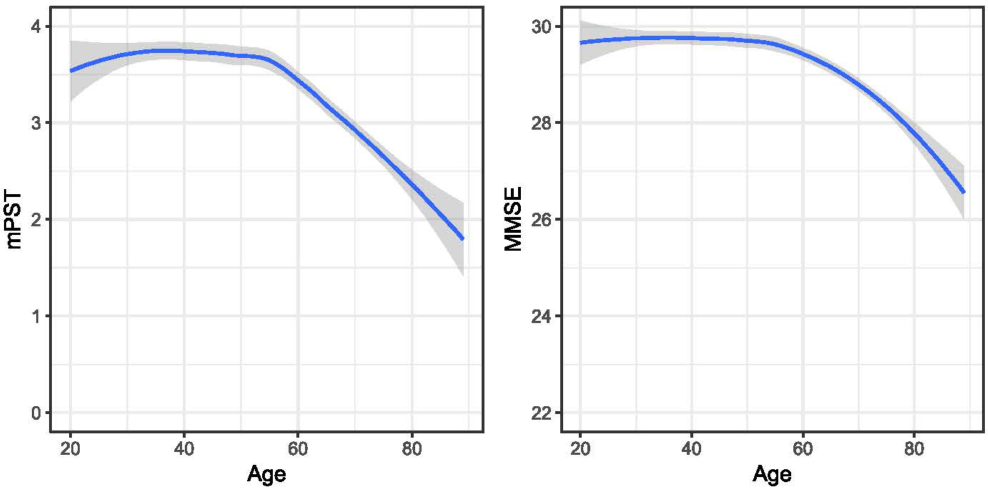

Figure 2. Age-dependent decline of mPST scores (a) and MMSE scores (b) for each participants are shown with loess smoothed curves (blue) and the gray area indicates 95% confidence intervals for the loess smoothing.

linked to an age-dependent decline in olfactory identification function (Table 1). The comparison between self-reported and mPST-based smell dysfunction indicates the validity to use mPST because of high accuracy between these (Table 2). The trend in our study is similar to NHANES outcomes [8]. Thus, mPST appears to be an unbiased tool to understand the status of smell function.

Our data indicated a gender difference as previously reported [19,20] as seen in table 3, with male seeing an earlier decline in olfactory function compared to females according to age (Table 1). These findings are similar to previous studies conducted in other Asian countries including Japan [1,12,21,22]. We also analyzed the OR of olfactory dysfunction in each age subgroups. The increasing tendency of OR of olfactory dysfunction in older subgroups in this study was similar to those of NHANES [12]. From a cultural aspect, these findings indicate that there appears to be no difference between Caucasians and Asians in regards to olfactory function decline and aging.

Our study also clarifies the slight, but clear age-dependent decrease in cognitive function score by MMSE. Similar slopes of mPST and MMSE decline in relation to age were observed (Figure 2a and b). The statistical analysis using polyserial method showed 0.3650, 0.2967 and 0.3313 as the correlation coefficient in male, female and all-comers, respectively, suggesting weak correlation between olfactory function and cognitive function. It seems to be reasonable because there might be a time-lag between the initiation of olfactory impairment and that of mental decline [11,23-26]. Table 1 indicates the age categories firstly showing the smell loss (defined as less than 3) and mental decline (defined as less than 28) are 70-79 (2.65) and 80+ (27.6), respectively. It suggests an initial apparent decrease in olfactory identification capabilities followed by the decrease in cognitive function, as observed previously [11,23-26]. Since this was cross-sectional study, further confirmation to assess clearly if olfactory loss occurs prior to mental fitness decline will be required in a prospective study. It also might be good to use B-SIT or UPSIT for more thorough assessment of mental fitness decline association with olfactory dysfunctions [11]. In future study, the impact of education years and gender in both olfactory and cognitive functions should be evaluated to confirm the results in this study that shows being male increased the OR of both olfactory impairment and mental decline, and that education years, at least, decreased the OR of mental decline. It will also be interesting to assess if smell tests such as mPST could be used as non-invasive mean to monitor early efficacy of amyloid β-lowering drugs once available since loss of smell has been associated with amyloid deposition in brain and thinner entorhinal cortex [27].

Limitations

This study has two important limitations. The design of our observation study was cross-sectional so it was difficult to clarify the exact causal connections among the parameters, such as mPST score, MMSE score and clinical characteristics. A longitudinal follow-up study will be required. In addition, all participants in this study were volunteers, who were interested in their health condition and may be healthier than other local residents who did not join the study. This selection bias must be considered when a general population is targeted.

Conclusion

This is the first report to show the association between olfactory impairment and decline of mental fitness in a more than 1000 Japanese general population. Our study clarifies the mean value in 4-item mPST in each age category, supporting further researches. mPST is a rapid, non-invasive, useful screening tool to detect olfactory impairment, suggesting potential sign of mental fitness change.

Acknowledgements

The authors thank all coworkers in this study for their contributions on the data collection (Masaki Oguma and Masaharu Morimoto), the data management (Koichi Murashita, Ken-ichi Kawatani) and the preparation of modified 4-item PST Japanese version (Kazumasa Nagayama, Yoshie Tanigawara, Yohei Kijima, and Hiromi Kamba). The Iwaki Project is supported by Center-of-Innovation in Japan Science and Technology Agency.

The authors would like to express their special appreciation to Professor Richard L. Doty from University of Pennsylvania, the Smell & Taste Center, for his useful suggestions for the preparation of mPST and how to conduct the smell identification test for our study.

Author contributions

Mamoru Yanagimachi conceived and directed the Olfactory test study and contributed to prepare the manuscript. Kentaro Takahashi conducted the data processing and the statistical analysis with the direction from Ippei Takahashi, the study director of Iwaki Project. Francois Bernier contributed to manuscript preparation and data analysis. Yuki Mikuniya and Akira Sasaki contributed the study design, data collection, management and analysis. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work.

Disclosure and conflict of interest

All authors have no competing financial interests. Mamoru Yanagimachi, Francois Bernier, Kentaro Takahashi, and Toshiya Komine are employees of Eisai Co., Ltd. They also contributed to conducting mPST and MMSE in this study.

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