

# Spectrum of Non-Motor Symptoms in Parkinson's Disease

Maithrayie Kumaresan<sup>1</sup>, Safeera Khan<sup>2</sup>

1. Neurology, California Institute of Behavioral Neurosciences & Psychology, Fairfield, USA 2. Internal Medicine, California Institute of Behavioral Neurosciences & Psychology, Fairfield, USA

**Corresponding author:** Maithrayie Kumaresan, maithrayiek@gmail.com

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## Abstract

Parkinson's disease is predominantly classified as a movement disorder. Beyond the textbook definition of rigidity, tremors, and bradykinesia, Parkinson's disease encompasses an entire entity of non-motor symptom complexes that can precede the motor features by many years. Despite their significant clinical importance, the awareness of non-motor symptoms is quite negligible. Sleep disorders, gastrointestinal dysfunction, olfactory disturbances, anxiety, and depressive episodes are some of the most common non-motor presentations. The wide-spread occurrence of olfactory symptoms and the low cost of the assessment, is favoring olfactory dysfunction as a potential biomarker in Parkinson's. Sleep disorders may manifest before the motor and autonomic symptoms and might be linked to concomitant sleeping disorders like insomnia, REM sleep disorders, restless leg syndrome, narcolepsy, or obstructive sleep apnea. Non-motor symptoms can deteriorate the quality of life in Parkinson's patients. Early detection of non-motor symptoms can help in the diagnosis of Parkinson's disease and can fairly improve the survival and prognosis of these patients.

**Categories:** Internal Medicine, Neurology, Gastroenterology

**Keywords:** parkinson's disease, non-motor symptoms, sleep disorders, olfactory dysfunction, gastrointestinal disorders

## Introduction And Background

The characteristic feature of Parkinson's disease (PD) is the loss of dopaminergic neurons in the substantia nigra and the presence of alpha-synuclein protein Lewy body, named after the German neuropathologist Friedrich Heinrich Lewy. Parkinson's disease affects two per 1000 population at any given time. The prevalence of PD increases with age and is more common in men than in women [1]. The triad of parkinsonism is often defined by rigidity, bradykinesia, and tremors. However, non-motor symptoms (NMS) in PD is a common occurrence and was recognized first in 1817 by James Parkinson in his essay "Shaking Palsy" [2].

NMS can manifest at any stage of the disease, sometimes even in the early and pre-motor phases. Around 30 different NMS have been highlighted in PD [2]. Braak and colleagues proposed that the varying degrees of synuclein pathology depicted a temporal sequence of events that could be classified into six stages [3]. They postulated that environmental neurotoxins gain entry into the gastrointestinal tract via the nasal cavity, initiating Lewy body pathogenesis. Similarly, there was another hypothesis stating the spread of Lewy pathology (LP) from the peripheral to the cerebrospinal nervous system.

Motor impairments in PD may be heralded by non-motor symptoms such as depressive disorders, olfactory deficit, rapid eye movement (REM) sleep disorders, constipation, and anxiety, by even up to ten years. Sleep disturbances are highly prevalent in patients with PD and are indicators of poor caliber of life. The assessment of sleep disorders in these patients is complex. As a host of primary medical disorders, psychiatric conditions, increasing age, or the neuropathophysiology of PD itself may affect the sleep cycle [4]. Olfactory deficits are common and often supersede the diagnosis of PD by years, signifying prior initiation of Lewy body pathology. Olfactory dysfunction coupled with other non-motor features of PD and may serve as an indicator of cognitive decline [5]. Despite their vast clinical relevance, NMS is often overlooked by physicians and dismissed by patients. Usage of a patient-based screening tool such as a non-motor symptom questionnaire (NMS quest) draws attention to and strengthens the early management of NMS [6]. For the effective care of PD patients, a multidisciplinary approach encompassing both pharmacological and non-pharmacological treatment is mandatory. In this literature study of 50 review articles, the pathophysiology and features of three main non-motor symptoms have been highlighted.

## Review

The three most common non-motor symptoms in Parkinson's disease have been analyzed below from 50 review studies. All studies highlight the importance of non-motor symptoms in the early detection of Parkinson's disease and talk about the precedence of NMS over motor symptoms. On-going clinical trials and existing hypotheses on the pathophysiology of NMS have also been elicited.

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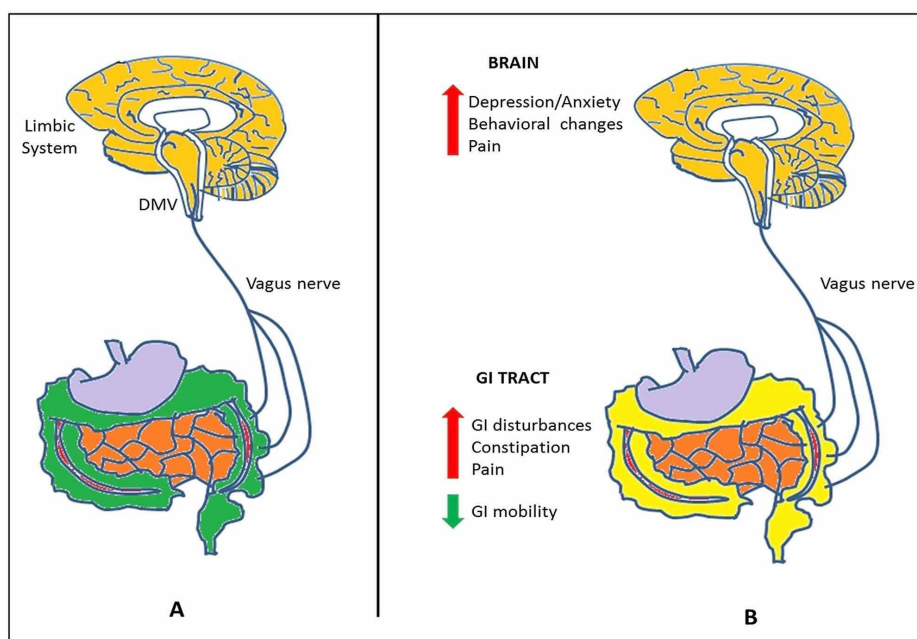
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## Gut dysfunction in Parkinson's disease

Gastrointestinal (GI) or gut dysfunction in PD can be caused by both motor and non-motor (dysautonomic) impairment. It has now been established that gut disturbances in patients with PD are quite a frequent occurrence [7]. Around 60% to 80% of the PD patients present with GI changes which serve as an early indicator for assessing the quality of life [8]. Gut dysfunctions such as sialorrhoea, hypogeusia, dysphagia, delayed gastric emptying, weight loss, and dyschezia present early in the disease is relatively high frequencies [9]. The gut may serve as a pathway for the PD toxin to reach the central nervous system (CNS). There is increasing evidence suggesting the gut microbiome's diverse and potent influence over CNS-related conditions apart from PD, including autism spectrum disorders and Alzheimer's disease [10]. Enteroendocrine cells are specialized intestinal cells that express various peptides/hormones and act as signaling channels, via which the gut microbiota communicates with the cerebrospinal nervous system through the X<sup>th</sup> cranial nerve (vagus) [11].

Animal trials have illustrated that  $\alpha$ -synuclein bundles can disseminate in a prion-like style via microtubule-associated transport along the axons and spread to neighboring brain regions. In short, alpha-synuclein functions as a prion-like protein, which can act as seeds for further aggregation and undergo transport along axons transferring to subsequent neurons and eventually cause neuronal degeneration in the substantia nigra. Though studies have linked vagotomy with a decreased risk of Parkinson's in humans, conclusive evidence to support the prion hypothesis and the cerebral origin of alpha-synuclein aggregates is still amiss. It is also to be noted that patients with neural grafting in Parkinson's disease have developed alpha-synuclein pathology. Alpha-synuclein from PD patients is also known to cause nigrostriatal degeneration in mice and other mammals (Figure 1, Table 1) [12].



**FIGURE 1: The brain-gut axis in Parkinson's disease. (A) Two-way communication between the brain and the gut via the vagus nerve. (B) Non-motor symptoms of Parkinson's disease.**

| Author                          | Year of publication | Type of study    | Purpose of the study  | Intervention studied   | Result/conclusion   |
|---------------------------------|---------------------|------------------|---|--|---|
| Caputi and Orion [13]           | 2018                | Review           | Newer treatment   | Microbiome-gut-brain axis and Toll-like receptor ligands in PD.    | Prebiotics, probiotics, and synbiotics can be used effectively for the prophylaxis and treatment of neurodegeneration. Probiotics produce anti-inflammatory cytokines through Toll-like receptors and can suppress inflammatory activity. |
| Mukherjee et al. [14]           | 2016                | Review           | The study focused on various gut dysfunctions associated with PD  | Microbiota and GI system   | The study revealed that in PD, the gut is involved extensively in the pathophysiology of the disease.   |
| Cryan et al. [15]               | 2019                | Review           | To study the role of microbiota in regulating the gut-brain axis.   | Microbiota-gut-brain axis  | The gut microbiota is important for adequate maintenance of cerebral activity.  |
| Perez-Pardo et al. [16]         | 2017                | Review           | To study the gut-brain axis in Parkinson's disease as well as identifying the possibilities for food-based therapies  | Alpha-synuclein aggregates and enteric nervous system involvement. | The study supports the theory that PD could originate in the gut  |
| Liddle [17]                     | 2018                | Research article | Possibility of PD originating in the gut in light of the recent unveiling of an enteroendocrine cell – neural circuit and the discovery of $\alpha$ -synuclein in enteroendocrine cells.                            | Immuno-histological staining of a CCK type EEC cell.               | Ingested toxins in the gut microbiome can induce $\alpha$ -synuclein aggregation and subsequently cause PD.   |
| Pfeiffer [18]                   | 2018                | Review           | To determine the potential of gut microbiota in the genesis of PD.  | Gut microbiome   | Small intestinal dysfunction may play a role in Parkinson's disease, especially concerning erratic responses to Parkinson medication  |
| Sharma et al. [19]              | 2019                | Review           | The use of probiotics and prebiotics as a new treatment modality to retain normal gut flora and prevent PD-like symptoms.   | Gut-brain axis   | The alteration of gut flora leading to inflammation of the enteric system and aggravating prion manner synuclein pathology leading to PD.   |
| Klingelhofer and Reichmann [20] | 2017                | Review           | Clinical and pathological review to substantiate the theory that PD originates in the gut and spreads via trans-synaptic cell-to-cell transfer through the autonomic nervous systems to the central nervous system. | GI and the enteric nervous system.                                 | Rostro-cranial transmission of PD from the olfactory bulb/ ENS to the substantia nigra, questioning the involvement of environmental triggers in the pathogenesis of the disease.   |
| IJzendoorn and Derkinderen [21] | 2019                | Review           | The intestinal barrier in PD.   | Microbiota and the enteric nervous system                          | Studying the possibility of intestinal permeability in neurodegenerative conditions.  |

**TABLE 1: Previous studies about gut dysfunction in Parkinson's disease.**

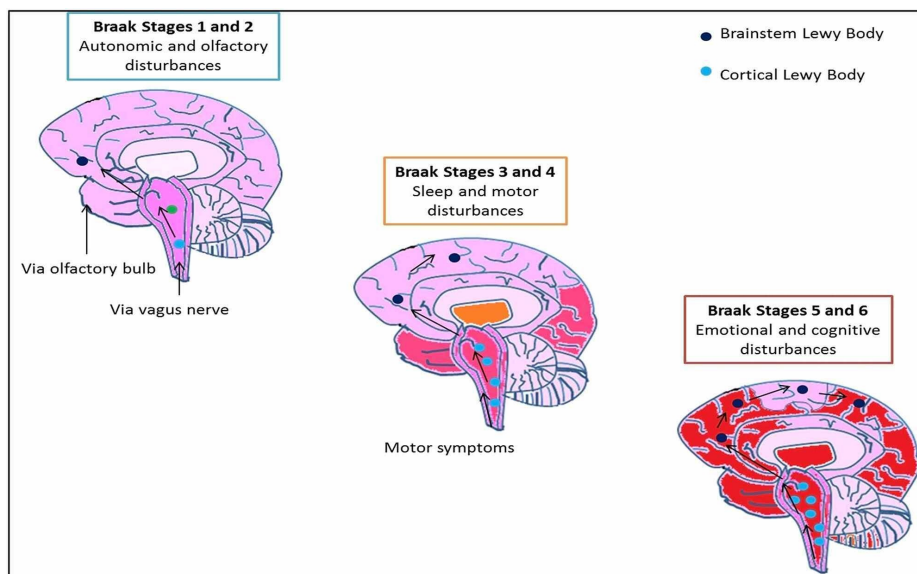
PD- Parkinson's disease; GI- gastro-intestinal; CCK- cholecystokinin; EEC- enteroendocrine cell; ENS- enteric nervous system

## Olfactory disorders in Parkinson's disease

Olfactory dysfunction is a distinct early feature of Parkinson's disease. Research has indicated that >95% of PD patients have impairment of olfactory function. Deficits in the sense of smell may precede clinically relevant motor symptoms by many years and can be used as an early assessment tool for Parkinson's disease in asymptomatic individuals [22]. Ample studies are looking into olfactory disorders in the pre-motor stages of PD. The Honolulu-Asia Aging Study, a longitudinal study following 2267 men between 71 years and 95 years of age without known PD, reported an odds ratio of 5.2 for PD development in subjects within the lowest quartile odor identification test after a four-year follow-up [23].

The presence of Lewy bodies (alpha-synuclein as the main component) in the substantia nigra and Lewy neuritis is characteristic of Parkinson's disease. Braak et al. believed that Lewy body pathogenesis originated in the olfactory bulb and dorsal motor nucleus of the tenth cranial nerve [24]. Alpha-synuclein deposition in olfactory structures occurs before deposition in the substantia nigra This happens in the initial stages of the Braak hypothesis. By Braak stage 3, LB pathology involves the medulla and pontine tegmentum by moving up the brainstem [25]. Motor symptoms become prominent at this stage. Neuropathological studies in normal human brains identified Lewy body isolates. Braak documented that when only a part of the brain is affected with incidental Lewy bodies, it was most likely to be the olfactory bulb [26]. Incidental Lewy bodies have been studied in the olfactory bulb, anterior olfactory nucleus, and the cortices of the olfactory tract in patients with neurodegeneration. The beginning of the Lewy pathology can be traced to the thin olfactory nerve sheath; it then spreads to the olfactory bulb's glomeruli from where it projects to the mitral and tufted cells. The pathology extends from the dendrites of the mitral cells to the nucleus of the amygdala in the cortex [27]. Early alpha-synuclein deposition and neuronal degeneration prior to the appearance of motor features, sometimes even as early as four years, can be traced back to this part of the cortex. Upcoming

functional genomics studies are identifying alteration in the cortical olfactory and taste receptors in PD patients (Figure 2, Table 2).



**FIGURE 2: Braak staging steps 1-6. The pink shading represents the pattern of spread of alpha-synuclein from the olfactory region to the cortex.**

| Author                    | Year of publication | Type of study    | Purpose of the study   | Intervention studied   | Result/conclusion   |
|---------------------------|---------------------|------------------|--|--|---|
| Roos et al. [28]          | 2019                | Research article | To evaluate the relationship between hyposmia and motor features of PD.                                  | MMSE   | Hyposmia in PD is directly linked to the degree of nigrostriatal dopaminergic degradation.  |
| Marin et al. [29]         | 2018                | Review           | Olfactory function assessment and quantification.  | Olfaction as a clinical marker for neurodegenerative diseases.                                     | Understanding the mechanisms underlying olfactory dysfunction and its association with neurodegenerative disorders.                 |
| Oh et al. [30]            | 2018                | Research article | Specialized MRI guided techniques to assess the status of the dopamine active transporter in the cortex. | MRI, PET image   | Importance of gut microbiota to maintain normal brain functions.  |
| Leonhardt et al. [31]     | 2019                | Research article | Assessing the awareness of olfactory impairments in Parkinson's.   | Odor identification test and the subjective olfactory capability.                                  | Anosmia and decreased respiratory function could serve as a marker for cognitive decline in PD.                                     |
| Fullard et al. [32]       | 2017                | Research article | Recognizing early biomarkers in Parkinson's.   | Olfaction as a potential biomarker for early recognition of Parkinson's.                           | Linking early biomarkers to cognitive decline function.   |
| Tarakad and Jankovic [33] | 2017                | Review           | To determine the association of anosmia and ageusia in Parkinson's Disease                               | Evaluation of olfactory thresholds, smell identification and discrimination, and olfactory memory. | Olfactory disorders are more prominent in Parkinson's disease compared to other neurodegenerative conditions.                       |
| Taniguchi and Takeda [34] | 2017                | Review           | To study the olfactory dysfunction as a clinically detectable motor sign for PD                          | Smell tests.   | Smell tests seem to be a feasible diagnostic tool for early PD and a potentially useful biomarker for Parkinson's disease dementia. |
| Domellöf et al. [35]      | 2017                | Research article | The presentation and evolution of olfactory deficits from the time of PD diagnosis.                      | Brief smell identification test.   | The risk of dementia increased ten times manifold in PD patients with anosmia.  |
| Iannilli et al. [36]      | 2017                | Research article | Studying the co-relation of EEG with olfactory function assessment.                                      | 64-channel electroencephalography and psychophysical tests.  | The difference in the mechanism of olfactory dysfunction in patients with and without Parkinson's.                                  |

**TABLE 2: Previous studies about olfactory disorder in Parkinson's disease.**

PD- Parkinson's disease; PET- positron emission tomography; EEG- electroencephalography; MMSE: mini-mental state examination

## Sleep disorders in Parkinson's disease

Sleep disorders are the most common NMS associated with PD and have been studied in 58-98% of PD patients [37]. James Parkinson himself mentioned the poor sleep quality in PD patients in his famous monograph about the disease. Sleep disorders like olfactory dysfunctions can occur years before the appearance of motor features [38]. Decreased sleep quality, daytime fatigue, and nocturnal awakenings characterize sleep in PD [39]. These disorders may precede motor and autonomic symptoms like akinesia, rigidity, dystonia, and nocturia and might be linked to concomitant sleeping disorders like insomnia, REM sleep disorders, narcolepsy, or sleep apnea. Daytime somnolence, sudden sleep attacks, and other diurnal sleep disturbances can be caused by the levodopa treatment or the neuropathology of PD itself. The early recognition and management of sleep disorders in PD are essential because of their negative impact on life quality. Studies have reported an early morning "sleep benefit" (improved motor function on waking up) prior to medication intake in PD patients [40]. Högl et al. described that the graph linking levodopa concentrations and polysomnographic studies shared a similar pattern between PD patients with and without the sleep benefit. However, PD patients with sleep benefit demonstrated a different response curve to levodopa - the immensity of motor function deterioration after levodopa intake was higher in PD patients with the sleep benefit compared to patients without it [41]. Previous studies have also reported a high prevalence of obstructive sleep apnea (OSA) in PD patients (approximately 20-60%). The hypothesis surrounding OSA is PD related loss of functioning neurons in myofibers and their subsequent atrophy, degeneration of the peripheral nerves innervating the oropharyngeal muscles, alpha-synuclein deposition in the fibers of the vagus nerve, supplying the laryngeal and pharyngeal muscles, and the episodic upper airway movement disorders caused by nocturnal dyskinesia may play a pivotal role in the development of obstructive sleep apnea. Nevertheless, the clinical relevance of OSA in PD remains a topic for further debate (Table 3).

| Author                            | Year of publication | Type of study    | Purpose of the study  | Intervention studied  | Result/conclusion   |
|-----------------------------------|---------------------|------------------|---|---|---|
| Chahine et al. [42]               | 2017                | Review           | Sleep wakefulness cycle in PD.  | A systematic review on REM sleep behavior disorders, periodic limb movements, sleep-disordered breathing, and circadian rhythm disorders. | There is an influence of the medications used in the treatment of PD on the sleep cycle.                                      |
| Doregowska and Rudzińska-Bar [43] | 2019                | Review           | The study discussed sleep physiology, different sleep dysfunctions such as REM sleep behavior disorder, EDS, insomnia, obstructive sleep apnea syndrome, and their clinical manifestations. | Sleep physiology  | There is a coexistence of various non-motor symptoms such as pain, depression, or nocturia with sleeping disorders            |
| Falup-Pecurariu and Diaconu [44]  | 2017                | Review           | Detection and management of sleep disorders in PD.  | Sleep recording techniques-actigraphy or polysomnography.   | Insomnia, daytime somnolence, REM sleep disorders, and restless leg syndrome are all encountered in PD.                       |
| Shen and Liu [45]                 | 2018                | Editorial        | The study discussed the present status and future prospects of sleep disorders in PD.   | Genetic studies of sleep disorders.   | It's debatable if sleep disorders enhance PD progression.   |
| Crosta et al. [46]                | 2017                | Research article | The study looked into the occurrence of sleep-disordered breathing in a large consecutive outpatient series   | Epworth sleepiness scale, polysomnography   | The study suggested an increased frequency of obstructive sleep apnea syndrome and other SDB in PD and parkinsonism.          |
| Bollu and Sahota [47]             | 2017                | Review           | To study the various sleep disorders seen in PD patients  | Sleep fragmentation, wakefulness after sleep onset  | The study helps understand sleep issues in PD, which can help identify them early and result in optimal management.           |
| Barone and Henchcliffe [48]       | 2018                | Review           | The study looked into rapid eye movement sleep behavior disorder and its association with alpha-synucleinopathies.  | Alpha-synucleinopathy   | RBD alone is now recognized to be a significant causative factor of neuropathological ailments especially Lewy body dementia. |
| Sobreira-Neto et al. [49]         | 2017                | Research article | Frequency study of major sleep disorders in Parkinson's disease   | Standardized scales- Epworth Sleepiness Scale, PD questionnaire, Pittsburgh sleep quality index.  | The impact of day time somnolence on the quality of life.   |
| Kim et al. [50]                   | 2018                | Review           | To probe the significance of REM sleep behavior disorder as a prognostic factor in PD   | Baseline RBD.   | Studying the co-relation of RBD with the prognosis and mortality of PD patients.  |

**TABLE 3: Previous studies about sleep disorders in Parkinson's disease.**

PD- Parkinson's disease; REM- rapid eye movement; SDB- sleep-disordered breathing; RBD- REM sleep behavior disorder; EDS- excessive daytime sleepiness

## Conclusions

Despite the growing awareness of PD's non-motor symptoms, most clinical trials still focus on motor symptoms as the primary consequence. The prodromal NMS phase's basis relies on the Lewy pathology hypothesis, which starts outside the substantia nigra. Though backed by in vitro, in vivo, and clinical evidence, this hypothesis isn't widely accepted. Gut dysfunction, depression, REM sleep disorders amongst the many NMS can prove to be seriously disabling and can deteriorate the quality of life in Parkinson's patients. Early recognition and quantitation of NMS can thus aide in the management and sometimes even the early diagnosis of Parkinson's disease.

## Additional Information

### Disclosures

**Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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