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REVIEW

Olfactory Dysfunction as an Early Biomarker in Parkinson's Disease

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Abstract Olfactory dysfunction is common in Parkinson's disease (PD) and often predates the diagnosis by years, reflecting early deposition of Lewy pathology, the histologic hallmark of PD, in the olfactory bulb. Clinical tests are available that allow for the rapid characterization of olfactory dysfunction, including tests of odor identification, discrimination, detection, and recognition thresholds, memory, and tests assessing the build-up of odor intensity across increasing suprathreshold stimulus concentrations. The high prevalence of olfactory impairment, along with the ease and low cost of assessment, has fostered great interest in olfaction as a potential biomarker for PD. Hyposmia may help differentiate PD from other causes of parkinsonism, and may also aid in the identification of "pre-motor" PD due to the early pathologic involvement of olfactory pathways. Olfactory function is also correlated with other non-motor features of PD and may serve as a predictor of cognitive decline. In this article, we summarize the existing literature on olfaction in PD, focusing on the potential for olfaction as a biomarker for early or differential diagnosis and prognosis.

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Introduction

Parkinson's disease (PD) is a common neurodegenerative disease that affects 10 million people globally and at least 1.5 million in the United States, numbers that are expected to double by the year 2030 due to the aging population [1, 2]. A clinical diagnosis of PD is currently made based on motor features, including tremor, bradykinesia, rigidity, and postural instability. However, it has been increasingly recognized that the clinical spectrum of PD includes far more than motor symptoms, and many non-motor features may predate the classic motor features by years. Olfactory impairment is one of the most common and best characterized non-motor features in PD with a prevalence of 50%–90%. Hyposmia is often one of the first manifestations of the disease [3–5], and the olfactory bulb (along with the lower brainstem) are thought to be induction sites for alpha-synuclein pathology, which later spreads through the rostral brainstem to the cerebral cortex [6, 7]. These observations, along with the ease of assessment and low cost of measuring olfactory function, have fostered great interest in olfaction as a potential biomarker in PD. In this review, we discuss the role of olfaction as a biomarker in PD for differential diagnosis, "pre-motor" diagnosis, and prognosis.

Potential Mechanisms and Pathological Correlates of Olfactory Impairment

The mechanisms involved in olfactory loss in PD are currently unknown, but may involve neuropathological

alterations and/or dysfunction caused by changes in neurotransmitter levels in the olfactory system.

Pathological Correlates of Olfactory Impairment

The presence of Lewy bodies in the substantia nigra is a pathological hallmark of PD. According to Braak staging, Lewy pathology begins in the olfactory bulb and dorsal motor nucleus of the vagus, consistent with the early onset of olfactory dysfunction [6]. Pathology then moves up the brainstem to involve the medulla and pontine tegmentum, and by Braak stage 3, it reaches the substantia nigra, at which point motor symptoms develop [8]. Further support for the olfactory bulb as a possible induction site for Lewy pathology comes from neuropathological studies examining brains of neurologically normal individuals who are found to have incidental Lewy bodies. Beach and colleagues found that when only one brain region was affected in those with incidental Lewy bodies, it was most commonly the olfactory bulb [9]. Lewy pathology in the olfactory bulb has also been shown to be 95% sensitive and 91% specific for identifying PD *versus* elderly controls, and accurately predicts the presence of pathology in other brain regions [10]. The synucleinopathy density scores in the olfactory bulb are correlated with UPDRS motor scores, suggesting that pathology develops early and continues to accumulate [10].

Pathological changes are also seen in other areas of the olfactory system, including the anterior olfactory nucleus (AON), cortical nucleus of the amygdala, piriform cortex, olfactory tubercle, entorhinal cortex, and orbitofrontal cortex. The AON is closely associated with the olfactory bulb, and Lewy pathology in the AON is correlated with neuronal loss in this region [11]. In the neuropathological study by Pearce *et al.* neuronal counts in the AON were greatly reduced in patients with the longest disease duration, and the olfactory nerves were grossly atrophic in all PD cases [11]. The cortical nucleus of the amygdala receives the primary olfactory bulb projections and demonstrates more alpha-synuclein pathology and neuronal loss than other nuclei in the amygdala [12]. The degree of pathology seen in the amygdala is strongly correlated with that seen in the AON [12]. It has been suggested that alpha-synuclein pathology may spread from peripheral to central olfactory structures as part of the olfactory vector hypothesis [13]. This is supported by a study of 10 PD cases and 12 controls (7 with incidental Lewy bodies), in which all of those with PD and incidental Lewy bodies demonstrated alpha-synuclein pathology in five sub-regions of the primary olfactory cortex. The temporal piriform cortex showed more alpha-synuclein pathology than the frontal divisions, the olfactory tubercle, and the anterior portions of the entorhinal cortex. All of these areas demonstrated more pathology than the orbitofrontal cortex [14]. These data suggest that early pathology in PD involves the olfactory bulb and associated structures and may progress from the periphery to central structures.

In addition to alpha-synuclein pathology, tau pathology has also been found in the AON in PD [15, 16]. Interestingly, patients with corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP), parkinsonian disorders with little or no olfactory loss, did not demonstrate tau pathology in the AON, suggesting that tau may contribute to olfactory impairment in PD [15, 16].

Neurotransmitter Alterations

Multiple neurotransmitters are altered in PD and several have demonstrated associations with olfactory loss, including dopamine, acetylcholine, and serotonin. A comprehensive review of the potential role of these changes in the pathogenesis of olfactory loss in PD is discussed in a review by Doty [17], which is briefly summarized here. Dopamine has long been known to play a major role in the pathogenesis of PD, but more recently its association with olfactory loss has been explored. Studies have shown correlations between olfactory tests and dopamine transporter (DAT) activity in the substantia nigra, striatum, and hippocampus in PD patients [18–20]. However, olfaction has not been found to be responsive to dopaminergic replacement therapy [21, 22]. Whether alterations in dopamine activity are directly associated with olfactory loss or whether there is a common underlying mechanism is unknown. Acetylcholine levels are also altered in PD. The nucleus basalis of Meynert is rich in acetylcholine-producing neurons and displays substantial neuronal loss in PD [23]. Damage to the nucleus basalis of Meynert is also seen in other neurodegenerative diseases with olfactory loss, most notably Alzheimer's disease (AD), whereas considerably less damage occurs in diseases with little or no olfactory loss, including PSP, amyotrophic lateral sclerosis, and multiple sclerosis [24]. These findings suggest that the association between changes in acetylcholine levels and olfactory impairment may not be specific to PD, and that a common mechanism may underlie olfactory impairment in neurodegenerative diseases. In addition, in a study using positron emission tomography, there was a moderate-to-strong correlation between University of Pennsylvania Smell Identification Test (UPSIT) scores and acetylcholinesterase activity in PD patients, further illustrating a potential association between acetylcholine and olfactory loss [25].

The third neurotransmitter with a possible role in the pathogenesis of olfactory dysfunction in PD is serotonin. Serotonin arises from the raphe nuclei, which send projections to the olfactory bulb [26]. In patients with PD, Lewy pathology is found in the raphe nuclei [27], along with marked depletion of serotonin in the olfactory bulb and other areas of the olfactory system [28]. Similar to the findings from studies of acetylcholine, relative preservation of serotonin was found in disorders with normal or near-normal olfaction, including PSP [29]. While the evidence is far from conclusive, these studies suggest that alterations in certain neurotransmitter levels may be involved in the olfactory loss in PD.

Measuring Olfaction

While olfactory impairment is common in PD, patients are most often unaware of the deficit. In one study, 72% of PD patients were unaware of their olfactory impairment prior to testing [4], and in a second study, 63% of patients overestimated their olfactory ability [30]. This finding is not limited to PD patients, as controls overestimate their olfactory ability as well, although to a lesser extent. In addition, in a separate population without neurodegenerative disease, awareness of olfactory deficits was inversely proportional to age, with older individuals less aware of their deficits [30]. These findings underscore the need for objective testing to accurately capture an individual's olfactory function.

Assessment of olfactory ability in the clinical setting typically consists of odor identification, odor discrimination, and odor detection threshold tasks. Odor identification methods involve the presentation of a suprathreshold concentration of an odor and participants must make a choice from several items. In odor discrimination tasks, participants are required to differentiate between, but not identify, odors. An odor may be presented in which a participant must discern that odor from a set of foils (scents that serve as a contrast to the odor in question). Similarly, an odor discrimination/memory test consists of smelling an odor and then identifying that odor from a set of alternatives after various delay intervals. Lastly, odor detection thresholds are frequently measured by presenting various concentrations of a given odor, usually in a forced-choice setting against blanks, in an ascending staircase series to determine the lowest concentration at which a subtle sensation can be perceived. In contrast, the lowest concentration at which an odor can be recognized is the recognition threshold and should be distinguished from the odor detection threshold [31].

Controversy exists over whether many of these tests measure a common source of variance [32] or whether certain tests, such as odor threshold, may assess more distinct properties of olfaction than odor identification and discrimination, both of which are based upon the presentation of suprathreshold odors [33]. In a meta-analysis of 43 studies of olfaction in PD, all tests showed relatively uniform impairment despite a small trend towards somewhat better performance on threshold measures than tests of recognition and identification [34] A principal components analysis by Doty *et al.* found that most tests of olfaction load on a single olfactory factor in healthy controls [32]. In addition, odor detection threshold tests have been shown to correlate highly with odor identification scores in controls and PD, and both load on the same component in a second principal component study [35]. While the various olfactory tests may be measuring a similar construct, the odor identification tasks are thought to require more cognitive and memory processing [36, 37].

Odor identification is the most frequently used measure of olfaction in the clinical setting. A commonly-used and well-characterized method is the UPSIT (sold as the Smell Identification Test, Sensonics, Inc., Haddon Heights, NJ), which is a "scratch 'n' sniff" test during which participants are sequentially presented with 40 microencapsulated odorants and required to choose among four descriptors for each odorant [38]. Since a number of odors are not universally recognized, the UPSIT has been adapted and validated for use in many different languages and cultures, and normative values for age and gender have been developed [39–42]. Additional "scratch 'n' sniff" odor identification tests include the 12-item Brief Smell Identification Test (B-SIT), also known as the Cross-Cultural Smell Identification Test (CC-SIT), which include universally recognizable items from the UPSIT [43]. A 3-item Pocket Smell Test™ and a 4-Item NHANES Pocket Smell Test™ are also available. These are all forced-choice odor identification tests that serve as screening tools of gross olfactory function and help determine which individuals should undergo a full UPSIT [44].

Tests of odor detection threshold include the Smell Threshold Test, which uses 17 squeeze-bottles of increasing concentrations of phenyl ethyl alcohol, and the Connecticut Chemosensory Clinical Research Center test, which consists of a smell detection threshold test using differing concentrations of butanol and a smell identification test [45]. "Sniffin' Sticks" are another well-characterized measure of olfactory performance that includes testing of odor identification, odor discrimination, and olfactory threshold, each of which can be tested alone or in combination [46, 47]. Pen-like odor dispensing devices are presented to the participant for each task and a combined "TDI score" is obtained when all tests are performed. Lastly, a newer threshold test includes the Snap & Sniff ® test in which different concentrations of a stimulus are presented using hand-held "wands". This test allows for the rapid and reliable determination of detection thresholds [48].

The utility of an olfactory test in the clinical setting depends upon its validity in the population being studied, reliability, ease of use, and cost. Because olfactory function can be influenced by multiple factors, including age, gender, and smoking status, it is important that normative data be available for a given test in order to accurately classify a patient's olfactory impairment [49, 50]. A review of the strengths and weaknesses of the various tests available has been published [51], as well as a review of tests that have been validated in PD [52].

Olfaction as a Biomarker

Differential Diagnosis

As discussed above, PD is a clinical diagnosis that is made based on criteria such as the United Kingdom Parkinson's Disease Society Brain Bank Clinical diagnostic criteria [53]. The accuracy of a clinical diagnosis ranges from 53% to 93% in clinicopathologic studies, depending on whether a neurologist or movement disorder specialist is making the diagnosis [54–57], and how long the patients have been followed. In one study, accuracy was only 53% when patients were followed for <5 years [58]. Since diagnostic accuracy is lowest early in the disease, this is the time when a marker like olfaction may be useful in distinguishing idiopathic PD from common differential diagnoses including essential tremor (ET), atypical parkinsonian syndromes, drug-induced parkinsonism, and vascular or other causes of parkinsonism (Table 1). For example, patients with tauopathies associated with parkinsonism, such as CBD and PSP, tend to have fairly normal olfactory function. Doty and colleagues and Silveira-Moriyama and colleagues demonstrated that olfactory identification in PSP is not significantly different from controls [59, 60]. Likewise, odor identification and odor thresholds were found to be normal in a study of PSP and CBD patients, which helped differentiate these disorders from idiopathic PD and multiple system atrophy (MSA) [61]. Idiopathic PD displays the most severe and consistent olfactory deficit of the parkinsonian disorders, while MSA tends to have olfactory impairment intermediate between PD and the tauopathies [62–64]. Based on this evidence, the American Academy of Neurology suggests that olfactory testing be considered to differentiate idiopathic PD from the tauopathies, but not from MSA [65].

In dementia syndromes with parkinsonism, both dementia with Lewy bodies (DLB) and AD patients may display olfactory impairment. In two small studies, hyposmia was more common and more severe in DLB than AD, but could not reliably differentiate between the two diseases because of the overlap of olfactory dysfunction in both groups [66, 67]. In a study of 122 patients with mild cognitive impairment (MCI), those who went on to develop DLB had lower CC-SIT scores than those who developed AD or remained stable [68]. Both odor identification scores and performance on visual memory function tests were independent predictors of a diagnosis of DLB rather than AD. Lastly, in a small study investigating olfactory ability in normal pressure hydrocephalus (NPH), patients with NPH had UPSIT scores within the normal range compared to published normative data, but somewhat lower than controls [69].

Olfactory function can also be used to help distinguish idiopathic PD from other forms of parkinsonism and tremor syndromes, including drug-induced parkinsonism (DIP), vascular parkinsonism, and ET. Clinically, DIP and PD may be indistinguishable, but a correct diagnosis has significant implications for treatment and prognosis. When parkinsonism develops in patients exposed to antidopaminergic drugs, it may represent simple drug-induced parkinsonism, or, in some cases, "unmasking" of prodromal PD in a previously asymptomatic patient who likely would have gone on to clinically manifest motor disease. In many studies, clinically diagnosed DIP patients had normal or near-normal olfaction and were reliably distinguished from PD patients [70–73]. In a case series of 33 patients who were evaluated for DIP using DAT-SPECT scans, 7 had abnormal scans. Of these, 86% demonstrated anosmia on smell testing compared to only 9% of those with normal DAT-SPECT scans [74]. This evidence suggests that olfactory testing may be used to differentiate DIP from PD, especially when DAT-SPECT imaging may not be available. It may also aid in the identification of patients with "unmasked" PD with presumed DIP whose symptoms do not resolve over time.

Vascular parkinsonism is common in aging populations and can also be difficult to distinguish clinically from PD. In a small study comparing olfactory function in patients with vascular parkinsonism, PD, and normal controls, the patients with PD had significantly lower UPSIT scores, while those with vascular parkinsonism did not differ from controls [75]. Likewise, olfactory function has been investigated in patients with ET and found to be similar to normal controls, while PD patients had significantly worse performance, suggesting olfaction may be useful to distinguish ET from tremor-predominant PD [76–78]. However, one study found slightly lower olfaction scores in ET patients compared to controls, but the UPSIT scores remained higher than those typically found in PD [79].

Pre-motor Diagnosis

Because olfactory impairment manifests years prior to the onset of motor symptoms, it has the potential to serve as an early diagnostic marker of PD (Table 1). Identifying

Table 1 Use of olfactory function testing for differential diagnosis, pre-motor diagnosis and prognosis.

Use of olfactory testing	Study findings	References
Differential diagnosis		
PD *versus* tauopathies (progressive supranuclear palsy and corticobasal degeneration)	Odor identification in PSP and CBD is similar to controls. Olfactory deficit can aid in discrimination between PD and tauopathies	[39–41]
PD *versus* multiple system atrophy (MSA)	Olfactory impairment in MSA is intermediate between PD and tauopathies. Olfactory ability should not be used to distinguish PD and MSA	[42–45]
PD, DLB *versus* Alzheimer's disease (AD)	PD, DLB and AD all demonstrate olfactory impairment. Hyposmia tends to be more common and more severe in PD and DLB than AD, but significant overlap prevents differentiation based on olfaction alone	[46–48]
PD *versus* normal pressure hydrocephalus (NPH)	Subjects with NPH had UPSIT scores within the normal range, distinguishing them from PD	[49]
PD *versus* drug-induced parkinsonism (DIP)	DIP subjects have normal or near normal olfaction and can be reliably distinguished from PD using olfactory testing	[50–55]
PD *versus* vascular parkinsonism	Olfactory function in vascular parkinsonism does not differ from controls. Olfactory impairment can help differentiate vascular parkinsonism from PD	[55]
PD *versus* essential tremor (ET)	Subjects with ET have olfactory function similar to controls. Testing olfaction may help differentiate the two	[56–59]
"Pre-motor" diagnosis		
	In HAAS, men with worst olfactory function had a 5.2 fold increased risk of developing PD within 4 years. In PRIPS, the odds of developing PD was almost 4 times higher in those with olfactory impairment. Olfactory impairment may help identify those at higher risk of developing PD, especially when combined with other biomarkers	[60–64]
Prognosis		
Motor progression	Majority of evidence suggests that olfactory impairment is independent of disease severity and disease duration, making it unlikely to be a reliable marker of disease progression	[3, 4, 80–88]
Non-motor progression	Olfactory impairment has been associated with apathy, autonomic symptoms, anxiety and depression in cross-section studies. Longitudinal studies are needed to determine if olfactory impairment can serve as a predictor of development or progression of non-motor symptoms	[93–97]
Cognitive decline	Baseline olfactory impairment has been associated with a faster rate of cognitive decline in early PD and has been identified as an independent risk factor for the development of dementia	[80, 102, 103]

patients with "pre-motor" PD, when only the earliest pathological changes are present, is a major unmet need, as it may improve the chances of success for neuroprotective and disease-modifying trials. Many studies have demonstrated an association between olfactory impairment and an increased risk of developing PD. In the Honolulu-Asia Aging Study (HAAS), men in the lowest quartile of olfactory function had a 5.2-fold increased risk of developing PD within four years [80]. The Prospective Validation of Risk Factors for the Development of Parkinson Syndromes study followed 1850 patients prospectively and found that the odds of developing PD was 3.94-times higher in those with olfactory impairment [81]. These findings are supported by clinico-pathologic studies which demonstrate a higher odds (up to 11 fold in HAAS) of incidental Lewy body pathology on autopsy for hyposmic patients without clinical PD compared to normosmic participants [82–84].

While olfactory dysfunction is a disease-sensitive indicator of underlying PD, the specificity is low due to the many other causes of hyposmia in other disorders and the general population. Therefore, screening based on olfactory function alone is unlikely to be adequate. To improve the positive predictive value of olfaction as a screening tool, many studies have used a combination of PD markers, screening in a high-risk population, or a tiered approach to screening in an enriched population to identify those at highest risk for developing PD. For example, when pre-motor markers (impaired olfaction, constipation, slow reaction time, excessive daytime sleepiness, and impaired executive function) were combined in HAAS, men with 2 or more features had up to a tenfold increased risk for the development of PD [85]. Other studies have combined olfactory testing with imaging. Sommer and colleagues identified 30 patients with idiopathic olfactory loss and found that 11 had increased echogenicity of the substantia

nigra on transcranial sonography [86]. Five of these patients had abnormal DAT imaging while two had borderline findings, suggesting olfaction and transcranial sonography together may help identify individuals at a high risk for PD [86].

A second approach to improving the positive predictive value of olfaction includes using olfactory screening in a population known to be at a high risk for developing PD. Rapid eye movement sleep behavior disorder (RBD) is a known potential harbinger for the development of an alpha-synucleinopathy, including PD, MSA, and DLB [87, 88]. Studies have demonstrated a higher incidence of olfactory impairment in RBD patients compared to controls [89–93]. In one prospective study of 34 patients with polysomnogram-confirmed RBD, patients in the lowest olfactory tertile had a relative risk of 7.3 for developing an alpha-synuclein-mediated neurodegenerative disease compared to the top two tertiles [94]. However, olfactory dysfunction in this population cannot differentiate between the three types of alpha-synucleinopathy.

Using olfactory testing as a prescreening tool, Ponsen and colleagues identified a group of 40 hyposmics and 38 normosmics from a cohort of 361 clinically unaffected first-degree relatives of PD patients [95]. Five out of the 40 hyposmic subjects developed PD by year 5 of follow-up compared to none of the normosmic subjects. All of the hyposmic individuals who went on to develop PD had an abnormal DAT scan at baseline. While this suggests that olfaction may be a useful prescreening tool, this study was performed in an already enriched population [96]. If this tiered approach were undertaken in the general population, it would likely lead to overuse of DAT imaging in healthy individuals. Combining olfaction with other markers of premotor PD may improve the positive predictive value [97]. The Parkinson At Risk Study followed a similar tiered approach, in which first-degree relatives underwent the UPSIT and a questionnaire on prodromal features of PD [98]. In this cohort, 11% of hyposmic subjects had a DAT deficit at baseline compared to 1% of normosmic subjects [99]. When hyposmia, male sex, and constipation were combined as predictors of DAT deficit, >40% of the participants with a DAT deficit were identified.

Marker of Disease Progression

In addition to serving as a marker of "pre-motor" PD, olfactory function has also been studied as a potential marker of disease progression (Table 1). Olfactory impairment appears largely independent of disease severity and disease duration in the vast majority of studies. In the Parkinson's Progression Marker's Initiative (PPMI), in which participants with a disease duration <2 years were recruited, olfactory impairment was not associated with UPDRS part III scores, disease duration, or DAT deficit [100]. Findings have been similar in other cohorts with early disease [21, 101] and more advanced disease [3, 22, 102–106]. Levodopa use has also not been found to influence olfactory performance [21, 22]. These studies suggest that olfactory impairment develops early or prior to the motor symptoms of PD and is fairly stable as motor symptoms progress. This may, at first, seem to be at odds with the discovery that the synucleinopathy density scores in the olfactory bulb correlate with UPDRS motor scores [10]. However, there are several possible explanations for these findings, including that tests of olfactory dysfunction may be subject to a "floor-effect" so that small changes in olfaction in the most affected individuals are not detected by olfactory tests. In addition, the olfactory dysfunction that is detected may be caused by early pathology and further accumulation may do little to alter test scores.

While much of this work has been done using cross-sectional study designs, two studies have explored the change in olfaction over time. Doty and colleagues administered the UPSIT to 24 PD patients on two occasions separated by a mean of 2 years and found no significant changes in the odor identification scores between the two measurements [4]. In a second study, 27 patients were followed for a mean of 4.4 years, and while olfactory impairment was not stable over the study period, it did not deteriorate in a linear fashion [104]. Some participants displayed small improvements over time, while others' scores worsened. These two studies again demonstrate a lack of association between olfactory impairment and disease duration.

While this evidence suggests that olfaction is not a suitable biomarker for motor disease progression, a few studies have shown small group-wide associations between measures of olfaction and disease severity or duration. In one small study of early PD patients, odor discrimination (but not identification) was associated with disease severity [101]. A larger study of 400 PD patients found that odor discrimination worsened with increasing disease duration [3]. Other smaller studies have shown associations between olfactory impairment and measures of disease severity [107–109] and DAT imaging [19]. However, the balance of evidence suggests that serial measurement of olfaction is unlikely to be a reliable marker of disease progression, especially in an individual. It is possible that by the time a diagnosis of PD is made based on emergent motor symptoms, the extent of olfactory impairment may be near its peak and then remain relatively static throughout the disease. Therefore, subsequent measurements of olfaction remain stable. Other potential explanations include the possibility that olfactory performance does not decline linearly, that current olfactory assessments are not precise enough to measure the decline that occurs in one year, or that there is a "floor-effect" in current olfactory tests so that small changes near anosmia may not be detected.

Association with Non-motor Symptoms

While olfaction is not a reliable marker of motor symptoms, it may be associated with common non-motor manifestations of PD. Multiple cross-sectional studies have explored the relationship between olfactory function and non-motor symptoms in PD. In one study, participants with higher apathy scores performed worse on the B-SIT compared to those without apathy [110]. In a second study of 232 patients, apathy was again associated with lower olfactory function [111]. Self-reported autonomic symptoms were higher in those with worse olfaction, while another study demonstrated that anosmic patients had significantly worse clinical and physiological markers of autonomic dysfunction than those with mild-to-moderate hyposmia [112, 113]. Berendse and colleagues found that anxiety and depression scores were higher in patients with worse olfaction [114]. It cannot be determined from these cross-sectional studies if the degree of olfactory impairment in early PD can serve as a predictor of the development or progression of these clinical features; however, ongoing longitudinal studies are likely to provide relevant evidence.

The association between olfactory dysfunction and cognitive impairment has been examined in both cross-sectional and longitudinal studies. In one study, general measures of cognition, including the Mini-Mental Status Examination, were not associated with hyposmia [106], while others have shown associations between olfaction and specific cognitive domains, including episodic verbal learning and verbal memory [25, 115–117]. In a retrospective cohort study, worse baseline olfaction predicted self-reported cognitive impairment several years later, while a small longitudinal study demonstrated that severe hyposmia was an independent risk factor for the development of dementia within 3 years [118]. In a study of 125 newly diagnosed PD patients followed for a mean of 6 years, hyposmia at baseline was associated with an increased risk of developing dementia (hazard ratio = 3.29) [119]. In a second prospective cohort of early PD patients (diagnosis within 2 years), olfactory impairment was associated with a faster rate of decline in both global cognition and several cognitive domains, specifically verbal memory, executive function, and attention [100]. When combined with cerebrospinal fluid (CSF) biomarkers, worse olfaction was also associated with conversion to MCI over a 3-year period. Given that the olfactory system is one of the first areas affected by Lewy pathology [6], worse olfaction may reflect more severe extranigral disease and therefore be associated with earlier cognitive impairment through cortical involvement.

The combination of olfaction with other markers of disease progression may improve the prognostic ability of the biomarkers. In one study of 98 patients with early PD, those with RBD and hyposmia had worse global cognition and were more likely to exhibit the akinetic-rigid phenotype [120]. In a second study involving the PPMI cohort, the combination of age, UPSIT score, RBD screening questionnaire, CSF amyloid beta, and caudate uptake on DAT imaging was the best predictor of cognitive impairment at two years with an area under the curve of 0.80 [121]. Further prospective studies will be needed to assess how olfaction, alone or in combination with other biomarkers, may be a useful predictor for cognitive impairment or other non-motor symptoms.

Other Measures of the Olfactory System as Potential Biomarkers

Lastly, more recent studies have explored the use of other measures of the olfactory system, such as biopsies of olfactory epithelium, measurements of olfactory bulb volume, and functional neuroimaging, as potential biomarkers in PD. In one such study, Hummel and colleagues found no pathological changes in the nasal mucosa that were specific to PD patients compared to non-PD patients who had other causes of hyposmia, confirming earlier results [122–124]. In addition, when using magnetic resonance imaging (MRI) to measure olfactory bulb volume in 11 PD patients and 9 normosmic controls, this group found no significant differences in olfactory bulb volume between PD and controls, nor did volume correlate with degree of olfactory loss in the PD patients [122]. Subsequent studies, however, have had mixed results. Some have demonstrated smaller olfactory bulb volumes in PD patients compared to controls, including a recent meta-analysis of 6 case–control studies of 216 PD patients and 175 controls [125–129]. Other studies have shown no difference in olfactory bulb volumes between PD and controls, as well as no correlation between volume and disease features, such as disease duration, disease severity, or severity of olfactory impairment [130–132]. It should be noted, however, that there was significant heterogeneity among these studies, including country of origin and magnetic field intensity on MRI. Additional studies are needed to determine conclusively if measuring olfactory bulb volume by MRI can differentiate PD from non-PD patients.

Functional MRI has also been studied as a means to differentiate PD from controls. In a study of 12 hyposmic PD patients and 16 healthy controls, neuronal activity in the amygdala and hippocampus was reduced in the PD patients compared to controls [122]. In a second study, PD patients with hyposmia demonstrated altered functional activity in the primary olfactory cortices as well as the secondary olfactory structures compared to controls [133], although additional larger cohorts are needed to confirm these results.

Summary and Future Directions

Clinical measures of olfactory function are inexpensive and easy to administer, making olfaction an attractive biomarker for PD. In this review, we summarized the evidence for the use of olfaction as a biomarker for PD, including use for differential diagnosis, pre-motor diagnosis, and prognosis. Overall, olfactory testing may be useful in differentiating idiopathic PD from tauopathies (PSP and CBD), as well as from non-degenerative causes of parkinsonism, including NPH, DIP, vascular parkinsonism, and ET. Because of the overlap in olfactory impairment, olfactory testing is not recommended as a tool to discriminate PD from MSA or AD. Importantly, olfactory impairment may aid in the identification of "pre-motor" PD, which is essential for the conduct of neuroprotective trials. However, a sequential combination of markers of "pre-motor" PD may best identify an at-risk population where olfactory testing is a simple, sensitive—but non-specific—first step. Finally, we discussed the use of olfactory dysfunction as a marker of disease progression. Current evidence suggests the potential of olfaction to predict future cognitive impairment, especially in combination with other biomarkers, and ongoing prospective longitudinal studies are likely to shed more light on its utility. The potential use of other measurements of the olfactory system (i.e., clinical biopsy or radiological methods) remains in its infancy, and further studies are needed to assess the suitability of these methods as a biomarker for PD.

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