

Review

# The Anatomy and Clinical Significance of Sensory Disturbance in Parkinson's Disease

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## Abstract

The clinical features of Parkinson's disease (PD) include tremors and rigidity. However, paresthesia has not drawn clinical attention. PD involves the whole body and begins with gastrointestinal lesions, which do not start in the midbrain substantia nigra, but from the beginning of the medulla oblongata of the glossopharyngeal nerve nuclei, to the motor nerve dorsal nucleus of the vagus nerve, to the pons and midbrain, and finally to the neocortex. The human eye, ear, nose, tongue, and body perceive the external world. (1) Visual impairment in patients with PD can be easily confused with senile eye disease. This change in retinal pigment cells has many similarities to the degeneration of dopaminergic neurons in the substantia nigra in PD. (2) Selective high-frequency hearing impairment can cause a certain degree of communication barriers, only understanding the son's bass but not the daughter's soprano, and there is a certain relationship between hearing and body postural balance. (3) Olfactory loss is one of the earliest signs of PD and an important indicator for the early screening of PD. (4) Taste disorders, including loss of taste and taste memory, can cause cognitive impairment. (5) The body's sense of touch, pressure, pain, temperature, and position abnormalities interfere with the motor symptoms of PD and seriously affect the quality of life of patients. This article discusses vision, hearing, smell, taste, touch, and analyses of neuroanatomy and pathology, revealing its clinical significance.

**Keywords:** Parkinson's disease; paresthesia; anatomy;  $\alpha$ -synuclein

## 1. Introduction

The British physician James Parkinson first reported "parkinsonism" in 1817, and humans have never stopped researching "Parkinson's disease" (PD) for more than 200 years. According to the eighth edition of the Clinical Medicine's undergraduate neurology textbook in China, "Parkinson's disease, also known as parkinsonism, is a neurodegenerative disease commonly seen in middle-aged and elderly people and is clinically characterized by resting tremor, bradykinesia, rigidity, and postural balance disorders" [1]. According to this definition, people are only concerned with motor symptoms in PD and ignore sensory disturbances [2–7].

PD is characterized by degeneration and a sharp decrease in the number of dopamine and other pigment-containing neurons in the substantia nigra pars compacta, locus coeruleus, raphe nucleus, and dorsal vagus nucleus [8–15], as well as the appearance of eosinophilic inclusions (Lewy bodies) in the cytoplasm of the remaining neurons [16–18]. Patients with PD first exhibit abnormal  $\alpha$ -synuclein deposition in gastrointestinal tissues other than the brain [19–21], such as the antral mucosa, colonic mucosa, and tissues surrounding the submandibular gland [22–27]. PD is thus a disease that affects the entire body. Le-

sions in the brain do not begin in the substantia nigra of the midbrain but begin in the glossopharyngeal nucleus of the medulla oblongata, affect the dorsal motor nucleus of the vagus nerve, and then reach the pons, midbrain, and finally the neocortex. Multiple organ multi-target injuries account for a wide range of motor and sensory disturbances in PD, including motor and non-motor symptoms [28–31]. Humans use sensory organs, such as the eyes, ears, nose, tongue, and body, to detect changes in the external world and make appropriate adjustments. This is necessary for the survival and development of humans. Therefore, this paper examines and explains the neuroanatomical pathways associated with sensory disorders, such as visual, auditory, olfactory, gustatory, tactile, pressure, and pain sensations, in PD.

## 2. Visual Disturbance in PD

Diplopia, color discrimination disorder, contrast recognition disorder, saccadic dysfunction, spatial perception disorder, visual hallucinations, and dry eye are visual symptoms of PD [32–37]. Degeneration of the substantia nigra in the midbrain reduces dopamine production and release.  $\alpha$ -synuclein deposition is also present in the inner nuclear layer, inner lamella, and ganglion cell layer



of the retina away from the midbrain [38], which is similar to dopaminergic nerve cell dysfunction and results in decreased visual conduction efficacy and acuity. In patients with PD, retinal fluorescein angiography revealed reduced avascular areas and increased vascular density in the fovea, implying compensatory vascular proliferation with dopamine neuron injury [39].

In patients with PD, optical coherence tomography revealed weakening of the macular region and gradual aggravation of the retinal nerve fiber layer [40]. Before experiencing visual impairment, patients with PD have a slow metabolism and decreased dopamine activity in the primary visual cortex. Reduced dopaminergic neurons in the frontal and basal ganglia affect the modulation of pupillary light responses and saccadic eye movements [41].

Different waveforms of electroretinograms (ERG) reflect the functional status and changes in dopamine levels in the retina of patients with PD. Pattern ERG reflects ganglion cell function and ERG reflects the functional changes in retinal pigment epithelial cells and photoreceptors by measuring the changes in resting potentials in the anterior and posterior poles of the eyeball during dark and light adaptation [42–47]. Clinical studies [48] have shown that the granular cell layer is significantly damaged in the early stage of PD, and levodopa treatment can shorten the latency of visual evoked potentials (VEP) and improve the intermediate frequency of pattern ERG in PD patients. Theta values of global domain synchronization of EEG in patients with PD increased in the eyes-closed state and cortical responses decreased after intermittent stimulation [49].

### 3. Auditory Disorders in PD

Patients with PD are unable to differentiate high-frequency speech sounds, such as the daughter's voice, but can clearly hear the son's bass tone.

The auditory nerve first enters the cochlear nucleus, where it splits into two branches, one of which sends fibers to the anteroventral nucleus of the cochlear nerve and the other to the postventral nucleus of the cochlear nerve and posterior nucleus of the cochlear nerve. Low-frequency fibers extend ventrally, whereas high-frequency fibers are distributed dorsally according to an organized pattern of tonotopic projections that pass through the cochlear nucleus [50–56]. The electrical impulses from each nucleus on the auditory pathway from the auditory nerve to the auditory cortex are clinically recorded by brainstem auditory evoked potentials (BAEP), which then assess the functional state of each pathway based on the latency and amplitude of the waveform [57–59].

Auditory problems are linked to dementia and low mood, in addition to affecting afferents of sound impulses and communication with the outside world [60]. Patients with presbycusis and PD are deaf and deposit  $\alpha$ -synuclein in the efferent nerves of the inner ear [61]. PD patients have an uneven gait, which could be a sign of impaired auditory

nerve function [60,61].

PD patients experience “Dysphonia-Unable to perceive full range wavelength of sounds” because they have poor high-frequency hearing and are unable to perceive a full soundscape. For example, a palace commercial horn sign feather may only have thin timbre and timbre quality. PD patients with selective hearing loss in addition to articulation and airflow tremors over time may talk and hear differently from other people and experience social impairment [62–67].

### 4. Olfactory Disturbances in PD

Reactions to their surroundings, behavioral patterns, and memory are inextricably linked to olfaction; however, patients with PD experience olfactory impairment before motor symptoms. In the PD group, olfactory testing at the University of Pennsylvania Odor Recognition Experiment revealed higher taste thresholds and lower olfactory discriminating [68]. Olfactory memory impairment may be a symptom of PD disease.

Olfactory dysfunction is characterized by pathological alterations that are primarily found in the anterior olfactory nucleus, which also exhibits extensive aberrant  $\alpha$ -synuclein deposition and neuronal death [69–71]. In patients with PD, cortical nuclei also exhibit structural abnormalities in olfactory cells at low magnification, bilateral piriform and orbitofrontal cortical atrophy, and olfactory nerve atrophy [72]. The olfactory mucosa, olfactory nerve, and impaired olfactory afferent pathways are peripheral mechanisms of olfactory dysfunction. It is also possible that the causative agent enters the brain tissue directly through the olfactory mucosa and olfactory nerve, causing damage to the midbrain substantia nigra or prefrontal cortex. In addition, retrograde olfactory pathways are hampered, and dopamine neurons in the substantia nigra of the midbrain deteriorate [73–76]. However, dopamine has no obvious effect on olfactory disorders, which may be related to the route of administration and form of the dopamine drug.

Olfactory dysfunction examinations can be used to predict the likelihood of PD developing [77–81], and olfactory dysfunction is an independent risk factor for diseases such as PD [82–85].

Although there are now equipment and reagents suitable for the Chinese people, it is important to consider the variations in vast Chinese areas and customs. The devices currently in use should fully cover the regional culture, diet, and environmental conditions. Olfactory testing, particularly a thorough assessment of olfactory dysfunction in conjunction with PD motor symptoms, increases the sensitivity and specificity of early PD diagnoses.

### 5. Dysgeusia in PD

Taste is a special sensation that is instantly accompanied by a powerful emotional reaction and profoundly ingrained in the brain and digestive system. Distinct tastes

excite different receptors that are delivered to the taste center in the brain in various ways [86,87], whereas the same taste stimulates the same receptors differently for the same person during childhood and old age. There are connections between scent, taste, and tongue temperature [87].

Methods for conducting taste tests include electrotaste measurement, full-mouth taste testing, taste strip testing, and taste-evoked potential testing. Little research has been conducted on taste loss in PD patients. Electrogustometry and the University of Pennsylvania odor recognition test were used to examine taste and smell separately. In the PD group, the taste threshold was higher and olfactory discrimination was lower [87,88]. Because taste and scent changes are gradual, they are frequently unreported. Some people observed that their food had a mild, flavorless taste, or that they frequently added more salt or pepper. Although the loss of taste and smell is generally not a highly dangerous symptom, it can cause appetite loss. Tongue taste in patients with PD can be affected by tongue stiffness, numbness, pain, and burning sensations.

The taste sensation of the anterior two-thirds of the tongue is mainly innervated by the facial nerve, whereas that of the posterior one-third of the tongue is innervated by the glossopharyngeal nerve. Loss of taste is mainly due to nerve damage resulting in damage to the nerves innervating the taste buds, such as damage to the chorda tympani nerve, and attention should also be paid to the following conditions:

- (1) Physiological taste loss due to older age.
- (2) Pathological hypogeusia, such as gustatory nerve disorders caused by surgery, otitis media, intranasal tumors, rhinitis, turbinate hypertrophy, and other related diseases may also cause hypogeusia.
- (3) Drug-induced taste loss, such as the side effects caused by long-term use of drugs to treat rheumatism, levodopa causing a burning sensation in the mouth, and trihexyphenidyl hydrochloride (Antan) causing decreased salivary secretions, can affect the taste sensation in the tongue, teeth, lips, and gums.
- (4) Visceral diseases such as kidney or liver can also cause taste abnormalities.
- (5) PD tremors, particularly tongue tremors and other movement disorders, cause oral problems such as difficulty in cleaning, salivation, dysphagia, dry mouth, and tooth and gingival problems, and can also lead to dysgeusia.
- (6) In some patients, mood swings and insufficient motivation for depression can lead to loss of taste.

## 6. Somatosensory Disturbances in PD

Paresthesia in the skin of PD patients is very subtle and complicated, involving the feeling of touch or being touched, pressure, temperature, pain, and imbalance of the whole body when standing up or walking.

Unnameable pain is a special indicator of PD, and some people experience pain in many body regions in vari-

ous ways and at variable intensities before exhibiting movement symptoms. However, the nature and etiology of central and peripheral pain are quite different, and peripheral pain is mostly linked to poor vitamin B<sub>12</sub> metabolism [88,89]. Pain can be caused by small nerve fiber damage and damage to the pain pathway in the central or peripheral nervous systems.

Patients with PD usually experience unbearable bone-crushing pain. Patients with PD may also experience bone and joint discomfort, especially in those with low back pain. However, PD may result in inexplicable pain owing to stiffness, cramps, spasms, or other forms of muscle pain. Leg discomfort known as “restless of leg”, feels like a pain in the muscles and affects one-third of PD patients, is the most prevalent type of pain that many PD patients also experience insomnia concurrently.

In fact, discomfort such as unmeasurable pain in patients with PD is frequently caused by muscle rigidity. This is because uncomfortable symptoms typically worsen when the drug is not as effective as the onset of dopaminergic medication. However, the exact cause of the pain remains unknown. In some cases, patients with PD may be more sensitive to pain than are healthy individuals. Peripheral neuropathy is a risk factor for PD, and can be exacerbated by high-dose levodopa therapy. Burning pain, which is a side effect of levodopa, is a key symptom of peripheral neuropathy. Levodopa increases homocysteine levels and decreases vitamin B<sub>12</sub> intake [90]. PD and vitamin B<sub>12</sub>-deficiency increase the risk of uncontrollable pain [91].

Other commonly prescribed dopaminergic medications, including compound dopa, compound dopa + entacapone (Dalindox), dopamine receptor agonists (pramipexole), and monoamine oxidase inhibitor type B, also aid in the relief of PD pain, particularly pain related to motor fluctuations [92]. PD can also be managed using nondopaminergic medications. Targinact, a combination of the opioid agonist oxycodone and peripheral opioid antagonist naloxone, is clinically used to effectively treat chronic pain in PD. The semi-synthetic opioid oxycodone has long been used in medicine as a strong analgesic. Drug safety issues with this class of medicines have gained increasing attention in recent years as drug addicts using oxycodone-containing drugs have become more prevalent. Preparations made from oxycodone-containing compounds and other types are managed by relevant national authorities. Other opioid analgesics with neuropsychiatric and gastrointestinal adverse effects, such as tramadol, codeine, and morphine, have not been proven useful in treating PD pain [93].

PD pain can be effectively treated with duloxetine, a serotonin and norepinephrine reuptake inhibitor, with antidepressant and central analgesic properties. Pregabalin and gabapentin, two medications frequently used to treat neuropathic pain, do not appear to be beneficial in the treatment of PD pain. Botulinum toxin injections are safe and effective in treating localized PD discomfort. The PD

and pain were significantly relieved using neuromodulation techniques [94]. When moderate-to-severe pain is present in patients with PD, it may be challenging to obtain satisfactory results with drug therapy alone, or patients may be unable to take the medication continuously due to the side effects of drugs.

Using neuromodulation techniques, deep brain stimulation of the subthalamic nucleus may produce prolonged efficacy in treating PD discomfort such as pain. The pain associated with PD may be reduced by repetitive transcranial magnetic stimulation (rTMS) [95], a noninvasive method of cranial neuromodulation that modifies pain-related signaling systems.

After skin biopsy, the nature of pain can be determined by microscopic examination of tiny nerve fibers, quantitative sensory tests, and contact thermal pain-evoked potentials. In patients with PD, skin biopsies have revealed  $\alpha$ -synuclein accumulation in the epidermis of sensory and autonomic neurons [96], a reduction in the number of epidermal nerve fibers, and axonal enlargement of nerve fibers. The functions of the tiny fibers were examined using quantitative sensory testing. Elevated temperature perception and lowered thermal pain thresholds have been observed in PD patients. The contact thermal pain-evoked potential test is non-invasive and simple to use [97]. It measures the density of nerve fibers in the skin epidermis, and the amplitude is decreased in patients and is linked to special conditions.

Somatosensory evoked potentials (SEP) can be used to assess the health of somatosensory pathways carried by the gross tactile fibers. The vagus SEP can be used to measure the damage to the dorsal motor nucleus of the vagus nerve in PD. According to previous studies [98], PD patients had considerably longer vagal SEP latency, smaller P20-N30 peak-to-peak values for bilateral short-latency SEP, and amplitudes of N30 linked to blood flow in parietal cortical regions [99].

PD is characterized by various abnormalities in many body and organ systems, including autonomic dysfunction of the gastrointestinal, cardiovascular, genitourinary, and thermoregulatory systems. Heart rate variability and sympathetic skin responses were used to assess autonomic dysfunction. Cardiovascular autonomic function is dynamically monitored using heart rate variability [100]. Its amplitude reflects the simultaneous activation of efferent sympathetic nerve fiber discharges by sweat glands, and can be used as an indicator for cholinergic nerve function detection in patients with PD. Sympathetic skin responses can reflect autonomic dysfunction caused by damage to the peripheral and central nervous system damage [101]. Patients with PD have longer latency and diminished amplitude of sympathetic skin responses in both the upper and lower limbs, which may indicate impairment of the sympathetic nervous system.

Likewise, patients with position perception disorders are greatly affected. Position and hearing, which comprise

the functions of the eighth cranial nerve, have specific roles and are complementary to one another. Nerve impulses that originate from three semicircular canals perpendicular to one another emit links with various systems to establish positional sensations [102]. Dystonia, visual abnormalities, and compromised cortical control contribute to abnormal gait and posture, which characterize PD.

As a result of their clinical characteristics and inability to be entirely distinguished from motor symptoms, PD sensory disorders are postulated in relation to PD motor disorders and are classified as the primary “non-motor symptoms”. Since sensation and movement are intertwined, a thorough evaluation of sensory and motor impairments in PD is necessary to determine patients’ quality of life and likelihood of survival. There are no precise grading scales for sensory abnormalities because of their intricacy, yet they may come before PD motor symptoms. Despite the subjective nature of sensory disturbances, objective testing is the only way to diagnose them. To obtain early diagnosis and treatment, a combination of subjective and objective measures, clinical and neurophysiology, neuroimaging, and molecular biology must be used together.

This study has three limitations. This study focused solely on PD sensory impairment rather than motor symptoms. For example, the eighth cranial nerve carries hearing and balance sensations, cochlear nerve division hearing, and nerve division position sensations from the semicircular canal. Sensation and movement are inextricably linked. Additionally, sensory problems have a strong objective foundation; this review only searched for objective proof, and not in the subjective sector. The sensory perception fell within the subjective category.

This paper analyzed sensory disturbances based on the human eyes, ears, nose, mouth, and skin of the body, but comprehensive sensations may be more biologically meaningful, and this paper did not take people into account for the convenience of the narrative. PD is a systemic disease and this analysis may have greater clinical value. Paresthesia in patients with PD is not identical to the well-known nonmotor symptoms of PD. In the future, it may be possible to statistically assess different PD sensory problems, integrate them, and study them in conjunction with motor symptoms. This may be the key to early diagnosis and treatment of PD.

## 7. Summary

PD is clinically characterized by tremors and rigidity. However, sensory disturbances corresponding to these movement disorders have not aroused clinical concern. Recent studies have confirmed that PD affects the entire body. From the beginning of gastrointestinal lesions to the brain, brain lesions do not start in the substantia nigra of the midbrain as we already known, but from the glossopharyngeal nucleus of the medulla oblongata, followed by the dorsal motor nucleus of the vagus nerve, to the pons, midbrain, and

finally to the neocortex. Humans use sensory organs such as the eyes, ears, nose, tongue, and whole body to sense external world changes; therefore, this study analyzes the neuroanatomy and pathological changes one by one from sensory disturbances such as visual, auditory, olfactory, gustatory, tactile, and pressure sensations in PD and reveals its clinical significance.

### Availability of Data and Materials

Research data supporting this publication are available in the PubMed repository at [www.pubmed.org/download/](http://www.pubmed.org/download/).

### Author Contributions

BXM, JYZ, YLC and HMG—Participated in the research (they proposed research topics, designed the research programs, and implemented the research process). HMG wrote the article (research literature, design thesis framework, drafting papers, revising papers, and final thesis). YLC provided work support (access to technical and material support). All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

### Ethics Approval and Consent to Participate

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The protocol was approved by the Ethics Committee of Qingdao Binhai University Affiliated Hospital (approval number: 2022-11B23).

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### Conflict of Interest

The authors declare no conflict of interest.

### References

[1] Jia J, Chen S. *Neurology* (8th Edition). People's Medical Publishing House: Beijing. 2018.  
 [2] Beitz JM. Parkinson's disease: a review. *Frontiers in Bioscience* (Scholar Edition). 2014; 6: 65–74.  
 [3] Cabreira V, Massano J. Parkinson's Disease: Clinical Review

and Update. *Acta Médica Portuguesa*. 2019; 32: 661–670. (In Portuguese)  
 [4] Reich SG, Savitt JM. Parkinson's Disease. *The Medical Clinics of North America*. 2019; 103: 337–350.  
 [5] Hayes MT. Parkinson's Disease and Parkinsonism. *The American Journal of Medicine*. 2019; 132: 802–807.  
 [6] Cerri S, Mus L, Blandini F. Parkinson's Disease in Women and Men: What's the Difference? *Journal of Parkinson's Disease*. 2019; 9: 501–515.  
 [7] Opara J, Malecki A, Malecka E, Socha T. Motor assessment in Parkinson's disease. *Annals of Agricultural and Environmental Medicine: AAEM*. 2017; 24: 411–415.  
 [8] Tysnes OB, Storstein A. Epidemiology of Parkinson's disease. *Journal of Neural Transmission* (Vienna, Austria: 1996). 2017; 124: 901–905.  
 [9] Ghosh B, Mishra A, Sengupta P. Is Parkinson's disease a homogeneous disorder—what is the burden of Parkinson's disease in India. *Journal of the Indian Medical Association*. 2005; 103: 146, 148, 150 passim.  
 [10] Tolosa E, Wenning G, Poewe W. The diagnosis of Parkinson's disease. *The Lancet. Neurology*. 2006; 5: 75–86.  
 [11] Cummings JL, Henchcliffe C, Schaier S, Simuni T, Waxman A, Kemp P. The role of dopaminergic imaging in patients with symptoms of dopaminergic system neurodegeneration. *Brain: a Journal of Neurology*. 2011; 134: 3146–3166.  
 [12] Mollenhauer B, Locascio JJ, Schulz-Schaeffer W, Sixel-Döring F, Trenkwalder C, Schlossmacher MG.  $\alpha$ -Synuclein and tau concentrations in cerebrospinal fluid of patients presenting with parkinsonism: a cohort study. *The Lancet. Neurology*. 2011; 10: 230–240.  
 [13] Mollenhauer B. Quantification of  $\alpha$ -synuclein in cerebrospinal fluid: how ideal is this biomarker for Parkinson's disease? *Parkinsonism & Related Disorders*. 2014; 20: S76–S79.  
 [14] Mollenhauer B, Parnetti L, Rektorova I, Kramberger MG, Pikkarainen M, Schulz-Schaeffer WJ, *et al.* Biological confounders for the values of cerebrospinal fluid proteins in Parkinson's disease and related disorders. *Journal of Neurochemistry*. 2016; 139 Suppl 1: 290–317.  
 [15] Parnetti L, Paciotti S, Farotti L, Bellomo G, Sepe FN, Eusebi P. Parkinson's and Lewy body dementia CSF biomarkers. *Clinica Chimica Acta; International Journal of Clinical Chemistry*. 2019; 495: 318–325.  
 [16] Chiasserini D, Biscetti L, Eusebi P, Salvadori N, Frattini G, Simoni S, *et al.* Differential role of CSF fatty acid binding protein 3,  $\alpha$ -synuclein, and Alzheimer's disease core biomarkers in Lewy body disorders and Alzheimer's dementia. *Alzheimer's Research & Therapy*. 2017; 9: 52.  
 [17] Bougea A, Stefanis L, Paraskevas GP, Emmanouilidou E, Efthymiopoulou E, Vekrelis K, *et al.* Neuropsychiatric symptoms and  $\alpha$ -Synuclein profile of patients with Parkinson's disease dementia, dementia with Lewy bodies and Alzheimer's disease. *Journal of Neurology*. 2018; 265: 2295–2301.  
 [18] Bougea A, Stefanis L, Emmanouilidou E, Vekrelis K, Kapaki E. High discriminatory ability of peripheral and CFSF biomarkers in Lewy body diseases. *Journal of Neural Transmission* (Vienna, Austria: 1996). 2020; 127: 311–322.  
 [19] Chung SJ, Kim J, Lee HJ, Ryu HS, Kim K, Lee JH, *et al.* Alpha-synuclein in gastric and colonic mucosa in Parkinson's disease: Limited role as a biomarker. *Movement Disorders: Official Journal of the Movement Disorder Society*. 2016; 31: 241–249.  
 [20] Chung SJ, König IR, Lohmann K, Hinrichs F, Kim J, Ryu HS, *et al.* Association of SNCA variants with  $\alpha$ -synuclein of gastric and colonic mucosa in Parkinson's disease. *Parkinsonism & Related Disorders*. 2019; 61: 151–155.  
 [21] Keshavarzian A, Green SJ, Engen PA, Voigt RM, Naqib A, Forsyth CB, *et al.* Colonic bacterial composition in Parkinson's

- disease. *Movement Disorders: Official Journal of the Movement Disorder Society*. 2015; 30: 1351–1360.
- [22] Engen PA, Dodiya HB, Naqib A, Forsyth CB, Green SJ, Voigt RM, *et al*. The Potential Role of Gut-Derived Inflammation in Multiple System Atrophy. *Journal of Parkinson's Disease*. 2017; 7: 331–346.
- [23] Gerhardt S, Mohajeri MH. Changes of Colonic Bacterial Composition in Parkinson's Disease and Other Neurodegenerative Diseases. *Nutrients*. 2018; 10: 708.
- [24] Dodiya HB, Forsyth CB, Voigt RM, Engen PA, Patel J, Shaikh M, *et al*. Chronic stress-induced gut dysfunction exacerbates Parkinson's disease phenotype and pathology in a rotenone-induced mouse model of Parkinson's disease. *Neurobiology of Disease*. 2020; 135: 104352.
- [25] Liu J, Banskota AH, Critchley AT, Hafting J, Prithiviraj B. Neuroprotective effects of the cultivated *Chondrus crispus* in a *C. elegans* model of Parkinson's disease. *Marine Drugs*. 2015; 13: 2250–2266.
- [26] Yu H, Sun T, He X, Wang Z, Zhao K, An J, *et al*. Association between Parkinson's Disease and Diabetes Mellitus: From Epidemiology, Pathophysiology and Prevention to Treatment. *Ageing and Disease*. 2022; 13: 1591–1605.
- [27] Pietrucci D, Cerroni R, Unida V, Farcomeni A, Pierantozzi M, Mercuri NB, *et al*. Dysbiosis of gut microbiota in a selected population of Parkinson's patients. *Parkinsonism & Related Disorders*. 2019; 65: 124–130.
- [28] Chen GL, Zhang Y, Wang WY, Ji XL, Meng F, Xu PS, *et al*. Partners of patients with ulcerative colitis exhibit a biologically relevant dysbiosis in fecal microbial metacommunities. *World Journal of Gastroenterology*. 2017; 23: 4624–4631.
- [29] Sauerbier A, Jenner P, Todorova A, Chaudhuri KR. Non motor subtypes and Parkinson's disease. *Parkinsonism & Related Disorders*. 2016; 22 Suppl 1: S41–S46.
- [30] Pont-Sunyer C, Hotter A, Gaig C, Seppi K, Compta Y, Katzeneschlager R, *et al*. The onset of nonmotor symptoms in Parkinson's disease (the ONSET PD study). *Movement Disorders: Official Journal of the Movement Disorder Society*. 2015; 30: 229–237.
- [31] Barone P, Erro R, Picillo M. Quality of Life and Nonmotor Symptoms in Parkinson's Disease. *International Review of Neurobiology*. 2017; 133: 499–516.
- [32] Marinus J, Zhu K, Marras C, Aarsland D, van Hilten JJ. Risk factors for non-motor symptoms in Parkinson's disease. *The Lancet. Neurology*. 2018; 17: 559–568.
- [33] Zahodne LB, Fernandez HH. Pathophysiology and treatment of psychosis in Parkinson's disease: a review. *Drugs & Aging*. 2008; 25: 665–682.
- [34] Powell A, Ireland C, Lewis SJG. Visual Hallucinations and the Role of Medications in Parkinson's Disease: Triggers, Pathophysiology, and Management. *The Journal of Neuropsychiatry and Clinical Neurosciences*. 2020; 32: 334–343.
- [35] Borgemeester RWK, Lees AJ, van Laar T. Parkinson's disease, visual hallucinations and apomorphine: A review of the available evidence. *Parkinsonism & Related Disorders*. 2016; 27: 35–40.
- [36] Han G, Han J, Han K, Youn J, Chung TY, Lim DH. Visual Acuity and Development of Parkinson's Disease: A Nationwide Cohort Study. *Movement Disorders: Official Journal of the Movement Disorder Society*. 2020; 35: 1532–1541.
- [37] Yuki N, Yoshioka A, Mizuhara R, Kimura T. Visual hallucinations and inferior longitudinal fasciculus in Parkinson's disease. *Brain and Behavior*. 2020; 10: e01883.
- [38] Mammadova N, Summers CM, Kokemuller RD, He Q, Ding S, Baron T, *et al*. Accelerated accumulation of retinal  $\alpha$ -synuclein (pSer129) and tau, neuroinflammation, and autophagic dysregulation in a seeded mouse model of Parkinson's disease. *Neurobiology of Disease*. 2019; 121: 1–16.
- [39] Adam CR, Shrier E, Ding Y, Glazman S, Bodis-Wollner I. Correlation of inner retinal thickness evaluated by spectral-domain optical coherence tomography and contrast sensitivity in Parkinson disease. *Journal of Neuro-ophthalmology: the Official Journal of the North American Neuro-Ophthalmology Society*. 2013; 33: 137–142.
- [40] Cesareo M, Di Marco E, Giannini C, Di Marino M, Aiello F, Pisani A, *et al*. The Retinal Posterior Pole in Early Parkinson's Disease: A Fundus Perimetry and SD-OCT Study. *Clinical Ophthalmology (Auckland, N.Z.)*. 2021; 15: 4005–4014.
- [41] Del Pino R, Acera M, Murueta-Goyena A, Lucas-Jiménez O, Ojeda N, Ibarretxe-Bilbao N, *et al*. Visual dysfunction is associated with cognitive impairment in Parkinson's disease. *Parkinsonism & Related Disorders*. 2021; 92: 22–25.
- [42] Huang L, Zhang D, Ji J, Wang Y, Zhang R. Central retina changes in Parkinson's disease: a systematic review and meta-analysis. *Journal of Neurology*. 2021; 268: 4646–4654.
- [43] Latif S, Jahangeer M, Maknoon Razia D, Ashiq M, Ghaffar A, Akram M, *et al*. Dopamine in Parkinson's disease. *Clinica Chimica Acta; International Journal of Clinical Chemistry*. 2021; 522: 114–126.
- [44] Robbins CB, Thompson AC, Bhullar PK, Koo HY, Agrawal R, Soundararajan S, *et al*. Characterization of Retinal Microvascular and Choroidal Structural Changes in Parkinson Disease. *JAMA Ophthalmology*. 2021; 139: 182–188.
- [45] Netser R, Demmin DL, Dobkin R, Goldstein A, Roché M, Netser Zernik A, *et al*. Flash Electroretinography Parameters and Parkinson's Disease. *Journal of Parkinson's Disease*. 2021; 11: 251–259.
- [46] Mohana Devi S, Mahalaxmi I, Aswathy NP, Dhivya V, Balachandrar V. Does retina play a role in Parkinson's Disease? *Acta Neurologica Belgica*. 2020; 120: 257–265.
- [47] Lee JY, Ahn J, Shin JY, Jeon B. Parafoveal Change and Dopamine Loss in the Retina with Parkinson's Disease. *Annals of Neurology*. 2021; 89: 421–422.
- [48] Peppe A, Stanzione P, Pierelli F, Stefano E, Rizzo PA, Tagliati M, *et al*. Low contrast stimuli enhance PERG sensitivity to the visual dysfunction in Parkinson's disease. *Electroencephalography and Clinical Neurophysiology*. 1992; 82: 453–457.
- [49] Babiloni C, De Pandis MF, Vecchio F, Buffo P, Sorpresi F, Frisoni GB, *et al*. Cortical sources of resting state electroencephalographic rhythms in Parkinson's disease related dementia and Alzheimer's disease. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology*. 2011; 122: 2355–2364.
- [50] Smith PF. Vestibular Functions and Parkinson's Disease. *Frontiers in Neurology*. 2018; 9: 1085.
- [51] Gökyay NY, Gündüz B, Söke F, Karamert R. Evaluation of Effortful Auditory System and Hearing Quality in Parkinson's Disease: Is the Difficulty in Speech Understanding in Complex Listening Conditions Related to Neural Degeneration or Aging? *Journal of Speech, Language, and Hearing Research*. 2021; 64: 263–271.
- [52] Jafari Z, Kolb BE, Mohajerani MH. Auditory Dysfunction in Parkinson's Disease. *Movement Disorders: Official Journal of the Movement Disorder Society*. 2020; 35: 537–550.
- [53] Abur D, Subaciute A, Daliri A, Lester-Smith RA, Lupiani AA, Cilento D, *et al*. Feedback and Feedforward Auditory-Motor Processes for Voice and Articulation in Parkinson's Disease. *Journal of Speech, Language, and Hearing Research: JSLHR*. 2021; 64: 4682–4694.
- [54] Watson N, Ding B, Zhu X, Frisina RD. Chronic inflammation -inflammaging - in the ageing cochlea: A novel target for future presbycusis therapy. *Ageing Research Reviews*. 2017; 40: 142–148.

- [55] Johansson IL, Samuelsson C, Müller N. Patients' and communication partners' experiences of communicative changes in Parkinson's disease. *Disability and Rehabilitation*. 2020; 42: 1835–1843.
- [56] Shetty K, Krishnan S, Thulaseedharan JV, Mohan M, Kishore A. Asymptomatic Hearing Impairment Frequently Occurs in Early-Onset Parkinson's Disease. *Journal of Movement Disorders*. 2019; 12: 84–90.
- [57] Cicekli E, Titiz AP, Titiz A, Oztekin N, Mujdeci B. Vestibular evoked myogenic potential responses in Parkinson's disease. *Ideggyogyaszati Szemle*. 2019; 72: 419–425.
- [58] Anzak A, Tan H, Pogosyan A, Khan S, Javed S, Gill SS, *et al.* Subcortical evoked activity and motor enhancement in Parkinson's disease. *Experimental Neurology*. 2016; 277: 19–26.
- [59] Tremblay C, Emrich R, Cavazzana A, Klingelhoefer L, Brandt MD, Hummel T, *et al.* Specific intranasal and central trigeminal electrophysiological responses in Parkinson's disease. *Journal of Neurology*. 2019; 266: 2942–2951.
- [60] Panza F, Lozupone M, Sardone R, Battista P, Piccininni M, Dibello V, *et al.* Sensorial frailty: age-related hearing loss and the risk of cognitive impairment and dementia in later life. *Therapeutic Advances in Chronic Disease*. 2018; 10: 2040622318811000.
- [61] Elgoyhen AB. The  $\alpha 9\alpha 10$  nicotinic acetylcholine receptor: a compelling drug target for hearing loss? *Expert Opinion on Therapeutic Targets*. 2022; 26: 291–302.
- [62] Mehanna R, Jankovic J. Young-onset Parkinson's disease: Its unique features and their impact on quality of life. *Parkinsonism & Related Disorders*. 2019; 65: 39–48.
- [63] Ponsi G, Panasiti MS. Impulsive-compulsive disorders in Parkinson's Disease: influence on individual and social decision-making processes. *Rivista di Psichiatria*. 2020; 55: 213–221. (In Italian)
- [64] Vescovelli F, Sarti D, Ruini C. Subjective and psychological well-being in Parkinson's Disease: A systematic review. *Acta Neurologica Scandinavica*. 2018; 138: 12–23.
- [65] Caballero JA, Auclair Ouellet N, Phillips NA, Pell MD. Social decision-making in Parkinson's disease. *Journal of Clinical and Experimental Neuropsychology*. 2022; 44: 302–315.
- [66] Jiang X, Sanford R, Pell MD. Neural architecture underlying person perception from in-group and out-group voices. *NeuroImage*. 2018; 181: 582–597.
- [67] Jiang X, Pell MD. On how the brain decodes vocal cues about speaker confidence. *Cortex; a Journal Devoted to the Study of the Nervous System and Behavior*. 2015; 66: 9–34.
- [68] Cecchini MP, Federico A, Zanini A, Mantovani E, Masala C, Tinazzi M, *et al.* Olfaction and taste in Parkinson's disease: the association with mild cognitive impairment and the single cognitive domain dysfunction. *Journal of Neural Transmission (Vienna, Austria: 1996)*. 2019; 126: 585–595.
- [69] Walker IM, Fullard ME, Morley JF, Duda JE. Olfaction as an early marker of Parkinson's disease and Alzheimer's disease. *Handbook of Clinical Neurology*. 2021; 182: 317–329.
- [70] Marin C, Vilas D, Langdon C, Alobid I, López-Chacón M, Haehner A, *et al.* Olfactory Dysfunction in Neurodegenerative Diseases. *Current Allergy and Asthma Reports*. 2018; 18: 42.
- [71] Alonso CCG, Silva FG, Costa LOP, Freitas SMSF. Smell tests to distinguish Parkinson's disease from other neurological disorders: a systematic review and meta-analysis. *Expert Review of Neurotherapeutics*. 2021; 21: 365–379.
- [72] Ubeda-Bañon I, Saiz-Sanchez D, Flores-Cuadrado A, Rioja-Corroto E, Gonzalez-Rodriguez M, Villar-Conde S, *et al.* The human olfactory system in two proteinopathies: Alzheimer's and Parkinson's diseases. *Translational Neurodegeneration*. 2020; 9: 22.
- [73] Crespo Cuevas AM, Ispuerto L, Vilas D, Planas A, Planas A, Isern I, *et al.* Distinctive Olfactory Pattern in Parkinson's Disease and Non-Neurodegenerative Causes of Hyposmia. *Neurodegenerative Diseases*. 2018; 18: 143–149.
- [74] Bestwick JP, Auger SD, Schrag AE, Grosset DG, Kanavou S, Giovannoni G, *et al.* Optimising classification of Parkinson's disease based on motor, olfactory, neuropsychiatric and sleep features. *NPJ Parkinson's Disease*. 2021; 7: 87.
- [75] Oppo V, Melis M, Melis M, Tomassini Barbarossa I, Cossu G. "Smelling and Tasting" Parkinson's Disease: Using Senses to Improve the Knowledge of the Disease. *Frontiers in Aging Neuroscience*. 2020; 12: 43.
- [76] Fan W, Li H, Li H, Li Y, Wang J, Jia X, *et al.* Association between Functional Connectivity of Entorhinal Cortex and Olfactory Performance in Parkinson's Disease. *Brain Sciences*. 2022; 12: 963.
- [77] Goldman JG, Postuma R. Premotor and nonmotor features of Parkinson's disease. *Current Opinion in Neurology*. 2014; 27: 434–441.
- [78] Haehner A, Masala C, Walter S, Reichmann H, Hummel T. Incidence of Parkinson's disease in a large patient cohort with idiopathic smell and taste loss. *Journal of Neurology*. 2019; 266: 339–345.
- [79] Haehner A, Hummel T, Reichmann H. A clinical approach towards smell loss in Parkinson's disease. *Journal of Parkinson's Disease*. 2014; 4: 189–195.
- [80] Vengalil S, Agadi JB, Raghavendra K. University of Pennsylvania Smell Identification Test Abnormalities in Parkinson's Disease. *The Journal of the Association of Physicians of India*. 2016; 64: 32–36.
- [81] Bohnen NI, Gedela S, Kuwabara H, Constantine GM, Mathis CA, Studenski SA, *et al.* Selective hyposmia and nigrostriatal dopaminergic denervation in Parkinson's disease. *Journal of Neurology*. 2007; 254: 84–90.
- [82] Alonso CCG, Silva FG, Costa LOP, Freitas SMSF. Smell tests can discriminate Parkinson's disease patients from healthy individuals: A meta-analysis. *Clinical Neurology and Neurosurgery*. 2021; 211: 107024.
- [83] Xing F, Mo Y, Chen X, Liu T, Wang K, Hu P. Using the Chinese Smell Identification Test to explore olfactory function in Parkinson's disease. *Journal of Clinical and Experimental Neuropsychology*. 2021; 43: 156–162.
- [84] Cao M, Li Y, Gu Z, Mi T, Xu X, Ma C, *et al.* Validation of the utility of the Brief Smell Identification Test in Chinese patients with Parkinson's disease. *Journal of Clinical Neuroscience: Official Journal of the Neurosurgical Society of Australasia*. 2019; 60: 68–72.
- [85] Almeida WRPL, Gomes ADOC, Belo LR, Leal LB, Coriolano MDGWDS. Olfactive and taste perception in Parkinson's disease. *CoDAS*. 2021; 33: e20200038.
- [86] Marras C, Goldman S, Smith A, Barney P, Aston D, Comyns K, *et al.* Smell identification ability in twin pairs discordant for Parkinson's disease. *Movement Disorders: Official Journal of the Movement Disorder Society*. 2005; 20: 687–693.
- [87] Gao HM, Zhang JY, Ma LY. *Non Movement Symptoms of Parkinson's disease*. Scientific and Technical Literature Press: Beijing. 2021.
- [88] Polak T, Weise D, Metzger F, Ehlis AC, Langer JB, Schramm A, *et al.* Vagus nerve somatosensory evoked potentials in Parkinson's disease. *Journal of Neurology*. 2011; 258: 2276–2277.
- [89] Christine CW, Auinger P, Joslin A, Yelapaala Y, Green R, Parkinson Study Group-DATATOP Investigators. Vitamin B12 and Homocysteine Levels Predict Different Outcomes in Early Parkinson's Disease. *Movement Disorders: Official Journal of the Movement Disorder Society*. 2018; 33: 762–770.
- [90] Christine CW, Auinger P, Saleh N, Tian M, Bottiglieri T, Arning E, *et al.* Relationship of Cerebrospinal Fluid Vitamin B12 Sta-

- tus Markers With Parkinson's Disease Progression. *Movement Disorders: Official Journal of the Movement Disorder Society*. 2020; 35: 1466–1471.
- [91] Xie Y, Feng H, Peng S, Xiao J, Zhang J. Association of plasma homocysteine, vitamin B12 and folate levels with cognitive function in Parkinson's disease: A meta-analysis. *Neuroscience Letters*. 2017; 636: 190–195.
- [92] Ahmad MH, Rizvi MA, Ali M, Mondal AC. Neurobiology of depression in Parkinson's disease: Insights into epidemiology, molecular mechanisms and treatment strategies. *Ageing Research Reviews*. 2023; 85: 101840.
- [93] Karnik V, Farcy N, Zamorano C, Bruno V. Current Status of Pain Management in Parkinson's Disease. *The Canadian Journal of Neurological Sciences*. 2020; 47: 336–343.
- [94] Grassi G, Albani G, Terenzi F, Razzolini L, Ramat S. New pharmacological and neuromodulation approaches for impulsive-compulsive behaviors in Parkinson's disease. *Neurological Sciences: Official Journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*. 2021; 42: 2673–2682.
- [95] Lefaucheur JP, Aleman A, Baeken C, Benninger DH, Brunelin J, Di Lazzaro V, *et al*. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): An update (2014-2018). *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology*. 2020; 131: 474–528.
- [96] León-Bejarano F, Méndez MO, Alba A, Rodríguez-Leyva I, González FJ, Rodríguez-Aranda MDC, *et al*. Raman Spectroscopy Study of Skin Biopsies from Patients with Parkinson's Disease: Trends in Alpha-Synuclein Aggregation from the Amide I Region. *Applied Spectroscopy*. 2022; 76: 1317–1328.
- [97] Zhang W, Sun L, Yang X, Wang R, Wang H. Inhibition of NADPH oxidase within midbrain periaqueductal gray decreases pain sensitivity in Parkinson's disease via GABAergic signaling pathway. *Physiological Research*. 2020; 69: 711–720.
- [98] Cheron G, Piette T, Thiriaux A, Jacquy J, Godaux E. Somatosensory evoked potentials at rest and during movement in Parkinson's disease: evidence for a specific apomorphine effect on the frontal N30 wave. *Electroencephalography and Clinical Neurophysiology*. 1994; 92: 491–501.
- [99] Giza E, Katsarou Z, Georgiadis G, Bostantjopoulou S. Sympathetic skin response in Parkinson's disease before and after mental stress. *Neurophysiologie Clinique*. 2012; 42: 125–131.
- [100] Sariahmetoglu H, Soysal A, Sen A, Yuksel B, Celiker S, Ciftci-Kavaklioglu B, *et al*. Forehead sympathetic skin responses in determining autonomic involvement in Parkinson's disease. *Clinical Neurophysiology: Official Journal of the International Federation of Clinical Neurophysiology*. 2014; 125: 2436–2440.
- [101] Cuenca-Bermejo L, Almela P, Navarro-Zaragoza J, Fernández Villalba E, González-Cuello AM, Laorden ML, *et al*. Cardiac Changes in Parkinson's Disease: Lessons from Clinical and Experimental Evidence. *International Journal of Molecular Sciences*. 2021; 22: 13488.
- [102] Chen Y, Gao Q, He CQ, Bian R. Effect of Virtual Reality on Balance in Individuals With Parkinson Disease: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Physical Therapy*. 2020; 100: 933–945.