Neurological Sciences (2018) 39:557–564
https://doi.org/10.1007/s10072-018-3261-1

ORIGINAL ARTICLE

Comparison of odor identification among amnestic and non-amnestic mild cognitive impairment, subjective cognitive decline, and early Alzheimer's dementia

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Received: 10 November 2017 / Accepted: 22 January 2018 / Published online: 30 January 2018

Abstract

Olfactory impairment might be an important clinical marker and predictor of Alzheimer's disease (AD). In the present study, we aimed to compare the degree of olfactory identification impairment in each mild cognitive impairment (MCI) subtype, subjective memory impairment, and early AD dementia and assessed the relationship between olfactory identification and cognitive performance. We consecutively included 50 patients with amnestic MCI, 28 patients with non-amnestic MCI, 20 patients with mild AD, and 17 patients with subjective memory impairment (SMI). All patients underwent clinical and neuropsychological assessments. A multiple choice olfactory identification cross-cultural smell identification test was also utilized. Controlling for age and gender, olfactory impairment was significantly more severe in patients with AD and amnestic MCI compared with the results from the non-amnestic MCI and SMI groups. Higher scores on MMSE, verbal and non-verbal memory, and frontal executive function tests were significantly related to olfactory identification ability. In conclusion, olfactory identification is impaired in amnestic MCI and AD. These findings are consistent with previous studies. In amnestic MCI patients, this dysfunction is considered to be caused by underlying AD pathology.

Keywords Hyposmia · Alzheimer's disease · Mild cognitive impairment · Amnestic · Non-amnestic · Subjective memory impairment

Introduction

The presence of olfactory impairment in various neurodegenerative diseases has been documented. This is thought to be attributable to the deposition of pathological proteins and degeneration in the olfactory epithelium, olfactory bulb, entorhinal cortex, hippocampus, and secondary olfactory cortices [1].

Likewise, olfactory dysfunction in Alzheimer's disease (AD), which is the most common cause of dementia [2], has been well established by numerous epidemiologic studies [3–6]. The impairment has also been supported by several imaging studies, which showed a correlation between hippocampal atrophy and olfactory dysfunction [7–10], and autopsy studies [11, 12], which revealed a relationship between olfactory impairment and accumulation of neurofibrillary tangles in central olfactory regions.

In AD, odor identification deficit is the earliest and most prevalent form of olfactory impairment [1, 13]. Consequently, olfactory identification has been repeatedly examined in amnestic mild cognitive impairment (aMCI), which is known to be highly associated with progression to AD [14, 15], and loss of odor identification has been proposed as a predictive marker of conversion from aMCI to AD [16–20].

Meanwhile, to the best of our knowledge, there have been only a few reports regarding associations between odor identification deficit and different subtypes of MCI including non-amnestic MCI (naMCI) [21, 22], which is reported to less frequently convert to AD [23]. In addition, odor identification in subjective memory impairment (SMI), a self-perception of progressive cognitive deterioration,

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10072-018-3261-1) contains supplementary material, which is available to authorized users.

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has rarely been investigated, even though SMI is increasingly recognized as a possible preclinical stage of AD [24, 25].

In this study, we assessed odor identification performance in different subtypes of MCI and compared the results with those of participants with SMI and with early AD. We hypothesized that aMCI individuals would have lower odor identification scores than naMCI participants. We also expected that the olfactory function of SMI patients would be different from that of aMCI and AD patients. Furthermore, we analyzed the association between neuropsychological profile and olfactory identification score on the assumption that olfactory impairment is related to cognitive measures of the memory domain.

Methods

Subjects

A total of 115 participants with complaints of cognitive problems were recruited from the Department of Neurology, Seoul St. Mary's Hospital from January 2016 to December 2016. Clinical information, including age, sex, education status, disease duration, history of hypertension, diabetes mellitus, and smoking status, was obtained. Laboratory tests for variables that can affect cognitive function, including complete blood counts, blood chemistry, homocysteine, vitamin B_{12}, folate level, syphilis serology, and thyroid function, were performed, and patients with any abnormalities were excluded from the study. Apolipoprotein E (APO E) genotype was determined by real-time multiplex PCR blinded to participant status [26].

Subjects were excluded from the study if they presented with history of neurologic diseases (e.g., Parkinson's disease, stroke, epilepsy, brain tumor), a current psychiatric diagnosis, or rhinological disorders that can have a negative effect on olfaction.

The present study was approved by the local ethics committee, and informed consent was obtained from all participants.

Neuropsychological measures

All patients underwent the following set of neuropsychological tests at the time of enrollment in the study: Mini Mental State Examination (MMSE), Clinical Dementia Rating (CDR), Global Deterioration Scale (GDS), Neuropsychiatric Inventory (NPI), Barthel Index of Activities of Daily Living (ADL), and Seoul Neuropsychological Screening Battery (SNSB) [27]. Quantifiable tests on the SNSB comprise the five domains of attention and working memory, language, visuo-constructive function, verbal and visual memory, and frontal/executive function.

A consensus diagnosis was established using clinical criteria for AD [28] and MCI [29]. Depending on the impaired cognitive domain, MCI was further stratified into MCI with memory impairment (amnestic MCI) and MCI without memory impairment (non-amnestic MCI). In addition, patients who had more than two abnormal domains in the neuropsychological tests were classified as multi-domain MCI, while all others were classified as single-domain MCI. A diagnosis of SMI was made on the basis of a complaint of memory decline, despite the absence of any objective neuropsychological explanation provided by neuropsychological tests [30].

Olfactory assessment

Olfaction was assessed using the Cross-Cultural Smell Identification Test (CCSIT) [31], a widely used test of odor identification involving a scratch-and-sniff test of 12 microencapsulated odorants. Before the CCSIT, nasal problems that evoked olfactory dysfunction were evaluated using an otorhinolaryngological evaluation. CCSIT scores were dichotomized as less than 8 (hyposmia) versus 8 or greater (normosmia).

Statistical analysis

Statistics were calculated using SPSS version 24.0 (SPSS Inc., Chicago, IL, USA). Group differences were analyzed using chi-square test or independent sample t test for categorical variables and one-way analysis of variance (ANOVA) for continuous variables. Analysis of covariance (ANCOVA) was conducted to compare CCSIT scores after controlling for age, gender, smoking, education, diabetes mellitus, hypertension, and APO $\varepsilon 4$ status as covariates. In addition, correlations between CCSIT score and cognitive measures, NPI, and Barthel Index of ADL were evaluated using Spearman correlation analysis. Statistical significance was noted when the p value was less than 0.05.

Results

The demographic and clinical characteristics of the study populations are summarized in Table 1. Of the 115 participants, 17 (14.8%) were classified into the SMI group, 50 (43.5%) were placed into the aMCI group, 28 (24.3%) were placed into the naMCI group, and 20 (17.4%) were classified as early AD. The mean MMSE and CDR scores of the subjects were 24.5 ± 4.3 and 0.5 ± 0.2, respectively. Fifty-three (46.1%) of the subjects were normosmic, whereas 62 (53.9%) had hyposmia. The mean score of CCSIT was 6.9 ± 2.6.

CCSIT scores varied across studied groups, including different subtypes of MCI ($p < 0.001$) (Fig. 1). The SMI, naMCIsd, and naMCImd groups performed better than the aMCIsd, aMCImd, and AD groups. This trend remained consistent after regrouping MCI patients into aMCI and naMCI.

Table 1 Baseline characteristics of subjects

Variables		Value
Age, year		72.3 ± 7.8
Male, *n* (%)		32 (27.8%)
Disease duration		1.0 ± 0.9
Education		9.3 ± 5.1
Hypertension, *n* (%)		57 (49.6%)
Diabetes mellitus, *n* (%)		23 (20.0%)
Smoking	Nonsmoker, *n* (%)	96 (83.5%)
	Exsmoker, *n* (%)	19 (16.5%)
MMSE		24.5 ± 4.3
CDR		0.5 ± 0.2
SOB of CDR		1.9 ± 1.9
GDS		3.1 ± 0.8
Barthel ADL		19.7 ± 1.5
Cognitive status	SMI	17 (14.8%)
	Amnestic single domain MCI	9 (7.8%)
	Amnestic multi domain MCI	41 (35.7%)
	Nonamnestic single domain MCI	14 (12.2%)
	Nonamnestic multi domain MCI	14 (12.2%)
	AD	20 (17.4%)
APOE ε4		26 (22.6%)
CCSIT		6.9 ± 2.6
Normosmia		53 (46.1%)
Hyposmia		62 (53.9%)

Values represent mean with standard deviation or numbers of subjects (percentage)

MMSE mini-mental state examination, *CDR* clinical dementia rating, *SOB of CDR* sum of box of CDR, *GDS* global deterioration scale, *ADL* activity of daily living, *SMI* subjective memory impairment, *MCI* mild cognitive impairment, *AD* Alzheimer's dementia, *APOE* apolipoprotein E, *CCSIT* cross-cultural smell identification test

Furthermore, similar group differences were observed after dichotomizing odor identification scores into hyposmia and normosmia. However, ANCOVA showed that CCSIT score was not significantly influenced by APOE ε4 status [6.9 ± 2.6 for APOE ε4 non-carriers vs. 6.7 ± 2.6 for APOE ε4 carriers, $p = 0.747$].

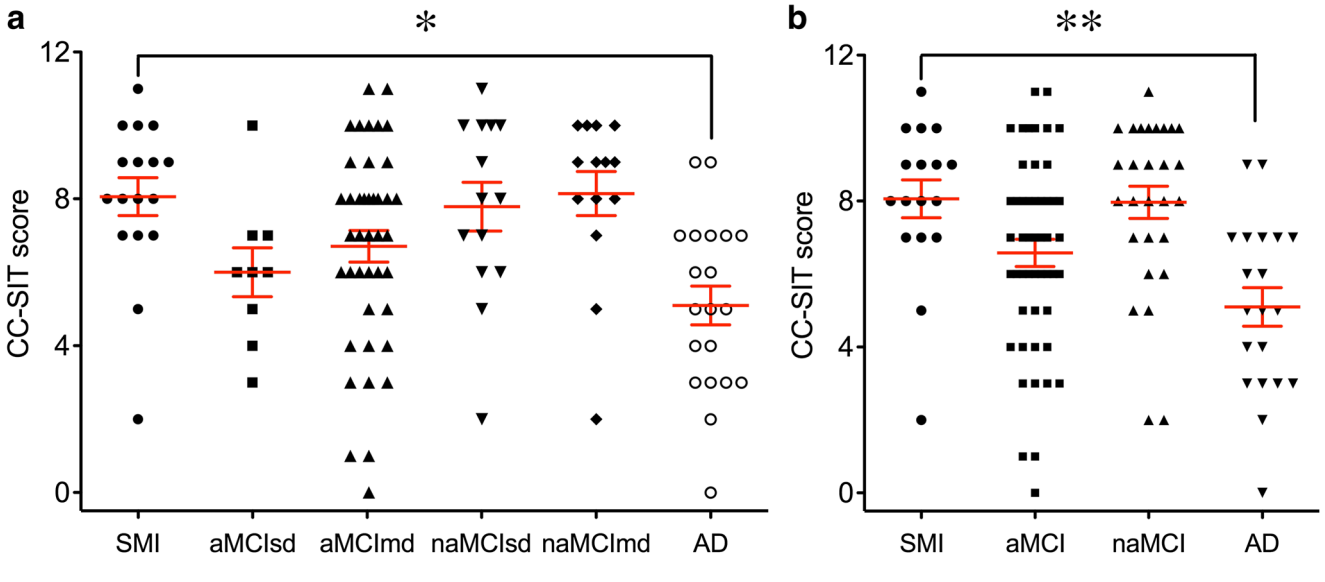
Spearman correlation analyses were conducted for the groups of participants to analyze the associations between neuropsychological measures and olfactory performance (Table 2). Moderate correlations were found between CCSIT score and memory tests, immediate and delayed recall in verbal learning test, as well as immediate and delayed recall in RCFT ($r = 0.395$, 0.467, 0.334, and 0.385, respectively); all were statistically significant ($p < 0.001$). A moderate correlation was also observed with semantic COWAT ($r = 0.507$, $p < 0.001$), while only a weak association was detected with phonemic COWAT ($r = 0.246$, $p = 0.011$). Additionally, results of the Boston naming test and Stroop tests (word and color) were moderately correlated with odor identification score ($r = 0.358$, $p = 0.002$; $r = 0.322$, $p = 0.001$; and $r = 0.309$, $p = 0.001$). On the other hand, calculation was not significantly correlated with CCSIT score ($p = 0.565$). Also, there were no meaningful associations between olfactory performance and digit span tests (forward and backward), which were designed to evaluate attention ($p = 0.809$ and 0.052, respectively).

In comparison with hyposmic participants, subjects with normosmia had better profiles in global cognition as measured by CDR and GDS (Table 3). Among neuropsychological measures, normosmic participants were significantly outperformed as compared with hyposmic subjects in delayed recall in verbal (5.0 ± 3.1 vs. 2.2 ± 2.7, $p = 0.006$) and visuospatial (11.9 ± 6.4 vs. 7.9 ± 5.6, $p = 0.039$) memory tests and semantic COWAT (28.0 ± 10.4 vs. 19.9 ± 7.1, $p = 0.014$). Results from digit span tests, calculation, and Rey Copy test were not significantly different between the two groups, consistent with the correlation analysis. While hyposmic participants were significantly older than subjects with normosmia (74.7 ± 6.9 vs. 69.6 ± 8.0, $p < 0.001$), the two groups were not different in other clinical characteristics, including gender, disease duration, diabetes mellitus, hypertension, smoking, and APOE ε4 status. Clinical and neuropsychological characteristics across different cognitive groups are summarized in the supplementary table.

Discussion

The important finding of our study is that the odor identification deficit of the aMCI group was comparable with that of the early AD group, while the naMCI group showed better olfactory performance, similar to that of the SMI group. These results are in line with results published in the literature, which found olfactory identification impairment in AD [11, 32–34] and its association with conversion from MCI to AD [8, 18, 35–38]. The relative preservation of odor identification in the naMCI group can be explained by the heterogeneous etiologies of naMCI, which might represent prodromal stages of dementias not related to AD, such as frontotemporal dementia (FTD) or dementia with Lewy bodies (DLB). This is in contrast with aMCI, most cases of which progress to AD dementia [15]. This explanation is supported in part by a previous study that reported milder impairment of olfactory identification in FTD patients compared with AD patients [39]. The differences in olfactory performance across MCI subtypes can also be explained by the results of our correlation analysis, which revealed significant associations between performance on memory tests and CCSIT score.

The present findings might be based on AD-related neurodegeneration of the olfactory bulb and brain regions, such as the entorhinal cortex and hippocampus, which are responsible



	SMI	aMCIsd	aMMCmd	naMCIsd	naMCImd	AD	p
Normosmia	12 (70.6%)	1 (11.1%)	19 (46.3%)	8 (57.1%)	11 (78.6%)	2 (10.0%)	<0.001
Hyposmia	5 (29.4%)	8 (88.9%)	22 (53.7%)	6 (42.9%)	3 (21.4%)	18 (90.0%)	

	SMI	aMCI	naMCI	AD	p
Normosmia	12 (70.6%)	20 (40.0%)	19 (67.9%)	2 (10.0%)	<0.001
Hyposmia	5 (29.4%)	30 (60.0%)	9 (32.1%)	18 (90.0%)	

Fig. 1 CCSIT scores of subjects. Values represent the mean with standard error of the mean (*SEM*) or numbers of patients (percentage). *SMI* subjective memory impairment, *aMCI* amnestic mild cognitive impairment, *naMCI* non-amnestic mild cognitive impairment, *sd* single-domain, *md* multi-domain, *AD* Alzheimer's dementia. Analyses were performed by the χ^2 test and analysis of covariance (*ANCOVA*) controlling with age, sex, hypertension, diabetes mellitus, and smoking. *$p < 0.05$; **$p < 0.01$

for memory and olfaction. In fact, many studies have reported accumulation of AD pathology (amyloid plaques, neurofibrillary tangles, and neuropil threads) and corresponding degenerative changes in the olfactory system and related brain regions [9, 11, 40–42]. Moreover, a few neuropathological studies have addressed the association of odor identification with severity of AD pathology [12, 37, 43].

However, considering the results of our correlation analysis, which showed a significant correlation between olfactory performance and memory, pathologic changes in the central olfactory areas, rather than involvement of the peripheral olfactory system, might be the neurobiological basis of the present findings. It has been demonstrated in a meta-analysis that, among several aspects of olfaction, AD patients are more strongly impaired on high-order olfactory tasks compared with low-level perceptual tasks [44]. In addition, an image study demonstrated that there was no significant correlation between olfactory bulb volume and olfactory function, suggesting that hyposmia in AD might be related to degeneration of the central structures of the olfactory system and subsequent cognitive impairment [45].

In particular, the entorhinal cortex, which mediates olfactory information from the primary olfactory system to the hippocampus, might play a central role in AD-related odor identification deficit. While the entorhinal cortex, which is one of the earliest involved sites in AD pathogenesis [46, 47], is well known for its role in generation and retrieval of long-term memories [48, 49], it also plays an important role in integration of sensory input [47]. Furthermore, olfactory structures are the only primary sensory system components that have direct projections to the entorhinal cortex [50]. Thus, presumably, based on the degeneration of the entorhinal cortex, olfactory dysfunction can appear in the very early stage of the disease process in AD, distinct from other sensory modalities. This is consistent with previous studies that have shown that the entorhinal cortex correlates best with initial appearance of cognitive symptoms in AD [33, 51], and the volume of the entorhinal cortex well differentiates converters to AD from non-converters before the onset of overt dementia [47].

In the present study, subjects with SMI displayed olfactory test outcomes similar to those obtained by the naMCI group. Recently, SMI has been proposed as a potential indicator of AD, as associations of SMI with AD biomarkers have been increasingly reported [52–55]. A cross-sectional study indicated that subjective memory complaints correlated with olfactory identification in elderly individuals [56]. Nonetheless, results from the present study were not consistent with the abovementioned reports, as the olfactory performance of the SMI group was significantly better than those of the aMCI and early AD groups. Several considerations should be addressed

Table 2 Correlation analysis results among the CC-SIT score and the neuropsychological test results

	Spearman correlation
MMSE	0.285 (0.002)**
CDR	−0.299 (0.001)**
SOB of CDR	−0.300 (0.001)**
GDS	−0.349 (< 0.001)**
NPI	−0.098 (0.351)
Barthel ADL	0.092 (0.331)
Digit span forward	0.023 (0.809)
Digit span backward	0.185 (0.052)
Calculation	−0.091 (0.565)
Rey-Osterrieth Complex Figure copy	0.235 (0.013)*
Boston naming test	0.358 (0.002)**
Verbal learning test, immediate recall	0.395 (< 0.001)**
Verbal learning test, delayed recall	0.467 (< 0.001)**
RCFT, immediate recall	0.334 (< 0.001)**
RCFT, delayed recall	0.385 (< 0.001)**
COWAT, semantic	0.507 (< 0.001)**
COWAT, phenomic	0.246 (0.011)*
Stroop word	0.322 (0.001)**
Stroop color	0.309 (0.001)**

Analyses were performed using the Spearman rank correlation coefficients

MMSE mini-mental state examination, *CDR* clinical dementia rating, *SOB of CDR* sum of box of CDR, *GDS* global deterioration scale, *NPI* neuropsychiatric inventory, *ADL* activity of daily living, *RCFT* Rey-Osterrieth Complex Figure test, *COWAT* Controlled Oral Word Association Test

$p^* < 0.05$; $^{**}p < 0.01$

Table 3 Comparison of clinical and neuropsychological characteristics between normosmia and hyposmia groups

	Normosmia ($n = 53$)	Hyposmia ($n = 62$)	*P*
Age, year*	69.6 ± 8.0	74.7 ± 6.9	< 0.001
Male, *n* (%)**	12 (22.6%)	20 (32.3%)	0.251
Disease duration, year*	0.9 ± 0.7	1.1 ± 1.0	0.265
Hypertension, *n* (%)**	23 (43.4%)	34 (54.8%)	0.221
Diabetes mellitus, *n* (%)**	10 (18.9%)	13 (21.0%)	0.779
Smoking** Nonsmoker, *n* (%)	45 (84.9%)	51 (82.3%)	0.703
Ex-smoker, *n* (%)	8 (15.1%)	11 (17.7%)	
APOE ε4**	9 (17.0%)	17 (27.4%)	0.182
MMSE	25.6 ± 3.2	23.5 ± 4.8	0.121
CDR	0.5 ± 0.2	0.6 ± 0.3	0.043
SOB of CDR	1.4 ± 1.1	2.4 ± 2.3	0.071
GDS	2.9 ± 0.7	3.4 ± 0.9	0.031
Barthel ADL	19.7 ± 2.1	19.7 ± 0.9	0.459
NPI	4.6 ± 8.9	5.9 ± 8.0	0.449
Digit span forward	5.5 ± 1.6	5.4 ± 1.2	0.776
Digit span backward	3.4 ± 1.2	3.0 ± 0.9	0.174
Calculation	9.5 ± 2.3	9.9 ± 3.1	0.882
Rey-Osterrieth Complex Figure copy	30.1 ± 6.2	27.6 ± 8.8	0.471
Boston naming test	11.7 ± 2.3	9.9 ± 2.6	0.074
Verbal learning test, immediate recall	16.8 ± 5.9	13.4 ± 5.0	0.240
Verbal learning test, delayed recall	5.0 ± 3.1	2.2 ± 2.7	0.006
RCFT, immediate recall	12.0 ± 6.9	8.3 ± 6.1	0.239
RCFT, delayed recall	11.9 ± 6.4	7.9 ± 5.6	0.039
COWAT, semantic	28.0 ± 10.4	19.9 ± 7.1	0.014
COWAT, phenomic	19.8 ± 9.9	15.7 ± 9.3	0.221
Stroop word	107.0 ± 18.8	95.0 ± 30.1	0.059
Stroop color	71.4 ± 26.8	50.1 ± 25.9	0.081

Analyses were performed by analysis of covariance (ANCOVA) controlling with age, sex, education duration, hypertension, diabetes mellitus, and smoking; independent sample *t* test*, and the χ^2 test**

APOE apolipoprotein E, *MMSE* mini-mental state examination, *CDR* clinical dementia rating, *SOB of CDR* sum of box of CDR, *GDS* global deterioration scale, *ADL* activity of daily living, *NPI* neuropsychiatric inventory, *RCFT* Rey-Osterrieth Complex Figure test, *COWAT* Controlled Oral Word Association Test

regarding these findings. First, as previously reported, SMI is related to various conditions affecting older adults, such as personality traits, medical disorders, and medications, but these were not considered in our study. In particular, psychiatric conditions like depression can be associated with SMI [24, 56, 57] and should have been controlled for in the analysis. Second, according to recent recommendations, SMI with concerns should be distinguished from SMI without concerns [57, 58], which was not presumed to be associated with increased risk of AD dementia. In other words, SMI with concerns is truly relevant to AD dementia, and different outcomes might be revealed if we excluded SMI without concern.

Few studies have discussed odor identification in different subtypes of MCI. The results of this study are consistent with previous longitudinal cohort and case-control studies, which showed an association among olfactory impairment, incident aMCI, and progression from aMCI to AD dementia [21, 38]. In contrast to previous findings, other cross-sectional studies [8, 22] have observed a conflicting result which showed similar degree of odor identification deficit in naMCI patients and aMCI patients. Some authors also reported the olfactory impairment of naMCI as a condition precedent of FTLD, or DLB, which appears to accompany profound olfactory impairment [59, 60]. However, a noteworthy finding of each study is that the degree of olfactory identification impairment was consistently correlated with the results of memory tests among various cognitive measures. Further, even in the study that directly compared aMCI and naMCI with odor identification [22], olfactory deficit in naMCI was not associated with any cognitive correlates. Namely, on the basis of the

correlation analysis, it can be postulated that aMCI, which is characterized by deficit in memory measures, rather than naMCI has a legitimate relationship with impairment of odor identification.

There was no significant influence of the APOE ε4 allele in odor identification. Some studies have reported that APOE ε4 allele carriers have stronger associations between impaired olfaction and cognitive impairment than do non-carriers [61–63], while several longitudinal studies [8, 17, 38] did not find a significant association between olfactory performance and APOE genotype. Overall, the interaction between odor identification and APOE genotype is not consistent or strong, and the pathophysiological basis for such an association remains unclear [2].

Several limitations of the present study must be noted. First, there are questions regarding generalizability, because of the relatively small sample size, restricted ethnicity, and large proportion of female participants. Second, as the study design was cross-sectional, we could not make precise conclusions regarding the disease trajectory of our MCI subjects. Third, we did not conduct odor detection tests, and some degree of odor detection deficit could have influenced our results. The results of odor detection tests are known to be highly correlated with those of odor identification tests [5]. Lastly, it is well documented that many conditions, including drug intake, exposure to chemical agents, head trauma, systemic diseases like chronic kidney and liver diseases, and chronic alcohol abuse, can interfere with olfactory function [64–67], but we were unable to exclude people with those conditions.

In conclusion, our findings demonstrated that degree of olfactory impairment is different across MCI subtypes and is mainly driven by deficit in memory measures. Based on these results, it can be suggested that olfactory impairment is related to the pathological process of AD. Longitudinally designed studies with larger sample sizes are needed to validate this suggestion.

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