The Relationship Between Dysarthria, Primary Motor Profile, and Cognition in Idiopathic Parkinson's Disease

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Abstract

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While previously considered purely a motor disorder, Parkinson's disease (PD) is now recognized as a complex constellation of motor and non-motor symptoms. Current research to better understand the heterogeneity of symptoms has uncovered potential links between motor and non-motor features. Specifically, converging evidence suggests an association between the presence of dysarthria and cognitive decline, and that this relationship may be mediated by primary motor phenotype (i.e., tremor-dominant and non-tremor dominant). The aim of this study is to examine this purported relationship through two distinct, yet related, experiments.

Experiment 1 utilized perceptual ratings of naturalness, articulatory precision, and intelligibility to examine the relationship between dysarthria, primary motor presentation (tremor versus non-tremor), and cognition in 9 individuals with PD. 10 experienced SLPs used a visual analog scale to rate naturalness and articulatory precision. Orthographic transcription was used to calculate intelligibility. Cognition was assessed with the Parkinson's Disease Cognitive Rating Scale (PD-CRS) and primary motor presentation was rated with the Unified Parkinson's Disease Rating Scale (UPDRS). Results aligned with the hypothesis and indicated that participants with increased non-tremor symptom severity had more impaired ratings of speech naturalness and articulatory precision. Furthermore, participants with mild cognitive impairment (MCI) had more impaired speech ratings than individuals without cognitive impairment, which is consistent with a small, but growing, literature.

In Experiment 2, 192 individuals with PD were examined from the Parkinson's Progression Marker Initiative (PPMI) – a longitudinal, controlled database of individuals with de novo PD. Speech ratings, and tremor and non-tremor symptom severity, as measured by the UPDRS, in early PD (T_1) were examined as predictive factors of cognitive status 4-5 years later (T_2). Results are consistent with the hypothesis and suggest that speech functioning around the time of diagnosis is associated with a non-tremor dominant motor profile, and is predictive of dementia 5-7 years post diagnosis. Additionally, the tremor dominant group performed worse or equal to the non-tremor dominant group across cognitive domains, which is contrary to the literature that suggests worse cognitive functioning in non-tremor dominant PD.

Findings from both experiments align, in part, with current literature implicating breakdowns in cholinergic-mediated channels, thought to be more severely depleted in individuals with pervasive cognitive decline and a non-tremor presentation, as a possible contributor to dysarthria from PD. More research is needed to better understand these relationships.

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Dedication

To Grandpa L.

Chapter 1: Introduction

Overview

Parkinson's disease (PD) is the second most common age-related neurodegenerative disease, affecting up to 1 million people in the United States. Features most notably associated with PD include tremor at rest, rigidity, akinesia (or bradykinesia), and postural instability (Jankovic, 2008). These four cardinal signs represent the chief features of PD, but are merely the tip of the iceberg. PD was once thought to present as a pure motor disorder. However, with medical advances, specifically, the introduction of levodopa therapy, secondary motor and nonmotor characteristics have received increased focus in the literature. As such, PD is now recognized as a disease that spans multiple motor and nonmotor systems.

As a result of this increased breadth of characterization, attempts to elucidate the full range of motor and nonmotor features have emerged in recent literature (Chaudhuri & Sauerbier, 2016; Levy et al., 2000a; Marras & Chaudhuri, 2016; Olanow et al., 2011). Secondary motor symptoms – motor disruptions that are in addition to cardinal motor features - are being carefully examined and described (Klopfenstein, 2016; Rektorova et al., 2016; Weir-Mayta et al., 2017). Additionally, there has been an amplified focus on nonmotor features, such as altered cognition, neuropsychiatric symptoms, sleep disorders and fatigue.

Studies of potential associations between motor and nonmotor features in PD are rapidly expanding. For example, there has been increased attention given to cognitive changes that may be associated with well-known motor traits (Burn, 2006; Gago et al., 2009a; Herman et al., 2014; Moustafa et al., 2016). Emerging from this line of research are studies suggesting that dysarthria may uniquely link to cognitive impairment (Paulo Bugalho & Viana-Baptista, 2013; Domellöf et

al., 2011; Elgh et al., 2009; Levy et al., 2000a; Rektorova et al., 2016; Schneider et al., 2015). The purpose of this proposed study is to better understand this purported relationship between the motor characteristic of dysarthria and the nonmotor characteristic of cognitive impairment.

Functional Anatomy

Critical to this discussion is an understanding of the non-diseased state of key mechanisms that play a role in the development of motor and non-motor features of PD. Although PD pathology attacks a range of vulnerable nerve cells, the basal ganglia are chiefly implicated, due to their prominent roles in cognition and motor control. The basal ganglia are a group of functionally-connected cell bodies that integrate and process complex motor, cognitive, and limbic information (Albin et al., 1989; DeLong & Wichmann, 2007; Olanow et al., 2011). The primary basal ganglia structures are the caudate nucleus (including head, body, and tail), putamen, globus pallidus (internal and external segments), subthalamic nucleus, and subtantia nigra (pars reticulate and pars compacta). The caudate nucleus and putamen are commonly referred to as the striatum (or dorsal striatum).

The basal ganglia are viewed as a functionally connected network, where different functions and circumstances result in distinct activation areas and patterns (Olanow et al., 2011). Signals arise from the cerebral cortex and thalamus and reach the basal ganglia for processing and integration (Olanow et al., 2011) before information is conveyed back to the appropriate cortical region or brainstem. Nuclei of the basal ganglia are broadly characterized as input, output, or intrinsic nuclei. Input nuclei receive incoming information, most often from the cerebral cortex, thalamus, or substantia nigra, while output nuclei send information to the thalamus for further transfer to the cerebral cortex. Intrinsic nuclei act as ephemeral processing channels that relay information between the input and output nuclei (DeLong & Wichmann,

2007; Lanciego et al., 2012). Along with other brain regions such as the cerebral cortex, thalamus, and brainstem, basal ganglia nuclei form a complex network of channels, termed the basal circuits. Comprised of direct and indirect pathways, the basal ganglia circuits inform several models of PD and will be examined further in a model-specific context.

Neuropathology of PD

The pathological hallmark of PD is dopaminergic cell loss due to the invasion of Lewy body proteins. PD is considered a synucleinopathic disease, marked by the ongoing accumulation of these proteins. Braak and colleagues (2005 & 2009) propose that Lewy body pathology attacks a specific type of vulnerable neuron, resulting in brain lesions that evolve in a predictable and relatively consistent manner across individuals. This framework, the Braak Model, is a staging model that suggests that PD pathology begins at two sites and progresses in a sequential, and predicable, pattern (Braak & Del Tredici, 2009) invading vulnerable cells along its path.

There are many types of nerve cells within the nervous system, yet only a few have been shown to be susceptible to the abnormal Lewy proteins (Braak & Del Tredici, 2009). Historically, cells vulnerable to PD pathology were considered based solely on the type of neurotransmitter synthesized in the neuron. More recently, Braak and colleagues determined that criterion to be insufficient. Nerve cells that are vulnerable to PD pathology share several properties and are a specific type of projection neuron (see Figure 1). Susceptible neurons feature an axon that is disproportionately long and slender relative to the size of the cell body. Conversely, Lewy proteins do not invade projection cells with a relatively short axon (Braak et al., 2006). Neurons with a relatively thick myelin sheath are also resistant due to the protective nature of the myelin coating in preventing pathological growth.

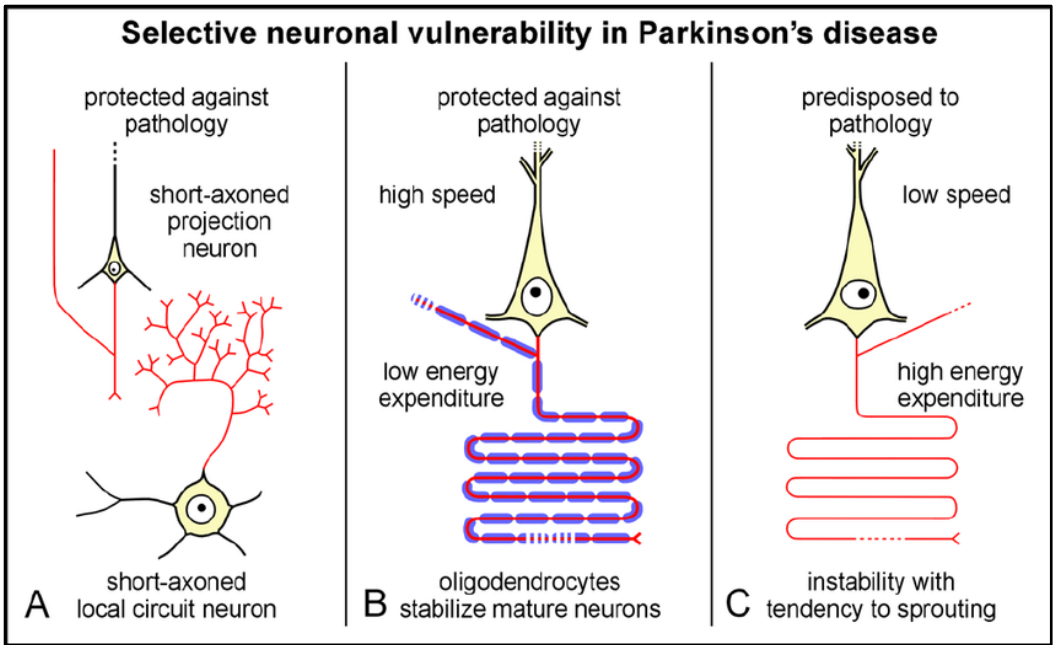

Figure 1. (A) Projection neurons with short axons do not become involved. (B) Projection neurons with a sturdy myelinated axon are resistant. (C) Poorly myelinated or unmyelinated projection neurons are vulnerable to Lewy pathology (Braak & Del Tredici, 2009).

In addition, all vulnerable cells contain the presynaptic protein α-synuclein (Del Tredici & Braak, 2012). This protein is thought to act as a modulator of synaptic transmission in non-diseased neurons (Stefanis, 2012), giving α-synuclein a central role in neurotransmitter release. An abnormal aggregation of α-synuclein leads to a buildup that comprises the bulk of the Lewy body protein, leading to eventual neuron dysfunction and death in most cases.

The Braak Model of Disease Progression

The Braak Model accounts for the span of PD pathology from the earliest known prodromal phase through end stage, marked in six stages. Initial growth within the lower medulla oblongata and the anterior olfactory structures (Braak & Del Tredici, 2009; Daniel & Hawkes, 1992; Rolheiser et al., 2011) mark Braak stage 1. From here, Lewy body pathology is thought to appear in the dorsal motor nucleus of the vagus nerve. Along with decreased olfaction, autonomic symptoms such as constipation, urinary and sexual dysfunction, and blood flow changes are important pre-motor symptoms that are attributed to this early Lewy pathology (Palma & Kaufmann, 2014). In recent years, these symptoms have been studied with increased

frequency and are part of a growing body of evidence to support early detection of PD (Palma & Kaufmann, 2014).

Lesions in the dorsal motor nucleus are more severe in stage 2. In addition, protein aggregates are said to occur in the brainstem beyond the medulla to the pons (Braak & Del Tredici, 2009). Stage 2 specifically implicates the locus coeruleus, a prominent noradrenergic nucleus with a role in integration of sensory information and maintenance of homeostasis (Samuels & Szabadi, 2008). Throughout stage 2, Lewy bodies remain isolated to areas outside of the brain and the disease is said to be progressing in an "asymptomatic" state; however, this is more accurately described as a premotor state, where subtle changes are often brushed off as typical age-related changes, and PD is not suspected due to the absence of motor symptoms. Breakdowns of the noradrenergic system in stage 2 have been deemed responsible for changes in the sleep/wake cycle and arousal (Benarroch, 2009; Samuels & Szabadi, 2008).

Braak stage 3 is marked by involvement of the amygdala as well as cholinergic axons in the basal forebrain. The substantia nigra is also invaded during stage 3, where a dense, and thus particularly vulnerable, population of poorly myelinated dopaminergic neurons reside. Braak and colleagues propose that once Lewy pathology reaches the substantia nigra, affected neurons decline more rapidly than in previous stages. Individual differences and environmental factors influence the timing and neurodegeneration, and clinically-recognized symptoms will emerge for some at this stage (Braak et al., 2006; Braak & Del Tredici, 2009). Emerging symptoms include the hallmark signs of PD such as bradykinesia, tremor, and rigidity. Currently, it is estimated that approximately one-third of dopaminergic neurons in the substantia nigra are depleted when clinical motor symptoms emerge (Braak & Del Tredici, 2009; Del Tredici et al., 2002; Stefanis,

2012), a lower figure than the 50%-80% depletion that was traditionally cited to mark the symptomatic phase (Cheng et al., 2010; Goldenberg, 2008).

The neocortex remains uninvaded throughout stage 4, with Lewy pathology involving more of the mesocortex (Braak et al., 2004). PD pathology in the mesocortex is said to result in changes to emotion, including anxiety, depression, and avolition. Motivation and reinforcement learning/reward processing are important cognitive processes influenced by the mesolimbic system, which are thought to become impaired during Braak stage 4 (Schott et al., 2007).

From this point, Lewy proteins will progress to the neocortex, marking stage 5 of the disease. Severity of degeneration increases at sites previously invaded in earlier stages, and the autonomic, limbic, and somatomotor systems exhibit substantial functional impairments (Braak & Del Tredici, 2009). Balance disruptions emerge and the disease is said to correleate with Hoehn and Yahr stages III and IV (Braak & Del Tredici, 2009; Hawkes et al., 2010). As Lewy pathology settles in the neocortex, sensory association areas are affected. Visual disturbances manifest as difficulty reading, diplopia, and visuospatial misjudgments (Hawkes et al., 2010; Weil et al., 2016). Visual hallucinations are thought to occur later in the disease course and are considered a risk factor for dementia (Weil et al., 2016).

Stage 6 is the final stage of the Braak model, where PD pathology has spread to its fullest topographic extent. Specifically, the primary fields of the neocortex to include the first order sensory association fields and premotor areas are affected (Braak et al., 2003, 2004). Preexisting damage is compounded and individuals are likely to become immobile (Del Tredici & Braak, 2012).

While the Braak Model provides important insight into the neuropathological disease process, it is based on the assumption that PD progresses in a predictable and consistent pattern

across individuals, with only speed of progression and individual factors altering the course. Thus, the Braak model alone is unable to account for cognitive and motor heterogeneity that is increasingly observed in PD.

Clinical Course

Initial PD diagnosis is dependent upon presentation of cardinal motor features (i.e., tremor, bradykinesia, etc.), absence of exclusionary symptoms, and response to levodopa; however, diagnosis can be clouded when presentation is non-classical (Jankovic, 2008). Furthermore, current views suggest that a prodromal phase likely occurs for many years before hallmark symptoms emerge. This pre-diagnostic phase has been reported to begin as many as 20 years before primary motor presentation (Olanow et al., 2011) and may be marked with olfactory, sleep, or psychiatric changes, indicating disease activity in the olfactory bulb and lower brainstem (Del Tredici & Braak, 2012; Postuma & Berg, 2019).

Motor Characteristics of PD

Primary motor symptoms typically present in an insidious manner and are often overlooked initially. Secondary motor symptoms include dysarthria, dysphagia, freezing, as well as occasional reemergence of the glabellar and palmomental primitive reflexes; these characteristics frequently co-occur and may be present at diagnosis (Jankovic, 2008; Olanow et al., 2011). Collectively, primary and secondary motor features span multiple neural systems. See Table 1.1 for further description of these motor features.

Motor Subtypes in PD

Although PD pathology is thought to invade in sequential stages (Braak et al., 2006), clinical presentation of symptoms often differs across individuals (Kehagia et al., 2010). In an

effort to navigate the heterogeneity of the disease, subtypes based on clusters of motor and non-motor symptoms have been proposed (Alves et al., 2006; Herman et al., 2014; Jankovic, 2008). Empirically derived and contingent upon predominant symptoms, as measured by the Unified Parkinson's Disease Rating Scale (UPDRS) (Goetz et al., 2007), classification commonly involves grouping individuals as either tremor-dominant disease, non-tremor dominant disease, or mixed/indeterminate type (Jankovic, 2008; Kotagal, 2016; Moustafa & Poletti, 2013). This stratification is particularly valuable when exploring relationships between PD characteristics.

Table 1. Primary and secondary motor features of PD (Duffy, 2013; Jankovic, 2008; Kim et al., 2015).

Primary Motor Feature	Characteristics
Tremor	Typically a resting tremor
	Decreases during voluntary movement
	Rate of 3-8 Hz
	Typically unilateral
	May involve lips, tongue, jaw, and chin
Bradykinesia or Hypokinesia	Slowness of movement
	Decreased amplitude of movement
	Difficulty with planning, initiating, and executing movement
	Difficulty executing repetitive movements
	Reduced reaction time
	Reduced arm swinging
	Masked facies
	Micrographia
Rigidity	Resistance to passive stretch
	Cogwheeling
	Paucity of movement
Akinesia	Freezing/ motor blocks
	Start or turn hesitation
Postural Instability	Flexed neck and trunk posture
	Flexed elbows and knees
	Decreased postural reflexes
Secondary Motor Feature	**Characteristics**
Dysarthria	Impaired voice
	Increased rate
	Prosodic abnormalities
	Articulatory imprecision
	Reduced utterance length
	Reduced respiratory support
Dysphagia	Incoordination with mastication and lingual motion during oral prep and bolus transport
	Increased speed of swallow
	Delayed initiation of pharyngeal swallow
Dystonia	Foot or hand cramping
	Generalized twitching and cramping secondary to levodopa therapy
Reflexes	Reemergence of primitive glabellar reflex
	Reemergence of palmomental reflex

The tremor-dominant subtype, which represents a more purely dopaminergic manifestation of PD, is characterized by tremor, rigidity, and bradykinesia, as well as slower disease progression initially and more pronounced response to dopaminergic therapy (Jankovic, 2008). Conversely, the non-tremor subtype is characterized by a relative resistance to dopaminergic therapy, and is associated with more rapid disease progression, and increased severity of disease (Jankovic, 2008; Levy et al., 2000b). Table 1.2 contrasts distinguishing features among the tremor-dominant and non-tremor subtypes of PD, revealing distinct motor and cognitive profiles.

Table 2. Primary characteristics of tremor-dominant and non-tremor subtypes of Parkinson's disease (PD).

	PD Subtypes	
	Tremor Dominant	**Non-Tremor Dominant (PIGD / Akinetic-Rigid)**
Prognosis	Good prognosis with slower progression	Poorer prognosis with more rapid progression
Dopaminergic response	Good response to levodopa	Not as responsive to levodopa
Motor profile	Tremor, as well as bradykinesia, rigidity	Bradykinesia, rigidity Postural instability, gait difficulty
Cognitive profile	Mild cognitive impairment; Executive dysfunction (problems with rule shifting, planning, attentional set-shifting, working memory, feedback-based learning)	More rapid cognitive decline with higher likelihood of progression to dementia; Problems with semantic fluency, auditory verbal learning, visuospatial skills, verbal and visual memory

Note. Based on Eggers et al., 2012; Eggers, Kahraman, Fink, Schmidt, & Timmermann, 2011; Factor et al., 2011; Jankovic, 2008; Kehagia et al., 2013; Moustafa & Poletti, 2013; Sauerbier et al., 2016; Thenganatt & Jankovic, 2014)

It is posited that tremor-dominant and non-tremor phenotypes represent unique pathophysiological underpinnings evidenced by lesion variation and differing involvement of the

basal ganglia and cerebello-thalamic circuits (Helmich et al., 2012). This is further supported through evidence of neurochemical distinctions among subtypes (Schiess et al., 2000; Schiess, Zheng, Soukup, Bonnen, & Nauta, 2000), suggesting that tremor-dominant and non-tremor phenotypes represent divergent groups that can be classified on an intrinsic level beyond clinical presentation (Spiegel et al., 2007).

The non-tremor subtype is often further categorized as (or used interchangeably with) a postural instability/gait difficulty (PIGD) subtype (Gago et al., 2009a; Herman et al., 2014) an akinetic-rigid subtype (Eggers et al., 2012), or an axial[1] subtype (reflecting posture and gait difficulty). While the nomenclature is varied in the literature, the PIGD, akinetic-rigid, and axial classifications represent a non-tremor dominant subtype.

Dysarthria in PD

Central to the proposed study is the secondary motor symptom of dysarthria. Speech impairment is pervasive in individuals with PD; nearly 90% will develop dysarthria at some point during the course of the disease (Fox & Ramig, 1997). Hypokinetic dysarthria, the most commonly associated dysarthria with PD, may impair any or all levels of speech (Duffy, 2013). Resulting deficits are imbued throughout aspects of speech motor control and present clinically as decreased flexibility, speed, amplitude, and range of speech (Spencer, 2007; Spencer et al., 2009; Spencer & Rogers, 2005).

While hypokinetic dysarthria can lead to impairment across the range of speech subsystems, including the respiratory, laryngeal, velopharyngeal, and articulatory components (Duffy, 2013; Ramig et al., 2007), the most evident perceptual characteristics of this

[1] Axial motor signs are associated with midline body structures, and typically include postural instability, gait difficulty, and speech disruption (Gago et al., 2009). They are often contrasted with appendicular motor signs, associated with limb function, such as tremor and bradykinesia.

dysarthria are impaired voice, articulation, and prosody. In particular, reduced loudness, monopitch, monoloudness, reduced stress, repeated phonemes, and rapid rate are considered distinguishing characteristics (Chenausky et al., 2011; Duffy, 2013).

The perceptual characteristics of hypokinetic dysarthria can vary across individuals. Regardless of the presentation, these speech changes often lead to reduced intelligibility (Fox & Ramig, 1997; Sapir, 2014) and naturalness (Klopfenstein, 2016; Weir-Mayta et al., 2017), and can considerably impact communicative participation and quality of life (McAuliffe et al., 2017; Miller et al., 2007). Most germane to the proposed study are the constructs of naturalness, articulatory precision, and intelligibility.

Naturalness of Speech in PD

Naturalness of speech refers to the degree to which speech conforms to an expected or conventional speech pattern. This perceptual characterization is garnered from overall adequacy of prosodic properties such as rate, rhythm, intonation, and intensity, as well as voice quality (Duffy, 2013; Weir-Mayta et al., 2017). The prosodic changes emanate from deviations to speech subsystems that span respiratory, laryngeal, velopharyngeal, or articulatory components. (see Table 1.3). Pausing characteristics may also be affected in hypokinetic dysarthria, altering naturalness of speech, although this is a lesser studied phenomenon that may not always be present, even when naturalness is impaired (Duffy, 2013).

Table 3. Speech subsystem deviations that may affect naturalness in individuals with hypokinetic dysarthria (Adapted from Duffy, 2013).

Respiratory
Reduced strength and endurance
Reduced airflow volume
Irregular breathing patterns
Reduced vital capacity
Laryngeal
Decreased intensity
Decreased pitch range and variability
Increased voice tremor and flutter
Poor pitch control
Velopharyngeal
Increased nasalization
Articulatory
Reduced or increased speech rate or variability (connected or AMRs)
Intensity variations within and between syllables

Naturalness of speech is largely responsible for undertone signals that send additional cues related to a speaker's message. The monotonous quality associated with reduced naturalness can lead to negative connotations and mixed messages by reducing an individual's ability to signal emphatic meaning (Duffy, 2013). This phenomenon is commonly described in the stuttering literature, where reduced speech naturalness also occurs, particularly as a consequence of compensatory strategies (Martin et al., 1984). Naturalness is thus considered a useful functional outcome measure due to its value as an independent contributor to an individual's ability to communicate (Anand & Stepp, 2015) as well as influence on communicative participation (Eadie et al., 2006). While aspects of naturalness can be measured

acoustically with discrete variables (e.g., related to pitch or stress placement), it is often measured holistically via perceptual ratings, such as rating scales or a visual analog scale (VAS). VAS, in particular, has been shown to be valid and reliable in the perceptual judgments of dysarthric speech (Spencer et al., 2009; Stipancic, Tjaden & Widling, 2016; Weir-Mayta et al., 2017).

Articulatory Precision in PD

Articulatory precision refers to how accurately speech sounds are produced. Errors such as phoneme distortions, deletions, additions, and/or substitutions degrade articulatory precision. These errors likely stem from, at least in part, impairments affecting a variety of components in the speech subsystem, including lips, tongue, and jaw (see Table 1.3). As a result of these changes, individuals with hypokinetic dysarthria might demonstrate articulatory undershooting, resulting in indistinct speech sound production or syllable boundary (Duffy, 2013). It has also been suggested that phonetic complexity plays an important role in articulatory precision, such that articulatory decrement is increased as greater demands are placed on articulators (Kuruvilla-Dugdale et al., 2020).

Table 4. Deviations that may affect articulation in individuals with hypokinetic dysarthria (Adapted from Duffy, 2013).

Lip
Reduced amplitude or velocity of movement
Reduced amplitude and duration of muscle action potentials
Articulatory undershoot
Rigidity or stiffness
Tremor at rest, during sustained postures, and active or passive movement
Tongue
Reduced endurance and strength
Jaw
Reduced stability during vowel prolongation
Tremor at rest, during sustained postures, and active or passive movement
Poor visuomotor tracking of movements
Poor maintenance of depressor and elevator temporal reciprocity

Intelligibility of Speech in PD

Intelligibility of speech, defined as speech clarity or the extent to which a listener can understand a speaker's message, is a perceptual measurement influenced by respiration, phonation, articulation, prosody, and resonance (Fox & Ramig, 1997; Sapir, 2014). Intelligibility ratings are considered a reflection of the acoustic signal created by the speaker (Duffy, 2013) and can objectively determine the accuracy with which the speaker's intended message was received by the listener (Kate Bunton, Ray D. Kent, Jane F. K, 2001). Of note, intelligibility is distinct from comprehensibility, which includes contextual information that may improve understanding. A related, but distinct, measure of speech is understandability. Ratings

of understandability of speech are considered a perceptual estimate of intelligibility (Yorkston & Beukelman, 1978).

Taken together, naturalness, articulatory precision, and intelligibility serve as relatively holistic measurements of speech dysfunction. When examining dysarthria in complex, heterogeneous populations, such as those with PD, global measures are beneficial as they are less influenced by the individual variability associated with discrete measures, such as pitch, rate of speech, or presence of dysfluencies (Tjaden, 2008; Tjaden, Lam, et al., 2013; Tjaden, Richards, et al., 2013).

Nonmotor Characteristics of PD

Nonmotor characteristics of PD have received increased focus in recent literature. Symptoms include, but are not limited to, sensory disturbance, autonomic dysfunction, gastrointestinal symptoms, sleep disturbance, neuropsychiatric disturbance, and cognitive decline. Individuals with PD consistently rate nonmotor symptoms as most troublesome on self-report tools (Politis et al., 2010) and as the principle factor impacting their quality of life (Martinez-Martin, Rodriguez-Blazquez, Kurtis, Chaudhuri, 2011; Sauerbier, Jenner, Todorova, & Chaudhuri, 2016). Table 3 provides an overview of nonmotor symptoms of PD.

Nonmotor symptoms tend to co-occur with other nonmotor symptoms, particularly pain, sweating, anxiety and fatigue; they are considered to interact with, and amplify, other nonmotor symptoms (Ehgoetz Martens & Shine, 2018). For example, significant interactions of anxiety and fatigue have been documented (Fabbri et. al, 2017). Some nonmotor features are thought to predate motor symptoms by as much as 10 to 15 years (Chaudhuri & Sauerbier, 2016). While not recognized as a distinct clinical entity prior to PD diagnosis, symptoms such as disordered

sleep, olfactory dysfunction, constipation, and depression, that occur before the start of motor symptoms, have been retroactively attributed to the disease.

Table 5. An overview of select nonmotor symptoms of PD (Marras & Chaudhuri, 2016; Olanow et al., 2011; Stacy, 2011)

Nonmotor Feature	Example Characteristics
Cognitive	Executive dysfunction
	Visuospatial deficits
	Memory deficits
	Dementia
	Language deficits
Neuropsychiatric	Anxiety
	Depression
	Hallucinations
	Impaired Impulse control
Sensory	Loss of olfaction (anosmia)
	Loss of taste
Autonomic	Urinary dysfunction
	Sexual dysfunction
	Gastrointestinal disturbances
	Orthostatic hypotension

Cognitive Impairment in PD

Cognitive symptoms are now recognized as independent nonmotor symptoms of PD that may occur at any stage of the disease (Bohlhalter & Kaegi, 2011). Nearly half of individuals are estimated to have a mild cognitive impairment within the first 3-5 years post diagnosis (Dag Aarsland & Kurz, 2010; Kehagia et al., 2010). Dementia is also noted as a potential consequence of PD. True prevalence is not known, although estimates from 32%-80% have

been reported (Janvin et al., 2006; Rosenthal et al., 2010), with differences in study design and diagnostic criteria likely influencing the wide range.

Coupled with this increased focus comes improved characterization of deficits, which affect various domains such as memory, executive function, language and visuospatial function (Adler, 2009; Janvin et al., 2006; Mamikonyan et al., 2009). A "dysexecutive" profile is common in PD. This profile is characterized by impairment in higher-order cognitive skills such as organization, which includes planning, working memory, cognitive flexibility, and regulation, and relies upon integration of skills such as initiation of action, self-control, and decision-making (Emre et al., 2007; Kelly et al., 2015; Rosenthal et al., 2010). These deficits significantly impact daily function in individuals with PD, across all levels of cognitive impairment (Rosenthal et al., 2010).

While cognitive impairment is prevalent in PD, it is increasingly recognized as non-uniform. Traditionally, mild cognitive impairment in PD has been used as an umbrella term to describe any impairment in a stage that is between normal function and dementia (Kehagia et al., 2013; Robbins & Arnsten, 2009). This "single-track" view is problematic. Increasingly, studies describing patterns of mild cognitive impairment have revealed distinct presentations that are not merely a function of disease progression; rather, specific types of deficits are now suggested to be predictive of progression to dementia (Dag Aarsland & Kurz, 2010; Alves et al., 2006; Janvin et al., 2006; Mills et al., 2016; Rosenthal et al., 2010). Models of cognitive impairment that account for underlying neuropathological differences, such as the dual syndrome hypothesis (Kehagia et al., 2010, 2013), may help explain this cognitive heterogeneity and progression to dementia in PD.

The Dual Syndrome Hypothesis

The Dual Syndrome Hypothesis, developed by Kehagia, Barker, and Robbins (2010 & 2013), considers the cognitive heterogeneity in PD through the window of distinct neurotransmitter involvement. The authors combine data from neuropsychological task performance, neuroimaging, genetic differences, and pharmacological manipulation to explain cognitive heterogeneity and reveal distinct cognitive profiles. The varied neurodegeneration that occurs throughout the disease process, affecting each individual at different rates, is viewed as the impetus for the specific cognitive profile with which an individual may present.

According to the Dual Syndrome Hypothesis, there are two distinct clinical presentations of cognitive impairment in PD: (1) a mild deficit with executive dysfunction, stemming from depleted dopamine-dependent channels, and (2) a profile of more pervasive deficits that involves additional neurotransmitters and progresses to dementia (see Figure 2).

The first presentation, a dopaminergically mediated profile, presents with impairment in the fronto-striatal loop connecting the basal ganglia with the pre-frontal cortex. This compromised pathway results in a mild cognitive impairment with executive function deficits impacting rule shifting, planning, attentional set shifting, and working memory (Kehagia et al., 2013). This cognitive profile is thought to correspond with a tremor-dominant motor profile (Kehagia et al., 2013).

The second track purported by the Dual Syndrome Hypothesis largely implicates cholinergic pathways, and presents with prodromal visuospatial deficits and impaired semantic fluency. This cognitive profile is more commonly associated with progression to dementia (Alves et al., 2005, 2006; Emre et al., 2007; Herman et al., 2014; Levy et al., 2000b; Rosenthal et al., 2010). Specifically, impaired semantic fluency and pentagon copying at baseline have been

found to be significant predictors of development of global cognitive decline at follow-up (Williams-Gray et al., 2007). It has been suggested that this cognitive profile corresponds with a non-tremor motor phenotype, characterized by a dominance of non-tremor motor symptoms, such as postural instability and gait disturbance (Kehagia et al., 2013).

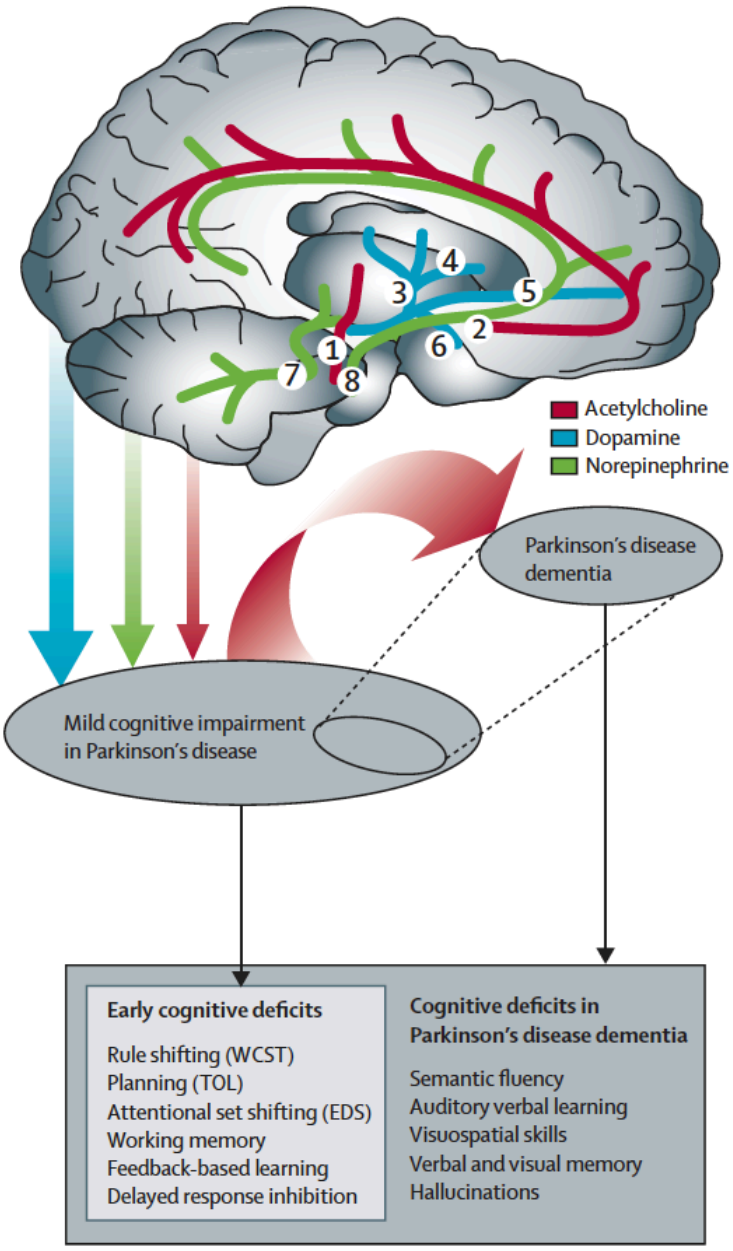

Figure 2. The Dual Syndrome Hypothesis in PD. Distinct cognitive profiles are contrasted. Pathways outlined are those compromised by the disease and implicated in cognitive impairment. The neuropsychological deficits characterizing the dysexecutive syndrome in the mild cognitive impairment are mediated mainly by fronto-striatal dopaminergic dysfunction (blue). Noradrenergic dysfunction (green) is thought to underlie attentional set shifting deficits, which forms part of the dysexecutive syndrome. Some frontal cholinergic deficit (red) also compromises early Parkinson's disease cognition. Increased cholinergic involvement is thought underlie visuospatial and memory deficits and to have a key role in progression to dementia.

Taken from Kehagia, Barker, & Robbins, 2013.

Identification of cognitive change in PD has been increasingly acknowledged as an important component of managing nonmotor aspects of the disease, as it may be a risk factor for worsening cognitive decline and subsequent dementia (Janvin et al., 2006; Mamikonyan et al., 2009). Thus, there has been a surge in the recurrent use of cognitive screening tools from both clinical and research standpoints (Mamikonyan et al., 2009). However, these measures need to be carefully considered in the context of the typical presenting deficits. For instance, one commonly used cognitive measure, the Mini-Mental State Examination (MMSE) has questionable sensitivity to subtle cognitive impairment in PD (Burdick et al., 2014; Mamikonyan et al., 2009). In addition, because the MMSE primarily examines memory and language skills, it lacks the breadth needed to capture the range of domains that may be affected by PD (Zadikoff et al., 2008).

The Go/NoGo Model

Frank and colleagues' Go/NoGo model is another model of cognitive impairment in PD. This neurocomputational model is grounded in reinforcement learning and has been used to explain cognitive and motor impairment in PD (Collins & Frank, 2016; Frank et al., 2004). In the Go/NoGo model, the basal ganglia are described as having structurally-alike circuits that connect distinct regions of the cortex (see Figure 3). These are described as two opposing pathways that facilitate and suppress behaviors (Velseboer et al., 2016; Wiecki & Frank, 2010). Specifically, striatal neurons project from the striatum to the globus pallidus and substantia nigra via these two main circuits. The "Go" pathway is a direct pathway wherein excitation creates a gating function allowing for the thalamus to receive further signals from other projections (Frank, 2005), facilitating action plans from the frontal lobe. Conversely, the indirect, "NoGo" pathway inhibits the thalamus and suppresses action execution. Dopamine signals mediate these

loops, as dopamine signals occur as the result of reward or punishment, driving learning and modulating behavior response and inhibition (Frank, 2005; Frank et al., 2004).

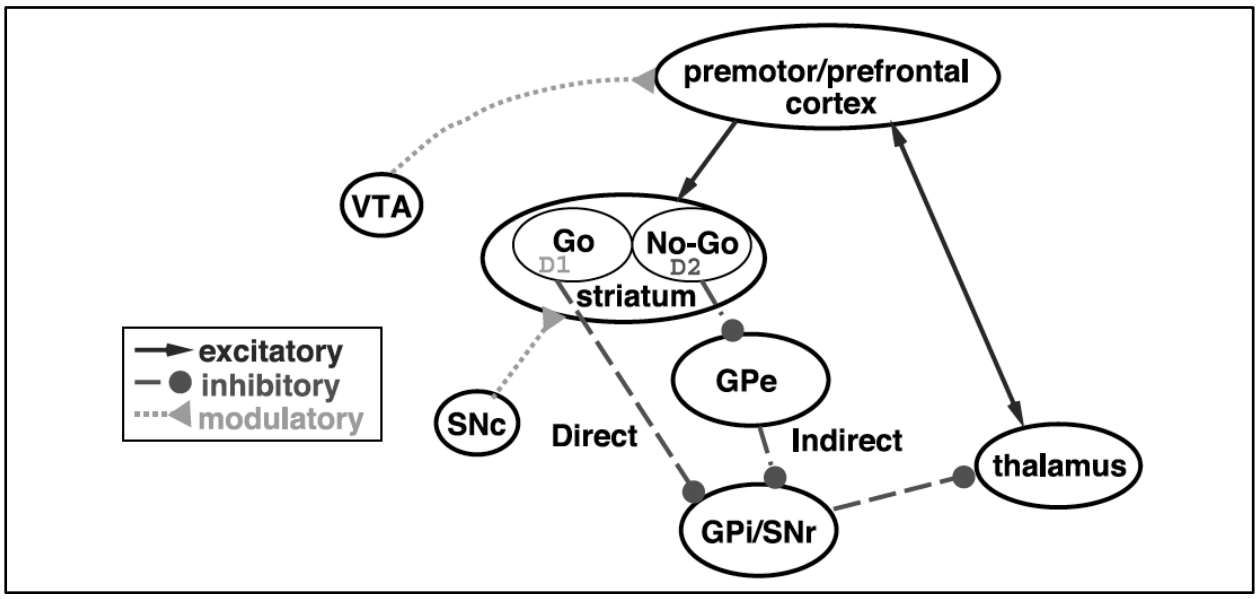

Figure 3. Schematic of the direct and indirect pathways of the bsasal ganglia in the Go/NoGo model of cognitive deficits in PD. GPi = internal segment of globus pallidus; GPe = external segment of globus pallidus; SNc = substantia nigra pars compacta; SNr =substantia nigra pars reticulate; VTA = ventral tegmental area (Frank, 2005).

In this model, the basal ganglia does not encode specific motor responses, but instead modulates execution of responses by signaling Go versus NoGo. Therefore, Go and NoGo pathways compete with each other and result in execution of desired behavior with simultaneous inhibition of unwanted behavior. Reinforcement learning results when repetition of a specific context causes dopamine to flood and stimulate the direct/Go pathway. On the contrary, a lack of dopamine surging reinforces the indirect/NoGo pathway, contributing to an increased likelihood of suppression of desired behavior during future encounters. Furthermore, as dopamine

decreases, the indirect NoGo pathway is no longer suppressed, and unwanted behaviors are executed.

Neural Networks Framework

This framework, introduced by Gratwicke, Jahanshahi, and Foltynie (2015) provides an important perspective on cognitive impairment in PD. The Neural Networks Framework views cognitive processes as a group of widely dispersed, yet deeply interconnected, networks that can be differentially influenced by the neurotransmitter deficits found in PD (Gratwicke et al., 2015). Four domains are discussed in the context of the neural networks model, executive function, attention, memory, and visuospatial domains (see Figure 4).

In an attempt to capture a more complex picture of the interconnectedness of neural circuits in relation to executive dysfunction, the neural networks framework implicates the mesocortical dopamine network (Gratwicke et al., 2015) in addition to recognizing the involvement of fronto-striatal (nigrostriatal) loops. The mesocortical network originates in the midbrain ventral tegmental area and projects to the prefrontal, insular, and cingulate cortices (Gratwicke et al., 2015). This network releases dopamine that mediates prefrontal receptors involved in cognitive flexibility (Floresco & Magyar, 2006). Specifically, the authors suggest that the mesocortical dopaminergic network facilitates recruitment of other cognitive networks, a core component of cognitive flexibility. Non-dopaminergic networks are also cited by the neural networks framework as modulators of executive function.

Attention is another domain accounted for by the neural networks framework. Previous theoretical frameworks describe attention as a task requiring three cortical networks working together to attend to the salient environmental stimuli (Mesulam, 1990). Networks within the frontal lobe, cingulate cortex, and posterior parietal lobes converge to involve motor, spatial, and

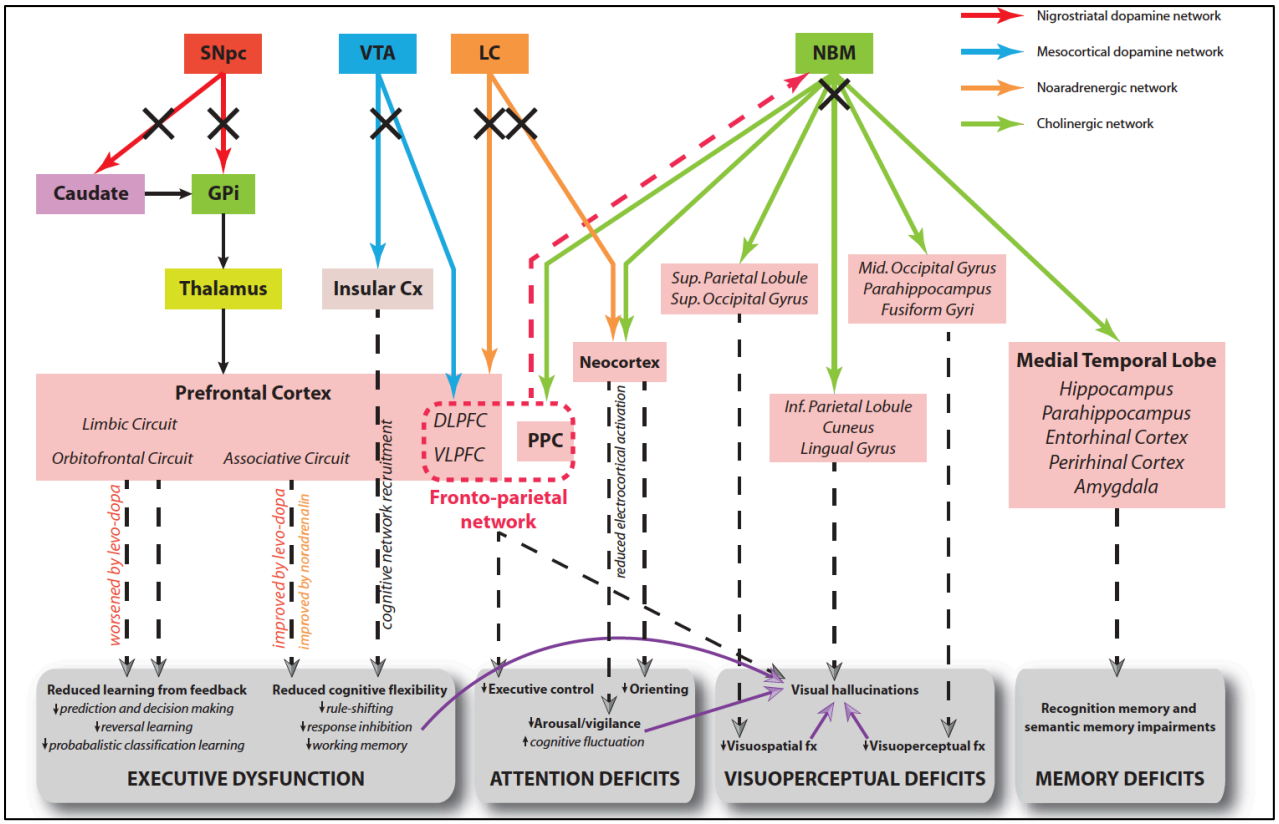

Figure 4. Schematic of the neural networks framework. Solid arrows represent direct pathways, while dashed lines connect network with corresponding cognitive deficit. Purple arrows represent deficits in one domain contributing to another. The red dashed arrow represents prefrontal contribution to top-down initiation of attention in the nucleus basalis of Meynert (NBM) cholinergic network. Cx = cortex; DLPFC = dorsolateral prefrontal cortex; fx = function; GPi = globus pallidus (internus); LC = locus ceruleus; PPC = posterior parietal cortex; SNpc = substantia nigra pars compacta; VLPFC = ventrolateral prefrontal cortex; VTA = ventral tegmental area (Gratwicke et al., 2015).

sensory components, respectively (Mesulam, 1990). Gratwicke et. al (2015) builds upon this with the neural networks framework, delineating executive control, orienting, and alerting as the three requisite subsystems contributing to attention, all mediated by a cholinergic network.

Medial temporal lobe structures including the hippocampus, parahippocampus, entorhinal and perirhinal cortices, and amygdala are considered the dominant structures for storage and retrieval of information. The neural networks framework describes memory impairment in PD as

an interruption in one of these areas, which are regulated by the cholinergic network (Gratwicke et al., 2015), seemingly independent of frontal lobe processes. However, memory is an interdependent process that relies on executive function and attention and must be considered accordingly.

Visuoperceptual impairment, the final affected domain detailed in the neural networks model, is a well-documented deficit in PD (Davidsdottir et al., 2005; Weil et al., 2016). Deficits in peripheral vision, object and motion perception, visuospatial construction, mental rotation, and even facial recognition are common. Visual hallucinations are another symptom of PD seen in the later stages. The neural networks framework considers these visual deficits to result from atrophy across several lobes, thus implicating multiple neural networks. As shown in Figure 4, many networks influence visuoperceptual deficits, to include bottom-up and top-down processes regulated by dopaminergic, cholinergic, and noradrenergic neurotransmitters (Gratwicke et al., 2015).

The Relationship between Motor and Cognitive Characteristics

The interplay of motor and nonmotor characteristics has garnered increased attention in the last decade (Chaudhuri & Sauerbier, 2016; Marras & Chaudhuri, 2016; Olanow et al., 2011; Stacy, 2011). Of specific interest is the growing literature supporting an association between motor symptoms and cognition. To date, no single model has emerged as a standard to account for the general interaction of motor and cognitive breakdowns; however, evidence now exists to support a connection between cognition and motor profile of PD. Specifically, more severe posture and gait symptoms have been associated with global and rapid cognitive decline, as well as increased risk for developing dementia (D. Aarsland, Hutchinson, & Larsen, 2003; Dag

Aarsland, Andersen, Larsen, & Lolk, 2003; Burn, 2006; Gago et al., 2009; Herman et al., 2014; Kelly et al., 2015; Kim et al., 2015). Longitudinal studies have supported this claim, finding that a non-tremor dominant motor presentation at baseline was predictive of global cognitive decline at a 5-year follow-up (Williams-Gray et al., 2007). Alternatively, tremor dominant motor profiles have been associated with less severe cognitive profiles and higher test scores across memory, executive function, attention, and visuospatial cognitive domains (Wojtala et al., 2019).

The Link Between Dysarthria and Cognition in PD

One specific motor feature has received increased attention regarding its possible connection to cognition. That is, an intriguing association has been posited between the presence of dysarthria and worsened cognitive decline in PD. Studies to date are summarized below.

A study by Elgh and colleagues (2009) examined cognitive function in 88 newly-diagnosed, drug-naïve participants. Global cognitive function was assessed using the MMSE, cognitive domains (episodic memory, working memory, visuospatial function, verbal fluency, naming, and executive function) were assessed with neuropsychological tests, and the UPDRS was utilized for motor evaluation. In addition to comparing scores against healthy controls, the authors categorized individuals with PD into groups with and without cognitive impairment. The authors found disruption to speech, in addition to reduced facial expression, rigidity, and bradykinesia, to be significantly worse in participants who presented with a co-morbid cognitive decline, compared to those with PD with intact cognition. Conversely, no significant difference on tremor score was found when comparing the two groups (Elgh et al., 2009). A significant difference in disease duration was found between the groups, with a shorter disease duration found in the group with impairment in one or more cognitive domains; the authors did not adjust

for disease severity. These findings support the notion that pathophysiological mechanisms that underlie the motor symptoms of dysarthria, rigidity, and bradykinesia may also influence cognitive deficits in PD.

As a follow-up study, Domellof, Elgh, & Forsgren (2011) further probed this relationship. However, the authors introduced a composite score of the sum of speech and facial expression (termed bulbar score). Facial expression on the UPDRS is rated in a similar way as speech, using a 5-point scale, with 0 suggesting no observed impairment of facial expression, and a higher number indicating more severe impairment. In their analyses, Domellof and colleagues compared cognition between ratings of tremor, bradykinesia, rigidity, axial impairment (rated as posture and gait scores), and the bulbar construct. While tremor was not significantly correlated with the cognitive measures, the bulbar score was found to be significantly negatively correlated with the cognitive and language measures of verbal fluency, the trail making test, and the Boston Naming Test (Domellöf et al., 2011). These results are congruent with the aforementioned study suggesting that cognitive and non-tremor motor symptoms may be influenced by shared pathways.

Bugalho and Viana-Baptista (2013) explored predictors of cognitive decline in a group of 75 individuals with PD. Participants were assessed at baseline and again, using the same instruments, two years later. Cognition was assessed using two screening tools: the MMSE and the Frontal Assessment Battery. The authors found that a higher speech score, suggesting greater impairment, was significantly associated with a decline in performance on the Frontal Assessment Battery (Paulo Bugalho & Viana-Baptista, 2013). As with the previous studies, speech impairment was measured using one question on the UPDRS rating scale (see Figure 5),

calling into question the sensitivity of the speech metric. However, when taken with other work, these results further confirm the potential for shared underpinnings of cognition and speech.

More recently, Schneider, Sendek and Yang (2015) examined the relationship between speech and cognition in 94 participants with PD. For this study, the authors used the UPDRS for motor evaluation as well as the previously described composite score of speech and facial expression. Cognition was assessed using the MMSE as well as seven additional neuropsychological tests: 1) Brief Test of Attention, 2) Controlled Oral Word Association, 3) Wisconsin Card Sorting Test, 4) Ruff-Light Trail Learning Test, 5) Conditional Associative Learning Task, 6) Stockings of Cambridge Test, and 7) CANTB Spatial Working Memory Test. Individuals with an MMSE < 24 were excluded in an attempt to limit the sample to those without dementia or pronounced cognitive decline. Significant correlations were reported between the speech/facial expression composite score and numerous cognitive measures, including the Ruff-Light Trail Learning Test, Stockings of Cambridge Test, Wisconsin Card Sorting Test, and the Spatial Working Memory Test (Schneider, Sendek, & Yang, 2015). The speech/facial expression score was also positively correlated with disease duration. Tremor was also found to correlate with disease duration; however, unlike the impaired speech/facial expression variable, no correlation was found between tremor and cognitive performance. These results provide insight into potential links between dysarthria and cognitive dysfunction and support the notion that these two symptoms may result from impairment of shared circuits. However, there are several methodological limitations to the study, such as the use of a speech and facial expression composite score and the lack of adjustment for multiple statistical comparisons.

3.1 SPEECH	SCORE
Instructions to examiner: Listen to the patient's free-flowing speech and engage in conversation if necessary. Suggested topics: ask about the patient's work, hobbies, exercise, or how he got to the doctor's office. Evaluate volume, modulation (prosody) and clarity, including slurring, palilalia (repetition of syllables) and tachyphemia (rapid speech, running syllables together). 0: Normal: No speech problems. 1: Slight: Loss of modulation, diction or volume, but still all words easy to understand. 2: Mild: Loss of modulation, diction, or volume, with a few words unclear, but the overall sentences easy to follow. 3: Moderate: Speech is difficult to understand to the point that some, but not most, sentences are poorly understood. 4: Severe: Most speech is difficult to understand or unintelligible.	☐

Figure 5. UPDRS Part III, motor evaluation rating scale to elicit examiner's perceptual judgement of level of speech impairment.

Also probing an association between dysarthria and cognitive decline in PD, Rektorova and colleagues (2016) conducted a longitudinal study to assess whether baseline speech parameters would predict cognitive decline across two years. Global cognition was measured using Addenbrooke's Cognitive Examination (ACE-R). Ten acoustic parameters were chosen for analysis and speech samples were obtained using a Czech dysarthria protocol (Rektorova et al., 2016). Two speech parameters emerged as a significant link between dysarthria and cognitive decline in PD: speech index of rhythmicity and pitch variation range (F_0VR). Speech index of rhythmicity is an acoustic component of the perceptual parameter of speech naturalness, capturing the alternation between pauses and speech, calculated as the number of inter-pauses per minute. The authors found the speech index of rhythmicity to significantly predict cognitive decline at a 2-year follow-up with 73.2% accuracy (sensitivity 87.1%, specificity 30.0%). Thus, a lower speech index of rhythmicity (suggestive of less natural speech) indicated an increased probability of worsening cognitive status. Disease duration was not statistically significant when

combined with the speech index of rhythmicity parameter, suggesting that this link is likely not merely a function of time post onset of PD. Instead, the authors posit that measuring the number of speech inter-pauses per minute may serve as a useful predictor of cognitive decline. Additionally, the most significant acoustic variable predicting change in the ACE-R was F_0VR. That is, less pitch variation predicted worse cognitive performance. According to the authors, this link is due to the specific role of the cholinergically-mediated amygdala in pitch control in PD. More broadly, speech prosody seems to be more strongly associated with axial non-dopaminergic motor symptoms than with limb motor symptoms and dopaminergic impairment. Thus, this study was the first study to elevate the notion that impaired prosodic features may uniquely link to cognition.

In sum, studies directly examining speech and cognition in PD have suggested an intriguing association between dysarthria and cognitive impairment in PD, but are limited in both quantity and robustness of speech, and sometimes cognitive, dependent measures. Examining speech in a more comprehensive and theoretically motivated manner could provide valuable insight into the possible link between, and the predictive ability of, speech change as it relates to cognitive change. Equally important is the examination of the role that primary motor characteristics play in this relationship. Such research, when considered through the lens of current models of cognitive impairment in PD, could inform both clinical and research practice and aid in treatment at all stages of PD.

The overarching goal of this study is to examine this purported link through two distinct, but related, experiments.

Chapter 2: Experiment 1

Research Questions

The aim of Experiment 1 is to systematically examine the perceptual speech constructs of intelligibility, articulatory precision, and naturalness, and their relationship to global cognitive performance in PD.

Specifically, Experiment 1 is designed to answer the following questions:

1) What is the relationship between listener ratings of speech (intelligibility, articulatory precision, and naturalness) and measures of global cognitive functioning in individuals with idiopathic PD? Specifically, can intelligibility, articulatory precision, or naturalness of speech predict performance on the Parkinson's Disease Cognitive Rating Scale in individuals with idiopathic PD?
2) Does PD motor subtype inform the relationship between speech (intelligibility, articulatory precision, and naturalness) and global cognitive functioning?

Hypotheses

Based on extant literature and current models of cognitive impairment in PD, it is hypothesized that greater speech impairment will be predictive of greater cognitive impairment. More specifically, it is anticipated that perceptual ratings of decreased speech intelligibility, articulatory precision, and naturalness will be predictive of poorer performance on a measure of global cognition. This finding would support the premise that a breakdown in shared neural channels results in changes to speech and cognitive performance. Additionally, it is hypothesized that there will be a significant interaction between motor subtype and speech/cognitive ratings. Specifically, participants classified as non-tremor dominant are anticipated to have greater disruption of speech naturalness, decreased articulatory precision,

reduced intelligibility, and poorer cognitive performance (see Table 2). This finding would align with research supporting the association between speech prosody and axial non-dopaminergic motor systems (Rektorova et al., 2016). It would also support the notion that individuals with a non-tremor dominant motor profile present with more impaired global cognition than individuals with a tremor-dominant phenotype.

Table 6. Proposed questions, hypotheses, and analyses for Experiment 1.

Question	Hypothesis	Analysis
1. What is the relationship between listener ratings of speech (intelligibility, articulatory precision, and naturalness) and a measure of global cognitive functioning in individuals with idiopathic PD? Specifically, can intelligibility, articulatory precision, or naturalness of speech predict performance on the Parkinson's Disease Cognitive Rating Scale in individuals with idiopathic PD?	Perceptual ratings of decreased speech intelligibility, articulatory precision, and naturalness will be predictive of poorer performance on a measure of global cognition.	Multiple linear regression will examine ratings of speech intelligibility, articulatory precision, and naturalness as predictive factors of cognitive performance.
2. Does PD motor subtype inform the relationship between speech (intelligibility, articulatory precision, and naturalness) and global cognitive functioning?	Participants classified as non-tremor dominant are anticipated to have greater disruption of speech naturalness, articulatory precision, intelligibility, and cognition.	Interaction term of motor subtype will be included in regression analysis.

Methods

Participants

Speakers

A total of 9 participants[2] were recruited from the Washington State Parkinson's Disease Registry as well as local support groups, retirement homes, and speech pathology clinics. Speaker demographics can be found in Table 7. Inclusion criteria were (1) diagnosis of idiopathic PD by neurologist (per self-report), (2) native speaker of American English, (3) typical speech, language, and cognitive developmental history, (4) adequate vision (able to read line 20/30 at 2.3 feet from the Snellen chart) and hearing (thresholds < 50 dB at 500, 1000, and 2000 Hz in one ear).

Table 7. Characteristics of speakers with Parkinson's Disease.

Speaker	Gender	Age	Years of Education	Years Since Diagnosis	H&Y	Motor Subtype	PD-CRS	Intelligibility (percent)
S01	F	72	16	10	3	Non-Tremor	99	97
S02	M	79	20	14	4	Non-Tremor	79	82
S03	M	83	18	13	3	Non-Tremor	105	94
S04	M	76	18	3	2	Tremor	93	99
S05	M	62	16	6	2	Tremor	113	94
S06	M	65	16	6	3	Non-Tremor	94	98
S07	M	80	18	3	3	Non-Tremor	62	98
S08	M	75	14	4	3	Non-Tremor	78	88
S09	F	79	18	6	3	Non-Tremor	93	98
Mean	--	74.56	17.11	7.22	2.89	--	90.67	94
SD	--	7.06	1.76	4.15	0.60	--	15.47	6

Note. PD-CRS = Parkinson's Disease Cognitive Rating Scale (134 = total score; 81 = cutoff for PD Mild Cognitive Impairment (Pagonabarraga et al., 2008; Rosca & Simu, 2020). H&Y = Hoehn and Yahr Parkinson's Disease Severity Rating Scale.

[2] Recruitment was halted due to public health restrictions ensuing from COVID-19 pandemic.

All speakers presented with hypokinetic dysarthria. Presence of hypokinetic dysarthria was based on determination of perceptible characteristics of speech disruption by two independent investigators during the initial telephone screening/interview and speech recordings.

Exclusion criteria were (1) history of any surgical procedure to treat PD, (2) diagnosis of secondary Parkinsonism, (3) severe depression per Beck Depression Inventory II (BDI-II) score > 29 (Beck, 1996), (4) neurologic compromise beyond PD (e.g., stroke, traumatic brain injury), (5) alcohol or drug dependency, (6) currently taking sedatives or tranquilizers, and (7) severe cognitive impairment such that an individual was unable to make informed consent. No participants were excluded based on these criteria. Participants were assessed while remaining on their current medication routine, approximately 1-2 hours after ingestion of anti-Parkinsonian medications.

Listeners

Ten Speech-Language Pathologists with a minimum of five years of clinical experience working with individuals with dysarthria from PD were recruited to serve as experienced listeners (see Table 8). Clinically experienced listeners were chosen over untrained listeners given their specialized training related to this population and the metrics of intelligibility and naturalness. Experienced listeners completed perceptual ratings of naturalness and articulatory precision. Three research assistants completed intelligibility calculations. All listeners were native speakers of American English with no history of hearing impairment and successful completion of hearing screening.

Table 8. Characteristics of experienced listeners.

Listener	Gender	Age	Years of Practice	Primary Setting
L01	F	34	8	Academic Medical Center
L02	F	35	10	Acute / rehab
L03	F	45	21	Outpatient
L04	F	33	9.5	Acute / Rehab
L05	F	52	29	Academic Medical Center
L06	F	37	9	Acute
L07	F	29	5	Acute
L08	F	31	7	Acute / Rehab
L09	F	42	15	Academic
L10	F	40	17	Academic
Mean	--	37.80	13.05	--
SD	--	7.04	4.47	--

Procedure

Speaker Session

Demographic and Disease-Related Information

Information specific to participant disease history was collected in an interview format. Motor function was assessed using the UPDRS (Part III); following guidelines of the International Parkinson and Movement Disorder Society (MDS), a trained examiner conducted the UPDRS rating. This exam entails examination and "rate what you see" assessment of the motor signs of PD, and includes 18 questions with five response options (ranging from 0-4), with higher scores indicating greater impact of PD symptoms.

Speech Sample

It has been demonstrated that speech naturalness can be enhanced when individuals with PD are cued with a reading task, and thus not reflective of typical speech performance (Weir-Mayta et al., 2017). Additionally, speakers with PD may alter their speech by employing compensatory strategies when aware that their speech is being recorded. Thus, speech samples were obtained via monologue during a covert recording. To elicit a covert speech sample, participants were fitted with the microphone and told that a recording will begin at some point during the session, but they would not be alerted to the specific moment when the recording would begin. After consent, the examiner then engaged participants in a casual conversation. A three-minute speech sample was obtained by the experimenter asking open-ended questions. Sounds files were clipped and processed in sound editing software (Adobe Audition 9.0). The first 30 seconds of continuous speech that met extraction criteria were used for the listener rating task and were also transcribed by naïve listeners for the objective measure of intelligibility. Extraction criteria were based on Sidtis, Cameron, Bonura, & Sidtis (2012); samples were free of proper nouns, low frequency words, formulaic expressions, and specialty vocabulary. To preserve naturalness, samples were clipped to the nearest sentence's end; thus, sample length varied negligibly. See Appendix for complete extraction criteria.

Cognitive Assessment

The Parkinson's Disease Cognitive Rating Scale (PD-CRS) was administered to participants. The PD-CRS is a PD specific cognitive scale designed to capture and measure functional changes across the continuum of cognitive severity, including subtler mild impairments (Serrano-Dueñas et al., 2017). The PD-CRS uses a broader range of tasks compared to a cognitive screener (Chou, et. al, 2010), and examines the following domains:

immediate and delayed verbal memory, confrontation naming, sustained attention, working memory, clock drawing, and verbal fluency. Administration time for the PD-CRS typically ranges from 17 minutes for non-demented individuals to 26 minutes for those with more severe cognitive dysfunction (Pagonabarraga et al., 2008). The PD-CRS has been rated as a valid tool for studying cognitive impairment in PD, with a 94% sensitivity and 99% specificity, and statistically significant power at discriminating dementia in PD (Kulisevsky et al., 2013; Serrano-Dueñas et al., 2017). A PD-CRS score of 81 (out of 134) has been shown to be an optimal cutoff score for detection of MCI in PD (Fernández de Bobadilla et al., 2013; Fernández-Bobadilla et al., 2017; Rosca & Simu, 2020).

Motor Classification

Motor presentation was characterized using three self-report scores from the UPDRS Part II and thirteen examiner ratings from Part III (see Table 9). Participants were categorized into tremor-dominant or non-tremor motor subtypes. Subtyping aligned with the approach of Jankovic et al. (1990), updated using the most recent UPDRS version (Goetz et al., 2007; Stebbins et al., 2013), where total tremor score (TD) was calculated as a sum of tremor-

Table 9. Ratings from the UPDRS used to determine motor subtype.

Tremor Items	**Non-Tremor Items**
2.10 tremor	2.12 walking and balance
3.15 postural tremor	2.13 freezing
3.16 kinetic tremor	3.10 gait
3.17 rest tremor	3.11 freezing of gait
3.18 constancy of rest tremor	3.12 postural stability

related items, and total non-tremor score (NT) was calculated as a sum of non-tremor items. Tremor dominance was defined as individuals with a ratio of TD/NT of ≥ 1.5, whereas a ratio of TD/NT ≤ 1.0 indicates non-tremor dominance. A ratio of > 1.0 but < 1.5 indicated an indeterminate phenotype.

Listener Session

Naturalness and Articulatory Precision Ratings

Experienced listeners listened to speech samples and rated them on the constructs of naturalness and articulatory precision using two 100-point visual analog scales (VAS). VAS has been used to successfully identify and characterize changes to speech from PD (Sussman & Tjaden, 2012; Tjaden et al., 2014; Weir-Mayta et al., 2017). Due to in-person restrictions related to COVID-19 closures, the VAS was created to be a specific interface designed for listeners to access from their personal computers. Using the Gorilla Experiment Builder perceptual interface, naturalness and articulatory precision continuous scales were developed with numerical values from 0-100.

Each speech sample was rated by each listener with counterbalanced presentation of naturalness and articulatory precision. Each listener heard a random order of samples and could not pause or replay samples during the rating task.

Participants were instructed to be seated in a quiet location in their home where they would be free of distractions and to best minimize ambient noise. Prior to rating speech samples, listeners were presented with an instruction screen followed by an informational screen to familiarize them with the scale and definitions. The following definitions were provided to the experienced listeners: *Naturalness* – "how speech conforms to standard expectations of prosody-

such as rate, rhythm, intonation, and stress," – with VAS anchors of "completely unnatural" and "completely natural" (see Figure 6); and *Articulatory Precision* – "how accurately speech sounds are produced…" – with VAS anchors of "completely imprecise; speech is fully degraded from articulation errors" and "completely precise; no perceived articulation errors" (see Figure 7). Definitions were available to the listeners throughout the listening session.

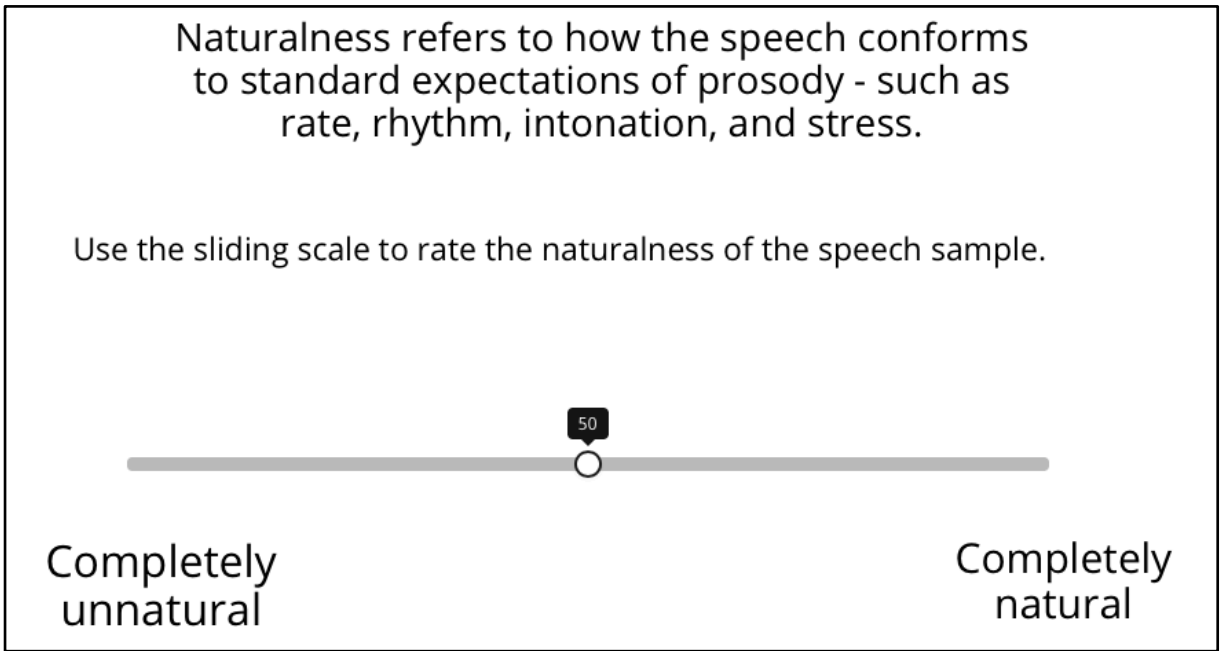

Figure 6. Visual Analog Scale (VAS) for rating speech naturalness.

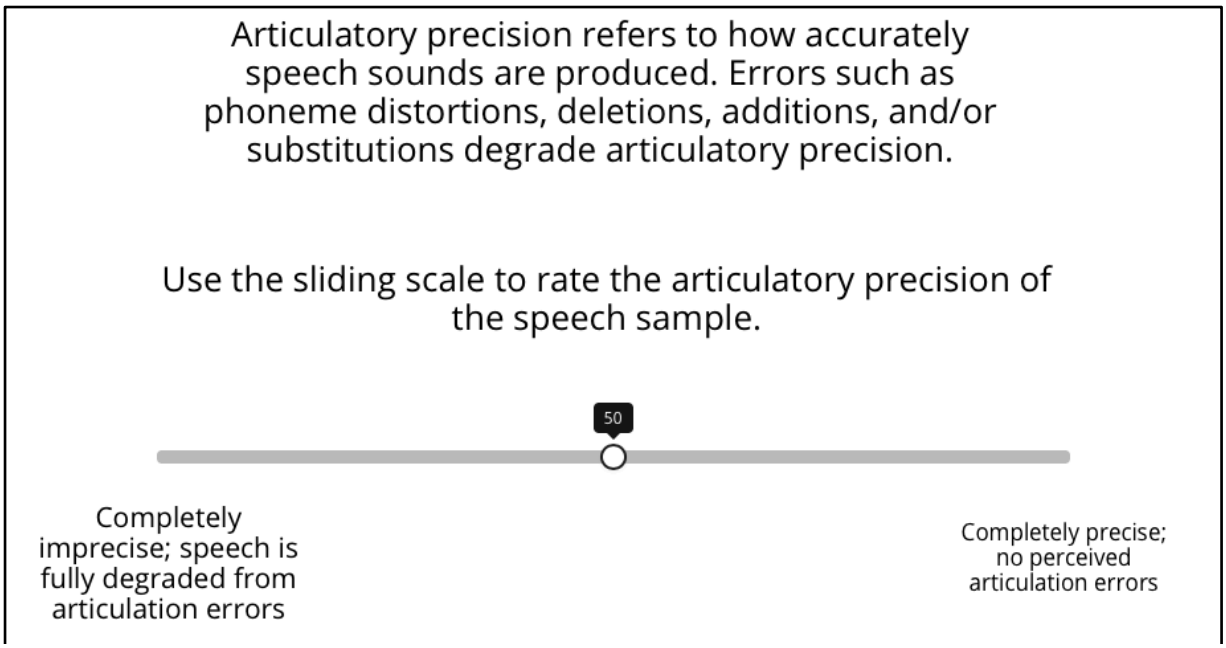

Figure 7. Visual Analog Scale (VAS) for rating articulatory precision.

Calculating Intelligibility

Intelligibility of the speech sample was scored via transcription by three research assistants to provide a mean intelligibility calculation. Listeners produced a written transcription of each speech sample. Intelligibility calculations were determined by counting the number of correctly identified words and dividing by total number of words in the 30-second sample elicited from the covert monologue.

Statistical Analyses

SPSS 26 was used for the analyses. Reliability was measured using a point-to-point approach and intraclass correlations. Associations between motor and cognitive domains were first examined using Pearson Product-Moment correlation. Specifically, correlations between ratings of tremor severity, non-tremor severity, naturalness, articulatory precision, intelligibility

and global cognition were conducted. Next, independent samples t-tests were performed to test for significant group differences on speech parameters between individuals with MCI and those without.

Results

Reliability

Approximately 20% of speech samples were repeated for each experienced listener for the calculation of intra-rater reliability of naturalness and articulatory precision ratings. Thus, each of the experienced listeners heard and rated 11 speech samples (9 novel samples, 2 randomly-selected repeated samples), providing ratings for naturalness and articulatory precision for each sample. Intra-rater reliability was determined by the percent of repeat ratings that fell within a predetermined range on the VAS (Bijur et al., 2001; Spencer & France, 2016). Of the 20 repeat ratings (10 listeners x 2 repeated files) for articulatory precision, 85% were within 10 points on the 100-point VAS scale, and 100% were within 20 points. No raters were inconsistent (> 20-point difference) in their perception of articulatory precision. For naturalness, 70% of repeat ratings were within 10 points, and 90% were within 20 points. Two ratings (10%) were inconsistent (> 20-point difference).

Inter-rater reliability was assessed using intraclass correlation coefficient (ICC), two-way mixed-effects model. Excellent overall inter-rater reliability was achieved for ratings of naturalness (ICC = 0.904, range = 0.77–0.97) and articulatory precision (ICC = 0.934, range = 0.84-0.98) (Koo & Li, 2016).

Speech Constructs and PD-CRS

Research Question 1 aimed to examine the relationship between listener ratings of speech (intelligibility, articulatory precision, and naturalness) and cognitive functioning in participants with PD. Mean ratings of experienced listener's judgements of naturalness and articulatory precision can be found in Table 10 along with intelligibility ratings.

Table 10. Mean listener ratings across speech constructs for each speaker with Parkinson's disease.

Speaker	Naturalness	Articulatory Precision	Intelligibility
	M (*SD*)	*M* (*SD*)	*M* (*SD*)
S01	79.3 (23.69)	94.2 (4.44)	97 (0.96)
S02	32.5 (16.31)	43.1 (25.40)	82 (9.85)
S03	73.5 (13.79)	77.5 (24.61)	94 (1.14)
S04	77.8 (17.50)	92.1 (7.46)	99 (0.00)
S05	85.5 (10.23)	88.9 (14.48)	94 (1.75)
S06	84.4 (15.54)	96.1 (3.93)	98 (2.55)
S07	63.0 (27.46)	86.9 (12.31)	98 (1.52)
S08	65.0 (20.05)	56.9 (25.21)	88 (4.41)
S09	61.7 (27.38)	84.3 (19.69)	98 (2.78)
Mean	**69.2 (16.40)**	**80.0 (18.21)**	**94 (5.72)**

Pearson Product-Moment correlations were conducted to examine the relationship between cognitive and speech variables. Correlation coefficients between PD-CRS scores and ratings of naturalness, articulatory precision, and intelligibility can be found in Table 11. Correlations did not reach significance (p values = 0.086, 0.288, and 0.557, respectively).

Table 11. Pearson Product-Moment correlations coefficients (r) between global cognition (PD-CRS) and speech variables.

PD-CRS	***r***	***p***
Speech variables		
Naturalness	0.60	0.086
Articulatory Precision	0.40	0.288
Intelligibility	0.23	0.557

Note. PD-CRS = Parkinson's Disease Cognitive Rating Scale.

Next, independent samples t-tests were used to test for group differences on speech constructs between individuals with MCI and those without. As noted previously, a PD-CRS score of 81 (out of 134) has been shown to be an optimal cutoff score for detection of MCI in PD (Fernández de Bobadilla et al., 2013; Fernández-Bobadilla et al., 2017; Rosca & Simu, 2020). Three participants (S02, S07, S08) fell below the cut-off.

Results from independent samples t-test[3] indicated that individuals with MCI, as determined via the PD-CRS, were rated as having speech that was significantly less natural than individuals with cognitive scores above the MCI cutoff ($t(7) = 2.72$, $p = 0.029$). The effect size for this analysis ($d = 1.65$) was found to exceed Cohen's (1988) convention for a large effect ($d = 0.80$). Welch's *t*-test indicated that speech ratings of articulatory precision did not differ significantly between MCI and individuals with cognitive scores above the MCI cutoff, although there was a large effect size ($d = 1.60$). Similarly, intelligibility did not differ between MCI and

[3] Intelligibility and articulatory precision did not meet homogeneity of variance assumptions per Levene's test, therefore Welch's *t*-test was used for these comparisons (see Table 12).

those with scores above the MCI cutoff, but the effect size was large (d = 1.24). Results are summarized in Table 12.

Table 12. Independent samples t-test examining speech constructs between MCI and normal cognition groups.

	MCI (n = 3)	No-MCI (n = 6)					
Speech Construct	Mean (SD)	Mean (SD)	Diff	*df*	*t*	*p*-value	*d*
Naturalness	53.50 (18.21)	77.03 (8.71)	23.53	7	2.72	**0.029***	1.65
Articulatory Precision	62.30 (22.39)	88.85 (6.95)	26.55	2.20	2.00	0.171	1.60
Intelligibility	89.33 (8.08)	96.67 (2.16)	7.34	2.14	1.54	0.254	1.24

Note. * = $p \leq 0.05$; MCI = mild cognitive impairment; No-MCI = cognitive performance above MCI cutoff (> 81) on Parkinson's Disease Cognitive Rating Scale.

Visualization of the relationship between speech constructs and cognitive test performance is included in Figures 8-10. Figure 8 shows cognitive performance on the PD-CRS relative to naturalness ratings. Three participants scored below the MCI cutoff of 81 (S02, S07, and S08) and are designated with green bars. As reflected in the independent sample *t*-test (see Table 12), participants with MCI demonstrated lower ratings of naturalness than most participants with PD-CRS scores above the MCI cutoff.

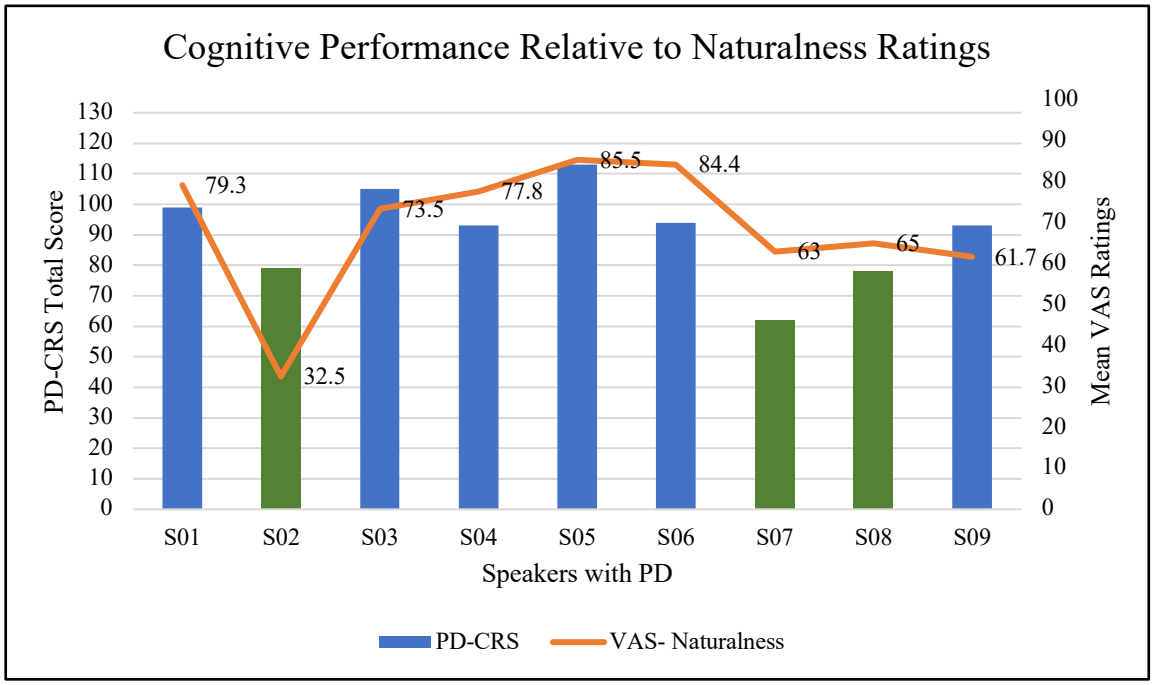

Figure 8. Parkinson's Disease Cognitive Rating Scale (PD-CRS) performance relative to naturalness ratings. Participants with lower cognitive performance (≤ 81) are shown in green.

Cognitive performance relative to articulatory precision is shown in Figure 9. Visual analysis indicates two of the three participants with PD-CRS scores below the MCI cutoff (S02 and S08) were rated as the least precise of the sample. S07 was also below the MCI cutoff but had relatively high ratings of articulatory precision (86.9). This speaker had a slow rate of speech (38 words produced in the 30-second sample; group mean = 73 words) which disrupted naturalness (Figure 8), but likely resulted in speech that was more precise (Tjaden et al., 2014).

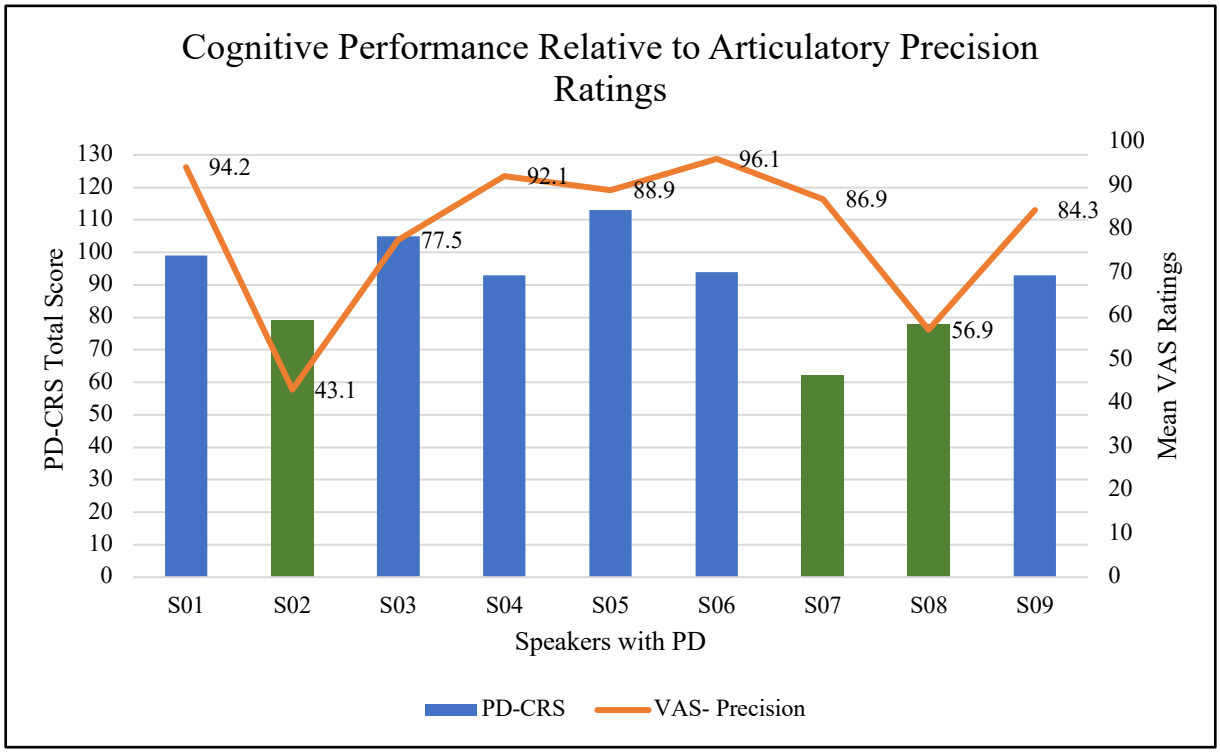

Figure 9. Parkinson's Disease Cognitive Rating Scale (PD-CRS) performance relative to articulatory precision ratings. Participants with lower cognitive performance (≤ 81) are shown in green.

Figure 10 shows cognitive performance relative to transcribed intelligibility. Visual analysis indicates relatively stable intelligibility ratings across speakers. The two speakers with the lowest ratings of intelligibility performed below MCI cutoff on the PD-CRS (S02 and S08), while S07 achieved an average intelligibility rating of 98. Similarly to articulatory precision, the slower rate of speech is consistent with increased intelligibility (Tjaden et al., 2014).

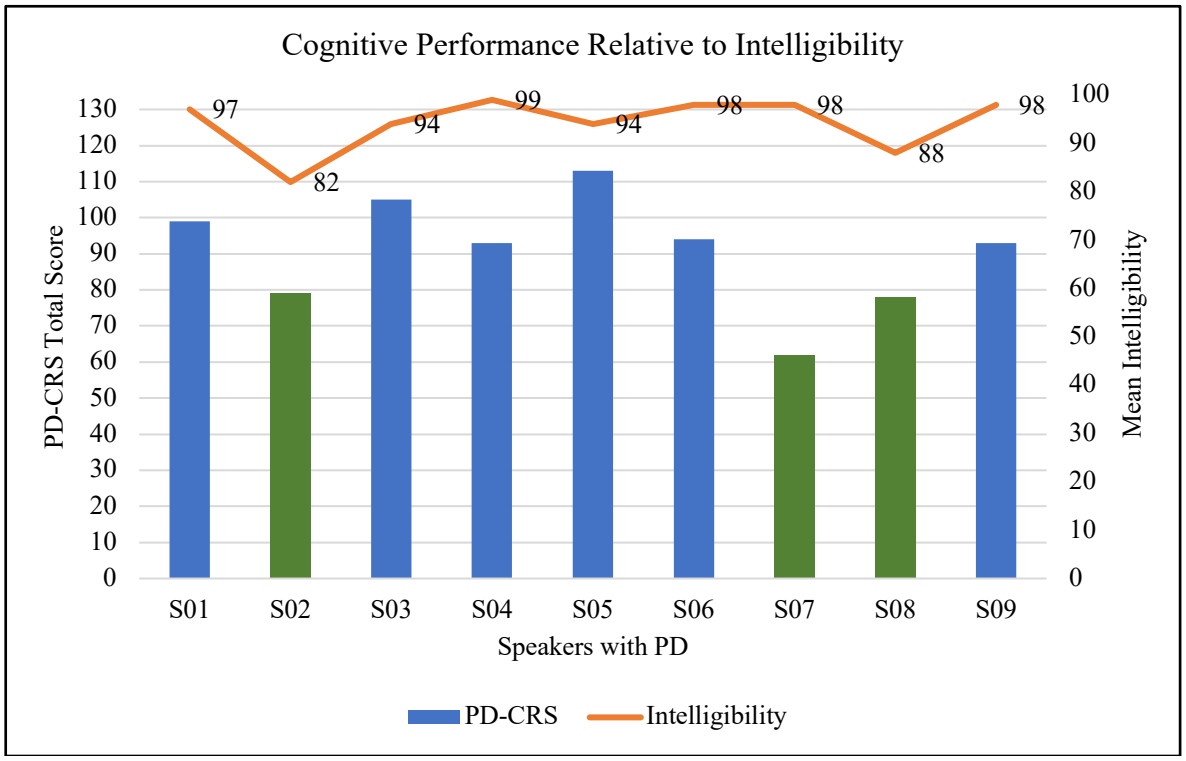

Figure 10. Parkinson's Disease Cognitive Rating Scale (PD-CRS) performance relative to intelligibility ratings. Participants with lower cognitive performance (≤ 81) are shown in green.

Influence of Primary Motor Symptoms

Research Question 2 examined whether primary motor presentation influences the relationship between speech constructs and cognitive test performance. Pearson-Product Moment correlations were calculated for tremor severity, non-tremor severity, and speech constructs of naturalness, articulatory precision, and intelligibility. Results can be found in Table 13. Non-tremor severity, calculated as the sum of non-tremor items on the UPDRS, was significantly negatively correlated with listener ratings of naturalness ($p = 0.020$) and articulatory precision ($p = 0.028$), but not intelligibility. Correlation coefficients indicated that the strength of this relationship is strong. Thus, an increase in non-tremor symptom severity was strongly associated with decreased ratings of naturalness and decreased ratings of articulatory precision. Tremor severity, which represents the sum of all tremor items on the UPDRS, was not significantly correlated with speech constructs.

Table 13. Pearson Product-Moment correlations coefficients (r) between primary motor characteristics and speech.

	Primary Motor Characteristic			
Speech Construct	**Tremor Severity**		**Non-Tremor Severity**	
	r	*p*	r	*p*
Naturalness	0.53	0.140	**- 0.75**	**0.020***
Articulatory Precision	0.37	0.334	**- 0.72**	**0.028***
Intelligibility	0.13	0.749	- 0.62	0.076

Note. * = $p \leq 0.05$

The relationship between speech and motor profile is also depicted in Figures 11 and 12. In Figure 11, average ratings of naturalness, articulatory precision, and intelligibility are graphed by tremor severity relative to the group mean of 4.22. That is, speakers were grouped by low (≤ 1 *SD* below group mean = 0.83), average (within 1 *SD* of the group mean = 4.22), and high (≥ 1 *SD* above group mean = 7.61) severity of tremor symptoms, as rated per the UPDRS. As indicated in Figure 11, intelligibility remained relatively constant across tremor symptom severity levels, while average ratings of naturalness and articulatory precision appeared lower in individuals with less severe tremor symptoms. Thus, individuals with less tremor had speech that was rated as less natural and less precise because these individuals had more predominant non-tremor symptoms (as shown in Figure 12).

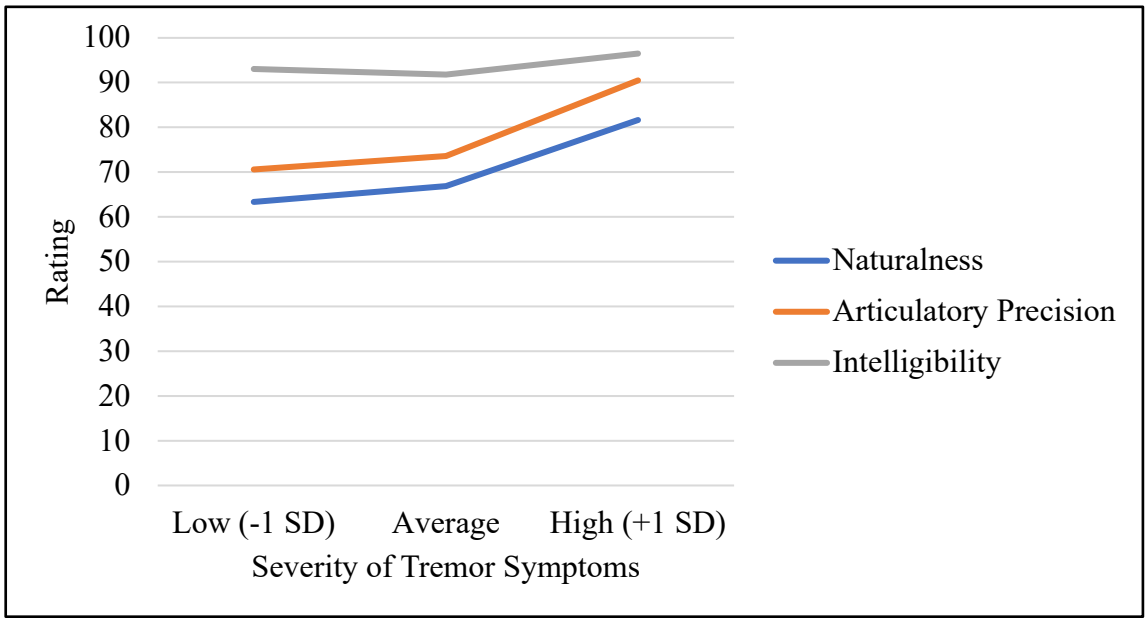

Figure 11. Average ratings of naturalness, articulatory precision, and intelligibility across low (≤ 1 *SD*), average, and high (≥ 1 *SD*) ratings of tremor symptom severity.

In Figure 12, average ratings of naturalness, articulatory precision, and intelligibility are visualized between speakers with low (≤ 1 *SD* below group mean = 3.33), average (within 1 *SD* of the group mean of 10), and high (≥ 1 *SD* above group mean = 16.67) levels of severity of non-tremor symptoms relative to the group, as rated per the UPDRS. Intelligibility was variable across non-tremor severity levels. Individuals with more severe non-tremor symptom severity had lower average ratings of naturalness and articulatory precision, which is consistent with the significant negative correlation between severity of non-tremor symptoms and perceptual ratings of naturalness and articulatory precision.

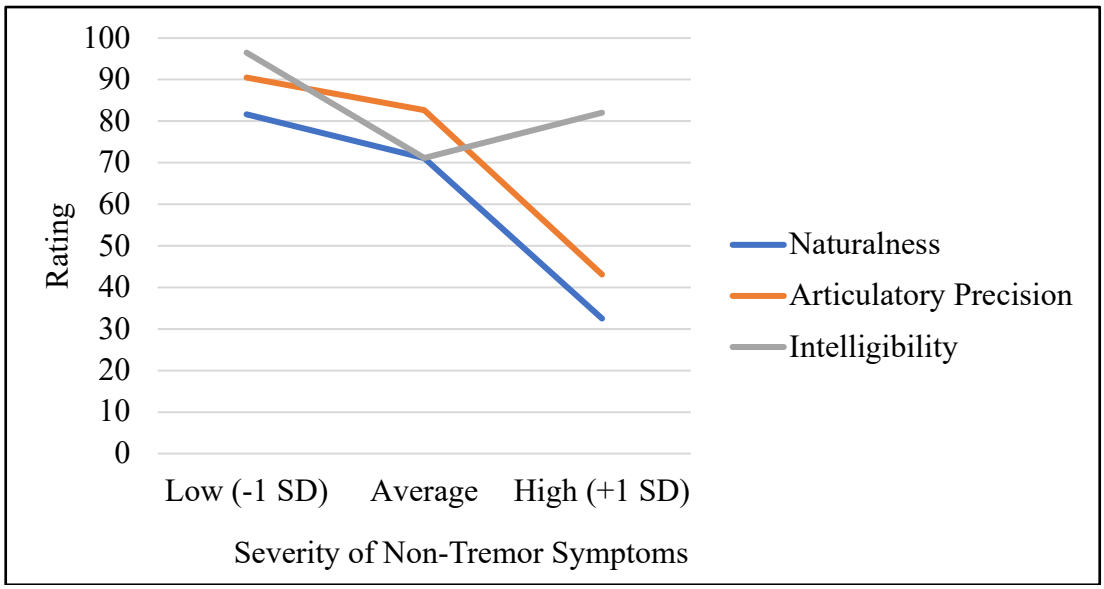

Figure 12. Average ratings of naturalness, articulatory precision, and intelligibility across low (≤ 1 *SD*), average, and high (≥ 1 *SD*) ratings of non-tremor symptom severity.

Discussion

Experiment 1 was motivated by extant literature and models of PD disease that suggest non-tremor symptoms, such as postural instability or gait disturbance, may be associated with different patterns of speech disruption (Burk & Watts, 2018; Goberman, 2005; Skodda & Schlegel, 2008) and cognitive dysfunction (Kehagia et al., 2013; Rektorova et al., 2016). The goal of this experiment was to examine the speech constructs of intelligibility, articulatory precision, and naturalness, and their relationship to a measure of global cognitive performance in PD.

Orthographic transcription was used to calculate intelligibility ratings, while a 100-point visual analog scale was used for ratings of naturalness and articulatory precision. This enabled the capture of more comprehensive perceptual judgments compared to the more commonplace 5-point UPDRS rating scale (see Figure 5) in the existing literature. Similarly, analyzing tremor and non-tremor symptoms as continuous variables instead of dichotomizing participants into tremor and non-tremor motor subtype allowed for a more nuanced analysis of the relationship of speech constructs with primary motor presentation. The PD-CRS, a PD specific cognitive test, was also utilized to examine cognitive performance across a wider range of tasks than a cognitive screener, integrating performance on domains of immediate and delayed verbal memory, confrontation naming, sustained attention, working memory, clock drawing, and verbal fluency.

It was hypothesized that decreased ratings of speech intelligibility, articulatory precision, and naturalness would be associated with poorer cognitive performance on the PD-CRS. In addition, it was posited that reduced ratings across all three speech constructs would correlate with increased severity of non-tremor symptoms. Conversely, individuals who had speech that

was rated as more natural, more precise, and more intelligible, were expected to have better cognitive test scores and lower severity of non-tremor motor symptoms. Despite the small sample size, an emerging relationship between speech and cognition in PD was present, and the hypotheses were partially supported.

Perceptual ratings of naturalness and articulatory precision appeared more sensitive to disruption of speech, while intelligibility scores were similar across many of the speakers. Overall, these results suggest that utilizing VAS ratings of naturalness and articulatory precision might uniquely capture a wider breadth of changes to speech in PD than intelligibility measures alone. This finding may be of particular importance when assessing speech changes in individuals with mild hypokinetic dysarthria, where intelligibility ratings may not suitably represent initial speech changes. This is consistent with the idea that naturalness is a distinct construct that serves as an independent contributor to an individual's ability to communicate (Anand & Stepp, 2015). Similarly, perceptual ratings of articulatory precision extend beyond traditional intelligibility measures by allowing nuanced detection of changes to speech patterns.

Speech Ratings and Cognitive Performance

Three individuals received scores below the cutoff for MCI on the PD-CRS. While correlations between the speech ratings of intelligibility and articulatory precision and performance on the PD-CRS did not reach significance, individuals with cognitive scores in the MCI range had speech that was rated as significantly less natural than speakers who had cognitive scores above the MCI cutoff. This finding partially aligns with the hypothesis that individuals with poorer performance on the PD-CRS would have speech that was rated as more impaired. While the small sample size likely influenced statistical power, effect sizes and

descriptive data suggest an emerging relationship between speech constructs and cognition in PD.

Of the speech variables, the construct of naturalness had the strongest relationship with cognition. One explanation for this finding relates to the specific role that the amygdala plays in prosodic functioning. The amygdala has been posited as a central regulator of pitch control, a major component of naturalness (Rektorova et al., 2016), and has been associated with perceived intensity in non-verbal vocalizations as well (Fecteau et al., 2007; Leitman, 2010), suggesting a role in modulating and interpreting prosodic elements. The amygdala is functionally connected to the medial prefrontal cortex and is innervated by cholinergic projections stemming from the basal forebrain (Elfmarková et al., 2016). Degeneration of the basal forebrain, and the resulting acetylcholine depletion, has been implicated as a predictor of subsequent dementia in PD (Pereira et al., 2020), thus serving as an anatomical link between observed cognitive and speech changes. Breakdowns in the cholinergic network have been implicated by models of disease pathology for their role in cognitive dysfunction and are considered a component of a non-tremor phenotype (Bohnen & Albin, 2009; Kehagia et al., 2013; Moustafa et al., 2016; Peter et al., 2016). Additionally, cholinergic deficits are considered an impetus to more severe cognitive dysfunction, and subsequent dementia, than that which occurs when breakdowns are contained to dopaminergic channels (Dag Aarsland & Kurz, 2010; Gratwicke et al., 2015; Pereira et al., 2020). While the amygdala is thought to be impacted by Lewy PD pathology in Braak disease Stage 4 (Braak & Del Tredici, 2009), greater amounts of atrophy are found in the amygdala and hippocampus in individuals with dementia compared to those without (Junqué et al., 2005). Thus, it is likely that more severe cholinergic depletion is required before changes to speech naturalness result, explaining why this pattern would not be expected in all individuals with PD.

A possible relationship between cognitive functioning and the two speech metrics of articulatory precision and intelligibility was also apparent based on visual analysis, as well as the large effect sizes when comparing these speech constructs between the MCI and no-MCI groups. Specifically, the two individuals with the lowest rating of articulatory precision also scored below the MCI cutoff on the PD-CRS. The third individual with poor PD-CRS performance (S07), however, was rated as having articulatory precision that was above average when compared to the sample's mean. This speaker had a slow rate of speech which disrupted naturalness, which likely resulted in speech that was more precise (Tjaden et al., 2014) and intelligible. This discrepancy between speech that is rated as less natural but simultaneously highly intelligible highlights the importance of utilizing ratings of naturalness as distinct outcome measures, particularly when considering the influence that impaired naturalness may have on communicative participation (McAuliffe et al., 2017).

The relationship between cognition and speech in individuals with PD is supported by a growing literature (Paulo Bugalho & Viana-Baptista, 2013; Domellöf et al., 2011; Elgh et al., 2009). For example, Schneider and colleagues (2015) reported that more impaired speech (aggregated with UPDRS facial expression) was associated with poorer performance on the Ruff-Light Trail Learning Test (visuospatial learning), Stockings of Cambridge (planning and problem solving), the Wisconsin Card Sorting Test (set-shifting), and the Spatial Working Memory test. Despite the limitations inherent to a small sample size, our initial findings align with these investigations, which purported that shared neuropathological mechanisms underlie dysarthria and PD-related cognitive changes, but not tremor (Elgh et al., 2009). Elgh and colleagues specifically highlight the potential role of the pedunculopontine nucleus, a structure

linked to the basal ganglia via cholinergic networks, which has been demonstrated to have a role in the genesis of PD (Lee et al., 2000) as well as cognitive deficits (Mori et al., 2016).

Influence of Tremor and Non-tremor Motor Presentation

The influence of PD motor profile on speech constructs was also examined, and the results suggested non-tremor symptom severity was associated with perceptual ratings of naturalness and articulatory precision. To examine gradations of motor presentation, primary motor symptoms were measured as continuous variables to characterize severity of tremor and non-tremor symptoms. Thus, every individual received a tremor and a non-tremor score. This method of capturing primary motor presentation was preferred over dichotomization into motor subtype due to the small sample size. When examining the relationship between severity of primary motor symptoms and the speech constructs, a significant negative association of non-tremor symptom severity was observed with ratings of naturalness and articulatory precision, suggesting that increased severity of non-tremor symptoms was associated with decreased/poorer ratings of speech.

The pattern of an association between non-tremor motor symptoms and disrupted speech is in line with the hypothesis for this experiment, and previous studies linking these characteristics. For example, Goberman (2005) found strong associations between non-tremor characteristics and pause parameters in reading tasks, and monologue speech rate, although the author examined discrete motor variables instead of dichotomizing them into tremor and non-tremor scores as in this study. Skodda et al. (2011, 2012) found similar associations, linking pause parameters with gait and overall axial severity, based on speech sampled from a reading task. While the methodology of this study differs slightly from previous literature, the overall

findings support the notion that a link between speech changes and non-tremor phenotype is present, and likely detectable across a range of tasks.

These findings can be largely explained by the cholinergic breakdowns which are implicated in more severe non-tremor symptom presentation in PD (Perez-Lloret & Barrantes, 2016), particularly postural instability and gait disturbance (Karachi et al., 2010; Rochester et al., 2012). Moreover, results are consistent with the notion that speech disruption is an axial motor sign, an idea that has been proposed in previous studies (Burk & Watts, 2018; Defazio et al., 2016; Novotný et al., 2020; Skodda & Schlegel, 2008). However, Goberman (2005) purports that speech is too multidimensional of a construct to be considered an axial component, citing their finding of an association between rest tremor and decreased fundamental frequency standard deviation as evidence. It is important to note that Goberman's study was conducted during a reading task on a small sample (9 participants), and should be considered in the context of other studies which did not find a significant relationship between speech and tremor (Cantiniaux et al., 2010; Dias et al., 2016; Skodda et al., 2011, 2012).

The method of examining speech through more holistic speech constructs, rather than discrete acoustic variables, likely contributed to the significant findings and positive trends in the present study. Previous studies examining the association of acoustic variables and PD motor features (Midi et al., 2007), or between tremor and non-tremor groups (Brown & Spencer, 2020; Tykalová et al., 2020), failed to find significant associations. However, Tykalová and colleagues (2020), using an aggregate of discrete acoustic variables, found significant differences between tremor and non-tremor groups.

The relationship between cognition and primary/secondary motor characteristics does not appear to be driven by disease duration or severity alone. Regarding disease duration, two of the

three participants with MCI had a relatively short disease duration compared to the group mean. Hoehn and Yahr disease severity ratings also do not appear to account for this relationship as the majority of participants received a Hoehn and Yahr rating of three or greater, despite only three participants presenting with MCI.

Clinical Implications

The results of Experiment 1 highlight the interconnectedness of primary motor characteristics, secondary motor characteristics, and cognition in PD. This line of research may inform clinical practice, as clinicians might anticipate a greater likelihood of cognitive challenges in clients with dysarthria and a non-tremor dominant motor phenotype. Converging evidence, and the results of the present experiment, support this premise.

The findings of this study also suggest that clinicians should not rely on the single speech metric of intelligibility to determine level of speech functioning—a common clinical approach. Rather, rating scales that capture naturalness/prosody, in particular, would allow for a more comprehensive representation of the severity and impact of dysarthria in PD. In addition, it is important for clinicians to consider measures of naturalness in their speech assessments over time given the influence of prosody on communicative participation and quality of life. As noted in Anand & Stepp (2015), changes to naturalness likely account for negative listener- and self-perception of speech in PD, and these changes may be significantly limiting even when intelligibility is relatively unaffected (Anand & Stepp, 2015; Yorkston et al., 2004).

For the purpose of this study, speech samples were recorded in a noise-free setting and rated while listeners were in a quiet room. While important for research consistency, this condition is not reflective of more typical daily communication situations, which often include

background noise and competing speech signals. When examining the effect of changes to naturalness, articulatory precision, or intelligibility, it is important for clinicians to consider the effect of background noise in typical communication settings, which has been shown to negatively impact communicative success, even in speakers with mild dysarthria (Chiu & Forrest, 2018; Chiu & Neel, 2020).

Limitations and Future Directions

Several limitations existed for Experiment 1. First and foremost, the small sample size resulting from premature study shutdown pursuant to COVID-19 restrictions limited the ability to conduct the planned recruitment and statistical analyses. Thus, the small study sample is not representative of the local PD community, and results, particularly those showing low, average, and high group ratings are relative only to this sample and cannot be generalized. A larger sample size is particularly warranted when investigating subgroup differentiation.

Proper nouns, low frequency words, formulaic expressions, and specialty vocabulary words were removed from speech samples to standardize speech samples (Sidtis et al., 2012), making speech samples less natural than in typical conversation. Future work may address this limitation by using more representative speech samples.

Chapter 3: Experiment 2

Research Questions

Experiment 2 was designed to address the following research questions:

1) What is the association between primary motor signs (ratings of tremor and non-tremor symptoms), secondary motor signs (ratings of speech severity), and cognition (global and discrete variables) during the de novo time period (T_1) and 4-5 years post (T_2)? Cognitive variables will include verbal learning, visuospatial functioning, working memory, semantic fluency, and global cognitive performance.
2) Do participants classified as having tremor-dominant or non-tremor dominant PD differ on ratings of speech and cognition (global and discrete variables) during the de novo time period (T_1) and 4-5 years post (T_2)?
3) Are early motor signs predictive of later cognitive decline? Specifically, do primary motor signs (ratings of tremor and non-tremor symptoms) or secondary motor signs (ratings of speech severity) in early PD predict general cognitive status (normal cognition, cognitive complaint, MCI, or PDD) 4-5 years post?

Hypotheses

Drawing on the Dual Syndrome Hypothesis, as well as the extant literature, increased severity of non-tremor symptoms is expected to correlate with decreased verbal learning, decreased visuospatial functioning, reduced semantic fluency, and lower scores on global cognitive testing, as well as more severe speech ratings. In contrast, increased severity of tremor symptoms is expected to be associated with decreased working memory. It is also hypothesized

for Question 1 that perceptual ratings indicating more impaired speech at T_1 will be related to increased non-tremor motor severity, as well as decreased verbal learning, decreased visuospatial functioning, reduced semantic fluency, and poorer global cognition at T_2.

Individuals with PD are often subtyped based on primary motor symptom, and it is widely documented that these subtypes differ in terms of general disease path characteristics. Specifically, evidence suggests that individuals within these two phenotypes will differ in measures of cognition and speech. It is predicted that analyses for Question 2 will reveal significant group differences in speech and cognitive variables.

Finally, it is expected that individuals who present with more severe speech impairment or more severe non-tremor symptoms at T_1 will belong to the dementia group at T_2. By contrast, it is hypothesized that more severe tremor symptoms at T_1 will be predictive of either normal cognition, MCI, or cognitive complaint status at T_2. The interaction of speech and motor subtype will also be examined. It is hypothesized that a significant interaction between speaker's motor subtype and cognitive status will be revealed. Specifically, it is expected that more severe speech ratings and a non-tremor primary motor profile will be associated with progression to dementia. This result would support current evidence that suggests that primary and secondary motor symptoms influence cognitive status, aligning with view that shared mechanisms underlie distinct profiles in PD. Research questions and hypotheses are summarized in Table 14.

Table 14. Proposed questions, hypotheses, and analyses for Experiment 2.

Question	Hypothesis	Analysis
1. What is the association between primary motor signs (ratings of tremor and non-tremor symptoms), secondary motor signs (ratings of speech severity), and cognition (global and discrete variables) during the de novo time period ($T_{1)}$ and 4-5 years post (T_2)? Cognitive variables will include verbal learning, visuospatial functioning, working memory, semantic fluency, and global cognitive performance.	More severe non-tremor symptoms and more impaired speech will correlate with more impaired cognition – both global and discrete measures.	Correlations will be run with nonparametric Spearman's rho.
2. Do participants classified as having tremor-dominant or non-tremor dominant PD differ on ratings of speech and cognition (global and discrete variables) during the de novo time period (T_1) and 4-5 years post (T_2)?	Tremor and non-tremor motor subtypes will differ in terms of secondary motor (speech) and cognition.	Between group differences will be examined with an ANOVA adjusted for multiple comparisons.
3. Are early motor signs predictive of later cognitive decline? Specifically, do primary motor signs (ratings of tremor and non-tremor symptoms) or secondary motor signs (ratings of speech severity) in early PD predict general cognitive status (normal cognition, cognitive complaint, MCI, or PDD) 4-5 years post?	Speech rating at T_1 will be a predictor of cognitive status at T_2. Specifically, more severe speech ratings are expected to predict progression to dementia.	Logistic regression will test ability of primary and secondary motor variables to predict cognitive status.

Methods

Dataset

Experiment 2 utilized pre-existing data to further examine the relationship between speech and cognition in PD at a time when in-person data collection is not feasible. Specifically, data presented here are from the Parkinson's Progression Markers Initiative (PPMI) public dataset. Sponsored by the Michael J. Fox Foundation, the PPMI is a longitudinal study with the aim to help researchers identify biomarkers of PD progression. PPMI data collection sites are located across the United States, Europe, Israel, and Australia, and researchers complete rigorous training to ensure uniformity in the data collection process. The complete PPMI protocol encompasses clinical assessments, neuroimaging data, and biological samples, however, only cognitive, motor, and demographic data were used for this study.

Participants

The complete PPMI dataset contains several cohorts of individuals; however, this study examined data only from those participants enrolled in the *de novo* cohort. Subjects included in this cohort have had PD for ≤ 2 years and have not begun pharmacological treatment at the time of enrollment. Participants attend follow-up visits at set increments of at least every 6 months for the first 5 years, and yearly thereafter.

Inclusion criteria were primary diagnosis of idiopathic PD and age ≥ 50 years at time of screening. Exclusion criteria were premature withdrawal, exclusion by examiner for any reason, indeterminate cognitive status (see cognitive status, below), and those who were identified as belonging to the Scans Without Evidence of Dopaminergic Deficit (SWEDD) cohort. The SWEDD cohort includes individuals who present clinically as having PD, but who do not show

evidence of dopaminergic deficit on a DaTSCAN neuroimaging test. The DaTSCAN is an FDA-approved diagnostic tool which has been shown to have high specificity and sensitivity in detecting PD (De La Fuente-Fernandez, 2012; Grachev, 2014). Initial data included 619 participants. Healthy controls (n = 196) were removed, followed by individuals in the SWEDD cohort (n = 81), those with age < 50 at screening (n = 106), and participants with indeterminate cognitive status (n = 45), leaving a total of 191 participants included in Experiment 2.

Speech Rating

Speech presentation at T_1 was determined by the examiner's response to question 3.1 of the Unified Parkinson's Disease Rating Scale (UPDRS) (Goetz et al., 2007) (see Figure 3). This scale is designed to capture overall ease of understanding, as well as aspects of prosody ("loss of modulation", "loss of volume") and precision ("loss of diction"). The sensitivity of using a single 5-point perceptual rating scale to capture changes to speech, particularly in the early stages when any impairment is likely mild, is questionable. However, previous studies of speech and cognition in PD have suggested adequate sensitivity to change (Paulo Bugalho & Viana-Baptista, 2013; Domellöf et al., 2011; Elgh et al., 2009; Schneider et al., 2015).

Motor Classification

Motor presentation from T_1 was characterized using the same methods described in Experiment 1 (see Table 5). Participants were categorized into tremor and non-tremor groups using the same UPDRS subtyping methodology. In addition, tremor and non-tremor severity was determined by the sum of all tremor items, and sum of all non-tremor items, respectively. These

scores were analyzed as continuous variables; thus, each participant received a tremor score and a non-tremor score, in addition to a motor subtype.

Cognitive Performance

Each participant underwent neuropsychological testing by PPMI examiners measuring a range of cognitive functions. Four discrete cognitive assessments, one cognitive screening test, and one global cognitive measure were included in the cognitive test battery given to participants at 12-month intervals. For the purpose of this study which aimed to examine discrete and global measures, the Symbol Digit Modalities Test, a cognitive screening tool, was not included. Thus, four discrete tests and the one global test were used to examine cognitive performance, described below.

1. *Verbal Learning*. The Hopkins Verbal Learning Test (HVLT) examines verbal short-term memory and new learning, which requires rapid encoding of information. The HVLT includes three immediate recall trials, one delayed recall trial, and one delayed recognition trial, for a total of 5 trials worth 12 points each. Scores across trials are summed for a total verbal learning score out of 60.
2. *Visuospatial Skills*. The Benton Judgement of Line Orientation measures visuospatial processing. For this test, participants are asked to estimate angular relationships by visually matching line segments that share the same slope. Thirty trials are presented, with a total score of 30.
3. *Working Memory*. The Letter Number Sequencing subtest of the Wechsler Memory Scale, 3rd edition, tests verbal working memory. In this test, participants are read a combination of numbers and letters and asked to recall and state the numbers first, in

ascending order, followed by the letters in alphabetical order. The test consists of seven items, with three trials each. One point is given for each correct trial, with a total score of 21.

4. *Semantic Fluency*. Semantic fluency is measured by requesting participants to orally name as many animals as they can in a one-minute period. This procedure was repeated with the sematic categories of vegetable and fruit. Scores are summed across the three trials to produce an overall semantic fluency score.
5. *Global Cognition*. The Montreal Cognitive Assessment (MoCA) is a global cognitive measure developed to be more sensitive to patients presenting with mild cognitive complaints. The MoCA assesses short-term and working memory, visuospatial skills, executive function, attention, concentration, language, and orientation. Total score ranges from 0 to 30.

Cognitive Categorization

Using cognitive test performance, participant/caregiver report, and examiner's judgment, participants are categorized into five cognitive status groups: 1) normal cognition, 2) cognitive complaint (made by patient or informant), 3) mild cognitive impairment (MCI), 4) Parkinson disease dementia (PDD), or 5) indeterminate. Participants with an indeterminate cognitive status were excluded from the present study. See Table 15 for classification criteria.

Cognitive categorization data are updated annually after the first year. This study will use the cognitive status at year 5 (T_2; 5-7 years post diagnosis) as the outcome variable of interest. Cognitive status at T_1 ($\leq$ 2 years following diagnosis) will also be recorded to contextualize the relationship between early speech and cognitive functioning. Cognitive tests used by PPMI

examiners for determination of MCI and PDD included: 1) Hopkins Verbal Learning Test, 2) Benton Judgment of Line Orientation, 3) Letter Number Sequencing subtest of the Wechsler Memory Scale, 4) Semantic Fluency subtest of the Neurosensory Center Comprehensive Examination for Aphasia, 5) Symbol Digit Modalities Test, and 6) Montreal Cognitive Assessment.

Table 15. PPMI study protocol criteria for cognitive categorization of mild cognitive impairment and Parkinson disease dementia (taken from PPMI, http://www.ppmi-info.org/).

Diagnosis of Mild Cognitive Impairment was determined by the following factors:	**Diagnosis of Parkinson Disease Dementia was determined by the following factors:**
1. Cognitive complaint by either the patient or informant (spouse, family member or friend). 2. Cognitive impairment defined as at least 2 test scores (out of 6 scores) from at least 1 domain (out of 4) >1.0 SD below the standardized mean. 3. No functional impairment as a result of cognitive impairment.	1. History of cognitive decline determined by the investigator based on information from the patient, other informant (spouse, family member or friend) and the investigator's judgment. 2. Cognitive impairment defined as at least 1 test score (out of 6 scores) from at least 2 domains (out of 4 domains) >1.5 SD below the standardized mean. 3. Functional limitation as a result of cognitive impairment.

Statistical Analysis

Statistical analyses were conducted using SPSS 26. As highlighted in Table 14, nonparametric Spearman's rho was used to examine correlations between primary motor, speech, and cognitive variables at T_1 and again at T_2. Next, differences in demographic (age, gender, and

years of education), speech, and cognitive variables between the tremor and non-tremor groups at T_1 and T_2 were analyzed using an analysis of variance, with adjusted alpha value. A third analysis was used to examine the relationship between cognitive test scores and clinical variables at T_1 and the presence of cognitive decline at T_2. Specifically, logistic regression was used to determine whether speech, severity of tremor symptoms, or severity of non-tremor symptoms at T_1 could uniquely predict cognitive status at T_2.

Results

Reliability

Intra- and inter-rater reliability was conducted for accuracy of data extraction from the PPMI database. For intra-rater reliability, the investigator re-extracted data for twenty randomly chosen participants (approximately 10% of the sample) across four primary variables (approximately 20%). Pearson product-moment correlations between original and repeated samples revealed perfect (r = 1.00) correlations with significance of $p < 0.001$ for speech rating, cognitive categorization, semantic fluency T_1, and semantic fluency T_2. To assess inter-rater reliability, a second trained research assistant independently extracted data from the same primary variables for twenty randomly chosen participants. Correlations were significant at the level of $p < 0.001$ for speech rating (r = 0.95), cognitive categorization (r = 0.98), and semantic fluency at T_1 (r = 1.00) and T_2 (r = 0.94), suggesting strong inter-rater reliability.

Participant Demographics

Participant demographics were examined between tremor-dominant and non-tremor groups on variables of gender, age, years of education, and Hoehn &Yahr disease severity rating

(see Table 16). Tremor-dominant and non-tremor dominant groups did not differ significantly in demographic variables of years of education ($p = 0.730$), age at baseline ($p = 0.316$), gender ($p = 0.260$), or Hoehn & Yahr disease severity ($p = 0.208$; see Table 16).

Table 16. Participant demographics between tremor-dominant (TD) and non-tremor (NT) groups.

	TD ($n = 153$)	NT ($n = 37$)			
Demographic	Mean (SD)	Mean (SD)	Difference	$F(1,188)$	p - value
Gender	102 male; 51 female	21 male; 16 female	--	1.28	0.260
Age (at baseline)	62.38 (7.66)	60.97 (7.33)	1.41	1.01	0.316
Years of Education	15.79 (2.71)	15.62 (2.52)	0.17	0.12	0.730
Hoehn & Yahr	1.69 (0.48)	1.81 (0.66)	0.12	1.60	0.208

Correlations between Motor and Cognitive Variables

Nonparametric Spearman's rho correlations were conducted to address research question 1, examining the association between primary motor subtype (tremor and non-tremor), primary motor signs (ratings of tremor and non-tremor severity), secondary motor signs (ratings of speech severity), and cognition (both global and discrete variables) during T_1 and T_2, and are presented in Table 17.

Table 17. Spearman rho correlation coefficients (r_S) between motor variables at T_1 (speech and primary motor) and cognitive variables at T_1 and T_2.

	Primary and Secondary Motor Variables			
Cognitive Variable (T_1)	**Speech (T_1)**	**Motor Subtype (T_1)**	**TD Severity (T_1)**	**NT Severity (T_1)**
Visuospatial	0.06	0.11	-0.13	0.10
Verbal Learning	- 0.08	**0.17***	-0.10	- 0.02
Working Memory	- 0.13	**0.17***	**- 0.15***	- 0.12
Semantic Fluency	- 0.13	**0.22****	**-0.22****	- 0.08
Global Cognition	0.05	**0.16***	**- 0.18***	**- 0.15***
Cognitive Variable (T_2)				
Visuospatial	- 0.04	0.06	- 0.11	- 0.12
Verbal Learning	- 0.14	0.06	- 0.07	- 0.07
Working Memory	**- 0.19***	- 0.02	- 0.12	- 0.13
Semantic Fluency	**- 0.18***	**0.17***	- 0.13	< 0.00
Global Cognition	- 0.09	0.11	**- 0.15***	**- 0.21****
Motor Variable (T_1)				
Speech	--	0.11	0.06	**0.30****

Note. * = $p \leq 0.05$; ** = $p < 0.001$; TD Severity = Tremor-dominant symptom severity; NT Severity = non-tremor dominant symptom severity.

Cognition at T_1 and Motor Presentation

When examining cognition in early PD in relation to speech and motor presentation, *speech* rating at T_1 was not significantly associated with T_1 discrete or global cognitive variables. However, *motor subtype* at T_1 was significantly associated with the cognitive variables of verbal learning, working memory, semantic fluency, and global cognition (see Table 17).

Further examination of motor symptom severity and cognition revealed a negative association between severity of *tremor symptoms* and T_1 cognitive variables of working memory ($p = 0.043$), semantic fluency ($p = 0.002$), and global cognition ($p = 0.012$), although the strength of these associations was weak. The negative association indicates that an increase in tremor severity was associated with a decrease in performance on the aforementioned cognitive measures. When examining *non-tremor symptom* severity and cognition, no discrete cognitive variables were significantly associated. However, non-tremor symptom severity was significantly negatively correlated with global cognition ($p = 0.035$), although the strength of this correlation was also weak. It is important to highlight that decreased global cognition (MoCA score) was associated with an increase in both tremor and non-tremor severity, suggesting that this relationship might be driven by disease severity and not specific motor presentation.

Cognition at T_2 and Motor Presentation

The relationship between cognitive performance at T_2, and T_1 ratings of speech and motor subtype was also examined. Results indicated significant negative correlations between *speech rating* at T_1 and working memory ($p = 0.012$) and semantic fluency ($p = 0.014$) at T_2. Thus, poorer performance on discrete cognitive measures of working memory (Letter Number Sequencing) and semantic fluency 5-7 years post diagnosis were found to be associated with increased ratings of speech severity on the UPDRS at baseline, although Spearman coefficients were weak. Correlations between cognitive variables at T_2 and *motor subtype* revealed one significant association between semantic fluency and motor subtype ($p = 0.017$), although the strength of this association was also weak.

When examining correlations between T_1 *tremor symptom severity* and later cognitive performance, a significant negative correlation was found between tremor symptom severity and global cognitive performance at T_2 ($p = 0.038$), indicating that higher (worse) early tremor scores were associated with poorer later MoCA scores. However, the correlation coefficients suggest that the strength of this relationship is weak. Tremor symptom severity was not significantly associated with any discrete variables.

In a similar pattern, T_1 non-tremor symptom severity was not associated with discrete cognitive variables at T_2, but was significantly negatively correlated with T_2 MoCA score ($p = 0.005$). As with T_1, decreased global cognition (MoCA score) at T_2 was also significantly correlated with both tremor and non-tremor symptom severity ratings, a likely indicator that this relationship might be driven by disease severity and not specific motor presentation.

Speech and Motor Presentation

Finally, the relationship between speech rating at T_1 and primary motor presentation at T_1 was examined. While speech rating was not found to be significant with motor subtype or severity of tremor symptoms, speech severity ratings were found to be significantly associated with non-tremor symptom severity ($p < 0.001$). This finding indicates that as speech ratings increased, indicative of more severe dysarthria, non-tremor symptom severity ratings also increased; the strength of this relationship was moderate.

Tremor Versus Non-Tremor Subtype Comparisons

To address Research Question 2, analysis of variance was conducted to examine whether individuals with tremor-dominant and non-tremor dominant PD differ on ratings of speech and

cognition at T_1 and T_2. Data met assumptions of the planned ANOVA, including normality, homogeneity of variance, and independence. One participant was classified as an indeterminate subtype and was excluded from these analyses.

Between-group comparisons for speech and cognitive variables at T_1 are shown in Table 18. Results indicated that performance on several cognitive measures was significantly worse in the tremor-dominant versus non-tremor dominant group. Specifically, significant between-group differences were found for verbal learning (p = .015), working memory (p = 0.006), semantic fluency (p = 0.001), and MoCA scores (p = .026).

Table 18. Comparison of tremor-dominant (TD) and non-tremor dominant (NT) groups across speech and cognitive variables for T_1.

	TD (n = 153)	NT (n = 37)			
T_1 variables	Mean (SD)	Mean (SD)	Difference	F(1,188)	p - value
Speech Rating	0.55 (0.61)	0.73 (0.84)	0.18	2.25	0.135
Visuospatial	24.98 (4.66)	26.38 (3.23)	1.40	2.98	0.086
Verbal Learning	45.07 (9.85)	49.54 (10.46)	4.47	6.01	**0.015***
Working Memory	10.40 (2.46)	11.65 (2.54)	1.25	7.58	**0.006***
Semantic Fluency	49.53 (9.91)	55.81 (12.77)	6.28	10.62	**0.001***
MoCA	26.57 (2.80)	27.68 (2.16)	1.11	5.06	**0.026***

Note. ***** = significant at $p \leq 0.05$

Between-group analyses examining cognitive variables at T_2 revealed that significantly lower scores remained in the semantic fluency domain for the tremor-dominant group compared to the non-tremor group ($p = 0.012$), but not for the other T_2 cognitive variables (see Table 19).

Table 19. Differences in cognitive variables for tremor-dominant (TD) and non-tremor dominant (NT) groups at T_2.

	TD (n = 153)	NT (n = 37)			
T_2 variables	Mean (SD)	Mean (SD)	Difference	F(1,188)	p - value
Visuospatial	23.82 (4.84)	24.38 (4.64)	0.56	0.41	0.523
Verbal Learning	46.61 (11.56)	47.84 (13.23)	1.23	0.32	0.575
Working Memory	9.61 (2.95)	9.54 (2.77)	0.07	0.16	0.900
Semantic Fluency	42.67 (14.65)	49.76 (17.90)	7.09	6.38	**0.012***
MoCA	25.86 (4.35)	27.06 (3.10)	1.20	2.45	0.119

Note. * = significant at $p \leq 0.05$

Factors Predicting Cognitive Status at T_2

To address research question 3, four binary logistic regression models were conducted to examine whether early motor signs (subtype and speech ratings) were predictive of later cognitive decline. By follow-up at T_2, 108 participants remained with normal cognition, 56 had cognitive complaint status, 10 were rated as MCI, and 17 progressed to PDD. Speech rating, tremor symptom severity, and non-tremor symptom severity at T_1 were used in each model to predict cognitive status at T_2. Models for normal cognition, cognitive complaint, MCI, and PDD were completed; see Tables 20-23. All predictors were entered into the models simultaneously.

To account for multiple comparisons, *p*-value was adjusted to 0.025 using Bonferroni correction method.

Results of the binary logistic regression Model 1, shown in Table 20, indicated that T_1 factors of speech severity rating, tremor severity, and non-tremor severity were not significant predictors of normal cognition status at T_2. This suggests that neither speech nor primary motor presentation in early PD predicted normal cognitive status in later PD.

Table 20. Model 1 examining motor variables at T_1 as predictive factors for normal cognition (*n* = 108) at T_2.

Overall model fit				Value
- 2 log likelihood	--	--	--	258.78
Nagelkerke R^2	--	--	--	0.019
Predictor	B	SE	Exp(B)	*p* - value
Speech Rating	- 0.10	0.23	0.91	0.673
Tremor Severity	- 0.05	0.04	0.95	0.196
Non-Tremor Severity	- 0.08	0.11	0.93	0.483
Constant	0.71	0.31	2.03	0.023

Similarly, in Model 2, ratings of speech, tremor, and non-tremor severity were not found to be significant predictors of cognitive complaint status at T_2 (see Table 21), suggesting that these characteristics in early PD are not predictive of later development of cognitive complaint.

Table 21. Model 2 examining motor variables at T_1 as predictive factors for cognitive complaint (n = 56) at T_2.

Overall model fit				Value
- 2 log likelihood	--	--	--	228.22
Nagelkerke R^2	--	--	--	0.021
Predictor	B	SE	Exp(B)	p - value
Speech Rating	- 0.38	0.27	0.68	0.150
Tremor Severity	- 0.03	0.04	1.03	0.463
Non-Tremor Severity	- 0.12	0.123	1.12	0.328
Constant	- 0.10	0.34	0.37	0.003

In Model 3, binary logistic regression examining predictors for MCI at T_2 indicated that neither speech rating, tremor symptom severity, nor non-tremor symptom severity in early PD (T_1) were predictive of development of MCI 4-5 years later (T_2; see Table 22).

Table 22. Model 3 examining motor variables at T_1 as predictive factors for MCI (n = 10) at T_2.

Overall model fit				Value
- 2 log likelihood	--	--	--	73.52
Nagelkerke R^2	--	--	--	0.076
Predictor	**B**	**SE**	**Exp(B)**	***p*** **- value**
Speech Rating	0.35	0.57	1.42	0.534
Tremor Severity	0.02	0.09	1.02	0.820
Non-Tremor Severity	- 0.86	0.46	0.43	0.063
Constant	- 2.45	0.68	0.09	< 0.001

Finally, model 4 examined primary and secondary motor presentation in early PD as predictors of development of PDD 4-5 years later. The predictor variable, speech rating at T_1, was found to significantly contribute to the model predicting PDD cognitive status at T_2. A test of the full model with all three predictors against a constant-only model was statistically significant, $\chi 2(3, N = 191) = 10.53$, $p = .015$, indicating that the predictors, as a set, significantly distinguished between individuals with PDD and those without (see Table 23).

Table 23. Model 4 examining motor variables at T_1 as predictive factors for PDD (n =17) at T_2.

Overall model fit				Value
- 2 log likelihood	--	--	--	104.16
Nagelkerke R^2	--	--	--	0.12
Predictor	B	SE	Exp(B)	p - value
Speech Rating	0.96	0.39	2.60	**0.014***
Tremor Severity	0.07	0.06	1.07	0.250
Non-Tremor Severity	0.14	0.16	1.15	0.396
Constant	- 3.74	0.66	0.02	< 0.001

Note. ***** = significant at adjusted value of $p \leq 0.02$

Discussion

The goal of Experiment 2 was to examine the relationship between speech, primary motor presentation, and cognitive performance in individuals with PD. By utilizing a *de novo* cohort, this study was able to capture cognitive, speech, and primary motor presentation in an early disease state and examine the association with cognitive performance 4-5 years later. Discrete variables of visuospatial performance, verbal learning, working memory, and semantic fluency, were considered as well as global cognitive performance. In addition to examining the relationship between these variables, differences in cognitive performance and speech ratings between tremor dominant and non-tremor phenotypes were considered. Finally, regression models were conducted to test the ability of early speech and primary motor symptom severity to

predict cognitive categorization status (normal, cognitive complaint, MCI, or PDD) 5-7 years post PD diagnosis.

It was hypothesized that increased severity of non-tremor symptoms would be associated with decreased verbal learning, decreased visuospatial functioning, reduced semantic fluency, and lower scores on global cognitive testing, as well as more severe speech ratings. In contrast, increased severity of tremor symptoms was posited to be associated with decreased working memory. It was also hypothesized that perceptual ratings indicating more impaired speech at T_1 would be related to increased non-tremor motor severity, as well as decreased verbal learning, decreased visuospatial functioning, reduced semantic fluency, and poorer global cognition at T_2. Additionally, between-group differences were anticipated on measures of cognition and speech ratings, in alignment with current models of cognitive impairment in PD that link dysexecutive dysfunction to a tremor-dominant phenotype and more global cognitive deficits, including visuospatial and semantic fluency, to a non-tremor profile. Lastly, it was expected that speech rating at T_1 would be uniquely predictive of PDD cognitive status at T_2.

Associations between Cognitive Variables and Motor Characteristics

To address Research Question 1, correlations were used to test associations between cognition, primary motor characteristics, and speech severity. Perhaps the most compelling finding related to Research Question 1 is that early speech severity (T_1) was significantly associated with early non-tremor dominant symptom severity, but not tremor symptom severity. This result is consistent with previous literature linking dysarthria and non-tremor symptoms, specifically changes to gait (Cantiniaux et al., 2010; Lord et al., 2014; Moreau et al., 2007; Morgante et al., 2013) or bradykinesia (Dias et al., 2016; Goberman, 2005; Skodda et al., 2011).

Even mild dysarthric changes have been linked to non-tremor symptoms after controlling for disease severity (Moreau et al., 2007), providing further support of the notion that speech should be clustered with axial signs. Taken together, these findings confirm early speech changes as an important clinical symptom that may serve to inform the presence of a more pervasive disease (see General Discussion).

With respect to the association between cognition and primary/secondary motor characteristics, several significant relationships were found, but interpretation is limited by the relatively weak strength of the correlations. For instance, increased tremor symptom severity in early PD was significantly associated with decreased early working memory and semantic fluency performance. Numerous investigations have reported an association between a tremor-dominant symptoms and working memory resulting from impaired fronto-striatal loops (Moustafa et al., 2016; Papagno & Trojano, 2018). The well-documented amelioration of both tremor and working memory deficits from dopaminergic supplementation further solidifies this link (Lewis et al., 2005; Lewis & Barker, 2009; Owen et al., 1995), which is also reflected in the Dual Syndrome Hypothesis (Kehagia et al., 2010, 2013) and the Go/NoGo Model (Frank et al., 2004).

However, the significant link between tremor severity and semantic fluency was not expected as this cognitive-linguistic measure is routinely linked to the non-tremor dominant symptoms (Obeso et al., 2012; Williams-Gray et al., 2007) and the posterior-cortical profile of the Dual-Syndrome Hypothesis. One explanation for this unexpected finding is the presence of postural tremor in the tremor severity ratings. Postural tremor has been demonstrated to more frequently occur in individuals with an akinetic-rigid PD presentation (Helmich et al., 2012). Another explanation for this unexpected finding is the potential interaction between semantic

fluency and side of presentation, a concept which has limited, but important, empirical support (Jaywant et al., 2014), purporting that individuals with right-sided symptom onset have poorer performance on semantic and verbal fluency tasks due to left frontal lobe mediation (Baldo et al., 2001), although side of onset was not controlled for in this study. Differences in methodology may have also contributed to this unexpected finding. Specifically, semantic fluency in the PPMI dataset was measured as the number of items counted in a 60-second period, repeated for three trials. However, in the influential work of Williams-Gray et al. (2007) semantic fluency was measured as number of items named in 90-seconds. Thus, these results are not directly comparable due to the substantial time difference during testing.

Poorer performance on the MoCA in both early PD and again 5-7 years post diagnosis was significantly associated with both tremor and non-tremor symptom severity, suggesting this association is driven by disease severity instead of motor profile. In addition, MoCA scores were not associated with speech ratings. Thus global cognitive scores are not likely to contribute meaningfully to the differentiation between motor subtypes or speech ratings, which suggests that this screening tool does not provide unique information beyond an understanding of general cognitive functioning.

Finally, early speech severity (T_1) was significantly associated with poorer performance on working memory and semantic fluency 5-7 years post diagnosis (T_2), suggesting a potential link between speech and discrete cognitive domains. While the strength of the correlations with these specific measures was considered weak, the connection between speech and cognition was more comprehensively addressed with the regression models in research question 3, and will be further discussed in that section.

Cognitive Performance Between Tremor and Non-Tremor Phenotype

For research question 2, analysis of variance was used to examine differences in cognitive performance between tremor and non-tremor groups at two time points—in the early, *de novo* state and 5-7 years post diagnosis. The aim of this analysis was to build upon the relationships highlighted in research question 1 by examining variables between primary motor phenotypes. The primary finding of this subtype comparison was that early performance on verbal learning, working memory, semantic fluency, and global cognition was significantly worse in the tremor-dominant group. This maps, in part, onto the Dual Syndrome Hypothesis, which suggests that impaired working memory is part of the tremor-dominant profile. Conversely, more impaired verbal learning and semantic fluency in the tremor-dominant group were not an expected finding. Interestingly, although there were significant between-group differences on verbal learning at T_1, this cognitive domain was not associated with motor symptom severity (research question 1). While this finding was not expected, one possible explanation for this can be found in the dopamine overdose hypothesis (Cools, 2006; Fallon et al., 2015; Vaillancourt et al., 2013), which suggests that dopaminergic supplementation may impair sensitive cognitive channels, particularly those related to learning. Thus, poorer performance on verbal learning tasks in the tremor dominant group may be a reflection of dopaminergic medication in this group.

When examining the cognitive performance of the tremor and non-tremor groups at 5-7 years post diagnosis, the only between-group difference that remained was semantic fluency. However, as noted with research question 1, the nature of this finding was inconsistent with the Dual Syndrome Hypothesis. That is, impaired semantic fluency has been more strongly associated with a non-tremor motor profile, as discussed in the previous section.

Early Motor Signs as a Predictor of Later Cognitive Status

Research question 3 examined whether early motor symptoms were predictive of later cognitive decline. Specifically, this question aimed to test whether primary motor signs (ratings of tremor and non-tremor symptoms) or ratings of speech severity in early PD could predict general cognitive status (normal cognition, cognitive complaint, MCI, or PDD) 4-5 years later.

Results aligned with the hypothesis, and suggested that early speech ratings in the early *de novo* period were significantly predictive of PD dementia status at T_2. As there were no significant differences in Hoehn & Yahr disease severity ratings between PDD and non-PDD groups, this relationship does not appear to be driven by disease severity. These results suggest that early presentation of dysarthria may be indicative of rapid cognitive decline, even during a relatively short follow-up period (Paulo Bugalho & Viana-Baptista, 2013; Rektorova et al., 2016). Incidence of dementia in this study was slightly lower than expected in the larger PD population, with 17 of the 191 participants progressing to dementia (incidence equivalence of 89 per 1,000), compared to more conventional rates of 95.3 per 1,000. This is likely due to the relatively early follow-up period in this study, and further supports the importance of early speech changes.

An increasing body of work has linked speech with cognitive performance, although few have examined speech as a focal predictor of progression to dementia. Quantifying this relationship is critical, however, as cognitive decline in PD substantially impacts quality of life and leads to increased caregiver burden (Biundo et al., 2016). Our findings provide support for early identification based upon clinical presentation, which is a critical component to implementation of proactive interventions.

Furthermore, the key finding of early dysarthria as a predictor of later dementia further strengthens the notion of shared neural underpinnings, as noted by prior empirical studies (Paulo Bugalho & Viana-Baptista, 2013; Gago et al., 2009a; Rektorova et al., 2016). Specifically, these studies implicate depletion of shared cholinergically-mediated channels as the likely impetus of changes to speech, particularly prosodic changes (Chiu & Neel, 2020). When taken with models of cognitive impairment that suggest cholinergic breakdowns underlie progression to dementia (Karachi et al., 2010; Kehagia et al., 2013), our findings further corroborate these claims.

Experiment 2 also served to demonstrate that significant speech changes can be identified even in early stages of the disease, and even slight changes can be telling of a more pervasive disease path, a notion that has been demonstrated previously (Defazio et al., 2016), and suggests that speech should be considered as an important variable throughout the course of PD. Specifically, of the 17 participants who progressed to PDD, 4 had mild ratings, 11 had speech changes rated as slight, and 2 were rated as having normal speech at baseline, suggesting that even mild disruption is a useful metric. In addition, the single, 5-point speech rating scale of the UPDRS appears sufficient to capture even slight changes to speech, although it remains unclear which specific changes to speech (e.g., intelligibility, prosody) prompted examiners to give more severe ratings; a more nuanced assessment would yield additional clinically relevant information.

Limitations and Future Directions

This study used a cohort of newly diagnosed individuals with a relatively short follow-up period. Due to this, the number of individuals who progressed to dementia was relatively small compared to the expected prevalence over the course of the disease. Another limitation of this study is that dopaminergic medication was not taken into account. Although all individuals were unmedicated at baseline, many individuals likely began dopaminergic medication at some point

during the study. The effect of dopaminergic medication on speech and cognition is not well known, as the effects are likely variable at the individual level. Further work is also needed to expand speech ratings, specifically by discerning the nature of speech changes that may inform progression to dementia.

Chapter 4: General Discussion

The overarching goal of these experiments was to examine the interplay between dysarthria and cognition in PD, while also considering the role that primary motor presentation plays on this relationship. Several clinical features have been shown to be associated with increased risk for cognitive impairment in PD, such as speech (Paulo Bugalho & Viana-Baptista, 2013; Domellöf et al., 2011; Rektorova et al., 2016) and non-tremor motor symptoms (Factor et al., 2011; Giladi et al., 2001; Herman et al., 2014). This study expanded on these findings by providing additional evidence that early changes to speech are predictive of later development of dementia.

Additionally, speech impairment has been linked to the presence of non-tremor motor symptoms (Cantiniaux et al., 2010; Herman et al., 2014; Karachi et al., 2010), such as bradykinesia and changes to gait. This non-tremor presentation has been demonstrated as a distinct PD profile (Eggers et al., 2012; Factor et al., 2011; Moustafa et al., 2016), indicative of more pervasive disease presentation with a poorer prognosis (see Table 2). Results of both Experiments 1 and 2 revealed significant associations between dysarthria and non-tremor symptom severity, further confirming this notion that speech changes are a likely feature of the non-tremor profile.

Speech and Cognition in PD

As discussed previously, speech changes have been demonstrated to have uniquely predictive associations with overall cognitive decline and incident dementia (Gago et al., 2009a; Levy et al., 2000b; Rektorova et al., 2016). While Experiment 1 did not reveal a significant relationship between speech and cognition, findings from Experiment 2 support this notion. Specifically, Experiment 2 highlighted speech severity rating in early PD as a significant

predictive factor of PDD cognitive status at follow-up, 4-5 years later. This finding aligns with Levy et al. (2000) and Gago et al. (2009), which demonstrated speech severity rating on the UPDRS as a significant predictor of progression to dementia. In a slightly different approach, Bugalho and Viana-Baptista (2013) dichotomized the UPDRS speech rating into impairment (> 0) and non-impairment (0) groups and reached a similar conclusion, indicating that a rating of >0 on the UPDRS was a significant predictor of a decline in cognitive test scores (frontal assessment battery), further corroborating the speech and cognition link. Authors of these studies have suggested that their results implicating speech changes as predictive of worse cognitive decline likely stem from impairments in non-dopaminergic channels, specifically cholinergic dysfunction. This notion is also supported by previously discussed models of PD. For example, Gratwicke's (2015) Neural Networks Framework suggests atrophy within the medial temporal lobe network leads to hypoactivation of the hippocampus, parahippocampus, entorhinal and perirhinal cortices, and amygdala; structures critical for memory storage and retrieval. Similarly, the Braak Model notes these areas are likely invaded with disease pathology around late stage 3, to early stage 4, although Braak acknowledges additional factors such as individual neuronal reserves or preexisting comorbidities influence the timing of overt symptoms (Braak & Del Tredici, 2009).

While these networks are also implicated by behavioral studies (Bohnen & Albin, 2009; Peter et al., 2016), some individuals with PD have been described as having cortical Lewy pathology presence, confirmed post mortem, without a clinical presentation of dementia (Colosimo, 2003; Rietdijk et al., 2017). Colosimo and colleagues (2003) take this as evidence that there is not a clear quantifiable threshold for Lewy pathology to distinguish between individuals progressing to dementia versus those who do not. Furthermore, the authors suggest

that presence and quantity of Lewy pathology might be unrelated to cognitive impairment (Colosimo, 2003), a notion that continues to be supported by Rietdijk and colleagues (2017).

Another possible explanation for the presence of the expected pattern of Lewy pathology in individuals who do not present with dementia is presented by Braak and colleagues, suggesting that these discrepancies are representative of general heterogeneity related to individual differences such as amount of neuronal reserve, which may prevent or delay more pervasive cognitive deficits in some individuals (Braak & Del Tredici, 2009). This discrepancy has led to the emergence of a relatively new theory of PD progression, the Threshold Theory (Engelender & Isacson, 2017), which purports that individual body systems have distinct thresholds and that PD pathology, along with natural age-related deterioration, differentially impact these systems, thus, PD symptoms would be expected to appear at different rates. This theory diverges from the Braak Hypothesis, which suggests that PD pathology spreads in an ascending pattern, and instead suggests that there is simultaneous parallel degeneration. Thus, according to the Threshold Theory, PD pathology have invaded multiple cortical areas, but, due to a lower functional threshold, classic symptoms emerge first (Engelender & Isacson, 2017).

As stated by Gago et al (2009) and Alves (2006), early axial changes should not be ignored as they might signify a greater likelihood of PD progression to worse cognitive decline or dementia. The results of this study support this notion that speech changes, even in early PD represent important characteristics that are likely mediated, at least in part, by cholinergic channels. Furthermore, consideration of dysarthria as an axial, or non-tremor symptom, may facilitate improved identification and management of other more deleterious changes such as severe cognitive decline.

Dysarthria and Primary Motor Presentation

Speech changes, specifically to naturalness and articulatory precision, were found to be strongly associated with non-tremor symptom severity in Experiment 1. Similarly, dysarthria, measured as severity of impairment, was found to be significantly correlated with severity of non-tremor symptoms in Experiment 2, although results indicated that the strength of this relationship was weak. However, when taken together, and considered with previous research and models of impairment, results from Experiments 1 and 2 support unique associations within PD between speech and non-tremor characteristics. Findings from this study echo Cantiniaux et al. (2009), which demonstrated individuals with more impaired gait also demonstrated reduced speech velocity. Although participants in Cantiniaux et al. underwent deep brain stimulation during the study, the authors concluded that shared neuropathological mechanisms underlie speech and gait dysfunction. Similarly, Skodda et al. (2011) and (Dias et al. (2016) found worsening of axial symptoms to be associated with prosodic changes, as did Gobeman (2005). Equally important in the argument for a speech and non-tremor link is the lack of significant associations between speech changes and tremor symptoms. The majority of studies examining the speech and primary motor presentation link failed to reveal significant associations with tremor symptoms. One exception to this pattern is Goberman (2005), who found an association between increased rest tremor and fundamental frequency, although this relationship was only present during a reading task. Due to the known effects that a reading task may have on speech, this association alone should not be considered as evidence against a speech and non-tremor link. Goberman also noted an association between postural tremor and changes to articulation (F2 vowel slope) and prosody (pausing parameters in monologue). While Goberman cites this as evidence against consideration of speech as an axial feature, recent work suggests that a postural

tremor more frequently occurs in the akinetic-rigid subtype (also a non-tremor categorization; Helmich et al., 2012). Thus, the author's findings might be better taken as support for an distinct relationship between speech and non-tremor characteristics.

Non-tremor presentation has been well-described in the literature as a sign of a more pervasive disease, characterized by more predominant posture, rigidity, and gait disturbance, and more rapid cognitive decline. The demonstrated link between these characteristics and speech changes suggests that speech might serve as an additional indicator of the presence of non-tremor PD phenotype. Furthermore, it is possible that the same neural breakdown responsible for non-tremor symptom emergence also underlies changes to speech. When considered in tandem with extant research suggesting a role of acetylcholine in cognitive decline, posture and gait impairment (Karachi et al., 2010; Rochester et al., 2012), as well as speech naturalness (Rektorova et al., 2016) and intelligibility (Chiu & Neel, 2020), Experiment 1 and 2 results provide further support of this notion.

Additional Considerations

The Role of Acetylcholine

At a cellular level, Lewy pathology impairs sensitive channels beyond the dopamine-dependent networks which are responsible for cardinal tremor presentation, potentially involving additional neurotransmitters such as acetylcholine, serotonin, and norepinephrine. Theoretical and empirical evidence largely implicates differential neurotransmitter involvement as underling the unique relationship that may exist between motor and non-motor characteristics. Of specific interest is the role that acetylcholine plays in cognition, speech, and primary motor presentation, as it is largely recognized in current models of PD.

Synthesizing current theories of PD progression can help explain results from Experiments 1 and 2. In Experiment 1, participants with greater severity of non-tremor symptoms demonstrated more impaired speech naturalness and articulatory precision. As speech is relatively refractory to dopamine supplementation (Cavallieri et al., 2021; Spencer et al., 2009), it is possible that non-tremor symptom presentation and changes to speech naturalness result from a shared neural mechanism. Further considering the purported role that the amygdala, a cholinergically-mediated limbic structure, plays in prosodic control (Rektorova et al., 2016) provides additional evidence that cholinergic deficits are underlying the perceptual speech changes and non-tremor symptom association revealed in Experiment 1. Results of Experiment 2 further support this notion, as cognitive impairment has also been shown to result from depleted cholinergic networks in experimental studies (Perez-Lloret & Barrantes, 2016; Rizzi & Tan, 2017) as well as models of impairment (Gratwicke et al., 2015; Kehagia et al., 2013). Thus, acetylcholine should be considered as an influential neurotransmitter which may underlie many motor and non-motor features in PD.

The Role of Auditory Perception in PD

One characteristic of individuals with hypokinetic dysarthria in PD is impaired self-perception of loudness (De Keyser et al., 2016; Fox & Ramig, 1997) and rate (Tjaden, 2000). It has been well established that individuals with PD demonstrate the ability to improve loudness when provided with external cues (Fox & Ramig, 1997; Liotti et al., 2003; Sapir et al., 2011). Amelioration of dysarthric characteristics such as breathy, monotone, and reduced volume of speech have been documented through successful "recalibration" of self-perception, particularly through the Lee Silverman Voice Treatment, the gold-standard treatment for voice impairment in

individuals with PD (Fox & Ramig, 1997; Liotti et al., 2003; Ramig et al., 2007; Sapir et al., 2011). Impaired self-perception is an important component of the link between cognition and speech in PD. At this time, the underlying mechanism of impaired self-perception in PD is not known. However, research suggests that the cause is not due to impaired ability to integrate auditory feedback, but perhaps a deficit in motor planning related to sensory integration (Brajot et al., 2016).

Medication Status

The potential effects of dopaminergic supplementation are widely documented, though not well understood due to individual differences in medication response. Theories such as the dopamine overdose hypothesis highlight the deleterious effects that dopamine can have on sensitive cognitive channels (Cools, 2001, 2006; Vaillancourt et al., 2013). Considering this, it is possible that the significantly poorer performance on cognitive tests of verbal learning, working memory, and semantic fluency see in individuals with a tremor-dominant presentation in Experiment 2, are the result of a disruption to these cognitive channels related to potential dopaminergic medication.

Speech as an Axial Feature

Classifying speech as an axial feature is both useful and well-reasoned. Namely, numerous studies have linked dysarthria to non-tremor primary motor symptoms (Cantiniaux et al., 2010; Dias et al., 2016; Moreau et al., 2007; Skodda et al., 2011), a finding that was also confirmed in both Experiments 1 and 2 of this study. A link between speech and cognitive changes emerged from Experiment 2, which demonstrated speech as a significant predictor of

later dementia, in addition to observed associations between dysarthria and the cognitive domains of working memory and semantic fluency. This intriguing relationship was also present in previous work examining both holistic and discrete changes to speech and their association with cognition (Paulo Bugalho & Viana-Baptista, 2013; Domellöf et al., 2011; Elfmarková et al., 2016; Rektorova et al., 2016; Tykalová et al., 2020).

In addition to observed relationships among symptom presentation, the notion of shared neural underpinnings between speech and a non-tremor profile is well-supported. Specifically, it has been demonstrated that speech changes are likely the result of impaired cholinergic channels (Alves et al., 2006; Chiu & Neel, 2020; Gago et al., 2009a; Rektorova et al., 2016). Depletion within these channels are the purported impetus for more pervasive cognitive deficits, such as those seen in the non-tremor subtype, and described in PD models. For example, according to the Neural Networks Framework (Gratwicke et al., 2015), a lack of adequate acetylcholine results in observed deficits to cognitive functions such as attention, visuospatial skills, and memory. This is the result of hindered acetylcholine-dependent structures, including the hippocampus, parahippocampus, and amygdala. The amygdala has also been suggested to play a role in the modulation of prosodic elements of speech, serving as additional support for speech as an axial feature, as described previously (Fecteau et al., 2007; Junqué et al., 2005; Rektorova et al., 2016).

The proposition of speech as an axial feature is also supported by the lack of amelioration of dysarthria from dopaminergic medication. While tremor symptoms consistently respond to dopamine, speech has shown little to no effects of levadopa (Cavallieri et al., 2021; Elfmarková et al., 2016; Ramig et al., 2007; Spencer et al., 2009). This lack of an effect on speech has been shown to be present even when motor performance has improved (Fabbri et al., 2017).

Consideration of speech as an axial feature also offers clinical and research benefits. Namely, this would elevate the viewpoint of speech as a germane indicator of the potential presence of a more pervasive PD, such as that seen in the non-tremor profile. This would help inform clinical and research practice by indicating more vulnerable populations earlier in the disease process, which may lead to the development or implementation of therapeutics to preserve cognitive and/or speech function.

Clinical Implications

When viewed through a clinical lens, results of this study provide useful insight into potential patterns of disease presentation. Consideration of early changes to speech as a potential predictive factor of progression to dementia highlights the importance of dysarthric characteristics as important and distinct features. Furthermore, this highlights the need for nuanced evaluation of individual speech constructs, beyond just intelligibility, which appears to be lacking as a metric of overall speech degradation.

While patterns between dysarthria and non-tremor characteristics have emerged, clinicians must continue to consider the role of natural variation. Measuring speech is particularly more challenging than task performance, which can be judged as correct or incorrect, due to the complex nature of speech and the array of parameters that are influenced by PD, such as speech rate, pausing characteristics, dysfluencies, and prosodic variation. Clinicians should consider this during assessment and intervention, as tracking subtle changes to speech parameters over time may prove fruitful to inform individualized recommendations. While the 5-point speech rating scale of the UPDRS appears sufficient to capture even slight changes to speech, other metrics such as the Robertson Dysarthria Profile (Robertson & Thomson, 1987), or

the VAS ratings demonstrated in Experiment 1, have been shown to correlate with non-tremor symptom severity (Defazio et al., 2016) and likely provide additional relevant clinical information.

In addition, an improved understanding of clinical symptoms that are more likely to present together, such as non-tremor symptoms and dysarthria can aid clinicians in managing PD symptoms as well as working to provide more individualized care when recommending supports or systems for proactive care.

Limitations

Limitations for Experiment 1 are largely related to the small sample size, which stemmed from time constraints and pandemic restrictions. The small sample size limited statistical analyses as well as generalization of results, as discussed previously. In Experiment 2, although early speech severity ratings were found to be significantly predictive of dementia cognitive status, little information about specific changes to speech is garnered from the 5-point rating scale.

Limitations of PD Models in Clinical Application

More general limitations are important to acknowledge, particularly surrounding current disease models. While useful in providing a framework to overlay neural underpinnings with clinical presentation, the models of PD discussed do not overtly account for changes to speech. This poses a substantial limitation when using these models to inform the results of this study.

Another limitation of current models of PD is the difficulty accounting for the multifaceted manner in which cognitive networks overlap and interact. This interdependence

clearly muddles dissociation of neural networks and reduces the ability to implicate distinct neurotransmitters relative to specific symptom presentation. Thus, dividing cognitive functions into distinct domains is perhaps as spurious as it is helpful. This is a confound for any attempt to model cognition, particularly from a clinical perspective. In addition, the discussed models do not quantify the amount of breakdown that is needed before cognitive symptoms arise.

The lack of accounting for individual differences, such as contextual factors described in biopsychosocial models, needs to be considered when using models to explain behavioral results. Environmental influences such as family or caregiver support, socio-economic status, and access to care likely influence outcomes as well as an individual's perceived outlook towards the experience of having a degenerative disease. Personal factors such as level of resilience also likely influence treatment outcomes, quality of life, and disease management. Further, the role of these contextual factors as a protective or preventative mechanism against cognitive decline in PD has not been examined. Considering how personal and environmental factors influence the prevalence, rate, and general nature of cognitive decline in a neurodegenerative disease has important and far reaching outcomes. Both clinical and research communities would benefit from an improved understanding of cognitive impairment through the lens of a biopsychosocial model.

Future Directions

Future work is needed to better understand the relationship between motor and non-motor characteristics in PD. Research should include a nuanced examination of clinical presentation rooted in models of impairment. This may help elucidate shared neural mechanisms underlying cognition and speech, as well as the role of neurotransmitter depletion in symptom emergence. In addition, future research should continue to examine speech in a holistic manner, recognizing changes to perceptual characteristics such as naturalness and articulatory precision as distinct constructs. Assessing speech and cognition in a focused manner and over the course of the disease could provide valuable insight into the nature of speech and cognitive changes across individuals. Such research, when considered through the lens of current models of PD, could inform both clinical and research practice and aid in treatment at all stages of PD.

Appendix

Speech Sample Extraction Criteria
(Based on Sidtis, Cameron, Bonura, & Sidtis, 2012)

The first 30 seconds of speech that meets extraction criteria will be used for speech sample.

Extraction criteria:

1. Sample does not include examiner's voice/prompts.
2. Sample is free of unexpected environmental noise.
3. No proper nouns.
4. No low frequency words (e.g, "The plans drew the ire of the townspeople.")
5. No formulaic expressions (e.g., "Be that as it may.")
6. No specialty vocabulary.
7. Sample will be rounded to the nearest sentence's end.

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