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Olfactory identification in amnestic and non-amnestic mild cognitive impairment and its neuropsychological correlates

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ABSTRACT

Background: Olfactory identification impairment in amnestic mild cognitive impairment (aMCI) patients is well documented and considered to be caused by underlying Alzheimer's disease (AD) pathology, contrasting with less clear evidence in non-amnestic MCI (naMCI). The aim was to (a) compare the degree of olfactory identification dysfunction in aMCI, naMCI, controls and mild AD dementia and (b) assess the relation between olfactory identification and cognitive performance in aMCI compared to naMCI.
Methods: 75 patients with aMCI and 32 with naMCI, 26 patients with mild AD and 27 controls underwent the multiple choice olfactory identification Motol Hospital Smell Test with 18 different odors together with a comprehensive neuropsychological examination.
Results: Controlling for age and gender, patients with aMCI and naMCI did not differ significantly in olfactory identification and both performed significantly worse than controls ($p < 0.001$), albeit also better than patients with mild AD ($p < .001$). In the aMCI group, higher scores on MMSE, verbal and non-verbal memory and visuospatial tests were significantly related to better olfactory identification ability. Conversely, no cognitive measure was significantly related to olfactory performance in naMCI.
Conclusion: Olfactory identification is similarly impaired in aMCI and naMCI. Olfactory impairment is proportional to cognitive impairment in aMCI but not in naMCI.

1. Introduction

Olfactory impairment has been demonstrated in Alzheimer's disease (AD) [10,20,36], presumably as a consequence of early degeneration of olfactory bulb, olfactory nerve and olfactory cortex situated predominantly in the medial temporal lobe [1,2,3]. Among the three major types of olfactory ability (detection, discrimination and identification), the olfactory identification is impaired earlier compared to the olfactory detection in AD patients [50]. So far, most studies with cognitively impaired patients have investigated only olfactory identification, which strongly correlates with olfactory threshold and is easier to test [9, 11,12]. The olfactory identification deficit seems to be specifically linked mainly to the temporal lobe including the amygdala, hippocampus and parahippocampal gyrus, but even anterior temporal damage is sufficient to provoke olfactory identification impairment [21].

Dementia syndrome in AD and in other degenerative disorders is almost always preceded by mild cognitive impairment (MCI) syndrome in which the patients have objective cognitive impairment on neuropsychological examination but do not show substantial deficits in activities of daily living [43,45].

MCI patients with objective memory impairment are labeled amnestic MCI (aMCI). These patients progress mainly to AD dementia [15,42,44], aMCI patients with isolated memory (amnestic) impairment are labeled as the single domain aMCI (aMCIsd), and aMCI patients with an additional impairment in the other cognitive domains beyond memory (e.g., executive impairment, language, visuospatial) are called multiple domain aMCI (aMCImd) [42,44].

Among aMCI patients, olfactory identification impairment has been demonstrated in a number of studies with a cross sectional design [8, 14,23,59]. To our best knowledge only one study also investigated other olfactory modalities beyond olfactory identification in patients with aMCI and it reported impaired olfactory detection and identification. There was also an olfactory discrimination deficit but that was

Abbreviations: MHST, Motol Hospital Smell Test.

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accounted for by an abnormal olfactory threshold [8]. Finally, olfactory impairment in aMCI represents a risk factor for subsequent cognitive decline and conversion to AD dementia, as was demonstrated by some longitudinal studies [6,53,54].

MCI patients with normal memory function but with cognitive impairment in non-memory domains (e.g. executive functions, visuospatial functions, language) are classified as non-amnestic MCI (naMCI). Patients with naMCI may convert more frequently to non-AD dementias [42,44], especially to frontotemporal lobar degeneration (FTLD), Parkinson disease and Lewy body disease (LBD) in which olfactory identification impairment is frequently found [20,29,36,46].

However, there have been only a few studies investigating olfactory functions in naMCI, which report inconsistent results [7,23,59]. Considering the evidence of olfactory identification impairment in these non-AD dementias, which are typically preceded by naMCI subtype, we would expect large olfactory impairment in patients with naMCI that may resemble that of patients with aMCI.

Association between olfactory and cognitive impairment in AD and MCI patients is not yet fully understood. The association between memory and olfactory identification performance was demonstrated only in a mixed cohort of healthy elderly and MCI patients and in a mixed cohort of MCI and dementia patients [7,8,23,48,60]. To our best knowledge the relation between olfactory identification and cognitive performance in MCI, specifically in the amnestic versus non-amnestic MCI subtypes, has not been assessed.

Because of anatomical and functional proximity of brain areas responsible for memory and olfaction (both situated predominantly in the medial temporal lobe), we would expect proportional degree of olfaction and memory impairment in pre-dementia and dementia stages of AD.

To build on previous research, the aim of this study was to:

1) Compare olfactory identification deficit in patients with aMCI vs. naMCI, as well as aMCI and naMCI vs. controls and mild AD.
2) Compare olfactory identification between patients with single vs. multiple domain aMCI.
3) Analyze the association between olfactory identification and cognitive performance in aMCI vs. naMCI.

2. Methods

2.1. Subjects

All subjects were recruited from referrals to the Memory Disorders Clinic at Motol Hospital, an affiliate of Charles University in Prague, and signed an informed consent approved by the local ethics committee. They underwent standard protocol which consisted of magnetic resonance imaging, neurological, medical and laboratory evaluation, questionnaires and complex neuropsychological assessment mentioned below. A total of 160 participants were included in the analyses.

The MCI group subjects met the revised Petersen's criteria for MCI [43]. The participants had cognitive complaints reported by themselves or by their caregiver, they were impaired on objective cognitive tasks, not demented with largely intact functional activities with CDR (Clinical Dementia Rating scale) of 0.5.

The MCI patients (n = 107) were further classified into the following groups: (*a*) *patients with naMCI* (n = 32) or (*b*) *patients with aMCI* (n = 75).

All aMCI patients had memory complaints and scored more than 1.5 of standard deviation (SD) lower than age matched controls in verbal memory tests (Auditory Verbal Learning Test [AVLT] and Enhanced Cued Recall [ECR] test).

Patients with naMCI had impairment only in the non-memory cognitive domains, manifesting in all patients as attentional-executive deficit, in addition 5 patients suffered from language deficit and 3 patients from visuospatial deficit.

Of the 75 broadly defined aMCI cases, only 18 had pure amnesia (all other tests were within the normal range — aMCIsd), while the remaining participants, labeled as aMCImd, suffered from other subtle semantic, visuoconstructive or attention-executive function deficits (more than 1.5 SD), or both.

Two other groups were used in this study:

–The control group (n = 27) Reported no cognitive problems, which was subsequently confirmed by neuropsychological testing and a CDR score of 0.0. They were recruited from staff and patient's relatives and were selected to be as similar as possible to the other groups in terms of age, education and gender.

–The mild probable AD group (n = 26) Met the Diagnostic and Statistical Manual of Mental Disorders IV criteria for dementia and the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer Disease and Related Disorders Association criteria for probable AD [32]. Patients with dementia had an impairment of memory and another cognitive domain, impaired functional activities, and their CDR was 1.0 or higher. They didn't have significant vascular impairment on brain MRI (Fazekas scale 0 or 1) [16]. All AD patients were on a stable dose of cholinesterase inhibitors for at least 3 months.

2.2. Exclusion criteria

Subjects with history of smoking in past 10 years, acute or chronic rhinitis or another ORL diagnosis causing potential hyposmia or subjects with preexisting hyposmia of another etiology (posttraumatic, professional exposure to toxics) and subjects with depression (scoring more than 5 on Geriatric Depression Scale) were excluded from the study.

2.3. Neuropsychological assessment

Following neuropsychological tests and questionnaires were administered: Clinical Dementia Rating (CDR) [38], and 15-item Geriatric Depression Scale [62]. Additional neuropsychological testing included the Mini Mental State Examination (MMSE) [17], verbal memory tests: Auditory Verbal Learning Test (AVLT) [51], 16-item version Grober and Buschke's Test with Enhanced Cued Recall (ECR) procedure [19], nonverbal memory test and visuospatial test: Rey–Osterrieth Complex Figure Test (ROCF) copy and reproduction [37], working memory attention: digit span (DS) forward and reversed [58], Trail Making Tests (TMT) A [47], executive functions: Category Fluency and Initial Letter Fluency (FAS) tests [26] and TMT B.

2.4. Smell identification assessment

In all subjects, smell identification was assessed using the Motol Hospital Smell Test (MHST) — a multiple-choice smell identification test developed and evaluated at our memory clinic [29,30]. MHST is composed of 18 odors very well known among elderly Czech population (pine-tree, peach, lemon, rose, cherry, grapefruit, clove, lavender, peppermint, orange, cinnamon, vanilla, coffee, honey, lilac, strawberry, black currant, rum). Odors are presented as essential oils in special phials in the amount of 200 μl to both nostrils simultaneously. The essential oils are replaced every 2 months in the phials in order to prevent degradation of the odor. After sniffing the odor, subjects are asked to