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Long-term Olfactory Functions in Patients with Subjective Cognitive Decline and Mild Cognitive Impairment

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Abstract

Introduction Olfactory function is known to be impaired in patients with Alzheimer's disease (AD) as well as in subjective cognitive decline (SCD) and mild cognitive impairment (MCI), which are generally considered at-risk states for developing AD. The aim of the study at hand was to identify predictors of self-reported olfaction capability (SOC), self-reported capability of perceiving specific odors (SRP), olfaction-related quality of life (ORQ), and odor identification (OIT) in patients with SCD, naMCI, and aMCI.

Methods The sample consisted of 33 patients with SCD, 88 with naMCI, and 43 with aMCI who consulted the Department of Neurology, Medical University of Vienna, due to memory complaints between January 2001 and May 2018. Olfactory function was assessed objectively by means of the Sniffin' Sticks odor identification test (OIT) and subjectively by means of the ASOF-scores SOC, SRP, and ORQ at two to three points in time, with an average time interval of 39 months between the first and second examination, and 24 months between the second and third examination. Linear mixed models were used in order to identify clinical and demographic variables as predictors of mean SOC, SRP, ORQ, and OIT throughout the observation period.

Results There was a statistically significant — albeit small — time-related decline of SOC and ORQ in the SCD group but not in other groups. Throughout the observation period, estimated ORQ was significantly higher in the SCD group than in the naMCI and estimated OIT was significantly higher in the naMCI group than in the aMCI group after adjusting for time of measurement and other covariates. Positive relationships between OIT and all three ASOF-scores, negative relationships between BDI-II and SOC and ORQ, and a positive relationship between WST-IQ and SRP were identified.

Conclusion There is a statistically significant, albeit small, time-related decline of uncertain clinical relevance in subjective measures of olfactory capability and olfaction-related quality of life in patients with SCD.

Implications In all subgroups, objectively measured odor-identification scores have a significant impact on subjective scores over time. The study at hand confirms previous observations regarding the negative influence of depression on subjective perception of olfactory capabilities known from cross-sectional studies.

Keywords Cognitive dysfunction · Neuropsychology · Olfaction · Memory

Introduction

The underlying pathophysiological processes of Alzheimer's disease (AD) precede the onset of AD dementia by many years. Mild cognitive impairment (MCI) and subjective cognitive decline (SCD) are diagnostic entities that are associated with increased probabilities of developing AD and are frequently referred to as prodromal stages of dementia. By nature, these diagnoses fit highly heterogeneous groups of patients. Underlying etiology and progression vary considerably between patients.

Olfactory deficits are well-documented in MCI and AD. There is increasing evidence for reduced odor identification in SCD (Jobin et al. 2021). Typically the domain that is most impaired is odor identification, which leads to significantly poorer performance in odor identification tests such as UPSIT odor identification test (OIT) or Sniffin' Sticks OIT (Roalf et al. 2017).

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Subjective over- and underestimations of odor identification capability are commonly observed in both healthy and olfaction-impaired samples. Underestimation was found to be more common in patients with depression (Hur et al. 2018) while over-estimation occurs more frequently in neurodegenerative diseases such as AD or Parkinson's disease (Devanand et al. 2000; Leonhardt et al. 2019), with increasing age and decreasing cognitive capabilities (Nordin et al. 1995; Devanand et al. 2000; Wehling et al. 2011).

Reports regarding the correlation between subjective reports on olfactory function and objective assessments vary. Using a relatively small sample, Bahar-Fuchs et al. found that correlations between subjective and objective assessments of olfactory function were poor in both healthy elderly controls and patients with aMCI and AD (Bahar-Fuchs et al. 2011), suggesting that unawareness of olfactory impairment occurs in both healthy aging and neurodegenerative disease.

Contrarily, Tahmasebi et al. used the Subjective Olfactory Capability (SOC) scale, which asks patients to rank their olfactory capabilities on a scale from one to ten and found a significant moderate correlation between the objective OIT score and the SOC score in patients with AD, aMCI, and SCD and small but still significant correlation in patients with naMCI (Tahmasebi et al. 2019).

While evidence implies that subjective ratings of olfactory capability are not sufficient to detect hyposmia in patients with AD or its putative prodromal stages, the discrepancy between subjective and objective ratings might be relevant for predicting conversion to AD (Devanand et al. 2000).

Olfaction plays an important role in many aspects of life, including but not limited to avoidance of danger, mating, preparation and consumption of food, personal hygiene, and even professional life.

Different studies observed various effects of olfactory dysfunction, including increased or decreased BMI (Patel et al. 2015; Fluitman et al. 2019), decreased number of sexual relationships in males and decreased perceived relationship security in women (Croy et al. 2013), impairments in professional life (Temmel et al. 2002; Brämerson et al. 2007), and reduced health-related quality of life (Neuland et al. 2011).

While it is evident that olfactory dysfunction can impair various aspects of daily life, correlation between subjective ratings and objective measures of olfactory function, such as the Sniffin' Sticks test, has been found to be either moderate, weak, or non-existent, depending on the sample and instruments for assessing subjective perception that have been used (Marschner et al. 2010; Bahar-Fuchs et al. 2011; Neuland et al. 2011; Pusswald et al. 2012). Consequently, the necessity arises to assess how daily life of an individual is affected by olfactory dysfunction.

The goal of the study at hand was to investigate the influence of time, diagnostic subgroup, and other demographic and clinical variables on SOC, SRP, ORQ, and OIT in patients with SCD, naMCI, and aMCI in a longitudinal setting. We hypothesized that all olfaction-related scores would decline over time and would correlate negatively with age and depression scores and correlate positively with MMSE scores. Furthermore, we hypothesized that subjective olfaction scores (SOC, SRP, ORQ) would correlate with OIT and that group differences in olfaction scores would exist between diagnostic subgroups (SCD, naMCI, aMCI).

Materials and Methods

Participants

All patients came to the Department of Neurology, Medical University of Vienna, due to memory complaints. The sample for the first and second assessment consisted of a total of 164 patients (43 with an initial diagnosis of aMCI, 88 with naMCI, 33 with SCD). The sample for the third assessment consisted of 56 patients (13 with an initial diagnosis of aMCI, 29 with naMCI, 14 with SCD).

Inclusion criteria required patients to satisfy the diagnostic criteria of either SCD, naMCI, or aMCI on at least two consecutive examinations. No longer satisfying the diagnostic criteria for either of the three subgroups led to exclusion of four patients (two who had developed AD and two who no longer reported neither subjective nor objectively measurable cognitive impairment at the second examination), while conversion between diagnostic entities did not lead to exclusion and patients remained in the same diagnostic subgroup they were initially assigned to.

Exclusion criteria included (a) current radiologic or clinical evidence or past history of stroke, (b) traumatic brain injury, (c) psychiatric disorders other than (sub-) depressive symptoms, (d) dementia, and (e) other severe medical conditions (such as cardiac or respiratory disorders) significantly affecting cognitive abilities.

Psychometric Testing

The Vienna Neuropsychological Test Battery (NTBV) was used for assessment of cognitive performance and diagnosis of SCD and MCI. It covers multiple domains of cognition commonly affected by neurodegenerative disease (Lehrner et al. 2007). The NTBV consists of multiple tests, covering the domains of attention, language, executive functioning, and memory which are commonly affected by Alzheimer's disease and other forms of dementia.

Furthermore, Mini Mental State Test (MMSE) (Folstein et al. 1975) which is commonly used in both clinical practice

and literature as a screening tool for cognitive decline and the Wortschatztest (WST-IQ) which aims to assess comprehension of language and verbal intelligence have been performed with every patient.

Presence and severity of depressive symptoms was assessed by means of the Beck-Depressions-Inventar, version II (BDI-II) (Hautzinger et al. 2009). BDI is a screening tool for depression consisting of 21 multiple-choice items that aim to capture aspects of life commonly impaired in depression, such as mood, quality of sleep, sexual life, and appetite throughout the past 4 weeks. Items of BDI-II haven been designed to match the DSM-IV criteria for diagnosis of major depression.

Subjective and Objective Assessment of Olfaction

Patients rated their olfactory function by means of the questionnaire for the assessment of self-reported olfactory functioning and olfaction-related quality of life (ASOF) (Pusswald et al. 2012).

The ASOF-questionnaire consists of 12 questions, covering three independent domains that aim to capture subjective reports on different aspects of olfaction:

- *Subjective Olfactory Capability (SOC)* domain, consisting of a single item rated 0–10 asking the patient to rate his subjective olfactory capability within the last 4 weeks.
- *Smell-Related Problems (SRP)* domain, consisting of five items rated 1–5 asking the patient to state how frequently he faced specific olfaction-related problems (e.g., perceiving one's own body odor) within the last 4 weeks.
- *Olfaction-Related Quality of life (ORQ)* domain, consisting of 6 items rated 1–5, asking the patient to rate the degree of impairment in specific areas of daily living (e.g., sexual life).

The SOC score ranges from 0 to 10 and is equivalent to the response to the related single-item question. For the SRP and ORQ score, arithmetic means are calculated. All three scores have been shown to have very good psychometric properties (reliability and validity) in normosmic patients as well as in patients with olfactory dysfunction (Pusswald et al. 2012) and have been shown to discriminate significantly between healthy controls and a sample of 35 patients with olfactory dysfunction due to posttraumatic, postviral, or idiopathic causes.

The ASOF-questionnaire is available at www.psimistri.com.

Objective olfactory function was tested by means of the Sniffin' Sticks odor identification test (OIT). This test consists of 16 multiple-choice items, each of which asks candidates to identify an odor dispensed by a pen-like odor-dispensing device. The test includes multiple stimuli that only trigger olfactory nerve-responses, multiple stimuli that trigger both olfactory-nerve and trigeminal nerve-responses, a single stimulus that triggers only trigeminal responses, and a negative control.

This test has been shown to be highly sensitive to age-related decline of olfactory functions and is highly suitable for clinical use (Hummel et al. 2007).

Procedure

Tests were conducted at two or three different points in time between January 2001 and May 2018, with an average time interval of 26.7 months between the first and second assessment and 24.9 months between the second and third assessment.

At the first examination, patients received a thorough neurologic examination, a standard blood examination, and psychometric testing. Most of them received either a CT- or MRI-examination.

Diagnosis of the at-risk states for developing AD (SCD, naMCI, or aMCI) was made by a consensus committee, considering the results of all executed examinations and using the scores on the Vienna Neuropsychologische Testbatterie (NTBV) (Lehrner et al. 2007) in order to differentiate between SCD and MCI.

Patients with objectively measurable cognitive deficits, defined as having a z-score of −1.5 SD or less below the age- and education-corrected norms, revealed through neuropsychological tests were diagnosed with MCI based on the Petersen criteria (Petersen et al. 1999).

Patients with MCI who showed impairment in the domain of memory, defined as having a z-score of −1.5 SD or less on a memory test, were assigned the diagnosis amnestic MCI (aMCI), while patients who only showed impairment in other domains, but not in the domain of memory, were diagnosed with non-amnestic MCI (naMCI).

Patients with subjectively perceived cognitive deterioration who did not show objectively measurable cognitive deficits (achieving a z-score above −1.5 SD) were diagnosed with SCD (Jessen et al. 2014).

Patients received the recommendation of undergoing further examination within 2 years of the last examination but were free to choose whether or not and when to take part in the examinations. As a result, follow-up periods were highly variable between patients and many patients have not yet undergone a third examination until May 2018.

At each examination, self-reported measures of olfactory capability (by means of ASOF-scores), objective measures of olfactory capability (by means of Sniffin' Sticks OIT), and psychometric tests (MMSE, WST-IQ, BDI-II) were captured. Furthermore, diagnosis was reevaluated at each examination, but patients remained in the same subgroup according to their initial diagnosis for statistical analysis.

Statistical Methods

All statistics have been calculated using IBM SPSS Statistics 25. Significance level for all tests was set to $\alpha = 0.05$. A two-level linear mixed model was calculated separately for each olfaction score (SOC, SRP, ORQ, OIT) in order to identify demographic and clinical variables as predictors of olfaction scores. An unstructured covariance structure was used. Inclusion of random effects was evaluated where applicable, but no random effects were kept in any of the models as they were not found to improve the fit in any case, essentially resulting a form of analysis that is equivalent to multivariate regression. For each patient, either two or three data points were included in the model, depending on how many examinations the patient took part in. Only data points where the patient satisfied diagnostic criteria of SCD, naMCI, or aMCI were included in the analysis, leading to the a priori exclusion of four patients who no longer satisfied diagnostic criteria of SCD, naMCI, or aMCI by the second examination (two who had developed AD, two who were considered healthy) and exclusion of the third data point for two more patients who had developed AD by examination three.

Results

Refer to Table 1 for descriptive evaluation of demographic and clinical properties of the sample.

Conversion Between Diagnostic Entities

Between the first and second examination, conversions to diagnostic entities further downstream the putative trajectory towards AD occurred at the following rates: In patients initially diagnosed with SCD (33), 9 (27%) had developed naMCI and 6 (18%) had developed aMCI. In patients initially diagnosed with naMCI (85), 15 (18%) had developed aMCI and 2 (2%) had developed AD and were thus excluded from the analysis.

In patients who underwent three examinations, conversion rates between the second and third examination were as follows: Out of 14 patients diagnosed with SCD, 4 (29%) converted to naMCI, one converted to aMCI (7%), out of 29 patients with naMCI, 3 (10%) converted to aMCI, and one (3%) converted to AD. One patient (8%) with aMCI converted to AD.

The remaining patients either remained stable or converted to diagnostic entities further upstream the putative directory towards dementia (e.g., from aMCI to SCD).

Predictors of SOC

Initial diagnosis did not significantly predict Subjective Olfactory Capability (SOC) in this model ($F(2, 159.206) = 2.477$, $p = 0.087$), but the interaction between time of measurement and diagnosis significantly predicted SOC ($F(2, 220.154) = 5.016$, $p = 0.007$).

Table 1. Demographic and clinical variables

	SCD			naMCI			aMCI		
	Assessment 1	Assessment 2	Assessment 3	Assessment 1	Assessment 2	Assessment 3	Assessment 1	Assessment 2	Assessment 3
N	33	33	14	88	88	29	43	43	13
Age*	64 (59, 70)	67 (61, 74)	65.5 (60, 74.75)	66 (59, 72)	70 (63, 75)	71 (64, 74)	69 (61, 72)	70 (63, 75)	72 (66, 74)
Sex	52% female	52% female	57% female	67% female	67% female	72% female	44% female	44% female	53% female
Education**	12 (9, 16)	12 (9, 16)	12 (11.25, 13.75)	11 (8, 14)	11 (8, 14)	12 (8, 16)	12 (9, 16)	12 (9, 16)	15 (10, 18)
MMSE*	29 (29, 30)	28 (28, 29)	29 (27.5, 30)	29 (27, 29)	29 (27, 29)	28 (27, 29)	28 (27, 29)	28 (27, 29)	28 (27, 29)
BDI-II*	8 (4, 14)	9 (4, 13)	9 (2.25, 13.5)	10 (5, 15)	8 (6, 15)	10 (4, 14)	9 (6, 15)	8 (5, 14)	6 (1, 11)
WST-IQ*	118 (107, 122)	114 (110, 122)	118 (111, 125)	110 (101, 118)	110 (99, 118)	110 (97, 116)	111 (101, 118)	114 (104, 118)	114 (99, 125)
SOC*	8.5 (8, 10)	8 (5, 9)	9 (7, 10)	8 (5.5, 9)	8 (5, 9)	8 (6.5, 9)	8 (5, 9.5)	7 (5, 9)	8 (4.75, 9)
SRP*	4.9 (4.15, 5)	4.6 (4.35, 5)	5 (4.4, 5)	4.6 (3.8, 5)	4.6 (3.8, 5)	4.4 (3.7, 5)	4.6 (3.6, 5)	4.2 (3.4, 4.8)	4.6 (4.35, 5)
ORQ*	5 (5, 5)	5 (4.5, 5)	5 (2.5, 5)	5 (3, 5)	5 (1.4, 5)	5 (4.4, 5)	5 (1.4, 5)	5 (1.4, 5)	5 (1.4, 5)
OIT*	13 (11, 14)	13 (9.75, 14)	13 (11, 14)	13 (11.5, 14)	12 (11, 14)	13 (11, 14)	12 (9.5, 13)	11 (9, 13)	12 (8.75, 13)

*Median (Q1 | Q3)

**Years of education in school

In patients with SCD, there was a significant negative relationship between time of measurement and SOC, $b = -0.0181$ ($p < 0.001$), indicating an estimated decline of approximately 0.19 scale points per year. In aMCI, there was a similar, albeit non-significant negative trend in SOC over time ($b = -0.015$, $p = 0.054$). In naMCI, time of measurement did not significantly predict SOC ($b = 0.002$, $p = 0.655$).

The OIT score significantly predicted SOC ($b = 0.218$, $p < 0.001$). BDI-II had a negative relationship with SOC ($b = -0.051$, $p = 0.003$). While the relationship between OIT and SOC remained significant in all subgroups, the relationship between BDI and SOC only remained significant in patients with SCD.

Predictors of SRP

Neither diagnosis ($F(2, 161.828) = 0.106$, $p = 0.899$), time of measurement ($F(1, 242.739) = 3.479$, $p = 0.063$), nor the interaction between diagnosis and time significantly predicted capability of perceiving specific odors (SRP). Highly significant positive relationships were identified between SRP and both the OIT score ($b = 0.104$, $p < 0.001$) and the WST-IQ score ($b = 0.017$, $p < 0.001$).

Predictors of ORQ

Initial diagnosis significantly predicted Olfaction-related quality of life (ORQ) ($F(2, 155.366) = 4.355$, $p = 0.014$). Estimated ORQ after adjusting for other covariates was significantly higher in patients with SCD (4.790) than in patients with naMCI (4.625) ($p = 0.004$).

Time of measurement did not significantly predict ORQ ($F(1, 147.613) = 2.675$, $p = 0.104$), but the interaction between diagnosis and time of measurement significantly ($F(2, 145.087) = 4.104$, $p = 0.018$) predicted ORQ. In patients with SCD, there was a small but significant negative trend in ORQ over time ($b = -0.005$, $p = 0.012$). In naMCI ($b = 0.002$, $p = 0.150$) and aMCI ($b = 0.000$, $p = 0.536$), there was no significant relationship between time of measurement and ORQ.

Predictors of OIT

Initial diagnosis significantly predicted Sniffin' Sticks score ($F(2, 153.867) = 3.826$, $p = 0.024$). Estimated mean Sniffin' Sticks score after adjusting for covariates was significantly lower in aMCI than in naMCI. Other subgroup differences were not significant.

Neither time ($F(1, 207.330) = 2.551$, $p = 0.112$) nor the interaction between time and diagnosis significantly predicted Sniffin' Sticks score. MMSE had a highly significant positive relationship with Sniffin' Sticks score ($b = 0.307$, $p < 0.001$). Age had a highly significant negative impact on Sniffin' Sticks score ($b = -0.093$, $F(1, 159.715) = 22.131$, $p < 0.001$).

Discussion

SOC, SRP, ORQ, and OIT in patients with SCD, naMCI, and aMCI have been analyzed cross-sectionally in previous studies. The aim of this study was to investigate the progression of SOC, SRP, ORQ, and OIT in patients diagnosed with the diagnostic entities mentioned above longitudinally.

Cross-sectional studies found no significant difference in mean SOC, SRP, and ORQ between patients with SCD, naMCI, and aMCI. Significant differences were found however, when comparing mean ASOF-scores of patients with SCD, naMCI, and aMCI to healthy controls or patients with AD (Ruttinger 2019; Tahmasebi et al. 2019).

Note that the study at hand did not include healthy controls or patients with AD. In general, prior findings regarding predictors of SOC, SRP, and ORQ from cross-sectional studies (Sniffin' Sticks OIT, BDI-II, and SRP) have been confirmed in this longitudinal setting.

Similar to cross-sectional studies that found no difference in mean SOC, SRP, and ORQ between diagnostic subgroups, this study found that initial diagnosis did not significantly predict SOC or SRP. The diagnostic subgroup was however significantly predictive of ORQ and a significant difference between patients with SCD in naMCI in estimated mean ORQ after adjusting for other covariates was identified.

Regarding objectively measured odor identification scores, the diagnostic subgroup predicted OIT scores. Patients with naMCI had a higher estimated mean Sniffin' Sticks OIT after adjusting for other covariates than patients with aMCI. Other pairwise differences were not significant. This is not concordant with previous findings by Tahmasebi, who found significantly lower mean OIT scores in patients with aMCI than patients with naMCI and SCD (Tahmasebi et al. 2019). While this study did not adjust for covariates such as age, group differences in these variables were non-significant.

One issue that comes with the longitudinal design of this study is that diagnoses of SCD, naMCI, and aMCI are unstable by nature. This is reflected by the relatively high conversion rates that were found in this study. Conversion occurred not only to diagnostic entities that are located further downstream on the theoretical trajectory towards AD, but also in the opposite direction (e.g., conversion from MCI to SCD). These findings were to be expected due to how heterogeneous these groups of patients and the underlying etiologies of their (perceived) cognitive impairment are. It is reasonable to assume that in a significant portion of patients, cognitive impairment was due to transient, non-AD-related causes.

For this study, patients were assigned to subgroups based on their initial diagnosis. Note that only initial diagnosis was considered when evaluating the influence of diagnosis on the progression of SOC, SRP, ORQ, and OIT.

Objectively measured odor-identification capability significantly predicted SOC, SRP, and ORQ throughout the follow-up period, implying that subjective reports on olfactory capabilities reflect actual objectively measured olfaction skills at least to some degree in this sample of patients. These findings are in line with previous studies, which found weak to moderate correlations between SOC, SRP, and ORQ in patients with SCD, naMCI, and aMCI in cross-sectional studies (Ruttinger 2019; Tahmasebi et al. 2019).

Correlations between measured OIT scores and self-reported olfactory capabilities were also reported using instruments other than ASOF to capture subjective ratings. Welge-Luessen et al. used a visual analog scale for rating subjective olfactory capability and identified a significant correlation between subjective reports and objectively measured OIT scores (Welge-Luessen et al. 2005). Furthermore, they found that anosmic individuals perceived their olfactory capabilities to be significantly lower than hyposmic and normosmic individuals.

On the other hand, multiple earlier studies using instruments other than ASOF and one study using the SOC score (Pusswald et al. 2012) for assessing subjective perception of olfactory capability showed poor prediction of objective odor identification capability by subjective reports and either weak or no correlation between subjective scores and objectively measured odor identification scores (Marschner et al. 2010; Bahar-Fuchs et al. 2011). Landis et al. performed both objective odor identification tests and subjective rating of olfactory capability in healthy individuals and found that correlation between OIT and subjective ratings only existed, when capturing subjective ratings after objective testing (Landis et al. 2004). This may lead to the conclusion that subjective ratings of olfactory capability are rather unreliable in predicting actual olfactory capability in healthy individuals due to limited attention to sense of smell in everyday life. Note that the study performed by Landis and Konnerth included patients with airway infections and that nasal patency was measured and correlated strongly with subjective ratings of olfactory capability when asking patients to rate olfactory capability before conducting smell tests.

SOC and ORQ showed a small, albeit significant time-related decline in patients with SCD but not in patients with naMCI and aMCI. Literature suggests cut-off values for clinical relevance of impairment of SOC (Pusswald et al. 2012), but not for time-related changes, making it hard to judge the clinical relevance of this finding. Extrapolating the amount of decline of estimated SOC and ORQ, by means of multiplying the slope calculated in the regression model, might serve in making these findings more intuitively understandable. This yields a hypothetical decline of −1.08 scale points for SOC and −0.3 scale points for ORQ in a 5-year period. One might reasonably assume that such a small change would not be clinically relevant. The fact that SOC and ORQ remained more stable in patients with (n) aMCI is concordant with the previous finding that awareness of hyposmia is considerably lower in patients with naMCI and aMCI than in patients with SCD and healthy controls (Tahmasebi et al. 2019).

Previous studies using a longitudinal design and a sample of elderly participants with three examinations similar to this study found a significant age-related decline in OIT (Wehling et al. 2011, 2016). While the study at hand confirmed previous findings regarding correlation between baseline age and OIT, there was no significant time-related decline in OIT as shown in the other studies.

Besides the obvious differences in sample, limitations regarding study design might explain why the study at hand failed to show a time-related decline in OIT. While mean observation periods were only slightly longer in the previously mentioned studies, variance in observation periods and number of missing values on the third examination were considerably lower, what might be the reason why time-related decline was not significant in this study. Regarding SRP, one might hypothesize that encounters of smell-related problems did not tend to increase with time as patients might have been less involved tasks requiring intact olfaction (e.g., cooking) with increasing age.

The association between SRP and WST-IQ, as previously identified by Ruttinger in a cross-sectional context, has been confirmed — in the sense of WST-IQ being a predictor of SRP — in this longitudinal setting (Ruttinger 2019).

Regarding depression, it was found that that both SOC and ORQ decreased significantly with increasing BDI-II scores. These results are in line with multiple previous studies reporting that patients with depression generally rated their olfactory capabilities lower than patients without depression and other studies finding higher prevalence of depression in patients with olfactory impairment. Furthermore, this is concordant with findings by Ruttinger and Tahmasebi who found significant correlation between BDI-II scores and the SOC, SRP, and ORQ scores cross-sectionally (Ruttinger 2019; Tahmasebi et al. 2019). Besides the effect depression has on the perception of one's olfactory capability, Croy proposed that olfactory impairment itself might play a role in the development of depression due to its impact on quality of life (Croy et al. 2011).

Regarding objectively measured odor identification scores, as previously established, age and MMSE significantly predicted OIT scores (Deems et al. 1991; Devanand et al. 2000; Wehling et al. 2016).

Surprisingly, SOC, SRP, and ORQ were not related to age at baseline in both the study at hand and in a previous study

using a sample of healthy controls and patients with olfactory deficits due to postviral, posttraumatic, or idiopathic etiologies (Pusswald et al. 2012). The fact that age did not predict subjective ratings of olfactory capability is particularly interesting when considering that negative correlations between age and odor identification scores are well established in literature (Deems et al. 1991; Wehling et al. 2016).

Limits and Outlook

Follow-up periods varied considerably between patients and only a limited number of patients underwent all three examinations as recommended. Patients who had developed AD by the time of the second examination were excluded from the sample. Furthermore, the rate of conversion to AD throughout the follow-up period was relatively small in this sample when compared to other studies (Mitchell and Shiri-Feshki 2009). One might hypothesize that patients who had more favorable long-term outcomes were more likely to take part in a second and third examination. It is therefore reasonable to suspect a certain amount of selection bias towards patients with more benign etiologies of SCD, naMCI, and MCI being overrepresented in the sample. This might explain why OIT tended to remain relatively stable throughout the observation period.

Future longitudinal studies with less variance in observation period between patients and less missing values could possibly reveal significant time-related trends in SOC, SRP, and ORQ and Sniffin' Sticks OIT in a comparable sample. Furthermore, insight might potentially be gained from analyzing long-term progression of SOC, SRP, and ORQ in healthy individuals.

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Declarations

Conflict of Interest The authors declare no competing interests.

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