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Featured Article

Olfactory dysfunction in Alzheimer's disease– and Lewy body–related cognitive impairment

Han Soo Yoo[a,1], Seun Jeon[b,1], Seok Jong Chung[a], Alan C. Evans[b], Mijin Yun[c], Phil Hyu Lee[a], Young Ho Sohn[a], Byoung Seok Ye[a,*]

[a]*Department of Neurology, Yonsei University College of Medicine, Seoul, Korea*
[b]*McGill Center for Integrative Neuroscience, Montreal Neurological Institute, McGill University, Montreal, Canada*
[c]*Department of Nuclear Medicine, Yonsei University College of Medicine, Seoul, Korea*

Abstract

Introduction: Olfactory dysfunction is common in Alzheimer's disease– and Lewy body–related disorders, but its neural correlates have not been clearly elucidated.

Methods: We retrospectively recruited 237 patients with Alzheimer's disease–related cognitive impairment (ADCI) and 217 with Lewy body–related cognitive impairment (LBCI). They were identically evaluated using the Cross-Cultural Smell Identification Test, neuropsychological tests, and brain magnetic resonance imaging.

Results: LBCI had more severe olfactory dysfunction than ADCI. Patients with more severe cognitive dysfunction had worse olfactory function in both groups. In ADCI, lower Cross-Cultural Smell Identification Test scores correlated with a lower cortical thickness in brain regions typically affected in Alzheimer's disease, most prominently in the right parahippocampal cortex, whereas in LBCI, the scores correlated with white matter abnormalities in regions vulnerable to Lewy body, including subcortical regions of the orbitofrontal and frontoparietal cortices.

Discussion: Our results suggest that cortical atrophy in ADCI and white matter abnormalities in LBCI play important roles in olfactory dysfunction.

Keywords: Olfaction; Alzheimer's disease; Parkinson's disease; Dementia with Lewy bodies; Cognitive impairment; Cortical atrophy

Olfactory dysfunction is common in patients with neurodegenerative diseases, including Alzheimer's disease (AD) and in Lewy body (LB)–related disorders including Parkinson's disease (PD) and dementia with Lewy bodies (DLBs) [1–3]. However, the exact neural correlates for olfactory dysfunction remain poorly understood.

Previous clinical-pathological studies have shown that olfactory dysfunction is associated with LB pathology in the limbic and neocortical regions [4], and AD tangle pathologies in the entorhinal cortex and the hippocampus in the elderly [5]. Although olfactory dysfunction is present even in the prodromal stage of AD- or LB-related disorders [6,7], clinical-pathological correlation studies have investigated far-advanced dementia patients and used long intervals between olfactory function tests and pathologic evaluations. Recent advances in neuroimaging have provided new opportunities to reveal the brain changes in Alzheimer's disease–related cognitive impairment (ADCI) and Lewy body–related cognitive impairments (LBCIs). Previous imaging and pathological studies exhibited that ADCI is characteristically a gray matter disease [8], whereas LBCI is characterized by white matter microstructural changes identified on diffusion tensor imaging (DTI) [9]. Therefore, comparative evaluations of olfactory dysfunction in ADCI and LBCI using cortical thickness and DTI could lead to a better understanding of these two most common neurodegenerative diseases.

The authors have declared that no conflict of interest exists.

[1]These authors contributed equally to this work.

*Corresponding author. Tel.: +82-2-2228-1601; Fax: +82-2-393-0705.
E-mail address: romel79@gmail.com

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We investigated the relationship of olfactory deficits with cognitive dysfunction and brain structural changes in ADCI and LBCI patients who were identically evaluated using olfactory identification tests, neuropsychological tests, and brain structural magnetic resonance imaging (MRI) for cortical thickness and DTI analyses. We hypothesized that there are two different neural correlates explaining olfactory dysfunction in ADCI and LBCI.

1. Methods

1.1. Study participants

From a university hospital-based memory and movement disorders clinics, we consecutively recruited 950 patients complaining of cognitive decline. Among them, 496 patients were excluded for the following reasons (Fig. 1 and Supplementary Methods): pure vascular cognitive impairment; concomitant ADCI and LBCI; severe white matter hyperintensities (WMHs) on Fazekas scale [10]; incomplete evaluation in olfactory identification test, neuropsychological test, or brain MRI; other conditions explaining participants' cognitive or olfactory dysfunction; and chronic alcohol abuse. Accordingly, we enrolled 237 patients with ADCI (99 with probable AD dementia [11], 62 with amnestic mild cognitive impairment [MCI] [12], and 76 with subjective cognitive decline [SCD]) and 217 patients with LBCI (33 with PD dementia [13], 15 with DLB [14], 83 with PD-MCI [15], 16 with prodromal DLB, and 70 with PD-SCD). All clinical diagnoses were performed at Yonsei University Medical Center from March 2012 to February 2017. Patients who complained of subjective memory problems but had a normal neuropsychological profile and showed no Parkinsonism were defined as SCD in the ADCI group. Two neurologists (L.P.H. and Y.B.S.) confirmed the absence of Parkinsonism, visual hallucinations, and rapid eye movement sleep behavior disorder in these patients. PD was diagnosed if patients fulfilled the UK PD Society Brain Bank diagnostic criteria for PD [16]. Patients with PD who had normal cognition on neuropsychological evaluations were defined as PD-SCD. Patients with prodromal DLB were defined as patients with MCI meeting probable DLB criteria except for the presence of dementia [17]. All patients with LBCI underwent [^{18}F] N-(3-Fluoropropyl)-2β-carbon ethoxy-3β-(4-iodophenyl) nortropane positron emission tomography scanning and showed the presence of appropriate defects in dopamine transporter activity [18].

All patients underwent a neurologic examination, an olfactory identification test, a detailed neuropsychological tests battery [19], and a three-dimensional volumetric brain MRI assessment. All diagnostic workup procedures were carried out within 6 months. This study was approved by the Institutional Review Board of the Yonsei University Medical Center. The requirement for patient consent was waived, given the retrospective nature of the study.

1.2. Neuropsychological evaluation

All participants underwent a standardized neuropsychological battery called the Seoul Neuropsychological Screening Battery [19], which contains the following scorable tests: digit span (forward and backward); Korean version of the Boston Naming Test; Rey-Osterrieth Complex Figure Test (copying, immediate and 20-min delayed recall, and recognition); Seoul Verbal Learning Test (immediate recall, 20-min delayed recall, and recognition), phonemic and semantic Controlled Oral Word Association Test; Stroop Test (word and color reading); and Mini–Mental State Examination (MMSE) [20].

1.3. Evaluation of olfactory function

Olfactory function (identification) was assessed with the Cross-Cultural Smell Identification Test (CCSIT), which

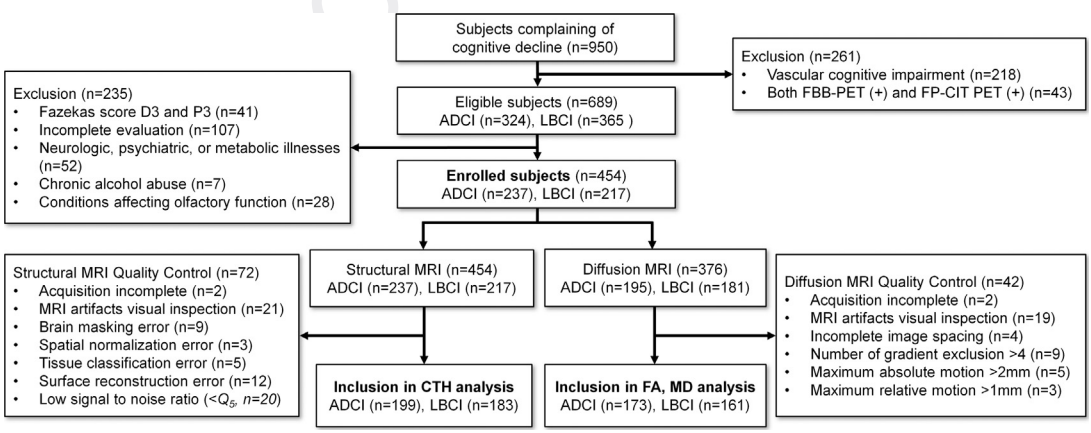

Fig. 1. Flowchart of the study participants. Abbreviations: ADCI, Alzheimer's disease–related cognitive impairment; CTH, cortical thickness; FA, fraction anisotropy; FBB-PET, ^{18}F-florbetaben positron emission tomography; FP-CIT PET, [^{18}F] N-(3-Fluoropropyl)-2β-carbon ethoxy-3β-(4-iodophenyl) nortropane positron emission tomography; LBCI, Lewy body–related cognitive impairment; MD, mean diffusivity; MRI, magnetic resonance imaging.