Research Highlights

1. Impaired human cognitive abilities are reflected by loss of olfactory abilities.
2. We examined olfactory abilities in three neurogenerative disorders.
3. Parkinson's disease, Type 1 myotonic dystrophy and Alzheimer's disease were tested.
4. All patients exhibited decreased or impaired odor-recognition compared with age-matched controls.

**Markers of brain illness may be hidden in your olfactory ability:
A Japanese Perspective**

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Conflict of Interest

The authors declare that they have no conflict of interests.

Abstract

There is evidence that impaired human cognitive abilities are reflected by loss of olfactory abilities. Declining olfactory perception may be a biomarker for impairment of cognitive function and of impending illnesses in neurogenerative disorders. As olfactory perception may differ between culture and ethnic group, we sought to confirm this relationship with Japanese participants. In this study, we examined possible relationships between age and olfactory abilities in healthy Japanese subjects (control subjects) over a wide range of ages and compared this relationship with that observed in three neurodegenerative disorders; patients with Parkinson's disease (PD), Type 1 myotonic dystrophy (DM1) and Alzheimer's disease (AD). In control subjects, both threshold and recognition abilities decreased with age. Ability to detect odors was generally intact in most control subjects, however, we found that the abilities of individuals in the three different patient populations to recognize odors were impaired relative to control subjects. All three types of patients exhibited decreased or impaired odor-recognition compared with age-matched controls.

Previous studies showed the causes of olfactory impairments in PD and AD patients have been attributed to pathological changes and MRIs' signal abnormalities in limbic

areas, including the amygdala (AMG), entorhinal cortex (ENT), hippocampus (HI), and orbitofrontal cortex (OFC). Another study reported that DM1 patients have bilateral lesions in anterior temporal areas, including the subcortical white matter, AMG, ENT and insula. Our findings underscore the need to pay careful attention to significant decreases of odor identification abilities caused by diverse forms of abnormal brain function, especially in the AMG, ENT and HI.

Keywords: olfaction, recognition, detection, age, normal subjects, Parkinson's disease,

Type 1 myotonic dystrophy, Alzheimer's disease

Olfaction and the processing of olfactory information represents an early evolutionary system that is highly developed in many animals, and it is linked to various essential functions, from detecting appropriate food and avoiding dangerous substances, to choosing a mate and engaging in social interactions. Such abilities involve key brain regions in limbic and frontal (especially orbitofrontal) regions [17]. Importantly, these regions are relevant to the processing of social suggesting that olfaction [11] and social cognition are intimately linked [21]. Further, the olfactory sense has a direct path into the limbic brain regions and this may have important survival value [26]. In humans, however, the olfactory system is a less critical sensory modality, and humans can live relatively normal lives following the loss of olfactory perception. Nevertheless, there is evidence that human cognitive abilities are impaired by loss of olfactory abilities. Indeed, declining olfactory abilities may be a biomarker for impairment of cognitive function and of impending illnesses, such as Parkinson's disease (PD) [5, 8, 15], Alzheimer's disease (AD) [15, 16, 24], and psychiatric disorders including schizophrenia [2, 25].

Previously, we have examined olfactory detection and recognition tests and brain activities in healthy Japanese subjects (control subjects) [12]. It is noteworthy however that Japanese subjects may differ from those of different cultures [3] as many

cannot readily identify the odor of root beer, while the smell of a skunk may not be familiar in countries unfamiliar to such animals. It is important therefore to establish normative data relevant to each culture. Clinicians in different countries employ specific odor identification tests validated and approved for use with their populations. Most studies conducted in the United States and Europe report olfactory results obtained using the University of Pennsylvania Smell Identification Test (UPSIT) [5, 6, 8], whereas researchers in Japan typically use the T & T olfactometer [9,11,12,14]. Fortunately, the results of these two tests are highly correlated, as reported elsewhere [10, 20].

In previous studies we also tested olfactory abilities in Japanese patients with one of two neurological disorders [11, 13, 14, 21]. To compare olfaction tests between these patients and age-matched controls, we collected data in subjects over a wide range of ages [11, 13, 14, 21]. In this study, we compared new data from olfaction tests in Japanese AD patients to previously collected data [11-14, 21]. Given difference between olfactory abilities between Japanese and other cultures, as noted above, we sought to extend previous reports of the relationship between age and olfactory abilities and between this relationship and three neurodegenerative disorders. All patients were recruited from a population of outpatients regularly treated at Department of

Neurology (patients with PD and Type 1 myotonic dystrophy: DM1) and Department of Psychiatry (patients with AD) at Showa University Hospital. Healthy subjects under the age of 60 years were volunteers from medical students and office staff of Showa University (N=34: 18 male and 16 female). Control subjects over the age of 60 years were recruited from an agency for senior citizen and paid for their participants. These control subjects were education-matched to the patients (N=33: 17 male and 16 female; total number of controls, N=67: 35 male and 32 female). All patients and control subjects were provided written informed consent, and the study was approved by the Ethics Committee of the Showa University School of Medicine.

Olfactory abilities are generally evaluated using tests of threshold detection and recognition of distinct classifications of odors. Threshold tests determine the minimum concentration of an odor a subject can detect. Recognition tests determine whether a subject can identify a specific odor, presented at suprathreshold levels. The olfactory threshold depends on processing in brain regions including the piriform cortex (Pir), entorhinal cortex (ENT), amygdala (AMG), and hippocampus (HI) [18, 23]. Olfactory identification requires higher areas in the orbitofrontal cortex (OFC) that are para-limbic and cortical [7, 19] but also depends on personal history and culture.

Figures 1 and 2 show the relationships between detection and recognition in

three neurological disorders compared with control subjects as determined by the T & T olfactometer in Japanese adults from the 3rd to 9th decades of life. The lower y-axis indicates impaired olfactory detection or recognition, and the higher y-axis indicates a high sensitivity to the odor. In normal subjects (indicated by the closed circles), both threshold and recognition abilities decrease with age (Pearson linear regression analysis, detection $r = 0.6$, $P < 0.001$; recognition, $r = 0.8$, $P < 0.001$). The regression lines for each detection score versus age comparison and recognition versus age comparison were parallel (no interaction), as confirmed by analysis of covariance (ANCOVA) ($r = 0.2$, $P = 0.7$). Therefore, both the detection and recognition of odors appear to decline with age in control subjects.

We also obtained new data in patients with AD (N = 16: 9 male and 7 female; disease duration, 4.6 ± 2.2 years; therapy duration, 2.5 ± 1.4 years; all diagnosed as having mild AD; indicated by the asterisks). Each AD diagnosis was based on clinical history of the subject and their neurological and neuropsychological examinations, and was supported by structural and functional imaging. The AD patients fulfilled the diagnostic criteria of AD according to NINCDS-ADRDA and Diagnostic and Statistical Manual of Mental Disorders, Six Edition (DSM-VI) and were taking donepezil and were tested in the “on” condition. All subjects gave informed consent, and the study was

approved by the ethics committee at the Showa University School of Medicine, Tokyo, Japan. We then extended our comparison by including detection and recognition data previously obtained in patients with PD (N = 18: 16 male and 2 female; Hoehn-Yahr scale 2–3; disease duration, 6.2 ± 1.1 years; indicated by the closed triangles) [13, 14], previously obtained in patients with DM 1 (N = 7: 3 male and 4 female; disease duration, 13.3 ± 8.2 years; indicated by the open squares) [11].

In patients with PD, there were no significant differences in detection abilities compared with age-matched control subjects [13, 14]. Three out of 16 AD patients (2 male and 1 female) were not able to detect specific odors, whereas the remaining 13 subjects (7 male and 6 female) had odor detection abilities that were comparable to the 15 control subjects (8 male and 7 female; normal subjects mean age: 78.9 ± 5.4 , AD patients mean age: 79.8 ± 5.4 ; there were no significant differences in age between two groups, Mann-Whitney U test, $P = 0.69$; normal subjects mean threshold score: 0.78 ± 1.2 , AD patients mean threshold score: 0.8 ± 0.8 ; no significant differences were observed in detection level between the two groups, Mann-Whitney U test, $P = 0.76$). DM1 patients also had normal olfactory detection, except in one 35-year-old [11]. These data suggest *odor detection* is generally intact in most normal control subjects and in many individuals diagnosed with the three neurological conditions of interest.

In contrast, patients in each specific neurological condition exhibited decreased or impaired *odor recognition* abilities. We have previously reported that the recognition abilities of PD patients are significantly worse than control subjects, and four patients in our sample had impaired recognition [13, 14]. Similarly, the three DM1 patients also showed poor odor identification and one DM1 patient had completely lost the ability to identify odors [11]. In addition to these data, we confirmed that most of the AD patients showed impairments in odor identification. It was striking that no patients with PD, AD, or DM1 understood that they could not identify odors, even when they had both impaired detection and recognition.

The causes of olfactory impairments in PD and AD patients have been attributed to pathological changes and MRIs' signal abnormalities in limbic areas, including the AMG, ENT, HI, and OFC [5, 8, 14-16, 24]. DM1 patients have bilateral lesions in anterior temporal areas, including the subcortical white matter, AMG, ENT and insula [11, 21]. Lesions of these areas were severe in DM1 patient aged 35 years, who had both impaired odor detection and recognition [11]. These brain areas are important for both the detection and recognition of odors.

The decline in olfactory abilities may be a natural phenomenon associated with aging, and may be related to both peripheral and central factors [4], however, our

findings underscore the need to pay careful attention to significant decreases of odor identification abilities. Abnormalities of the AMG, ENT, HI may begin in the earliest stages of disease, and accordingly, the decline in olfactory function associated with these areas may decline prior to the appearance of primary disease symptoms [1, 5, 8, 14-16, 22, 24].

Our observations of olfactory abilities in healthy Japanese control subjects and patients with neurological disorders extend the growing body of evidence gathered with subjects from North American and European studies confirming the utility of using sensitive test of olfactory function as a biomarker of neurodegenerative disease [4-6, 8, 15, 16, 24]. We were also particularly interested to observe in both normal Japanese subjects as well as in patients with AD, PD or DM1, that recognition of pleasant odors was impaired significantly more than recognition of unpleasant odors [13]. This finding raises the possibility that individuals experiencing deficits in the recognition of pleasant odor may also experience impaired odor-induction of pleasant emotions. The relationship of this finding to the presence of mood disorders in both PD and AD patients may be a worthwhile topic for future research.

Acknowledgements

This study was supported by Showa University School of Medicine Fund.

The authors thank the clinic staff for their continued support and help with subject recruitment and the research staff who assisted with data collection.

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Figure legends

Figure 1

Relationships between age and olfactory detection levels in healthy control subjects (●) and subjects with one of three neurological disorders (patients with Parkinson's disease, ▲; Type 1 myotonic dystrophy, ◆; Alzheimer's disease, *). X-axis indicates ages from 20^s to 90^s time of life. Y-axis indicates grades of concentration of odor. Downward y-axis indicates as "+" which means subjects can able to detect the odor with higher odor concentration. It means an impaired olfactory detection. Upward y-axis means subjects can able to detect the odor with lower odor concentration, indicating sensitive toward odor.

Figure 2

Relationships between age and olfactory recognition levels in healthy control subjects and subjects with one of three neurological disorders. X-axis indicates ages from 20^s to 90^s time of life. Y-axis indicates grades of concentration of odor. Downward y-axis

indicates as “+” which means subjects can able to identify the odor with higher odor concentration. It means an impaired olfactory identification. Upward y-axis means subjects can able to identify the odor with lower odor concentration, indicating sensitive toward odor.

Figure

Fig.2

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Title:

Markers of brain illness may be hidden in your olfactory ability: A Japanese perspective

Date:

2013-08-09

Citation:

Masaoka, Y., Pantelis, C., Phillips, A., Kawamura, M., Mimura, M., Minegishi, G. & Homma, I. (2013). Markers of brain illness may be hidden in your olfactory ability: A Japanese perspective. *NEUROSCIENCE LETTERS*, 549, pp.182-185. <https://doi.org/10.1016/j.neulet.2013.05.077>.

Publication Status:

Accepted manuscript

Persistent Link:

<http://hdl.handle.net/11343/41919>