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Neurocognitive testing in predicting conversion to Alzheimer's disease

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Abstract

Introduction Alzheimer's disease (AD) is a neurodegenerative disorder that affects memory, thinking, attention, and emotion or AD. Smelling problems are frequent symptoms of dementia. The aim of this study was to evaluate whether it is possible to predict if someone with anosmia or hyposmia has a higher risk of getting dementia or even AD.

Methods This study was a retrospective longitudinal study, and the data used were part of a larger research project, the Vienna Conversion to Dementia Study. The 173 participants were divided into four groups based on cognitive features such as healthy control (HC), subjective cognitive decline (SCD), non-amnestic mild cognitive impairment (naMCI), and amnestic mild cognitive impairment (aMCI). Olfactory assessment and neurocognitive assessment were administered.

Results We found that 30.5% of aMCI patients converted into AD after an average of about two years. The corresponding ROC analyses for olfactory testing showed that Sniffin' Sticks revealed significant results regarding the conversion to AD, whereas the Assessment of Self-Reported Olfactory Functioning and olfaction-related quality of life (ASOF) inventory using the Subjective Olfactory Capability (SOC) subscale, the Smell-Related Problems (SRP) subscale, and the Olfaction-Related Quality of life (ORQ) did not. A logistic regression showed that among the olfactory test procedures, only the Sniffin' Sticks enabled a relevant prognosis. Including neurocognitive measures in the model, only VSRT and the Trail Making Test-B. The other predictors did not contribute to the prediction of conversion to AD.

Conclusion Unlike self-reporting of olfactory functioning, olfactory testing using standardized tests may have potential for predicting dementia, especially AD. However, olfactory tests have lower predictive power than neurocognitive tests such as verbal memory and divided attention tests.

Implications Diagnostic tools for predicting dementia as accurately and early as possible are important. Olfactory assessment, compared to neurocognitive tests for verbal memory and divided attention, is inferior in predicting the prognosis of AD.

Keywords Dementia · Neuropsychological testing · Olfactory function · Quality of life · Smelling ability

Introduction

Olfactory deficits have been found to be relatively prevalent in large population-based studies (Yang and Pinto 2016). They occur as either qualitative or quantitative impairments occur due to various etiologies, including trauma, viral upper respiratory tract infections, nasal or sinus disease, and neurodegenerative diseases. Among the neurodegenerative diseases, it is not only Alzheimer's disease (AD) that displays olfactory dysfunction but also other forms of dementia like vascular dementia, Parkinson's disease, and frontotemporal dementia (Alves et al. 2014). The prevalence of olfactory dysfunction is estimated to be 3.8% in adults between the ages of 21 and 84 and to increase with age, from 0.6% in those < 35 years to 13.9% among those ≥ 65 years. There is a higher prevalence in men (Schubert et al. 2012).

There are differences between AD and other dementias when it comes to a decrease in olfactory function. For one Olfactory function is highly impaired in AD. More precisely, it occurs in 100% of these patients, compared to 96% of patients with frontotemporal dementia (Pardini et al. 2009) and about 15% of patients with vascular dementia (Duff et al. 2002). Patients with Parkinson's disease show similar impairment as AD patients (Chou and Bohnen 2009).

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Years before AD is diagnosed, patients can experience several preclinical stages, which can start with subjective cognitive decline (SCD) not yet severe enough to be measured in objective memory tests. The next stage begins when patients suffer mild cognitive impairment (MCI). Unlike patients with impairments in cognitive function, participants with normal cognitive function are aware of subtle memory deficits. These are just not yet severe enough to be measured in objective memory tests. Therefore, subjective memory complaints can predict cognitive decline only in individuals with normal baseline cognition (Geerlings et al. 1999; Murphy and Levine 2010; Wehling et al. 2011). There are theories that the frontal lobe can compensate and help retain objective memory performance (Erk et al. 2011). Thus, these findings demonstrate that subjective memory complaints are early markers of dementia in the elderly population, despite the apparently low reliability of memory self-assessments, and this might also be true when it comes to complaints about olfactory function (Stanciu et al. 2014).

The question of interest is whether participants within the normal rage of cognitive function, but in a preclinical stage of a dementia form, are able to notice olfactory deficits by themselves. The awareness of a dysfunction and the knowledge of its importance could influence an individual to see a doctor and possibly take precautions. There are few studies that have investigated self-assessed olfactory impairments among elderly participants, and these have found a low correlation between self-assessment of olfactory ability and real performance on standardized tests of olfactory functions (Stanciu et al. 2014).

When participants without generalized cognitive impairment rated their sense of smell as "worse than normal," they had 2.17 times the odds of dementia conversion within a 10-year timespan. The effect present not only in AD but also in other dementia forms like vascular dementia and remained stable after controlling for demographic variables, cognitive ability, odor identification ability, and symptoms of depression. These results showed that subjective olfactory complaints may play a role in the early detection of dementia and that a multi-factorial approach to predicting and evaluating dementia would have significant impact (Schmand et al. 1996; Stanciu et al. 2014; Alveset al. 2014).

A study from Tahmasebi et al. (2019) analyzed the relationship between olfactory and semantic memory impairment among participants with SCD or (MCI) at baseline. The results showed that for olfactory impairment, only the Sniffin' Sticks tests were significantly different between converted and non-converted participants, indicating that converted participants had a lower odor-identification ability than the other group (Tahmasebi et al. 2019). Olfactory function is often impaired in participants with AD, particularly in patients with mild cognitive impairment amnestic type (aMCI), which could be used as a predictive marker for AD (Conti et al. 2013; Djordjevic et al. 2008; Fusetti et al. 2010).

Tahmasebi et al. (2019) also showed that objective olfactory assessments were highly useful for prediction of conversion to AD among MCI participants, but their low sensitivity appeared to be a problem. Thus, combining them with a neuropsychological test would be far more useful for the estimation of the risk of AD development (Tahmasebi et al. 2019).

The aim of this study was to evaluate whether patients with anosmia or hyposmia have a higher risk of converting to AD. Furthermore, we were interested in determining if methods for evaluating olfactory ability and the self-assessment of smelling capability are useful in making predictions about AD risks.

Material and Methods

Patients

This study was a retrospective analysis of data collected by the Vienna Conversion to Dementia Study at the Department of Neurology of the Medical University of Vienna between 2008 and 2017. Data collection was performed in accordance with the Helsinki Declaration and was approved by the Ethical Committee of the Medical University of Vienna. Patients either were referred to the study site by physicians or were self-referrals. Patients underwent underwent a neurological examination and extensive neuropsychological testing. Patients were excluded from the study if any of the following conditions applied: age younger than 50 years; evidence of stroke as defined by neuroradiological and clinical examination; a history of severe head injury or current psychiatric diagnoses, excluding patients with subdepressive symptoms that often occur in elderly patients according to the International Classification of Diseases (ICD)-10 (Dilling et al. 2015); or any medical condition associated with severe cognitive deterioration, including renal, respiratory, cardiac, and hepatic disease.

One hundred seventy-four participants were divided into four groups based on cognitive features, as follows: SCD, aMCI, on-amnestic mild cognitive impairment (naMCI), and AD. An SCD classification required the presence of subjective memory deterioration, manifested by the seeking of medical help for memory problems, and the concurrent absence of any objectively measurable cognitive deficits (Jessen et al. 2014). aMCI was determined by a mean *z*-score for the memory domain below1.5 SD, and naMCI was determined by a mean *z*-score in at least one cognitive domain other than the memory domain below SD (Pusswald et al. 2013). The

diagnosis of AD was determined by a consensus committee that included a neuropsychologist, a neurologist, and other study personnel who were involved in the evaluation of the patients' cognitive status. AD was diagnosed according to criteria established by the National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (Mckhann et al. 1984) and the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) (Sass 2003). Cognitively healthy control participants were recruited by means of advertisements. Control participants underwent a rigorous evaluation involving a standardized clinical interview and cognitive screening.

Demographic and clinical characteristics are shown in Table 1.

Psychometric Testing

Neuropsychological Assessment

The Wortschatztest (WST) (Schmidt 1992) was used to estimate premorbid verbal intelligence, the Beck Depression Inventory (BDI-II)(Hautzinger et al. 2006) was conducted for assessment of depression and the Mini-Mental State Examination (MMSE) (Folstein et al. 1975) was used as a screening tool. The Neuropsychological Test Battery Vienna (NTBV) (Sass 2003) was administered to assess cognitive function. This battery includes several tests that examine domains of attention, executive functioning, language, and memory (Lehrner 2007). Attention was assessed using the Alters-Konzentrationstest (AKT) (Gatterer 1990), a geriatric cancelation test; the digit symbol subtest of German Wechsler Adult Intelligence Scale (WAIS-R); the symbol counting subtest of the cerebral insufficiency test (C.I.) (Lehrl 1999); and the Stroop Test from the Nürnberger Alters-Inventar (NAI) (Oswald and Fleischmann 1993). Psychomotor speed was examined using the symbol counting subtest of the C.I. Semantic verbal fluency was assessed by having patients name as many animals, supermarket items, and tools as possible within one minute each. Naming as many words as possible beginning with the letters *b, f,* and *I* each within one minute, was used as a measure of lexical verbal fluency. The Boston Naming Test (mBNT) assessed naming performance in patients (Goodglass et al. 2001). Episodic memory was tested using the Verbal Selective Reminding Test (VSRT) (Lehrner et al. 2006). Trail Making Test B (TMT) was administered to assess divided attention. The score difference between Parts A and B of the TMT (Reitan 1958), the Five-Point Test (Regard et al. 1982), and the Maze Test from the NAI Test Battery were used to examine executive functions.

Odor Assessment

All participants filled in a 12-item questionnaire for the assessment of self-reported olfactory functioning and olfaction-related quality of life (ASOF) (Pusswald et al. 2012; Psimistri, 2022). This tool can be subdivided into three domains: the one-item, subjective olfactory capability (SOC) scale, with a cut-off score of > 3; the five-item self-reported capability of perceiving specific odors (SRP) scale, with a cut-off score of < 2.9, and the six-item olfactory-related quality of life (ORQ) scale, with a cut-off score of > 3.7. Each subject's olfactory function was assessed using the Sniffin' Sticks odor identification test (OIT), with a cut-off score of 10 (Hummel et al. 1997).

Procedure

The participants underwent these assessments twice (at baseline T1 and at time point T2). The interval between examinations at T1 and T2 was between 12 and 48 months.

Statistical Analysis

The statistical calculations were performed with the IBM SPPS® Version 25 analysis software. The significance level within the context of inferential statistics was set at $\alpha = 5\%$. The standardized effect size r according to Cohen's classification was used to assess the relevance of results in terms of content. The odds ratio (OR) was calculated as an approximation of relative risk.

The distribution of parametric variable mean (M) and standard deviation for skewed distributions median (Md) and interquartile range (IQR) were calculated. For proportional values of nominally scaled variables, the corresponding confidence interval [95%-CI: lower level, LL%; upper level, UL%] was also calculated using the expression. For the 5% error probability of the CI, the corresponding bilateral z value of 1.96 was used.

We calculated the Kruskal–Wallis (KW) test and the Mann–Whitney U-test for comparison and the one-way analysis of variance (ANOVA) for normal distribution data. The χ^2 test was applied for distribution analysis. Furthermore, a binary logistic regression was used as a multiple method in the context of model testing as prognosis to differentiate between AD and non-AD patients. We used the significant parameters among those used for logistic regressions for receiver-operating characteristic (ROC) analyses.

Table 1 Characteristics of participants in terms of sociodemographic, neurocognitive, and olfactory parameters at Baseline (T1)

Parameter	Patient groups				*p*
	HC (*N* = 16)		SCD (*N* = 23)	naMCI (*N* = 75)	aMCI (*N* = 59)	
Gender female	11 (68.8%)		10 (43.5%)	43 (57.3%)	32 (54.2%)	.453
Age	56.3 ± 5.8		66.1 ± 10.0	67.9 ± 8.2	68.9 ± 7.4	< .01**
Education	18.5 (14.6–20.0)		13.0 (10–16)	11.0 (8–16)	12.0 (8–17)	< .01**
MMSE	29 (29–30)		29 (28–30)	29 (27–29)	28 (26–29)	< .01**
BDI II T1	3 (0–3.8)		8 (2–13)	10 (4.5–13.5)	8 (4–15)	< .01**
WST-IQ T1	118.2 ± 9.1		116.4 ± 11.2	111.7 ± 12.5	110.2 ± 13.2	< .05*
Sniffin' Sticks	13 (12–13)		13 (11–14)	13 (11–14)	11 (8–13)	< .01**
ASOF SOC	8 (7.0–10.0)	8 (8.0–19.0)		8 (6.0–19.0)	7 (5.0–10.0)	.16
ASOF SRP	5 (4.45–5.0)	5 (4.2–4.0)		4.80 (4.0–5.0)	4.40 (3.6–5.0)	.08
ASOF ORQ	5.0 (5.0–5.0)	5.0 (4.93–5.0)		5.0 (4.55–5.0)	5.0 (4.55–5.0)	< .05*
Neuropsychological Test Battery Vienna (NTBV) subtests						
AKT T1	22.5 (21.3–29.3)		28 (24–31)	35 (28–46)	37 (31–45)	< .01**
AKT TT T1	2.42 (1.84–2.59)		1.96 (1.74–2.21)	1.50 (1.19–1.80)	1.46 (1.20–1.77)	< .01**
T1	36.5 (29.5–41.0)		35.0 (31.0–41.0)	25.0 (20.0–32.0)	25.0 (18.0–33.0)	< .01**
Five Point Test perseveration errors. T1	3.0 (.25–4.75)		2.0 (.00–4.00)	1.0 (.00–3.13)	1.0 (.00–4.00)	.60
Digit-symbol T1	52.13 ± 13.46		52.0 ± 10.13	41.08 ± 11.33	38.80 ± 12.46	< .01**
C.I. symbols T1	18.5 (17.0–22.0)		19.0 (16.0–22.0)	21.0 (18.0–28.0)	23.0 (18.0–27.0)	< .09**
TMT A T1	29.0 (24.0–38.0)		32.0 (29.0–41.0)	41.0 (33.0–49.0)	48.0 (36.0–67.0)	< .01**
TMT B T1	65.5 (46.0–91.25)		75.0 (56.0–90.0)	104.0 (81.0–143.0)	108.0 (83.0–182.0)	< .01**
SWT T1	76.62 ± 13.89		62.04 ± 11.70	54.88 ± 12.28	48.42 ± 10.19	< .01**
PWT T1	45.31 ± 13.15		36.48 ± 7.30	31.85 ± 11.19	30.61 ± 10.20	< .01**
BNT	15.0 (15–15)		15.0 (15–15)	15.0 (14–15)	14.0 (14–15)	< .01**
VSRT immediate	10.0 (9.25–11.0)		8.0 (7.0–9.0)	8.0 (7.0–9.0)	6–0 (5.0–7.0)	< .01**
VSRT total learning	59–63 ± 8.37		54.43 ± 10.16	50–95 ± 8.05	39.16 ± 9.47	< .01**
VSRT delayed	12.62 ± 2.55		12.17 ± 2.67	10.73 ± 2.15	6.69 ± 3.30	< .01**
VSRT recognition	15.0 (15–15)		15.0 (14–15)	15.0 (14–15)	13.0 (11–14.5)	< .01**
Stroop color T1	19.5 (18.0–22.5)		21.0 (18.0–23.0)	24.0 (22.0–27.0)	26.0 (21.0–28.0)	< .01**
Stroop words T1	36.0 (32.5–42.5)		36.0 (34.0–46.0)	46.0 (40.0–53.0)	50.0 (43.0–64.0)	< .01**
Stroop TT T1	.97 ± .25		.96 ± .267	.78 ± .18	.68 ± .23 (*n* = 59)	< .01**
Stroop difference T1	16.0 (12.25–19.0)		15.0 (13.0–23.0)	23.0 (18.0–28.0)	26.0 (20.0–40.0)	< .01**
Planning Maze T1	31.0 (19.25–39.75)		29.0 (25.0–41.0)	39.0 (32.0–47.0)	47.0 (32.0–67.0)	< .01**
Planning Maze TT T1	.50 (.31–.82)		.52 (.37–.64)	.39 (.29–.48)	.31 (.20–.50)	< .01**
TMT B-A T1	26.5 (17.25–59.50)		39.0 (27.0–54.0)	58.0 (40.0–87.0)	53.0 (37.0–116.0)	< .01**
Interference C. I T1	17.5 (15.25–21.50)		19.0 (17.0–22.0)	23.0 (20.0–26.0)	24.0 (20.0–29.0)	< .01**
Interference C.I. TT T1	1.94 ± .51		1.76 ± .34	1.50 ± .36	1.41 ± .40	< .01**

** $p \leq .01$, * $p \leq .05$ (mean ± SD = standard deviation; median (IQR = interquartile range); MMSE, Mini Mental State Examination; BDI II, Beck Depression Inventar; WST, Wortschatz Test; Konz, Maze Test; ASOF, assessment of self-reported olfactory functioning; SOC, subjective olfactory capability scale; SRP, self-reported capability of perceiving specific odors scale; ORQ, olfactory-related quality of life; AKT, Alters Konzentrations Test; TT, total/time; TMT B, Trail Making Test Version B; C.I., cerebral insufficiency; TMT A, Trail Making Test Version A; SWT, Semantic verbal fluency test; BNT, Boston Naming Test; VSRT, verbal selective reminding test; PWT, lexical verbal fluency Test

Results

Table 1 shows sociodemographic and neurocognitive variables, NTBV subtests, and olfactory performance depending on the participants' (patients') categories at baseline (time point T1). Analyses revealed significant differences in age and years of education. *Post hoc* pairwise procedures according to Bonferroni revealed that the participants in the healthy control group (HC) were younger than in the other groups. On average, participants in the HC also had more years of education than the other groups (p's ≤ 0.001). The analyses also showed

significant differences in MMSE, BDI-II, and WST among the participant groups at T1. Test results revealed significant differences in all NTBV subtests among the participant groups at T1 except on the Five Point Test preserve. Furthermore, significant differences in Sniffin' Sticks performance and ASOF ORQ scores among the participant groups at T1 were found.

Of the 173 participants, a total of 95 (54.9%) had the same diagnosis at both times, whereas 44 (25.4%) were shown to be worsening, and 34 (19.7%) showed an improvement. The results of $\chi^2 = 1.282$, $p = 0.308$ demonstrated no significance. Specifically, 18 of the 59 aMCI (30.5%; 95% CI [18.8%; 42.3%]) patients showed conversion to AD after an average of two years, whereas the other 18 of the 59 aMCI showed an improvement, 13 (7.5%) toward naMCI, and 5 (2.9%) toward SCD. Additionally, there was no conversion of the SCD and naMCI patients to AD. As a result, we were able to categorize 41 patients as non-AD and the remaining 18 as AD.

Table 2 shows the results of relevant olfactory performance and neuropsychological subtests at time point two (T2) depending on the different diagnostic groups within the sample. The examination of group differences in olfactory function at T2 was carried out by KW testing. Test results revealed significant differences in all subtests of the neuropsychological test-battery among the participant groups at T2 except the Five Point Test preserve as well as Sniffin' Sticks and ASOF SOC scores.

Table 2 Olfactory and neurocognitive performance at assessment two (T2)

Parameter	Category (*n*)					*p*
	HC (16)	SCD (34)	naMCI (62)	aMCI (43)	AD (18)	
Sniffin' Sticks	13 (11–14)	12 (10–14)	11.5 (9–13.8)	11.5 (8.3–13.8)	8.5 (3.3–13)	.275
AOSF-SOC	8.0 (7.0–9.0)	8.0 (6.0–10.0)	7.5 (5.0–10.0)	8.0 (6.0–9.0)	7.0 (3.0–10.0)	.918
AOSF-SRP	5 (4.5–5.0)	4.60 (4.0–5.0)	4.20 (3.35–4.85)	4.60 (3.8–5.0)	3.50 (2.85–4.65)	.009**
AOSF-ORQ	5.00 (5.0–5.0)	5.0 (4.83–5.0)	5.00 (4.5–5.0)	5.00 (4.74–5.0)	4.35 (3.30–5.0)	.028*
Neuropsychological Test Battery Vienna (NTBV) subtests						
AKT	23.5 (19–28.3)	33.0 (24.8–38.8)	37.0 (29.8–46.5)	33.0 (30.0–43.0)	42.0 (35.5–68.5)	< .001**
AKT TT	2.35 ± .60	1.80 ± .56	1.55 ± .54	1.60 ± .39	1.14 ± .43	< .001**
Five point Test	39.63 ± 10.40	31.65 ± 10.18	26.38 ± 10.08	27.71 ± 7.49	18.38 ± 7.76	< .001**
Five point Test perseveration errors.	2.0 (.00–3.0)	1.0 (.00–3.0)	1.5 (.00–4.0)	2.0 (.00–5.25)	3.5 (2.25–6.75)	.053
Digit-symbol	51.5 (41.8–62.0)	46.5 (38.8–51.0)	38.5 (33.0–46.8)	37.0 (34.0–50.5)	23.5 (20.3–32.0)	< .001**
C.I. symbols	18.06 ± 3.96	21.61 ± 4.58	26.13 ± 8.63	22.28 ± 5.11	28.53 ± 9.97	< .001**
TMT A	27.5 (24.0–31.0)	37.5 (27.5–45.3)	44.0 (33.8–55.0)	42.0 (33.0–49.0)	72.0 (41.8–79.3)	< .001**
TMT B	59.5 (45.3–66.5)	78.5 (62.0–100)	111 (90.0–166.5)	93 (73.0–128.8)	240 (203–300)	< .001**
SWT	78.44 ± 13.88	52.82 ± 10.11	51.17 ± 12.60	51.71 ± 14.79	41.25 ± 9.82	< .001**
PWT	45.06 ± 11.16	36.47 ± 8.67	31.70 ± 12.41	32.98 ± 10.95	25.88 ± 12.04	< .001**
VSRT immediate	10.0 (8–11)	8.0 (6–9)	7.0 (6–9)	5.0 (5–7)	5.0 (4–6)	< .001**
VSRT total learning	60.81 ± 8.10	50.91 ± 9.73	48.63 ± 9.0	36.37 ± 7.71	26.88 ± 8.17	< .001**
VSRT delayed	14.0 (12–15)	11.0 (9–13)	11.0 (8.75–13)	5.0 (3–8)	3.0 (1–5.75)	< .001**
VSRT recognition	15.0 (15–15)	15.0 (14–15)	14.5 (14–15)	12.5 (11–14.5)	10.0 (7.8–12.3)	< .001**
Stroop color	20.0 (18.3–21.5)	22.0 (20.0–25.3)	25.0 (22.0–29.0)	23.5 (20.8–26.3)	33.5 (28.8–35.0)	< .001**
Stroop words	33.0 (30.3–39.5)	41.5 (34.8-49.3)	50.0 (38.0-55.0)	44.5 (39.0-56.3)	75.5 (50.0-88.3)	< .001**
Stroop TT	1.1 (.91–1.19)	.87 (.72–1.04)	.72 (.63–.95)	.79 (.63–.90)	.46 (.29–.70)	< .001**
Stroop difference	15.31 ± 7.37	18.94 ± 7.57	23.85 ±1 0.86	23.20 ± 9.95	44.38 ± 21.83	< .001**
Planning Maze	30.0 (22.0–35.0)	36.5 (27.8–46.3)	45.0 (32.0–64.0)	36.0 (31.0–55.0)	59.0 (40.5–105.5)	< .001**
Planning Maze TT	.51 (.43–.70)	.41 (.33–.55)	.34 (.22–.50)	.38 (.24–.52)	.24 (.15–.41)	< .001**
TMT B-A	30.0 (20.0–38.8)	43.0 (25.0–60.5)	69.0 (46.0–120.0)	49.0 (33.5–84.0)	180 (150–215)	< .001**
Interference C. I.	16.5 (15.3–20.8)	20.0 (18.8–23.0)	25.0 (21.0–30.0)	21.0 (19.0–27.0)	32.0 (24.5–40.0)	< .001**
Interference C.I. TT	1.98 ± .59	1.64 ± .33	1.38 ± .45	1.51 ± .41	1.07 ± .34	< .001**

**$p \leq .01$, *$p \leq .05$;(mean ± SD = standard deviation; median (IQR = interquartile range); MMSE, Mini Mental State Examination; BDI II, Beck Depression Inventar; WST, Wortschatz Test; Konz, Maze Test; ASOF, assessment of self-reported olfactory functioning; SOC, subjective olfactory capability scale; SRP, self-reported capability of perceiving specific odors scale; ORQ, olfactory-related quality of life; AKT, Alters Konzentrations Test; TT, total/time; TMT B, Trail Making Test Version B; C.I., cerebral insufficiency; TMT A, Trail Making Test Version A; SWT, Semantic verbal fluency test; BNT, Boston Naming Test; VSRT, verbal selective reminding test; PWT, lexical verbal fluency Test

Model testing using binary and logistic regression was performed to predict the AD criterion. Initially, the explanatory values of the Sniffin' Sticks and ASOF subtests were examined using the stepwise backward method in order to identify those tests that made a meaningful contribution. The Hosmer–Lemeshow test indicated model fit, $p = 0.71$. Table 3 shows the results for the prediction of the AD criterion. It should be noted that 14 participants were not included in this analysis because they did not have complete records of olfactory performance at T1. Therefore, a sample size of $n = 159$ was used for this binary logistic regression.

The result showed that only the Sniffin' Sticks ($p = 0.01$, OR = 0.73; 95% CI [0.61; 0.88], $R^2 = 17.7\%$) enabled a relevant prognosis.

The corresponding ROC analyses for olfactory testing at T1 revealed that Sniffin' Sticks outperformed the ASOF regarding the prediction of conversion to AD (see Fig. 1 for details).

In the next step, the explanatory value of the NTBV subtests was examined using the stepwise backward method in order to identify those tests that made a meaningful contribution to the prediction of conversion to AD.

A total of six subtests (AKT TT, C.I. Symbols, TMT B, Phonematische Wortflussigkeit (PWT), VSRT total, and VSRT recognition) showed a significant effect on the prediction of the conversion to AD. See Table 4 for details.

A logistic regression showed that among the olfactory test procedures, only the Sniffin' Sticks enabled a relevant prognosis. Therefore, we did not include the ASOF subtests in the following analysis. The significant NTBV subtests were then subjected to this further model, together with olfactory performance (Sniffin' Sticks) and sociodemographic characteristics (sex, age, and education years).

The weight of the first block was 15.0%, including only Sniffin' Sticks. The first and second block had a combined weight of 19.6%, with the sociodemographic variables included. The additional inclusion of the NTBV subtest services increased the prognosis resulting in a declared variance level of 72.4%. "Risk for AD was indicated by low scoring on the learning subtest of the VSRT ($p = 0.01$, OR = 0.83; 95% CI [0.73; 0.94]), recognition ($p = 0.01$, OR = 0.67; 95% CI [0.45; 0.996]), and higher values for divided attention (TMT B) ($p = 0.01$, OR = 1.03; 95% CI [1.01; 1.05]) indicated a risk for AD. The other predictors did not contribute to a correct prognosis for AD.

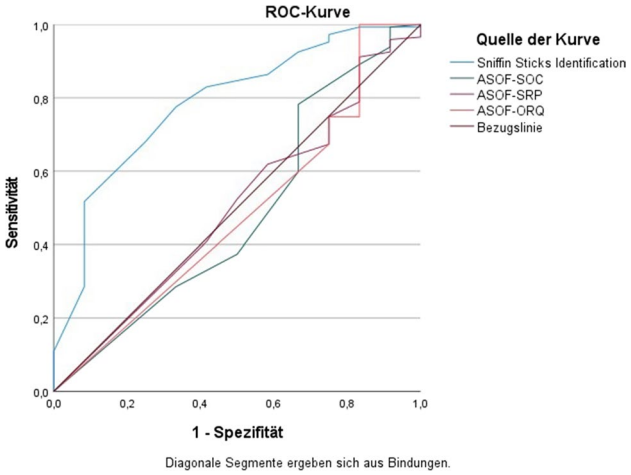

Fig. 1 The corresponding ROC analyses for Sniffin' sticks and ASOF subtests at baseline (T1). Subjective Olfactory Capability scale (SOC)-Subjektives Riechvermögen; SOC (self-reported capability of perceiving specific odors scale (SRP)-Beeinträchtigung der Wahrnehmung von Alltagsdüften; (olfactory-related quality of life (ORQ)-Riechbezogene Lebensqualität

The corresponding ROC analyses for the relevant neuropsychological subtests at T1 showed that the subtests of the VSRT, Learning and Recognition, and the TMT B for testing divided attention showed satisfactory validity regarding the prognosis of AD (see Fig. 2 for details).

Visual inspection shows that the neurocognitive measures are outperforming the olfactory measures in terms of predicting AD.

Discussion

In the present study, the data protocols of 173 participants, aged ≥ 50 years, were analyzed. The main objectives were to examine the prognostic validity of neuropsychological and odor assessment tools with regard to conversion into AD. We wanted to answer the question of whether someone with anosmia has a higher risk of dementia and whether Sniffin' Sticks and ASOF can predict the risk. We examined whether age, sex, and years of education as covariates, together with the applied neurocognitive tests, could provide a prognosis of the probability of the conversion to AD.

Table 3 Coefficients of relevant olfactory T1 performance criterion: AD vs. non-AD at T2 OR odds ratio; B beta; SE standard error, CI confidence interval

Odor identification test	*B*	SE	Wald χ^2 (df = 1)	*p*	OR	95% CI OR	
						LL	UL
Sniffin' Sticks	− .313	.092	11.58	.001**	.731	.611	.876
Constant	.768	.914	.706	.401	2.156		

**$p \leq .01$, *$p \leq .05$

Table 4 Coefficients of relevant subtests of the Neuropsychological Test Battery Vienna at T1: AD vs. non-AD T2 OR odds ratio; B beta; SE standard error, CI confidence interval

NTBV subtest	*B*	SE	Wald χ^2 (df = 1)	*p*	OR	95% CI OR	
						LL	UL
AKT TT	− 3.119	1.563	3.982	.046*	.044	.002	.946
C.I. symbols	− .185	.104	3.159	.075	.831	.677	1.019
TMT B	.027	.009	8.990	.003**	1.027	1.009	1.045
PWT	.084	.048	3.072	.080	1.088	.990	1.195
VSRT total learning	− .231	.076	9.143	.002**	.794	.683	.922
VSRT recognition	− .343	.176	3.813	.051	.709	.503	1.001
Constant	13.461	5.252	6.568	.010	701,387.7		

**$p \leq .01$, *$p \leq .05$; VSRT, verbal selective reminding test; PWT, lexical verbal fluency

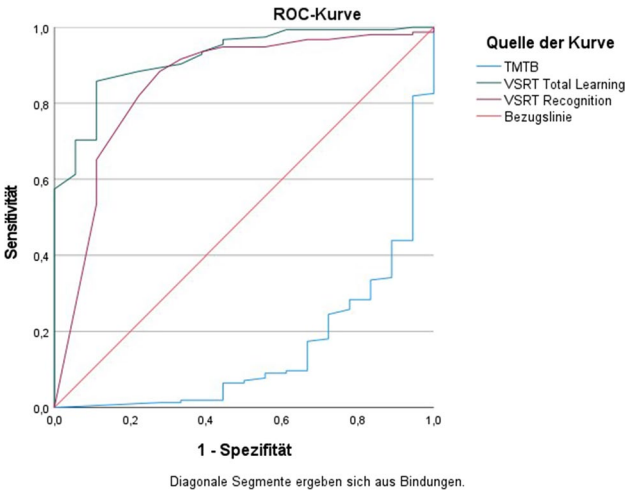

Fig. 2 The corresponding ROC analyses for the relevant subtests of the Neuropsychological Test Battery Vienna (NTBV) at baseline (T1). VSRT (Verbal Selective Reminding Test Learning), VSRT Recognition, TMT B (Trail Making Test)

Participant groups showed differences in age and years of education; HC were younger than in the other groups and had more education. The analysis also showed differences in the MMSE, BDI II, and WST among the participant groups at T1. Results of olfactory function procedures at T1 depending on the different diagnostic groups within the sample indicated differences in Sniffin' Sticks performance and ORQ, part of the ASOF questionnaire.

With regard to olfactory performance, the patient groups at T2 differed only on the subtests of the ASOF questionnaire in SRP and ORQ, whereas participant groups did not differ on Sniffin' Sticks and SOC results. Again, test results revealed significant differences in all NTBV subtests among the participant groups at T2, except perseveration errors in the Five Point Test. The remaining subtests of the NTBV were then subjected to a further model analysis, together with the olfactory performance (Sniffin' Sticks) and the sociodemographic characteristics (sex, age, and education years). The additional inclusion of the NTBV subtests with the Sniffin' Sticks and sociodemographic variables increased the predictive validity. Risk for AD was predicted by low scoring in verbal memory, and low attention. The other predictors did not contribute to the prognosis for AD.

The corresponding ROC analyses for olfactory testing showed that Sniffin' Sticks had a satisfactory validity regarding the prognosis of AD, whereas the ASOF measures showed low validity. Compared to the Sniffin' Sticks, the NTBV subtests for memory and attention showed superior predictive validity in the ROC analysis.

Jessen et al. (2014) already focused on predictors of AD and found that several studies used gender, age, the mini-mental status test (MMSE), individual CSF biomarker data, MRI-based hippocampal volumes, model to make predictions. The studies showed that gender and age did not provide an accurate prediction of dementia risk (Rostamzadeh and Jessen 2020). This is consistent with our results, which showed that gender and age do not make an impact.

Our results supported the results of the study by Tahmasebi et al. (2019). That study showed that the Sniffin' Sticks performance was significantly lower in AD patients compared to healthy controls, SCD, naMCI, and aMCI patients; significantly lower in aMCI patients compared to healthy controls, SCD, and naMCI patients; and significantly lower in naMCI patients compared to healthy controls. The Sniffin' Sticks also produced significant results in the ROC analyses (Tahmasebi et al. 2019).

Stanciu et al. (2014) also conducted a logistic regression as the main analysis, in which age, gender, years of education, MMSE score, olfactory identification performance, and reporting olfactory impairment were used as predictor variables and conversion to dementia, with a period of 10 years, as the criterion variable. They showed that after adjustment for demographic variables and MMSE scores, olfactory identification and subjective olfactory impairment significantly and independently predicted conversion to dementia. Patients who rated their sense of smell as "worse than normal" were more likely to be diagnosed with dementia

within 10 years than patients who did not report olfactory impairment. Adding reports of olfactory complaints in the last step of the regression significantly improved the variance explained by the logistic model and increased the the accuracy of dementia predictions.

This improvement of explained variance through reporting olfactory complaints could not be shown in our results. However, gender and years of education had no independent influence on the probability of conversion to dementia, just as our results showed. It is worth mentioning that Stanciu et al.'s (2014) study examined participants over 10 years. In our study, the time interval of examination was on average 24 months.

Limitations and Preview

One limitation that should be mentioned is that participant groups showed differences in age, education years, and some basic clinical data. This fact should not be ignored when discussing the results. The study was also limited due to the circumstance that only those test protocols that were completely available on the two examination dates could be considered. Furthermore, it should be noted that the patient sample at T2 had a comparatively small number of AD patients.

Conclusion

Using a retrospective longitudinal study design, we examined the extent to which standard neurocognitive diagnostic procedures provide prognostic value in the correct identification of AD patients when combined with olfactory measures. Sniffin' Sticks were identified as a measure with satisfactory predictive validity for conversion to AD. However, predictive validity disappeared when used together with standard neurocognitive measures of memory and attention. In conclusion, olfactory assessment might be a useful tool in assessing conversion to dementia but might be inferior predicting to conversion to dementia compared to standard neurocognitive measures of memory and attention.

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Declarations

Conflict of Interest The authors have no competing interest, except for JL who is the CEO of psimistri GmbH which owns the website www.psimistri.com.

Ethics Approval and Consent Participate All participants gave written informed consent.

The study was approved by the local Institutional Review Board (Medical University of Vienna) and was conducted in accordance with the Declaration of Helsinki.

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