UNIVERSITY OF IOANNINA

SCHOOL OF HEALTH SCIENCES

DEPARTMENT OF SPEECH AND LANGUAGE THERAPY

Speech difficulties and dysphagia in Parkinson's disease and their neuroimaging correlates

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HIGHLY SPECIALIST SPEECH AND LANGUAGE THERAPIST

PhD THESIS

IOANNINA 2025

ΠΑΝΕΠΙΣΤΗΜΙΟ ΙΩΑΝΝΙΝΩΝ

ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑΣ

ΤΜΗΜΑ ΛΟΓΟΘΕΡΑΠΕΙΑΣ

Διαταραχές ομιλίας και δυσφαγία στη Νόσο του Πάρκινσον και οι νευροαπεικονιστικοί τους συσχετισμοί

ΣΩΤΗΡΙΟΣ ΠΟΛΥΧΡΟΝΗΣ

ΛΟΓΟΘΕΡΑΠΕΥΤΗΣ ΥΨΗΛΗΣ ΕΞΕΙΔΙΚΕΥΣΗΣ

ΔΙΔΑΚΤΟΡΙΚΗ ΔΙΑΤΡΙΒΗ

ΙΩΑΝΝΙΝΑ 2025

«Η έγκριση της διδακτορικής διατριβής από το Τμήμα Λογοθεραπείας του Πανεπιστημίου Ιωαννίνων δεν υποδηλώνει αποδοχή των γνωμών του συγγραφέα»

Ημερομηνία αίτησης του κ. Πολυχρόνη Σωτήριου: 28/02/2020

Ημερομηνία ορισμού Τριμελούς Συμβουλευτικής Επιτροπής: Γ.Σ. αριθμ. 9η/23-09-2020

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«Speech difficulties and dysphagia in Parkinson's disease and their neuroimaging correlates»

ΟΡΙΣΜΟΣ ΕΠΤΑΜΕΛΟΥΣ ΕΞΕΤΑΣΤΙΚΗΣ ΕΠΙΤΡΟΠΗΣ: 118η/08-10-2025

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Έγκριση Διδακτορικής Διατριβής με βαθμό **«ΑΡΙΣΤΑ»** στις **05-11-2025**

ΠΡΟΕΔΡΟΣ ΤΟΥ ΤΜΗΜΑΤΟΣ ΛΟΓΟΘΕΡΑΠΕΙΑΣ
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Η Γραμματέας του Τμήματος

ΕΛΛΗΝΙΚΗ ΔΗΜΟΚΡΑΤΙΑ ΣΧΟΛΗ ΕΠΙΣΤΗΜΩΝ ΥΓΕΙΑΣ ΤΜΗΜΑ ΛΟΓΟΘΕΡΑΠΕΙΑΣ ΠΑΝΕΠΙΣΤΗΜΙΟ ΙΩΑΝΝΙΝΩΝ

Χρυσούλα Κοτρώτσιου

Ιωάννινα 11-11-2025

“When silence begins in the brain,

science strives to speak…”

Sotirios Polychronis

Preface

This doctoral thesis was written as part of my PhD studies at the University of Ioannina, within the Department of Speech and Language Therapy. The research presented here explores the complex relationship between speech difficulties, dysphagia, and their neuroimaging correlates in Parkinson's disease. It reflects both my academic interests and my clinical commitment to understanding and supporting individuals affected by neurodegenerative disorders.

The journey of this thesis has been shaped by the guidance, encouragement, and generosity of many people. I would like to express my deepest gratitude to my supervisors: Prof. Grigorios Nasios, for entrusting me with the opportunity to pursue this research, and for his unwavering support and enduring commitment at every stage of this work; Prof. Gennaro Pagano, for his invaluable mentorship, sharp scientific intuition, and thoughtful guidance throughout this journey; and Prof. Efthimios Dardiotis, for his expertise and insightful contributions on this research. Special thanks go to my fellow researchers and friends for their continuous encouragement and enriching discussions.

Finally, I dedicate this work to my family, whose love and belief in me have been a source of strength through every stage of this journey.

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Section I - Introduction

Chapter 1: Overview of Parkinson's disease

1.1 Introduction

Parkinson's disease (PD) is a neurodegenerative disease that significantly impact on the patient's quality of life. Many patients suffering from PD will eventually present a form of speech dysfunction and/or swallowing difficulties that may become an additional source of anxiety and a possible hurdle to their communication.

1.2 Parkinson's disease overview

PD is recognised as the second most frequent neurodegenerative disease after Alzheimer's (Delamarre & Meissner, 2017). James Parkinson first documented the condition in 1817 (Ostheimer, 1922). PD predominantly impacts the motor system, characterised by the progressive degeneration of dopaminergic neurones in the substantia nigra, an area located in the midbrain. The ensuing reduction in dopamine levels within the striatum, an essential brain region for motor regulation, results in motor manifestations including tremors, bradykinesia, stiffness, and postural instability. Besides motor symptoms, PD impacts various neuronal cell types, leading to non-motor symptoms including cognitive impairment, mood problems, sleep abnormalities, and autonomic dysfunction.

1.3 Epidemiology

Parkinson's disease affects between 1-2% of those aged 65 and older, with the prevalence rising to 3-5% for those aged 80 and above (Fahn, 2003). The underlying cause of PD remains largely unspecified, but current theories propose that it arises from many factors, including genetic and environmental influences (Elbaz et al., 2016; Delamarre & Meissner, 2017). Epidemiological studies have shown that PD prevalence is age-dependent, with the condition rarely manifesting prior to the age of 50, with a progressive increase in prevalence post-60 (Elbaz et al., 2016). Hirsch et al.'s meta-analysis (2016) indicates that PD prevalence is 0.41‰ for those aged 40-49, while it increases significantly to 19.03‰ for individuals older than 80 years.

Furthermore, research has demonstrated that PD is more frequent in men than in women within specific age groups (Hirsch et al., 2016; Elbaz et al., 2007; Taylor et al., 2007). Hirsch et al.'s meta-analysis (2016) reveals that men are more affected, especially in the 50-59 age group, where the prevalence is 1.34‰ compared to a mere 0.41‰ in women. In other age groups studied, men exhibited slightly higher, albeit not statistically significant, incidence rates than women. The later manifestation of PD symptoms in women could be attributed to the neuroprotective effects of oestrogen, differences in occupational exposures such as pesticide use, or X-linked genetic factors (Elbaz et al., 2016; Shulman, 2007).

Ethnicity appears to significantly influence the gender prevalence of PD. Alves et al.'s study (2008) found that the male-to-female PD ratio was 1.58 in most investigations involving Western populations, while the ratio was almost equal in Asian populations. This suggests that there may be additional genetic or environmental factors specific to different ethnic groups that impact to the progression of PD. Understanding these factors could offer significant understanding of the mechanisms underlying PD and guide new preventive and treatment approaches.

1.4 Genetics

Over the past 20 years, particularly the last decade, research has increasingly concentrated on the genetics of PD. This focus has led to the discovery of many genes associated with familial monogenic types of PD. Furthermore, numerous gene loci have been discovered to be associated with either autosomal-dominant (e.g., *LRRK2, SNCA, CHCHD2*, *EIF4G1* and *VPS35*) or autosomal-recessive (e.g., *PINK1, DJ1, ATP13A2, Parkin, PLA2G6, RAB39B, DNAJC6* and *FBXO7*) inheritance of Parkinsonism (Delamarre & Meissner, 2017).

Additionally, genome-wide association studies (GWAS) have revealed single nucleotide polymorphisms (SNPs) across several genes, including the *SNCA* gene that encodes alpha-synuclein, to be associated with a higher likelihood of manifesting PD (Nalls et al., 2011). Certain gene mutations are linked with juvenile or cases where the disease begins at an earlier age, while others, such as SNP mutations, seem to cause sporadic Parkinsonism in both clinical and demographic aspects (Alves et al., 2008). All these affected genes have a significant impact on intracellular functions, including mitochondrial function, lysosomal and endosomal pathways, synaptic transmission, vesicle trafficking, and quality control, which are subsequently disrupted (Elbaz et al., 2016; Delamarre & Meissner, 2017).

1.5 Risk and protective factors

The impact of a wide range of environmental factors on PD has been the subject of numerous studies, yet the results have often been contradictory or inconclusive (Lai et al., 2002; Elbaz & Tranchant, 2007). Despite the inconsistencies, certain environmental factors have emerged as potential risk factors contributing to the manifestation of PD. These factors include contact with pesticides or other environmental chemicals, such as solvents, as well as methamphetamine use, the occurrence of melanoma skin cancer, traumatic brain injury, and an increased consumption of dairy products (Alves et al., 2008; Ascherio & Schwarzschild, 2016; Delamarre & Meissner, 2017; Elbaz et al., 2016).

On the other hand, several factors have been identified that may lower the likelihood of developing PD. Among the most significant protective factors are tobacco smoking, coffee or caffeine consumption, elevated urate levels, the utilisation of non-steroidal anti-inflammatory drugs (NSAIDs) and engaging in regular vigorous physical activity or exercise (Ascherio & Schwarzschild, 2016; Elbaz et al., 2016).

1.6 Neurological underpinnings

The principal source of classic PD symptoms is the degeneration of dopaminergic neurones in the substantia nigra pars compacta (SNc) and the resulting decrease in striatal dopamine levels (Dickson et al., 2009). A neuropathological diagnosis necessitates evidence of Lewy bodies, Lewy neurites, and reduced dopamine in nuclei such as the SNc, and eventually, some cortical regions (Braak et al., 2004), or even throughout the brain, as observed in post-mortem examinations of PD brains (Pavese & Brooks, 2013). Lewy bodies are eosinophilic inclusions composed of a dense core encircled by a faintly stained halo of radiating filaments, with alpha-synuclein as a key component (Dexter & Jenner, 2013). However, this does not encompass the entire neuropathology of PD, as various non-dopaminergic nuclei also experience degeneration and Lewy body pathology. Jellinger (2012) lists affected nuclei such as the locus coeruleus, brainstem's reticular formation, vagus nerve's dorsal motor

nucleus, raphes nucleus, Meynert's basal nucleus, the hippocampus and the amygdala. Depending on which of these nuclei are impacted, patients may exhibit an array of non-motor symptoms (Dexter & Jenner, 2013).

The involvement of multiple cortical and subcortical brain regions in basal ganglia functions can account for the wide range of non-motor and motor manifestations associated with PD.

1.7 The role of the basal ganglia

The basal ganglia, in conjunction with related nuclei, are a collection of subcortical cell groups that are predominantly involved in executive functions, behaviour, emotions, motor control, and motor learning. Nuclei located deep within the cerebral hemispheres, including the striatum (caudate-putamen) and globus pallidus, are the subject of these terms. Structures situated in the diencephalon (subthalamic nucleus), mesencephalon (SN), and pons (pedunculopontine nucleus) are examples of related nuclei (Lanciego et al., 2012).

The basal ganglia and its related nuclei are structured into input, output, and intrinsic nuclei. The input nuclei, comprising the caudate nucleus, putamen, and nucleus accumbens, receive information from cortical, thalamic, and nigral brain regions. Conversely, output nuclei, including the internal segment of the globus pallidus (GPi) and substantia nigra pars reticulata (SNr), transmit information from the basal ganglia to the thalamus and several cortical regions in the frontal lobe (DeLong et al., 1990). Intrinsic nuclei, such as the external portion of the globus pallidus (GPe), subthalamic nucleus (STN), and substantia nigra pars compacta (SNc), are situated between output nuclei in the information relay pathway (DeLong et al., 1990).

The optimal functioning of the basal ganglia depends on dopamine release in the input nuclei. Dysfunction in dopamine release, particularly in projections from the substantia nigra pars compacta to the striatum, is linked to many movement disorders, including PD and dystonia (Lanciego et al., 2012).

In PD, changes in dopamine-dependent synaptic plasticity may interfere with the coordinated activity of the basal ganglia. Dopamine deficiency alters the activity balance towards the indirect pathway, resulting in heightened activity in the STN, which subsequently overexcites the GPi/SNr. The increased activity from the GPi/SNr excessively suppresses the thalamocortical projection, reducing cortical neuronal activation related to movement initiation (Calabresi et al., 2014).

As a consequence of the degeneration of dopamine neurones in PD, the indirect pathway experiences increased activity, and the thalamus remains in an overly inhibited state. With the thalamus suppressed, the signal to the motor cortex cannot function properly, resulting in challenges with movement initiation or speech for individuals with PD.

1.8 Progression and clinical manifestations

PD is a neurodegenerative disease that usually starts to develop long before noticeable motor dysfunction and the subsequent diagnosis. In prodromal (early), stage of PD, non-motor symptoms emerge, such as constipation, depression, sleep disturbances and anosmia (Schapira et al., 2017). The manifestation and

advancement of these symptoms may differ among persons; these non-motor features of PD can appear more than a decade before the onset of motor impairments and diagnosis. By the time the first motor symptoms arise, 50-60% of dopamine neurons have already been depleted (Fearnley & Lees, 1991; Gibb & Lees, 1991; Schapira et al., 2017). This significant loss of dopamine neurons has a considerable impact on the patient's motor control and coordination.

Moreover, the course of the disease after diagnosis varies depending on the treatment received. If the disease is left untreated, the symptoms progress quickly, significantly affecting the patient's quality of life. It is crucial to note that while dopamine replacement therapy can alleviate symptoms, it does not terminate the underlying loss of dopamine-producing nerve cells. Consequently, the disease will continue to progress over time, and the effectiveness of the treatment may diminish (Schapira et al., 2017).

1.9 Non-motor symptoms

Non-motor symptoms (NMS) of PD are diverse and can manifest in individuals diagnosed with PD at any point during the disease's progression (Pfeiffer et al., 2005; Jankovic, 2008; Kempster et al., 2010). These symptoms may follow a different progression pattern than motor symptoms (Antonini et al., 2012). Schapira et al. (2017) recently categorised non-motor symptoms into four main groups: *sensory impairments, neuropsychiatric features, sleep disturbances, and autonomic dysfunction*.

Sensory impairments include olfactory deficits, such as hyposmia/anosmia (reduced or complete loss of sense of smell), and visual issues like hallucinations, diplopia (double vision), pain, and somatosensory disturbances. Other sensory symptoms may involve altered taste perception and abnormal skin sensations (Schapira et al., 2017).

Neuropsychiatric features cover a wide range of disorders, including anxiety, depression, apathy, fatigue, cognitive deficits, dementia, and psychosis. These symptoms may profoundly affect the quality of life for individuals with PD and may require specialised treatment and support from healthcare professionals (Schapira et al., 2017).

Sleep disturbances are prevalent in PD and include excessive daytime sleepiness (EDS), insomnia, REM sleep behaviour disorder (RBD), and restless leg syndrome (RLS). Addressing sleep issues can significantly improve the overall well-being of individuals with PD (Schapira et al., 2017).

Autonomic dysfunction in PD is characterised by symptoms affecting various body systems. Bladder dysfunction can lead to urinary urgency, frequency, and incontinence, while gastrointestinal issues may result in constipation, gastroparesis, and swallowing difficulties. Sexual dysfunction can manifest as erectile dysfunction in men and arousal difficulties in women. Cardiovascular features, such as orthostatic hypotension, may cause dizziness or fainting upon standing (Schapira et al., 2017).

Some non-motor symptoms, like hyposmia, depression, and subtle cognitive impairments, may be present at the time of PD diagnosis and can become more

pronounced as the disease progresses, particularly in its later stages (Chaudhuri et al., 2006).

1.10 Motor symptoms

Basic motor processes, such as selecting suitable motor actions, coordinating, and sequencing movements, accurately executing a series of movements, and integrating perceptual input with timing information (Moustafa et al., 2016), underlie motor actions like walking, speaking, and handwriting. In PD, these processes are impaired, leading to motor movements characterised by an asymmetrical manifestation of four principal motor symptoms: resting tremor, postural instability, bradykinesia and cogwheel rigidity (Jankovic, 2008; Braak et al., 2004). Additional prevalent signs of PD include episodes of freezing and a stooped posture (Jankovic, 2008). Research frequently classifies individuals into three overarching categories based on these principal symptoms: tremor-dominant, akinetic-rigid dominant, and mixed phenotype (Lee et al., 2006; Jankovic et al., 1999).

Dopamine loss in the basal ganglia is closely connected to dyskinesia and rigidity (Helmich et al., 2011; Rodriguez-Oroz et al., 2009). Dyskinesia arises due to excessive activation of striatal neurons in the indirect pathway, leading to reduced motor output and a greater perceived effort to move (Collins & Frank, 2014). Additionally, Berardelli et al. (2001) proposed that excessive inhibitory output from the basal ganglia to the cortex might underlie bradykinesia's neural mechanism. No definitive evidence links dopamine depletion in the basal ganglia to tremor presence. However, some pharmacological studies suggest that different tremor types (e.g., resting, kinetic, and postural) show varying responses to dopaminergic therapies, with kinetic and postural tremors being the most dopamine-dependent (Spiegel et al., 2007). Tremor has also been linked to abnormalities in the cerebellum, thalamus, and STN (Helmich et al., 2011; Kassubek et al., 2002).

As PD progresses, patients' quality of life worsens due to their diminished ability to carry out everyday motor activities like walking, writing, eating with utensils, and swallowing, as well as impaired communication abilities, even before the overall underlying decline becomes severe. This gradual, life-altering bodily change, affecting movement and speech production, is attributed to the four primary motor symptoms of PD and the motor mechanism's neuropathological changes (Cantiniaux et al., 2008; Jankovic, 2008; Braak et al. 2004; Ackermann & Ziegler 1991).

Clinically, bradykinesia refers to slowed movement involving difficulties in planning, initiating, and executing movement. These difficulties also interfere with performing sequential or simultaneous/dual tasks (Jankovic, 2008; Berardelli et al., 2001). Patients may exhibit slow movements and increased reaction times (Giovannoni et al., 1999; Cooper, Sagar, Tidswell & Jordan, 1994) across a wide range of motor abilities. This impairment can affect actions from facial expressions to fine motor skills. Patients may experience hypomimia (i.e., masked face) and struggle with activities like writing (i.e., micrographia), buttoning, playing musical instruments, and using utensils. They may also have significant difficulty rising from a chair or walking at a normal pace without shuffling. Voice quality, speech rate, and swallowing patterns may also change (Hou & Lai, 2008; Jankovic, 2008).

Resting tremor is often the earliest and most easily observed clinical sign of PD, typically described by a low-frequency tremor (3-8Hz) that predominantly affects the upper extremities and usually presents unilaterally (Ahlskog, 2000). This hand tremor is commonly referred to as a supination-pronation or pill-rolling tremor (Jankovic, 2008) and is influenced by patients' anxiety levels. In the initial stages of PD, postural tremor may share similar amplitude and frequency with resting tremor. As the disease advances, both resting and postural tremors become more prevalent, affecting patients' daily functioning and further complicating their motor symptoms (Jankovic et al., 1999).

Rigidity, defined as heightened resistance to passive limb movement due to increased muscle tone, is another hallmark symptom of PD (Magrinelli et al., 2016). This rigidity often co-occurs with the cogwheel phenomenon, particularly during passive movements of the trunk, neck and limbs (Magrinelli et al., 2016). The resistance to external movements presents as slow movement without a specific speed or angle threshold, posing difficulties for patients to carry out daily activities (Magrinelli et al., 2016). Rigidity may also contribute to further complications, including dystonia and abnormalities in posture, ultimately contributing to postural instability (Magrinelli et al., 2016).

More prevalent in advanced PD, postural instability arises from a combination of rigidity and bradykinesia, leading to diminished postural reflexes and difficulty with positional adjustments (Palakurthi et al, 2019). Postural reflexes are responsible for generating adequate muscular contractions to maintain a particular stance (Weismer G., 2000). Various gait-related activities, including walking pace, gait initiation, and turns, are severely impacted, leading to a decline in patients' mobility and independence. PD patients' gait patterns may also be altered, exhibiting festinations and freezing of gait while walking, which can raise the risk of injuries and falls. Over time, patients may experience significant challenges in maintaining an upright position during walking, standing, or even sitting, further exacerbating how PD impairs their ability to maintain a good quality of life (Nonnekes et al., 2019).

Chapter 2: Overview of Speech Difficulties in Parkinson's disease

2.1 Epidemiology

Speech impairments are common and clinically significant features of PD, affecting up to 90% of individuals as the condition progresses, with considerable consequences for quality of life and social engagement (Ho et al., 1999; Logemann et al., 1978). These deficits are not limited to advanced stages; evidence shows they may also be present in the early, untreated phases of PD (Polychronis et al., 2019). In fact, approximately 42.8% of *de novo* PD patients report speech difficulties in addition to other motor symptoms (Polychronis et al., 2019). Importantly, alterations in voice and speech may emerge as early as five years before a formal diagnosis is made (Harel et al., 2004).

Such impairments represent a critical area of concern within the broader context of the epidemiology of the condition. The occurrence of speech and voice impairments in early stages of PD signals the potential role of these difficulties as early indicators of the disease (Qi et al., 2023), which has important implications for disease detection and management strategies. The far-reaching implications of speech difficulties in PD necessitate further investigation into the epidemiological factors contributing to their prevalence (Rahman et al., 2023).

2.2 Effects of Parkinson's disease on speech

It is evident that PD affects speech output in a variety of ways, impacting articulation, speech tempo, voice volume, and pitch. The link between dopaminergic dysfunction and general speaking ability is yet unknown (Skodda et al., 2013). It has therefore been proposed that speech and voice changes in PD may arise not only from deficits in internal cueing, sensorimotor processing, and speech motor control but also from non-dopaminergic pathways (Kompoliti et al., 2000; Goberman et al., 2002; Goberman, 2005).

Hypokinetic Dysarthria (HKD) is a catch-all term for the speech symptoms that typically appear in PD patients (Darley et al., 1975). HKD is a rare and complex motor condition that can impact all aspects of speech production, including breathing, phonation, articulation, and speech intonation, among other areas. As a result, speech intelligibility is also impacted and, depending on the degree of HKD, can range from articulatory imprecision to completely unintelligible speech (Duffy, 2013; Freed, 2011; Ho et al., 1999).

According to Darley et al. (1975), features such as reduced stress, monoloudness, imprecise consonants, repeated phonemes, monopitch, low pitch, brief rushes of speech, inappropriate pauses, harsh or breathy vocal quality, increased rate within segments and variable speech rate are the most typical speech characteristics of HKD. These characteristics are discussed in relation to all dysarthrias in their landmark book on motor speech disorders, which was initially released in 1975 (Darley et al., 1975). Their guiding principle was that the dysarthrias can be differentiated primarily based on the sound of the speech. The core motor characteristics of stiffness, bradykinesia, and tremor are connected to the hypokinetic dysarthria. Muscular rigidity can explain symptoms like the expressionless face, monotonous volume and pitch, diminished volume, and slurred articulation. Bradykinesia, or difficulty starting

movements, explains why reactions are sluggish. The lips, tongue, jaw, and voice can all exhibit trembling. According to Gillivan-Murphy et al. (2016), tremors in the voice are most likely caused by oscillatory movement in the vocal cords.

All these speech deviations can be attributed to patients' limited resources to monitor their speech production due to the basal ganglia dysfunction in PD (Dagenais et al., 1999). Overall, physiology, acoustic and kinematic studies confirm most of the initial perceptual observations of Darley et al. (1975) about HKD and contribute to creating a detailed and precise profile of this distinct type of dysarthria.

The descriptions of deep brain stimulation (DBS) are consistent with the possibility that these traditional dysarthria symptoms are brought on by the motor elements of PD. The scale of postoperative dysarthria can vary depending on the electrodes' positions, bipolar directional steering, and setting amplitudes. To maximise speech clarity and understandability, careful electrode placement and stimulation settings are necessary (Little et al., 2013; Reker et al., 2016).

2.3 Pathophysiology of speech difficulties

Speech difficulties in PD are a prevalent and multifaceted problem that can profoundly impact the quality of life for affected individuals (Miller et al., 2006). The pathophysiology of speech impairments in PD is intricate, involving disruptions in various motor, sensory, and cognitive processes related to speech production.

Tremor, bradykinesia, and rigidity, the primary motor features of PD, can adversely affect key speech subsystems such as breathing, voice production, articulation, and intonation (Sapir et al., 2010). Additionally, axial motor symptoms, like reduced trunk mobility and impaired facial muscle control, can further exacerbate speech difficulties in PD by affecting the respiratory support, vocal fold function, and articulatory precision required for normal speech production (De Keyser et al., 2017).

Bradykinesia, characterised by slowness of movement, can cause reduced speech rate, increased pauses, and difficulties with initiating speech (Skodda, 2013). Rigidity, or increased muscle tone, can lead to stiffness in the muscles responsible for speech production, contributing to reduced vocal range, monotone speech, and imprecise articulation (Polychronis et al., 2019). Tremor may also impact the stability and control of the muscles involved in speech, further affecting voice quality and articulation (Jankovic, 2008).

Moreover, the underlying neurodegenerative processes in PD, particularly the progressive loss of dopaminergic cells in SN and the consequent dopamine deficit in the basal ganglia, have been linked to the disruption of speech motor control (Alm, 2004). This disruption affects the planning, execution, and coordination of speech movements, leading to alterations in speech rate, rhythm, and fluency (Yorkston et al., 2007). The role of other neurotransmitters, such as serotonin and norepinephrine, in the pathophysiology of speech difficulties in PD has also been suggested, as they may contribute to the complex interaction of neural networks involved in speech production (Rusz et al., 2016).

In addition to motor-related issues, sensory and cognitive deficits in PD also contribute to speech difficulties. Impairments in auditory and somatosensory feedback processing can hinder the individual's ability to monitor and adjust their speech production, resulting in reduced intelligibility and abnormal prosody (Ludlow & Hoit, 2008). Furthermore, cognitive deficits, such as executive dysfunction, attentional impairments, and working memory limitations, can affect the planning and organisation of speech content, contributing to disfluencies and communication challenges (Yorkston et al., 2007).

Lastly, it is important to consider the effect of PD medications and DBS on speech production. While dopaminergic medications can improve some motor symptoms, their effects on speech can be variable, with some patients experiencing improved speech performance and others experiencing worsening of speech symptoms (Ciucci et al., 2008). Similarly, DBS can lead to significant motor improvements in PD but may result in variable and sometimes adverse effects on speech production (Tripoliti et al., 2011).

In conclusion, the pathophysiology of speech difficulties in PD is a complex interplay of motor, sensory, and cognitive impairments resulting from the neurodegenerative processes underlying the condition, as well as the influence of treatments such as medications and DBS (Alm, 2004). These disruptions lead to a range of speech impairments, including reduced speech rate, altered prosody, and decreased intelligibility, which may severely compromise the person’s ability to communicate and diminish their quality of life (Miller et al., 2006).

2.4 Imaging assessment: presynaptic dopaminergic function

Polychronis et al. (2019) highlighted that speech difficulties in early PD are associated to enhanced striatal dopaminergic deficits and more severe symptoms. Interestingly, the variations in dopaminergic function observed between patients with and without speech difficulties did not seem to be directly connected to the severity of clinical symptoms or motor phenotype displayed by PD patients experiencing speech difficulties. This finding suggests that other factors may also play a role in speech impairments in PD.

Previous neuroimaging studies employing positron emission tomography (PET) (Liotti et al., 2003; Narayana et al., 2009, 2010; Pinto et al., 2004) and functional magnetic resonance imaging (fMRI) (Elfmarkova et al., 2016; Maillet et al., 2012) have shed light on the neural underpinnings of speech impairments in PD. These investigations revealed abnormal activation patterns within the basal ganglia–cerebellum–cortex circuitry, as well as altered engagement of the orofacial motor cortex, supplementary motor area, and cerebellum. Notably, PD patients receiving dopaminergic therapy exhibited increased recruitment of premotor and prefrontal cortical regions (Elfmarkova et al., 2016; Maillet et al., 2012), highlighting the involvement of compensatory mechanisms. Collectively, these findings suggest that speech difficulties in PD arise from a complex network of dysfunctional and adaptive brain processes.

In a more recent fMRI study, Elfmarkova et al. (2016) investigated the impact of levodopa on resting-state functional connectivity and prosodic speech control in both ON and OFF medication states. The authors identified a link between levodopa-induced modulation of caudate–dorsolateral prefrontal cortex connectivity and improvements in speech production. This finding supports the association between dopaminergic dysfunction and speech impairments in PD. Nonetheless, not all studies have indicated a direct correlation between levodopa medication and enhancement of speech. For example, Skodda et al. (2011) evaluated the influence of levodopa on speech using a syllable repetition paradigm and found no association between levodopa administration and vocal pace performance. This finding indicates that dysfunctional basal ganglia circuits responsible for maintaining speech motor programs might not respond uniformly to short-term dopaminergic stimulation, and other mechanisms could be contributing to speech difficulties in PD.

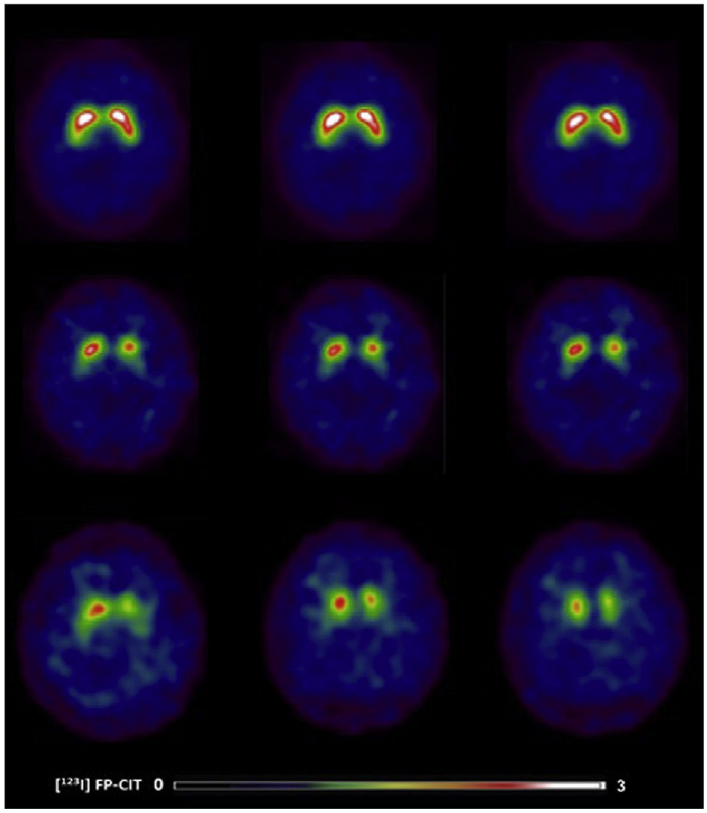


Figure 1. [^{123}I]FP-CIT SPECT images in Parkinson's disease patients with and without speech difficulties adapted from 'Polychronis, S., Niccolini, F., Pagano, G., Yousaf, T., & Politis, M. (2019). Speech difficulties in early de novo patients with Parkinson's disease. *Parkinsonism & Related Disorders, 64*, 256–261'.

(Top) A 55-year-old healthy control presenting typical [^{123}I]FP-CIT specific binding ratios in the caudate and putamen.

(Middle) A 55-year-old male without speech difficulties showcasing minor dopaminergic deficits as indicated by [^{123}I]FP-CIT specific binding ratios in the caudate and putamen.

(Bottom) A 55-year-old male with speech difficulties displaying more significant striatal dopaminergic deficits as revealed by [^{123}I]FP-CIT specific binding ratios in the caudate and putamen.

2.5 Neurobiological basis of speech difficulties and their Imaging assessments

To comprehend the neurological foundation of speech difficulties in PD, it is essential to examine particular functional linkages between the cortex and the basal ganglia that may distinctly influence speech symptoms. Cortico–basal ganglia circuits play a vital role in normal speech production; however, the precise contributions of basal ganglia pathways to speech processes remain incompletely understood.

Advanced neuroimaging techniques, including positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), have significantly advanced our understanding of how these structures contribute to both typical and disordered speech. Among the basal ganglia components, the putamen has been consistently implicated in speech and voice control, as supported by various neuroimaging studies (Bohland & Guenther, 2006; Brown et al., 2009; Manes et al., 2014; Tourville & Guenther, 2011). Evidence from these studies shows robust bilateral activation of the putamen during both speech-related and non-speech oromotor tasks (Brown et al., 2009; Chang et al., 2009; Parkinson et al., 2012).

Evidence from PET imaging with D2/D3 receptor radioligands indicates left-lateralized striatal dopamine release during speech production, suggesting that the left hemisphere may be more crucial for speech-related functions than the right hemisphere (Simonyan et al., 2013).

The globus pallidus, in conjunction with the striatum, has been implicated in the neural control of normal speech production. A meta-analysis of functional activation patterns within the internal segment of the globus pallidus (GPi) and the subthalamic nucleus revealed considerable overlap with regions involved in speech processing, including the left putamen, insula, and the ventrolateral nucleus of the thalamus (Manes et al., 2014). These findings align with the Directions Into Velocities of Articulators (DIVA) model, which posits that both the globus pallidus and putamen contribute to the initiation of speech movements through their reciprocal connections with the supplementary motor area (SMA) (Tourville & Guenther, 2011).

Considering the crucial function of basal ganglia circuits in speech production, it is unsurprising that illnesses impacting these areas, such as Parkinson's and Huntington's disease, lead to considerable speech deficits. Nonetheless, uncertainties persist regarding the specific basal ganglia-cortex connectivity implicated in speech disorders and if these pathways are separate from those linked to general motor symptoms. Multiple cortical regions implicated in speech production, including the supplementary motor area, sensorimotor cortex, superior temporal gyrus and inferior frontal gyrus may be influenced by alterations in basal ganglia functionality (Tourville & Guenther, 2011; Manes et al., 2014; Brown et al., 2005).

Resting-state connection investigations in PD have revealed atypical connectivity between the basal ganglia and areas like motor cortices (Kwak et al., 2010; Baudrexel

et al., 2011; Kurani et al., 2015) and the cerebellum (Hacker et al., 2012). These results underline that altered connectivity can cause speech problems in PD. Additionally, the basal ganglia may also be linked to cortical areas that are not directly engaged in motor control processes, such as the superior temporal gyrus (STG). During a sentence production task, Simonyan et al. (2013) observed a correlation between BOLD responses in the left anterior putamen and the left superior temporal gyrus, raising the possibility that changes in basal ganglia-STG connectivity might contribute to speech impairments in PD.

Resting-state fMRI connectivity analysis offers a method to estimate the robustness of connections between cortical regions and basal ganglia. This approach allows researchers to observe intrinsic brain network organization, free from the influence of task execution (Di Martino et al., 2008; Biswal et al., 1995). While numerous studies have identified disrupted resting-state connectivity in PD, few have examined how these changes relate to speech impairments (Helmich et al., 2010; Hacker et al., 2012; Kurani et al., 2015). Two studies have specifically investigated the association between speech impairments and connectivity in PD using seed-based resting-state analysis. According to New et al. (2015), the reduction in interhemispheric connectivity between the bilateral putamen was associated with speech impairment scores. Similarly, a study by Elfmarkova et al. (2016) identified a reduction in connectivity between the right caudate nucleus and dorsolateral prefrontal cortex in PD patients, providing further evidence of the relationship between striatal connectivity and speech function. However, these studies did not exclusively focus on patients with speech impairments, leaving questions about the specific brain circuits involved in PD-related speech dysfunction.

Chapter 3: Overview of Dysphagia in Parkinson's disease

3.1 Epidemiology

Dysphagia, or swallowing difficulties, is a prevalent issue in PD, affecting a prominent proportion of patients, particularly in advanced stages of the illness (Kalf et al., 2012). The reported frequency of dysphagia varies considerably due to differences in classification, measurement techniques, and the stage of the disease being studied (Kalf et al., 2012). Based on pooled prevalence data, oropharyngeal dysphagia is subjectively estimated at 35% and increases to 82% when objective, instrumental measures, such as fibreoptic endoscopic evaluation of swallowing (FEES) or video fluoroscopic swallowing study (VFSS), are used (Kalf et al., 2012).

It is crucial to note that swallowing impairments can manifest even in the early stages of PD, with mild oropharyngeal symptoms and oesophageal dysfunctions often occurring before more severe symptoms develop (Potulska et al., 2003; Noyce et al., 2012; Sung et al., 2010; Thomas & Haigh, 1995). In certain instances, these first swallowing difficulties may manifest as the primary symptom of the disease, marking the prodromal stage of PD (Potulska et al., 2003; Noyce et al., 2012; Sung et al., 2010; Thomas & Haigh, 1995). While aspiration episodes can happen early on, severe dysphagia involving chronic aspiration and significant clinical complications are more commonly associated with advanced stages of PD (Potulska et al., 2003; Noyce et al., 2012; Sung et al., 2010).

Moreover, research has stressed that over 50% of PD patients who subjectively report no dysphagia exhibit oropharyngeal disorders when evaluated using objective measures, such as FEES or VFSS (Fuh et al., 1997; Bird et al., 1994). In some cases, silent aspiration, where food or liquid enters the airway without any noticeable signs or symptoms, is observed in approximately 15% of PD cases (Ali et al., 1996).

3.2 Effects of Parkinson's disease on swallowing

Swallowing involves four stages, all of which are governed by a complex, sequential response that is primarily automatic and minimally voluntary (Simons et al., 2017). In PD, disturbances may impact any stage of the swallowing process -including preoral, oral, pharyngeal, and oesophageal phases- as well as associated systems such as respiration, smell, and salivation (Simons et al., 2017). The literature widely agrees that swallowing dysfunctions in PD resulting from delayed motor execution, constrained movement range, diminished physical power, and possible perceptual impairments (Simons et al., 2017).

There is a diverse range of swallowing pathomechanisms and consequent symptom presentation in PD, according to the various swallowing phases:

Phase of swallowing	**Dysfunctional mechanisms and resulting symptom characteristics**
1. Pre-oral phase and oral preparation phase	Swallowing disturbances and symptoms include reduced sense of smell and taste, impaired sensory and tactile-kinesthetic orofacial perception, lack of tongue proprioception, decreased oral

	strength and endurance and disturbed motion dynamics of jaw muscles and tongue movements. As a result, patients may struggle with insufficient saliva production, incomplete chewing and abnormal bolus preparation and formation. They may also experience choking, hawking, and coughing. Therefore, they may present with issues associated with anterior bolus leakage and drooling, posterior leakage or premature bolus spillage, pharyngeal pooling, predeglutitive penetration or aspiration (including silent aspiration) and difficulty or inability in bolus preparation and swallowing.
2. Oral phase, which includes oral propulsion, oral processing, and transportation	Swallowing disturbances and symptoms involve reduced oral bolus control and diminished oropharyngeal bolus transport, with the tongue festinating onto the soft palate. Symptoms may present as repetitive rocking and rolling festination-type motion of the tongue, piecemeal deglutition and choking, hawking, or coughing. Therefore, they may present with issues associated with posterior leakage or premature bolus spillage, pharyngeal pooling, predeglutitive penetration or aspiration (including silent aspiration), oral residues and delayed oral transit time.
3. Pharyngeal phase of swallowing	Swallowing disturbances and symptoms include disturbed swallow triggering, reduced velopharyngeal closure, diminished backward movement of the tongue, and decreased elevation of the velum, hyoid bone, and larynx. Other issues involve reduced contraction of pharyngeal structures, disturbed pharyngeal bolus transport, increased hypopharyngeal intrabolus pressure,

	decreased pharyngeal and laryngeal sensitivity, disturbed coordination of breathing and swallowing, and insufficient laryngeal vestibule closure with dysfunction of the epiglottis and incomplete closure of arytenoids, false cords and true vocal cords. Symptoms may manifest as liquid dribbling out of the nose, pharyngeal residues, pharyngeal or cricopharyngeal pooling, choking, hawking, coughing and delayed pharyngeal transit time. Therefore, they may present with issues associated with nasal penetration, delayed pharyngeal swallow and pooling, reduced rate of spontaneous swallows and saliva pooling, extended pharyngeal transit time, somatosensory deficits, reduced airway protection, postdeglutitive penetration or aspiration, silent aspiration and decreased pharyngeal clearance.
Swallow-related symptoms and additional limitations They involve various disturbances and pathomechanisms, including reduced swallow frequency, levodopa-induced xerostomia, disturbed expiratory muscles, reduced force of glottal or supraglottal explosion, dopamine-induced swallow difficulties, disadvantageous head and body postures, disturbed hand-mouth coordination, motor disabilities (such as freezing phenomenon, tremor or rigor, akinesia, hyperkinesia, restless legs or restlessness) and psychomental stresses (e.g., limited perception and attention, anxiety, depression, dementia, fatigue, exhaustion, insomnia, and medically induced psychosis). These disturbances manifest in a variety of dysphagia symptoms across all phases of swallowing, with additional symptoms like pseudohypersalivation and hyposalivation. Main findings associated with these disturbances include drooling, difficulty swallowing or disturbed swallow triggering, difficulty swallowing specific consistencies, mixed consistencies or pills or tablets, reduced laryngeal and pharyngeal clearance, on/off medication fluctuations and secondary enhanced swallow problems and health threats.	
Other clinical complications and coexisting conditions that might affect swallowing ability and nutritional well-being These may include health problems such as physical weakness or frailty, weight loss, malnutrition, sarcopenia, dehydration, and lung infections or pneumonia.	

Nonmotor problems, such as hypokinetic-rigid dysarthrophonia, can also contribute to swallowing difficulties. Additionally, other gastrointestinal dysfunctions, like obstipation, diarrhea, and gastroparesis, may further impact a patient's ability to swallow and maintain proper nutritional status. It is essential to consider these factors when evaluating and managing swallowing issues in individuals with PD.
According to (Alfonsi, Versino, Merlo, Pacchetti, et al., 2007; Ali et al., 1996; Bird et al., 1994; Castell et al., 2001; Chou, Evatt, Hinson, & Kompoliti, 2007; Davydov & Botts, 2000; Ebihara et al., 2003; Edwards, Quigley, Hofman, & Pfeiffer, 1993; Edwards, Quigley, & Pfeiffer, 1992; Johnston, Li, Castell, & Castell, 1995; Kalf, Bloem, & Munneke, 2012; Leopold & Kagel, 1997; Leow, Beckert, Anderson, & Huckabee, 2012; Leslie, Drinnan, Ford, & Wilson, 2005; Logemann, 1998; Mari et al., 1997; Marks, Turner, O'Sullivan, Deighton, & Lees, 2001; Moreau, Ozsancak, Blatt, et al., 2007; Nobrega et al., 2008; Pehlivan et al., 1996; Pfeiffer, 2003; Pinnington, Muhiddin, Ellis, & Playford, 2000; Proulx, de Courval, Wiseman, & Panisset, 2005; Rodrigues, Nobrega, Sampaio, Argolo, & Melo, 2011; Su, Gandhy, Barlow, & Triadafilopoulos, 2017; Troche, Huebner, Rosenbek, et al., 2011; Tumilasci et al., 2006; Umemoto, Tsuboi, Kitashima, et al., 2011).

Table 1. Swallowing pathomechanisms and relating PD symptom characteristics in different swallowing phases.

3.3 Pathophysiology of dysphagia

The symptoms of PD-related neurogenic dysphagia are well documented, yet its intricate neural pathophysiology is still not fully understood and warrants further exploration (Suttrup et al., 2016). Swallowing is governed by a complex, semi-automatic, and repetitive motor program coordinated by the medulla influenced by bolus volume and consistency, as well as peripheral and central feedback from afferent involvement (Suttrup et al., 2016).

Impairments in brainstem regions involved in the swallowing central pattern generator, together with degeneration of the substantia nigra, are believed to play a key role in the underlying pathology of PD (Suntrup et al., 2013). Disturbances in dopaminergic mechanisms and non-dopaminergic neural networks, such as serotonergic and cholinergic systems, may be major contributing factors to swallowing dysfunction (Suntrup et al., 2013; Chaudhuri et al., 2006).

In addition to the dopaminergic basal ganglia system—primarily implicated in the supramedullary control of swallowing (Leopold & Daniels, 2010)—Lewy body pathology in PD also affects non-dopaminergic brainstem and cortical regions involved in swallowing regulation, as described in Braak's staging model (Braak et al., 2003). According to this model, the progression of Lewy body deposition extends across multiple cortical and subcortical structures critical for the coordination of swallowing. Notably, the accumulation of Lewy bodies in medullary areas directly responsible for swallowing control has been linked to severe dysphagia in individuals with PD (Braak et al., 2003). Early stages of the pathological process (Stages I–II) are marked by Lewy body involvement in the dorsal motor nuclei of cranial nerves IX and X, as well as the locus coeruleus—regions largely associated with non-motor symptoms. As the disease advances to Stages III–IV, pathology extends to the substantia nigra, mesocortex, and neocortex, which coincides with the emergence of motor manifestations (Braak et al., 2003).

Given the ascending pattern of Lewy body pathology, the early involvement of brainstem regions responsible for swallowing would suggest the presence of related symptoms in the initial stages of PD (Polychronis et al., 2019). However, severe dysphagia is more commonly observed in individuals with advanced PD (Polychronis et al., 2019). This apparent discrepancy may be explained by the recruitment of compensatory mechanisms in cortical regions during the early phases of the disease, which may temporarily mitigate the clinical manifestation of swallowing difficulties (Polychronis et al., 2019).

Moreover, recent research has hypothesised that the disease may originate in the gut and progress in a rostral direction to medulla regions, with gastrointestinal manifestations occurring as the disease advances (Mu et al., 2013). This theory is supported by findings of alpha-synuclein deposition in peripheral sensory and motor nerves innervating the pharyngeal muscles, with more pronounced pathology observed in dysphagic PD patients compared to those without dysphagia (Mu et al., 2013).

Cholinergic dysfunction, specifically in the parasympathetic nervous system, may also be linked to dysphagia in early PD (Lee et al., 2015). Abnormal short-latency afferent inhibition values could be indicative of dysphagia risk, serving as a useful biomarker (Lee et al., 2015). This highlights the potential role of cholinergic pathways in the pathophysiology of dysphagia in PD.

Another pathological contributor to dysphagia in PD is the reduced concentration of substance P in the sputum of affected individuals (Troche et al., 2014; Ebihara et al., 2003). Substance P is a neuropeptide implicated in nociception and the modulation of several physiological functions, including those related to airway protection (Troche et al., 2014; Ebihara et al., 2003). In PD patients, decreased levels of substance P may impair critical protective reflexes -such as swallowing, coughing, and throat clearing- thereby increasing the risk of aspiration, including silent aspiration (Troche et al., 2014; Ebihara et al., 2003).

3.4 Imaging assessment: presynaptic dopaminergic function

The supramedullary network governing swallowing relies on the functional integrity of dopaminergic neurons within the basal ganglia (Leopold et al., 2010). In neurologically healthy individuals, swallowing is associated with bilateral activation of basal ganglia structures, including the putamen and globus pallidus (Suzuki et al., 2003). Based on this evidence, it is anticipated that individuals with PD -characterised by dopaminergic depletion- would demonstrate impaired functioning of the supramedullary swallowing control system (Suzuki et al., 2003).

Moreover, whole-head magnetoencephalography studies have demonstrated that PD patients without dysphagia exhibit distinct alterations in cortical activity, particularly in the lateral regions of the premotor, motor, and inferolateral parietal cortices, alongside reduced activation in the supplementary motor area (Polychronis et al., 2019). Notably, these changes are absent in PD patients with dysphagia, suggesting the presence of adaptive neuroplastic responses involving parallel motor networks that may serve to preserve swallowing function. However, when neurodegeneration exceeds a critical

threshold, these compensatory mechanisms may become insufficient, leading to the clinical emergence of dysphagia (Braak et al., 2003; Polychronis et al., 2019).

Polychronis et al. (2019) demonstrated a significant association between dysphagia and reduced striatal dopaminergic function in patients with early, drug-naïve PD. Specifically, patients presenting with dysphagia exhibited significantly lower striatal [^{123}I]FP-CIT uptake, with the most pronounced reductions observed in the caudate nucleus, compared to their non-dysphagic counterparts. Furthermore, the degree of decline in presynaptic dopaminergic function was correlated with the severity of dysphagia. While dopaminergic terminal loss in the caudate nucleus is generally considered a marker of overall PD severity, these findings suggest it may also play a role in the underlying pathophysiology of dysphagia in early-stage PD, potentially reflecting both peripheral and central nervous system involvement (Polychronis et al., 2019).

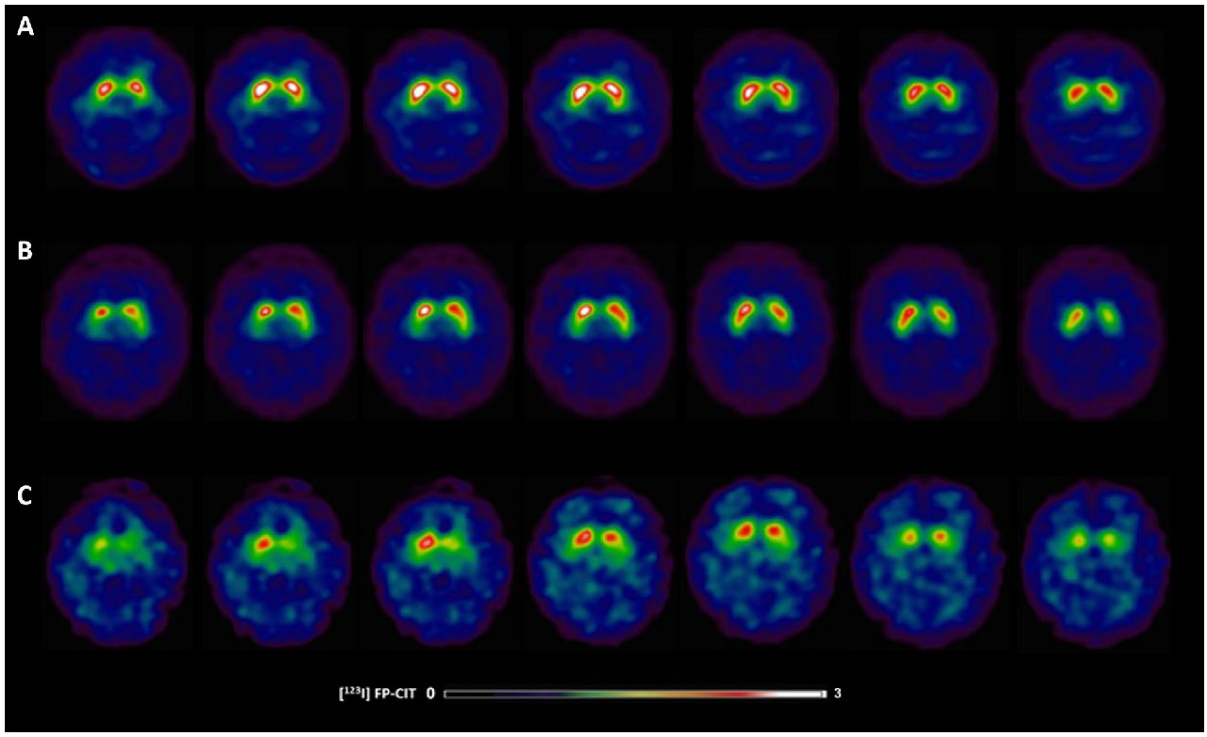


Figure 2. [^{123}I]FP-CIT SPECT images in Parkinson's disease patients with and without dysphagia adapted from 'Polychronis, S., Dervenoulas, G., Yousaf, T., Niccolini, F., Pagano, G., & Politis, M. (2019). Dysphagia is associated with presynaptic dopaminergic dysfunction and greater non-motor symptom burden in early drug-naïve Parkinson's patients. *PloS one*, *14*(7), e0214352.'

(A) 63-year-old healthy control exhibiting typical [^{123}I]FP-CIT specific binding ratios in the caudate and putamen.

(B) 63-year-old male without swallowing issues showing mild dopaminergic deficits, as indicated by [^{123}I]FP-CIT specific binding ratios in the caudate and putamen.

(C) 63-year-old female with swallowing problems displaying more pronounced striatal dopaminergic deficits, as evidenced by [^{123}I]FP-CIT specific binding ratios in the caudate and putamen.

Chapter 4: Overview of Drooling in Parkinson's Disease

4.1 Introduction

Drooling frequently presents in individuals with PD due to excessive saliva production, salivary incontinence, or dysphagia (Alhajj, M., & Babos, M., 2021). The condition may result from excessive saliva production in the oral cavity or altered salivary clearance resulting from impaired swallowing or reduced ability to retain saliva in the mouth (Alhajj, M., & Babos, M., 2021). Numerous studies have investigated the mechanism of drooling in PD (Ali, G. N. et al. (1996); Bagheri, H. et al. (1999); Baijens, L. W. J. et al. (2011); Barbe, A. G. et al. (2017); Bateson, M. et al. (1973); Benamer, H. T. et al. (2000); Braak, H. et al. (2003); Bushmann, M. et al. (1989); Calabresi, P. et al. (2010); Cantuti-Castelvetri, I. et al. (2007); Ciucci, M. R. et al. (2011); Conforti, R. et al. (2013); Cotzias, G. C. et al. (1967); David, N. (2021); Del Tredici, K. et al. (2010)).

Drooling prevalence throughout the course of PD varies widely, ranging from 9.26% to 70% (Ding, C. et al., 2017; Durcan, R. et al., 2019; Fasano, A. et al., 2015; Fereshtehnejad, S. M. et al., 2017; Haaxma, C. A. et al., 2007). It is more pronounced in males (Fasano, A. et al., 2015; Hou, Y. et al., 2016; Hyson, H. C. et al., 2002; Kalf, J. G. et al., 2011) than in females, and the risk of drooling increases with longer disease duration (Ding, C. et al., 2017; Durcan, R. et al., 2019; Kalf, J. G. et al., 2011; Karakoc, M. et al., 2016) and progression (Cotzias, G. C. et al., 1967; Ding, C. et al., 2017; Durcan, R. et al., 2019; Hou, Y. et al., 2016; Kalf, J. G. et al., 2011; Karakoc, M. et al., 2016; Koga, T. et al., 2003). Furthermore, higher drooling prevalence has been linked to both increased age and more pronounced Levodopa-induced dyskinesia. A singular study indicated that drooling may, in certain instances, serve as a prodromal symptom of PD (Fereshtehnejad, S. M. et al., 2017). Despite the contradictory data regarding the correlation between cognitive performance and drooling (Ding, C. et al., 2017; Hou, Y. et al., 2016; Hyson, H. C. et al., 2002; Karakoc, M. et al., 2016; Leclair-Visonneau, L. et al., 2018; Leopold, N. A. & Kagel, M. C., 1996; Luchesi, K. F. et al., 2015; Malek, N. et al., 2017), evidence suggests a link between drooling and the presence of sleep disorders (Hou, Y. et al., 2016; Hyson, H. C. et al., 2002), dysautonomic symptoms (Hou, Y. et al., 2016; Hyson, H. C. et al., 2002; Mao, C. J. et al., 2018), speech difficulties (Hyson, H. C. et al., 2002), dysphagia (Ding, C. et al., 2017; Hyson, H. C. et al., 2002; Karakoc, M. et al., 2016; Marg, S. et al., 2004; Marinus, J. & van Hilten, J. J., 2015; Meningaud, J. P. et al., 2006; Merello, A. et al., 1997), hypomimia (Kalf, J. G. et al., 2011; Koga, T. et al., 2003; Miller, N. et al., 2019), bradykinesia (Koga, T. et al., 2003), and a more symmetric pattern of PD presentation (Kalf, J. G. et al., 2011; Mito, Y. et al., 2020). Neuroimaging studies indicate that *de novo* PD patients have shown reduced functional connectivity in the putamen, indicating that drooling may reflect a broader underlying neuropathology (Morgan, J. & Sethi, K. D., 2005), which poses treatment challenges (Ali, G. N. et al., 1996). Subsequent research ought to investigate the correlation between drooling and additional facets of PD symptomatology (Nascimento, D. et al., 2021; Nicaretta, D. H. et al., 2008), along with the impact of other prevalent treatments for PD and their effects on drooling (Nienstedt, J. C. et al., 2018).

4.2 Pathophysiology of Drooling

Drooling is controlled by the sympathetic and parasympathetic nerve systems (Nóbrega, A. C. et al., 2008). The secretion process of salivary glands predominantly entails cholinergic transmission via parasympathetic neurones and neuropeptide signalling, such as substance P and adrenergic pathways mediated by sympathetic innervation. Stimulation of the parasympathetic nervous system leads to the activation of acetylcholine receptors, while sympathetic stimulation enhances alpha-receptor activation, resulting in smooth muscle contraction and increased volumetric flow (Nóbrega, A. C. et al., 2008). Drooling tends to be more pronounced during off-medication periods in PD patients (Ali et al., 1996). The pathophysiology of drooling is primarily attributed to two key factors: abnormalities in salivary production and retention within the oral cavity, and impaired salivary clearance (Ali, G. N. et al., 1996). The excessive production of saliva might lead to drooling. Research indicates that PD patients exhibit reduced saliva production relative to healthy controls (Bagheri, H. et al., 1999; Baijens, L. W. J. et al., 2011; Barbe, A. G. et al., 2017), potentially attributable to dopamine insufficiency. The precise process underlying diminished salivary production is inadequately clarified (Baijens, L. W. J. et al., 2011).

Research utilising animal models has demonstrated that saliva secretion is regulated by dopamine (Bateson, M. et al., 1973; Benamer, H. T. et al., 2000). Animal studies have shown that salivary secretion is mediated by both central and peripheral dopamine receptor activation (Benamer et al., 2000). This finding is supported by lesion studies, which demonstrate a significant decrease in salivary output following damage to the globus pallidus, its efferent projections -particularly the lateral mesencephalic reticular formation- and the striatum (Braak et al., 2003). Furthermore, pathological examinations have identified the presence of Lewy bodies in structures involved in autonomic regulation of salivation, including the superior cervical ganglion, cervical sympathetic trunk, peripheral vagus nerve, and submandibular glands (Bushmann et al., 1989).

A follow-up study by Costa et al. (2008) evaluated and compared salivary output and excretion velocity of the parotid gland in individuals with PD and healthy controls. The results revealed no significant differences in overall saliva production between the two groups. However, the rate of parotid salivary excretion in response to a specific stimulus was significantly higher in the PD group (Ou et al., 2015). These findings suggest that increased salivary secretion is unlikely to be the primary cause of drooling in PD, although it may contribute to its pathophysiology.

Dysphagia during the oral and/or pharyngeal phases of swallowing represents another key contributor to drooling in PD. In this population, bradykinesia can result in oropharyngeal dysphagia. Animal studies have provided supporting evidence: rats administered 6-hydroxydopamine (6-OHDA) demonstrated significantly reduced tongue protrusion compared to healthy controls (Calabresi et al., 2010). Similarly, in a videofluorographic analysis, parkinsonian rats treated with 6-OHDA exhibited a higher frequency of abnormal food bolus movements relative to controls (Cantuti-Castelvetri et al., 2007). In humans, a videofluoroscopic swallowing study (VFSS) by Ciucci et al. (2011) revealed a direct association between the severity of dysphagia and the presence of drooling in PD patients. These findings suggest that dysfunction in the

oropharyngeal phase of swallowing may be a principal factor underlying the pathophysiology of drooling in PD.

Moreover, Kikuta T. Et al. (2011) posited that advanced PD patients exhibit diminished maximal tongue pressure relative to those in early or moderate stages of the condition, and that there exists a negative association between oropharyngeal transit time and tongue movement (Conforti, R. et al., 2013). Consequently, inadequate tongue muscle control and bradykinesia may influence the aetiology of dysphagia and perhaps contribute to drooling.

Hypomimia, involuntary mouth opening, bent upper body posture, and a dropped head can impair patients' ability to retain saliva in the oral cavity, thus leading to drooling in PD (Cotzias, G. C. et al., 1967). Ultimately, research utilising manometry shown that compromised mobility of the upper oesophageal sphincter (UES) may influence dysphagia and drooling in patients with PD. This cannot be the exclusive cause of dysphagia in individuals with sufficient clearance mechanisms and pharyngeal propulsion forces (David, N., 2021; Del Tredici, K. et al., 2010).

4.3 Symptomatology associated with Parkinson's Disease and Drooling

Drooling in individuals with PD has been associated with various clinical characteristics, encompassing both motor and non-motor symptoms.

4.3.1. Common Clinical Characteristics

The reported incidence of drooling in PD ranges from 9.26% to 70%, reflecting both the heterogeneity of the disease and the variability in assessment tools used across studies (Ding, C. et al., 2017; Durcan, R. et al., 2019; Fasano, A. et al., 2015; Fereshtehnejad, S. M. et al., 2017; Haaxma, C. A. et al., 2007; Hou, Y. et al., 2016; Hyson, H. C. et al., 2002; Kalf, J. G. et al., 2011; Karakoc, M. et al., 2016; Pazo, J. H. & Belforte, J. E., 2002; Pirker, W., 2003; Proserpio, C. et al., 2017). It may present early in the disease (Fereshtehnejad, S. M. et al., 2017), although it is not categorised as a prodromal symptom in PD according to the current MDS research criteria. According to Braak’s staging of PD pathology and the proposed model of alpha-synuclein (aSyn) propagation, aSyn accumulation is thought to originate in the gastrointestinal tract and subsequently ascend to the brain via the vagus nerve (Proulx, M. et al., 2005). Consequently, it may be proposed that gastrointestinal tract characteristics need to be a significant early indication of PD. Nonetheless, further scientific investigation is required to explore the potential significance of drooling in the diagnosis of PD.

The incidence of drooling is greater in males (Fasano, A. et al., 2015; Hou, Y. et al., 2016; Hyson, H. C. et al., 2002; Kalf, J. G. et al., 2011) compared to females, as women with PD exhibit a less severe phenotype (Qin, X. et al., 2019), likely due to oestrogen activity in females which may postpone the onset of PD symptoms (Rana, A. Q. et al., 2012).

Furthermore, an extended duration and progression of the disease correlate with an elevated risk of drooling. Drooling primarily results from a reduced frequency of saliva clearance in the oral cavity, along with posture-related difficulties, oral motor dysfunction, and face impairments such as bradykinesia, stiffness, and hypomimia.

These deficits are believed to become more prevalent and severe as the disease advances.

Age is an essential factor in determining predominance. Drooling increases in frequency with advancing age (Ding, C. et al., 2017; Hou, Y. et al., 2016; Kalf, J. G. et al., 2011; Karakoc, M. et al., 2016). Age-related alterations can affect saliva regulation as we advance in years. As individuals age, there is a natural, ongoing loss of brain tissue associated with a decline in neurological abilities and a drop in muscular mass (Reynolds, H. et al., 2018). Reduced strength in orofacial muscles -such as the tongue, orbicularis oris, and buccinator- may contribute to the accumulation of saliva in the oral cavity and increase the risk of both anterior and posterior drooling (Reynolds et al., 2018). However, the lack of a control group in these studies limits the generalisability of the findings, highlighting the need for further research with more rigorous methodological designs.

The prevalence of drooling is higher among PD patients with more severe Levodopa-induced dyskinesia (LID) (Hou, Y. et al., 2016; Hyson, H. C. et al., 2002). This phenomenon is observed in more advanced patients, who typically receive higher doses of levodopa (Cotzias, G. C. et al., 1967; Ding, C. et al., 2017; Durcan, R. et al., 2019; Hou, Y. et al., 2016; Kalf, J. G. et al., 2011; Karakoc, M. et al., 2016; Koga, T. et al., 2003; Leclair-Visonneau, L. et al., 2018; Rosenberg-Katz, K. et al., 2013; Russell, J. A. et al., 2013).

4.3.2 Non-Motor Symptoms, Motor Symptoms, and Drooling

A range of non-motor and motor symptoms may manifest throughout the progression of PD (Sánchez-Martínez, C. M. et al., 2019). Concerning cognitive function, research has yielded inconsistent results regarding the relationship between cognitive performance and drooling (Ding, C. et al., 2017; Hou, Y. et al., 2016; Hyson, H. C. et al., 2002; Karakoc, M. et al., 2016; Leopold, N. A. & Kagel, M. C., 1996; Luchesi, K. F. et al., 2015); nonetheless, certain studies indicate a correlation between drooling and cognitive decline (Leclair-Visonneau, L. et al., 2018; Malek, N. et al., 2017). According to Reynolds et al. (2018), cognition contributes to the regulation of drooling and saliva in ways that surpass autonomic or reflexive mechanisms (Leopold, N. A. & Kagel, M. C., 1996). The research indicated that impaired divided attention worsens drooling in individuals with PD, using a paradigm in which attention to saliva control and the frequency of swallowing declined during engagement in a cognitively demanding task (Leopold, N. A. & Kagel, M. C., 1996). Disturbances in sleep are linked to the occurrence of drooling (Hou, Y. et al., 2016; Hyson, H. C. et al., 2002). In patients with PD, superior sleep quality was associated with reduced motor symptoms in the morning (Schiffman, S. S. & Miletic, I. D., 1996). As a result, poor sleep quality may exacerbate motor symptoms and contribute to increased drooling (Hou, Y. et al., 2016). Dysautonomias, encompassing urine dysfunction, sexual impairment (Hyson, H. C. et al., 2002), obstipation (Hou, Y. et al., 2016), varied gastrointestinal disturbances alongside orthostatic hypotension, were recognised as correlated with drooling. The autonomic system is affected by alterations in the vagus nerve (Mao, C. J. et al., 2018), which may result in various dysfunctions, such as drooling, gastrointestinal problems, and constipation. Impairment in speech (Hyson, H. C. et al., 2002) and dysphagia (Ding, C. et al., 2017; Hyson, H. C. et al., 2002; Karakoc, M. et al., 2016) are correlated with

drooling. Speech, swallowing, and salivary control rely on overlapping anatomical structures; thus, dysfunction in one domain often leads to impairments in the others. The oral musculature -including the jaw, lips, tongue, cheeks, pharynx and larynx- is particularly susceptible to the effects of rigidity, bradykinesia, and hypokinesia, which are hallmark motor features commonly observed in PD (Marg, S. et al., 2004; Marinus, J. & van Hilten, J. J., 2015). Individuals with PD often exhibit several oromotor abnormalities -such as an altered swallowing reflex (Meningaud et al., 2006), lingual tremor, lingual pumping, prolonged tongue elevation, and abnormal mandibular excursion- which may contribute to impaired salivary control (Merello et al., 1997). Hypomimia was correlated with drooling (Kalf, J. G. et al., 2011; Koga, T. et al., 2003), resulting in diminished lip closure in certain PD patients, which impacts saliva management (Miller, N. et al., 2019). Bradykinesia has been associated with drooling (Koga, T. et al., 2003), since it can affect the orofacial musculature (Marinus, J. & van Hilten, J. J., 2015). Reduced movement speed of the lips, tongue, jaw, and cheeks can compromise the ability to manage saliva within the oral cavity and facilitate its transit to the oropharynx.

Patients displaying a prominent tremor associated with PD did not demonstrate an increased incidence of drooling (Hou, Y. et al., 2016). However, one study reported that PD patients presenting with non-dominant hand tremor had a higher incidence of drooling (Hou et al., 2016). This finding may be explained by evidence showing that individuals with non-dominant tremor exhibit more pronounced reductions in grey matter volume and functional connectivity within motor-related brain regions (Seibyl et al., 1995), in addition to a greater burden of Lewy body pathology in cortical areas (Selikhova, M. et al., 2009). These patients also display more pronounced lingual motor dysfunction and increased rigidity in the oropharyngeal region (Conforti et al., 2013). Moreover, drooling has been linked to a more symmetrical presentation of PD symptoms (Kalf et al., 2011). Individuals with a higher overall burden of motor symptoms are more likely to exhibit a symmetric motor pattern, which may further contribute to impaired salivary control (Mito, Y. et al., 2020). Hence, it can be anticipated that drooling is more prevalent in individuals with a symmetric motor presentation. However, *de novo* PD patients with drooling have not been extensively studied, and existing findings may be influenced by the effects of pharmacological treatments, such as Levodopa. Levodopa is the principal pharmacological treatment employed in the management of PD; yet, prolonged administration may result in dyskinesia and motor fluctuations (Srivanitchapoom, P. et al., 2014). Dyskinesia is typically a progressive motor complication that can involve multiple body regions, including the orofacial muscles, neck, tongue, and jaw (Stanković et al., 2019). When present in these areas, dyskinesia-related motor impairments may further exacerbate drooling. While the relationship between dopamine transporter (DAT) binding in the striatum and drooling has not been thoroughly investigated, Tajima et al. (2020) proposed that the severity of motor symptoms -particularly axial features associated with the akinetic-rigid subtype and bradykinesia- may be linked to drooling in *de novo* PD patients. Notably, this association was not observed with tremor or the Specific Binding Ratio (SBR) (Mito, Y. et al., 2020). Consequently, it can be posited that the mechanism underlying the exacerbation of drooling resembles that of bradykinesia and axial symptoms, as prior

research indicates a correlation between DAT binding and both bradykinesia and axial symptoms, rather than parkinsonian tremor (Morgan, J. & Sethi, K. D., 2005; Nascimento, D. et al., 2021; Nicaretta, D. H. et al., 2008). Nonetheless, the effects of Levodopa are ambiguous (Ali, G. N. et al., 1996; Nascimento, D. et al., 2021), suggesting that processes beyond the nigrostriatal dopamine pathway contribute to drooling.

A functional MRI study by Hou et al. (2016) investigated functional connectivity within the basal ganglia in *de novo* PD patients, comparing those with and without drooling. The results revealed that patients with drooling exhibited significantly reduced functional connectivity between the putamen and several cortical regions, including bilateral sensory cortices, the inferior and superior parietal lobules, as well as areas in the right occipital and right temporal lobes (Nicaretta, D. H. et al., 2008). Consequently, it may be deduced that drooling is a manifestation of a prevalent condition and cannot be ascribed to a singular causative element.

Managing drooling is complex, as identifying treatment options for this widespread problem can be challenging. Pharmacological and non-pharmacological interventions have been proposed to address drooling in PD (Ali, G. N. et al., 1996). In the initial management of drooling in PD, patients should discontinue medications known to exacerbate salivation, particularly cholinesterase inhibitors, as well as antipsychotics such as quetiapine and clozapine (Ali et al., 1996). Following this, efforts should be directed toward optimising motor symptom control either through dopaminergic therapy or interventions such as DBS (Ali et al., 1996).

Finally, it is important to highlight that no study to date has specifically investigated the effects of DBS on drooling in PD patients. Behavioural interventions and radiotherapeutic approaches have been proposed as adjunctive treatments (Ali et al., 1996). However, these strategies offer only partial relief, underscoring the need for the development of more targeted and effective therapeutic interventions for the management of drooling in PD.

4.4 Limitations and Future Directions

Future research should prioritise the use of drooling-specific rating instruments -such as the Drooling Severity and Frequency Scale (DSFS), the Sialorrhea Clinical Scale for Parkinson's Disease (SCS-PD), and the Drooling Rating Scale (DRS)- rather than relying solely on subjective reports or patient complaints for the assessment of drooling in PD (Ali et al., 1996). In addition, the evaluation of salivary biochemical characteristics—including appearance, viscosity, flow rate, and volume—should be integrated into study protocols. These measures should be analysed in relation to clinical features and drooling severity. Notably, the Radboud Oral Motor Inventory for PD—Saliva subscale (ROMP-saliva) has been identified as the only tool with sufficient clinimetric validation in PD populations (Van Wamelen et al., 2020). Furthermore, several underexplored areas warrant further investigation. Of particular interest is the potential relationship between saliva production and olfactory function. Salivary secretion can be modulated by olfactory stimuli (Nienstedt et al., 2018), as exposure to food-related scents has been shown to increase salivation (Zhang et al., 2016), and hyposmia is a common non-motor symptom in PD. Investigating this link may offer novel insights into the mechanisms underlying salivary control impairments in PD. Furthermore, given that drooling is linked to fatigue and sensory impairments,

including visual anomalies, frequently observed in people with PD as their condition advances (Sánchez-Martínez, C. M. et al., 2019), it is essential to determine whether drooling affects early PD patients to assess any correlation with a more severe phenotype in latter stages of the disease.

Finally, comprehensive guidance is essential for the pharmaceutical management of drooling, especially given that botulinum toxin injection is currently considered the standard of care, and its possible beneficial or adverse consequences on other clinical symptoms. At present, it is recognised that anticholinergic medications used to diminish drooling may induce side effects, including hallucinations or delirium (Zlotnik, Y. et al., 2015). Ultimately, the inclusion of a control group would facilitate more dependable data and more secure conclusions.

4.5 Conclusions

The precise mechanism of drooling in patients with PD remains inadequately described. A deeper comprehension of the correlation between drooling and clinical characteristics will elucidate whether these factors aggravate drooling or just coexist.

Excessive drooling in PD has been associated with a greater burden of non-motor symptoms, as well as increased severity of motor fluctuations and bradykinesia. Additionally, DaTSCAN imaging has revealed reduced dopamine transporter (DAT) binding in the striatum, further supporting the link between drooling and underlying dopaminergic dysfunction.

All in all, excessive drooling in PD cannot be ascribed to a singular cause, but rather to a confluence of circumstances, as part of a multifaceted illness that is challenging to manage.

Chapter 5: Overview of Cerebrospinal Fluid (CSF) Biomarkers in Parkinson's Disease

Due to the complex pathophysiology of PD, the exploration for reliable biomarkers has emerged as a crucial area of research, given that early detection and monitoring of the disease could significantly improve clinical management and therapeutic interventions (Cova & Priori, 2018).

One promising avenue for biomarker development is the analysis of CSF, which provides a direct window into the biochemical changes occurring in the central nervous system (Magdalinou et al., 2014). Several key CSF biomarkers have been investigated in the context of PD, including amyloid-beta, tau, phosphorylated tau, and alpha-synuclein (Constantinescu & Mondello, 2013).

Amyloid-beta

Amyloid-beta, a peptide that is associated with the pathology of Alzheimer's disease, has also been studied in PD (Constantinescu & Mondello, 2013). Patients with PD and concurrent cognitive impairment have been shown to exhibit a faster decline in CSF amyloid-beta levels compared to those without cognitive impairment (Baek et al., 2021). These findings suggest a potential association between amyloid-beta pathology and the onset of dementia in individuals with PD (Baek et al., 2021).

Tau and phosphorylated tau

Tau and phosphorylated tau, two proteins involved in the formation of neurofibrillary tangles, have also been investigated as potential biomarkers in PD (Baek et al., 2021). CSF levels of tau and phosphorylated tau have been found to be elevated in PD patients, particularly those with cognitive impairment (Kang et al., 2016). This indicates that the accumulation of tau proteins may contribute to the cognitive deficits observed in a subset of PD patients (Baek et al., 2021).

Alpha-synuclein

Alpha-synuclein, the principal constituent of Lewy bodies, plays a central role in the pathogenesis of PD (Kim, 2013). Studies have demonstrated that CSF levels of alpha-synuclein are significantly reduced in PD patients compared to healthy controls, suggesting its potential utility as a biomarker for disease diagnosis and progression (Grassi et al., 2018). Moreover, patients with PD and concurrent cognitive impairment have been found to exhibit a faster decline in alpha-synuclein levels over time, suggesting that the progression of alpha-synuclein pathology may be associated with the development of cognitive deficits (Baek et al., 2021).

In conclusion, the analysis of CSF biomarkers, including amyloid-beta, tau, phosphorylated tau, and alpha-synuclein, has provided valuable insights into the underlying pathological processes in PD. These biomarkers may not only facilitate the early detection of PD but also enhance our understanding of its heterogeneous nature, particularly in relation to the association between cognitive impairment and underlying neuropathological alterations.

Chapter 6: Aims and Hypotheses

The aims of this research are:

- Aim 1: To describe and compare the demographic characteristics, clinical characteristics, CSF pathology levels and presynaptic dopaminergic levels of PD patients with and without speech difficulties in the early treatment-naïve stage and the early levodopa-treated stage.
- Aim 2: To describe and compare the demographic characteristics, clinical characteristics, CSF pathology levels and presynaptic dopaminergic levels of PD patients with and without dysphagia in the early treatment-naïve stage and the early levodopa-treated stage.

The hypotheses of this study are:

- Hypothesis 1: Early PD treatment-naïve patients with speech difficulties have greater disease severity, CSF pathology and presynaptic dopaminergic deficits than early PD treatment-naïve patients without speech difficulties.
- Hypothesis 2: Early PD levodopa-treated patients with speech difficulties have greater disease severity, CSF pathology and presynaptic dopaminergic deficits than early PD levodopa-treated patients without speech difficulties.
- Hypothesis 3: Early PD treatment-naïve patients with dysphagia have greater disease severity, CSF pathology and presynaptic dopaminergic deficits than early PD treatment-naïve patients without dysphagia.
- Hypothesis 4: Early PD treatment-naïve patients with dysphagia have greater disease severity, CSF pathology and presynaptic dopaminergic deficits than early PD treatment-naïve patients without dysphagia.

Section II – Empirical Research

Chapter 7: Methodology

7.1 Data source

This study extensively utilizes clinical data, evaluations, participant demographics, and biological specimens from the Parkinson's Progression Markers Initiative (PPMI) dataset. Access to this information is granted upon request and is subject to approval by the PPMI Data Access Committee. The PPMI study enforces standardized protocols and stringent quality controls in all aspects of data collection, transmission, and analysis, as well as in the handling of biospecimens. These protocols are designed to promote uniformity and reduce variability across the dataset. Comprehensive details on the research methodologies and study structure can be found at www.ppmi-info.org/study-design.

7.2 Participants

This study utilised data from the Parkinson's Progression Markers Initiative (PPMI) database (www.ppmi-info.org/data), using the curated data cut dated 29 January 2024 (v.2024-01-29). Only participants with a diagnosis of sporadic PD were included in the analyses.

Inclusion criteria:

- Diagnosis of PD for two years or less
- Age 30 years or older at the time of PD diagnosis
- Presence of at least two of the following motor symptoms: resting tremor, bradykinesia, or rigidity (with a mandatory presence of either tremor or bradykinesia)
- Hoehn and Yahr stage I or II at baseline
- Dopamine transporter deficit confirmed through imaging

Exclusion criteria:

- Current use of PD medications (e.g., levodopa, dopamine agonists)
- Use of medications known to affect dopamine transporter imaging within six months prior to screening
- Medical conditions rendering lumbar puncture hazardous (e.g., spinal pathology, coagulopathy)

All participants included in this analysis were enrolled in the PPMI study as sporadic PD cases who met the above criteria. Two independent groups were defined for the purposes of this study:

- **Early PD treatment-naive**: participants assessed at baseline (Year 0) who had not yet initiated any PD-specific pharmacological treatment.
- **Early PD levodopa-treated**: a separate group of participants assessed at Visit 6 (Year 2), who had initiated levodopa treatment by that time.

These two groups consisted of different individuals (with distinct participant codes in the PPMI dataset) and were analysed as separate cross-sectional samples.

7.3 Clinical evaluation

For the clinical evaluation, the following assessment were performed:

- Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part I
- MDS-UPDRS Part II
- MDS-UPDRS Part III
- MDS-UPDRS Part IV
- Montreal Cognitive Assessment (MoCA)
- Hoehn and Yahr scale

The severity of motor symptoms was evaluated using the MDS-UPDRS-III and classified according to the Hoehn and Yahr (H&Y) scale. The MDS-UPDRS-III score was computed without including Item 3.1 (Speech). The MDS-UPDRS-II score was computed eliminating Item 2.3 (Chewing and Swallowing).

7.4 Dopaminergic image acquisition

SPECT images were obtained 4 hours (targeting ± 30 minutes) after administering an injection of 3–5 mCi (111–185 MBq) of [^{123}I]DaTscan™, or 3.5 hours (targeting ± 30 minutes) after an injection of 25 mCi (925 MBq) of ^{99m}Tc-TRODAT-1. All SPECT scans were acquired and processed following the PPMI SPECT Technical Operations Manual (https://www.ppmi-info.org/study-design/research-documents-and-sops).
Raw SPECT data was acquired into a 128x128 matrix using a step-and-shoot protocol for a total of 120 projections over a 360° rotation. The acquisition used an energy window cantered on 159 keV (±10%) for [^{123}I]DaTscan™ or 140 keV (±10%) for ^{99m}Tc-TRODAT-1. The total scan duration was 60 minutes, with a frame time of 30 seconds per projection with a total of 120 projection. Following acquisition, images were reconstructed by each imaging centre according to their local standard protocol for clinical brain SPECT scans.
For quantification, SPECT image volumes were spatially normalized to an Ioflupane template. The eight axial slices best depicting the striatum were summed, after which a standardized volume of interest (VOI) template was applied. VOI analyses were conducted for the left and right caudate and putamen, using the occipital cortex as the reference region. Specific binding ratios (SBR) were derived by dividing the count density of the caudate or putamen VOIs by that of the occipital cortex and subtracting one. This metric provides an approximation of the binding potential (BPND) when the tracer has reached equilibrium at the target site, as previously described for Ioflupane SPECT.

7.5 CSF collection and analysis

The CSF collection involves lumbar punctures at baseline and follow-up visits. The levels of amyloid-beta, alpha-synuclein, tau and p-tau were analysed for the purpose of this study.

7.6 Statistical analysis

7.7.1 Analysis A

7.7.1.1 Study population and Speech Difficulties classification

Statistical analyses and graph illustrations were performed with SPSS (Version 29). A total of 376 early PD treatment-naïve patients were included in the analysis, with 167 patients presenting with speech difficulties and 209 patients without speech difficulties. A total of 133 early PD levodopa-treated patients were included in the analysis, with

76 presenting with speech difficulties and 57 without speech difficulties. The presence of speech difficulties served as both an inclusion and exclusion criterion for the stratification of these subgroups. Speech difficulties were identified and quantified according to the MDS-UPDRS Part-III, Item 3.1 (Speech). This item is a clinician-administered scale with 5 scores, rated between 0 (normal) to 4 (most severe impairment). Speech difficulties were defined as a score of ≥ 1 on item 3.1.

7.7.1.2 Group comparisons and Independent t-tests

Comparisons among groups were performed independently for early PD treatment-naïve and early PD levodopa-treated patients, comparing those with and without speech difficulties. For all variables, assumptions of variance homogeneity and normality were assessed using Levene's test for equality of variances and descriptive statistics. Levene's test was used to determine whether the assumption of equal variances was met before conducting t-tests, ensuring that appropriate statistical adjustments were applied if variances were unequal. Independent t-tests were performed to determine whether there were significant differences in clinical, demographic, and neuroimaging variables between the two groups. The t-test provided t-values and p-values, which were used to assess statistical significance.

Handling of Missing Data

Missing data were assessed for each variable, and the percentage of missing values per group was documented. If the absence of data surpassed 20% in either group, sensitivity analysis was deemed necessary. If missing data exceeded 20% in either group, sensitivity analyses were considered. Cases with missing data were excluded pairwise to maximize data retention without introducing bias. All statistical comparisons were based on available cases with no missing or out-of-range values.

Correction for Multiple Comparisons

Given the multiple comparisons performed, results were interpreted with caution to account for the risk of Type I error. While no formal correction (e.g., Bonferroni) was applied due to the exploratory nature of the analysis, findings were considered in conjunction with effect sizes and clinical relevance to avoid overinterpretation of statistical significance.

Effect Size Reporting

In addition to p-values, effect sizes (Cohen's d) were calculated to assess the magnitude of group differences where relevant. This allowed for a more meaningful interpretation of statistically significant results, distinguishing clinically relevant effects from trivial differences.

Selection for Multivariate Analysis

Variables that demonstrated significant differences in the independent t-tests ($p < .05$) were considered for inclusion in subsequent multivariate analyses. This step ensured that predictors showing between-group differences were further examined in a controlled statistical model to assess their independent contributions while accounting for potential confounders.

7.7.1.3 Multivariate Binary Logistic Regression

Two multivariate binary logistic regressions were performed to assess the independent contributions of clinical, CSF and neuroimaging variables to the likelihood of speech

difficulties in early PD patients. One model focused on early PD treatment-naïve patients, while the other analyzed early PD patients receiving Levodopa treatment. Predictor variables were initially selected based on their statistical significance in prior independent-samples t-tests, ensuring that only variables showing between-group differences were considered for further modeling. To ensure model accuracy and interpretability, a variable selection process was implemented. First, a correlation matrix was examined to identify multicollinearity ($r > 0.7$) between predictors. Highly correlated variables were removed to avoid redundancy and statistical instability, ensuring that each retained predictor contributed unique variance to the model. Additionally, variables that became non-significant in the multivariate regression ($p > .05$) were considered for removal to refine the model and prevent overfitting. The final models retained only those predictors that demonstrated independent associations with the outcome variable while adjusting for the influence of other factors.
All logistic regression assumptions were tested prior to analysis. Multicollinearity was assessed using Variance Inflation Factor (VIF), ensuring that all retained variables met the acceptable threshold ($VIF < 10$). Model fit was evaluated using the Hosmer-Lemeshow goodness-of-fit test and Nagelkerke's R^2, and significance of individual predictors was determined using Wald's test. The final results are presented as odds ratios (Exp(B)) with 95% confidence intervals.

7.7.2 Analysis B

7.7.2.1 Study population and Dysphagia classification

Statistical analyses and graph illustrations were performed with SPSS (Version 29). A total of 377 early PD treatment-naïve patients were included in the analysis, with 51 patients presenting with dysphagia and 326 patients without dysphagia. A total of 133 early PD levodopa-treated patients were included in the analysis, with 23 presenting with dysphagia and 110 without dysphagia. The presence of dysphagia served as both an inclusion and exclusion criterion for the stratification of these subgroups. Dysphagia was identified and quantified according to the MDS-UPDRS Part-II, Item 2.3 (Chewing and Swallowing). This item is a clinician-administered scale with 5 scores, ranging from 0 (normal) to 4 (most severe impairment). Dysphagia was defined as a score of ≥ 1 on item 2.3.

7.7.2.2 Group comparisons and Independent t-tests

Comparisons between groups were conducted independently for early PD treatment-naïve and early PD levodopa-treated patients, comparing those with and without dysphagia. For all variables, assumptions of variance homogeneity and normality were assessed using Levene's test for equality of variances and descriptive statistics. Levene's test was used to determine whether the assumption of equal variances was met before conducting t-tests, ensuring that appropriate statistical adjustments were applied if variances were unequal. Independent t-tests were performed to determine whether there were significant differences in clinical, demographic, and neuroimaging variables between the two groups. The t-test provided t-values and p-values, which were used to assess statistical significance.

<u>Handling of Missing Data</u>

Missing data were assessed for each variable, and the percentage of missing values per group was documented. If the absence of data surpassed 20% in either group, sensitivity analysis was deemed necessary. Cases with missing data were excluded

pairwise to maximize data retention without introducing bias. All statistical comparisons were based on available cases with no missing or out-of-range values.

Correction for Multiple Comparisons

Given the multiple comparisons performed, results were interpreted with caution to account for the risk of Type I error. While no formal correction (e.g., Bonferroni) was applied due to the exploratory nature of the analysis, findings were considered in conjunction with effect sizes and clinical relevance to avoid overinterpretation of statistical significance.

Effect Size Reporting

In addition to p-values, effect sizes (Cohen's d) were calculated to assess the magnitude of group differences where relevant. This allowed for a more meaningful interpretation of statistically significant results, distinguishing clinically relevant effects from trivial differences.

Selection for Multivariate Analysis

Variables that demonstrated significant differences in the independent t-tests ($p < .05$) were considered for inclusion in subsequent multivariate analyses. This step ensured that predictors showing between-group differences were further examined in a controlled statistical model to assess their independent contributions while accounting for potential confounders.

7.7.2.3 Multivariate Binary Logistic Regression

Two multivariate binary logistic regressions were performed to assess the independent contributions of clinical, CSF, and neuroimaging variables to the likelihood of dysphagia in early PD patients. One model focused on early PD treatment-naïve patients, while the other analyzed early PD patients receiving Levodopa treatment. Predictor variables were initially selected based on their statistical significance in prior independent-samples t-tests, ensuring that only variables showing between-group differences were considered for further modeling. To ensure model accuracy and interpretability, a variable selection process was implemented. First, a correlation matrix was examined to identify multicollinearity ($r > 0.7$) between predictors. Highly correlated variables were removed to avoid redundancy and statistical instability, ensuring that each retained predictor contributed unique variance to the model. Additionally, variables that became non-significant in the multivariate regression ($p > .05$) were considered for removal to refine the model and prevent overfitting.

Neuroimaging and CSF biomarkers were initially screened for multicollinearity, leading to the selection of Mean Putamen and pTau as the representative markers. However, in the final regression model, Mean Putamen did not retain statistical significance, while Mean Caudate remained a significant predictor. Similarly, while MoCA was initially included based on prior significance in t-tests, it did not remain significant in the presence of pTau in the final model. Despite this, MoCA was retained in the model alongside pTau to assess whether cognitive impairment had an independent contribution to dysphagia when controlling for CSF tau pathology. Including MoCA allowed for comparison between univariate and multivariate results and provided insight into the role of cognitive function in the presence of neurodegenerative biomarkers.

The final models retained only those predictors that demonstrated independent associations with the outcome variable while adjusting for the influence of other factors. All logistic regression assumptions were tested prior to analysis. Multicollinearity was assessed using Variance Inflation Factor (VIF), ensuring that all retained variables met the acceptable threshold (VIF < 10). Model fit was evaluated using the Hosmer-Lemeshow goodness-of-fit test and Nagelkerke's R^2, and significance of individual predictors was determined using Wald's test. The final results are presented as odds ratios (Exp(B)) with 95% confidence intervals.

7.7 Ethical consideration

This research is a secondary analysis of data obtained from the PPMI database (ClinicalTrials.gov Identifier: NCT01141023). The PPMI study was conducted in accordance with the Declaration of Helsinki and received ethical approval from the Institutional Review Boards of all participating sites. Written informed consent was obtained from all participants prior to inclusion in the PPMI study. The present analysis used fully de-identified data available to qualified researchers via the PPMI data repository. This study was conducted and reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (von Elm et al., 2007).

Chapter 8: Results

8.1 Speech difficulties in early Parkinson's disease treatment-naïve patients

8.1.1 T-test analyses

8.1.1.1 Demographic characteristics

In early treatment-naïve PD patients, the group with speech difficulties (N = 167) was compared to the group without speech difficulties (N = 209). The mean age of patients with speech difficulties was significantly higher at 63.78 years (±8.8) compared to 60.33 years (±9.9) for those without speech difficulties ($p < .001$). The sex ratio (male/female) was also significantly different, with a ratio of 0.71 in the speech difficulties group compared to 0.61 in the group without speech difficulties ($p = 0.04$). Disease duration was similar between the two groups, with a mean of 6.63 years (±6.1) for patients with speech difficulties and 6.65 years (±6.8) for those without, showing no significant difference ($p = 0.98$) (Table 2).

8.1.1.2 Clinical characteristics

Compared to patients without speech difficulties, patients with speech difficulties had a higher burden of non-motor symptoms (MDS-UPDRS Part I: 6.1 vs 5.0, $p = 0.01$) (Figure 3) and worse motor symptom severity in the OFF state (MDS-UPDRS Part II: 7.2 vs 4.9, $p < .001$; MDS-UPDRS Part III: 24.1 vs 18.5, $p < .001$; Figure 3), as well as in the ON-state (MDS-UPDRS Part III: 24.1 vs 18.5, $p < .001$; H&Y: 1.7 vs 1.5, $p < .001$; Figure 3). Patients with speech difficulties also exhibited overall greater disease burden than patients without speech difficulties in the OFF-state (MDS-UPDRS Total: 37.4 vs 28.5, $p < .001$) and in the ON-state (MDS-UPDRS Total: 37.4 vs 28.5, $p < .001$). The cognitive performance, measured by the MoCA score, did not significantly differ between patients with and without speech difficulties (mean = 27.0 vs 27.3; $p = 0.20$) (Table 2; Figure 3).

8.1.1.3 CSF biomarkers

No differences in any CSF biomarkers were observed between patients with and without speech difficulties (Table 2).

8.1.1.4 [^{123}I]FP-CIT SBR

The [^{123}I]FP-CIT SBR values revealed significant differences between the two groups. PD patients with speech difficulties had significantly reduced [^{123}I]FP-CIT SBR in the bilateral caudate (1.8 vs 2.1; $p < .001$), as well the caudate contralateral (1.7 vs 1.9; $p = 0.002$) and ipsilateral (2.0 vs 2.2; $p < .001$) to the most affected side. The putamen values showed similar trends. PD patients with speech difficulties had significantly reduced [^{123}I]FP-CIT SBR in the bilateral putamen (0.7 vs 0.87; $p < .001$), as well the putamen contralateral (0.6 vs 0.7; $p < .001$) and ipsilateral (0.8 vs 1.0; $p < .001$) to the most affected side. The striatum values were also significantly different between the groups. PD patients with speech difficulties had significantly reduced [^{123}I]FP-CIT SBR in the bilateral striatum (1.3 vs 1.5; $p < .001$), as well the striatum contralateral (2.3 vs 2.6; $p < .001$) and ipsilateral (2.8 vs 3.3; $p < .001$) to the most affected side (Table 2; Figure 4; Image 1).

8.1.1.5 Summary

These results indicate significant differences in demographic characteristics, clinical features, and [^{123}I]FP-CIT SBR values between early PD treatment-naïve patients with and without speech difficulties. Specifically, patients with speech difficulties were significantly older, had a significantly different sex ratio, and exhibited higher MDS-UPDRS scores across several subscales, indicating significantly worse motor and non-motor symptoms. Additionally, the [^{123}I]FP-CIT SBR values were significantly lower in the speech difficulties group across multiple regions. However, cognitive performance and CSF biomarkers did not show significant differences between the groups.

	Early PD treatment-naïve patients with speech difficulties (N = 167)	Unavailable data's ratio (%)	Early PD treatment-naïve patients without speech difficulties (N = 209)	Unavailable data's ratio (%)	*P* value
Demographic characteristics					
Age (years) [mean (±SD)]	63.78 (±8.8)	-	60.33 (±9.9)	-	**<.001**
Sex [mean (±SD)]	0.71 (±0.4)	-	0.61 (±0.4)	-	**0.04**
Disease duration (months) [mean (±SD)]	6.63 (±6.1)	-	6.65 (±6.8)	-	0.98
Cognitive performance					
MoCA [mean (±SD)]	26.98 (±2.3)	-	27.29 (±2.3)	-	0.20
Clinical characteristics					
MDS-UPDRS Part I [mean (±SD)]	6.13 (±3.9)	-	5.04 (±4)	-	**0.01**
MDS-UPDRS Part II [mean (±SD)]	7.16 (±4.5)	-	4.94 (±3.6)	-	**<.001**
MDS-UPDRS Part III [mean (±SD)]	24.14 (±8.5)	-	18.47 (±8.2)	-	**<.001**
MDS-UPDRS Part III(ON-state) [mean (±SD)]	24.14 (±8.5)	-	18.47 (±8.2)	-	**<.001**
MDS-UPDRS Part IV [mean (±SD)][a]	0	-	0	-	-

MDS-UPDRS Total [mean (±SD)]	37.42 (±13)	-	28.45 (±12)	-	**<.001**
MDS-UPDRS Total (ON-state) [mean (±SD)]	37.42 (±13)	-	28.45 (±12)	-	**<.001**
Holen & Yard (ON-state) [mean (±SD)]	1.67 (±0.47)	-	1.49 (±0.50)	-	**<.001**
CSF biomarkers					
abeta [mean (±SD)]	829.01 (±296.1)	12%	830.55 (±288.3)	9%	0.96
tau [mean (±SD)]	173.12 (±61.8)	5%	165.80 (±53)	4%	0.23
ptau [mean (±SD)]	15.23 (±5.7)	11%	14.49 (±4.8)	10%	0.20
asyn [mean (±SD)]	1536.85 (±711.1)	4%	1495.23 (±636.1)	<1%	0.55
[^{123}I]FP-CIT SBR					
contralateral_caudate [mean (±SD)]	1.71 (±0.5)	-	1.88 (±0.5)	-	**0.002**
ipsilateral_caudate [mean (±SD)]	1.97 (±0.5)	-	2.24 (±0.5)	-	**<.001**
mean_caudate [mean (±SD)]	1.84 (±1.8)	-	2.06 (±0.5)	-	**<.001**
contralateral _putamen [mean (±SD)]	0.63 (±0.2)	-	0.72 (±0.2)	-	**<.001**
ipsilateral _putamen [mean (±SD)]	0.83 (±0.2)	-	1.03 (±0.3)	-	**<.001**
mean_putamen [mean (±SD)]	0.73 (±0.2)	-	0.87 (±0.2)	-	**<.001**
contralateral _striatum [mean (±SD)]	2.34 (±0.6)	-	2.60 (±0.7)	-	**<.001**
ipsilateral _striatum [mean (±SD)]	2.81 (±0.8)	-	3.27 (±0.8)	-	**<.001**
mean_striatum [mean (±SD)]	1.29 (±0.3)	-	1.46 (±0.3)	-	**<.001**
[a]t cannot be computed because at least one of the groups is empty.					

Table 2. Demographic characteristics, Cognitive performance, Clinical characteristics, CSF biomarkers and [^{123}I]FP-CIT SBR in early PD treatment-naïve patients with and without speech difficulties. SBR=Signal-Binding-Ratio.

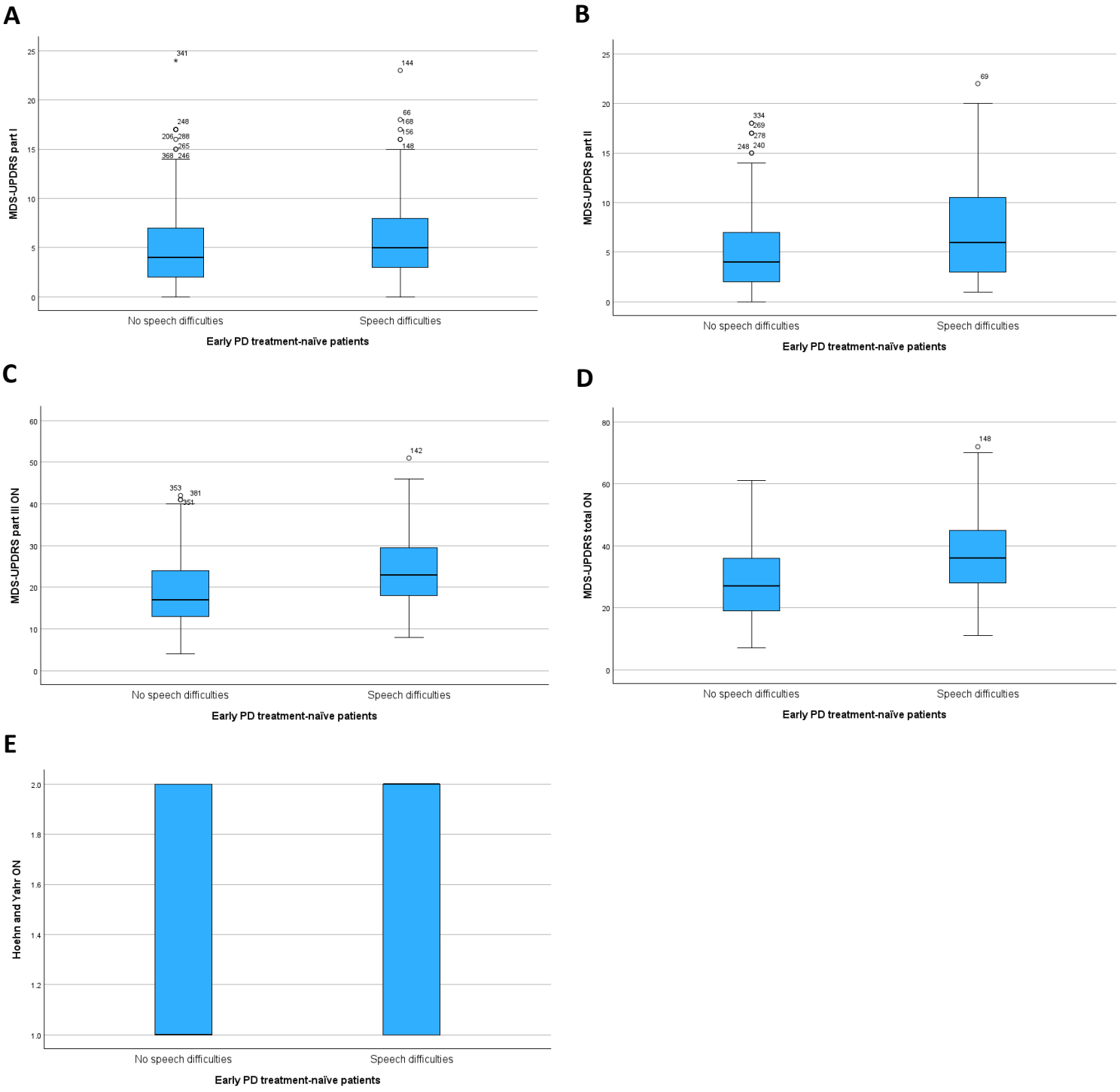
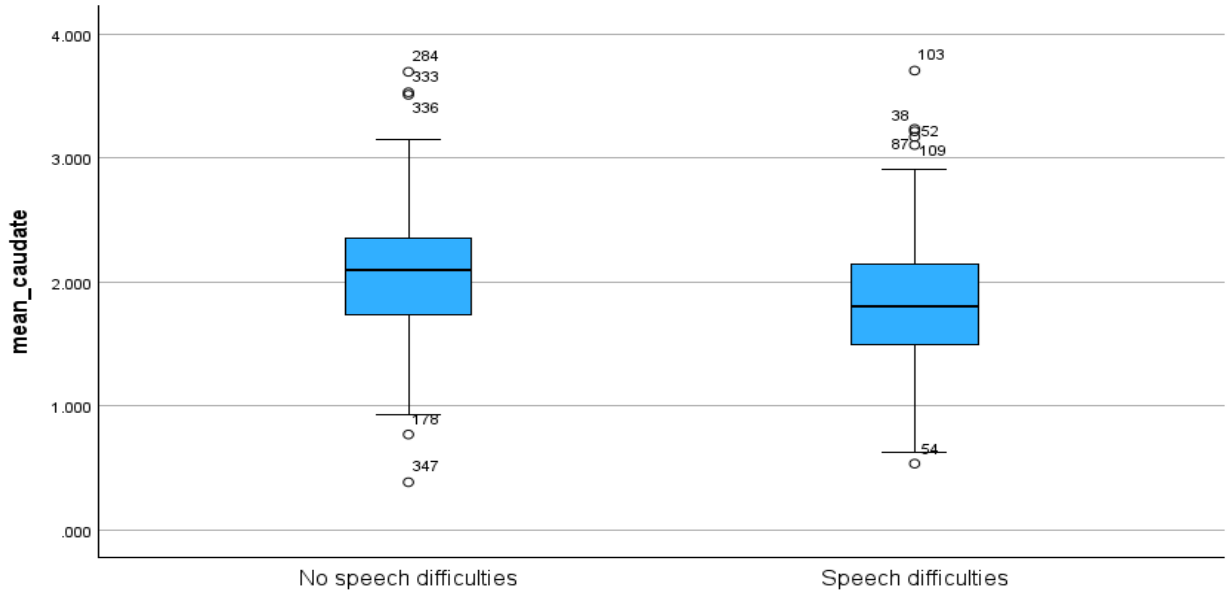


Figure 3. A) MDS-UPDRS Part I scores in early PD treated-naïve patients with and without speech difficulties.
B) MDS-UPDRS Part II scores in early PD treated-naïve patients with and without speech difficulties.
C) MDS-UPDRS Part III (ON-state) scores in early PD treated-naïve patients with and without speech difficulties.
D) MDS-UPDRS total (ON-state) scores in early PD treated-naïve patients with and without speech difficulties.
E) Hoehn and Yah (ON-state) scores in early PD treated-naïve patients with and without speech difficulties.

A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3.000
2.000
1.000
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333
336
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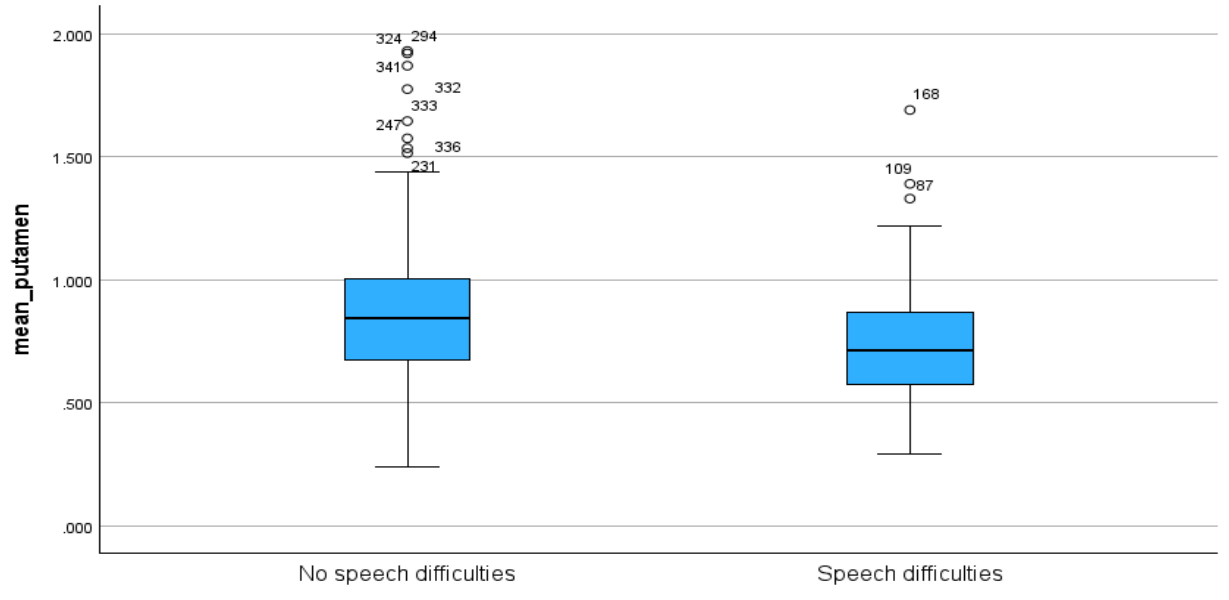
347
103
38
52
87
109
54
No speech difficulties
Speech difficulties
Early PD treatment-naïve patients

B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333
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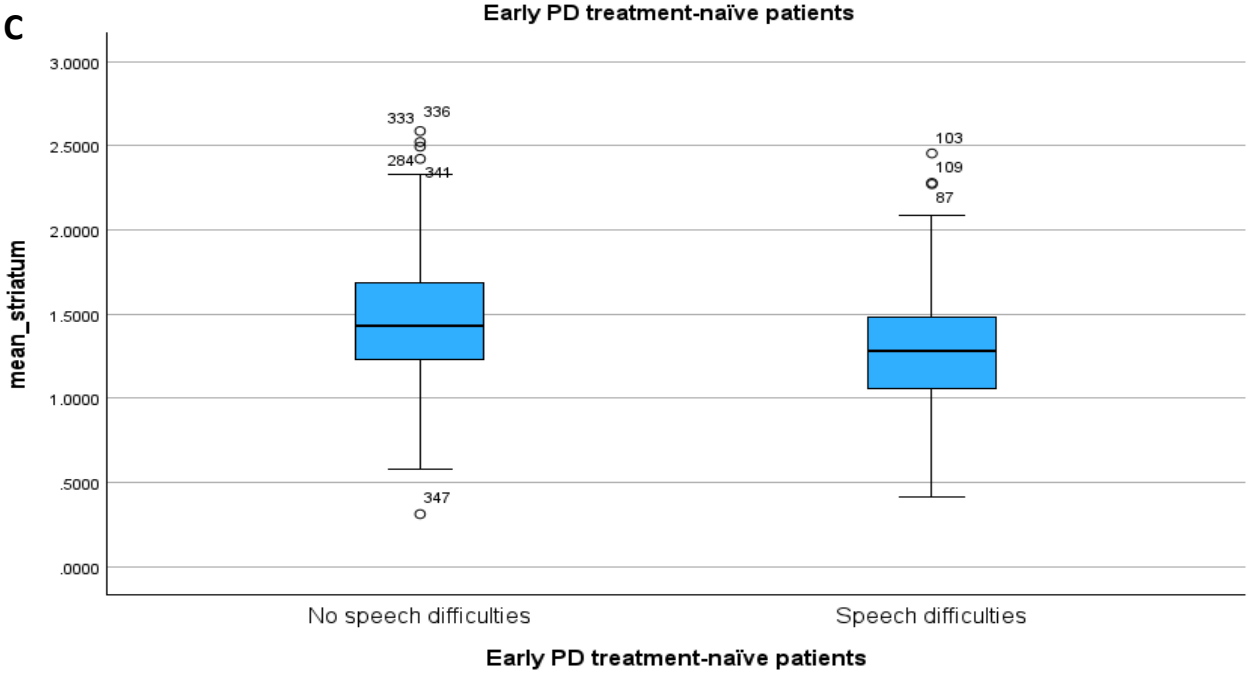
No speech difficulties
Speech difficulties
Early PD treatment-naïve patients

C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2.0000
1.5000
1.0000
.5000
.0000
333
336
284
341
347
103
109
87
No speech difficulties
Speech difficulties
Early PD treatment-naïve patients

Figure 4. A) [^{123}I]FP-CIT SBR in bilateral caudate of early PD treatment-naïve patients with and without speech difficulties.

B) [^{123}I]FP-CIT SBR in bilateral putamen of early PD treatment-naïve patients with and without speech difficulties.

C) [^{123}I]FP-CIT SBR in bilateral striatum of early PD treatment-naïve patients with and without speech difficulties.

SBR=Signal-Binding-Ratio.

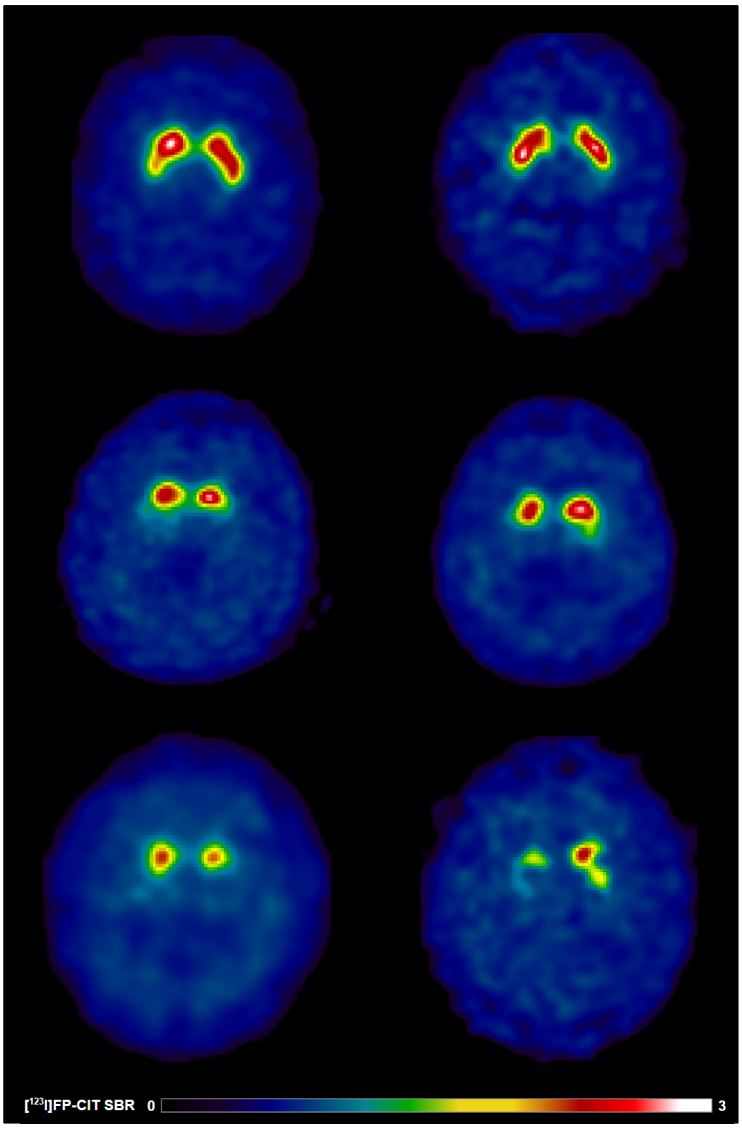


Image 1. [^{123}I]FP-CIT SPECT images in early untreated PD patients with and without speech difficulties.

(Top) A 63-year-old healthy control male (left) showing typical [^{123}I]FP-CIT specific binding ratios in the caudate (SBR: 3.03) and putamen (SBR: 2.26) and a 69-year-old healthy control female (right) showing typical [^{123}I]FP-CIT specific binding ratios in the caudate (SBR: 3.21) and putamen (SBR: 2.79).
(Middle) A 63-year-old male (left) without speech difficulties exhibiting slight dopaminergic deficits as reflected by [^{123}I]FP-CIT specific binding ratios in the caudate (SBR: 1.98) and putamen (SBR: 0.52) and a 69-year-old female (right) without speech difficulties exhibiting slight dopaminergic deficits as reflected by [^{123}I]FP-CIT specific binding ratios in the caudate (SBR: 2.45) and putamen (SBR: 0.79).
(Bottom) A 63-year-old male (left) with speech difficulties demonstrating larger striatal dopaminergic deficits as reflected by [^{123}I]FP-CIT specific binding ratios in the caudate (SBR:1.16) and putamen (SBR: 0.37) and a 69-year-old male (right) with speech difficulties demonstrating larger striatal dopaminergic deficits as reflected by [^{123}I]FP-CIT specific binding ratios in the caudate (SBR: 1.33) and putamen (SBR: 0.77).

8.1.2 Multivariate Binary Logistic Regression analysis

The initial multivariate logistic regression included all predictors that were significant in the t-tests. However, due to high multicollinearity and redundancy among predictors, certain variables were excluded to refine the model. Specifically, UPDRS Part III, UPDRS Total Score, and MDS-UPDRS Total ON showed high correlations ($r > 0.8$) and were therefore reduced to a single representative variable, MDS-UPDRS Part III ON, which remained the most clinically relevant predictor of motor impairment in this cohort. Similarly, among the neuroimaging variables, mean caudate and mean striatum were highly correlated with mean putamen ($r > 0.7$), and therefore, only mean putamen was retained as the most significant marker of neurodegeneration.

After refining the model, a final logistic regression was conducted with age, sex, MDS-UPDRS Part III ON, Hoehn and Yahr ON, and mean putamen values as independent predictors (Table 3). The model was statistically significant, $\chi^2(5) = 61.420$, $p < .001$, indicating that the included variables collectively distinguished between patients with and without speech difficulties (Table 3). Nagelkerke's $R^2 = 0.202$ suggested that the model explained 20.2% of the variance in speech difficulties (Table 3). The Hosmer-Lemeshow test was non-significant ($p = 0.588$), indicating a good model fit (Table 3).

Higher MDS-UPDRS Part III ON scores were significantly associated with increased odds of speech difficulties (OR = 1.074, $p < .001$), suggesting that greater motor impairment in the ON state strongly contributes to the condition (Table 3). Lower mean putamen values were also a significant predictor (OR = 0.198, $p < .001$), reinforcing the role of neurodegeneration in the development of speech difficulties (Table 3). Additionally, age was significantly associated with speech difficulties (OR = 1.028, $p = 0.028$), indicating that older patients are at higher risk, with a 2.8% increase in odds per year of age (Table 3).

In contrast, sex ($p = 0.104$) and Hoehn and Yahr ON ($p = 0.393$) were not retained as significant predictors, suggesting that their initial significance in univariate analyses was likely driven by shared variance with stronger predictors such as UPDRS Part III ON and mean putamen (Table 3).

These findings highlight the importance of age, motor function, and neurodegeneration in predicting speech difficulties in early PD treatment-naïve patients, with the final model providing a statistically robust and clinically interpretable representation of these relationships.

	B	S.E.	Wald	df	Sig.	Exp(B)
Age	.027	.012	4.836	1	**0.028**	1.028
Sex at birth (1)	.388	.239	2.649	1	.104	1.474
MDS-UPDRS part III ON	.071	.016	18.704	1	**<.001**	1.074
Hoehn and Yahr ON (1)	-.237	.278	.728	1	.393	.789

mean_putamen	-1.620	.483	11.257	1	**<.001**	.198

Table 3. Multivariate Binary Logistic Regression analysis of predictor variables on early PD treatment-naïve patients with and without speech difficulties.

8.2 Speech difficulties in Early Parkinson's Disease levodopa-treated PD patients

8.2.1 T-test analyses

8.2.1.1 Demographic characteristics

In early PD levodopa-treated patients, the group with speech difficulties (N = 76) was compared to the group without speech difficulties (N = 57). Mean age, sex ratio and disease duration were comparable between patients with and without speech difficulties (Table 4).

8.2.1.2 Clinical characteristics

Levodopa-treated PD patients with speech difficulties had significantly worse motor symptoms compared to those without (UPDRS Part II: 8.7 vs 6.2, p=0.003; Figure 5); UPDRS Part III OFF-state: 29.3 vs 21.9, p < .001; UPDRS Part III ON-state: 24.0 vs 17.0, p < .001; H&Y: 1.8 vs 1.6, p = 0.045; Figure 5), as well as higher overall disease burden both OFF and ON medication (UPDRS Total OFF-state: 45.6 vs 34.0, p < .001; UPDRS Total ON-state: 40.0 vs 29.6, p < .001; Table 4). No differences were observed in cognitive function, as measured by MoCA, motor complications, as measured by MDS-UPDRS part IVand non-motor symptom burden as measured by MDS-UPDRS part I between those with and without speech difficulties (Table 4).

8.2.1.3 CSF biomarkers

The analysis of CSF biomarkers showed no significant differences between patients with and without speech difficulties (Table 4; Figure 5).

8.2.1.4 [^{123}I]FP-CIT SBR

The [^{123}I]FP-CIT SBR values revealed significant differences between the two groups. Compared to patients without speech difficulties, those with speech difficulties exhibited reduced [^{123}I]FP-CIT SBR in the contralateral caudate (1.4 vs 1.6, p = 0.02), ipsilateral caudate (1.7 vs 1.9, p = 0.02) and bilateral caudate (1.5 vs 1.7, p = 0.01). The putamen values showed similar trends. Compared to patients without speech difficulties, those with speech difficulties exhibited reduced [^{123}I]FP-CIT SBR in the contralateral putamen (0.5 vs 0.6, p = 0.003), ipsilateral putamen (0.7 vs 0.8; p = 0.008) and bilateral putamen (0.6 vs 0.7, p = 0.002). The striatum values were also significantly different between the groups. Compared to patients without speech difficulties, those with speech difficulties exhibited reduced [^{123}I]FP-CIT SBR in the contralateral striatum (1.9 vs 2.2, p = 0.008), ipsilateral striatum (2.3 vs 2.7; p = 0.01) and bilateral striatum (1.1 vs 1.2, p = 0.007) (Table 4; Figure 6; Image 2).

8.2.1.5 Summary

These results indicate significant differences in clinical features and [^{123}I]FP-CIT SBR values between early PD levodopa-treated patients with and without speech difficulties. Patients with speech difficulties exhibited significantly higher MDS-UPDRS scores across several subscales, indicating worse motor symptoms, as well as higher Hoehn and Yahr stage scores. Additionally, the [^{123}I]FP-CIT SBR values were significantly lower in the speech difficulties group across multiple regions. However, demographic characteristics, cognitive performance and CSF biomarkers did not show significant differences between the groups.

	Early PD levodopa-treated patients with speech difficulties (N = 76)	Unavailable data's ratio (%)	Early PD levodopa-treated patients without speech difficulties (N = 57)	Unavailable data's ratio (%)	*P* value
Demographic characteristics					
Age (years) [mean (±SD)]	63.53 (±7.9)	-	60.63 (±10)	-	0.66
Sex [mean (±SD)]	0.71 (±0.4)	-	0.63 (±0.4)	-	0.33
Disease duration (months) [mean (±SD)]	5.82 (±5.9)	-	4.7 (±6.2)	-	0.33
Cognitive performance					
MoCA [mean (±SD)]	25.70 (±3.5)	-	26.25 (±3.3)	-	0.36
Clinical characteristics					
MDS-UPDRS Part I [mean (±SD)]	7.95 (±5.4)	-	6.40 (±4.3)	-	0.08
MDS-UPDRS Part II [mean (±SD)]	8.72 (±5.3)	-	6.23 (±3.7)	-	**0.003**
MDS-UPDRS Part III [mean (±SD)]	29.26 (±10.3)	18%	21.94 (±8.3)	45%	**<.001**
MDS-UPDRS Part III(ON-state) [mean (±SD)]	24.03 (±9.9)	11%	17.02 (±8.1)	5%	**<.001**
MDS-UPDRS Part IV [mean (±SD)][a]	0.05 (±0.2)	1%	0.0 (±0.0)	-	0.15
MDS-UPDRS Total [mean (±SD)]	45.63 (±15)	18%	34.03 (±12.6)	45%	**<.001**

MDS-UPDRS Total (ON-state) [mean (±SD)]	40.55 (±15.6)	11%	29.63 (±11.3)	5%	**<.001**
Holen & Yard (ON-state) [mean (±SD)]	1.81 (±0.46)	11%	1.63 (±0.48)	5%	**0.045**
CSF biomarkers					
abeta [mean (±SD)]	734.39 (±293)	23%	788.78 (±261.1)	35%	0.36
tau [mean (±SD)]	169.01 (±68.5)	14%	174.44 (±75.7)	29%	0.70
ptau [mean (±SD)]	14.55 (±5.8)	23%	15.87 (±7.6)	38%	0.34
asyn [mean (±SD)]	1425.80 (±623.2)	14%	1463.12 (±660)	28%	0.77
[^{123}I]FP-CIT SBR					
contralateral_caudate [mean (±SD)]	1.39 (±0.4)	-	1.58 (±0.4)	1%	**0.02**
ipsilateral_caudate [mean (±SD)]	1.67 (±0.5)	-	1.88 (±0.5)	1%	**0.02**
mean_caudate [mean (±SD)]	1.53 (±0.4)	-	1.73 (±0.4)	1%	**0.01**
contralateral_putamen [mean (±SD)]	0.51 (±0.1)	-	0.60 (±0.1)	1%	**0.003**
ipsilateral_putamen [mean (±SD)]	0.66 (±0.2)	-	0.78 (±0.2)	1%	**0.008**
mean_putamen [mean (±SD)]	0.58 (±0.1)	-	0.69 (±0.1)	1%	**0.002**
contralateral_striatum [mean (±SD)]	1.90 (±0.5)	-	2.18 (±0.6)	1%	**0.008**
ipsilateral_striatum [mean (±SD)]	2.33 (±0.7)	-	2.66 (±0.7)	1%	**0.01**
mean_striatum [mean (±SD)]	1.06 (±0.3)	-	1.21 (±0.3)	1%	**0.007**

Table 4. Demographic characteristics, Cognitive performance, MDS-UPDRS Scales, CSF biomarkers and [^{123}I]FP-CIT SBR in early PD levodopa-treated patients with and without speech difficulties. SBR=Signal-Binding-Ratio.

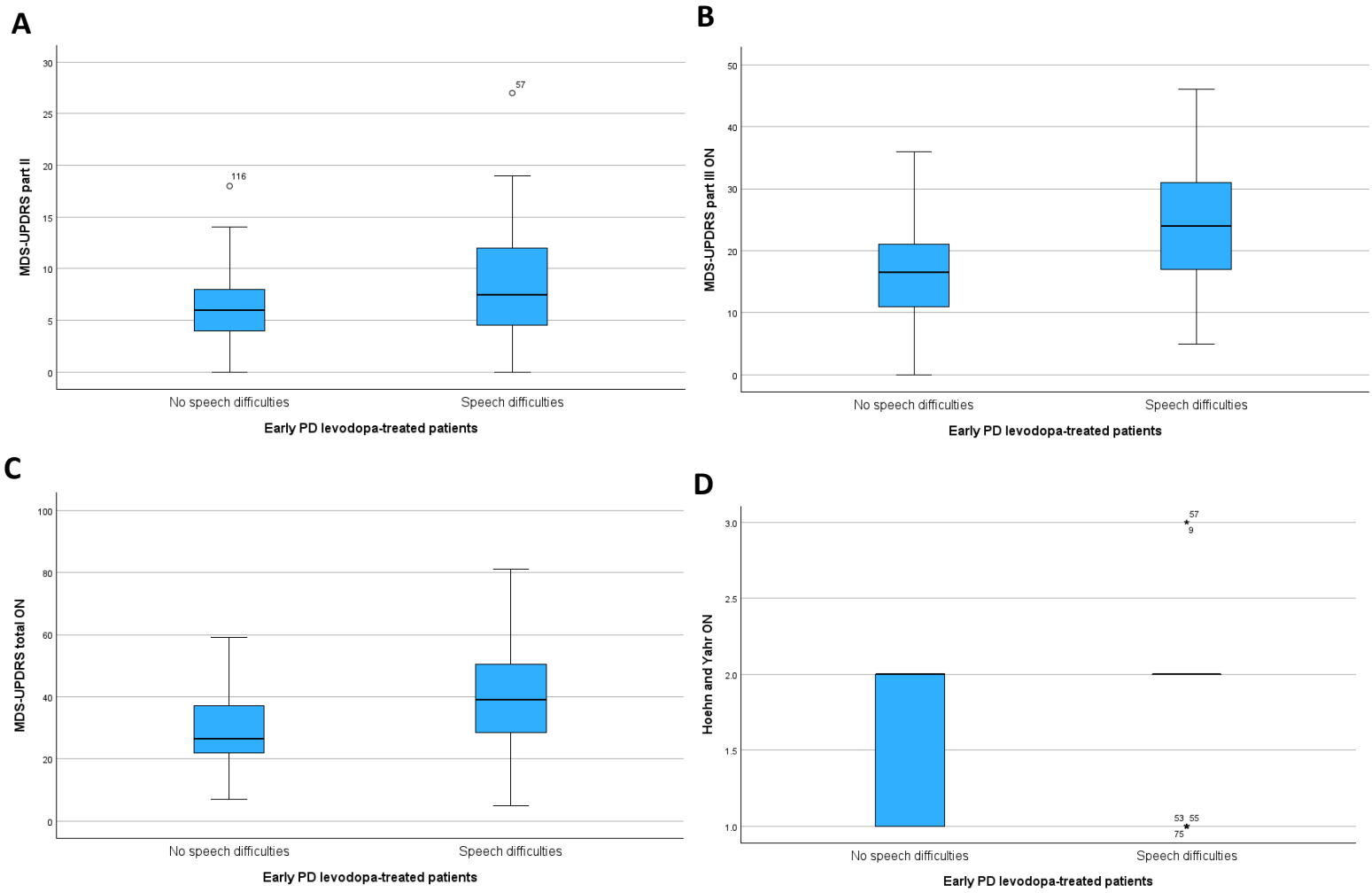
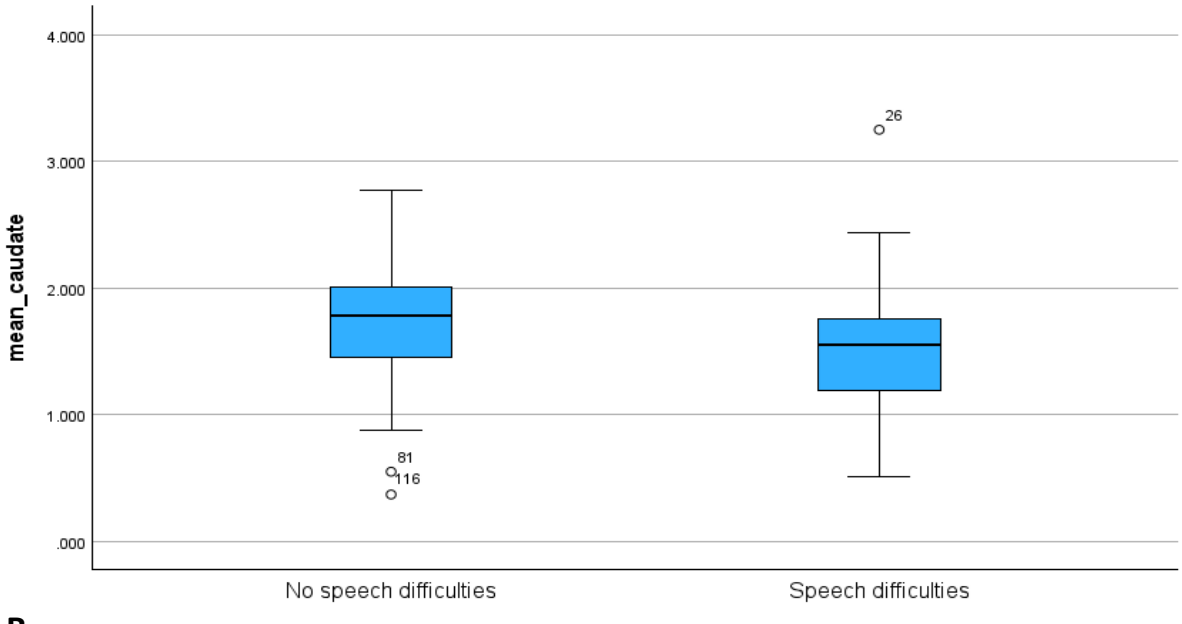


Figure 5. A) MDS-UPDRS Part II scores in early PD levodopa-treated patients with and without speech difficulties.
B) MDS-UPDRS Part III (ON state) scores in early PD levodopa-treated patients with and without speech difficulties.
C) MDS-UPDRS total (ON state) scores in early PD levodopa-treated patients with and without speech difficulties.
D) Hoehn and Yah (ON-state) scores in early PD levodopa-treated patients with and without speech difficulties.

A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26
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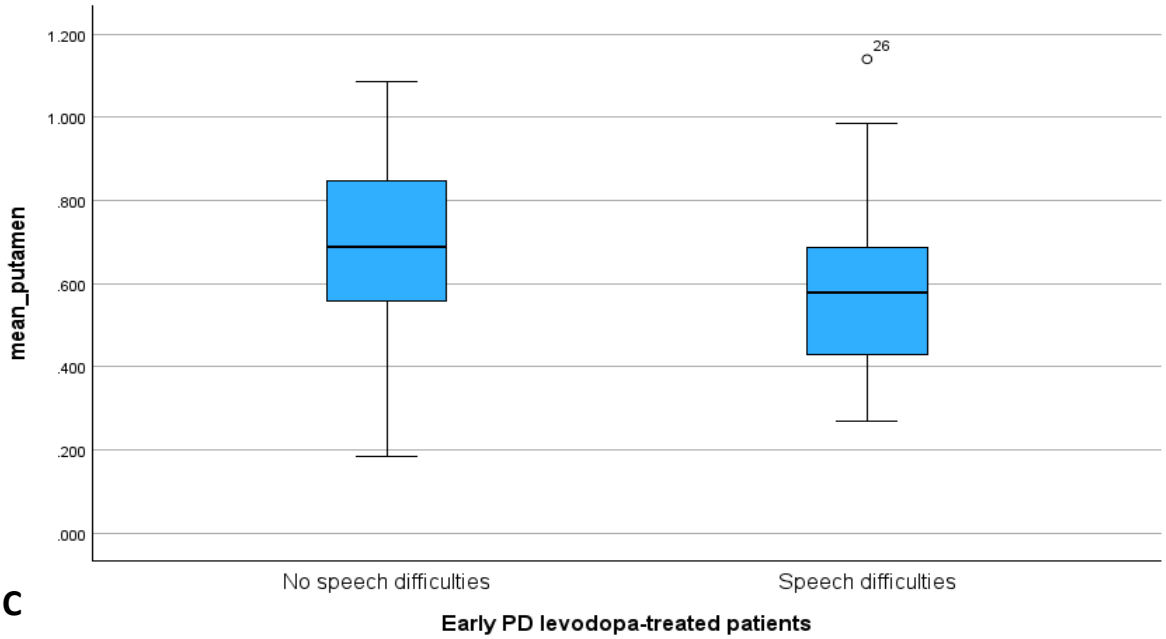
116
No speech difficulties
Speech difficulties
Early PD levodopa-treated patients

B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.000
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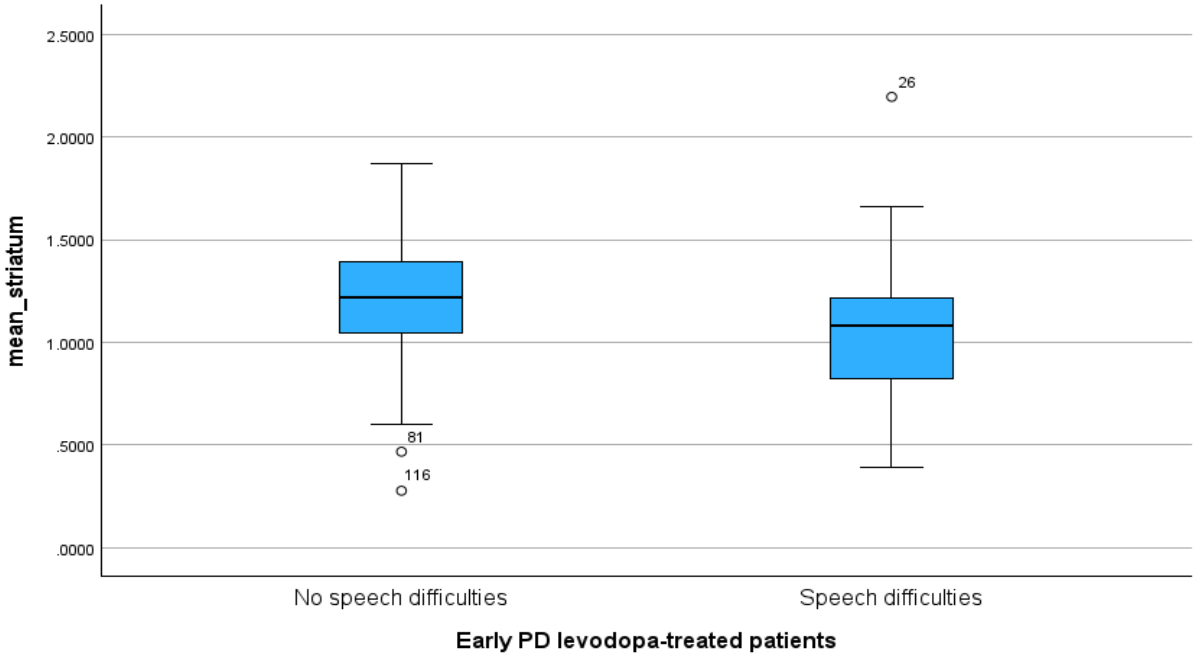
Speech difficulties
Early PD levodopa-treated patients

C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26
81
116
No speech difficulties
Speech difficulties
Early PD levodopa-treated patients

Figure 6. A) [^{123}I]FP-CIT SBR in bilateral caudate of early PD levodopa-treated patients with and without speech difficulties.

B) [^{123}I]FP-CIT SBR in bilateral putamen of early PD levodopa-treated patients with and without speech difficulties.

C) [^{123}I]FP-CIT SBR in bilateral striatum of early PD levodopa-treated patients with and without speech difficulties.

SBR=Signal-Binding-Ratio.

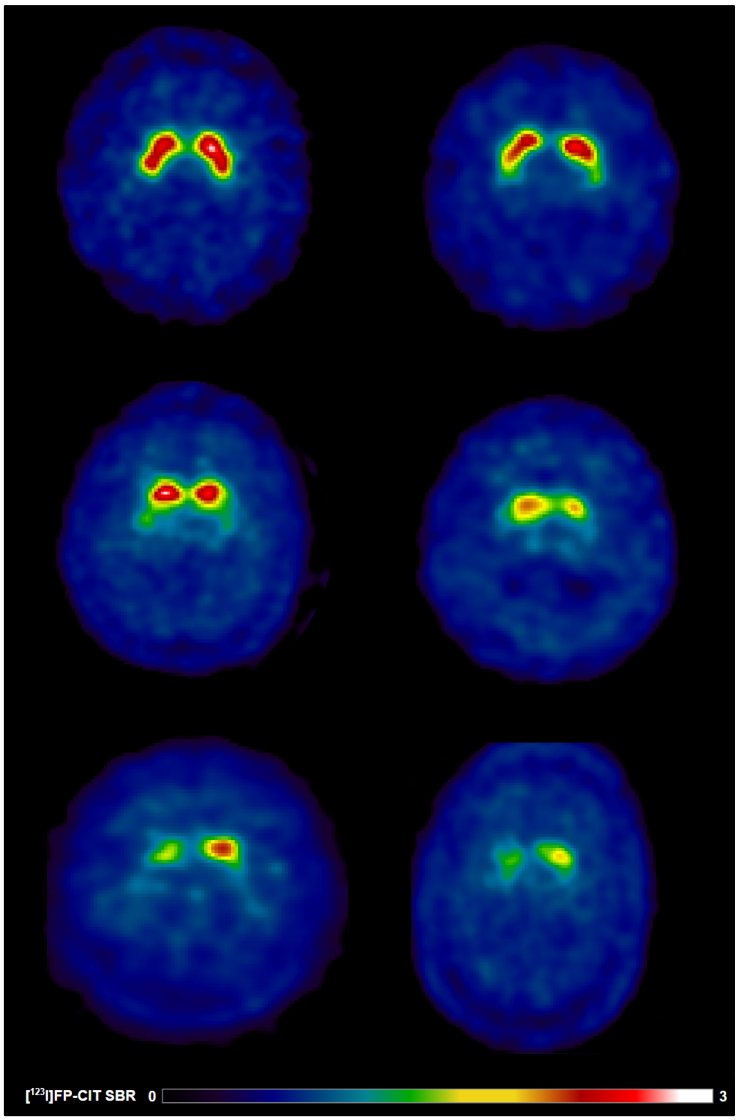


Image 2. [^{123}I]FP-CIT SPECT images in early treated PD patients with and without speech difficulties.

(Top) A 65-year-old healthy control male (left) showing typical [^{123}I]FP-CIT specific binding ratios in the caudate (SBR: 4.15) and putamen (SBR: 2.89) and a 69-year-old healthy control male (right) showing typical [^{123}I]FP-CIT specific binding ratios in the caudate (SBR: 2.75) and putamen (SBR: 1.85).
(Middle) A 65-year-old male (left) without speech difficulties exhibiting slight dopaminergic deficits as reflected by [^{123}I]FP-CIT specific binding ratios in the caudate (SBR: 2.38) and putamen (SBR: 0.99) and a 69-year-old female (right) without speech difficulties exhibiting slight dopaminergic deficits as reflected by [^{123}I]FP-CIT specific binding ratios in the caudate (SBR: 1.4) and putamen (SBR: 0.54).
(Bottom) A 65-year-old male (left) with speech difficulties demonstrating larger striatal dopaminergic deficits as reflected by [^{123}I]FP-CIT specific binding ratios in the caudate (SBR: 0.92) and putamen (SBR: 0.45) and a 69-year-old male (right) with speech difficulties demonstrating larger striatal dopaminergic deficits as reflected by [^{123}I]FP-CIT specific binding ratios in the caudate (SBR: 1.36) and putamen (SBR: 0.71).

8.2.2 Multivariate Binary Logistic Regression analysis

The initial multivariate logistic regression included all predictors that were significant in the t-tests. However, due to high multicollinearity and redundancy among predictors, certain variables were excluded to refine the model. Specifically, UPDRS Part III, UPDRS Total Score, and MDS-UPDRS Total ON showed high correlations ($r > 0.8$) and were therefore reduced to a single representative variable, MDS-UPDRS Part III ON, which remained the most clinically relevant predictor of motor impairment in this cohort. Similarly, among the neuroimaging variables, mean caudate and mean striatum were highly correlated with mean putamen ($r > 0.7$), and therefore, only mean putamen was retained as the most significant marker of neurodegeneration.

After refining the model, a final logistic regression was conducted with MDS-UPDRS Part III ON and mean putamen as independent predictors (Table 5). The model was statistically significant, $\chi^2(2) = 22.907$, $p < .001$, indicating that the included variables collectively distinguished between patients with and without speech difficulties (Table 5). Nagelkerke's $R^2 = 0.231$ suggested that the model explained 23.1% of the variance in speech difficulties (Table 5). The Hosmer-Lemeshow test was non-significant ($p = 0.809$), indicating a good model fit (Table 5).

Higher MDS-UPDRS Part III ON scores were significantly associated with increased odds of speech difficulties (OR = 1.075, $p = 0.002$), suggesting that greater motor impairment in the ON state strongly contributes to the condition (Table 5). Lower mean putamen values were also a significant predictor (OR = 0.082, $p = 0.016$), reinforcing the role of neurodegeneration in the development of speech difficulties (Table 5).

In contrast, UPDRS Part II and Hoehn and Yahr ON, which were significant in t-tests, were not retained in the final model due to their lack of independent contribution when controlling for other factors ($p > .05$; Table 5). This suggests that their initial significance in univariate analyses was likely driven by their shared variance with stronger predictors, such as UPDRS Part III ON and mean putamen.

These findings highlight the importance of both motor function and neurodegeneration in predicting speech difficulties in early PD patients, with the final model providing a statistically robust and clinically interpretable representation of these relationships.

	B	S.E.	Wald	df	Sig.	Exp(B)
Hoehn and Yahr ON			.582	2	.748	
Hoehn and Yahr ON(1)	-.390	.511	.582	1	.446	.677
Hoehn and Yahr ON(2)	19.335	28024.390	.000	1	.999	249410221.953
MDS-UPDRS part II	.014	.053	.073	1	.788	1.014

MDS-UPDRS part III ON	.079	.028	7.913	1	**0.005**	1.082
mean_putamen	-2.405	1.098	4.801	1	**0.028**	.090

Table 5. Multivariate Binary Logistic Regression analysis of predictor variables on early PD levodopa-treated patients with and without speech difficulties.

8.3 Dysphagia in early Parkinson's Disease treatment-naïve patients

8.3.1 T-test analyses

8.3.1.1 Demographic characteristics

Early PD treatment-naïve patients with dysphagia (N = 51) were compared to those without dysphagia (N = 326). Both groups were comparable in mean age (63.0 years vs 61.7 years), sex ratio (male/female) (0.6 vs 0.7), and disease duration (7.0 months vs 6.5 months; Table 6).

8.3.1.2 Clinical characteristics

Compared to PD patients without dysphagia, those with dysphagia had a higher burden of non-motor symptoms (UPDRS Part I 8.5 vs 5.0, $p < .001$; Figure 7), worse motor experiences of daily living (UPDRS Part II: 9.8 vs 5.3, $p < .001$; Figure 7) and overall disease severity (Total UPDRS OFF-state: 40.6 vs 31.1, $p < .001$; Total UPDRS ON-state: 40.6 vs 31.1, $p < .001$). Cognitive function, as measured by MoCA, and motor symptom severity, as measured by MDS-UPDRS Part III, MDS-UPDRS Part III (ON-state) and H&Y, did not differ between groups (Table 6).

8.3.1.3 CSF biomarkers

No significant differences in any CSF biomarkers were observed between PD patients with dysphagia and patients without dysphagia (Table 6).

8.3.1.4 [^{123}I]FP-CIT SBR

The [^{123}I]FP-CIT SBR values revealed significant differences between the two groups. Early PD treatment-naïve patients with dysphagia had reduced [^{123}I]FP-CIT SBR in the contralateral caudate (1.6 vs 1.8, $p < .001$), ipsilateral caudate (1.8 vs 2.2, $p < .001$), and bilateral caudate (1.7 vs 2.0, $p < .001$) compared to patients without dysphagia. The putamen values showed similar trends. Early PD treatment-naïve patients with dysphagia had reduced [^{123}I]FP-CIT SBR in the contralateral putamen (0.6 vs 0.7, $p = 0.031$), ipsilateral putamen (0.8 vs 1.0, $p = 0.027$), and bilateral putamen (0.7 vs 0.8, $p = 0.015$) compared to patients without dysphagia. The striatum values were also significantly different between the groups. Early PD treatment-naïve patients with dysphagia had reduced [^{123}I]FP-CIT SBR in the contralateral striatum (2.2 vs 2.5, $p < .001$), ipsilateral striatum (2.7 vs 3.1, $p < .001$), and bilateral striatum (1.2 vs 1.4, $p < .001$) compared to patients without dysphagia (Table 6; Figure 8; Image 1).

8.3.1.5 Summary

These results indicate significant differences in clinical features and [^{123}I]FP-CIT SBR values between early PD treatment-naïve patients with and without dysphagia. Patients with dysphagia exhibited significantly higher MDS-UPDRS scores, indicating significantly worse motor and non-motor symptoms, and significantly lower [^{123}I]FP-CIT SBR values across multiple regions. However, demographic characteristics, cognitive performance and CSF biomarkers did not show significant differences between the groups.

	Early PD treatment-naïve patients with dysphagia (N = 51)	Unavailable data's ratio (%)	Early PD treatment-naïve patients without dysphagia (N = 326)	Unavailable data's ratio (%)	*P* value
Demographic characteristics					
Age (years) [mean (±SD)]	63.01 (±7.9)	-	61.69 (±9.8)	-	0.365
Sex [mean (±SD)]	0.63 (±0.4)	-	0.66 (±0.4)	-	0.687
Disease duration (months) [mean (±SD)]	6.98 (±6.1)	-	6.58 (±6.5)	-	0.684
Cognitive performance					
MoCA [mean (±SD)]	27.39 (±1.8)	-	27.10 (±2.4)	-	0.408
Clinical characteristics					
MDS-UPDRS Part I [mean (±SD)]	8.53 (±5.2)	-	5.04 (±3.6)	-	**<.001**
MDS-UPDRS Part II [mean (±SD)]	9.82 (±5.1)	-	5.31 (±3.6)	-	**<.001**
MDS-UPDRS Part III [mean (±SD)]	22.25 (±8.3)	-	20.77 (±8.9)	-	0.267
MDS-UPDRS Part III(ON-state) [mean (±SD)]	22.55 (±8.3)	-	20.77 (±8.9)	-	0.267
MDS-UPDRS Part IV [mean (±SD)][a]	0[a]	-	0[a]	-	-
MDS-UPDRS Total [mean (±SD)]	40.61 (±14.4)	-	31.12 (±12.6)	-	**<.001**
MDS-UPDRS Total (ON-state) [mean (±SD)]	40.61 (±14.4)	-	31.12 (±12.6)	-	**<.001**

Holen & Yard (ON-state) [mean (±SD)]	1.65 (±0.48)	-	1.56 (±0.49)	-	0.235
CSF biomarkers					
abeta [mean (±SD)]	804.31 (± 273.7)	5%	833.63 (±293.9)	11%	0.519
tau [mean (±SD)]	168.03 (±59.7)	1%	169.03 (±56.6)	5%	0.996
ptau [mean (±SD)]	14.62 (±5.4)	7%	14.85 (±5.2)	11%	0.775
asyn [mean (±SD)]	1421.73 (±531.4)	1%	1527.26 (±687.0)	2%	0.300
[^{123}I]FP-CIT SBR					
contralateral_caudate [mean (±SD)]	1.57 (±0.52)	-	1.84 (±0.52)	-	**<.001**
ipsilateral_caudate [mean (±SD)]	1.81 (± 0.59)	-	2.17 (±0.55)	-	**<.001**
mean_caudate [mean (±SD)]	1.69 (±0.5)	-	2.01 (±0.51)	-	**<.001**
contralateral_putamen [mean (±SD)]	0.61 (±0.2)	-	0.69 (±0.2)	-	**0.031**
ipsilateral_putamen [mean (±SD)]	0.84 (±0.4)	-	0.96 (±0.3)	-	**0.027**
mean_putamen [mean (±SD)]	0.72 (±0.3)	-	0.82 (±0.2)	-	**0.015**
contralateral_striatum [mean (±SD)]	2.18 (±0.7)	-	2.54 (±0.7)	-	**<.001**
ipsilateral_striatum [mean (±SD)]	2.66 (±0.9)	-	3.14 (±0.8)	-	**<.001**
mean_striatum [mean (±SD)]	1.21 (±0.3)	-	1.42 (±0.3)	-	**<.001**
[a]t cannot be computed because at least one of the groups is empty.					

Table 6. [^{123}I]FP-CIT SBR in early PD treatment-naïve patients with and without dysphagia. SBR=Signal-Binding-Ratio.

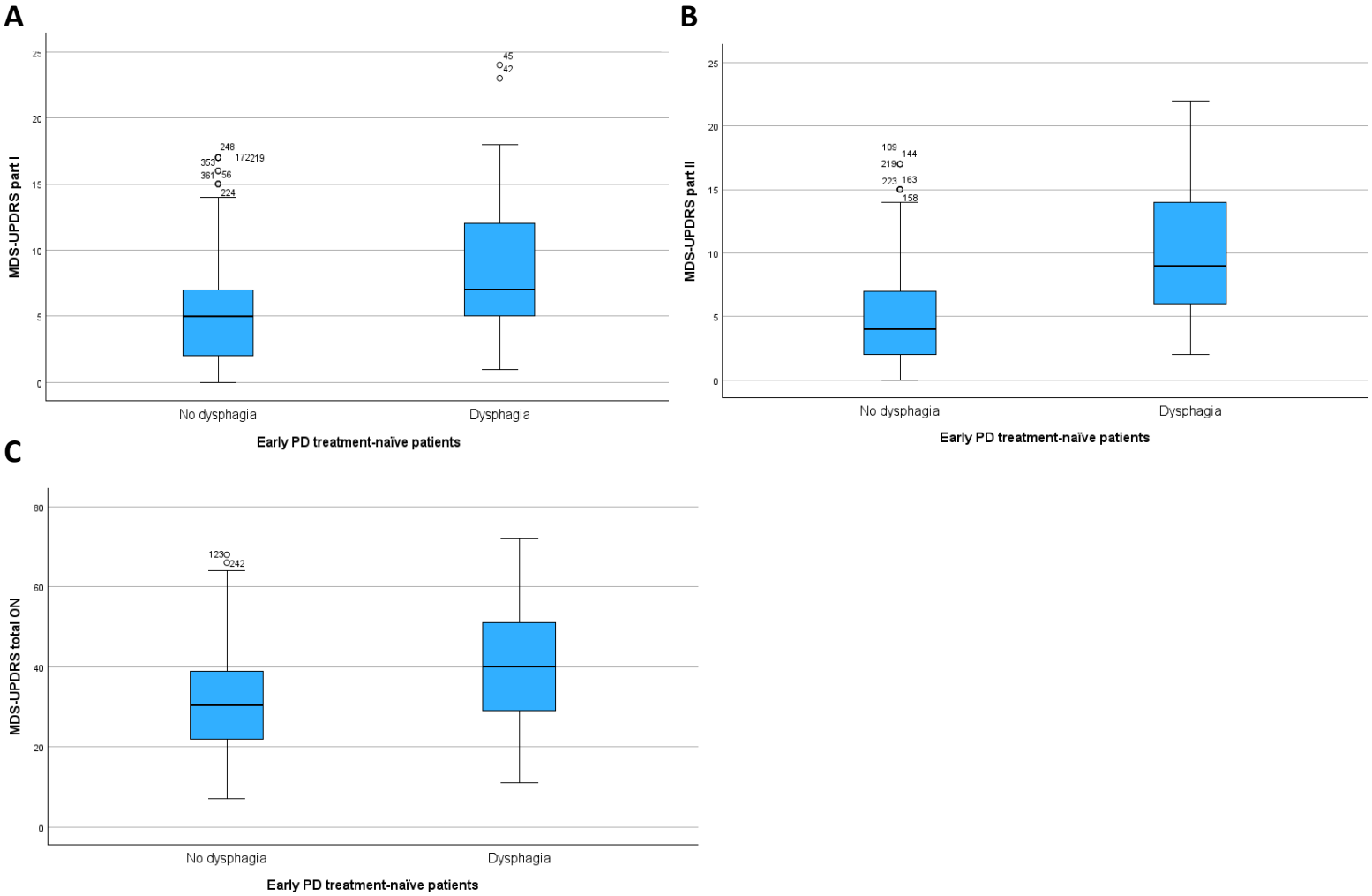
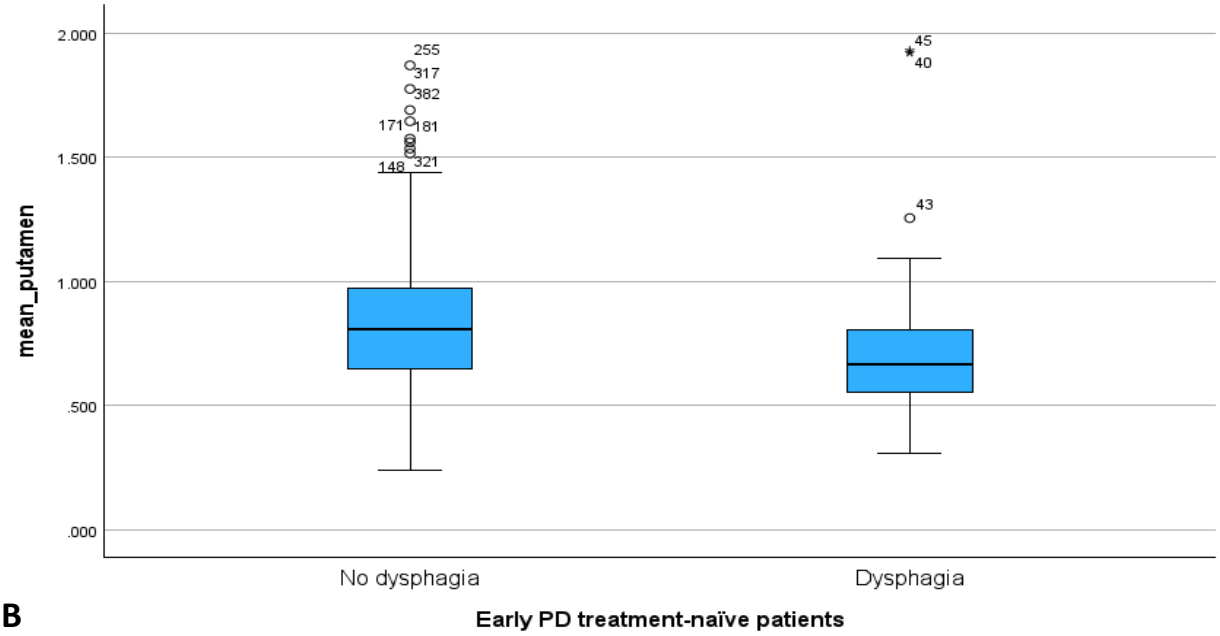
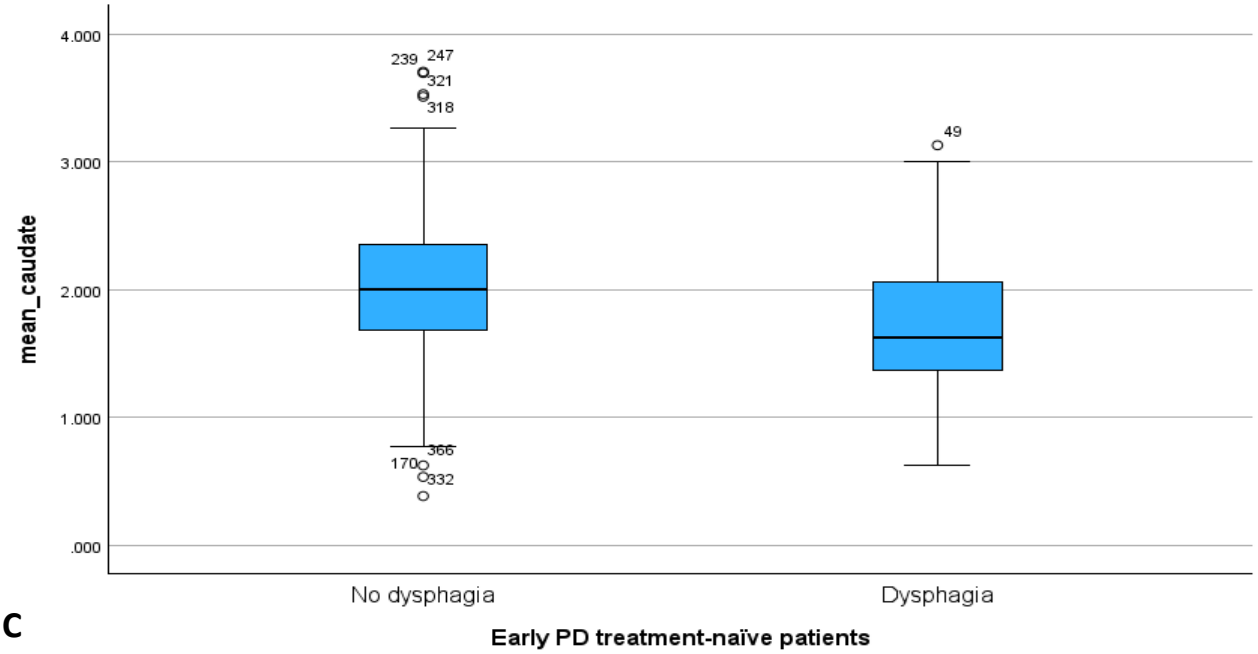


Figure 7. A) MDS-UPDRS Part I scores in early PD treatment-naive patients with and without dysphagia
B) MDS-UPDRS Part II scores in early PD treatment-naive patients with and without dysphagia.
C) MDS-UPDRS Part II scores in early PD treatment-naive patients with and without dysphagia.

A


mean_putamen
2.000
1.500
1.000
.500
.000
255
317
382
171
181
148
321
45
40
43
No dysphagia
Dysphagia
Early PD treatment-naïve patients

B


mean_caudate
4.000
3.000
2.000
1.000
.000
239
247
321
318
366
170
332
49
No dysphagia
Dysphagia
Early PD treatment-naïve patients

C

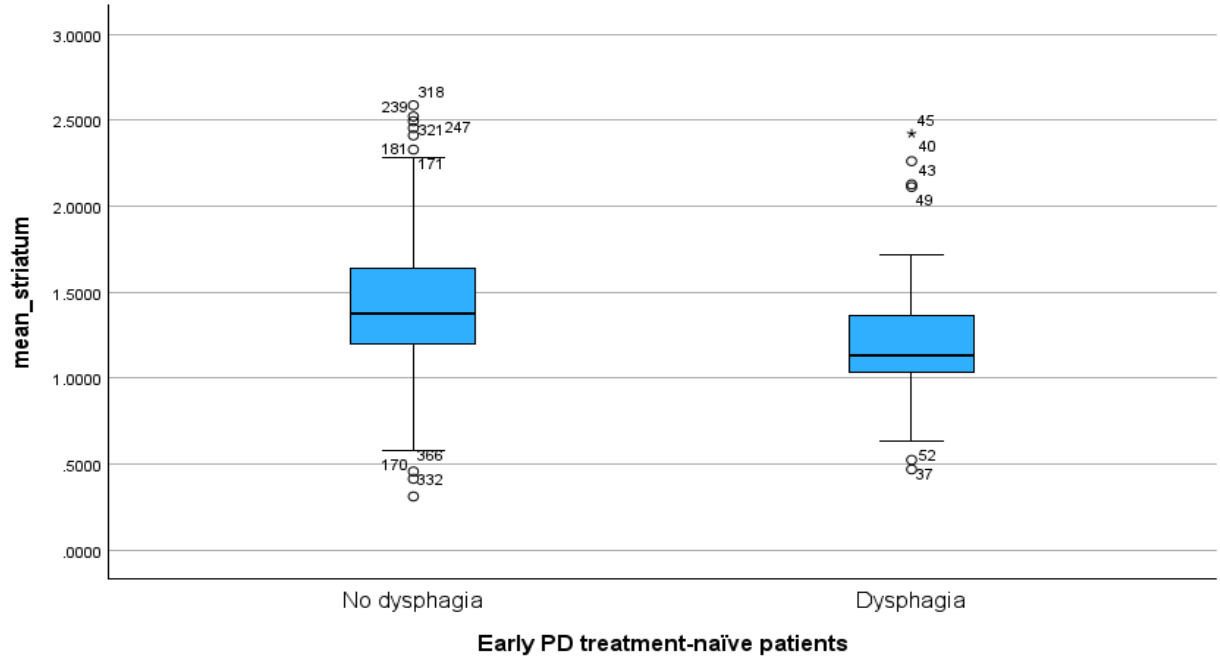

mean_striatum
3.0000
2.5000
2.0000
1.5000
1.0000
.5000
.0000
318
239
321
247
181
171
366
170
332
45
40
43
49
52
37
No dysphagia
Dysphagia
Early PD treatment-naïve patients

Figure 8. A) [^{123}I]FP-CIT SBR in bilateral caudate of early PD treatment-naive patients with and without dysphagia.

B) [^{123}I]FP-CIT SBR in bilateral putamen of early PD treatment-naive patients with and without dysphagia.

C) [^{123}I]FP-CIT SBR in bilateral striatum of early PD treatment-naive patients with and without dysphagia.

SBR=Signal-Binding-Ratio.

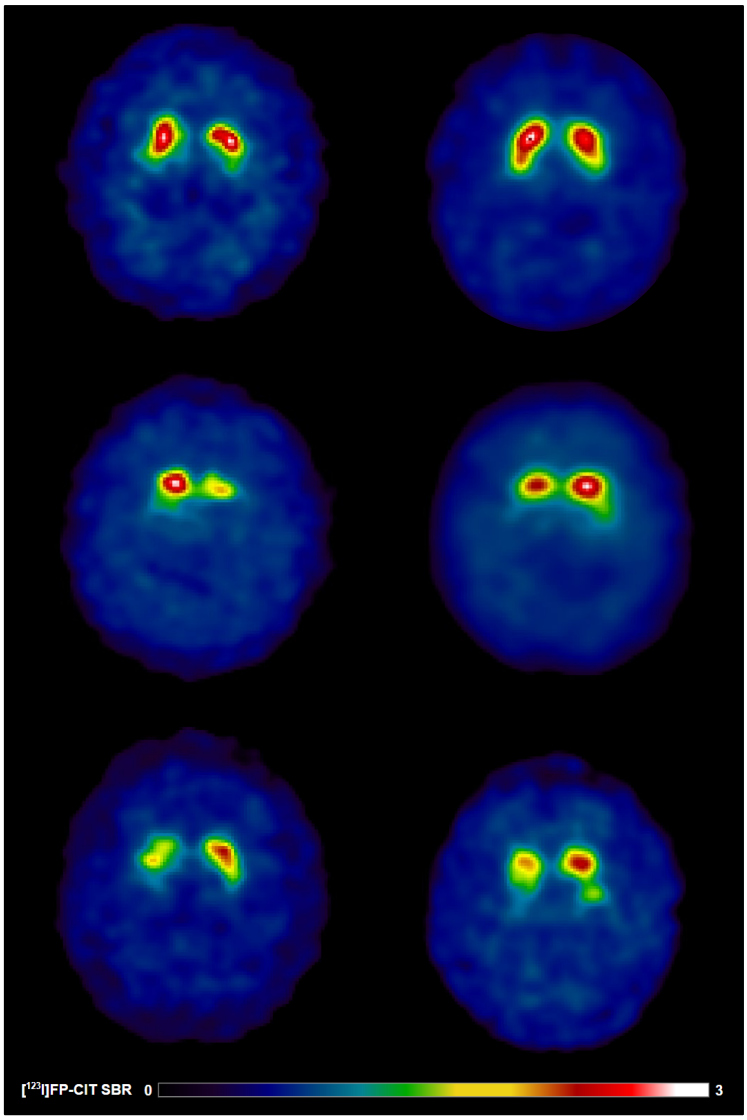


Image 3. [^{123}I]FP-CIT SPECT images in early untreated PD patients with and without dysphagia.

(Top) A 64-year-old healthy control male (left) showing typical [^{123}I]FP-CIT specific binding ratios in the caudate (SBR: 2.34) and putamen (SBR: 1.54) and a 67-year-old healthy control female (right) showing typical [^{123}I]FP-CIT specific binding ratios in the caudate (SBR: 3.01) and putamen (SBR: 1.84). **(Middle)** A 67-year-old male (left) without dysphagia exhibiting slight dopaminergic deficits as reflected by [^{123}I]FP-CIT specific binding ratios in the caudate (SBR: 1.77) and putamen (SBR: 0.58) and a 67-year-old female (right) without dysphagia exhibiting slight dopaminergic deficits as reflected by [^{123}I]FP-CIT specific binding ratios in the caudate (SBR: 2.14) and putamen (SBR: 0.83) **(Bottom)** A 67-year-old male (left) with dysphagia demonstrating larger striatal dopaminergic deficits as reflected by [^{123}I]FP-CIT specific binding ratios in the caudate (SBR: 2.6) and putamen (SBR: 1.93) and a 67-year-old male (right) with dysphagia demonstrating larger striatal dopaminergic deficits as reflected by [^{123}I]FP-CIT specific binding ratios in the caudate (SBR:1.34) and putamen (SBR: 0.74).

8.3.2 Multivariate Binary Logistic Regression analysis

The initial multivariate logistic regression included all predictors that were significant in the t-tests. However, due to high multicollinearity and redundancy among predictors, certain variables were excluded to refine the model. Specifically, neuroimaging variables were initially screened, leading to the selection of Mean Putamen as the representative marker of striatal degeneration. However, in the final regression model, Mean Putamen did not retain statistical significance, while Mean Caudate remained a significant predictor. Therefore, the final model retained the neuroimaging variable that provided the strongest independent contribution to dysphagia.

After refining the model, a final logistic regression was conducted with MDS-UPDRS Part I, MDS-UPDRS Part II, and Mean Caudate as independent predictors (Table 7). The model was statistically significant, $\chi^2(3) = 58.676$, $p < .001$, indicating that the included variables collectively distinguished between patients with and without dysphagia (Table 7). Nagelkerke's $R^2 = 0.263$ suggested that the model explained 26.3% of the variance in dysphagia (Table 7). The Hosmer-Lemeshow test was non-significant ($p = 0.463$), indicating a good model fit (Table 7).

Higher MDS-UPDRS Part I scores were significantly associated with increased odds of dysphagia (OR = 1.098, $p = 0.026$), suggesting that greater non-motor symptom burden is an independent risk factor (Table 7). Similarly, higher MDS-UPDRS Part II scores significantly increased the odds of dysphagia (OR = 1.183, $p < .001$), reinforcing the role of functional motor impairment in dysphagia development (Table 7). Additionally, lower mean caudate values were a significant predictor (OR = 0.380, $p = 0.004$), suggesting that neurodegeneration in the caudate contributes to dysphagia (Table 7).

The final model retained only significant predictors, ensuring a robust and interpretable analysis of independent risk factors for dysphagia in early PD patients. These findings highlight the importance of non-motor symptoms, functional motor impairment, and caudate degeneration in predicting dysphagia, providing further insights into disease progression in PD.

	B	S.E.	Wald	df	Sig.	Exp(B)
MDS-UPDRS part I	.093	.042	4.976	1	**0.026**	1.098
MDS-UPDRS part II	.168	.041	17.075	1	**<.001**	1.183
mean_caudate	-.969	.334	8.395	1	**0.004**	.380

Table 7. Multivariate Binary Logistic Regression analysis of predictor variables on early PD treatment-naive patients with and without dysphagia.

8.4 Dysphagia in early Parkinson's Disease levodopa-treated patients

8.4.1 T-test analyses

8.4.1.1 Demographic characteristics

Early PD levodopa-treated patient with dysphagia (N = 23) were comparable to those without dysphagia (N = 110) in age (64.7 years vs 61.2 years), sex ratio (male/female) (0.7 vs 0.7) and disease duration (5.0 months vs 5.5 months) (Table 8).

8.4.1.2 Clinical characteristics

Compared to PD patients without dysphagia, those with dysphagia had significantly worse cognitive function, as measured by MoCA (24.0 vs 26.0, p=0.001; Figure 9). Non-motor symptoms burden, as measure by MDS-UPDRS Part I, motor experiences of daily living, as measured by MDS-UPDRS Part II, motor symptom severity, as measured by MDS-UPDRS Part III and MDS-UPDRS Part III (ON-state), motor complications, as measured by MDS-UPDRS IV, overall disease severity as measured by MDS-UPDRS Total and MDS-UPDRS Total (ON-state) and H&Y did not significant differ between the groups (Table 8).

8.4.1.3 CSF Biomarkers

Compared to PD patients without dysphagia, those with dysphagia had significantly higher CSF tau (199.2 pg/mL vs 164.1 pg/mL, p = 0.042; Figure 10) and ptau (19.0 pg/mL vs 14.2 pg/mL, p = 0.005; Figure 10). No differences in CSF Aβ or α-syn were observed between the two groups (Table 8).

8.4.1.4 [^{123}I]FP-CIT SBR

No significant differences were observed in [^{123}I]FP-CIT SBR in the caudate, putamen or striatum in PD patients with dysphagia compared to those without (Table 8; Image 4).

8.4.1.5 Summary

These results indicate significant differences in CSF biomarkers, specifically Tau and phosphorylated Tau (p-Tau) levels, between early PD treatment-naïve patients with and without dysphagia. Higher levels of Tau and p-Tau were observed in the dysphagia group, suggesting a potential link to the presence of dysphagia in these patients. However, there were no significant differences in amyloid-beta (Aβ) or alpha-synuclein (α-syn) levels between the groups. Additionally, [^{123}I]FP-CIT SBR values did not reveal significant differences between the groups, indicating similar striatal dopaminergic function regardless of dysphagia status.

	Early PD levodopa-treated patients with dysphagia (N = 23)	Unavailable data's ratio (%)	Early PD levodopa-treated patients without dysphagia (N = 110)	Unavailable data's ratio (%)	*P* value
Demographic characteristics					

Age (years) [mean (±SD)]	64.67 (±8.4)	-	61.79 (±9.0)	-	0.163
Sex [mean (±SD)]	0.65 (±0.4)	-	0.68 (±0.4)	-	0.784
Disease duration (months) [mean (±SD)]	5.04 (±5.0)	-	5.45 (±6.2)	-	0.768
Cognitive performance					
MoCA [mean (±SD)]	23.87 (±4.6)	-	26.36 (±2.9)	-	**0.001**
Clinical characteristics					
MDS-UPDRS Part I [mean (±SD)]	8.52 (±5.6)	-	7.03 (±4.9)	-	0.197
MDS-UPDRS Part II [mean (±SD)]	7.78 (±4.6)	-	7.63 (±4.9)	-	0.890
MDS-UPDRS Part III [mean (±SD)]	27.35 (±8.5)	-	26.64 (±10.8)	36%	0.778
MDS-UPDRS Part III(ON-state) [mean (±SD)]	22.78 (±9.2)	-	20.46 (±9.8)	10%	0.306
MDS-UPDRS Part IV [mean (±SD)][a]	0.09 (±0.4)	-	0.02 (±0.1)	<1%	0.159
MDS-UPDRS Total [mean (±SD)]	43.65 (±14.5)	-	41.14 (±15.5)	36%	0.497
MDS-UPDRS Total (ON-state) [mean (±SD)]	39.09 (±14.5)	-	34.88 (±14.9)	10%	0.224
Holen & Yard (ON-state) [mean (±SD)]	1.83 (±0.38)	-	1.70 (±0.50)	10%	0.277
CSF biomarkers					
abeta [mean (±SD)]	744.97 (±296.0)	34%	757.57 (±279.8)	27%	0.874
tau [mean (±SD)]	199.21 (±85.5)	8%	164.05 (±65.7)	23%	**0.042**
ptau [mean (±SD)]	19.03 (±6.9)	26%	14.17 (±6.1)	30%	**0.005**

asyn [mean (±SD)]	1598.91 (±892.2)	8%	1401.04 (±553.5)	22%	0.202
[^{123}I]FP-CIT SBR					
contralateral_caudate [mean (±SD)]	1.48 (±0.4)	-	1.47 (±0.4)	<1%	0.882
ipsilateral_caudate [mean (±SD)]	1.67 (±0.5)	-	1.78 (±0.5)	<1%	0.397
mean_caudate [mean (±SD)]	1.58 (±0.4)	-	1.62 (±0.4)	<1%	0.695
contralateral_putamen [mean (±SD)]	0.57 (±0.1)	-	0.54 (±0.1)	<1%	0.549
ipsilateral_putamen [mean (±SD)]	0.65 (±0.1)	-	0.72 (±0.2)	<1%	0.227
mean_putamen [mean (±SD)]	0.61 (±0.1)	-	0.63 (±0.2)	<1%	0.619
contralateral_striatum [mean (±SD)]	2.06 (±0.5)	-	2.02 (±0.6)	<1%	0.764
ipsilateral_striatum [mean (±SD)]	2.32 (±0.7)	-	2.50 (±0.7)	<1%	0.309
mean_striatum [mean (±SD)]	1.09 (±0.3)	-	1.13 (±0.3)	<1%	0.657

Table 8. [^{123}I]FP-CIT SBR in early PD levodopa-treated patients with and without dysphagia. SBR=Signal-Binding-Ratio.

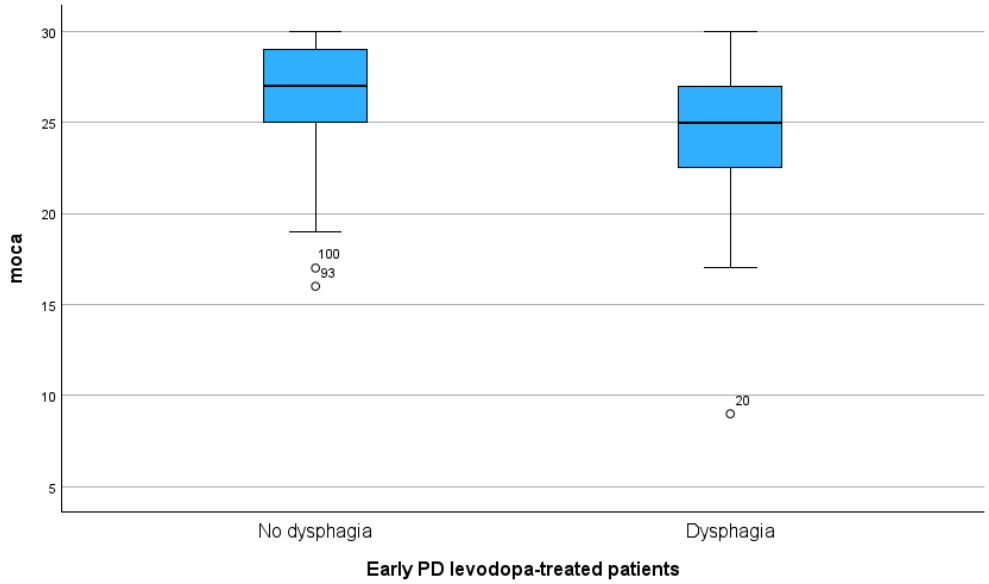


Figure 9. MoCA scores in early PD levodopa-treated patients with and without dysphagia.

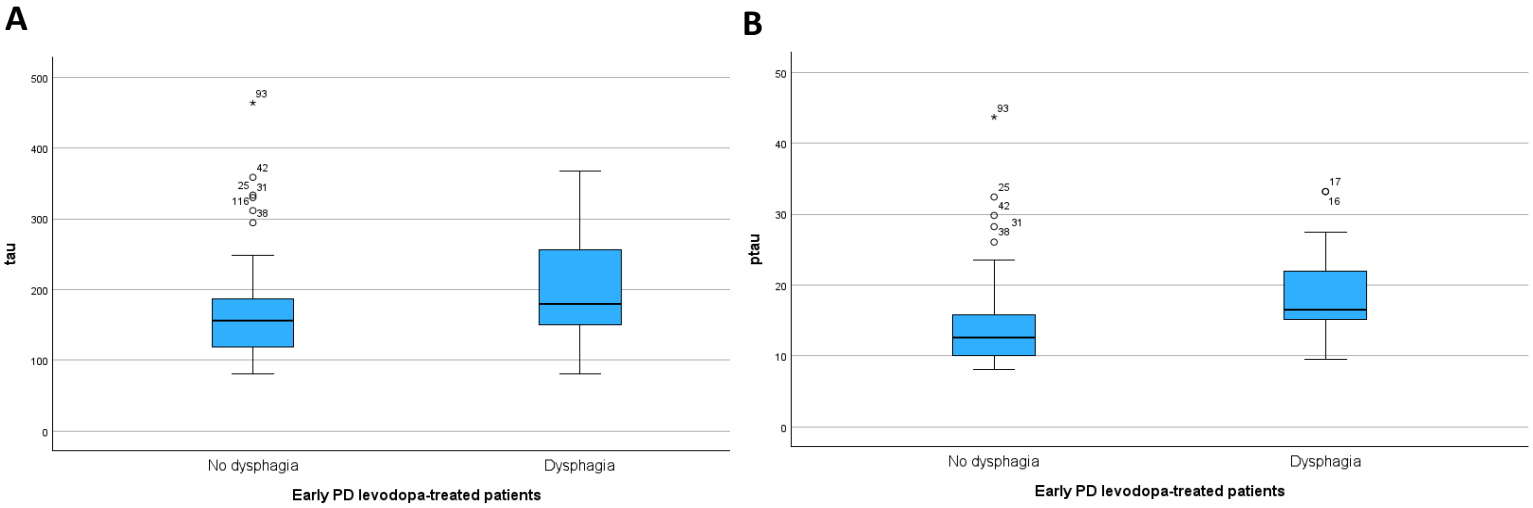


Figure 10. A) CSF tau scores in early PD levodopa-treated patients with and without dysphagia. **B)** CSF ptau scores in early PD levodopa-treated patients with and without dysphagia.

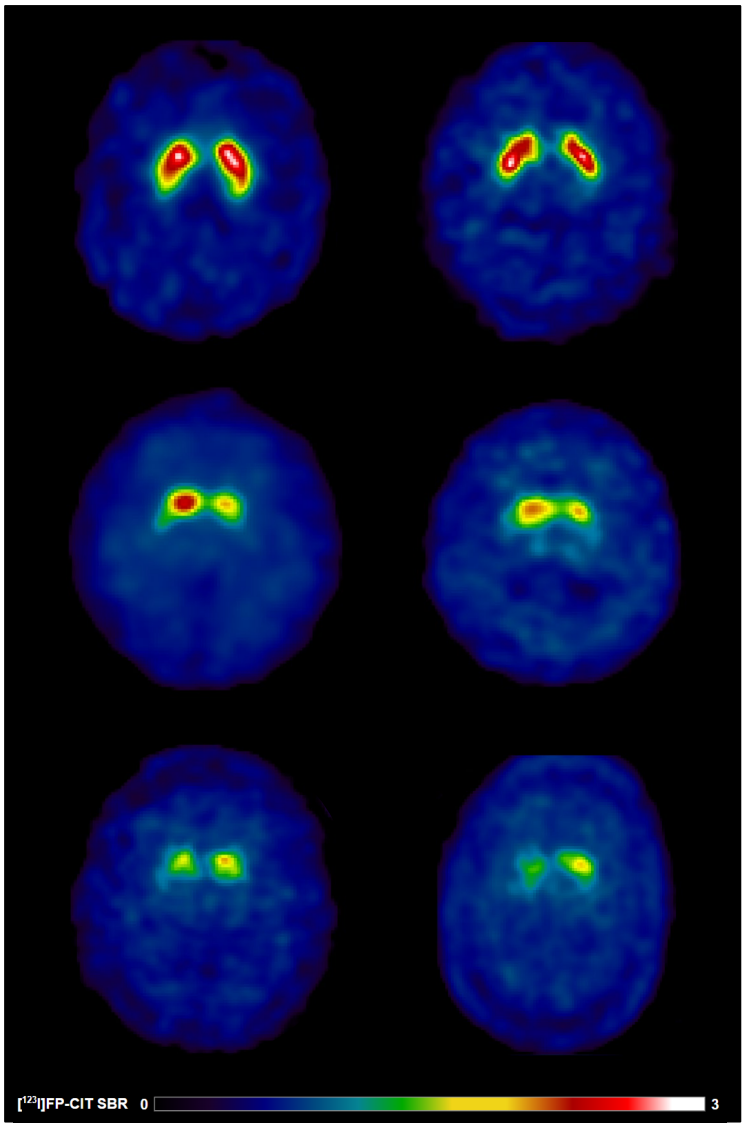


Image 4. [^{123}I]FP-CIT SPECT images in early treated PD patients with and without dysphagia.

(Top) A 66-year-old healthy control male (left) showing typical [^{123}I]FP-CIT specific binding ratios in the caudate (SBR: 3.24) and putamen (SBR: 2.62) and a 69-year-old healthy control female (right) showing typical [^{123}I]FP-CIT specific binding ratios in the caudate (SBR: 3.21) and putamen (SBR: 2.79). **(Middle)** A 66-year-old male (left) without dysphagia exhibiting slight dopaminergic deficits as reflected by [^{123}I]FP-CIT specific binding ratios in the caudate (SBR: 1.53) and putamen (SBR: 0.71) and a 69-year-old female (right) without dysphagia exhibiting slight dopaminergic deficits as reflected by [^{123}I]FP-CIT specific binding ratios in the caudate (SBR: 1.4) and putamen (SBR: 0.54). **(Bottom)** A 66-year-old male (left) with dysphagia demonstrating larger striatal dopaminergic deficits as reflected by [^{123}I]FP-CIT specific binding ratios in the caudate (SBR: 1.97) and putamen (SBR: 0.66) and a 69-year-old male (right) with dysphagia demonstrating larger striatal dopaminergic deficits as reflected by [^{123}I]FP-CIT specific binding ratios in the caudate (SBR: 1.36) and putamen (SBR: 0.71).

8.4.2 Multivariate Binary Logistic Regression analysis

The initial multivariate logistic regression included all predictors that were significant in the t-tests. However, due to high multicollinearity and redundancy among predictors, certain variables were excluded to refine the model. Specifically, neuroimaging and CSF biomarkers were initially screened, leading to the selection of pTau and MoCA for further analysis. Although MoCA was significant in the univariate analyses, it did not remain significant in the presence of pTau in the final model. Despite this, MoCA was retained to examine whether cognitive impairment had an independent contribution to dysphagia when controlling for CSF tau pathology.

After refining the model, a final logistic regression was conducted with pTau and MoCA as independent predictors (Table 9). The model was statistically significant, $\chi^2(2) = 8.734$, $p = 0.013$, indicating that the included variables collectively distinguished between patients with and without dysphagia (Table 9). Nagelkerke's $R^2 = 0.146$ suggested that the model explained 14.6% of the variance in dysphagia (Table 9). The Hosmer-Lemeshow test was non-significant ($p = 0.323$), indicating a good model fit (Table 9).

Higher pTau levels were significantly associated with increased odds of dysphagia (OR = 1.091, $p = 0.033$), suggesting that tau pathology plays a crucial role in the development of dysphagia in early PD (Table 9). In contrast, MoCA did not remain a significant predictor in the final model ($p = 0.148$, OR = 0.867), suggesting that cognitive impairment, as measured by MoCA, does not independently predict dysphagia when accounting for CSF tau pathology (Table 9).

The final model retained only significant predictors, ensuring a robust and interpretable analysis of independent risk factors for dysphagia in early PD patients. These findings highlight the importance of CSF tau pathology as a key biomarker in predicting dysphagia, while also demonstrating that cognitive function (MoCA) may not play an independent role in this association when controlling for neurodegeneration markers. This suggests that tau pathology might have a more direct effect on dysphagia than cognitive decline in this patient cohort.

	B	S.E.	Wald	df	Sig.	Exp(B)
ptau	.087	.041	4.556	1	**0.033**	1.091
moca	-.142	.098	2.089	1	0.148	.867

Table 9. Multivariate Binary Logistic Regression analysis of predictor variables on early PD levodopa-treated patients with and without dysphagia.

Chapter 9. Discussion

9.1 Speech Difficulties in Early Parkinson's Disease Treatment-Naïve and Levodopa-Treated Patients

9.1.1.1 Demographic Characteristics and Speech Difficulties in Early Parkinson's Disease Treatment-Naïve Patients

This study provides valuable insights into the demographic characteristics of early PD treatment-naïve patients with and without speech difficulties. The findings indicate that speech impairment can manifest even in *de novo* PD patients, aligning with previous research (Polychronis et al., 2019).

Age emerged as a significant predictor of speech difficulties, with an increased risk per year of age. This finding is consistent with evidence suggesting that aging contributes to reduced neuromuscular control, decreased neural plasticity, and progressive neurodegeneration, all of which exacerbate speech impairment in PD (Brabenec et al., 2017; Kent & Rosen, 2004). Older PD patients may also struggle with compensatory mechanisms as basal ganglia and cortical degeneration worsen, further affecting speech motor control (Simonyan & Horwitz, 2011). While Polychronis et al. (2019) found no significant age differences between PD patients with and without speech difficulties, they did report a higher prevalence of speech impairment in those with the akinetic-rigid motor subtype.

Sex differences were also explored, revealing that males were more prevalent in the group with speech difficulties. However, sex was not a significant predictor when accounting for motor severity and neurodegeneration, suggesting that speech difficulties occur at similar rates in men and women. While some studies indicate that male PD patients may experience greater reductions in vocal intensity, these differences often become negligible when controlling for disease severity (Skodda et al., 2012).

Despite these demographic differences, disease duration was comparable between the two groups, consistent with previous findings (Polychronis et al., 2019). This suggests that speech difficulties in early PD treatment-naïve patients may be more closely associated with aging and motor phenotype rather than the length of disease progression.

9.1.1.2 Demographic Characteristics and Speech Difficulties in Early Parkinson's Disease Levodopa-Treated Patients

Similarly, this study explores the demographic characteristics of early PD levodopa-treated patients with and without speech difficulties. The findings confirm that speech impairment can occur even in this cohort, in line with previous research (Martínez-Sánchez et al., 2016). However, unlike in treatment-naïve patients, no significant differences were observed in age, sex ratio, or disease duration between levodopa-treated patients with and without speech difficulties, a pattern also reported in earlier studies (Martínez-Sánchez et al., 2016).

The absence of significant demographic differences in this group suggests that factors beyond age and sex, such as treatment effects, motor phenotype, or underlying neurodegenerative processes, may play a more prominent role in speech impairment. While aging remains a key factor influencing neuromuscular decline and speech motor control in PD, levodopa treatment may attenuate some of these effects, potentially masking differences observed in treatment-naïve patients.

9.1.1.3 Summary

This study highlights that speech difficulties can emerge in early PD patients regardless of treatment status. In treatment-naïve patients, age was a significant predictor of speech impairment, likely due to age-related neuromuscular decline and progressive neurodegeneration. Additionally, while more males presented with speech difficulties, sex was not a significant predictor when considering motor severity. In contrast, no significant demographic differences were observed in levodopa-treated patients, suggesting that dopaminergic treatment may influence the relationship between age, sex, and speech impairment. These findings emphasize the complexity of speech difficulties in PD and the need to consider multiple interacting factors.

Factor	Treatment-Naïve Patients	Levodopa-Treated Patients
Speech Impairment	Present in *de novo* PD	Present in treated PD
Age	Significant predictor of speech difficulties	No significant differences observed
Sex	Males more prevalent but not a significant predictor	No significant differences observed
Disease Duration	Comparable between groups	Comparable between groups
Potential Influences	Aging, neuromuscular decline, motor phenotype	Treatment effects, motor phenotype, neurodegeneration

Table 10. Summary of demographic characteristics and their associations with speech difficulties in early PD treatment-naïve and levodopa-treated patients.

9.1.2.1 Clinical Characteristics and Speech Difficulties in Early Parkinson's Disease Treatment-Naïve Patients

The findings of this study reveal that early PD treatment-naïve patients with speech difficulties demonstrate significantly higher scores across multiple subscales of the MDS-UPDRS. Specifically, these patients exhibited elevated scores on:

- MDS-UPDRS Part I, reflecting greater severity of non-motor symptoms,
- MDS-UPDRS Part II, indicating a more pronounced burden on motor experiences of daily living,
- MDS-UPDRS Part III (both ON and OFF medication), suggesting more severe motor symptoms, including bradykinesia, rigidity, and tremor,
- H&Y scale (ON medication), pointing to higher severity and progression of motor symptoms, and

- MDS-UPDRS Total (both ON and OFF medication), representing a worse overall profile of motor and non-motor symptoms.

Of particular note, higher MDS-UPDRS Part III ON scores were significantly associated with speech difficulties, reinforcing the role of motor impairment in speech dysfunction. This aligns with the well-established understanding of hypokinetic dysarthria as a motor speech disorder in PD, primarily caused by bradykinesia, rigidity, and reduced coordination in respiratory and articulatory muscles (Ho et al., 1998; Duffy, 2013). Furthermore, speech dysfunction in PD has been strongly associated with axial motor symptoms (e.g., rigidity and bradykinesia) rather than tremor (Tykalová et al., 2014). This is further supported by Polychronis et al. (2019), who found that speech difficulties were significantly more prevalent in akinetic-rigid PD patients compared to tremor-dominant patients (69.9% vs. 18.9%), highlighting the dominant role of bradykinesia in speech impairment.

Interestingly, Hoehn & Yahr (ON) was not a significant predictor of speech difficulties, suggesting that speech impairment is not solely a function of overall disease stage. This is consistent with previous findings indicating that speech difficulties do not necessarily correlate with global PD progression but are instead linked to localized neural degeneration affecting motor speech control (De Letter et al., 2007). However, cognitive performance, as measured by the MoCA, did not significantly differ between patients with and without speech difficulties.

9.1.2.2 Clinical Characteristics and Speech Difficulties in Early Parkinson's Disease Levodopa-Treated Patients

Similarly, early PD levodopa-treated patients with speech difficulties showed significantly higher scores on several MDS-UPDRS subscales. These patients scored higher on:

- MDS-UPDRS Part II, indicating a greater burden on motor experiences of daily living,
- MDS-UPDRS Part III (both ON and OFF medication), reflecting more severe motor symptoms, such as bradykinesia, rigidity, and tremor,
- H&Y scale (ON medication), suggesting higher severity and progression of motor symptoms, and
- MDS-UPDRS Total (both ON and OFF medication), representing a worse overall profile of motor and non-motor symptoms.

Notably, MDS-UPDRS Part III ON scores (motor impairment in the medicated state) emerged as a strong predictor of speech difficulties. This aligns with previous findings that motor impairments, particularly bradykinesia and rigidity, significantly impact speech articulation and phonation in PD (Ho et al., 1998). While levodopa therapy improves general motor function, its effects on speech are inconsistent, with many patients continuing to experience persistent speech difficulties despite improvements in limb motor symptoms (Duffy, 2013).

Interestingly, Hoehn and Yahr stage (H&Y ON) and UPDRS Part II were not retained in the final regression model. Although these variables were significant in univariate tests, their effects overlapped with MDS-UPDRS Part III ON and mean putamen values. This suggests that while H&Y staging reflects overall disease progression, it may not accurately predict speech impairment when motor function is already accounted for (De Letter et al., 2007). In contrast, no significant differences were observed in other MDS-UPDRS subscales (i.e., Part I and Part IV) or in cognitive performance as measured by the MoCA between the two groups.

9.1.2.3 Summary

This study demonstrates that speech difficulties in both early PD treatment-naïve and levodopa-treated patients are closely associated with increased motor severity, particularly in MDS-UPDRS Part III ON scores. While Hoehn & Yahr staging was not a significant predictor in either group, these findings emphasize that speech impairment is primarily driven by motor dysfunction rather than overall disease stage. Cognitive function did not significantly differ between groups, supporting the notion that speech difficulties in early PD are predominantly motor-driven.

Factor	Treatment-Naïve Patients	Levodopa-Treated Patients
Speech Impairment	Associated with higher motor severity	Associated with higher motor severity
MDS-UPDRS Part I	Significantly higher (non-motor symptoms)	No significant differences
MDS-UPDRS Part II	Increased burden on daily motor function	Greater burden on daily motor function
MDS-UPDRS Part III ON	Strong predictor of speech difficulties	Strong predictor of speech difficulties
H&Y Scale (ON)	Not a significant predictor	Not retained in final model
MoCA	No significant differences	No significant differences

Table 11. Summary of clinical characteristics and their associations with speech difficulties in early PD treatment-naïve and levodopa-treated patients.

9.1.2.4 Literature Context: Clinical Characteristics and Speech Difficulties in Early Parkinson's Disease

9.1.2.4.1 The Effect of Motor Symptoms

Speech impairment in PD is closely linked to the severity of overall motor dysfunction. The underlying mechanism for this relationship involves the disruption of motor control networks responsible for coordinating speech production components, including respiration, phonation, articulation, resonance, and prosody (Moreau & Pinto, 2019; Polychronis et al., 2019).

Speech difficulties in PD are more prevalent in patients with an akinetic-rigid motor phenotype than in those with a tremor-dominant phenotype (Polychronis et al., 2019). Akinetic-rigid symptoms, such as bradykinesia and rigidity, directly impact the motor control of speech musculature. Notably, the progression of speech impairment in PD

often occurs independently of overall motor symptom progression, indicating the role of non-dopaminergic pathways in speech dysfunction.

Longitudinal studies have highlighted the relationship between speech impairment and motor symptoms in PD. For instance, Rusz et al. (2016) found that poorer speech performance, assessed through quantitative acoustic measures and UPDRS-III item 3.1 (speech), was associated with higher UPDRS-III motor scores, particularly bradykinesia subscores. At follow-up, improvements in speech were significantly linked to dopamine replacement therapy, correlating with overall motor function improvements, especially bradykinesia (Rusz et al., 2016).

Additionally, research has identified a strong relationship between speech impairments and axial symptoms, particularly freezing of gait, in moderate PD patients receiving dopamine replacement therapy (Skodda et al., 2012; Park et al., 2014; Skodda et al., 2011). In advanced stages, speech dysfluency is increasingly recognized as a motor speech control disorder, potentially sharing underlying pathophysiological mechanisms with freezing of gait (Ricciardi et al., 2016).

9.1.2.4.2 The Effect of Non-Motor Symptoms

Beyond motor symptoms, speech difficulties in PD are also associated with non-motor symptoms. Polychronis et al. (2019) found that early PD treatment-naïve patients with speech difficulties exhibited more severe non-motor symptoms than those without speech difficulties. These patients demonstrated greater autonomic dysfunction, increased daytime sleepiness, and a higher occurrence of REM sleep behavior disorder (RBD) symptoms. However, there were no significant differences in anxiety, depression, or cognitive function between the two groups at baseline. Interestingly, speech difficulties were linked to a higher risk of cognitive decline over time, though they did not affect motor symptom progression over a three-year follow-up period (Polychronis et al., 2019).

These findings highlight that speech impairment in PD extends beyond motor dysfunction, encompassing non-motor symptoms that may influence disease progression and quality of life.

9.1.2.4.3 The Effect of Cognitive Performance

Cognitive performance plays a significant role in speech and communication difficulties in PD. Deficits in temporal processing, attention, working memory, and executive function impact speech production and language use, leading to disruptions in connected speech, communication breakdowns, and social withdrawal.

9.1.2.4.3.1 Temporal Processing and Neural Networks

PD disrupts temporal processing in both motor and perceptual systems, affecting speech production and cognitive assessments (Johari & Behroozmand, 2018; Singh et al., 2021). Neuroimaging studies have revealed decreased connectivity and blood flow in fronto-striatal and parietal networks, impairing motor behavior and speech control (Burton et al., 2004; Kendi et al., 2008). Altered neural connections also affect

phonological planning and sequencing, which are crucial for detecting speech errors (Manes et al., 2018).

9.1.2.4.3.2 Speech Impairments as Predictors of Cognitive Decline

Speech impairments may serve as early markers of cognitive decline. Gago et al. (2009) found that the progression of speech impairment, measured by the UPDRS-III speech item, was a strong predictor of dementia development over six years in early-stage PD. Rektorova et al. (2016) demonstrated that variations in fundamental voice frequency and speech rhythmicity could predict cognitive status changes with 73.2% accuracy over two years.

9.1.2.4.3.3 Working Memory and Attention in Connected Speech

PD-related deficits in working memory and attention impact speech fluency, lexical retrieval, and syntactic complexity (Cotelli et al., 2007; Lieberman et al., 1992). Patients exhibit longer pauses, more grammatical errors, and fewer information units in connected speech (Roberts & Post, 2018). Episodic memory deficits further exacerbate these difficulties, as demonstrated by increased disfluency in story retelling compared to picture descriptions (Roberts, 2014).

9.1.2.4.3.4 Cognitive Demands and Motor Speech Impairments

Motor speech impairments, particularly hypokinetic dysarthria, occur in 70–90% of PD patients (Ramig et al., 2008). Speech timing deficits worsen under higher cognitive loads, such as spontaneous speech tasks compared to reading (Huber & Darling-White, 2017; Lowit et al., 2018). These findings highlight the need to assess both cognitive and motor factors when evaluating speech difficulties in PD.

9.1.2.4.3.5 Conversations and Communication Challenges

PD patients frequently report difficulties in conversation due to cognitive and motor impairments (Miller, 2017; Wolff & Benge, 2019). Overlapping speech, prolonged pauses, and lower voice volume contribute to communication breakdowns (Griffiths et al., 2012; Rinne & Roberts, 2019). Semantic and syntactic difficulties, such as vague language and word retrieval issues, further impact social interactions (Saldert et al., 2014; Saldert & Bauer, 2017).

9.1.2.4.3.6 Social Cognition and Non-Verbal Communication

PD affects social cognition, leading to difficulties in interpreting emotional and prosodic cues (Dara et al., 2008; Pell et al., 2014; Schwartz and Pell, 2017). Non-verbal communication is also impaired due to hypomimia (reduced facial expressions) and diminished spontaneous gestures, making interactions more challenging (Prenger et al., 2020; Gomez et al., 2023).

9.1.2.4.3.7 Implications for Functional Communication

Cognitive impairments substantially influence functional communication in PD, affecting speech, language, and social interaction. The interplay between motor, cognitive, and linguistic impairments necessitates a comprehensive methodology for evaluating and addressing communication needs.

9.1.2.4.3.8 Summary

Speech difficulties in PD are influenced by motor, non-motor, and cognitive factors. Akinetic-rigid motor symptoms, particularly bradykinesia and rigidity, are strongly associated with speech impairments, whereas tremor-dominant patients are less affected. Speech impairments may progress independently of global motor symptoms, indicating potential involvement of non-dopaminergic pathways. Non-motor symptoms such as autonomic dysfunction and REM sleep disturbances also contribute to speech difficulties. Additionally, cognitive deficits, including impaired temporal processing, working memory, and attention, significantly impact speech and language abilities. Speech impairments may serve as early markers of cognitive decline, with increased speech disfluencies correlating with worsening cognitive function. PD patients experience communication breakdowns due to word retrieval deficits, prolonged pauses, and reduced non-verbal expressiveness. These challenges highlight the need for comprehensive assessments that consider both cognitive and motor contributions to speech impairment.

Factor	**Effect on Speech Impairment in PD**
Motor Symptoms	Akinetic-rigid subtype more affected than tremor-dominant subtype
Bradykinesia & Rigidity	Strong predictors of speech difficulties
Dopamine Therapy	Improves motor symptoms but has inconsistent effects on speech
Freezing of Gait	Associated with speech impairments in moderate to advanced PD
Autonomic Dysfunction	More severe in patients with speech difficulties
REM Sleep Behavior Disorder	Higher prevalence in patients with speech impairments
Temporal Processing	Disrupts motor and perceptual speech timing
Neural Networks	Decreased connectivity in fronto-striatal and parietal regions
Speech as Predictor of Cognitive Decline	Speech impairment progression predicts dementia
Working Memory & Attention	Impacts verbal fluency and syntactic complexity
Cognitive Load	Worsens speech timing and coordination
Conversation Challenges	Increased speech overlaps and pauses
Social Cognition	Difficulty interpreting emotions and prosody
Non-Verbal Communication	Reduced facial expressions and gestures

Table 12. Literature summary of clinical characteristics and their associations with speech difficulties in early PD treatment-naïve and levodopa-treated patients.

9.1.3.1 CSF Biomarkers and Speech Difficulties in Early Parkinson's Disease Treatment-Naïve Patients

The present findings indicate no significant differences in the examined CSF biomarkers between early PD treatment-naïve patients with and without speech difficulties. This suggests that the mechanisms underlying speech impairment in early PD may not be directly linked to the pathological processes reflected by these specific biomarkers.

Although CSF biomarkers were not directly analysed in this model, previous research suggests that neuroinflammation and neurodegeneration-related biomarkers (e.g., α-synuclein, tau, amyloid-beta) may contribute to speech difficulties. Specifically:

- Lower CSF α-synuclein levels have been correlated with worsening motor function, which may extend to speech-related brain regions (Hall et al., 2015).
- CSF tau and amyloid-beta levels have been associated with cognitive decline, potentially impairing motor planning and executive function, which are critical for speech production (Montembeault et al., 2016).
- Neuroinflammatory markers such as IL-6 and TNF-α have been linked to worsening motor and non-motor symptoms, which may also negatively affect speech production (Brockmann et al., 2016).

These findings suggest that while no direct associations were observed in the present study, it remains possible that more subtle interactions between neurodegenerative processes and speech function exist. Incorporating longitudinal designs and multimodal biomarkers may provide deeper insights into the complex interplay between neuroinflammation, cognitive function, and motor control in early PD speech impairment.

9.1.3.2 CSF Biomarkers and Speech Difficulties in Early Parkinson's Disease Levodopa-Treated Patients

Similarly, the analysis of CSF biomarkers in early PD patients receiving levodopa treatment revealed no significant differences between those with and without speech difficulties. Levels of amyloid-beta, tau, phosphorylated tau (p-Tau), and alpha-synuclein (α-syn) were comparable across both groups, suggesting that these specific biomarkers may not play a direct role in the pathophysiology of speech impairment in PD.

Although CSF biomarkers were not directly included in the regression model, their established relevance to neurodegeneration suggests a potential indirect effect on speech difficulties. Previous studies have shown:

- Lower CSF α-synuclein levels and elevated neuroinflammatory markers (e.g., IL-6, TNF-α) are associated with neurodegeneration and motor decline, which may contribute to speech impairments (Hall et al., 2015; Brockmann et al., 2016).
- Abnormalities in amyloid-beta and tau proteins, commonly observed in neurodegenerative diseases, have been linked to cognitive and speech impairments in PD, particularly in later stages (Montembeault et al., 2016).

While no direct relationships between these biomarkers and speech impairment were identified in this study, it remains possible that levodopa treatment modulates speech-related neural pathways in ways not captured by CSF biomarker analysis alone. Investigating interactions between levodopa response, biomarker changes, and functional neuroimaging findings may help clarify the underlying mechanisms contributing to speech difficulties in treated PD patients.

9.1.3.3 Summary

The findings indicate no significant differences in CSF biomarkers between early PD treatment-naïve and levodopa-treated patients with and without speech difficulties. While direct links between these biomarkers and speech impairment were not identified, previous research suggests that neuroinflammatory and neurodegenerative markers such as α-synuclein, tau, and amyloid-beta may contribute to motor decline and cognitive dysfunction, both of which are relevant to speech impairment. In treatment-naïve patients, neuroinflammatory markers may play a role in worsening motor symptoms, indirectly impacting speech function. In levodopa-treated patients, potential interactions between dopaminergic treatment, neurodegenerative processes, and speech-related neural pathways warrant further investigation. Future studies using longitudinal and multimodal biomarker approaches may provide deeper insights into the complex mechanisms underlying speech impairment in PD.

Biomarker	Potential Effect on Speech Impairment
α-Synuclein	Lower levels linked to motor decline, potentially affecting speech regions
Tau & Amyloid-Beta	Associated with cognitive decline, impairing motor planning and speech production
IL-6 & TNF-α	Linked to worsening motor and non-motor symptoms, possibly affecting speech
Dopaminergic Treatment	May modulate neural pathways related to speech but requires further study

Table 13. Summary of CSF biomarker associations with speech difficulties in early PD treatment-naïve and levodopa-treated patients.

9.1.3.4 Literature Context: CSF Biomarkers and Speech Difficulties in Early Parkinson's Disease

9.1.3.4.1 The Effect of CSF Biomarkers

Previous studies have highlighted the association between cognitive impairment, amyloid-beta pathology, and the accelerated decline of alpha-synuclein levels in PD, contributing to faster neurodegeneration and cognitive deterioration (Baek et al., 2021). According to Baek et al. (2021), cerebrospinal fluid (CSF) levels of α-synuclein and amyloid-beta (Aβ) decline in a negative exponential pattern even before the onset of motor symptoms. Simultaneously, levels of total tau (t-tau), phosphorylated tau (p-tau), and neurofilament light chain (NfL) increase in both CSF and serum.

Cognitive impairment seems to expedite biomarker alterations, resulting in a more significant reduction in Aβ and α-syn levels, as well as heightened increases in t-tau, p-tau, and NfL relative to those without cognitive dysfunction. Likewise, PD patients with diminished baseline Aβ levels demonstrate faster declines in α-syn, accelerated rises in t-tau, p-tau, and NfL, and more rapid cognitive decline compared to those with elevated baseline Aβ (Baek et al., 2021). These findings suggest that cognitive impairment and initial Aβ burden influence the trajectory of biomarker progression, making PD patients with Aβ pathology more susceptible to early α-synuclein

abnormalities, accelerated axonal damage, and heightened neurodegeneration, ultimately leading to faster cognitive decline.

However, the present findings suggest that the presence of speech difficulties alone, in the absence of cognitive deficits, may not necessarily follow this pattern of biomarker changes. This raises the possibility that speech difficulties in early PD may be more closely linked to motor and neurophysiological dysfunction rather than the proteinopathies typically associated with cognitive decline. Further research is needed to determine whether distinct neurobiological mechanisms underlie speech impairment in early PD, independent of cognitive deterioration.

9.1.3.4.2 Summary

Research indicates that CSF biomarkers, particularly α-synuclein, amyloid-beta, tau, and neurofilament light chain, play a crucial role in the progression of cognitive impairment in PD. Cognitive decline is associated with lower baseline Aβ and α-synuclein levels and increased tau-related markers, which accelerate neurodegeneration. However, speech difficulties in early PD, when cognitive deficits are absent, may not follow the same biomarker trajectory. Instead, speech impairment may be more closely linked to motor dysfunction and neurophysiological changes.

Biomarker	Associated Effect on PD Progression
α-Synuclein	Lower levels linked to motor and cognitive decline
Amyloid-Beta	Declining levels associated with cognitive impairment
Total Tau & p-Tau	Increased levels correlate with neurodegeneration and cognitive decline
Neurofilament Light Chain (NfL)	Higher levels indicate axonal damage and disease progression
Speech Impairment	May be linked more to motor dysfunction than cognitive decline

Table 13. Literature summary of CSF biomarker associations with speech difficulties and cognitive decline in early PD treatment-naïve and levodopa-treated patients.

9.1.4.1 Dopaminergic Alterations and Speech Difficulties in Early Parkinson's Disease Treatment-Naïve Patients

The findings indicate significant differences in [^{123}I]FP-CIT SBR values between early PD treatment-naïve patients with and without speech difficulties, suggesting that impairments in speech production may be linked to striatal dopaminergic deficits in both the caudate and the putamen. These results highlight the potential role of nigrostriatal dysfunction in the emergence of speech difficulties in early PD, reinforcing the idea that speech impairments may stem from broader motor control deficits associated with dopamine depletion.

Regression analysis further supports this association, revealing that lower mean putamen values were a significant predictor of speech difficulties, reinforcing the role of basal ganglia dysfunction in speech impairment. The putamen plays a central role in speech motor regulation, and its degeneration disrupts articulation, timing, and speech fluency (Simonyan & Horwitz, 2011; Pinto et al., 2004). Neuroimaging studies

have shown that putaminal atrophy is associated with reduced dopamine transporter activity, which has been linked to worsening speech symptoms in PD (Polychronis et al., 2019).

Despite the well-documented role of dopaminergic loss in motor impairment, speech deficits in PD often persist even with levodopa treatment, suggesting that speech control relies on both dopaminergic and non-dopaminergic pathways. Levodopa therapy has shown limited benefits for speech, as motor speech control involves complex circuits beyond the basal ganglia (Mollaei et al., 2013). De Letter et al. (2007) reported that while levodopa improved limb motor symptoms, it had minimal impact on speech articulation and intelligibility. These findings highlight the need to investigate additional neural mechanisms contributing to speech dysfunction in PD beyond dopaminergic depletion alone.

9.1.4.2 Dopaminergic Alterations and Speech Difficulties in Early Parkinson's Disease Levodopa-Treated Patients

Similar findings were observed in early PD levodopa-treated patients, where significant differences in [^{123}I]FP-CIT SBR values were detected between those with and without speech difficulties. This suggests that striatal dopaminergic deficits, particularly in the putamen, play a key role in speech production impairments.

Regression analysis confirmed that lower mean putamen values were a significant predictor of speech difficulties, reinforcing the role of dopaminergic neurodegeneration in speech impairment. The putamen is essential for regulating motor control, including speech articulation, and its degeneration disrupts speech fluency and coordination (Simonyan & Horwitz, 2011).

Neuroimaging studies have demonstrated that dopamine depletion in the putamen correlates with reduced speech volume (hypophonia) and articulation deficits in PD patients (Pinto et al., 2004; Mollaei et al., 2013). Although levodopa therapy partially restores dopamine levels in the putamen, speech motor control appears to involve non-dopaminergic pathways as well. This may explain why speech difficulties persist despite medication, highlighting the complexity of speech regulation in PD (Duffy, 2013).

9.1.4.3 Summary

The findings suggest that speech difficulties in early PD, both in treatment-naïve and levodopa-treated patients, are associated with striatal dopaminergic deficits, particularly in the putamen. Regression analysis indicates that lower mean putamen values predict speech difficulties, reinforcing the role of basal ganglia dysfunction in speech motor control. While levodopa therapy improves general motor symptoms, its effects on speech are limited, suggesting the involvement of non-dopaminergic pathways in speech regulation. These findings highlight the intricacy of speech impairments in PD and the necessity for additional investigation into different brain processes that contribute to speech dysfunction.

Factor	Effect on Speech Impairment in PD
Striatal Dopaminergic Deficits	Associated with speech production impairments
Putamen Degeneration	Predicts reduced speech fluency and articulation
Dopamine Transporter Activity	Correlates with worsening speech symptoms
Levodopa Therapy	Improves limb motor function but has limited effects on speech
Non-Dopaminergic Pathways	May contribute to persistent speech difficulties

Table 14. Literature summary of dopaminergic alterations and their associations with speech difficulties in early PD treatment-naïve and levodopa-treated patients.

9.1.4.4 Literature Context: Dopaminergic alterations and speech difficulties in Early Parkinson's Disease

9.1.4.4.1 Imaging Assessment

Consistent with the findings of the present study, previous research has shown that early PD treatment-naïve patients with speech difficulties exhibit significantly lower striatal [^{123}I]FP-CIT uptake compared to those without speech difficulties, suggesting that reduced presynaptic dopaminergic function is associated with greater speech impairment (Polychronis et al., 2019). Notably, differences in dopaminergic function between PD patients with and without speech difficulties do not appear to be solely responsible for the more severe clinical symptoms or motor profiles observed in those with speech difficulties, as these differences persist even after accounting for clinical covariates (Polychronis et al., 2019).

Earlier neuroimaging studies using positron emission tomography (PET) (Liotti et al., 2003; Narayana et al., 2009, 2010; Pinto et al., 2004) and functional MRI (fMRI) (Elfmarkova et al., 2016; Maillet et al., 2012) have demonstrated that speech difficulties in PD are associated with abnormal activity in the basal ganglia–cerebellum–cortex circuit. These alterations involve differences in the engagement of the orofacial motor cortex, supplementary motor cortex, and cerebellum, as well as increased activation of the premotor and prefrontal cortices in PD patients undergoing dopamine replacement therapy with moderate disease severity.

Specifically, Elfmarkova et al. (2016) used fMRI to investigate the effects of levodopa on resting-state functional connectivity in patients during ON and OFF medication phases, focusing on speech prosody. Their findings imply that levodopa-induced alterations in connectivity between the caudate and dorsolateral prefrontal cortex correlate with enhancements in speech, indicating a possible association between dopamine deprivation and speech impairments in PD. Conversely, Skodda et al. (2011) investigated the influence of levodopa on speech, using a syllable repetition task, and discovered no substantial effect on speech rate, implying that the basal ganglia circuits responsible for regulating speech motor programs may not respond to short-term dopamine stimulation.

The findings indicate that although dopaminergic insufficiency contributes to speech difficulties in PD, the underlying brain mechanisms are complex and likely encompass broader motor and cognitive networks beyond the basal ganglia. Additional investigations employing multimodal neuroimaging techniques may help elucidate the specific contributions of these circuits to speech dysfunction in PD.

9.1.4.4.2 Pathomechanisms and Compensatory Efforts in Parkinson's disease

Consistent with the current study's findings, previous research has identified key pathomechanisms underlying speech difficulties in PD and the compensatory efforts employed to mitigate these deficits. Arnold et al. (2013) used functional MRI (fMRI) to compare speech-related brain activity and connectivity in early-stage PD patients without overt speech symptoms and matched controls. Their results indicated that while both groups activated prefrontal regions and the caudate nucleus (CN) during speech preparation, PD patients exhibited significant hypo-connectivity between the CN and key prefrontal areas, including the inferior frontal gyrus (IFG), dorsolateral prefrontal cortex (DLPFC), and supplementary motor area (SMA). This impaired connectivity was present regardless of medication status, suggesting that it is a direct consequence of subcortical pathology rather than a dopaminergic medication-responsive issue.

Given that early PD primarily affects subcortical structures (Braak & Braak, 2000), these findings suggest that dysfunction in cortico-basal loops contributes to hypophonia, a speech symptom characterized by reduced vocal intensity (Alexander & Crutcher, 1990). The CN plays a crucial role in modulating prefrontal activity via cortico-striatal projections (Zhiu et al., 2024), and prefrontal dysfunction in PD patients may lead to impaired cognitive preparation for speech. This impairment manifests as a reduction in energization, which involves action initiation (Kouneiher et al., 2009; Stuss & Alexander, 2007), and task rule coding, which supports the coordination of brain regions for speech execution (Dosenbach et al., 2006; Sakai & Passingham, 2006).

Arnold et al. (2013) further proposed that motor planning for speech in PD patients may shift toward execution rather than preparation, contributing to hypophonia as a non-motor deficit. While general hypokinesia in PD typically improves with levodopa, hypophonia often persists, suggesting that reduced energization only partially explains speech impairment. Additionally, increased muscle stiffness may contribute to monotonic, flat prosody. Their study found no significant deficits in speech initiation in early-stage PD patients, suggesting the presence of compensatory mechanisms.

Levodopa appears to facilitate compensatory efforts in early PD by increasing effective connectivity during speech preparation between the associative CN and motor putamen (Arnold et al., 2013). Dopamine intake enhances connectivity between the dorsal premotor cortex (dPMC) and SMA, suggesting that dopamine restoration activates an alternative compensatory mechanism involving the dorsal premotor regions (Arnold et al., 2013). Additionally, the recruitment of the SMA has been

associated with levodopa-induced improvements in both general hypokinetic symptoms (Haslinger et al., 2001) and voice symptoms (Liotti et al., 2003) in PD. Arnold et al. (2013) proposed that while striato-prefrontal hypo-connectivity during cognitive preparation may eventually contribute to motor initiation deficits, early PD patients may counteract this through subcortical plasticity. On dopaminergic medication, hyper-connectivity in medial and lateral dPMC regions likely facilitates compensatory mechanisms, with the medial dPMC supporting self-initiated movements and the lateral dPMC mediating externally guided actions (Jahanshahi et al., 1995). This compensatory mechanism may explain why external cueing strategies remain effective in PD symptom management (Arnold et al., 2013).

In addition to motor impairments, Arnold et al. (2013) found that early PD patients exhibited overactivation in prefrontal regions involved in feedforward processing and executive control during speech preparation, even in the absence of overt speech deficits. This overactivation was accompanied by diminished suppression of the auditory cortex (AC) during speaking, regardless of medication status. Typically, AC suppression during speech enhances sensitivity to external auditory feedback, likely through motor-auditory interactions such as corollary discharge (Arnold et al., 2013; Chang et al., 2012; Eliades & Wang, 2008). Reduced connectivity between auditory and premotor cortices in PD may indicate impaired self-monitoring of speech, aligning with earlier behavioural studies (Ho et al., 2000; Mollaei et al., 2013). This dysfunction may be linked to subcortical pathology, as the left AC is functionally connected to the nigrostriatal dopaminergic system during speech (Simonyan et al., 2013).

Arnold et al. (2013) further suggested that faulty self-monitoring of speech intensity, a key factor in PD-related hypophonia, stems from a diminished ability to use auditory feedback. If PD patients were fully aware of their hypophonia, they might adjust their motor drive accordingly. This failure to integrate external auditory feedback may also degrade speech motor representations, which are critical for maintaining accurate speech production throughout life (Hickok et al., 2011). Neural mapping of sensory-motor functions may become less efficient in PD due to increased neural noise (Frank, 2005), leading PD patients to rely more on executive control mechanisms for speech compensation.

Despite these challenges, Arnold et al. (2013) found that levodopa improved effective connectivity between the PUT, left prefrontal cortex (including the DLPFC, dPMC, and IFG), and the left superior temporal sulcus (STS), suggesting that dopamine restoration enhances sensorimotor mapping for speech production. While speech remained normal in both ON and OFF levodopa states, hyper-connectivity in internal speech model regions during the OFF state suggests compensatory sensorimotor processing. Levodopa may reduce the need for this compensation by decreasing neural noise (Arnold et al., 2013).

Ultimately, diminished auditory feedback use, combined with reduced motor drive, may contribute to hypophonia and, over time, to dysarthria as phonetic speech motor

representations deteriorate (Arnold et al., 2013). However, even in later disease stages, patients can improve speech production with external feedback, such as therapeutic intervention (Fox et al., 2002). This suggests that some degree of plasticity remains within cortico-basal loops, though therapeutic efficacy may decline as PD progresses and prefrontal dysfunction worsens (Arnold et al., 2013).

In relation to prosody, Arnold et al. (2013) found that early-stage PD patients, despite lacking overt speech difficulties, were able to produce normal affective prosody with enhanced speech melody and intensity. However, these features deteriorated within two years, suggesting that affective prosody requires greater modulation of speech melody, which may decline as PD progresses. Notably, PD patients in this study could still imitate emotional speech, likely relying on an external model provided by the experimenter (Arnold et al., 2013). This aligns with previous findings that early-stage PD patients can produce normal affective prosody when guided by external cues (Möbes et al., 2008).

Furthermore, affective prosody preparation involves the functional interaction between the ventral and dorsal striatum and increased connectivity between the striatum and cortical regions involved in autobiographical memory (Pichon & Kell, 2013). Arnold et al. (2013) observed that in OFF-medication PD patients, reduced coupling between the right ventral and dorsal striatum was linked to impaired speech modulation by emotional states. However, as the affective prosody in their study was largely dependent on an external model, PD patients showed weaker access to limbic information compared to healthy controls. Additionally, PD patients exhibited abnormal cortical activity, with greater prefrontal engagement during cognitive preparation and delayed parietal cortex activation during execution suggesting an altered executive control of model learning (Arnold et al., 2013). These results indicate modified executive control of model learning, as neuroimaging research has associated the parietal cortex with speech adaption and self-monitoring (Shum et al., 2011).

Overall, Arnold et al. (2013) demonstrated that PD-related speech deficits involve both motor and cognitive dysfunction, with compensatory mechanisms emerging in early stages. Although external cueing and levodopa can mitigate some deficits, their effectiveness may decline as PD progresses, highlighting the need for targeted interventions that support both dopaminergic and non-dopaminergic pathways.

9.1.4.4.3 Functional Connectivity of the Putamen and Internal Globus Pallidus in Speech Impairment

Manes et al. (2018) investigated functional connectivity differences in the basal ganglia among older healthy controls (OHC), PD patients without speech impairments (PDN), and those with speech impairments (PDSI). Their study identified five main findings. Firstly, seed-to-whole-brain analysis revealed reduced connectivity between the left putamen and the left superior temporal gyrus (STG) in the PDSI group compared to both the OHC and PDN groups. Secondly, three cortical connections to the left globus pallidus internus (GPi) demonstrated enhanced connectivity in PDSI relative to PDN. Thirdly, these disparities in connectivity were not due to motor severity, as clinical

motor impairment ratings were included. Fourthly, in the PDN group, functional connectivity between the left GPi and left dorsal premotor cortex (PMd)/lateral motor cortex (LMC) exhibited an inverse correlation with the levodopa equivalent daily dose (LEDD), a correlation that was not seen in the PDSI group. Lastly, all notable group disparities were identified solely in the left hemisphere, indicating that malfunctioning of the left-hemisphere basal ganglia may be pivotal to speech impairments in PD.

The findings substantiate the idea that PD patients with speech impairment (PDSI) demonstrate atypical left-hemisphere striatal connection to cortical areas associated with speech production in contrast to OHCs (Manes et al., 2018). No significant alterations were noted between the left putamen and supplementary motor area (SMA) or premotor cortex; however, the PDSI group had diminished connectivity between the left putamen and both the sensorimotor cortex and the STG. In the comparison of PDSI to PDN, diminished left putamen connectivity to the STG—rather than to the motor cortices—was noted, underscoring the significance of STG connectivity in PD-related speech impairments. These findings correspond with Simonyan et al. (2013), who identified a positive association between activity in the left anterior putamen and the left STG during sentence production.

A possible explanation for this diminished connectivity is that compromised left putamen-STG coupling may obstruct the identification and rectification of speech mistakes. The STG is essential for the integration of speech perception and production, especially in the regulation of auditory feedback during speech (Hickok & Poeppel, 2007; Price, 2012; Behroozmand et al., 2015, 2016). Manes et al. (2018) determined that the impacted STG cluster corresponds to an anterolateral region of Heschl's gyrus, which is involved in real-time vocal error correction subsequent to the auditory perturbations (Behroozmand et al., 2016). Interestingly, patients with PD exhibit an overcompensation in response to rapid auditory feedback perturbations, suggesting a dependence on sensory feedback stemming from compromised feedforward speech control (Chen et al., 2013; Huang et al., 2016; Liu et al., 2012). The diminished connectivity between the left putamen and STG may exacerbate this impairment, making it more difficult for PD patients to integrate sensory feedback for effective speech modulation (Manes et al., 2018).

Additionally, PD patients exhibit reduced adaptation to long-term auditory feedback changes (Mollaei et al., 2013), further supporting the notion that weakened left putamen-STG connectivity may impair sensory information integration during speech production. Beyond articulatory control, the STG is also involved in phonological error monitoring, which has been reported as abnormal in PD (Gauvin et al., 2017; McNamara et al., 1992). Thus, the observed reduction in left putamen-STG connectivity may reflect broader deficits in speech error detection and correction in PD patients.

In addition to putaminal dysfunction, Manes et al. (2018) identified altered connectivity patterns between the left GPi and cortical regions. Compared to PDN, PDSI patients

exhibited stronger functional connectivity between the left GPi and three cortical regions: the left PMd/LMC, the left angular gyrus, and the right angular gyrus. Nevertheless, no statistically significant differences were seen between the PDN or PDSI groups in comparison to the OHCs. The absence of substantial differences between the OHC group and the PDN/PDSI groups suggests that the study may have lacked adequate statistical power to identify relevant variations (Manes et al., 2018). Additionally, the standard error for GPi connectivity was greater in the OHC group compared to PDN and PDSI, indicating that a larger sample size may be necessary to draw more certain results (Manes et al., 2018).

Notwithstanding these statistical constraints, a gradual enhancement in functional connectivity from OHC to PDN to PDSI groups was noted across all three left GPi linkages (PMd/LMC, left angular gyrus, and right angular gyrus). This suggests that these pathways may initially undergo a decline in connectivity due to disease progression, followed by increased compensatory connectivity as speech symptoms emerge (Manes et al., 2018). The left GPi's cortical connections may serve as compensatory mechanisms for deteriorating speech production. Since most individuals with PD eventually develop speech impairments, future research could investigate these pathways in PDN subjects longitudinally as they develop speech difficulties.

The increased connectivity between the left GPi and left PMd/LMC in PDSI patients is particularly noteworthy, as this region lies within the dorsal premotor cortex but is also functionally adjacent to the dorsolateral laryngeal motor cortex (Manes et al., 2018). This finding offers two potential interpretations. If this region is considered part of the premotor system, the enhanced GPi-PMd/LMC connectivity in PDSI may indicate greater reliance on external cues to compensate for deficits in internally guided speech production, a hallmark of PD (Jahanshahi et al., 1995; Siegert et al., 2002). Internal cueing impairments are known to contribute to dysarthria in PD, as speech performance improves when PD patients receive external prompts to increase loudness, clarity, or pacing (Dromey & Ramig, 1998; Ho et al., 1999; Sapir, 2014).

Alternatively, if this region is considered a primary motor area responsible for laryngeal control, the increased GPi connectivity may reflect a compensatory response to hypophonia (Simonyan, 2014). Given that voice abnormalities in PD include reduced loudness, pitch variability, and breathiness (Logemann et al., 1978; Darley et al., 1969; Duffy, 2013), this hyperconnectivity may represent a disease-related adaptation similar to the hyperconnectivity of the subthalamic nucleus to motor cortices in PD (Baudrexel et al., 2011; Kurani et al., 2015).

In either interpretation, the abnormal GPi-PMd/LMC connectivity provides a foundation for further exploration of GPi's role in speech and voice production in PD (Manes et al., 2018). Additionally, increased connectivity between the left GPi and bilateral angular gyrus aligns with prior research on compensatory resting-state connectivity in PD (Tahmasian et al., 2017). The angular gyrus, part of the inferior parietal lobule, is

involved in semantic processing, visuospatial attention, and multisensory integration (Spaniol et al., 2009; Rosenthal et al., 2009; Kim, 2010; Arsalidou & Taylor, 2011). Its posterior portion is a key component of the default mode network (DMN), which becomes deactivated during cognitive tasks but remains active during rest (Manes et al., 2018).

A meta-analysis of resting-state connectivity in PD found increased angular gyrus connectivity in PD patients compared to healthy controls, suggesting that this enhancement may reflect compensatory reorganization following dopaminergic neuron loss (Tahmasian et al., 2017). If increased GPi-angular gyrus connectivity in PDSI is compensatory, it may indicate a shift toward greater reliance on cortical regions for multisensory integration or higher cognitive processes during speech production (Manes et al., 2018).

Finally, Manes et al. (2018) found that speech-related connectivity differences were lateralized to the left hemisphere, consistent with the left-lateralized nature of speech production and striatal dopamine release during speech (Simonyan et al., 2013). Given that ~75% of PDSI patients in their study exhibited right-lateralized motor symptoms, these findings suggest that earlier degeneration in left basal ganglia pathways may predispose PD patients to speech impairments. Further research is needed to clarify the relationship between disease lateralization and speech function, particularly in longitudinal studies tracking speech changes over time (Manes et al., 2018).

9.1.4.4.4 Effect of Transcranial Magnetic Stimulation (TMS) on Speech Impairment in Parkinson's Disease

Transcranial Magnetic Stimulation (TMS) is a non-invasive neuromodulatory technique that has shown potential in alleviating both motor and non-motor symptoms in individuals with PD. By delivering magnetic pulses to targeted brain regions, TMS may modulate neural activity, leading to improvements in motor function, cognitive processing, and emotional regulation (Wu et al., 2008). Given the complex neural networks involved in speech production, researchers have explored whether TMS can help mitigate speech impairments in PD.

Dias et al. (2006) conducted one of the early studies on TMS and speech in PD, randomly assigning participants to receive either 10 sessions of 15Hz repetitive TMS (rTMS) to the left dorsolateral prefrontal cortex (DLPFC) or a sham treatment over two weeks. The results indicated no significant changes in vocal loudness or fundamental frequency in either group. However, both groups reported improvements in voice-related quality of life, suggesting a potential placebo effect rather than a direct neurophysiological impact.

More recently, Brabenec et al. (2019) investigated the effects of low-frequency (1Hz) rTMS targeting the right posterior superior temporal gyrus (STG) and found improvements in articulation and speech rhythm. Building on these findings, the same research group later conducted a sham-controlled study comparing PD patients who

received 1Hz rTMS over the right STG for 10 sessions across two weeks to a control group. The treatment group exhibited increased intrinsic connectivity in the right STG, caudate nucleus, and orofacial sensorimotor cortex, alongside enhancements in speech intelligibility and prosody. Notably, these benefits persisted post-stimulation in the treatment group but not in the sham group, suggesting a genuine neuromodulatory effect rather than a placebo response (Brabenec et al., 2021).

These studies indicate that interventions aimed at modulating neural connectivity may offer promising avenues for addressing speech deficits in PD. Previous research has shown that changes in connectivity between the right caudate nucleus and left sensorimotor cortex differentiate healthy individuals from those with PD. Additionally, reduced connectivity between the left STG and left putamen has been specifically linked to speech impairments in PD patients (Manes et al., 2018).

While further research is required to refine optimal stimulation parameters, target regions, and treatment duration, preliminary findings suggest that TMS, either as a standalone intervention or in combination with behavioural therapies, holds potential as a therapeutic tool for PD-related speech impairments (Chen et al., 2025). Future studies should explore long-term effects, individual responsiveness to stimulation, and the integration of TMS with established speech therapies to maximize clinical benefits.

9.1.4.4.5 Summary

Speech impairments in PD arise from a combination of dopaminergic and non-dopaminergic dysfunctions, affecting motor control, self-monitoring, and speech planning. Neuroimaging studies highlight reduced presynaptic dopaminergic function, particularly in the caudate and putamen, and abnormal activity in the basal ganglia–cerebellum–cortex circuits as key contributors to speech deficits. While levodopa modulates brain connectivity, its effects on speech remain inconsistent, indicating the role of broader motor and cognitive networks beyond the basal ganglia. Altered functional connectivity between the putamen, internal globus pallidus (GPi), and cortical regions further exacerbates speech impairments. Specifically, reduced left putamen-superior temporal gyrus (STG) connectivity impairs speech error detection and auditory feedback integration, while increased GPi connectivity to motor and sensory areas may reflect compensatory adaptations in PD patients as speech difficulties emerge.

Impaired self-monitoring mechanisms, particularly diminished auditory cortex suppression, prevent PD patients from perceiving their own reduced speech intensity, leading to hypophonia (reduced vocal loudness) and progressive speech motor degradation. Prosody, initially preserved, declines as striatal-limbic connectivity weakens, impairing speech modulation by emotional states. Compensatory mechanisms such as increased GPi-dorsal premotor cortex connectivity suggest a shift toward greater reliance on external cues for speech control, aligning with evidence that PD patients perform better with loudness and pacing prompts (Dromey & Ramig, 1998; Sapir, 2014). However, these compensatory mechanisms decline with

disease progression, reinforcing the need for targeted interventions addressing both motor and cognitive pathways involved in speech regulation.

Recent studies suggest Transcranial Magnetic Stimulation (TMS) as a potential therapeutic approach for PD-related speech impairments. While high-frequency (15Hz) TMS over the dorsolateral prefrontal cortex (DLPFC) showed no significant impact on vocal loudness or fundamental frequency (Dias et al., 2006), low-frequency (1Hz) rTMS targeting the right posterior STG demonstrated sustained improvements in articulation, speech rhythm, intelligibility, and prosody, along with increased connectivity in the right STG, caudate nucleus, and orofacial sensorimotor cortex (Brabenec et al., 2019, 2021). These findings reinforce the idea that targeted neuromodulation of speech-related networks may enhance sensorimotor integration and speech production in PD. However, further research is required to optimize stimulation parameters, treatment duration, and long-term efficacy, particularly in combination with behavioral speech therapies to maximize clinical outcomes.

Ultimately, PD-related speech difficulties stem from complex interactions between motor, sensory, and cognitive systems, with early basal ganglia dysfunction predisposing patients to progressive speech impairments. Longitudinal studies are needed to determine how disease lateralization influences speech progression and whether increased GPi connectivity or neuromodulation techniques like TMS can serve as viable therapeutic targets. Given the declining effectiveness of levodopa and external cueing strategies over time, multimodal approaches combining pharmacological, neuromodulatory, and behavioral interventions may offer the most promising path for managing speech impairments in PD.

Factor	**Effect on Speech Impairment in PD**
Presynaptic Dopamine Deficits	Reduced striatal dopamine impairs motor control and speech production.
Caudate and Putamen Dysfunction	Disrupts articulation, speech fluency, and coordination, contributing to hypophonia.
Basal Ganglia–Cerebellum–Cortex Circuit	Abnormal connectivity affects speech motor regulation and error detection.
Left Putamen-Superior Temporal Gyrus (STG) Connectivity	Reduced connectivity hinders auditory feedback processing and speech error correction.
Left GPi-Premotor Cortex Connectivity	Increased connectivity may reflect compensatory reliance on external cues for speech.
Left GPi-Angular Gyrus Connectivity	May indicate cortical compensatory mechanisms for impaired speech motor function.
Deficits in Internal Speech Cueing	PD patients struggle with self-initiated speech but improve with external cues (e.g., loudness prompts).
Hypophonia and Laryngeal Motor Dysfunction	GPi hyperconnectivity may attempt to compensate for reduced vocal intensity and pitch variability.

Prosody Alterations	Initially preserved but declines with disease progression due to weakened striatal-limbic connectivity.
Self-Monitoring Deficits	Reduced auditory cortex suppression impairs speech intensity regulation.
Compensatory Adaptations	Increased GPi connectivity suggests cortical reorganization as speech deficits progress.
Levodopa Therapy	Improves limb motor function but has inconsistent effects on speech regulation.
Transcranial Magnetic Stimulation (TMS) Interventions	May enhance speech articulation, rhythm, and prosody via targeted neuromodulation.
1Hz rTMS over Right Posterior STG	Improves speech intelligibility and increases intrinsic connectivity in speech-related networks.
15Hz rTMS over Left DLPFC	No significant improvement in vocal loudness, but reported enhancement in voice-related quality of life (placebo effect suspected).
Long-Term TMS Effects	Require further investigation; potential for integration with behavioral speech therapies.
External Cueing Strategies	Effective in early PD but lose efficacy as the disease progresses.
Multimodal Interventions	Combining pharmacological, neuromodulatory, and behavioral approaches may optimize speech outcomes.

Table 15. Literature summary of neurobiological mechanisms, compensatory adaptations, and therapeutic interventions for speech impairments early PD treatment-naïve and levodopa-treated patients.

9.1.5 Limitations and Future Studies

Despite the strengths of this study, several limitations should be acknowledged. First, the cross-sectional design limits the ability to establish causal relationships between speech difficulties, motor impairment, and neurodegenerative markers, underscoring the need for longitudinal studies to track disease progression and speech deterioration over time. Longitudinal designs could allow researchers to observe how symptoms evolve, providing insights into the trajectory of speech impairments and motor dysfunction (Schalling et al., 2017).

Additionally, the relatively small sample size, particularly in the levodopa-treated cohort, may reduce statistical power and limit generalizability, warranting replication in larger, more diverse populations. A small sample can hinder the ability to detect significant differences and trends that might be present within larger and more varied groups (Horin et al., 2019). Future studies should strive to include a more representative cohort to enhance the reliability of findings.

While this study identified motor impairment and neurodegeneration as key predictors of speech difficulties, the lack of detailed speech-specific assessments, such as acoustic or articulatory analyses, prevents a comprehensive characterization of these deficits. Previous research emphasizes the critical insight provided by acoustic measures that can reveal subtle changes in phonation and articulation, which are often overlooked (Polychronis et al., 2019; Rusz et al., 2011). Future investigations that

incorporate advanced speech analysis techniques—such as functional MRI or diffusion tensor imaging—could elucidate the neural mechanisms underpinning speech impairment in PD. Such multimodal imaging techniques would allow for a more refined understanding of how motor control and neural integrity are linked to speech production (Hlavnička et al., 2017).

Moreover, although cognitive function and non-motor symptom burden did not significantly differ between groups, other potential contributors—such as medication effects, compensatory mechanisms, and levodopa-induced dyskinesia—should be explored in future studies. Cognitive function, specifically executive functions, may contribute to the complexity of speech motor control, potentially bridging the connection between cognitive deficits and speech abnormalities (Yorkston et al., 2017). Additionally, understanding the interplay between levodopa treatment and speech impairments remains essential, as some research indicates that while levodopa may alleviate certain motor symptoms, its efficacy in improving speech quality can be limited (Smith et al., 2019).

Lastly, given the observed sex differences in demographic analyses, further research is needed to investigate potential sex-specific factors, including hormonal influences or differential compensatory strategies, that may contribute to speech impairment in PD. Investigating gender differences in presentation and progression of PD could illuminate variations in symptom expression and help tailor gender-sensitive treatment strategies (Janbakhshi & Kodrasi, 2021; Iwaki et al., 2021).

In conclusion, addressing these limitations through expanded cohort sizes, longitudinal tracking, detailed speech assessments, and an emphasis on potential psychosocial and sex-specific factors will enhance understanding of speech difficulties in PD and inform treatment strategies.

9.2 Dysphagia in Early Parkinson's Disease Treatment-Naïve and Levodopa-Treated Patients

9.2.1.1 Demographic Characteristics and Dysphagia in Early Parkinson's Disease Treatment-Naïve Patients

The study revealed no significant differences in age, sex ratio, or disease duration between early PD treatment-naïve patients with dysphagia compared to those without it. These findings align with those of Polychronis et al. (2019), who similarly observed no notable demographic distinctions between the two groups. In their research, they reported a dysphagia prevalence of 12.3% among drug-naïve patients, while other studies have identified a broader prevalence range from 9% to 82%. This variability largely hinges on the diagnostic methods and criteria applied, as noted in studies by Gong et al. (2022), Roshan et al. (2023), and Yao et al. (2023). Such discrepancies underscore the impact of geographical, methodological, and clinical assessment differences on the estimates of dysphagia prevalence.

Furthermore, Gong et al. (2022) conducted a systematic review and meta-analysis that established an association between age and dysphagia in PD patients, indicating that older individuals in this population are more likely to encounter swallowing difficulties. This observation suggests that age-related factors may substantially contribute to the onset and severity of dysphagia, warranting further examination of the relationship among age, disease progression, and dysphagia in early-stage PD patients. In addition, Gong et al. (2022) reported no significant association between male gender and the prevalence of dysphagia in PD patients, reflecting moderate heterogeneity across the studies included in their review. This discrepancy illuminates the complexity of the relationship between gender and dysphagia, as different studies may utilize varied assessment methods and patient cohorts, potentially affecting prevalence outcomes. It has been theorized that hormonal factors may contribute to the observed gender differences in dysphagia among PD patients and estrogen may play a protective role, with female patients typically exhibiting a later onset and maybe milder dysphagia relative to male individuals (Gong et al., 2022).

Our regression analysis corroborates this conclusion, as demographic variables did not prove to be significant predictors of dysphagia in early PD cases. Importantly, while the overall severity of the disease, as measured by the Hoehn and Yahr scale, may not predict swallowing difficulties, Polychronis et al. (2019) noted that specific motor subtypes, particularly the akinetic-rigid phenotype, were more frequently associated with dysphagia. Although demographic characteristics such as age and sex were generally comparable between patients with and without dysphagia in our analysis, prior research has identified age as a potential risk factor for developing swallowing difficulties in PD patients (Claus et al., 2020).

9.2.1.2 Demographic Characteristics and Dysphagia in Early Parkinson's Disease Levodopa-Treated Patients

Similar to the findings in early PD treatment-naïve patients, the study found no significant differences in age, sex ratio, or disease duration between early PD levodopa-treated patients with and without dysphagia. Research has demonstrated that dysphagia can manifest in various ways as PD progresses and typically

becomes more apparent as neurological degeneration advances (Cosentino et al., 2022; Altman, 2017). The fact that both groups in our study had similar demographic profiles suggests that dysphagia might not necessarily correlate with the duration of the disease or age, particularly in early stages. This raises the possibility that subgroup characteristics, rather than mere demographic factors, may play a more crucial role in understanding swallowing difficulties in PD patients.

While levodopa is a common treatment for PD, its role in exacerbating dysphagia is a matter of ongoing research. Some evidence suggests that higher daily levodopa doses could correlate with the severity of dysphagia symptoms as the disease progresses (Polychronis et al., 2019; Labeit et al., 2022). However, our sample includes patients at relatively early stages of PD, and it may be the case that the development of dysphagia is independent of the immediate effects of levodopa in this cohort. Studies have noted that swallowing dysfunction can occur very early in the disease process, often independent of treatment factors (Roshan et al., 2023; Argolo et al., 2015). The presence of dysphagia in these patients may suggest an intrinsic pathophysiological mechanism affecting the brain's motor control over swallowing before significant drug-related complications arise. The observation of dysphagia within our early PD cohort suggests that it may be an underappreciated aspect of the disease experience. The findings align with emerging evidence pointing to the broader spectrum of swallowing disorders associated with PD, which includes not only aspiration risk, but also functional deficits linked to the neural control of swallowing (Luca et al., 2021; Ueha et al., 2018).

Our regression analysis demonstrated that neither age nor sex is a significant predictor of dysphagia when accounting for cerebrospinal fluid (CSF) biomarkers and cognitive function. This aligns with recent literature which emphasizes the critical role of neurobiological factors over traditional demographics in understanding swallowing difficulties in PD (McGhee et al. 2013; Roshan et al., 2023). Current research supports the hypothesis that alterations in CSF biomarkers, such as neurofilament light chain and alpha-synuclein, are indicative of more profound neurodegenerative processes that could influence motor and non-motor symptoms in PD, including dysphagia (Herbert et al., 2015; Polychronis et al., 2019; Kang et al., 2016).

It also aligns with a broader consideration regarding the multifactorial origins of dysphagia in PD, especially concerning cognitive function. Cognitive decline has a significant association with dysphagia, as cognitive deficiencies might hinder the swallowing process. This corresponds with the developing perspective that dysphagia is not solely a manifestation of severe disease but may occur early in the clinical progression of PD, heavily influenced by neurocognitive variables (Roshan et al., 2023; Gao et al., 2016).

9.2.1.3 Summary

This study found no significant differences in age, sex, or disease duration between early PD patients with and without dysphagia, both in treatment-naïve and levodopa-treated groups, indicating that demographic factors alone may not account for the presence or early development of swallowing difficulties. Despite the wide variability in dysphagia prevalence reported across studies—likely due to methodological differences—age and sex were not significant predictors in our cohort. The findings indicate that dysphagia in early PD may be more closely linked to disease-specific

features, such as motor subtypes like the akinetic-rigid phenotype, and to early neural changes affecting the motor control of swallowing, rather than to demographic characteristics or treatment effects. Regression analyses further supported this view, showing that neither age nor sex predicted dysphagia when cognitive function and cerebrospinal fluid (CSF) biomarkers were taken into account, highlighting the potential role of neurodegenerative and cognitive mechanisms in the emergence of dysphagia in early PD.

Category	Early PD Treatment-Naïve	Early PD Levodopa-Treated
Age	No significant difference between patients with and without dysphagia	No significant difference between patients with and without dysphagia
Sex	No significant difference between patients with and without dysphagia	No significant difference between patients with and without dysphagia
Disease Duration	No significant difference observed	No significant difference observed
Treatment Effect	Not applicable (treatment-naïve)	Dysphagia appears independent of early levodopa treatment
Motor Subtypes	Akinetic-rigid subtype associated with greater dysphagia risk (based on previous findings)	Not assessed directly in current analysis
Predictive Value of Demographics	Age and sex not significant predictors after controlling for cognition and CSF biomarkers	Age and sex not significant predictors after controlling for cognition and CSF biomarkers
Implication	Dysphagia may reflect early neurodegenerative mechanisms rather than demographics	Dysphagia may reflect early neural dysfunction independent of treatment status

Table 16. Summary of demographic characteristics and their associations with dysphagia in early PD treatment-naïve and levodopa-treated patients.

9.2.2.1 Clinical Characteristics and Dysphagia in Early Parkinson's Disease Treatment-Naïve Patients

The study found no significant differences in cognitive performance, as measured by the Montreal Cognitive Assessment (MoCA) score, between early PD treatment-naïve patients with and without dysphagia. This is consistent with existing literature, which suggests that cognitive impairment is not necessarily a direct consequence of dysphagia in this patient group (Polychronis et al., 2019).

However, significant differences were observed in MDS-UPDRS scores between the two groups. Our regression model identified MDS-UPDRS Part I (non-motor symptoms) as a significant predictor of dysphagia, highlighting the role of non-motor symptom burden in swallowing difficulties. This finding aligns with Polychronis et al. (2019), who reported that PD patients with dysphagia exhibited greater autonomic dysfunction, depressive symptoms, REM sleep disturbances, and daytime sleepiness. These results reinforce the role of brainstem dysfunction and autonomic regulation in

swallowing impairments, as early neurodegeneration in PD affects regions involved in autonomic control and sensorimotor processing of swallowing.

Additionally, MDS-UPDRS Part II (functional motor impairment) was also a significant predictor of dysphagia, underscoring the role of oromotor dysfunction in swallowing difficulties. This is consistent with Polychronis et al. (2019), who reported that PD patients with dysphagia had significantly worse MDS-UPDRS Part II scores, reflecting greater functional motor impairments. These findings support the contribution of bradykinesia, rigidity, and axial motor dysfunction in disrupting the coordination of the swallowing process (Ertekin et al., 2002).

In contrast, MDS-UPDRS Part III (motor function assessment) did not significantly differ between the two groups, consistent with previous studies (Simons, 2017; Gong et al., 2022), which found no significant differences in motor function scores between PD patients with and without dysphagia. However, total MDS-UPDRS scores (ON and OFF medication) were significantly higher in the dysphagia group, suggesting that non-motor symptoms play a more prominent role in dysphagia development than motor impairments alone. These findings emphasize the need for early monitoring of non-motor symptoms as potential indicators of dysphagia risk, even when motor symptoms appear stable.

9.2.2.2 Clinical Characteristics and Dysphagia in Early Parkinson's Disease Levodopa-Treated Patients

Unlike in treatment-naïve patients, cognitive performance, as measured by the MoCA score, was significantly lower in patients with dysphagia compared to those without, suggesting a potential association between cognitive impairment and swallowing difficulties in early PD levodopa-treated patients. However, our regression analysis did not identify MoCA as a significant predictor of dysphagia, indicating that cognitive impairment does not independently predict swallowing difficulties when controlling for tau pathology.

In later-stage PD, studies have linked cognitive dysfunction to dysphagia, particularly where executive function and attention deficits impair swallowing coordination (Kalf et al., 2012). These findings suggest that cognitive decline and tau pathology may co-occur, meaning that while MoCA was not an independent predictor in this study, cognitive impairment may still contribute to dysphagia in combination with other neurodegenerative processes at a later stage.

9.2.2.3 Summary

The findings highlight distinct clinical associations with dysphagia in early PD, depending on treatment status. In treatment-naïve patients, dysphagia is more strongly associated with non-motor symptom burden and functional motor impairment rather than cognitive dysfunction or overall motor severity. Conversely, in levodopa-treated patients, lower MoCA scores suggest a potential relationship between cognitive impairment and dysphagia, although cognitive function was not an independent predictor when controlling for tau pathology. These results emphasize the need for a multifaceted approach to dysphagia risk assessment, incorporating both motor and non-motor symptom evaluation. Future research should further explore the

role of neurodegenerative markers in swallowing impairments across different PD stages to enhance early detection and intervention strategies.

Category	Early PD Treatment-Naïve	Early PD Levodopa-Treated
Cognitive Function	No significant differences in MoCA scores between patients with and without dysphagia.	MoCA scores were significantly lower in dysphagia patients, but not an independent predictor when controlling for tau pathology.
Motor Function	MDS-UPDRS Part II (functional motor impairment) was a significant predictor of dysphagia; Part III (motor function assessment) showed no significant differences.	No specific findings related to motor function reported in this analysis.
Non-Motor Symptoms	MDS-UPDRS Part I (non-motor symptoms) was a significant predictor of dysphagia, emphasizing autonomic dysfunction, depressive symptoms, REM sleep disturbances, and daytime sleepiness.	Not explicitly analyzed, but cognitive impairment was associated with dysphagia.
Key Findings	Dysphagia is more strongly linked to non-motor symptom burden and functional motor impairment rather than cognitive dysfunction or overall motor severity.	Cognitive impairment may contribute to dysphagia, though it is not an independent predictor when controlling for tau pathology.

Table 17. Summary of clinical characteristics and their associations with dysphagia in early PD treatment-naïve and levodopa-treated patients.

9.2.2.4 Literature context: Clinical characteristics and dysphagia in Early Parkinson's Disease

9.2.2.4.1 The effect of Cognitive and Motor symptoms

Kim et al. (2015) investigated the relationships between swallowing function, cognitive abilities based on neuropsychological profiles, and motor symptoms in PD patients. Their findings indicated that the oral phase of swallowing exhibited the strongest associations with frontal/executive and memory functions, whereas the pharyngeal phase showed a weaker but notable link to frontal functions. Additionally, motor abilities were correlated with oral residue and tongue base retraction, highlighting the interplay between motor dysfunction and swallowing impairments in PD.

Among cognitive impairments in PD, attention has been linked to the anticipatory phase of swallowing, which occurs before the oral phase and involves preparing and

introducing food into the mouth (Brodsky et al., 2012). Similarly, Miller et al. (2009) identified a moderate positive relationship between swallowing speed and cognition, although cognitive function in their study was assessed using a simpler screening tool. These findings suggest that cognitive decline may contribute to, and exacerbate, dysphagia in PD, though the specific effects of individual cognitive domains on swallowing function require further investigation (Kim et al., 2015).

To explore these relationships, Kim et al. (2015) examined cognitive function using detailed neuropsychological assessments and correlated the results with specific swallowing measures. Their study found that memory and learning skills, assessed via the Shiraz Verbal Learning Test, and executive functions, measured using the Controlled Oral Word Association Test and Stroop tests, were closely linked to the oral phase, particularly in bolus preparation and transport. These findings suggest that executive and memory impairments disrupt the coordination required for organized mastication and tongue movements, increasing the risk of dysphagia and aspiration in PD. In contrast, cognitive effects appeared less relevant during the pharyngo-esophageal phases, which are largely reflex-driven (Kim et al., 2015). This aligns with previous research suggesting that reflexive swallowing mechanisms are less susceptible to cognitive influences (Steele et al., 2010; Peyron et al., 2011).

In terms of motor function, mixed results were observed in MDS-UPDRS scores. No statistically significant differences were found between early PD levodopa-treated patients with and without dysphagia, suggesting that the relationship between dysphagia and motor symptom severity is complex and may not be straightforward. These findings underscore the importance of considering both motor and cognitive contributions to dysphagia in PD, as swallowing difficulties may arise from distinct yet interacting neural mechanisms.

9.2.2.4.2 The Relationship Between Disease Stage, Motor Symptoms and dysphagia

The association between disease stage and dysphagia risk in PD remains inconclusive, with some studies supporting a link while others do not (Kim et al., 2015). For instance, Leopold et al. (1996) reported more pre-pharyngeal abnormalities in advanced PD, whereas Ali et al. (1998) found no clear relationship between PD severity and dysphagia.

Evidence also suggests that the PD phenotype may affect swallowing impairments. Patients with the postural instability/gait disorder (PIGD) subtype typically demonstrate more significant swallowing deficits than those with tremor-dominant PD, reinforcing the idea that axial motor symptoms may contribute to dysphagia (Miller et al., 2009).

Additionally, Kim et al. (2015) found significant correlations between bradykinesia and oral residue, as well as between total UPDRS scores and impaired tongue base retraction. These findings suggest that hypokinesia in the oropharyngeal muscles may contribute to swallowing difficulties. As motor symptoms progress, dysphagia may

extend beyond the oral phase to include the pharyngeal phase, leading to more pronounced swallowing impairments.

However, Hoehn and Yahr (H&Y) stage did not correlate with specific swallowing issues in Kim et al.'s (2015) study. This may be due to their sample consisting primarily of early to middle-stage PD patients, with those experiencing severe dysphagia or advanced disease excluded to minimize the risks associated with swallowing assessments.

9.2.2.4.3 The Relationship Between Motor Symptoms and Swallowing Function

Nakamori et al. (2024) highlighted the broad spectrum of neurological symptoms in PD, including motor impairments and swallowing difficulties. Their study explored the relationship between swallowing function and specific motor symptom subscores, revealing that muscle rigidity was the strongest predictor of aspiration risk among PD patients. Specifically, higher muscle rigidity correlated with increased frequency of laryngeal penetration or aspiration, particularly when swallowing larger boluses (10 mL of water), whereas smaller bolus sizes did not show significant effects. These findings indicate that muscle rigidity, more so than other motor symptoms, increases the risk of aspiration, underscoring the necessity for modified swallowing strategies to prevent aspiration in PD patients with significant rigidity.

When swallowing 10 mL of water, more PD patients exhibited delayed peak laryngeal elevation, as measured by laryngeal elevation duration time (LEDT)—the interval between the bolus reaching the vallecula and the peak of laryngeal elevation (Miyaji et al., 2012). This delay was more pronounced with larger bolus sizes, likely due to PD-related bradykinesia and rigidity. However, no significant correlation was found between UPDRS subscores and LEDT, suggesting that other factors beyond standard motor severity measures contribute to swallowing dysfunction in PD.

PD symptoms are typically classified into limb and axial categories, with axial symptoms being more closely linked to falls and swallowing problems (Umemoto et al., 2020). Although Nakamori et al. (2024) assessed the postural instability/gait disorder (PIGD) subscore from UPDRS Part III, no significant association with swallowing impairment was found. Previous studies have reported a relationship between falls and swallowing difficulties (Umemoto et al., 2020), but discrepancies in findings may be attributed to differences in scoring methodologies. Nonetheless, a strength of Nakamori et al.'s (2024) study is its use of the UPDRS, a standardized PD assessment tool, combined with videofluoroscopic swallowing studies (VFSS) for objective swallowing evaluation.

Additionally, no significant correlations were found between UPDRS scores (including subscores) and other physiological markers such as tongue pressure and peak expiratory flow. Although certain studies and meta-analyses have associated age, tongue pressure, and hand grip strength with swallowing difficulties (Arakawa et al., 2021; Arakawa-Kaneko et al., 2022), these correlations were not evident in individuals with PD. Conversely, in other neurological conditions such as stroke, ALS, and

sarcopenia, disease severity scores correlate strongly with tongue pressure and an increased risk of aspiration or pneumonia (Nakamori et al., 2016; Hiraoka et al., 2017). In contrast to these disorders, PD does not typically cause paralysis; rather, it is characterized by impaired smooth movement due to bradykinesia, which may explain the weaker association between disease severity and tongue pressure in PD (Nakamori et al., 2024).

9.2.2.4.4 Summary

The relationship between cognitive, motor symptoms, disease progression, and dysphagia in PD is complex. Cognitive impairment, particularly in executive and memory functions, contributes to oral-phase swallowing difficulties, whereas motor dysfunction, especially rigidity, increases aspiration risk. The impact of disease severity on dysphagia remains inconclusive, with mixed findings on the correlation between H&Y stage and swallowing impairments. Additionally, while PIGD and bradykinesia have been linked to swallowing difficulties, findings vary depending on the methodology used.

Category	Findings
Cognitive Function	Executive and memory functions impact the oral phase; cognitive effects on dysphagia in levodopa-treated patients remain unclear.
Motor Function	No significant differences in MDS-UPDRS scores in treatment-naïve patients; muscle rigidity strongly predicts aspiration risk in levodopa-treated patients.
Disease Progression	No clear relationship between disease stage and dysphagia in treatment-naïve patients; dysphagia may extend from oral to pharyngeal phase over time in levodopa-treated patients.
Key Motor Symptom Associations	Bradykinesia correlates with oral residue and tongue base retraction; axial symptoms and rigidity impact swallowing biomechanics.
Clinical Implications	Dysphagia risk may not align with overall motor severity; tailored swallowing strategies needed for patients with rigidity.

Table 18. Literature summary of clinical characteristics and their associations with dysphagia in early PD treatment-naïve and levodopa-treated patients.

9.2.3.1 CSF Biomarkers and Dysphagia in Early Parkinson's Disease Treatment-Naïve Patients

This study found no significant differences in CSF biomarker levels (amyloid-beta, total tau, phosphorylated tau, and alpha-synuclein) between early, treatment-naïve PD patients with and without dysphagia.

The methodologies employed and participant selection in biomarker studies can greatly influence observed associations, as highlighted by Goldman et al. (2017). Our results demonstrate that, in the cohort of newly diagnosed patients, dysphagia does not meaningfully correlate with known CSF biomarkers, contrasting with evidence linking them to other motor or non-motor symptom profiles in PD patients, thus underscoring a notable gap in current neurological understanding (Atik et al., 2016).

Previous studies, such as those by Kang et al. (2013), have identified CSF biomarkers (e.g., β-Amyloid, T-tau, P-tau, and α-Synuclein) that correlate with certain motor subtypes of PD. Notably, these associations are often tied to the postural instability and gait difficulty (PIGD) subtype rather than dysphagia as a clinical feature (Kang et al., 2013; Roshan et al., 2023). This finding suggests that dysphagia may result from pathophysiological elements not effectively captured by commonly studied CSF biomarkers, further reiterating the multifactorial nature of swallowing difficulties that extend beyond mere biochemical indicators (Leverenz et al., 2011).

The literature also suggests that various factors -such as age, motor symptom severity, and cognitive function- play a significant role in the development of dysphagia within the PD population (Roheger, M., 2018). Our study's findings mirror this complexity, indicating that while CSF biomarkers offer insight into the underlying neurodegenerative process, they may not adequately reflect the intricacies of swallowing difficulties manifesting in early-stage PD.

Furthermore, existing research has indicated neurobiological factors that contribute to the onset of dysphagia, which may not be solely related to identifiable biomarkers (Sampedro et al., 2018). Many studies have pointed to the overlap of cognitive decline, which may influence dysphagia through deteriorating executive function and altered swallowing reflex, suggesting the need for a multi-faceted approach to assess swallowing difficulties (Kremer et al., 2021).

9.2.3.2 CSF Biomarkers and Dysphagia in Early Parkinson's Disease Levodopa-Treated Patients

The analysis revealed that early PD patients with dysphagia exhibited elevated levels of CSF tau and phosphorylated tau (pTau) compared to their counterparts without dysphagia. This finding aligns with studies that demonstrate tau pathology is associated with cognitive decline, further suggesting that tau plays an essential role in the dysphagia experienced by PD patients. Specifically, higher pTau levels show a correlation with increased odds of dysphagia, indicating that pTau may serve as a more direct biomarker of neurodegeneration compared to cognitive tests such as the Montreal Cognitive Assessment (MoCA) (Schrag et al., 2017; Kim et al., 2015). Observations resonate with existing research that links tau pathology to various neurodegenerative disorders, although more nuanced studies emphasize variables that impact dysphagia and cognitive function simultaneously (Dehaghani et al., 2021; Roshan et al., 2023).

Moreover, while cognitive function, as measured by MoCA, did not remain a significant predictor of dysphagia in the final multivariate analysis, initial findings provide valuable insights. The cognitive impairments observed in PD consistently intersect with other neurological processes, suggesting that while cognitive decline may not independently predict dysphagia, it is still relevant to understanding the multifaceted nature of swallowing disorders. Research has documented evidence that cognitive deficits and motor symptoms collectively exacerbate dysphagia in PD (Kim et al., 2015; Luca et al., 2021). This interplay is crucial, given that cognitive decline can influence attention and other cognitive resources essential for swallowing, as substantiated by dual-task studies (Troche et al., 2014)

Interestingly, previous research emphasizes the complexity surrounding the relationship between cognition and dysphagia. Some studies propose that cognitive impairment directly contributes to declines in swallowing function, while others indicate that motor control's neuroanatomical aspects may carry a more profound influence (Tian et al., 2025). In this regard, tau pathology appears to serve as a critical point linking neurodegeneration to dysphagia, potentially complicating cognitive tasks and enhancing the risk of swallowing difficulties by impairing neural networks involved in both cognitive and swallowing processes, particularly in early-stage PD patients (Bhattacharyya, 2014; Basagni et al., 2023).

The findings in this study contribute significantly to our understanding of dysphagia in levodopa-treated PD patients. Despite the nuanced role of cognitive impairment, evidence suggests that tau pathology remains a more consistent and critical biomarker for predicting dysphagia. Given that CSF biomarkers can elucidate underlying pathological processes in PD, future studies should further explore the metabolic pathways of tau and their implications for swallowing functions.

9.2.3.3 Summary

This study highlights the complex and multifactorial nature of dysphagia in early PD, revealing distinct patterns between treatment-naïve and levodopa-treated patients. Among treatment-naïve individuals, no significant differences were observed in cerebrospinal fluid (CSF) biomarker levels—including amyloid-beta, total tau, phosphorylated tau, and alpha-synuclein—between those with and without dysphagia, suggesting that these markers may not adequately reflect the early neurobiological changes contributing to swallowing difficulties. In contrast, levodopa-treated patients with dysphagia exhibited elevated CSF tau and pTau levels, indicating that tau pathology may play a more prominent role as the disease progresses or in response to treatment. These findings suggest that dysphagia in PD may not be solely linked to traditional motor symptoms or demographic factors but instead involves an interplay of cognitive, neurodegenerative, and potentially treatment-related mechanisms. While tau may serve as a more sensitive biomarker for dysphagia in levodopa-treated patients, its absence as a predictor in treatment-naïve cases underscores the importance of adopting a nuanced, stage-specific, and multi-dimensional approach to the assessment and management of swallowing dysfunction in PD.

Category	**Early PD Treatment-Naïve Patients**	**Early PD Levodopa-Treated Patients**
Overall CSF Biomarker Differences	No significant differences in CSF levels (Aβ, total tau, pTau, α-synuclein) between patients with and without dysphagia	Patients with dysphagia exhibited elevated CSF total tau and phosphorylated tau (pTau) levels compared to those without dysphagia
Interpretation	CSF biomarkers may not reflect dysphagia-related pathology in early, untreated PD	Tau pathology may be linked to swallowing dysfunction through neurodegenerative processes impacting cognitive and motor networks

Associated Clinical Factors	Dysphagia may be more strongly associated with age, motor severity, and cognitive function rather than with biochemical markers	Cognitive impairment did not predict dysphagia independently in multivariate analysis, but may interact with tau-related mechanisms to influence swallowing difficulties
Biomarker-Cognition Link	No clear biomarker-based explanation for dysphagia; need for multifactorial assessments	Elevated tau levels may serve as more sensitive indicators of dysphagia risk than cognitive screening tools like the MoCA

Table 19. Summary of CSF Biomarkers and their associations with dysphagia in early PD treatment-naïve and levodopa-treated patients.

9.2.4.1 Dopaminergic Alterations and Dysphagia in Early Parkinson's Disease Treatment-Naïve Patients

This study provides new insights into the relationship between striatal dopamine transporter (DAT) binding and dysphagia in early, treatment-naïve PD patients. The results showed that patients with dysphagia exhibited significantly lower [^{123}I]FP-CIT binding in the total striatum, caudate, and putamen compared to those without dysphagia. These findings suggest that the extent of dopaminergic denervation, as measured by FP-CIT imaging, is associated with dysphagia development in early PD.

Regression analysis identified lower mean caudate values as a significant predictor of dysphagia, whereas mean putamen values were not retained. This is consistent with Polychronis et al. (2019), who also found that early PD patients with dysphagia exhibited reduced presynaptic dopaminergic function in the caudate, but not in the putamen, using [^{123}I]FP-CIT SPECT imaging. The observed findings also align with established patterns of dopaminergic degeneration in PD (Innis et al., 1999; Wallert et al., 2022). These results suggest that DAT imaging may serve as an early biomarker for identifying dysphagia risk in PD, highlighting its potential role in early diagnosis and targeted intervention strategies.

These findings challenge the traditional view that swallowing dysfunction in PD stems solely from striatal motor deficits, emphasizing a specific role for caudate degeneration in dysphagia pathogenesis. Neuroimaging studies suggest that caudate dysfunction may impair the supramedullary swallowing network, which integrates basal ganglia circuits for voluntary and reflexive swallowing processes (Suzuki et al., 2003; Leopold & Daniels, 2010).

9.2.4.2 Dopaminergic Alterations in Early Parkinson's Disease Levodopa-Treated Patients

In contrast to treatment-naïve patients, striatal dopamine transporter (DAT) binding did not significantly differ between early PD levodopa-treated patients with and without dysphagia, as measured by [^{123}I]FP-CIT SPECT imaging. These results suggest that dopaminergic dysfunction alone may not fully explain the presence of dysphagia in this population, indicating the involvement of non-dopaminergic mechanisms in dysphagia pathophysiology.

Unlike previous studies that identified caudate degeneration as a key predictor of dysphagia, our findings highlight tau pathology as an independent risk factor for swallowing impairments. This suggests that dysphagia in levodopa-treated PD patients may be driven by non-dopaminergic neurodegeneration, particularly within tau-related pathways affecting swallowing control (Suzuki et al., 2003).

Research indicates that tau accumulation in the brainstem and cortical swallowing centres correlates with progressive dysphagia, independent of striatal dopaminergic dysfunction (Leopold & Daniels, 2010). These findings underscore the complex interplay between dopaminergic and non-dopaminergic neurodegeneration in PD-related dysphagia.

9.2.4.3 Summary

The relationship between dopaminergic dysfunction and dysphagia in early PD appears to differ between treatment-naïve and levodopa-treated patients. In treatment-naïve PD patients, lower DAT binding in the caudate was significantly associated with dysphagia, suggesting a caudate-specific role in swallowing impairment. In contrast, levodopa-treated PD patients showed no significant differences in DAT binding, indicating that dopaminergic dysfunction alone may not fully explain dysphagia in this group. Instead, tau pathology emerged as an independent predictor of dysphagia, highlighting the contribution of non-dopaminergic neurodegeneration. These findings suggest that DAT imaging may serve as a useful biomarker for identifying dysphagia risk in early PD, while tau accumulation may play a more prominent role in swallowing dysfunction as the disease progresses.

Category	**Early PD Treatment-Naïve Patients**	**Early PD Levodopa-Treated Patients**
Dopaminergic Dysfunction	Lower DAT binding in total striatum, caudate, and putamen in dysphagic patients.	No significant differences in DAT binding between dysphagic and non-dysphagic patients.
Key Predictor of Dysphagia	Lower mean caudate values were significantly associated with dysphagia.	Tau pathology emerged as an independent predictor of dysphagia.
Levodopa Response	Limited improvement in dysphagia with levodopa, suggesting non-dopaminergic compensatory mechanisms.	Dysphagia may be primarily influenced by non-dopaminergic neurodegeneration.
Neurobiological Mechanisms	Caudate dysfunction may impair the supramedullary swallowing network, affecting voluntary and reflexive swallowing.	Tau accumulation in brainstem and cortical swallowing centers correlates with progressive dysphagia.
Clinical Implications	DAT imaging may help identify dysphagia risk and serve as an early biomarker in PD.	Non-dopaminergic factors (e.g., tau pathology) should be considered in dysphagia management.

Table 20. Summary of dopaminergic alterations and their associations with dysphagia in early PD treatment-naïve and levodopa-treated patients.

9.2.4.4 Literature context: Dopaminergic alterations and dysphagia in Early Parkinson's Disease

9.2.4.4.1 Dopaminergic Dysfunction and dysphagia in Early treatment naive Parkinson's Disease patients

Polychronis et al. (2019) demonstrated that early, drug-naïve PD patients with dysphagia exhibited significantly reduced striatal [^{123}I]FP-CIT binding compared to those without dysphagia. The reduction in striatal presynaptic dopaminergic function correlated with dysphagia severity, marking the first reported association between

dopamine transporter deficits and dysphagia severity in PD. Patients with dysphagia showed greater loss of dopaminergic nigrostriatal terminals in the striatum, particularly in the caudate nucleus. Although caudate dopamine loss is typically seen an indicator of PD severity, it may also have a special role in the pathophysiology of dysphagia in early-stage PD, presumably arising from dysfunction in the peripheral or central nervous system. Given that the supramedullary swallowing network relies on dopaminergic signaling within the basal ganglia, disruptions in these circuits may contribute to swallowing impairments (Leopold et al., 2009).

Bilateral activation of the putamen and globus pallidus occurs during swallowing in healthy persons (Suzuki et al., 2003). Dopaminergic impairments in PD may compromise the supramedullary swallowing system, resulting in poor coordination of voluntary and reflexive swallowing mechanisms. Braak's staging of Lewy body pathology indicates that the initial stages of PD (Stage I-II) entail neurodegeneration in the dorsal nucleus IX and X, as well as the locus coeruleus, areas predominantly linked to non-motor symptoms. As disease progresses to the substantia nigra, mesocortex, and neocortex (Stages III-IV), motor symptoms become increasingly pronounced (Braak et al., 2003). Although brainstem structures associated with swallowing are impacted early in PD, severe dysphagia typically manifests in advanced stages, indicating the existence of compensatory mechanisms in cortical regions that postpone symptom manifestation during the initial development of the disease.

Findings from magnetoencephalography (MEG) investigations corroborates this concept, revealing modified brain activity patterns in PD patients without dysphagia (Proudfoot et al., 2014). These patients exhibit increased activity in the lateral premotor, motor, and inferolateral parietal cortex, coupled with reduced activity in the supplementary motor cortex, suggesting adaptive engagement of parallel motor networks to maintain swallowing function. In contrast, PD patients with dysphagia do not exhibit these compensatory cortical activity patterns, indicating a failure of these mechanisms as the disease progresses. This suggests that clinical dysphagia symptoms emerge once neurodegeneration surpasses a critical threshold, leading to the breakdown of both subcortical and cortical motor control of swallowing.

These findings underscore the complex interplay between dopaminergic degeneration, cortical compensation, and dysphagia onset in PD. Future studies should explore longitudinal changes in basal ganglia function and cortical adaptation to better understand how and when dysphagia develops in the course of PD progression.

9.2.4.4.2 Striatal Dopaminergic Dysfunction and Dysphagia Across Parkinson's Disease Stages

Kim et al. (2023) investigated striatal subregional dopaminergic loss associated with dysphagia across different stages of PD, highlighting potential implications for symptom-targeted neuromodulation. Their analysis of overlapping functional clusters revealed that reduced dopamine transporter (DAT) availability in the ventral striatum

correlated with significant dysphagia subitems, particularly pharyngeal-phase impairments linked to dopamine depletion from the anterior to posterior caudate. Despite some lateral differences, the regional patterns of dopaminergic dysfunction were bilaterally symmetrical, indicating a widespread impact of dopamine loss on swallowing function in PD.

9.2.4.4.2.1 Oral and Pharyngeal Phase Dysphagia and Striatal Dopamine Loss

Among seven oral phase subitems, only premature bolus loss was significantly associated with reduced DAT in the bilateral posterior-to-ventral putamen. This dysfunction occurs when the food bolus descends prematurely before the pharyngeal swallowing reflex, likely resulting from PD-related bradykinesia and rigidity impairing tongue movement, which is critical for smooth bolus transport (Nagaya et al., 1998; Wintzen et al., 1994). Dopamine depletion in the posterior putamen, a hallmark of PD, has been directly correlated with UPDRS akinesia-rigidity scores (Yang et al., 2017). Additionally, reduced DAT availability in the bilateral posterior putamen was associated with impaired laryngeal elevation, which is essential for preventing food aspiration (Logemann, 1992).

The study further identified that impaired triggering of the pharyngeal swallow and delayed pharyngeal transit time, both pharyngeal phase subitems, were strongly linked to dopamine depletion in the posterior to posteromedial caudate. Previous studies in stroke patients found that caudate lesions were associated with prolonged laryngopharyngeal response times, which affect pharyngeal bolus transit and swallow initiation (Im et al., 2018). The caudate's role in precise movement initiation supports these findings, as triggering pharyngeal swallowing relies on sensory inputs from multiple cranial nerves and coordinated muscle actions (Kitagawa, 2002; Villablanca, 2010). Additionally, 18F-FDG PET studies have linked swallowing initiation difficulties in PD to reduced metabolism in the anterior cingulate cortex, which functionally connects with the caudate (Kikuchi et al., 2013; Robinson et al., 2012).

9.2.4.4.2.2 Aspiration Risk and Dopaminergic Dysfunction in the Caudate

Food aspiration, the most severe dysphagia-related outcome in PD, was closely associated with dopamine depletion in the medial bilateral caudate. This finding aligns with stroke research, where caudate lesions have been shown to increase aspiration risk (Im et al., 2018). However, aspiration may result from dysfunction across multiple swallowing subitems, rather than being a direct consequence of caudate dopaminergic loss alone (Argolo et al., 2015).

Mapping of dysfunction-related clusters revealed significant overlap within the bilateral ventral striatum and anterior-to-posterior caudate, regions known to be activated during swallowing in healthy individuals (Hamdy et al., 1999). Further cluster analyses incorporating pharyngeal swallowing impairments showed that the ventral striatum had the highest overlap, consistent with animal studies demonstrating that this region facilitates swallowing reflexes via dopamine-related mechanisms (Weerasuriya et al., 1979).

9.2.4.4.2.3 Implications

These findings underscore the critical role of subregional dopaminergic loss in PD-related dysphagia, particularly within the caudate and putamen, and support the potential for targeted neuromodulation strategies to mitigate swallowing dysfunction.

9.2.4.4.2.4 Summary

The relationship between striatal dopaminergic dysfunction and dysphagia in PD varies based on disease stage and affected subregions. In early drug-naïve PD, caudate dopamine depletion correlates with dysphagia severity, disrupting swallowing-related basal ganglia circuits. Cortical compensation may temporarily maintain swallowing function, but as PD progresses, these adaptive mechanisms fail, leading to dysphagia onset.

Across PD stages, oral-phase impairments (e.g., premature bolus loss) are associated with posterior putamen dysfunction, while pharyngeal-phase impairments (e.g., delayed swallow initiation) are linked to caudate dysfunction. Aspiration risk is most strongly associated with medial bilateral caudate dopamine depletion, reinforcing its role in reflexive swallowing control. These findings suggest that swallowing impairments in PD are driven by regional dopaminergic loss, warranting further neuromodulatory interventions targeting affected circuits.

Category	Findings
Striatal Dopaminergic Dysfunction	Reduced DAT binding in the caudate and putamen correlates with dysphagia severity, with ventral striatum and caudate dysfunction linked to pharyngeal-phase impairments.
Compensatory Mechanisms	In early PD, cortical adaptation (premotor and parietal activity) may temporarily maintain swallowing function, but as PD progresses, these mechanisms fail, leading to clinical dysphagia.
Oral-Phase Dysphagia	Premature bolus loss is associated with posterior putamen dopamine depletion, likely due to PD-related bradykinesia and rigidity affecting tongue coordination.
Pharyngeal-Phase Dysphagia	Caudate dysfunction disrupts pharyngeal swallow initiation, with delayed swallow linked to caudate and anterior cingulate dysfunction.
Aspiration Risk	Medial bilateral caudate dopamine loss is strongly associated with aspiration, similar to findings in stroke patients.
Clinical Implications	Early identification of caudate and putamen dysfunction may help predict dysphagia onset; neuromodulation targeting striatal swallowing circuits could be a potential intervention.

Table 21. Literature summary of dopaminergic alterations and their associations with dysphagia in early PD treatment-naïve and levodopa-treated patients.

9.2.5 Limitations and Future Studies

The study of dysphagia in early PD provides critical insights, revealing various predictors linked to this condition. However, multiple limitations and avenues for future research warrant consideration. A primary limitation is the relatively small sample size, particularly within the levodopa-treated cohort. This limitation could restrict the statistical power and generalizability of the findings, necessitating larger, multicenter studies for robust confirmation of these outcomes (Mohamed et al., 2018; Suttrup & Warnecke, 2015). As suggested in the literature, the complexity of dysphagia in PD, influenced by both motor and non-motor symptoms, may require extensive cohorts to yield meaningful insights into its pathophysiology (Suttrup & Warnecke, 2015; Halabi et al., 2023).

Additionally, the cross-sectional nature of the current research design limits the ability to establish causality between dysphagia and associated factors such as neurodegeneration and cognitive impairment, underlining the necessity for longitudinal studies. Longitudinal assessments can enhance understanding of disease progression and reveal early biomarkers for dysphagia, which are vital for timely interventions (Suttrup & Warnecke, 2015; Wang et al., 2017). The identification of distinct predictors of dysphagia in treatment-naïve versus levodopa-treated patients—highlighting neuroanatomic changes such as caudate degeneration and CSF tau pathology—emphasizes the multifactorial nature of this condition (Schröder et al., 2019; Suttrup & Warnecke, 2015).

The study's findings on the lack of significant differences in dopaminergic imaging among levodopa-treated patients suggest that non-dopaminergic pathways may have a more significant impact on dysphagia development than previously thought, directing future studies to explore these pathways using multimodal imaging techniques, including functional MRI and targeted analyses of brainstem structures (Suttrup & Warnecke, 2015; Halabi et al., 2023). Cognitive impairment, indicated by lower MoCA scores in dysphagic patients, did not emerge as an independent predictor when accounting for tau pathology. This interplay suggests a potential overlap between cognitive decline and neurodegenerative processes impacting swallowing, meriting further exploration into the mechanisms at play (Schröder et al., 2019; Suttrup & Warnecke, 2015).

Future research should also consider detailed assessments of swallowing dysfunction through advanced methodologies like high-resolution manometry and videofluoroscopic swallow studies (Wang et al., 2017; Umemoto et al., 2021). Incorporating additional biomarkers, such as neurofilament light chains and glial fibrillary acidic protein, could enhance understanding of the pathophysiology underpinning dysphagia in PD, offering deeper insights into the neurodegenerative scope (Suttrup & Warnecke, 2015; Keage et al., 2014).

An important area for exploration includes the role of sex differences, medication effects, and comorbidities in dysphagia risk. Such factors may refine patient-specific predictors, enhancing tailored interventions to improve both swallowing function and

the overall quality of life for individuals with PD (Suttrup & Warnecke, 2015; Halabi et al., 2023). An inclusive approach accounting for diverse patient variables can deepen understanding and lead to improved clinical outcomes in managing dysphagia.

Chapter 10. Concluding Remarks

Speech and Swallowing Impairments in Early Parkinson's Disease

This thesis provides an in-depth exploration of two critical, underrecognized symptoms of early PD -speech difficulties and dysphagia- across both treatment-naïve and levodopa-treated patient groups. By integrating clinical, neuroimaging, cognitive, and biomarker data, the research highlights the multifactorial and stage-sensitive nature of these non-motor symptoms, challenging traditional views that they emerge only in advanced disease.

Common Themes Across Domains

Both speech and swallowing impairments were shown to be closely tied to specific motor and non-motor features as well as regional dopaminergic deficits within the striatum. Notably, caudate dysfunction emerged as a key neural correlate in both domains, reinforcing its broader role in sensorimotor integration and executive control. However, the limited impact of levodopa on these impairments suggests that non-dopaminergic mechanisms -including cortical network disruptions and tau-related neurodegeneration- are likely contributors, especially as the disease progresses.

Demographic variables such as age and sex did not consistently predict either speech or swallowing difficulties, supporting the view that these symptoms are not simply age-related sequelae but rather specific manifestations of PD pathophysiology. Furthermore, cognitive impairment -particularly in executive and working memory domains- was linked more clearly to speech difficulties than to dysphagia, where tau pathology appeared to play a more dominant role. These findings collectively point to shared yet distinct etiological pathways for communication and swallowing dysfunctions.

Implications for Clinical Practice

This thesis underscores the need for early, domain-specific assessments of speech and swallowing, even in the absence of overt motor or cognitive decline. Standard PD rating scales often fail to capture the nuance and complexity of these impairments. Therefore, targeted tools -including acoustic analysis, swallow studies, and functional imaging- are essential for timely identification and intervention. The data also advocate for a multidisciplinary treatment model that addresses both motor and non-motor contributors to communication and swallowing outcomes.

Emerging evidence for altered functional connectivity and cortical-striatal compensation further supports the use of neuromodulatory interventions (e.g., TMS) and external cueing strategies tailored to individual profiles. However, the heterogeneity of response, particularly in relation to disease stage and treatment status, reinforces the need for personalized and flexible treatment plans.

Research and Methodological Implications

From a research standpoint, the findings highlight the limitations of cross-sectional designs and the need for longitudinal, multimodal studies to capture symptom progression and identify early biomarkers. The differential involvement of tau pathology and dopaminergic depletion in speech versus swallowing suggests distinct trajectories that may require tailored monitoring strategies.

Future studies should also address the observed variability in symptom expression between treatment-naïve and levodopa-treated patients. Investigating how pharmacological and compensatory mechanisms interact over time will be essential to understand the shifting neural substrates of these symptoms. Furthermore, sex-specific analyses, high-resolution brainstem imaging, and advanced speech/swallow analytics will deepen our mechanistic understanding.

Final Reflection

Ultimately, this thesis advances a more integrated and neurobiologically grounded model of speech and swallowing impairment in PD. These symptoms, often overlooked in early-stage management, are now shown to reflect early disruption of complex sensorimotor networks. Recognizing and targeting them from the earliest stages of the disease offers a critical opportunity to improve quality of life, enhance communication, and prevent life-threatening complications such as aspiration.

In conclusion, managing PD-related speech and swallowing impairments requires a shift toward comprehensive, anticipatory care. By combining neurobiological insights with patient-centred clinical strategies, we move closer to a precision medicine framework for addressing the multifaceted challenges of PD.

Chapter 11. Περίληψη

Εισαγωγή
Οι διαταραχές στην ομιλία και η δυσφαγία είναι συχνά και λειτουργικά σημαντικά συμπτώματα της Νόσου του Πάρκινσον (ΝΠ), ωστόσο η εμφάνισή τους και οι υποκείμενοι μηχανισμοί στα αρχικά στάδια της νόσου παραμένουν ελλιπώς κατανοητοί. Η κατανόηση της σχέσης αυτών των διαταραχών με κλινικούς, νευροεκφυλιστικούς και ντοπαμινεργικούς δείκτες είναι καθοριστική για τη βελτίωση της πρώιμης διάγνωσης και παρέμβασης.

Σκοποί
Η παρούσα διατριβή είχε ως στόχο: (1) την περιγραφή και σύγκριση των δημογραφικών και κλινικών χαρακτηριστικών, των επιπέδων βιοδεικτών στο εγκεφαλονωτιαίο υγρό (ΕΝΥ), και των προσυναπτικών ντοπαμινεργικών ελλειμμάτων σε ασθενείς με ΝΠ στα αρχικά στάδια, χωρίς αγωγή και με αγωγή με λεβοντόπα, με και χωρίς διαταραχές ομιλίας και (2) την περιγραφή και σύγκριση των ίδιων μεταβλητών σε ασθενείς με και χωρίς δυσφαγία.

Μεθοδολογία
Τα δεδομένα ελήφθησαν από τη βάση δεδομένων Parkinson's Progression Markers Initiative (PPMI). Οι συμμετέχοντες κατηγοριοποιήθηκαν με βάση την κατάσταση αγωγής (χωρίς αγωγή vs. αγωγή με λεβοντόπα) και την παρουσία ή απουσία διαταραχών ομιλίας ή/και δυσφαγίας. Διενεργήθηκαν συγκρίσεις ομάδων και λογιστικές παλινδρομήσεις χρησιμοποιώντας κλινικές κλίμακες (MDS-UPDRS, Hoehn & Yahr, MoCA), βιοδείκτες ΕΝΥ (άλφα-συνουκλεΐνη, αμυλοειδές-βήτα, ολική tau, φωσφορυλιωμένη tau) και απεικόνιση DAT-SPECT της προσυναπτικής ντοπαμινεργικής λειτουργίας (δέσμευση στο κέλυφος και τον κερκοφόρο πυρήνα).

Αποτελέσματα
Οι διαταραχές στην ομιλία συσχετίστηκαν σημαντικά με αυξημένη κινητική σοβαρότητα και μειωμένη ντοπαμινεργική δραστηριότητα στο κέλυφος. Αντίθετα, η δυσφαγία συσχετίστηκε κυρίως με ντοπαμινεργικά ελλείμματα στον κερκοφόρο πυρήνα σε ασθενείς χωρίς αγωγή, και με αυξημένα επίπεδα tau και pTau στο ΕΝΥ σε ασθενείς που λάμβαναν λεβοντόπα. Ούτε οι διαταραχές ομιλίας ούτε η δυσφαγία προβλέφθηκαν σημαντικά από την ηλικία ή το φύλο. Η γνωστική έκπτωση συσχετίστηκε με τις διαταραχές ομιλίας, αλλά δεν αποτέλεσε σταθερό προβλεπτικό παράγοντα για τη δυσφαγία.

Συμπεράσματα
Οι διαταραχές στην ομιλία και την κατάποση στην αρχική φάση της ΝΠ αντικατοπτρίζουν πολύπλοκες αλληλεπιδράσεις μεταξύ κινητικών, γνωστικών και νευροεκφυλιστικών διεργασιών. Τα ντοπαμινεργικά ελλείμματα, ιδίως σε περιοχές του ραβδωτού σώματος, συμβάλλουν και στις δύο διαταραχές, ωστόσο διαφορετικοί μηχανισμοί -όπως η παθολογία tau και η τοπική απώλεια ντοπαμίνης- ενδέχεται να υποστηρίζουν την εκδήλωσή τους σε διαφορετικά στάδια και φάσεις αγωγής της νόσου. Τα ευρήματα υπογραμμίζουν την ανάγκη για πρώιμες, στοχευμένες και πολυδιάστατες προσεγγίσεις αξιολόγησης, με σκοπό τη βελτιστοποίηση της κλινικής διαχείρισης και την ανάπτυξη εξατομικευμένων παρεμβάσεων για διαταραχές επικοινωνίας και κατάποσης στη ΝΠ.

Λέξεις-κλειδιά: Νόσος του Πάρκινσον, Διαταραχές Ομιλίας, Δυσφαγία, Ντοπαμινεργικό Έλλειμμα, Βιοδείκτες Εγκεφαλονωτιαίου Υγρού

Chapter 12. Abstract

Introduction

Speech difficulties and dysphagia are prevalent and functionally significant symptoms in Parkinson's Disease (PD), yet their onset and underlying mechanisms in early-stage patients remain poorly characterized. Understanding how these impairments relate to clinical, neurodegenerative, and dopaminergic markers is critical for improving early diagnosis and intervention.

Aims

This thesis aimed to (1) describe and compare the demographic and clinical characteristics, CSF biomarker profiles, and presynaptic dopaminergic deficits of early treatment-naïve and early levodopa-treated PD patients with and without speech difficulties; and (2) describe and compare the same variables in patients with and without dysphagia.

Methods

Data were obtained from the Parkinson's Progression Markers Initiative (PPMI) database. Participants were grouped by treatment status (treatment-naïve vs. levodopa-treated) and by the presence or absence of either speech impairment or dysphagia. Group comparisons and logistic regression analyses were conducted using clinical scales (MDS-UPDRS, Hoehn & Yahr, MoCA), CSF biomarkers (α-synuclein, amyloid-β, total tau, phosphorylated tau), and DAT-SPECT imaging of presynaptic dopaminergic function (caudate and putamen binding).

Results

Speech difficulties were significantly associated with greater motor severity as well as reduced dopaminergic activity in the putamen. In contrast, dysphagia was more closely linked to caudate dopaminergic deficits in treatment-naïve patients and to elevated Cerebrospinal Fluid (CSF), tau and pTau levels in levodopa-treated patients. Neither speech nor swallowing impairments were significantly predicted by age or sex. Cognitive impairment contributed to speech difficulties but was not a consistent predictor of dysphagia.

Conclusions

Speech and swallowing impairments in early PD reflect complex interactions between motor, cognitive, and neurodegenerative processes. Dopaminergic deficits, particularly in striatal subregions, contribute to both impairments, but distinct mechanisms -such as tau pathology and regional dopamine loss- may underlie their expression at different disease stages and treatment phases. These findings underscore the need for early, targeted, and multidimensional assessment approaches to support clinical management and research into tailored interventions for communication and swallowing disorders in PD.

Key words: Parkinson's Disease, Speech difficulties, Dysphagia, Dopaminergic Deficit, Cerebrospinal Fluid Biomarkers

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