Odor Detection and Recognition Ability in Patients with Alzheimer’s Disease

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Abstract: Alzheimer’s disease (AD) manifests early with prominent olfactory dysfunction. The olfactory symptoms appear long before cognitive impairment and other typical AD symptoms. Here, we tested odor detection and recognition acuity in AD patients and in age-matched controls to determine the relationships between olfactory test scores and anxiety level, cognitive function, and disease and therapy duration.

We found that while AD patients had the same odor detection sensitivity as healthy subjects, most patients exhibited impaired odor recognition. AD patients had significantly lower cognitive function and trait anxiety scores than healthy subjects according to our assessments using the Mini-Mental State Examination (MMSE). Trait anxiety scores are thought to be lower in AD patients because of atrophy of the limbic system, particularly the amygdala (AMG). It has been reported that trait anxiety level is dependent on amygdala activity, therefore, the low activation of the AMG is linked to reduced trait anxiety in AD.

However, we found that trait anxiety correlated positively with odor detection ability in AD patients. Although the function of the AMG is reduced in AD patients, it still contributes to odor detection in AD patients with high trait anxiety.

Key words: Alzheimer’s disease, olfactory impairment, detection level, trait anxiety, the limbic system

Introduction

Neurodegenerative disorders such as Parkinson’s disease (PD)1, 2) and Alzheimer’s disease (AD)3, 4) manifest early with prominent olfactory dysfunction. In AD patients, the olfactory symptoms appear long before cognitive impairment and other typical AD symptoms3).

Olfactory information is projected directly to the limbic system, bypassing the thalamus.

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Human neuroimaging studies have shown that odor presentation activates the piriform (Pir) cortex, amygdala (AMG), hippocampus (HI), and orbitofrontal cortex (OFC) during. The Pir cortex, AMG, entorhinal cortex (ENT), and HI are involved in odor detection, memory retrieval, and emotional evaluation (pleasant or unpleasant), whereas the OFC plays a role in odor recognition filtered through emotion and memory via activation of the AMG and HI, which are brain regions involved in emotion and memory recognition.

We have examined odor detection and recognition acuity in PD patients and age-matched controls to determine the relationship between olfactory test scores and the function of brain regions involved in olfactory processing. All PD patients were able to detect odors to the same sensitivity as normal healthy subjects but had difficulty in recognizing odors. ENT is thought to play a role in odor detection and might also be involved in odor recognition. PD patients, who have impaired odor recognition but normal odor detection sensitivity, have decreased activation of ENT and limbic areas. It is also possible that the lower activity of these areas in PD patients might be below the threshold required to activate the OFC.

In AD, olfactory impairment is observed before the appearance of typical AD symptoms. To assist in predicting AD onset and in managing early treatment before the classic signs of the disease appear, it is important to understand the relationship between olfactory impairment and disease and therapy durations, and between olfactory deficit and cognitive function. To gain an understanding of these relationships, we tested odor detection and recognition acuity in AD patients and in age-matched controls and analyzed the relationships between olfactory test scores and anxiety level, cognitive function, and disease and therapy duration.

**Method**

Sixteen healthy normal subjects (mean 77.2 ± 5.1 years of age; all men) and 16 age-matched patients with AD (mean 79.6 ± 5.8 years of age; nine men and seven women) participated in this study. Diagnosis was based on clinical history as well as neurological and neuropsychological examinations, and was supported by structural and functional imaging. The AD patients were taking donepezil. All participants undertook the Mini-Mental State Examination (MMSE), for assessment of their cognitive function, and the Spielberger State-Trait Anxiety Inventory (STAI), to measure their anxiety levels.

All subjects gave informed consent, and the study was approved by the ethics committee of the Showa University School of Medicine.

**Olfactory test**

The olfactory test has been explained in detail elsewhere. Odor detection and recognition acuity were tested with a T&T olfactometer (Takasuna Co., Ltd., Tokyo, Japan) prior to commencement of the experiments. The results of these tests correlated positively with
those obtained by using the University of Pennsylvania Smell Identification Test\textsuperscript{11}. We tested five odors using the olfactometer including β-phenyl ethyl alcohol (odor A), methyl cyclopentenone (odor B), isovaleric acid (odor C), γ-undecalactone (odor D), and skatole (odor E). Each odorant was dissolved in propylene glycol and presented to the subjects in eight different concentrations and each consecutive concentration was 10 times stronger than the last. Concentrations were labeled from $-2$ to $+5$, being equal to a normal subject’s detection (odor A, $10^{-5.2}$ ppb; odor B, $10^{-5.6}$ ppb; odor C, $10^{-6.0}$ ppb; odor C; $10^{-6.0}$ ppb; odor D, $10^{-5.1}$ ppb; odor E, $10^{-6.1}$ ppb). The above odorants corresponded to the aroma of a rose or sweet odor (odor A), caramel or burnt sugar (odor B), rotten food or sweaty clothes (odor C), peach or sweet fruit (odor D), and fecal material or kitchen refuse (odor E). Subjects were presented with the end ($>1$ cm) of a strip of litmus paper ($14$ cm × $7$ mm wide) that had been dipped into a bottle containing the odorant. The five odorants were presented randomly but at the same concentration for each trial. The trials began with the lowest concentration of the odorants and were then repeated with progressively higher concentrations. The odorants were presented for 30 s each with an interval of 45 s between each presentation to minimize adaptation\textsuperscript{12}. At the end of each trial, the subjects were asked if they had perceived an odor. The concentration at which the odor was perceived but not identified was considered to be the detection level. The subjects were also asked if they could identify and describe the odors. As the concentration of the odorant increased, the subjects were able to identify the odors. The concentration at which an odor was first identified was considered to be the recognition level. The odor detection threshold for each subject was expressed as the average of threshold scores for each odor. The recognition threshold was expressed in the same manner.

\textit{Data analysis}

All statistical analyses were performed with SPSS statistical software (Version 11.0; SPSS, Tokyo, Japan). Differences in age, MMSE results, STAI scores, and results of the olfactory detection test between AD patients and healthy subjects were analyzed using the Wilcoxon signed-rank test. Correlation coefficients for the linear regression between the olfactory test score and age, MMSE score and olfactory detection level, disease duration and olfactory detection level, and therapy duration and olfactory detection level were calculated. Data in the Table 1 are shown as means with standard deviations, and the scattered plots in Figure 1 indicate the values obtained for each AD patient.

\textit{Results}

Detection and recognition scores of healthy subjects and AD patients are shown in Table 1. There was no significant difference in age between healthy subjects and AD patients ($P > 0.05$). Three out of 16 AD patients were not able to detect the odors, and 14 out of 16 patients had impaired odor recognition. There was no difference in detection levels between
healthy subjects (n = 11) and AD patients (n = 13) (P > 0.05). The MMSE scores were significantly lower in AD patients than in healthy subjects (P < 0.01). There was no difference in state anxiety between the two groups (P = 0.5). However, there were significantly lower scores for trait anxiety in AD patients (P < 0.05).

Fig. 1 shows the relationships between the measured variables in the 13 AD patients exhibiting impaired odor recognition, but intact odor detection ability. There was no correlation between the olfactory detection score and age (r = 0.2, P > 0.05), the olfactory detection score and the MMSE score (r = 0.2, P > 0.05), the olfactory detection score and disease duration (r = 0.4, P > 0.05), or the olfactory detection score and therapy duration (r = 0.1, P > 0.05). While there was no correlation between state anxiety score and olfactory detection score (r = 0.34, P > 0.05), there was a significant negative correlation between the trait anxiety score and the olfactory detection score (r = 0.78, P < 0.01). Taken together, these results indicate that AD patients with a lower olfactory detection score and able to detect low concentrations of odor had a higher trait anxiety score.

Discussion

Most AD patients in this study exhibited the same odor detection sensitivity as healthy subjects, with the exception of three patients (Subjects 1, 2 and 3), but exhibited impaired
Fig. 1. Correlation between age, state anxiety scores, trait anxiety scores, MMSE score, disease duration, therapy duration, and olfactory detection scores in AD patients.
odor recognition. These findings are consistent with a previous study showing that AD patients had normal smell detection but severely impaired olfactory identification ability. The neuropathological mechanisms underlying olfactory impairment remain unknown. There is a debate whether impaired odor detection ability reflects impairment at the semantic level caused by damage to the Pir cortex, primary olfactory cortex, or cortical-AMG connections. Some of the earliest changes in AD patients appear in the olfactory bulb and other studies have established that smell pathways are damaged in AD patients, but the maximum impact seems to be on the central rather than peripheral nervous system. Our results suggest that odor impairment in AD patients is indicative of damage to the central nervous system, namely a dysfunction in cortical-AMG connections.

In the process of odor detection, odor molecules reach the top of the nasal cavity and then interact with olfactory receptor cells that have cilia (dendrites) extending from the cell body into the nasal mucosa. Axons carry impulses to the olfactory bulb when the olfactory receptor is stimulated. The olfactory bulb then sends signals to the prepiriform and Pir cortices, the anterior olfactory nucleus, AMG, olfactory tubercle, and ENT. The OFC is involved in the convergence of higher-order information such as discrimination and representation. Odor recognition is impaired when connections between the AMG, ENT, and OFC are damaged in PD. Patients with PD are unable to recognize odors but retain the ability to detect odors within the normal range. Previous studies indicate that the olfactory deficits in PD have a neuropathological basis different from that of AD. Our findings here suggest that olfactory dysfunction in AD might result from damage to the central limbic areas rather than damage to the peripheral nervous system.

**Correlation between detection level and trait anxiety score**

We found that trait anxiety was lower in AD patients than in healthy subjects. Whereas the state anxiety scale evaluates how people feel ‘right now’ in various situations, the trait anxiety scale evaluates how people generally feel. State anxiety scores can change depending on the situation, but trait scores are generally stable. Subjects with high trait anxiety show strong activation in the AMG during exposure to negative emotional stimuli, and can be sensitive to olfactory stimuli. Unlike emotional responses, trait anxiety appears to be associated with the limbic areas and involve physiological responses co-expressed with emotional responses. Therefore, trait anxiety might be low in AD patients because of atrophy to the limbic system, particularly the AMG. It has been reported that trait anxiety level is dependent on amygdala activity, therefore, the low activation of the AMG is linked to reduced trait anxiety in AD.

The trait anxiety scores in AD patients were lower than in healthy subjects, and correlated with odor detection sensitivity. This result suggests that AD patients showing a high trait anxiety score tended to have increased odor detection sensitivity. This correlation was not observed in healthy subjects ($r = 0.4, P > 0.05$).
Among the sensory systems, olfactory perception is a unique process whereby information ascends directly to the olfactory limbic areas, bypassing the thalamus, and activates the Pir cortex, ENT, and AMG. Activation of these areas, especially the ENT and AMG, is required for odor detection. We have no direct evidence of a relationship between trait anxiety level and the stage of decreased AMG function in AD patients. It is possible that levels of trait anxiety and odor detection can be used to evaluate residual AMG function in AD patients. Further studies using brain imaging technology are thus required to clarify the relationship between activation levels in limbic areas and odor detection ability in AD patients with low and high trait anxiety.

References


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