Cognitive impairment, neurodegenerative disorders, and olfactory impairment: A literature review

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4Department of Public Health, Faculty of Medicine and Dentistry, Palacký University Olomouc, Czech Republic

ABSTRACT:

Introduction: The early detection and diagnosis of dementia are of key importance in treatment, slowing disease progression, or suppressing symptoms. The possible role of changes in the sense of smell is considered with regard to potential markers for early detection of Alzheimer’s disease (AD).

Materials and methods: A literature search was conducted using the electronic databases PubMed, Scopus, and Web of Science between May 30, 2022 and August 2, 2022. The term “dementia” was searched with keyword combinations related to olfaction.

Results: A total of 1,288 records were identified through the database search. Of these articles, 49 were ultimately included in the analysis. The results showed the potential role of changes in the sense of smell as potential biomarkers for early detection of AD. Multiple studies have shown that olfactory impairment may be observed in patients with AD, PD, MCI, or other types of dementia. Even though smell tests are able to detect olfactory loss caused by neurodegenerative diseases, they cannot reliably distinguish between certain diseases.

Conclusions: In individuals with cognitive impairment or neurodegenerative diseases, olfactory assessment has repeatedly been reported to be used for early diagnosis, but not for differential diagnosis.

KEYWORDS: Alzheimer’s disease, dementia, mild cognitive impairment, neurodegenerative disorders, olfactory impairment, Parkinson’s disease

ABBREVIATIONS

AD – Alzheimer’s disease
MCI – mild cognitive impairment
MRI – magnetic resonance imaging
PD – Parkinson’s disease
SARS-CoV-2 – severe acute respiratory syndrome coronavirus 2
TDI – comprehensive score of threshold, discrimination, and identification abilities

INTRODUCTION

Worldwide, the average life expectancy is increasing [1]. Population aging is associated with an increase in the prevalence of neurodegenerative diseases [2]. These are characterized by a loss of nerve cells and an abnormal accumulation of protein in brain cells. Clinically, neurodegenerative diseases are manifested by impaired cognitive function, tremor, muscle stiffness, motor impairment, and other signs and symptoms; over time, they get worse [2]. The prevalence of dementia has been on the rise globally [2, 3]. The word “dementia” does not refer to a single condition, but is rather an umbrella term for a whole group of symptoms occurring due to neurodegenerative disease. In 2015, there were 46.8 million people living with dementia around the world [3]. By 2021, the prevalence had risen to 55 million [4] and it is expected to reach 131.5 million by 2050 [3]. A rather common progressive neurological disorder is Alzheimer’s disease, considered the most frequent cause of dementia in people over 65 years of age [4]; in those aged 80 and older, there are multiple causes of dementia, such as mini-strokes [4].

In addition to the above manifestations of neurodegenerative diseases, olfactory impairment or loss may also occur [5–9]. Smell dysfunction has been documented as an early sign of neurodegenerative changes that may potentially become a marker for early diagnosis of conditions such as Alzheimer’s disease, Parkinson’s disease, or multiple sclerosis [7, 10–13].

As olfactory dysfunction varies among neurodegenerative diseases, the use of smell tests in differential diagnosis is considered [14]. In Parkinson’s disease, the olfactory impairment tends to be severe [14]. Some authors assume that it may occur as early as four to six years
prior to the onset of motor impairment [15]. In Huntington’s disease, by contrast, smell dysfunction accompanies typical clinical signs of the condition [14]. In patients with Creutzfeldt–Jacob disease, smell is impaired due to olfactory tract involvement of the prion protein. Finally, multiple sclerosis patients have olfactory impairment that is proportional to the formation of plaques in the subfrontal and subtemporal lobes and that fluctuates depending on exacerbation and remission periods [14]. Smell dysfunction has been shown to be associated with structural changes to different parts of the brain [16–18].

Smell impairment may also occur due to aging, since older age has a greater impact on decreased olfactory function than smoking [14]. Approximately 2% of people under 65 years of age report smell dysfunction; later, the proportion rises to 50% in those aged 65–80 years, reaching 75% in the over-80 population [14]. Age-related smell impairment is caused by age-related degenerative brain changes and cumulative damage to olfactory receptors throughout the lifespan, among other factors [14].

After the age of 65, the nasal microbiome composition changes [19]. A potential association between the shape of the nasal microbiome, chronic rhinosinusitis, and the development of Alzheimer’s disease was investigated [20]. Moreover, the nasal cavity represents an entry point of infection through which pathogens triggering or aggravating neurodegenerative disease may enter and spread through the central nervous system [21]. Adequate treatment of chronic rhinosinusitis or surgery have been reported to alleviate cognitive dysfunction [20].

The current diagnostics of olfactory impairment mainly relies on psychophysical testing of smell function to assess three parameters of human smell: odor threshold, odor discrimination, and odor identification. Over the past years, numerous smell tests have been developed globally that are capable of including and reliably assessing the above smell components. In their studies, researchers frequently combine such tests with objective methods able to provide information on the condition of the brain structures responsible for odor perception and discrimination. Worldwide, the following psychophysical smell tests are used: the Sniffin’ Sticks test [22], the University of Pennsylvania Smell Identification Test [23], the Cross-Cultural Smell Identification Test [24], the Connecticut Chemosensory Clinical Research Center test [25], and others. The Sniffin’ Sticks test is based on several pen-like devices dispensing odors used for three subtests that result in four scores: the olfactory threshold (T) score, the discrimination (D) score, the identification (I) score, and the global (TDI) score [22]. The University of Pennsylvania Smell Identification Test comprises 40 common microencapsulated odorants, each on a single page. It makes use of a “scratch’n sniff” method in which the test subject scratches an odorant strip, smells the emitted odor, and selects the right answer among four options. The total score ranges from 10 to 40 [23].

The test served as a basis for developing the Cross-Cultural Smell Identification test [24]. Developed and used in Japan, the Open Essence test consists of cards with 12 sealed odorants. The test subject rubs a card between their hands and identifies the odor by choosing one out of six options. The disadvantage is that the odorants cannot be resealed and used repeatedly [26].

The Mini-Mental State Examination, a simple, short, standardized instrument, is used widely around the world to assess cognitive function. First used in 1975 [27], the questionnaire contains 11 items and sections concerned with orientation, registration, attention, calculation, recall, and language. A maximum score of 30 points is possible [13].

The association between olfactory dysfunction or loss and clinical or preclinical stages of Parkinson’s and Alzheimer’s disease has been reported by many authors [6, 28–40].

The aim of this state-of-the-art review is to provide information on the literature concerned with assessing olfactory function in individuals with cognitive disorders or diagnosed with neurodegenerative diseases.

MATERIALS AND METHODS

Search strategy

A literature search was conducted using the electronic databases PubMed, Scopus, and Web of Science between May 30, 2022 and August 2, 2022. Keyword combinations related to cognition and olfactory impairment were searched.

Inclusion criteria

Eligible papers were selected using the following criteria: 1) they contain the keywords "olfactory loss", “olfactory dysfunction”, “olfactory impairment”, or “smell loss” and concerned the assessment of pathology in patients with cognitive impairment or particular neurodegenerative diseases; 2) the studies followed living participants whose mean age was 60 years or older and who were diagnosed with mild cognitive impairment, dementia, or particular neurodegenerative diseases at any phase of their progression; 3) they contain descriptions and definitions of the smell tests which were used; 4) the participants underwent subjective psychophysical smell testing or a combination of subjective testing and objective imaging methods to identify and monitor their olfactory pathology at a central nervous system level; 5) they were published between 2000 and 2022; and 6) they were published in English.

Exclusion criteria

From the records identified through the database search, duplicates appearing in multiple databases were removed, as were book chapters, conference proceedings, brochures, manuals, or similar publications.

Studies assessing the impact of olfactory impairment on respondents’ quality of life, eating patterns, physical and mental well-being, or the development and progression of depression or anxiety were not included. Studies on smell dysfunction due to infectious diseases, injury, or surgery were also excluded. Studies assessing the effects of any treatments on the olfactory system and articles with conclusions based merely on objective findings – for example, those obtained with magnetic resonance imaging (MRI) and no subjective psychophysical smell tests being administered to participants – were excluded. We excluded studies whose primary...
Identification

Records identified through database searching (n = 1288)
- Publications identified from PubMed (n = 450)
- Publications identified from Scopus (n = 363)
- Publications identified from Web of Science (n = 475)

Screening

Titles screened (n = 1288) → Records excluded (n = 1006)

Duplicates removing (n = 282) → Records removed (n = 157)

Abstracts screened (n = 125) → Records excluded (n = 46)

Eligibility

Articles assessed for eligibility (n = 79) → Articles excluded for not met our criteria (n = 30)

Included

Articles fitting all categories and included in review (n = 49)

- PD (n = 13)
- AD + MCI (n = 16)
- Other (n = 2)
- Reviews (n = 18)

Fig. 1. Flow diagram.
## Tab. I. Patients with Parkinson’s disease.

<table>
<thead>
<tr>
<th>AUTHOR, YEAR</th>
<th>NUMBER OF RESPONDENTS GROUPS (N = NUMBER OF PEOPLE)</th>
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<th>OBJECTIVE</th>
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<tbody>
<tr>
<td>Pekel et al., 2020</td>
<td>62 people (30 women, 32 men)</td>
<td>Patients 68.03 (SD = 6.09); Controls 65.48 (SD = 6.26)</td>
<td>Bursa, Turkey</td>
<td>BTT (Butanol Threshold Test); SST (Sniffin’ Sticks Test)</td>
<td>PD: 25; Controls: 25</td>
<td>To evaluate the association between the impairment of olfaction and cognitive functions in patients with PD and the feasibility of the use of olfactory tests to predict the risk for developing dementia in the population of Parkinson’s patients</td>
<td>In PD, olfactory impairment correlates with cognitive impairment and olfactory tests may be used to predict the likelihood of developing dementia in this patient population</td>
</tr>
<tr>
<td>Patel et al., 2020</td>
<td>60 people (27 women, 33 men)</td>
<td>Patients 64.3 (SD = 10.6); Controls 63.9 (SD = 10.2)</td>
<td>Mumbai, India</td>
<td>INSIT (Indian Smell Identification Test)</td>
<td>Aware of hyposmia: 29.25 (SD = 0.29); Unaware: 27.89 (SD = 1.1)</td>
<td>To evaluate olfactory impairment in patients with PD and to evaluate the unawareness of hyposmia among PD patients and controls and its correlation with cognitive impairment</td>
<td>Unawareness of hyposmia in patients with PD is higher than that of the elderly without PD. Population screening using INSIT could be used for early detection of PD in those who already harbor the earliest pathology of neurodegeneration</td>
</tr>
<tr>
<td>Fujio et al., 2019</td>
<td>56 people (29 women, 27 men)</td>
<td>67.8</td>
<td>Kobe, Japan</td>
<td>OE (Open Essence test); JSO (Jet Stream Olfactometry)</td>
<td>Baseline score: 22–30; 3rd year score: (19–23)</td>
<td>To examine the severity and frequency of smell disorder in PD and to verify the validity of olfactory tests as a predictor of cognitive symptom onset of PD</td>
<td>When the number of correct answers of 6 odors is 4 or less in patients with PD, there is a possibility that Mini-Mental-State Examination declines in 3 years</td>
</tr>
<tr>
<td>Camargo et al., 2018</td>
<td>80 people (34 women, 46 men)</td>
<td>Patients 61.4 (SD = 10); Controls 63.5 (SD = 8.9)</td>
<td>Ponta Grossa, Brazil</td>
<td>SST</td>
<td>PD: 23.05 (SD = 3.75); Controls: 27.37 (SD = 2.89)</td>
<td>To compare cognitive deficits and olfaction in PD patients</td>
<td>The prevalence of olfactory deficits in PD patients is significantly high. There may be a correlation between frontal lobe dysfunction and olfactory deficit</td>
</tr>
<tr>
<td>Campabadal et al., 2017</td>
<td>49 people (24 women, 25 men)</td>
<td>Patients 61.4 (SD = 10); Controls 63.5 (SD = 8.9)</td>
<td>Barcelona, Spain</td>
<td>UPSIT (University of Pennsylvania Smell Identification Test)</td>
<td>Not specified</td>
<td>To investigate the olfactory changes and their structural correlates in non-demented PD over a four-year follow-up</td>
<td>Olfactory loss over time in PD patients and controls is similar, but significant correlation was observed between this loss and basal ganglia volumes only in patients</td>
</tr>
<tr>
<td>Domellöf et al., 2017</td>
<td>125 people (50 women, 75 men)</td>
<td>Hyposomic PD patients (n = 91); Normosomic PD patients (n = 34)</td>
<td>Umeå, Sweden</td>
<td>B-SIT (Brief Smell Identification Test)</td>
<td>Hyposomic PD: 29.0; Normosomic PD: 29.0</td>
<td>To investigate the prevalence of olfactory dysfunction at PD diagnosis, how it evolves over time, and whether hyposmia increases the risk of dementia in PD</td>
<td>Olfactory dysfunction was common at the time of PD diagnosis and increased the risk of dementia up to ten years after PD diagnosis, regardless of baseline cognitive function</td>
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### Tab. I. ed. Patients with Parkinson’s disease

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<tr>
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<tr>
<td>Kawasaki et al., 2016</td>
<td>51 people (25 women, 26 men)</td>
<td>Patients with MCI 73.7 (SD = 6.4); Patients CN 66.8 (SD = 6.4); Controls 71.5 (SD = 4.7)</td>
<td>Tohoku, Japan</td>
<td>OE, C-TOT (Card-Type Olfactory Test); OQ (Olfactory Questionnaire)</td>
<td>PD-MCI: 26.7 (SD = 2.2); PD-CN: 28.8 (SD = 2.0); Controls: 28.8 (SD = 1.7)</td>
<td>To compare the degree of hyposmia self-awareness between Parkinson’s disease patients with mild cognitive impairment (PD-MCI) and cognitively normal Parkinson’s disease patients (PD-CN)</td>
<td>The loss of awareness of hyposmia is closely associated with mild cognitive impairment (MCI) in PD patients</td>
</tr>
<tr>
<td>Paschen et al., 2015</td>
<td>83 people (36 women, 47 men)</td>
<td>Patients 64.4 (SD = 8.7); Controls 62.6 (SD = 6.5)</td>
<td>Kiel, Germany</td>
<td>SST</td>
<td>PD: 28; Controls: 29</td>
<td>To investigate whether neuropathological findings on the olfactory bulb (OB) in idiopathic Parkinson’s disease (IPD) correspond to a detectable change in volume of the OB and to investigate the relationship between OB volume and residual olfactory function, clinical disease characteristics, and age</td>
<td>Compared to healthy controls, patients showed significant impairment in smell function for all subtests and the composite SST results (TDI score). The high-resolution MRI did not show a detectable volume loss of the OB in PD patients</td>
</tr>
<tr>
<td>Lee et al., 2014</td>
<td>119 people (59 women, 60 men)</td>
<td>PD-H 68.6 (SD = 7.1); PD-M 69.1 (SD = 3.9); PD-L 70.8 (SD = 7.5)</td>
<td>Seoul, Korea</td>
<td>CCSIT (Cross-Cultural Smell Identification test)</td>
<td>PD-H: 26.5 (SD = 2.6); PD-M: 26.3 (SD = 2.7); PD-L: 25.4 (SD = 2.9)</td>
<td>To explore whether olfactory performance acts as a cognitive reserve in non-demented patients with Parkinson’s disease (PD)</td>
<td>A high olfactory performance may compensate for gray matter volume loss in order to minimize the exhibition of cognitive impairment and thus may act as a cognitive reserve in non-demented patients with PD</td>
</tr>
<tr>
<td>Hanoglu et al., 2014</td>
<td>47 people (13 women, 34 men)</td>
<td>Patients, PD-stage 1: 59.6 (SD = 7.04); Patients, PD-stage 2: 67.94 (SD = 6.05); Controls 62.84 (SD = 6.01)</td>
<td>Istanbul, Turkey</td>
<td>UPSIT</td>
<td>PD-stage 1: 26.70 (SD = 1.77); PD-stage 2: 25.89 (SD = 2.05); Controls: 27.15 (16)</td>
<td>To investigate the relationship between olfactory dysfunction and cognitive impairment in early idiopathic Parkinson’s disease (PD)</td>
<td>IPD is characterized by low performance in episodic verbal memory, with accompanying olfactory dysfunction at the early stage</td>
</tr>
<tr>
<td>Homma et al., 2013</td>
<td>50 people (25 women, 25 men)</td>
<td>Patients, PD 69.0 (SD = 8.6); Patients, OND 67.3 (SD = 11.1); Controls 66.2 (SD = 11.2)</td>
<td>Tokyo, Japan</td>
<td>OE</td>
<td>PD: 27.4 (SD = 1.9); OND: 28.4 (SD = 1.5)</td>
<td>To evaluate the associations of olfactory loss with Parkinson’s Disease (PD) and to assess olfactory testing as a potential screening tool for early diagnosis of PD</td>
<td>The olfactory test scores for patients with PD were significantly lower than those for patients with other neurological diseases and the healthy controls</td>
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<tr>
<td>Santin et al., 2010</td>
<td>140 people (64 women, 76 men)</td>
<td>Patients, LOPD 67.8 (SD = 9); Patients, EOPD 45.0 (SD = 5.6); Controls 63.8 (SD = 10.5)</td>
<td>Porto Alegre, Brazil</td>
<td>SST</td>
<td>Not specified</td>
<td>To evaluate olfactory function using SST in healthy subjects, patients with EOPD, and those with LOPD</td>
<td>Both groups of patients present olfactory impairment, but those whose symptoms started before 45 years of age (EOPD) have better sense of smell than the LOPD patients</td>
</tr>
<tr>
<td>Meusel et al., 2010</td>
<td>19 people (5 women, 14 men)</td>
<td>PD patients (n = 19); No controls (n = 0)</td>
<td>Basel, Switzerland</td>
<td>SST</td>
<td>≥22</td>
<td>To test olfactory deficits in the early stages of Parkinson’s disease using olfactory event-related potentials</td>
<td>Electrophysiological measures showed a pattern of fluctuation in olfactory function comparable to that of the psychophysical results. These fluctuations do not seem to predict the course of the disease</td>
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</tbody>
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### Tab. II. Patients with Alzheimer’s disease or mild cognitive impairment.

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<tbody>
<tr>
<td>Payne et al., 2022</td>
<td>157 people (115 women, 42 men)</td>
<td>Patients, AD-mild stage (n = 63); Controls (n = 94)</td>
<td>Nice, France Quebec, Canada</td>
<td>NFOIT (New French Olfactory Identification test)</td>
<td>French: 27.5 (SD = 2.8); Canadian: 27.0 (SD = 3.2)</td>
<td>To use a new olfactory test to examine olfactory functions in Alzheimer’s patients and healthy people and to distinguish the French and Canadian populations</td>
<td>The test is able to significantly differentiate Alzheimer’s patients from healthy controls and to distinguish the French population tested from the Quebec population. The olfactory identification disorder is a target for early diagnosis of AD</td>
</tr>
<tr>
<td>Kashibayashi et al., 2021</td>
<td>218 (138 women, 80 men)</td>
<td>Patients, MCI; Patients, early AD (n = 218); No controls (n = 0)</td>
<td>Tatsuno, Japan</td>
<td>T&amp;T olfactometry (Thresholds for detection and identification of smells)</td>
<td>22.0 (SD = 4.0)</td>
<td>To elucidate brain regions associated with olfactory dysfunction in patients with mild cognitive impairment (MCI) and early Alzheimer’s disease (AD) by regional cerebral blood flow (CBF) detection</td>
<td>Olfactory identification dysfunction in patients with MCI and AD is attributable to reduced CBF of the left temporal pole, entorhinal area, and bilateral frontal pole</td>
</tr>
<tr>
<td>Lu et al., 2019</td>
<td>62 (33 women, 29 men)</td>
<td>MCI 72.8 (SD = 9.4); AD 73.7 (SD = 12.5); Controls 70.4 (SD = 10)</td>
<td>Hershey, Pennsylvania, USA</td>
<td>UPSIT (The University of Pennsylvania Smell Identification Test)</td>
<td>MCI: 26.63 (SD = 1.67); AD: 19.52 (SD = 5.66); Controls: 28.29 (SD = 1.64)</td>
<td>To investigate links between neurodegeneration, the olfactory network and the default mode network in Alzheimer’s Disease (AD)</td>
<td>Behaviorally, olfactory and memory scores showed a strong positive correlation in the study cohorts</td>
</tr>
</tbody>
</table>
Tab. II. cd. Patients with Alzheimer’s disease or mild cognitive impairment.

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<tr>
<td>Park et al., 2018</td>
<td>115 people (83 women, 32 men) Amnestic MCI (n = 50); Non-amnestic MCI (n = 28); Mild AD (n = 20); Patients with subjective memory impairment (n = 17)</td>
<td>72.3 (SD = 7.8)</td>
<td>Seoul, Korea</td>
<td>CCSIT (Cross-Cultural Smell Identification Test)</td>
<td>24.5 (SD = 4.3)</td>
<td>To compare the degree of olfactory identification impairment in each mild cognitive impairment (MCI) subtype, subjective memory impairment, and early Alzheimer’s disease (AD) dementia and to assess the relationship between olfactory identification and cognitive performance</td>
<td>Olfactory identification is impaired in amnestic mild cognitive impairment and Alzheimer’s disease</td>
</tr>
<tr>
<td>Hagemeier et al., 2016</td>
<td>80 people (47 women, 33 men) Patients, MCI (n = 19), Patients, AD (n = 42), Controls (n = 19)</td>
<td>MCI 73.6 (SD = 11.1); AD 76.0 (SD = 5.6); Controls 69.4 (SD = 2.9)</td>
<td>Buffalo, New York, USA</td>
<td>UPSIT</td>
<td>Not specified</td>
<td>To assess the association of volumetric differences in subcortical deep gray matter structures and odor identification deficit (OID) in subjects with amnestic mild cognitive impairment, those with AD, and normal controls</td>
<td>OID is a more specific marker of early pathological right mesial-temporal involvement than the currently regarded gold standard of right-sided memory. OID may be valuable in the longitudinal evaluation of disease modifying treatments in early disease course</td>
</tr>
<tr>
<td>Ryu et al., 2016</td>
<td>19 people (11 women, 8 men) Patients, MCI and reduced olfactory impairment (n = 10); Patients, MCI and relatively intact olfactory impairment (n = 9); No healthy controls (n = 0)</td>
<td>69.95 (SD = 8.2)</td>
<td>Daejeon, Korea</td>
<td>CCSIT, BTT (Butanol threshold test)</td>
<td>25.63 (SD = 1.89)</td>
<td>To explore how olfactory identification (OI) relates to white matter (WM) integrity, using diffusion tensor imaging in individuals with amnestic mild cognitive impairment (MCI)</td>
<td>Olfactory impairment contributes to WM microstructural alterations in individuals with amnestic MCI</td>
</tr>
<tr>
<td>Roberts et al., 2016</td>
<td>1,651 people (823 women, 828 men) Patients MCI (n = 221); Cognitive normal controls (n = 1,430)</td>
<td>Patients 82.1 (SD = 6); Controls 79.5 (SD = 5.3)</td>
<td>Rochester, Minnesota, USA</td>
<td>B-SIT (Brief Smell Identification Test)</td>
<td>Not specified</td>
<td>To examine associations of impaired olfaction with incident MCI subtypes and progression from MCI subtypes to AD dementia</td>
<td>Olfactory impairment predicts incident aMCI and progression from aMCI to AD dementia</td>
</tr>
<tr>
<td>Huart et al., 2015</td>
<td>39 people (22 women, 17 men) Patients, MCI (n = 13); Patients, post-infectious olfactory loss (PIO) (n = 13); Healthy controls (n = 13)</td>
<td>MCI 70.46 (SD = 5.97); PIO 52 (SD = 9.78); Controls 69.69 (SD = 8.35)</td>
<td>Brussels, Belgium</td>
<td>SST (Sniffin’ Sticks test)</td>
<td>≥24</td>
<td>To assess whether unihemispheric psychophysical and electrophysiological assessment of olfactory function can contribute to the diagnostic workup of mild cognitive impairment (MCI)</td>
<td>MCI patients exhibit a marked asymmetry of behavioral olfactory function, which could be useful for the diagnostic workup of MCI</td>
</tr>
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<tr>
<td>Vasavada et al., 2015</td>
<td>63 people (36 women, 27 men) Patients, MCI (n = 21); Patients, AD (n = 15); Controls (n = 27)</td>
<td>Hershey, Pennsylvania, USA</td>
<td>UPSIT</td>
<td>MCI: 26.5 (SD = 1.9), AD: 18.9 (SD = 5.4), Controls: 28.5 (SD = 1.5)</td>
<td>To test if structural degeneration of the primary olfactory cortex (POC) could be detected in AD as well as in MCI patients and would be correlated with olfactory functional magnetic resonance imaging (fMRI) alterations, reflecting loss of olfactory cortex activity</td>
<td>Decline in olfactory activity was correlated with the AD structural degeneration in the POC. A more prominent olfactory activity deficit than that of behavioral and tissue volume measurements was shown in the MCI stage</td>
</tr>
<tr>
<td>Makizako et al., 2014</td>
<td>220 people (112 women, 108 men) Patients, MCI and severe hyposmia (n = 36); Patients, MCI and non-severe hyposmia (n = 184); No controls (n = 0)</td>
<td>Obu, Japan</td>
<td>OE (Open essence test)</td>
<td>MCI and severe hyposmia: 25.4 (SD = 1.4), MCI and non-severe hyposmia: 26.8 (SD = 1.9)</td>
<td>To examine associations between olfactory function and cognitive performance scores</td>
<td>Olfactory impairment might be more closely associated with memory loss compared with other aspects of cognitive functioning in mild cognitive impairment subjects</td>
</tr>
<tr>
<td>Marigliano et al., 2014</td>
<td>18 people (9 women, 9 men) Amnestic MCI (n = 18); No controls (n = 0)</td>
<td>L’Aquila, Italy</td>
<td>SST</td>
<td>25.7 (SD = 1.12)</td>
<td>To verify the role of olfactory test and volumetric magnetic resonance imaging measurement of the hippocampus and to predict conversion from mild cognitive impairment to Alzheimer’s Disease (AD)</td>
<td>There is potential utility of the olfactory test and hippocampal volume loss for early detection of AD</td>
</tr>
<tr>
<td>Velayudhan et al., 2013</td>
<td>81 people (49 women, 32 men) Patients AD (n = 57); Controls (n = 24)</td>
<td>Leicester, UK</td>
<td>UPSIT</td>
<td>AD: 21.6 (SD = 3.7), Controls: 29.1 (SD = 0.9)</td>
<td>To evaluate the associations between olfactory identification impairment and cognition, illness severity, and progression in AD patients</td>
<td>There is an association between smell identification function and cognition and its utility as an adjunct clinical measure to assess severity in AD</td>
</tr>
<tr>
<td>Jimbo et al., 2011</td>
<td>117 people (80 women, 37 men) Patients, AD (n = 100); Controls (n = 17)</td>
<td>Tottori, Japan</td>
<td>OSTIT-J (Odor Stick Identification Test for the Japanese)</td>
<td>Not specified</td>
<td>To examine olfactory and other indexes to investigate correlations between them and the validity of an olfactory test for screening for AD</td>
<td>The olfactory tests such as the Odor Stick Identification Test for the Japanese can be useful for assessing severity of AD, including cognitive dysfunction</td>
</tr>
</tbody>
</table>
aim was to find and assess therapeutic and rehabilitation methods for restoring or improving participants’ smell function and those which used animals instead of living humans.

Among articles on the assessment of smell function in participants with dementia or particular neurodegenerative diseases, only original studies with subjects at a median age of 60 years or older were selected. Those assessing smell with multiple other factors such as speech, hearing, or gait impairments were subsequently excluded. Finally, articles which did not clearly state the methods used to assess smell or did not adequately describe the participants were also excluded.

RESULTS

Using the above-mentioned keywords and the 2000–2022 time frame, a total of 1,288 records were identified through the database search. A total of 1,052 records were excluded because they were not directly related to the issue of interest. Subsequently, 157 duplicates found in multiple databases were removed, as were another 30 articles which did not meet the inclusion criteria. Forty-nine articles were ultimately included in the analysis and divided into four subgroups. The entire search process is shown in Fig. 1.

Group 1 (PD; n = 13) includes studies in which the participants had Parkinson’s disease [8, 13, 15, 41–50]. Group 2 (AD + MCI; n = 16) includes studies whose participants had Alzheimer’s disease [7, 51–54] or mild cognitive impairment [11, 17, 55–58] as well as studies combining both types of patients [16, 18, 59–61]. Group 3 (Other; n = 2) includes studies whose participants had other neurodegenerative diseases, cognitive disorders, or combinations of them [62, 63]. Finally, Group 4 (Reviews; n = 18) consists of relevant reviews and systematic reviews [29, 64–80]. The most important characteristics of the studies classified into these groups are summarized in Tab. I.–IV.
The studies were conducted in the USA (n = 7) [11, 16, 18, 53, 54, 60, 63], Japan (n = 6) [42, 46, 49, 52, 56, 59], South Korea (n = 3) [17, 47, 61], Turkey (n = 2) [13, 48], Brazil (n = 2) [8, 50], France (n = 1) [7], Belgium (n = 1) [55], Italy (n = 1) [58], the United Kingdom (n = 1) [51], Poland (n = 1) [57], Denmark (n = 1) [62], India (n = 1) [41], Spain (n = 1) [43], Sweden (n = 1) [44], Germany (n = 1) [45], and Switzerland (n = 1) [15]. Between the years 2000 and 2005, one study and one review [54, 74] were published. Between 2006 and 2010, four studies [15, 50, 53, 63] and two reviews [64, 73] were published. Between 2011 and 2015, a total of 12 studies [18, 45, 47–49, 51, 52, 55–58, 62] and five reviews [66, 67, 70–72] were published. Between 2016 and 2020, a total of 12 studies [8, 11, 13, 16, 17, 41–44, 60, 61] and seven reviews [65, 68, 75–78, 80] were published. In the past two years, two studies [7, 59] and three reviews [29, 69, 79] have been published.

The numbers of participants in the studies ranged from 18 [58] to 1,651 [11]. Regarding gender distribution, the numbers of males varied depending on the study type, ranging from eight [17, 53] to 828 [11]; there were between five [15] and 823 [11] females included in the studies. The mean age, if stated by the authors, of all patients with neurodegenerative diseases ranged from 61.4 [43] to 82.1 years [11] and that of the controls ranged from 61.0 [62] to 79.5 years [11].

Across the studies, a wide variety of tests were used to assess smell. While some authors opted for a single test, others combined several. When considering only the widely used psychophysical smell tests, those most frequently reported in the articles were the Sniffin’ Sticks test [8, 13, 15, 45, 50, 53, 55, 57, 58] and the University of Pennsylvania Smell Identification Test [16, 18, 43, 48, 51, 53, 60, 62, 63], both used in nine studies. These were followed by the Cross-Cultural Smell Identification Test [17, 47, 61, 62] and the Open Essence test [42, 46, 49, 56], found in four studies each. Some authors administered their own smell tests to the participants [7], sometimes together with the widely used ones. All smell tests used in the studies are listed in Tab. V.

The selected records were classified as literature reviews, systematic reviews, or studies assessing olfaction in patients with Parkinson’s disease, Alzheimer’s disease, mild cognitive impairment, or other neurocognitive disorders.

Studies involving patients with Parkinson’s disease

The earliest study addressing the relationship between olfactory dysfunction and Parkinson’s disease was conducted by Meusel et al., who investigated long-term changes to so-called olfactory event-related potentials and their association with the course of the condition. They found an overall decrease in mean olfactory function [15].

In their 2013 study, Homma et al. [49] assessed the association between olfactory loss and Parkinson’s disease and the use of olfactory tests as a potential screening tool for early diagnosis of the condition. The participants were patients with Parkinson’s disease, those with other neurological diseases, and healthy controls. The authors found more severe olfactory loss in the subjects with Parkinson’s disease compared to the patients with other neurological diseases or the healthy controls [49].

A year later, the relationship between olfactory dysfunction and cognitive impairment was studied in patients with early idiopathic Parkinson’s disease. Once again, impaired olfactory function was confirmed in the early stages of the condition; in this study, it accompanied poor episodic verbal memory scores in selected patients [48]. In the same year, Lee et al. administered olfactory identification tests to Parkinson’s patients, classified them into subgroups according to their performance, and assessed the correlation between gray matter density – measured with MRI – and olfactory performance. They found that to minimize the exhibition of cognitive impairment, high olfactory performance may compensate for gray matter density loss [47].

In 2015, Paschå et al. used subjective smell tests and MRI to ascertain whether a detectable volume loss of the olfactory bulb can be
In 2020, the results of two studies were published. Patel et al. [41] examined olfactory impairment in Parkinson's patients, unawareness of hyposmia in both Parkinson's patients and controls, and its correlation with cognitive impairment. The patients' unawareness of hyposmia was higher than that of the elderly controls. The authors recommended that the Indian Smell Identification Test be used in population screening for early detection of Parkinson's disease at the earliest stage of neurodegeneration [41]. The last study in this section of the review was conducted in Turkey. Its aim was to assess associations between olfactory and cognitive impairment in Parkinson's patients and the feasibility of using smell tests to predict the development of dementia in these patients. The correlation was confirmed and the authors supported other experts' opinions that recommended smell tests as a predictor of the likelihood of dementia in Parkinson's patients [13].

According to the conclusions of the above-mentioned studies, olfactory dysfunction can be observed in patients with Parkinson's disease, even at the early stages of the disease.
They found a marked asymmetry of behavioral olfactory function and that patients with early Alzheimer’s disease exhibited olfactory impairment – namely, perceptual deficits in odor identification associated with disrupted odor quality coding in the posterior piriform cortex [53].

In 2010, a US study using functional MRI and smell tests observed that patients with early Alzheimer’s disease exhibited olfactory impairment – namely, perceptual deficits in odor identification associated with disrupted odor quality coding in the posterior piriform cortex [53].

A year later, Jimbo et al. studied the utility of smell tests as a potential tool for diagnosing Alzheimer’s disease. Unlike the controls, patients with Alzheimer’s disease, including the early stages, were shown to have olfactory dysfunction. Additionally, a correlation between cognitive and olfactory functions was confirmed. The authors concluded that smell tests may be useful for assessing the severity of Alzheimer’s disease and identifying cognitive impairment [52]. A 2011 Polish study aimed to investigate whether smell tests combined with neuropsychological testing and MRI may improve prediction of the development of dementia in patients with mild cognitive impairment. The authors confirmed correlations between olfactory impairment, cognitive impairment, and reduced hippocampal volume. They suggested that neuropsychological and smell testing may better predict the progression of mild cognitive impairment to dementia [57].

A 2013 study by British authors was concerned with associations of olfactory impairment with cognition and illness severity in Alzheimer’s patients. Once again, the relationship between smell and cognition was confirmed [51].

In the following year, Makizako et al. studied the association between olfactory function and cognitive performance scores in patients with mild cognitive impairment. They concluded that in these patients, olfactory impairment could be closely related to memory loss rather than other cognitive functions [56]. Marigliano et al. [58] wondered whether smell tests and hippocampal volume measurement by MRI could predict the progression of mild cognitive impairment to dementia. The hypothesis was confirmed, in line with other authors recommending smell tests combined with objective hippocampal volume measurement for early detection of Alzheimer’s disease [58].

In 2015, Huart et al. [55] published a study assessing whether smell tests may contribute to the diagnosis of mild cognitive impairment. They found a marked asymmetry of behavioral olfactory function exhibited by patients with mild cognitive impairment, a finding potentially useful for diagnosing the condition [55]. In the same year, a US study used functional MRI and smell tests to ascertain whether patients with mild cognitive impairment and those with Alzheimer’s disease show correlations between structural degeneration of the primary olfactory cortex and olfactory impairment. The study found that a decline in olfactory activity correlated with the degeneration in both Alzheimer’s patients and patients with mild cognitive impairment [18].

In the following year, Roberts et al. conducted a large study involving 1,651 participants to investigate the association between olfactory dysfunction and mild cognitive impairment subtypes and their progression to Alzheimer’s dementia. They confirmed that olfactory impairment may predict the development of mild cognitive impairment and progression to Alzheimer’s dementia [11].

Other US researchers studied the association between volumetric differences in subcortical deep gray matter structures and olfactory impairment in patients with amnestic mild cognitive impairment, Alzheimer’s patients, and healthy controls. Once again, their results confirmed that the Alzheimer’s patients had significant olfactory impairment and reduced brain volume; odor identification deficit in these patients was associated with bilaterally lower hippocampal and left amygdala volumes [16]. Finally, Ryu et al. investigated the association between olfaction and the integrity of the brain’s white matter in patients with amnestic mild cognitive impairment. They concluded that olfactory impairment contributes to microstructural changes to the white matter in these patients [17].

A 2018 South Korean study compared the degree of olfactory impairment in patients with mild cognitive impairment, Alzheimer’s disease, and subjective memory impairment. Additionally, the association between odor identification and cognitive performance was investigated. The study confirmed that smell was significantly more impaired in patients with Alzheimer’s disease and amnestic mild cognitive impairment, as compared with those with non-amnestic mild cognitive impairment or subjective memory impairment [61].

A year later, Lu et al. administered the psychophysical University of Pennsylvania Smell Identification Test with olfactory functional MRI to participants with mild cognitive impairment or Alzheimer’s disease and healthy controls to study associations between olfaction, memory, and neurodegeneration in terms of activity and connectivity of the olfactory and default mode networks. The study provided evidence suggesting vulnerability of the two networks in Alzheimer’s disease and showed that the approach is beneficial in predicting Alzheimer’s dementia [60].

In 2021, Kashibayashi et al. focused their study on brain regions associated with olfactory impairment in patients with mild cognitive impairment and Alzheimer’s disease. To that end, they used...
odor detection and identification tests combined with cerebral flow imaging. The authors found olfactory identification dysfunction to be associated with reduced blood flow in the left temporal pole, the entorhinal area, and the bilateral frontal pole [59].

The latest article included in this review was published by Payne et al. in 2022. The participants were French and Canadian patients with mild Alzheimer’s disease and healthy controls. They developed a new test to differentiate Alzheimer’s patients from controls and the French sample from the Canadian one. The study results showed that the new smell test was able to differentiate the subgroups. Additionally, the authors confirmed that olfactory impairment is a target for early diagnosis of Alzheimer’s disease [7].

Similar to Parkinson’s disease, in patients with Alzheimer’s disease, olfactory impairment or olfactory loss can be detected in the early stages. Some authors have confirmed that combining neuropsychological tests with olfactory tests can better predict the progression of mild cognitive impairment to dementia.

Studies involving patients with other neurodegenerative diseases

In 2008, Dulay et al. published the results of their study assessing three smell tests in 138 participants to ascertain how the test results are influenced by cognitive functioning. Of the three smell tests, two were found to be significantly influenced by some of the tested cognitive variables [63].

A 2014 longitudinal study comprising 129 patients aimed to find out whether smell tests combined with dopamine transporter imaging could predict their final diagnosis. The authors’ hypothesis relied on the finding that while most patients with idiopathic Parkinson’s disease or dementia with Lewy bodies are hyposmic, olfactory function remains unchanged in patients with other atypical disorders. They concluded that dopamine transporter imaging combined with smell tests may be used for diagnosis, since 91% of patients with idiopathic Parkinson’s disease or dementia with Lewy bodies were correctly identified, unlike those with other atypical disorders [62].

Patients with neurodegenerative diseases other than Parkinson’s and Alzheimer’s may also have olfactory impairment. The authors recommend the use of diagnostic tests in combination with smell tests for possible differential diagnosis.

LIMITATIONS

This review has several limitations, as listed below.

1. Although the database search yielded numerous studies on the association between smell and cognitive functioning, only 49 articles remained after the inclusion criteria were applied. The limitation is that other high-quality studies could have been published, but were not included in the review because they did not meet our criteria;
2. There were differences in smell testing methods used in the studies. While some authors used only subjective tests, others combined them with objective imaging methods. Articles reporting only objective findings were excluded;
3. Despite using similar methods, the specific study objectives varied to some extent;
4. The authors of the studies used different exclusion criteria, with some excluding patients with dementia, others excluding patients without dementia, and yet others excluding smokers, etc.;
5. Since various smell test methods were used across the studies, it was impossible to compare the results numerically.

Several authors confirmed that smell tests may serve as a screening tool for early detection of neurocognitive and neurodegenerative diseases and recommended they be introduced into clinical practice. They added, however, that the routine use of such screening methods requires long-term follow-up and subsequent assessment of their usefulness in clinical practice. Therefore, the issue should continue to be studied.
DISCUSSION

Olfactory dysfunction can arise from a variety of causes. Taste and olfactory impairment have been described in patients diagnosed with nasal polyps [81, 82], and the degree of olfactory impairment correlated significantly with the size of the pathological lesion [81]. Other causes of olfactory dysfunction have been identified as allergic rhinitis [83] or SARS-CoV-2 infection, among others [84, 85]. The investigation of the association between olfactory impairment and cognitive decline is also of current interest. Its relationship to neurocognitive disorders is frequently reported and discussed in the literature. Although the association between olfactory impairment and Parkinson's disease, mild cognitive impairment, or Alzheimer's disease is studied most frequently, other neurodegenerative disorders should also be mentioned. In these conditions, smell is often affected before other clinical manifestations are observed. Therefore, the use of smell tests as screening tools in clinical practice has been considered. Some authors have already attempted to use smell testing as a potential biomarker for early detection of neurodegenerative diseases [86]. However, practical implementation of such methods requires repetition, evaluation, and follow-up.

While some authors assess and describe participants' olfactory impairment only through subjective psychophysical smell testing [49, 56], others compared pathologies identified by objective evaluation with subjective smell test results [16–18]. The number of literature or systematic reviews already published proves the topic’s relevance.

Due to the large number of records identified, we decided against including a category of studies which assessed olfaction together with other abilities, such as hearing, speech, or gait [87]. Also, we were considering the inclusion of a 2008 population-based longitudinal study testing smell in the general population (n = 1,920). Five years later, the testing was repeated to assess the impact of olfactory dysfunction on the prediction of cognitive disorders. The authors found that a significantly higher proportion of participants with low San Diego Odor Identification Test final scores at baseline developed cognitive impairment than those with high test scores [5]. In the end, the study was excluded because the sample comprised the general population with no cognitive decline. Authors across the studies consistently concluded that unlike healthy controls, patients with neurocognitive disorders or neurodegenerative diseases exhibited olfactory impairment [8, 45, 51, 60] that worsened as their condition progressed. Many of them suggest that smell testing should be used for early diagnosis of neurodegenerative disorders.

CONCLUSIONS

Olfactory dysfunction was found to be present in patients with Alzheimer's disease, Parkinson's disease, mild cognitive impairment, and other neurodegenerative diseases. Given the fact that olfactory impairment may often be noticed as early as in the preclinical stage of neurodegenerative diseases, research has been conducted to find out whether smell testing could be used in clinical practice as a screening tool for early detection of neurocognitive disorders. Although many authors recommend that smell tests be introduced into practice, others are hesitant, stating that even though smell tests are able to detect olfactory loss caused by neurodegenerative diseases, they cannot reliably distinguish between certain diseases. At present, these issues are being addressed by many researchers, as seen from the many literature and systematic reviews that have been published. Continued and repeated research may draw more attention of both professionals and the public and may confirm the earlier findings.

ACKNOWLEDGEMENTS

Supported by the Czech Ministry of Health (project NU20-09-00119).

FUNDING

The authors declared that this study was financially supported by the Czech Ministry of Health (project NU20-09-00119). All rights reserved.

DATA AVAILABILITY STATEMENT

The study materials and the details of all analyses are available from the corresponding authors upon reasonable request.

REFERENCES


