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RESEARCH ARTICLE

HYPOSMIA IS RELATED TO COGNITIVE DETERIORATION AND HIPPOCAMPAL ATROPHY

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ABSTRACT

Dysosmia is found with mild cognitive impairment (MCI) and dementias including Alzheimer's disease (AD). The present study was conducted to assess the relations between smell sensitivity and cognitive function; between smell sensitivity and hippocampal size; and between cognitive function and hippocampal size. The results show that hyposmia is related to cognitive deterioration; hyposmia is related to hippocampal atrophy; and that cognitive deterioration is related to hippocampal atrophy. Hyposmia, thus, may be a crucial symptom to detect cognitive deterioration associated with hippocampal atrophy.

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INTRODUCTION

Accumulating evidence has pointed to dysosmia in Alzheimer's disease (AD)-related amnestic disorder; the smell disorder is detected from the earlier stage of AD and also in the AD pre-stage mild cognitive impairment (MCI) (Woodward *et al*., 2017; Marin *et al*., 2018; Yap *et al*., 2022; Mi et al., 2023). Smell validation, therefore, is expected as a beneficial biomarker of AD. The relations between smell sensitivity and cognitive function; between smell sensitivity and hippocampal size; and between cognitive function and hippocampal size, however, is far from understanding. To address this question, the present study carried out smell identification test assessing smell function, Mini-Mental State Examination (MMSE) assessing cognitive function, and magnetic resonance imaging (MRI) scan assessing the degree of hippocampal atrophy. The results show that hyposmia is related to cognitive deterioration; hyposmia is related to hippocampal atrophy; and that cognitive deterioration is related to hippocampal atrophy.

MATERIALS AND METHODS

Subjects: The present study was conducted in 359 subjects with the age ranging from 19 to 99 years old (average, 80 ± 0.5 years old) (157 males and 202 females), who had no disease of the nose such as chronic sinusitis affecting smell sensation. All of them took a neurological examination at Ohyama Hospital, a private hospital located at Nishiwaki, Japan.

Smell identification test: Smell identification test was carried out by the method modifying that described previously (Stamps *et al*., 2013). For the olfactory stimulus, 1 g of instant coffee grain was put in the bottom of acrylic box (30 cm in length of square and 40 cm in height) lacking at the top and one lateral side. The distance from the open one nostril to the stimulus upon its detection was measured using a 30 cm ruler by closing another nostril with hand. This trial was performed in each nose.

MMSE: Full marks of the MMSE score are 30, and subjects with more than 20 and below 19 were regarded as 'normal' and 'cognitive deterioration', respectively.

Analysis of hippocampal atrophy: Brain MRI scan was carried out and hippocampal atrophy was analysed in the coronal section imaging. The line connecting caudal edge of rostrum of the corpus callosum with caudal edge of splenium of the corpus callosum was initially put on the medial section of sagittal image. Subsequently, the second line connecting dorsal edge of the pons with the posterior commissure at an angle of 100° against the initial line was established, and T1-weighted coronal images were taken at a 5-mm interval rostrally and dorsally from the second line. Areas in the hippocampus and the cavity surrounding the hippocampus were measured at the section at which the Monro foramen is seen (Figure 1A). To normalize hippocampal size, the ratio of area in the hippocampus against area in the hippocampus plus the surrounding cavity was calculated (Figure 1B).

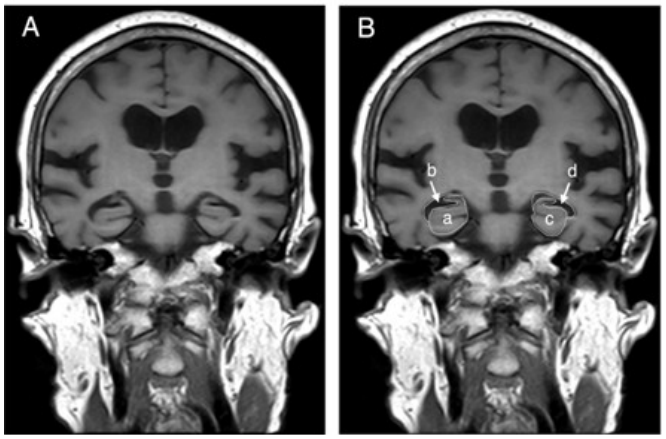

Figure 1. Analysis of hippocampal atrophy. In T1-weighted coronal images of MRI (A), areas in the hippocampus (a,c) and the cavity surrounding the hippocampus (b,d) were measured at the section at which the Monro foramen is seen (B). To normalize hippocampal size, the ratio of area in the hippocampus (a or c) against area in the hippocampus plus the surrounding cavity (a+b or c+d) was calculated

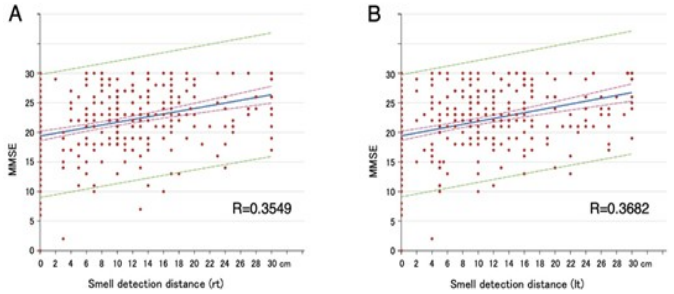

Figure 2. Hyposmia is related to cognitive deterioration. The relation between MMSE score and the smell detection distance was plotted in the right (rt) (A) and left (lt) nose (B) and the linear regression analysis was carried out (n=359). R, the correlation coefficient

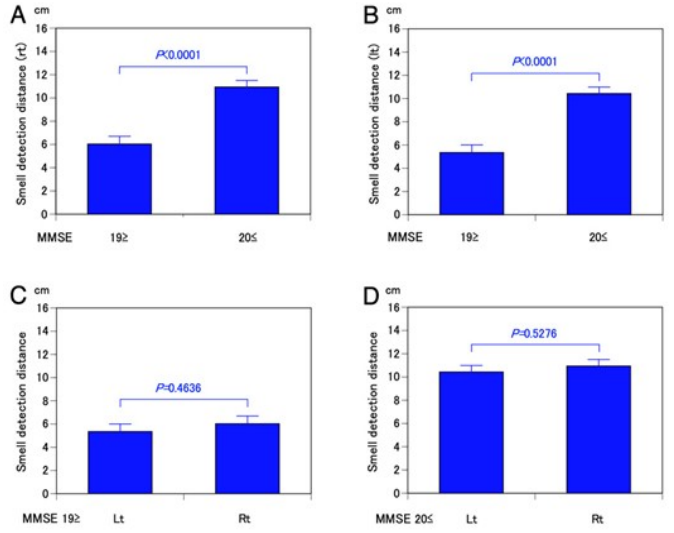

Figure 3. Hyposmia is accompanied by cognitive deterioration without laterality. The smell detection distance was analyzed in subjects with below 19 (n=120) and more than 20 of MMSE score (n=239) in the right (rt) (A) or left nose (lt) (B). The smell detection distance in the left (Lt) and right nose (Rt) was monitored in subjects with below 19 (n=120) (C) and more than 20 of MMSE score (n=239) (D). In the graphs, each column represents the mean (± SEM) smell detection distance. *P* values, ANOVA.

Statistical analysis: Statistical analysis was carried out using linear regression analysis and analysis of variance (ANOVA).

RESULTS

Hyposmia is related to cognitive deterioration: The smell detection distance was shortened in parallel with reduced score of MMSE, and the correlation coefficient (R) in the right and left nose was 0.3549 and 0.3682, respectively (Figure 2A,B).

The smell detection distance for subjects with below 19 of MMSE score was significantly shorter than the distance for those with more than 20 of MMSE score in both nose (P<0.0001, ANOVA) (Figure 3A,B). In contrast, there was no significant difference in the smell detection distance between left and right nose for subjects with below 19 of MMSE score or for those with more than 20 of MMSE (Figure 2C,D). Taken together, these results indicate that hyposmia is related to cognitive deterioration without laterality.

Hyposmia is related to hippocampal atrophy and hippocampal atrophy is related to cognitive deterioration: The smell detection distance was shortened along reduction of hippocampal size, with R of 0.3201 and 0.2960 in the right and left nose, respectively (Figure 4A,B). MMSE score decreased along reduction of hippocampal size, with R of 0.4322 and 0.4229 in the right and left nose, respectively (Figure 5A,B). Over all, these results indicate that hyposmia is related to hippocampal atrophy and that hippocampal atrophy is related to cognitive deterioration.

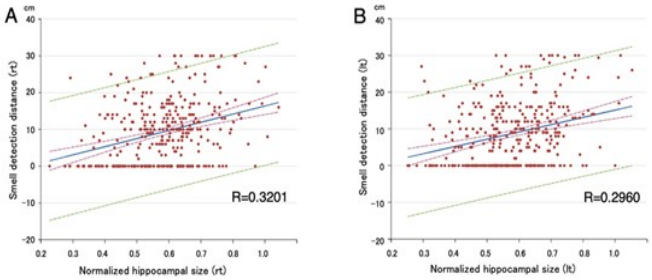

Figure 4. Hyposmia is related to hippocampal atrophy. The relation between the smell detection distance and normalized hippocampal size at the right (rt) (A) and left side (lt) (B) was plotted, and the linear regression analysis was carried out (n=239). R, the correlation coefficient

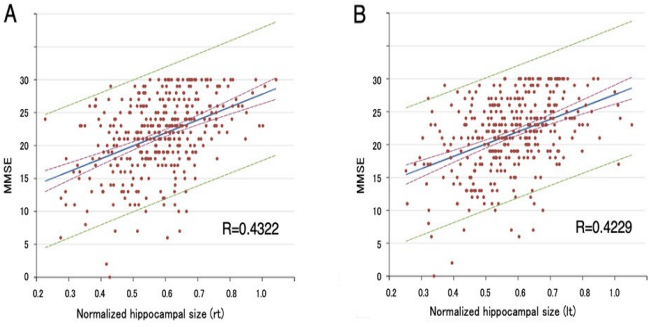

Figure 5. Cognitive deterioration is related to hippocampal atrophy. The relation between MMSE score and normalized hippocampal size in the right (rt) (A) and left hippocampus (lt) (B) was plotted and the linear regression analysis was carried out (n=239). R, the correlation coefficient

DISCUSSION

Early diagnosis of AD is a critical factor for an efficient treatment of AD. A variety of biomarkers for early diagnosis of AD have been proposed, and among them recent interest focuses on smell validation. It is recognized that dysosmia is found with in neurodegenerative diseases including AD (Woodward *et al*., 2017; Marin *et al*., 2018; Yap *et al*., 2022; Mi et al., 2023). In the present study, the smell sensitivity reduced in association with cognitive deterioration. An interest report shows that hyposmia is found with predominantly left nose, but not right nose, in AD patients (Stamps *et al*., 2013). Such finding, however, is not obtained with other AD-related olfactory studies (Doty *et al*., 2014). The results of the present study also demonstrate that there was no significant difference in the smell sensitivity between left and right nose for subjects with cognitive deterioration. One of the major findings in the present study is that hyposmia is related to hippocampal atrophy and further that hippocampal atrophy is related to cognitive deterioration. Olfactory sensation as well as sensations of vision, hearing, taste, and touch are closely connected to the limbic system including the hippocampus. Dysfunction of the limbic system, therefore, would perturb input of such sensations. This raises the possibility that hyposmia might be caused by hippocampal atrophy and the following cognitive deterioration. Overall, the results of the present study suggest that hyposmia may be a crucial symptom to detect cognitive deterioration associated with hippocampal atrophy.

CONCLUSION

Hyposmia is related to cognitive deterioration associated with hippocampal atrophy, and therefore, smell validation could become a beneficial biomarker of AD.

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