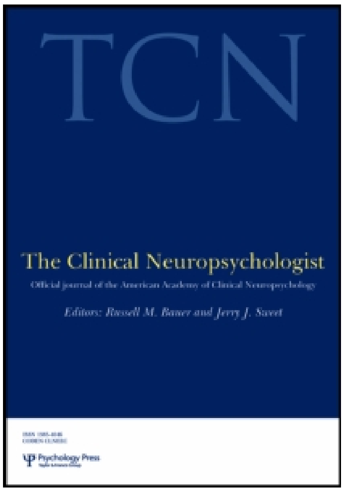

The Clinical Neuropsychologist
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713721659

Odor Identification and Self-reported Olfactory Functioning in Patients with Subtypes of Mild Cognitive Impairment

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First Published on: 11 February 2009

The Clinical Neuropsychologist, 2009, 1–13, iFirst
http://www.psypress.com/tcn
ISSN: 1385-4046 print/1744-4144 online
DOI: 10.1080/13854040802585030

ODOR IDENTIFICATION AND SELF-REPORTED OLFACTORY FUNCTIONING IN PATIENTS WITH SUBTYPES OF MILD COGNITIVE IMPAIRMENT

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Olfactory dysfunction is a very early symptom of Alzheimer's disease (AD), and olfactory dysfunction has also been found in mild cognitive impairment (MCI). The goal of the present study was to compare odor identification ability and self-reported olfactory functioning in patients with different types of MCI. We included 104 elderly participants classified into two groups: patients with mild cognitive impairment (MCI) and elderly controls (EC). Based on their performance in neuropsychological testing the study population was divided into four groups of participants based on cognitive features: amnestic MCI single domain (11), amnestic MCI multiple domain (19), non-amnestic MCI single domain (21) and non-amnestic MCI multiple domain (13), respectively. The MCI patients were compared to 40 elderly controls (EC) controls with no cognitive deficit. Comparison for odor identification revealed a significant difference between amnestic MCI multiple domain patients and the EC group. No other group comparison was significant. Statistical analyses for self-reported olfactory functioning revealed no significant group differences between any subgroup of MCI patients and the control group. Correlational analyses indicated that odor identification ability was related to cognition whereas no relationship was found for self-reported olfactory functioning. The present study showed that amnestic MCI patients with additional deficits in other cognitive domains have a specific odor identification impairment. Together with cognitive testing, olfactory testing may more accurately help predict whether or not a patient with MCI will convert to AD in the near future.

Keywords: Odor identification; Olfaction; Mild cognitive impairment subtypes; Alzheimer's disease; Dementia.

INTRODUCTION

In elderly people the transition from normal cognition to Alzheimer's disease (AD) is gradual. Affected individuals typically pass through a disease state recognized as mild cognitive impairment (MCI) with an increased risk for developing AD. Olfaction has gained increased attention in the clinical setting, and specific olfactory alterations have been found in neurodegenerative diseases.

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Accepted for publication: October 26, 2008. First published online: February 10, 2009.

Prior studies have documented decreased olfactory function in AD and MCI (Albers, Tabert, & Devanand, 2006).

Initial investigations of AD patients reported alterations in the ability to identify odorants (Doty, Reyes, & Gregor, 1987; Larsson et al., 1999; Lehrner, Brücke, Dal-Bianco, Gatterer, & Kryspin-Exner, 1997). Declined odor identification capabilities were observed in patients with questionable AD (Nordin & Murphy, 1996) and first-degree relatives of AD patients (Serby et al., 1996). Compared to age-matched controls MCI patients had inferior olfactory functions (Djordjevic, Jones-Gotman, De Sousa, & Chertkow, 2008). Odor identification deficit was not related to depression (Lehrner, Maly, Walla, Deecke, & Dal-Bianco, 2003). Electrophysiological results confirmed prior findings of olfactory dysfunction in patients with MCI (Peters et al., 2003). Impaired odor identification in individuals without overt dementia was associated with an AD-like memory impairment and an increased rate of cognitive decline (Royall, Chiodo, Polk, & Jaramillo, 2002). Among older persons without manifest cognitive impairment, difficulty in identifying odors predicted subsequent development of MCI (Wilson et al., 2007b). MCI patients who exhibited impaired odor identification had a greater risk of cognitive decline over time (Borenstein Graves et al., 1999) and were more likely to make the transition to clinical AD over a 2-year period (Devanand et al., 2000; Tabert et al., 2005).

Initially MCI was defined as a clinical condition with memory impairment with or without cognitive impairment in other domains (amnestic MCI multiple domain vs amnestic MCI single domain), implying a pre-AD state, and most research has focused on that clinical entity (Bäckman, Jones, Berger, Laukka, & Small, 2004; Petersen et al., 2001a, 2001b). However, in the meantime it has become apparent that several clinical subtypes of MCI exist and the concept of MCI has been expanded to include other types of cognitive impairment beyond memory, taking into account multiple etiologies or causes of cognitive impairment and dementia in older persons. Thus, a third clinical type of MCI is called non-amnestic MCI multiple-domain, and involves various degrees of impairment in multiple cognitive domains without memory impairment. A fourth type of MCI is non-amnestic MCI single-domain, in which a person has an impairment in a single non-memory cognitive domain. Whereas the amnestic type would likely represent a prodromal form of AD with an annual conversion rate of 10–20% per year (Bruscoli & Lovestone, 2004; Lehrner et al., 2005; Petersen et al., 2001b), the other subtypes showing impairments in non-memory domains may have a higher likelihood of progressing to a non-AD dementia such as vascular dementia, frontotemporal dementia, or dementia with Lewy bodies (Petersen, 2004; Petersen & Morris, 2005).

Due to the above-mentioned behavioral data and to neuropathological data suggesting that impaired odor identification in patients with memory impairment is partly due to the accumulation of neurofibrillary pathology in central olfactory and memory regions (Attems & Jellinger, 2006; Wilson et al., 2007a), we tested the hypothesis that patients with amnestic MCI show olfactory deficits. We also tested the hypothesis whether there is an association between cognitive scores and olfactory scores.

Thus, in the present study we investigated odor identification ability in patients with different subtypes of MCI. Furthermore, awareness of olfactory deficit as measured by self-reported olfactory functioning was also assessed. To our knowledge, no previous study has directly compared olfactory ability in MCI subtypes.

METHOD

Participants

We included 104 elderly participants classified into two groups: patients with mild cognitive impairment (MCI) and elderly controls (EC). The study protocol was in accordance with the Helsinki Declaration. The included area of the study was Vienna.

All participants received a complete neurological examination, standard laboratory blood tests, and psychometric testing. In most cases a CT scan or MRI scan of the brain was obtained. Electroencephalogram and single-photon emission computed tomography scans were performed on some patients. In determining significant cerebrovascular disease, both neuroimaging and clinical patient features were used.

Inclusion and exclusion criteria were similar to other studies. Patients were excluded from the study if any of the following conditions applied: (a) evidence of stroke as determined by neuroradiologic and clinical examination, (b) history of severe head injury, (c) current psychiatric diagnosis according to ICD-10 (Dilling, Mombour & Schmidt, 2000), however, patients with sub-clinical depression were included because (sub)-depressive symptoms often occur in elderly patients, (d) any medical condition that leads to severe cognitive deterioration including renal, respiratory, cardiac and hepatic disease, (e) less than 50 years of age, (f) diagnosis of dementia according to DSM IV (Saß, Wittchen, Zaudig, & Houben, 2003).

Neuropsychological measures

All participants were subjected to the Vienna Neuropsychological Test Battery (VNTB). The VNTB is a combination of established neuropsychological measures assessing psychomotor speed, concentration/attention, language, memory, and executive functioning domains (Lehrner, Gleiß, Maly, Auff, & Dal-Bianco, 2006; Lehrner, Maly, Gleiß, Auff, & Dal-Bianco, 2007; Lehrner et al., 2005; Lezak, 1995). Cognitive function tests were selected to assess a broad range of cognitive abilities commonly affected by AD and other dementias. Psychomotor speed was assessed using the symbol-counting task from the cerebral insufficiency test (CI; Lehrl & Fischer, 1997) and the Trail Making Test A (Reitan, 1979). The Alters-Konzentrations-Test (AKT) (Gatterer, 1990), a geriatric cancellation test, the digit symbol subtest of the German WAIS-R (Tewes, 1994), the Stroop Test from the NAI Test Battery (Oswald & Fleischmann, 1997) and the interference test from the C.I. (Lehrl & Fischer, 1997) were applied to assess attention. In order to test language functions we used verbal fluency tasks and a confrontation naming task (Goodglass & Kaplan, 1983). Naming as many animals, supermarket items, and tools that came to mind within 1 minute for each task was used to tap semantic verbal fluency. Naming as many words beginning with the letters b, f, and l, that came to mind within 1 minute for each task was used to tap phonemic verbal fluency. The modified Boston Naming Test (mBNT) (Morris et al., 1989) was used to assess naming capabilities. Episodic memory was tested using the Verbal Selective Reminding Test (VSRT: Lehrner et al., 2006), which is the Austrian paper/pencil version (Steiner, 1998) of the Memory Assessment Clinics (MAC) Grocery List Selective Reminding Test with the subtests of immediate recall, total recall, and delayed recall (Crook, Salama, & Gobert, 1986; Youngjohn, Larrabee & Crook, 1991). Executive functions were investigated using the Trail Making Test B (Reitan, 1979) as well as the score difference of the Trail Making Test A and B (Reitan, 1979), the Five-Point Test (Regard, Strauss & Knapp, 1982), and the Maze Test from the NAI Test Battery (Oswald & Fleischmann, 1997). In addition, participants completed the Geriatric Depression Scale (GDS) and the Beck Depression Inventory (BDI) in order to assess depressive symptoms.

Adequate normative data using cognitively normal participants (*N* ranging from 122 to 434 for single tests) for the VNTB were available, and a detailed description of the standardization procedures, norms, and validation is published elsewhere (Lehrner et al., 2007). Cognitively normal control participants of the normative sample were drawn from the General Hospital of Vienna including the Department of Neurology. The control participants underwent a standard medical evaluation, and were assessed as being in good health. Criteria for normal function were identified as being similar to those in the Mayo research studies (Ivnik et al., 1992; Petersen, 2004): (a) no active neurological or psychiatric disease, (b) no psychotropic medications, and (c) the participants may have medical disorders but neither they nor their treatment compromises cognitive function. They were required to have an MMSE score greater than or equal to 27 and a memory score greater than −1.5 standard deviations on the face recognition test of the MAC test battery (Crook et al., 1986).

In order to characterize the neuropsychological profile of the study sample, a *z*-score for each variable was calculated, which indicates the relative degree of impairment from normal in *SD* units, thereby allowing comparison across different cognitive tests. Because age, education, and gender effects on cognitive variables have been reported in the literature (Chandler et al., 2005), regression-based *z*-scores using the original healthy control sample (Lehrner et al., 2007) were calculated for each neuropsychological variable (after appropriate normalizing transformations if necessary; Berres, Monsch, Berasconi, Thalmann & Stähelin, 2000; Lehrner et al., 2007) using a multiple linear regression formula with age, education, and gender as regressors.

Olfactory evaluation

For assessing olfactory function we used the University of Pennsylvania Smell Identification Test (UPSIT). The UPSIT is a very commonly used odor identification test using 40 microencapsulated odors, with each presentation followed by a four-item forced choice of words. Norms have been established for age and gender (Doty, Shamson, & Dann, 1984). Patients also performed the one-item subjective olfactory capability scale (SOC), from the assessment of self-reported olfactory functioning and olfaction-related quality of life (ASOF) scale.

The SOC is a Likert scale ranging from 1 to 10 indicating olfactory performance, in which 1 indicates having a very bad sense of smell and 10 indicates very good sense of smell (Hufnagl, Lehrner & Deecke, 2003).

Procedure

Neurological examination, standard laboratory blood tests, and radiological evaluation was performed several days prior to neuropsychological testing. The neuropsychological assessment and the olfactory evaluation were performed in one session with a 30-minute break in between. In order to control for olfactory dysfunction due to nasal disease, all patients were screened for potential causes of olfactory dysfunction by interview. No patient was included if the common cold was present at examination, or complete smell loss was reported by the patients due to another reason. After the completion of the evaluation, a consensus committee meeting was held involving the neurologist, neuropsychologists, and other study personnel who had evaluated the patients in order to determine cognitive status of the participants.

Based on their performance on neuropsychological testing the study population was divided into four groups of participants based on cognitive features—Amnestic MCI single domain patients: the *z*-score of at least one memory test was below −1.5 *SD*, all other *z*-scores were greater than −1.5 *SD* (11 patients); Amnestic MCI multiple domain patients: the *z*-score of at least one memory test was below −1.5 *SD*, and at least one other *z*-score of the remaining tests was below −1.5 *SD* (19 patients); Non-amnestic MCI single domain patients: exactly one domain other than the memory domain where the *z*-scores within this domain were below −1.5 *SD* (21 patients); Non-amnestic MCI multiple domain patients: at least two tests from different domains other than memory tests below −1.5 *SD* (13 patients), respectively. The MCI patients were compared to 40 elderly controls (EC) with no cognitive deficit using the same methodological procedure including the neuropsychological test battery as described above.

See Table 1 for demographic details. The mean age did not differ among the MCI subgroups and the EC group ($p = .378$). Median education did not differ among the MCI subgroups and the EC group ($p = .523$). The percentage of females/males did not differ among the MCI subgroups and the EC group ($p = .443$). However, as expected, a Kruskal-Wallis Test revealed a significant group difference

Table 1 Demographic and clinical variables in MCI subtypes

Variables	Age (years)	Years of education median (quartiles)	Sex (male/female)	MMSE median (quartiles)
Elderly controls ($N = 40$)	66.5 ± 8.2	10.0 (8; 14)	19/21	29.0 (27.5; 29.0)
Amnestic MCI single domain ($N = 11$)	69.6 ± 7.5	12.0 (10; 16)	4/7	28.0 (26.0; 28.0)
Amnestic MCI multiple domain ($N = 19$)	68.4 ± 9.0	10.0 (8; 12)	8/11	27.0 (26.0; 28.0)
Non-amnestic MCI single domain ($N = 21$)	64.6 ± 9.3	10.0 (8; 12)	5/16	29.0 (28.0; 29.0)
Non-amnestic MCI multiple domain ($N = 13$)	64.1 ± 10.2	10.0 (9; 11)	4/9	27.0 (27.0; 28.0)

for the MMSE score ($p < .001$; H = 19.36, $df = 4$), indicating superior global cognitive performance for the EC group.

Statistical methods

The demographic variable age is described by means and standard deviation. Education and MMSE score are given as median and quartiles. Single group comparisons (EC group vs MCI subtypes) were calculated by means of the Wilcoxon Two-Sample Test. Wilcoxon Two-Sample testing was used due to the skewed distribution of the data sets and *p*-values are corrected for multiple testing (four comparisons each vs the control group) by means of the Bonferroni-Holm method. In order to examine the association between olfactory, demographic, and neuropsychological performances, correlation analysis was performed. Partial Spearman correlation coefficients between odor identification, subjective olfactory functioning, age, and MMSE score were calculated for the total group of participants, where MCI subtype was used as a partialized variable. Furthermore, partial Spearman correlation coefficients between odor identification, subjective olfactory functioning, and neuropsychological test battery variables were calculated for the total group of participants. Note that *p*-values relating to correlation coefficients were not corrected for multiplicity due to their exploratory character and have to be interpreted accordingly; *p*-values $< .05$ were considered to be statistically significant. All computations have been performed using SAS software Version 9.1 (SAS Institute Inc., Cary, NC, USA, 2001).

RESULTS

Statistical analyses comparing the EC group vs the MCI subtype groups were performed on smell identification and self-reported olfactory functioning scores. Comparison for the UPSIT revealed a borderline significant group difference between amnestic MCI multiple domain patients and the EC group after correction (corrected: $p = .05$, uncorrected: $p = .01$). No other group comparison was significant. See Figure 1 for details. The median scores for each group were as follows: EC = 33, a-MCI SD = 28, a-MCI MD = 25, Non a-MCI SD = 32, Non a-MCI MD = 28, respectively. Statistical analyses for self-reported olfactory functioning (SOC scale) revealed no significant group differences ($p = .288$) between any subgroup of MCI patients and the control group after Bonferroni-Holm correction. The median scores for each group were as follows: EC = 6, a-MCI SD = 8, a-MCI MD = 6, Non a-MCI SD = 7, Non a-MCI MD = 8, respectively. See Figure 2 for details.

Correlation analysis using partial Spearman correlation coefficients between odor identification, subjective olfactory functioning, age, and MMSE score was conducted for the total group of participants. The correlation between odor identification and subjective olfactory functioning was moderate ($r = .40$), the correlation between odor identification and age was also moderate (−.35), and the correlation between odor identification and MMSE score was also moderate ($r = .33$), all significant at $p < .001$. Because the a-MCI MD was the only MCI group that showed impaired odor identification, we calculated Spearman

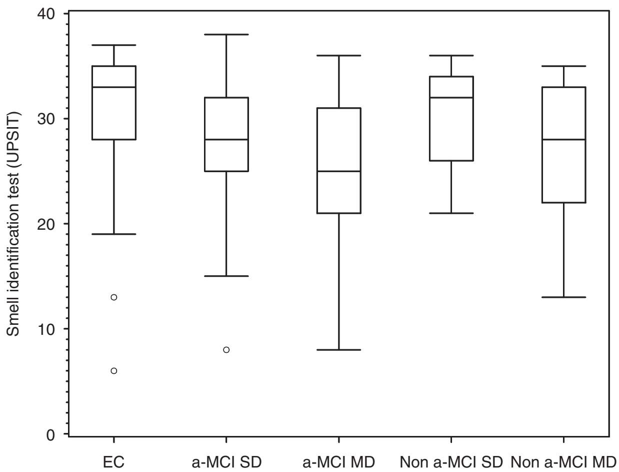

Figure 1 Performance of the elderly control group and the four MCI subtype patient groups on the Smell Identification Test (UPSIT) EC = Elderly control (N = 40); a-MCI SD = Amnestic MCI single domain (N = 11); a-MCI MD = Amnestic MCI multiple domain (N = 19); non a-MCI SD = Non-Amnestic MCI single domain (N = 21); non a-MCI MD = Non-Amnestic MCI multiple domain (N = 13).

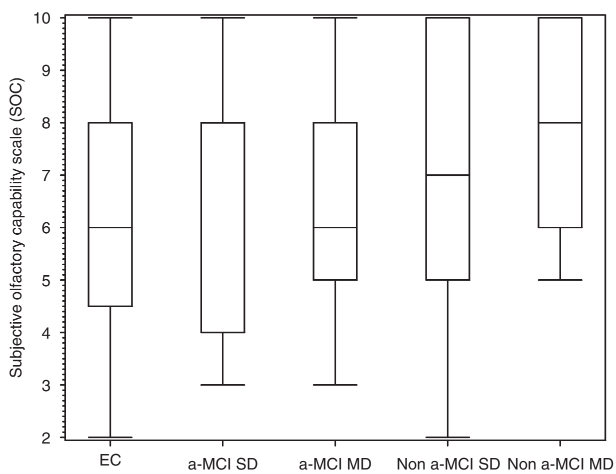

Figure 2 Performance of the elderly control group and the four MCI subtype patient groups on the subjective olfactory capabilities scale (SOC) EC = Elderly control (N = 40); a-MCI SD = Amnestic MCI single domain (N = 11); a-MCI MD = Amnestic MCI multiple domain (N = 19); non a-MCI SD = Non-Amnestic MCI single domain (N = 21); non a-MCI MD = Non-Amnestic MCI multiple domain (N = 13).

correlation coefficients between odor identification and subjective olfactory functioning for this group and the EC group. Similar moderate correlation coefficients were found ($r = .42$, $p = .08$ for the a-MCI MD group; $r = .30$, $p = .06$ for the EC group, respectively). Correlation analysis was also conducted between

Table 2 Partial Spearman correlation coefficients between performances on a battery of neuropsychological tests and odor identification, and subjective olfactory performance in the total sample of elderly controls and MCI patients

Cluster/Neuropsychological variable	UPSIT	SOC
Attention		
AKT	−.17	−.04
Digit-Symbol Test (WAIS-R)	.30**	.11
TMTA	−.16	.01
Stroop (NAI)	−.47***	−.15
Symbols counting (C.I.)	−.23*	−.06
Interference Test (C.I.)	−.28**	−.04
Memory		
Verbal memory immediate recall (VSRT)	.35***	.06
Verbal memory total recall (VSRT)	.37***	.09
Verbal memory delayed recall (VSRT)	.26**	.08
Executive function: shifting capability		
TMTB	−.26**	−.06
Difference score TMTB–TMTA	−.25*	−.07
Executive function: planning and nonverbal fluency		
Planning (Maze Test-NAI)	−.18	.00
Nonverbal Fluency (Five Point Test)	.15	.01
Language		
Semantic verbal fluency	.19	−.06
Lexical verbal fluency	.20	−.10
Boston Naming Test (mBNT)	.14	.05

AKT, Alters-Konzentrations-Test; WAIS-R, Wechsler Adult Intelligence Scale – Revised; TMTA, Trail Making Test Version A; TMTB, Trail Making Test Version B; NAI, Nürnberger Alters Inventar; C.I., Cerebral Insufficiency Test; VSRT, Verbal Selective Reminding Test; mBNT, modified Boston Naming Test; $*p < .05$, $**p < .01$, $***p < .001$.

odor identification, subjective olfactory functioning, and the tests of the neuropsychological battery. These correlation coefficients are shown in Table 2.

DISCUSSION

The present report directly compared, for the first time, odor identification and self-reported olfactory functioning in four different subtypes of mild cognitive impairment (MCI). As hypothesized, we could detect odor identification impairment in the amnestic MCI multiple domain subgroup. However, we found no reliable effect for the amnestic MCI single domain subgroup. There were no significant group differences between MCI subtypes regarding self-reported olfactory functioning.

Olfactory dysfunction in AD and MCI has been linked to neuropathological changes in the olfactory system. The olfactory bulb, olfactory anterior nucleus, and olfactory-related limbic structures are prime targets of AD pathology.

Early involvement of the olfactory bulb has been reported (Christen-Zaech et al., 2003; Jellinger & Attems, 2005; Kovacs, Cairns, & Lantos, 2001; Tsuboi, Wszolek, Graff-Radford, Cookson, & Dickson, 2003). AD-related changes affect central olfactory structures in the hippocampus, entorhinal cortex, piriform cortex, and amygdala in early stages (Averback, 1983; Braak & Braak, 1996; Reyes, Deems, & Suarez, 1993).

There is now good evidence that olfactory functions are affected early in the course of AD and it has been suggested, on both behavioral and neuropathological grounds, that the olfactory system is an early target of AD-related processes. Therefore, an early olfactory decline may be a clinical manifestation of early pathology in MCI, which has been viewed as the incipient stage of AD.

The results of our study support previous findings that odor identification is impaired in MCI patients (Albers et al., 2006). Furthermore, our data suggest that odor identification impairment is more pronounced in the aMCI–MD subtype than in other MCI subtypes. This is probably due to the fact that aMCI MD is a more progressed state of MCI with a higher conversion rate to AD compared to other MCI subtypes (Tabert et al., 2006). It is reasonable to believe that aMCI MD patients with low odor identification scores are at high risk to develop AD. This hypothesis is currently being investigated empirically in an ongoing research project in our study population.

Self-reported olfactory functioning was not related to MCI subtype status, indicating that MCI patients do not overrate their sense of smell as has been reported for AD patients (Nordin, Monsch, & Murphy, 1995). Specifically, the a-MCI MD group was the only MCI group that showed impaired odor identification, and as a group they did not overrate their sense of smell as they had similar median scores as the controls. Additional correlational analyses showed a moderate association between UPSIT scores and subjective olfactory functioning scores in both groups, indicating a similar relationship for objective and subjective olfactory functioning. However, Devanand and colleagues (2000) reported that patients with low olfaction scores, who reported no subjective problems with smelling, were more likely to develop AD. The role of self-reported olfactory functioning for the prediction of conversion to AD in our patient cohort is also currently being investigated.

Concerning the relationship between olfactory functioning and cognitive measurers, we found the postulated association between verbal memory and odor identification. Additionally, our analyses indicated an association between odor identification and measures of executive function (shifting capability) and measures regarding attention. Both measures can be conceptualized as working memory components, indicating that impaired olfaction as measured by the UPSIT may be due to compromised working memory function. An association between olfaction and cognition in MCI patients has also found by other researches (Djordjevic et al., 2008; Wilson et al., 2007b). Self-reported olfactory functioning was not related to cognitive test results. The finding of an association between olfactory status and memory status supports the view that perhaps memory dysfunction and olfactory dysfunction shared a common neuropathologic substrate at the time of testing. The fact that we also found an association with frontal-executive functions may indicate that there is a link between early frontal AD pathology and olfactory functions measured by means of odor identification.

The present study had a number of limitations. First, the findings are based on a selected group of MCI patients in a specialized memory outpatient clinic, and the results from this study may not generalize to other settings. Furthermore, it remains to be seen whether other research, using different neuropsychological measurers to define MCI subtypes, will support our findings. Finally, the small patient numbers of our MCI subtype groups limited the statistical power of the study.

In conclusion, the results of the present study show that amnestic MCI patients with additional deficits in other cognitive domains have a specific odor identification impairment. Future studies are needed to replicate this finding and further validate the association between cognitive dysfunction and olfactory deficit. Together with cognitive testing, olfactory testing may more accurately help predict whether or not a patient with MCI will convert to AD in the near future.

ACKNOWLEDGEMENT

We would like to thank Arinya Eller for proof reading the manuscript.

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