NORTHWESTERN UNIVERSITY

fMRI Correlates of Speech and Voice Impairment in Parkinson's Disease

A DISSERTATION

SUBMITTED TO THE GRADUATE SCHOOL
IN PARTIAL FULFILLMENT OF THE REQUIREMENTS

for the degree

DOCTOR OF PHILOSOPHY

Field of Neuroscience

By Jordan L. Manes

EVANSTON, ILLINOIS

September 2020

Abstract

Approximately 80-90% of individuals with Parkinson's disease (PD) develop motor speech impairments, predominantly in the form of voice dysfunction. It is known that the motor symptoms of PD arise from degeneration of the dopamine producing neurons in the substantia nigra and dysregulation of basal ganglia motor pathways. It is also known that motor cortical activity in PD patients is abnormal during movement. However, it is unclear how the changes in basal ganglia and motor cortical function relate to the speech and voice symptoms of PD. For this dissertation, I conducted three studies to further understand the contributions of the basal ganglia and motor cortices to speech and voice impairment in PD. In the first study (CHAPTER 2), I demonstrate that there are changes in functional cortico-basal ganglia connections that differentiate PD participants with speech impairment from PD participants without speech impairment. In the second study (CHAPTER 3), I demonstrate that performing speech tasks during continuous fMRI scanning elicits the Lombard effect comparably in both older healthy adults and individuals with PD and hypophonia. This study further demonstrates that this is independent of PD medication state (on medication vs. 12-hour withdrawal). In my third study (CHAPTER 4), I demonstrate that individuals with PD and hypophonia have hypoactivation in the dorsal premotor cortex when performing a sustained vowel task, and that activity in the dorsal premotor cortex is correlated with maximum phonation time. My third study also demonstrates spatial differences in the functional representation of the right laryngeal motor cortex between older healthy adults and individuals with PD and hypophonia. Together, the results of these three studies suggest that changes in multiple brain regions are associated with speech and voice impairment in PD. These include changes in the striatum, globus pallidus, laryngeal motor cortex, and dorsal premotor cortex. The work presented in this dissertation adds to our current understanding of the neurological changes involved in PD speech and voice impairment and presents several avenues for future research.

Acknowledgements

I would like to extend my sincerest gratitude towards my advisor, Dr. Daniel Corcos, and all of my committee members who have guided me throughout this process. Your mentorship has been invaluable, and you continue to inspire me with your talent and dedication to science. In addition, I would like to thank Dr. Donald Robin for encouraging me to pursue a career in neuroscience. Your mentorship and support led me on this incredible journey, and I could not be more grateful.

I would also like to extend a special thanks my colleagues Dr. Ajay Kurani and Ellen Herschel. Ajay, you have helped me further develop my neuroimaging skills in more ways than I can count. You have been a kind and patient mentor as I have worked towards developing my programming and technical skills. Ellen, you have helped me navigate the challenges of participant recruitment, data collection, and so much more. To both of you, thank you for your friendship over the past few years and for all of the help you have given to make this project a reality.

To all of my family and friends who have been with me throughout this journey, thank you so much for your continued love and support.

Finally, I would like to thank all of the participants who dedicated their time and energy to the pursuit of research in Parkinson's disease. Without you, this research would not be possible.

Funding sources:

The research presented in this dissertation was supported by the National Institutes of Health (NIH) Training Grant in the Neurobiology of Movement and Rehabilitation Sciences (T32 D057845-05) and by the National Institute on Deafness and Other Communication Disorders (NIDCD) National Research Service Award entitled, “fMRI Correlates of Speech and Voice Impairment in Parkinson’s Disease” (F31 DC015717).

The data presented in Chapter 1 were gathered from the Parkinson’s Progression Markers Initiative (PPMI). PPMI – a public-private partnership – is funded by the Michael J. Fox Foundation for Parkinson's Research and multiple funding partners, including Abbvie, Avid Radiopharmaceuticals, Biogen Idec, BioLegend, Bristol-Myers Squibb, Eli Lilly & Co., F. Hoffman-La Roche, Ltd., GE Healthcare, Genetech, GlaxoSmithKline, Golub Capital, Lundbeck, Merck, MesoScale, Pfizer, Piramal, Sanofi Genzyme, Servier, Takeda, Teva, and UCB. For up-to-date information on the study, visit www.ppmi-info.org.

Table of Contents

List of Figures

List of Tables

CHAPTER 1

Introduction

Speech difficulties (dysarthria) are pervasive among individuals with Parkinson's disease (PD), with estimates suggesting that 80-90% of those with PD will develop some form of speech impairment over the course of the disease (Sapir, 2014). Despite the prevalence of speech difficulties in PD, the neural mechanisms underlying dysarthria in PD are still unclear. Progress in understanding these mechanisms has been hindered, in part, by longstanding assumptions that speech and voice difficulties in PD arise from the same neural substrates as other non-speech motor symptoms. However, there is growing evidence to suggest that the mechanisms underlying speech and nonspeech motor symptoms are at least partially distinct. Over the past few decades, the availability of non-invasive brain imaging has provided researchers with new tools to address these assumptions and provide a more comprehensive understanding of the neural processes underlying speech impairment in PD. Still, the number of functional imaging studies investigating speech impairment in PD is limited and there remain methodological challenges to conducting speech experiments in the scanner.

This introduction includes (1) a brief overview of motor deficits in PD, (2) the characteristics of dysarthria in PD, (3) the presumed neurological similarities between speech and nonspeech motor deficits in PD, (4) potential neurological differences between speech and nonspeech motor deficits in PD, (5) the use of fMRI in understanding the neural substrates of dysarthria in PD, and (6) a brief summary of the studies conducted as part of this dissertation.

1.1 Motor deficits in PD

PD is a progressive neurological disorder that involves the degeneration of dopaminergic cells in the substantia nigra pars compacta (SNc). The clinical presentation of PD includes three cardinal motor features: bradykinesia (slowness of movement), tremor (involuntary rhythmic movements), and rigidity (increased muscle tone) (Jankovic, 2008; Postuma et al., 2015). Hypokinesia (reduced movement amplitude) and akinesia (difficulty initiating movement) are also frequently grouped under the term umbrella term of bradykinesia. However, disruptions to movement rate, amplitude, and initiation each represent their own distinct phenomenon (Hess & Hallett, 2017; Postuma et al., 2015; Schilder, Overmars, Marinus, van Hilten, & Koehler, 2017). In addition, many individuals with PD also present with secondary motor symptoms and non-motor disturbances (Jankovic, 2008).

1.2 Characteristics of dysarthria in PD

Speech and voice difficulties are among the secondary motor symptoms of PD. The earliest systematic description of deviant speech characteristics in parkinsonism was brought forth by Darley, Aronson, and Brown (1969a; 1969b), who used the term *hypokinetic dysarthria* to describe the constellation of speech abnormalities in PD. In their classic 1969 companion papers, Darely, Aronson and Brown (1969a; 1969b) used perceptual scaling methods to outline differential diagnostic patterns of dysarthria (1969a) as well as their corresponding clusters of deviant speech dimensions (1969b). The authors formulated a list of 38 dimensions, grouped into 7 broad categories (pitch, loudness, vocal quality, respiration, prosody, articulation, and “overall” or general impression), which could be used to describe the characteristics of dysarthria among specific neurological patient groups. For individuals with parkinsonism, the prominent dimensions of abnormal speech production included: monopitch, reduced

stress, monoloudness, imprecise consonants, inappropriate silences, short rushes of speech, harsh voice, breathy voice, low pitch, and variable rate. The majority of these dimensions were subsumed into an expanded cluster of prosodic insufficiency (monopitch, monoloudness, reduced stress, short phrases, variable rate, short rushes of speech, and imprecise consonants), while the breathy voice dimension fell into the cluster of phonatory incompetence.

1.3 Neurological similarities between speech and nonspeech motor deficits in PD

In addition to describing the deviant speech dimensions among the selected neurological populations, Darley, Aronson, and Brown (1969b) further drew upon the known motor and neurological deficits from each patient group in order to make generalized inferences about the underlying mechanisms. Among those with parkinsonism, the cluster of speech dimensions subsuming prosodic insufficiency was purported to be associated with reduced range of individual and repetitive movements as well as rigidity. To quote Darley, Aronson, and Brown (1969b, p. 470):

> *This cluster, PROSODIC INSUFFICIENCY, is considered to be due to REDUCED RANGE OF MOVEMENTS. The extension of this cluster consists of short rushes of speech, variable rate, and imprecise consonants. These appear to result from VERY FAST MOVEMENTS OF VERY REDUCED RANGE that are seen only in parkinsonism. Of the uncorrelated dimensions, inappropriate silences seems related to DIFFICULTY INITIATING MOVEMENTS. The occurrence of breathy voice, harsh voice, and low pitch would be presumed to be related to rigidity of laryngeal musculature. Because of the all-prevailing reduction of mobility, HYPOKINETIC DYSATHRIA is the appropriate designation for the speech of parkinsonism.*

Indeed, several of the speech characteristics observed in parkinsonism do appear to echo the

hypokinetic and rigid motor features of PD. With respect to scaling, individuals with PD exhibit reduced amplitude of lip and jaw movements during speech production (Connor, Abbs, Cole, & Gracco, 1989; Forrest, Weismer, & Turner, 1989; Hunker, Abbs, & Barlow, 1982; Walsh & Smith, 2012) as well as reduced vocal intensity, or hypophonia (Holmes, Oates, Phyland, & Hughes, 2000; Ramig, Sapir, Fox, & Countryman, 2001; Walsh & Smith, 2012). In addition, rigidity has been found to affect a number of muscles involved in speech production including those of the lips (Caligiuri, 1987; Hunker et al., 1982), jaw (Leopold & Kagel, 1996), vocal folds (Hanson, Gerratt, & Ward, 1984; Jiang, Lin, Wang, & Hanson, 1999; Jiang, O'Mara, et al., 1999), and rib cage (Hovestadt, Bogaard, Meerwaldt, van der Meche, & Stigt, 1989; Sabate, Rodriguez, Mendez, Enriquez, & Gonzalez, 1996; Solomon & Hixon, 1993).

The hypokinetic features of PD (including bradykinesia, hypokinesia, and akinesia) are linked to the overactivity of the GPi and excessive inhibition of thalamocortical outputs to the midline motor cortices. Under normal circumstances, dopaminergic input from the SNc serves to facilitate the execution of voluntary movements though the up regulation of the "direct" basal ganglia pathway and down regulation of the "indirect" basal ganglia pathway. However, when there is insufficient dopaminergic input to the striatum (as is the case in PD), the balance is shifted in favor of the indirect pathway and This leads to excessive inhibition of thalamocortical projections by the internal globus pallidus (GPi), and subsequently reduced activity in the motor cortices (Obeso et al., 2008). The neural mechanisms underlying rigidity are less well characterized, but it has been posited that rigidity arises from an overexcitation of the primary motor cortex (Cantello et al., 1991; Cantello, Gianelli, Civardi, & Mutani, 1995; Lefaucheur, 2005; Yu, Sternad, Corcos, & Vaillancourt, 2007), while hypokinesia arises from hypoactivation of the supplementary motor area (SMA) during volitional movement (Ellaway, Davey, Maskill, & Dick, 1995; Lefaucheur, 2005; Obeso et al., 2008). Critically, the cortical and subcortical brain regions involved in the cortico-basal ganglia motor circuitry are known to be important for speech motor control (Manes et al., 2014; Tourville & Guenther, 2011), and disruptions to motor cortical output may account for the hypokinetic and rigid features of dysarthria.

1.4 Potential neurological differences between speech and nonspeech motor deficits in PD

Still, there is evidence to suggest that the neural mechanisms underlying dysarthria in PD are at least partially distinct from other motor symptoms. The most compelling evidence for this is that speech difficulties are not typically improved by neurologically driven therapeutics for Parkinson's disease. Despite providing significant relief from limb motor symptoms, the effects of dopaminergic therapy on speech production are neither robust nor consistent (Fabbri et al., 2017; Ho, Bradshaw, & Iansek, 2008; Jiang, Lin, et al., 1999; Kompoliti, Wang, Goetz, Leurgans, & Raman, 2000; Skodda, Visser, & Schlegel, 2010). Similarly, deep brain stimulation of the subthalamic nucleus has variable effects on speech, leading to improvements in some subjects while worsening speech production in others (Aldridge, Theodoros, Angwin, & Vogel, 2016; Pinto, Ozsancak, et al., 2004). The discrepancy between the therapeutic effects on general motor function and the effects on speech and voice production suggests that there are changes in the neural processes underlying speech symptoms which differ from nonspeech motor symptoms of PD.

1.5 The use of fMRI in understanding the neural substrates of dysarthria in PD

Functional neuroimaging approaches can help to shed light on these changes. Researchers have used both positron emission tomography (PET) (Liotti et al., 2003; Narayana et al., 2010; Narayana et al., 2020; Pinto, Thobois, et al., 2004) and fMRI (Arnold, Gehrig, Gispert, Seifried, & Kell, 2014; Baumann et al., 2018; Elfmarkova et al., 2016; Maillet et al., 2012; Narayana et al., 2020; New et al., 2015; Pinto et al., 2011; Rektorova, Barrett, Mikl, Rektor, & Paus, 2007; Rektorova et al., 2012) to gain insight into the

mechanisms underlying dysarthria in PD. Studies investigating overt speech production in PD have reported changes in the activity of motor and premotor cortices, however, the direction of these changes appears to be mixed. Both instances of hypoactivation (Narayana et al., 2020; Pinto, Thobois, et al., 2004) and hyperactivation (Rektorova et al., 2007) have been reported in the primary motor cortex. In premotor regions of the cortex, two studies have reported hyperactivity in left PMd during overt speech production in PD (Arnold et al., 2014; Pinto et al., 2011), while another reported hypoactivity in left PMd (Narayana et al., 2020). Meanwhile, a study examining the neural correlates of the Lee Silverman Voice Treatment® (Ramig et al., 2001) in PD found that increased activity in right M1 and right PMd were linked to improved voice intensity following speech therapy (Narayana et al., 2010). Less is known about the function of the basal ganglia during active voice production in PD, however studies using resting-state fMRI have shown that individuals with PD have altered functional connectivity of the left and right putamen (New et al., 2015) and right caudate (Elfmarkova et al., 2016), all of which are known to play a role in speech production (Arnold et al., 2014; Brown, Ingham, Ingham, Laird, & Fox, 2005; Pichon & Kell, 2013; Robinson et al., 2012; Tourville & Guenther, 2011). Still the functional connections of other basal ganglia nuclei, such as the globus pallidus, have not been explored in relation to speech impairment in PD.

While functional imaging techniques show promise for understanding the neural substrates of speech impairment in PD, there are also methodological considerations to take into account. There is a strong ecological difference between performing speech tasks during fMRI and producing typical speech outside of the scanner. Two major changes include the change in body position from upright to supine and the addition of loud background acoustic noise during scanning. Speaking in the presence of background noise is known to cause a systematic increase in voice intensity – and effect which is known to be comparable between PD and OHC (Scott G Adams et al., 2006; Scott G Adams, Haralabous, Dykstra, Abrams, & Jog, 2005; Dykstra, Adams, & Jog, 2012a). However, speaking in the supine position might be exceptionally effortful in PD due to reparatory difficulties and the increased demand of supine speech

breathing (Hoit, 1995; Huber & Darling-White, 2017; Huber, Stathopoulos, Ramig, & Lancaster, 2003; Solomon & Hixon, 1993). There is thus a need to examine whether the impacts of the scanning environment differ between PD and OHC and to develop behavioral correlates that are more analogous to speech behavior during fMRI.

1.6 Summary of studies conducted as part of this dissertation

The purpose of this dissertation is to further understand the neural processes underlying speech and voice difficulties in PD. The work presented in this dissertation is a collection of three papers, each of which addresses a distinct need in the literature.

1.6.1 CHAPTER 2 Summary

First, in order to fully understand the neurological mechanisms underlying speech changes in Parkinson's disease, it is imperative that research establish not only the degree to which these mechanisms overlap with generalized motor symptoms, but also the degree to which they deviate. To that end, CHAPTER 2 of this dissertation provides an initial look at differences in basal ganglia connectivity between PD patients with speech impairment (PDSI), PD patients with no speech impairment (PDN), and older healthy controls (OHC) using resting-state fMRI data. Building upon prior research, which has found connectivity differences between PD and OHC in functionally relevant speech regions, this study provides the first evidence that basal ganglia connectivity to functional speech regions also differs between PDN and PDSI. In addition, this study is the first to show changes in the functional connectivity of the globus pallidus related to speech impairment in PD. This paper was published in *Brain and Behavior* and is presented in CHAPTER 2 with the published text and figures. Figure captions that did

not include figure titles have been edited to include figure titles.

The citation for the original publication is as follows:

> **Manes, J.L.**, Tjaden, K., Parrish, T., Simuni, T., Roberts, A., Greenlee, J., Corcos, D. M., & Kurani, A. S. (2018). Altered resting-state functional connectivity of the putamen and internal globus pallidus is related to speech impairment in Parkinson's disease. *Brain and Behavior*, *8*(9), e01073.

The author contributions are as follows:

Jordan L. Manes: Conceptualization, Methodology, Software, Formal Analysis, Data Curation, Writing – Original Draft, Visualization, Project administration, **Kris Tjaden:** Supervision, Writing – Reviewing and Editing, **Todd Parrish:** Resources, Methodology, Writing – Reviewing and Editing, **Tanya Simuni:** Resources, Writing - Reviewing and Editing, **Angela Roberts:** Writing – Reviewing and Editing, **Jeremy Greenlee:** Writing – Reviewing and Editing, **Daniel M. Corcos:** Supervision, Writing – Reviewing and Editing, **Ajay S. Kurani:** Supervision, Software, Methodology, Writing – Reviewing and Editing

1.6.2 CHAPTER 3 Summary

Second, in order to accurately interpret fMRI studies of speech production in clinical populations, it is important to consider the degree to which that behavior generalizes to behavior outside of the scanner. Even more critically, it is important to know whether the environmental changes in fMRI, such as body position and background noise, differentially impact speech production in the populations of interest. Given the known difficulties associated with speech breathing in PD and the increased respiratory demands of supine speech breathing, performing speech tasks during fMRI might be disproportionately effortful in this population. As this body of work is motivated by the desire to use fMRI in the study of PD speech, CHAPTER 3 of this dissertation focuses on understanding the influence

of the fMRI scanning environment on voice intensity in individuals with PD hypophonia and OHC. Using a mock MRI scanner, this study is the first to explicitly test the impact of supine posture and background noise on voice intensity during a simulated fMRI task. In addition, this is the first study to address whether body position and background noise affect voice intensity differently between PD and OHC populations. This study is currently under review for publication.

The author contributions are as follows: **Jordan L. Manes:** Conceptualization, Software, Methodology, Formal analysis, Investigation, Data Curation, Project Administration, Funding Acquisition, Writing – Original Draft, **Ellen Herschel:** Data Curation, Project Administration, Writing – Reviewing and Editing, **Kris Tjaden:** Supervision, Writing – Reviewing & Editing, **Todd Parrish:** Resources, **Tanya Simuni:** Resources, **Daniel M. Corcos:** Supervision, Resources, Funding Acquisition, Writing – Reviewing & Editing, **Angela Roberts:** Supervision, Resources, Writing – Reviewing & Editing

1.6.3 CHAPTER 4 Summary

Third, is it unclear whether the reduced vocal intensity in PD is related to hypoactivity in the motor cortices, as would be suggested by our current understanding of hypokinesia in PD. CHAPTER 4 of this dissertation focuses specifically on the neural mechanisms of hypophonia. Using the same group of participants from CHAPTER 3, this study compares brain activity between individuals with PD hypophonia and OHC during sustained vowel production and correlates fMRI findings with 1) voice intensity data from the fMRI simulation in CHAPTER 3, and 2) maximum phonation time. This study also describes differences in the spatial representation of the laryngeal phonatory area (or laryngeal motor cortex) between PD and OHC groups. This work is not yet published.

The author contributions are as follows:

Jordan L. Manes: Conceptualization, Software, Methodology, Formal analysis, Investigation, Data Curation, Project Administration, Funding, Writing – Original Draft, **Ajay S. Kurani:** Software, Methodology, **Ellen Herschel:** Data Curation, Project Administration, **Angela Roberts:** Supervision, Methodology, Resources, **Todd Parrish:** Methodology, Validation, Resources, **Kris Tjaden:** Supervision, Methodology, **Tanya Simuni:** Resources, **Daniel M. Corcos:** Supervision, Resources, Funding, Writing – Reviewing & Editing

CHAPTER 2

Altered resting-state functional connectivity of the putamen and internal globus pallidus is related to speech impairment in Parkinson's disease

Jordan L. Manes[1], Kris Tjaden[2], Todd Parrish[3], Tanya Simuni[4,5], Angela Roberts[6], Jeremy D. Greenlee[7], Daniel M. Corcos[1], Ajay S. Kurani[3]

[1] Department of Physical Therapy and Human Movement Sciences, Northwestern University, Chicago, IL

[2] Department of Communication Disorders and Sciences, University at Buffalo, Buffalo, NY

[3] Department of Radiology, Northwestern University, Chicago, IL

[4] Ken and Ruth Davee Department of Neurology, Northwestern University, Chicago, IL

[5] The Parkinson's Disease and Movement Disorders Clinic, Northwestern University, Chicago, IL

[6] Roxelyn and Richard Pepper Department of Communication Sciences and Disorders, Northwestern University, Evanston, IL

[7] Department of Neurosurgery, University of Iowa, Iowa City, IA

2.1 ABSTRACT

Speech impairment in Parkinson's disease (PD) is pervasive, with life- impacting consequences. Yet, little is known about how functional connections between the basal ganglia and cortex relate to PD speech impairment (PDSI). Whole-brain resting-state connectivity analyses of basal ganglia nuclei can expand the understanding of PDSI pathophysiology. Resting-state data from 89 right-handed subjects were downloaded from the Parkinson's Progression Markers Initiative database. Subjects included 12 older healthy controls ("OHC"), 42 PD patients without speech impairment ("PDN"), and 35 PD subjects with speech impairment ("PDSI"). Subjects were assigned to PDN and PDSI groups based on the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III speech item scores ("0" vs. "1–4"). Whole-brain functional connectivity was calculated for four basal ganglia seeds in each hemi- sphere: putamen, caudate, external globus pallidus (GPe), and internal globus pallidus (GPi). For each seed region, group-averaged connectivity maps were compared among OHC, PDN, and PDSI groups using a multivariate ANCOVA controlling for the effects of age and sex. Subsequent planned pairwise *t*-tests were performed to determine differences between the three groups using a voxel-wise threshold of $p < 0.001$ and cluster-extent threshold of 272 mm^3 (FWE<0.05). In comparison with OHCs, both PDN and PDSI groups demonstrated significant differences in cortical connectivity with bilateral putamen, bilateral GPe, and right caudate. Compared to the PDN group, the PDSI subjects demonstrated significant differences in cortical connectivity with left putamen and left GPi. PDSI subjects had lower connectivity between the left putamen and left superior temporal gyrus compared to PDN. In addition, PDSI subjects had greater connectivity between left GPi and three cortical regions: left dorsal premotor/laryngeal motor cortex, left angular gyrus, and right angular gyrus.

2.2 INTRODUCTION

Parkinson's disease (PD) is a progressive neurodegenerative disease involving degeneration of nigrostriatal dopaminergic pathways in the basal ganglia. While the impact of the disease on daily living typically manifests as impaired mobility, speech impairment is very common and can impair an individual's ability to communicate in daily life. It is estimated that 80-90% of individuals with PD develop dysarthria over the course of the disease (Sapir, 2014), with deviant perceptual characteristics including monopitch, monoloudness, reduced stress, variable rate, short rushes of speech, and imprecise consonants (Duffy, 2013). As a result, the perceived intelligibility and naturalness of speech in individuals with PD can be negatively affected (Frederic L Darley et al., 1969), leading to social withdrawal and impaired work-related performance (Miller, Noble, Jones, & Burn, 2006).

In order to understand the neurobiology of speech impairments in PD, it is important to determine whether there are specific functional connections between the basal ganglia and cortex that uniquely contribute to speech symptoms. Cortico-basal ganglia loops are critical for normal speech production. However, the specific contributions of basal ganglia circuits to speech production are not fully understood. Studies utilizing functional neuroimaging tools such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) provide insight into the role of the basal ganglia in both normal and disordered speech. Of the subcortical nuclei comprising the basal ganglia pathways, the putamen is most commonly associated with speech and voice production in neuroimaging studies (Bohland & Guenther, 2006; Brown et al., 2009; Manes et al., 2014; Tourville & Guenther, 2011). Researchers have reported increased bilateral putamen activation during both speech and non-speech vocal tract movements using fMRI (Brown et al., 2009; Chang, Kenney, Loucks, Poletto, & Ludlow, 2009; Parkinson et al., 2012). A recent PET study using D2/D3 receptor radioligands also demonstrated that speech production is accompanied by a left lateralized increase in endogenous dopamine release

within the striatum (Simonyan, Herscovitch, & Horwitz, 2013), suggesting that left hemisphere striatal regions may in fact play a more important role than those in the right hemisphere. In addition to the striatum, the role of the pallidum has also been described in relation to normal speech production. A meta-analysis of internal globus pallidus (GPi) and subthalamic nucleus co-activation maps revealed that the connectivity profiles of these two structures showed significant spatial overlap with brain regions involved in speech production, including the left putamen, left insula, and left ventrolateral nucleus of the thalamus (Manes et al., 2014). Both the globus pallidus and putamen have been incorporated in the Directions Into Velocity of Articulators (DIVA) computational model of speech production (Tourville & Guenther, 2011). Within this model, the globus pallidus and the putamen are involved in the initiation of speech movements through reciprocal functional connections with the supplementary motor area (SMA). Given the integral role of the basal ganglia in normal speech production, it is not surprising that basal ganglia disorders, such as PD and Huntington's disease, result in marked impairments in speech function. However, questions remain as to which functional connections between basal ganglia and cortex contribute to speech impairments in the presence of basal ganglia pathology and whether or not these are distinguishable from pathways contributing to non-speech motor symptoms.

There are several cortical regions supporting normal speech production that could be affected by functional changes in the basal ganglia. It is well established that speech production involves the sensorimotor cortex, SMA, inferior frontal gyrus/ventral premotor cortex (PMv), superior temporal gyrus (STG)/Heschl's gyrus, and cerebellum (Brown et al., 2005; Brown et al., 2009; Manes et al., 2014; Tourville & Guenther, 2011). These regions of the cortex are reliably active during speech and voice production tasks (Brown et al., 2005; Manes et al., 2014; Spaniol et al., 2009). Studies of whole brain resting-state connectivity in PD have documented that the basal ganglia have abnormal connectivity to the cerebellum (Hacker, Perlmutter, Criswell, Ances, & Snyder, 2012) and motor cortices, including sensorimotor cortex (Baudrexel et al., 2011; Hacker et al., 2012; Kurani et al., 2015; Kwak et al., 2010), premotor cortex (Baudrexel et al., 2011), and SMA (Baudrexel et al., 2011; Hacker et al., 2012; Kwak et

al., 2010). Given the critical role of these structures in speech production, it seems likely that changes in these connections contribute to speech problems in PD. However, it is also possible that speech impairments in PD involve abnormal basal ganglia connectivity to cortical brain regions that are not directly related to motor output, such as STG. Indeed, a study by Simonyan and colleagues (2013) found that the BOLD signal from the left anterior putamen was highly correlated with that of left STG when healthy individuals performed a sentence production task. In the presence of basal ganglia pathology, it is possible that, in addition to cortical regions involved in motor control, changes in the functional connectivity of the basal ganglia structures to STG may also be involved with speech impairment in PD.

Functional connectivity analysis of resting-state fMRI data provides a means for estimating the strength of functional basal ganglia connections to cortical and subcortical structures. By analyzing fMRI data in a task-free context, researchers can make inferences about the intrinsic organization of functional brain networks that might otherwise be masked by the effects of task performance (Biswal, Yetkin, Haughton, & Hyde, 1995; Di Martino et al., 2008; Smith et al., 2009). While several studies have identified abnormal resting-state basal ganglia connections in PD (Baudrexel et al., 2011; Hacker et al., 2012; Helmich et al., 2010; Kurani et al., 2015; Wu et al., 2009), little work has been done to assess the relationship of these connections with speech symptoms. Two studies have used seed-based resting-state analysis to study the mechanisms of speech impairment in PD by comparing the connectivity of functionally relevant brain regions between PD and controls. New and colleagues (2015) found that PD subjects had reduced connectivity between right and left putamen after performing a seed to seed resting-state connectivity analysis on thirteen regions involved in vocal motor control (Brown et al., 2005). The study further found that UPDRS Part III speech impairment scores were inversely correlated with right putamen connectivity to right cerebellum and left STG. A more recent study measured the whole brain resting-state connectivity of three right hemisphere structures involved in emotional prosody (orofacial sensorimotor cortex, anterior cingulate cortex, and the caudate) and found that PD patients had reduced connectivity between the right caudate and right dorsolateral prefrontal cortex compared to healthy

controls (Elfmarkova et al., 2016). Together these two studies provide evidence for a link between striatal functional connectivity and impaired voice and prosodic function in PD. However, it is important to note that neither study limited its PD group to only those patients who presented with speech impairments. Further, it remains unclear whether speech impairment in PD may involve connectivity changes in other basal ganglia or cortical structures.

The current study was designed to extend previously published literature in two ways. First, as prior resting-state studies of PD speech have only included striatal regions of the basal ganglia, we sought to investigate whether functional connections with the globus pallidus might also be linked to speech impairment in PD. Second, we chose to compare whole-brain basal ganglia connectivity between three groups: older healthy control subjects ("OHC"), PD subjects with no speech impairment ("PDN"), and PD subjects with speech impairment ("PDSI"). By separating our PD subjects into PDN and PDSI groups, we sought to identify changes in functional basal ganglia connections that were specific to PD speech impairments and independent of more global, disease-related motor impairments. If abnormal basal ganglia connectivity to motor cortices (sensorimotor cortex, SMA, premotor cortex) is in fact related to broader disease-related changes in motor function, we would expect to see these connections emerge from the comparison of OHC and PDSI, but not in the comparison of PDN and PDSI. By contrast, we would expect to see group differences in basal ganglia connectivity with STG when comparing PDN to PDSI, as such a connection would presumably be independent of global motor severity. We thus predicted that striatal connectivity to motor cortices and STG would differ between PDSI and OHC groups, but that we would observe differences only in striatal - STG connectivity when comparing PDN to PDSI. Given that striatal dopamine release appears to be left-lateralized during speech production (Simonyan et al., 2013), we further predicted that striatal connectivity differences between PDN and PDSI groups would occur in the left striatum. Although several speech models include the globus pallidus, none are predictive of whether there are resting-state connectivity changes related to

speech impairment in PD. As such, we made no specific predictions about connectivity between the globus pallidus and cortex.

2.3 MATERIALS AND METHODS

2.3.1 Data Source

This study leverages a large sample of resting-state fMRI data from the Parkinson's Progression Markers Initiative (PPMI; www.ppmi-info.org) in order to examine whether connections between the cortex and basal ganglia relate to speech impairment in PD. PPMI is an ongoing multi-center project aimed at identifying biomarkers of PD through the longitudinal tracking of standardized clinical, imaging, and biometric assessments across 21 sites (16 US and 5 European sites) (Parkinson Progression Marker Initiative, 2011). PPMI follows the progression of 423 PD subjects who were newly diagnosed (< 6 months) and not on antiparkinsonian medication at enrollment, as well as 196 age and sex matched OHC subjects. While structural MRI data were collected for all PPMI subjects, the collection of resting-state fMRI data was implemented at a later date across 6 of the twenty-one sites resulting in fewer subjects with available resting-state scans. For the purposes of this study, we searched the PPMI database for all subjects in the PD or OHC Cohorts who had received a resting-state fMRI scan. At the time of analysis, we identified 90 PD and 21 OHC subjects who had participated in resting-state fMRI scanning in addition to PPMI's standard data collection protocols. OHC subjects had completed their resting-state scans at either their Baseline, Year 1, or Year 4 visit. PD subjects had completed their resting-state scans at either their Baseline, Year 1, Year 2, or their visit prior to initiation of antiparkinsonian medication. From this sample of de-identified subjects, we accessed resting-state fMRI and structural MRI scans as well as clinical assessments describing PD features and severity, handedness, medication, cognitive function, and depression.

2.3.2 Inclusion/Exclusion Criteria

We restricted the final sample to include only right-handed subjects whose fMRI scans passed our quality assurance review. We selected only right-handed subjects to control for possible differences in the lateralization of speech and language representation in the cortex. For quality assurance, each resting-state scan was required to have at least 90% of time points (188/208 volumes) with < 0.5 mm frame wise displacement and with no outliers exceeding > 5% root mean squared change in BOLD signal. Of the initial 111 subjects identified from the PPMI database, 13 were excluded because they were not right-hand dominant and 9 were excluded because their scans did not meet our quality assurance criteria.

2.3.3 PD Group Assignment

Speech impairment scores on the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part III were used to assign PD subjects to either the PDN or PDSI group. While the scale provides only a coarse, global impression of speech severity, the availability of speech impairment scores through PPMI allows us to compare the resting-state connectivity of PDN and PDSI groups using large sample sizes that are less feasible to collect in a prospective study. Under this item, speech impairment was rated on a scale of '0-4' (0 = "No speech problems", 4 = "Most speech is difficult to understand or unintelligible"). PD subjects with a rating of '0' were assigned to the 'PDN' group (n=42) and PD subjects with a rating of '1-4' were assigned to the 'PDSI' group (n=35). Within the PDSI group, the median speech impairment score was '1' (33 subjects had a speech impairment rating of '1' and 2 subjects had a speech impairment rating of '2', mean = 1.06).

2.3.4 Characteristics of participants

Resting-state data were analyzed for 12 OHC, 42 PDN, and 35 PDSI subjects. Groups were similar across baseline characteristics. **Table I** demonstrates no differences in age, years of education, Geriatric Depression Scale (GDS), and Montreal Cognitive Assessment (MoCA) characteristics between the three groups; however, a less male gender preponderance was found for both PD groups compared to OHC. The identifiers for all analyzed subjects are presented in **Table II**.

Table I. PPMI subject characteristics for OHC, PDN and PDSI groups.

Variable	OHC (N=12)	PDN (N = 42)	PDSI (N = 35)	p-value (PDN vs. PDSI)	p-value (OHC vs. PDN)	p-value (OHC vs. PDSI)
Age				0.09	0.09	0.70
Mean	65.33	60.12	64.14			
(Min, Max)	(48,83)	(39, 79)	(38, 77)			
Sex				0.65	**0.02^**	**0.04^**
Male	12 (100.0%)	28 (66.7%)	25 (71.4%)			
Female	0 (0.0%)	14 (33.3%)	10 (28.6%)			
Education				0.68	0.10	0.07
< 13 Years	0 (0.0%)	8 (19.0%)	8 (22.9%)			
13-23 Years	12 (100.0%)	34 (81.0%)	27 (77.1%)			
> 23 Years	0 (0.0%)	0 (0.0%)	0 (0.0%)			
MoCA†				0.58	0.41	0.19
Mean	27.83	27.38	26.85			
(Min, Max)	(26,30)	(18,30)	(21,30)			
GDS				0.79	0.63	0.71
Mean	1.67	2.26	2.12			
(Min, Max)	(0,14)	(0,10)	(0,9)			

^p<0.05, Chi-squared test for independence
†Adjusted for years of education
Abbreviations: MoCA, Montreal Cognitive Assessment; GDS, Geriatric Depression Scale

Table II. PPMI subject identifiers, group assignment, and resting-state fMRI visit.

Sub ID	Group	Visit (Year)	Sub ID	Group	Visit (Year)	Sub ID	Group	Visit (Year)
3390	OHC	BL (Baseline)	3378	PDN	V04 (Year 1)	3119	PDSI	V04 (Year 1)
4032	OHC	BL (Baseline)	3380	PDN	V04 (Year 1)	3123	PDSI	ST (Year 1)
3310	OHC	V04 (Year 1)	3758	PDN	V04 (Year 1)	3327	PDSI	V04 (Year 1)
3318	OHC	V04 (Year 1)	3819	PDN	V04 (Year 1)	3374	PDSI	V04 (Year 1)
3769	OHC	V04 (Year 1)	3825	PDN	V04 (Year 1)	3575	PDSI	V04 (Year 1
3779	OHC	V04 (Year 1)	3826	PDN	V04 (Year 1)	3760	PDSI	V04 (Year 1)
4018	OHC	V04 (Year 1)	3828	PDN	V04 (Year 1)	3771	PDSI	V04 (Year 1)
3350	OHC	U01 (Year 4)	3829	PDN	V04 (Year 1)	3787	PDSI	V04 (Year 1)
3351	OHC	U01 (Year 4)	3832	PDN	V04 (Year 1)	3822	PDSI	V04 (Year 1)
3563	OHC	V10 (Year 4)	3838	PDN	V04 (Year 1)	3823	PDSI	V04 (Year 1)
3369	OHC	U01 (Year 4)	3863	PDN	V04 (Year 1)	3830	PDSI	V04 (Year 1)
3565	OHC	V10 (Year 4)	4019	PDN	V04 (Year 1)	3831	PDSI	V04 (Year 1)
3130	PDN	BL (Baseline)	4022	PDN	V04 (Year 1)	3834	PDSI	V04 (Year 1)
3134	PDN	BL (Baseline)	3108	PDN	V06 (Year 2)	3835	PDSI	V04 (Year 1)
3383	PDN	BL (Baseline)	3354	PDN	V06 (Year 2)	4013	PDSI	V04 (Year 1)
3385	PDN	BL (Baseline)	3359	PDN	V06 (Year 2)	3107	PDSI	V06 (Year 2)
3392	PDN	BL (Baseline)	3360	PDN	V06 (Year 2)	3113	PDSI	V06 (Year 2)
3593	PDN	BL (Baseline)	3364	PDN	V06 (Year 2)	3131	PDSI	V06 (Year 2)
4030	PDN	BL (Baseline)	3365	PDN	V06 (Year 2)	3352	PDSI	V06 (Year 2)
4035	PDN	BL (Baseline)	3366	PDN	V06 (Year 2)	3552	PDSI	V06 (Year 2)
4038	PDN	BL (Baseline)	3367	PDN	V06 (Year 2)	3556	PDSI	V06 (Year 2)
3118	PDN	V04 (Year 1)	3585	PDN	V06 (Year 2)	3574	PDSI	V06 (Year 2)
3120	PDN	V04 (Year 1)	3802	PDN	V06 (Year 2)	3586	PDSI	V06 (Year 2
3122	PDN	V04 (Year 1)	4021	PDN	V06 (Year 2)	3587	PDSI	V06 (Year 2)
3126	PDN	ST (Year 1)	3332	PDSI	BL (Baseline)	3800	PDSI	V06 (Year 2)
3128	PDN	ST (Year 1)	3386	PDSI	BL (Baseline)	3808	PDSI	V06 (Year 2)
3132	PDN	V04 (Year 1)	3387	PDSI	BL (Baseline)	3814	PDSI	V06 (Year 2)
3371	PDN	V04 (Year 1)	3589	PDSI	BL (Baseline)	3818	PDSI	V06 (Year 2)
3373	PDN	V04 (Year 1)	3869	PDSI	BL (Baseline)	4005	PDSI	V06 (Year 2)
3375	PDN	V04 (Year 1)	4034	PDSI	BL (Baseline)			

2.3.5 PD characteristics

All PD subjects had a diagnosis of idiopathic PD and had clear evidence of a lateralized dopaminergic deficit on DaTSCAN™. Subjects with a diagnosis of atypical Parkinsonism or those who showed no evidence of dopaminergic deficit were not included in the data analysis. The PDN and PDSI groups had similar baseline PD characteristics, including family history, Hoehn & Yahr scale, PD subtype, and MDS-UPDRS scores, and levodopa equivalent daily dose (LEDD; Tomlinson et al., 2010); however, those in the PDSI group were more likely to present with right-lateralized motor symptoms. Disease characteristics of the PDN and PDSI groups are provided in **Table III**. While all PD Cohort subjects were de novo when they enrolled in the PPMI study, some subjects were on dopaminergic therapy at the time of their resting-state fMRI scans. This resulted in a mixed group of subjects relative to PD medication use. Unlike limb motor symptoms, the effect of dopamine treatment on voice or speech is neither robust or consistent (Schulz & Grant, 2000, Pinto et al., 2004). We thus chose to include both medicated and non-medicated PD subjects. We performed additional analyses to look for potential relationships between LEDD and basal ganglia connectivity should they exist. PD subjects who had begun taking antiparkisonian medication were scanned while on medication, per PPMI protocol. For those subjects, we used on-medication MDS-UPDRS Part III scores to determine group assignment and motor severity.

Table III. Parkinson's disease characteristics for PDN and PDSI groups.

Variable	PDN (N = 42)	PDSI (N = 35)	p-value (PDN vs. PDSI)
Family History of PD			0.31
Family Members w/PD	14 (33.3%)	11 (22.9%)	
No Family Members w/PD	28 (66.7%)	27 (77.1%)	
MDS-UPDRS			
MDS-UPDRS Total Score	30.24	35.55	0.11
MDS-UPDRS Part I	6.4	6.77	0.75
MDS-UPDRS Part II	6.62	7.37	0.47
MDS-UPDRS Part III (Motor Exam)	17.21	21.17	0.06
Hoehn & Yahr			0.54
Stage 0	0 (0.0%)	0 (0.0%)	
Stage 1	13 (31.0%)	11 (31.4%)	
Stage 2	29 (69.0%)	23(65.7%)	
Stage 3-5	0 (0.0%)	1 (2.9%)	
TD/PIGD Classification			0.14
TD	31 (73.8%)	19 (54.3%)	
PIGD	5 (11.9%)	10 (28.6%)	
Indeterminate	6 (14.3%)	6 (17.1%)	
Side Most Affected			**0.00^**
Left	20 (47.6%)	9 (25.7%)	
Right	20 (47.6%)	26 (74.3%)	
Symmetric	2 (4.8%)	0 (0.0%)	
PD Medication Usage			0.54
PD Medication	26 (61.9%)	24 (68.6%)	
No PD Medication	16 (38.1%)	11 (31.4%)	
		0	
Levodopa Equivalent Daily Dose			0.81
Mean	219.56	231.65	
(Min, Max)	(0, 600)	(0,760)	

^ p<0.05, Chi-squared test for independence
Abbreviations: TD, tremor dominant, PIGD, postural instability and gait difficulty

2.3.6 Image Acquisition

Structural and functional brain images in the PPMI dataset were acquired using 3T Siemens TIM Trio MRI scanners across 6 sites with standardized imaging protocols. T1-weighted 3D anatomical scans were

acquired in the sagittal plane using a MPRAGE GRAPPA protocol (TR = 2300 ms, TE = 2.98 ms, flip angle = 9°, slice thickness = 1 mm, FOV = 256 mm x 256 mm, voxel size = 1 mm isotropic). BOLD T2*-weighted echo-planar images were acquired in 40 ascending slices (TR = 2400 ms, TE = 25 ms, flip angle = 80°, slice thickness = 3.3 mm, no gap between slices, FOV = 222 mm x 222 mm, voxel size = 3.29 mm x 3.29 mm x 3.3 mm). Each resting-state scan collected 212 volumes (8 minutes, 29 seconds). During all resting-state scans, subjects were asked to relax, keep their eyes open, and to keep their mind free of thought (Van Dijk et al., 2010).

2.3.7 Preprocessing

All data were pre-processed with a custom pipeline using AFNI and SPM 12 tools. The first four resting-state volumes were discarded to allow the MRI signal to reach equilibrium, leaving a total of 208 time points. Next, resting-state functional MRI scans were despiked, corrected for slice timing, and realigned to the reference volume (first time point) in AFNI. Time points with excessive motion (> 0.5 mm) and outliers (> 5% root mean squared change in the BOLD signal) were then identified for censoring at a later stage. T1-weighted structural MRI scans were co-registered to resting-state functional scans in AFNI before being segmented into white matter, gray matter, and cerebral spinal fluid (CSF) tissue classes in SPM12. As the default tissue probability priors in SPM12 often misclassify basal ganglia nuclei as white matter (particularly the globus pallidus), we took additional steps to subtract these nuclei from the white matter mask. Using the @Anaticor tool in AFNI, we then regressed out nuisance white matter and CSF signals as well as motion and motion derivatives. Resting-state scans underwent additional linear detrending and band-pass filtering (0.01 - 0.1 Hz). The data were then censored to remove time points that had > 0.5mm frame wise displacement or > 5% root mean squared change in the BOLD signal. The

functional data were then smoothed to reach a full-width-half maximum of 6 mm using 3dBlurtoFWHM in AFNI.

2.3.8 Basal ganglia seed definitions

We analyzed the functional connectivity of four basal ganglia seeds in each hemisphere. These were bilateral caudate, putamen, GPe, and GPi. The Basal Ganglia Human Area Template (BGHAT) was used to define the boundaries of seed locations for the caudate, putamen, GPe, and GPi in MNI space (Prodoehl, Yu, Little, Abraham, & Vaillancourt, 2008). Once defined in MNI space, basal ganglia seed definitions were transformed into subject-space to define individualized seed regions for each subject. To do this, a single nonlinear transform (comprised of affine and nonlinear warps) was calculated in order to normalize the co-registered T1-weighted structural scan to the MNI 2009c symmetric template brain (Fonov, 2009). The inverse transform was then applied to basal ganglia seed definitions, transforming them from MNI to subject-space, **Figure 1**. The outer edge of each seed region was then eroded by 1 mm to minimize partial volume signal from neighboring white matter and CSF. To confirm placement, we performed visual inspection of putamen, caudate, GPe, and GPi seeds on each subject's T1-weighted structural scan (co-registered with functional resting-state data).

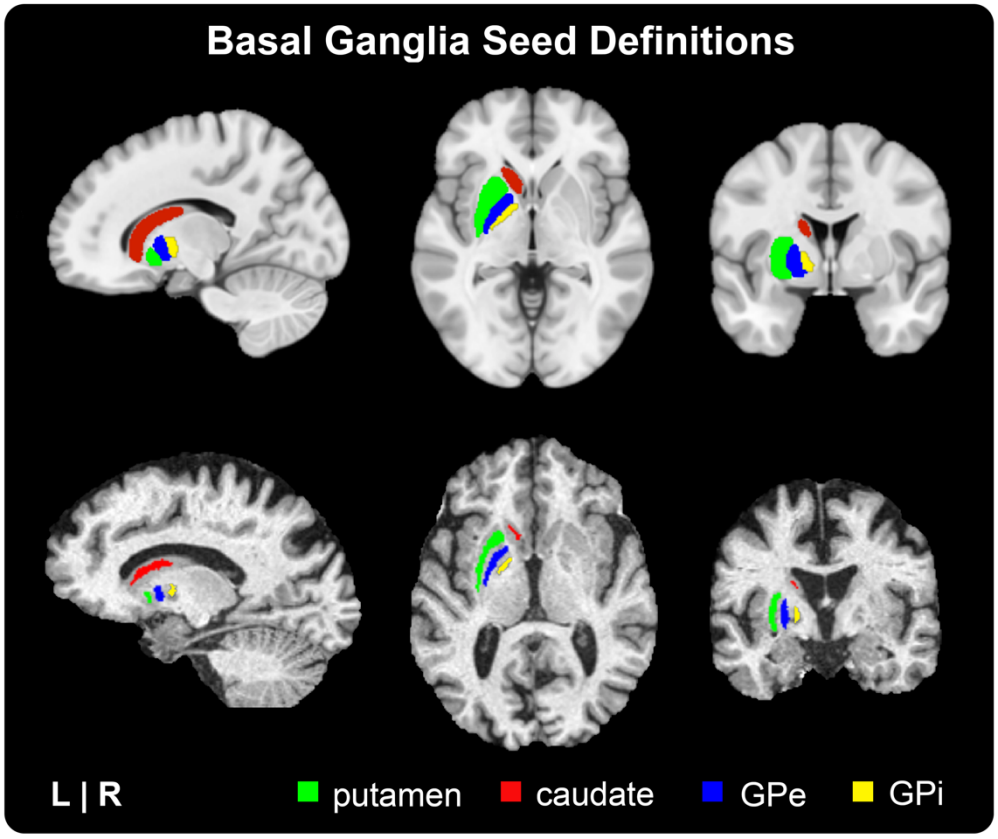

Figure 1. Basal ganglia seed definitions. Masks for the putamen, caudate, GPe, and GPi seeds were derived from the Basal Ganglia Human Area Template (BGHAT). Top row: BGHAT template regions overlaid onto the MNI template brain. Bottom row: BGHAT regions warped, eroded, and overlaid onto an individual subject's T1-weighted structural MRI. Abbreviations: external globus pallidus (GPe), internal globus pallidus (GPi).

2.3.9 Functional connectivity

Connectivity maps for each seed were calculated within each subject. Pearson correlations were calculated in subject-space to describe the connectivity between the seed and each voxel within the whole-brain mask. The resulting Pearson's *r* correlation maps were then converted to a *Z* score map via Fisher's transform. Each *Z* score map was then warped to 2 mm x 2 mm x 2 mm MNI space in preparation for a group analysis. Group-averaged *Z* score maps were calculated for OHC, PDN, and PDSI groups for statistical comparisons.

2.3.10 Statistical analysis

For each of the eight basal ganglia seeds, we performed a three-group analysis of covariance (ANCOVA) controlling for the effects of age and sex using the 3dMVM tool in AFNI. Planned, pairwise t-tests were then performed between-groups (OHC vs. PDN, OHC vs. PDSI, PDN vs. PDSI). To determine cluster-wise statistical thresholds for our between-groups comparisons, we first estimated the smoothness of noise in the resting-state scans using the spatial autocorrelation function in AFNI (Cox, Reynolds, & Taylor, 2016). This new approach to smoothness estimation was developed to address the recently identified issue of inflated false-positive rates resulting from the inappropriate smoothing calculations used by several imaging software packages (Cox et al., 2016; Eklund, Nichols, & Knutsson, 2016). Data smoothness was calculated for each subject individually using the preprocessed resting-state scans prior to nuisance signal regression in Anaticor (i.e., before removing noise) with the warp to MNI space applied. Smoothness estimates were then averaged across all subjects and entered into AFNI's 3dClustSim program. To reach a family-wise error (FWE) level of 0.05, statistical significance was

defined using a voxel-wise threshold of $p < 0.001$ and a cluster-wise threshold of 34 voxels (34 voxels x 8 mm^3 = 272 mm^3). To control for differences in brain coverage across subjects (specifically, clipping of slices at the top and bottom of the brain), our results were restricted to a group mask limited to voxels with at least 90% coverage across all subjects.

As motor severity and LEDD were not appropriate covariates to include with the OHC group, we conducted a two-group analysis using only the PD subjects to determine whether the motor severity or LEDD might influence the results of the PDN vs. PDSI comparisons within the three-group ANCOVA. The second set of ANCOVAs were performed on PDN and PDSI groups while controlling for the effects of age, sex, LEDD, and motor severity (MDS-UPDRS Part III) using the same statistical threshold. The results did not differ from PDN vs. PDSI comparisons in the three group ANCOVA.

2.3.11 Correlation with motor severity and PD medication

We also performed correlational analysis for PDN and PDSI groups separately to examine the relationship between connectivity values and MDS-UPDRS Part III aggregate scores as well as LEDD. Within each significant cluster, we extracted the averaged *Z* score for each individual PDN and PDSI subject. The subject-level *Z* scores were correlated with MDS-UPDRS Part III scores within the PDN and PDSI groups using a Pearson's *r* correlation ($p < 0.05$). To examine whether there was a relationship between group connectivity differences and use of antiparkinsonian medication, we further correlated *Z* scores of medicated PDN and PDSI subjects with LEDD using a Pearson's *r* correlation ($p < 0.05$).

2.4 RESULTS

Our results are organized by seed region (left putamen, right putamen, left caudate, right caudate, left GPe, right GPe, left GPi, right GPi).

2.4.1 Left putamen

A multivariate analysis of left putamen connectivity revealed a significant effect for group membership. Differences in left putamen connectivity were observed in all three pairwise comparisons (OHC vs. PDN, OHC vs. PDSI, PDN vs. PDSI) as shown in **Table IV**. Compared to the OHC group, PDN subjects had lower functional connectivity between the left putamen and left posterior cingulate cortex (**Figure 2,** top row, middle column). In addition, the PDN group had lower connectivity between the left putamen seed and a subset of voxels within the left putamen (**Figure 2**, top row, left and right columns). When compared to the OHC group, the PDSI group also had reduced connectivity between left putamen and left posterior cingulate cortex (**Figure 2**, fourth row, right column). Reductions in the connectivity between the left putamen seed and the subset of voxels within the left putamen were found when only the voxel-wise threshold was applied; however, the cluster did not meet our cluster extent threshold when comparing OHC vs. PDSI. In addition to the posterior cingulate cortex, the PDSI group had reduced connectivity between the left putamen and several other cortical regions, including sensorimotor cortex (**Figure 2**, second row, left column), cingulate motor area (**Figure 2**, fourth row, middle column), and two clusters in the left STG (**Figure 2**, middle row, right column). Compared to the PDN group, the PDSI group had significantly lower connectivity between left putamen and a single cluster in left STG (**Figure 2**, bottom row). **Figure 3** summarizes the mean functional connectivity (*Z*) between the left putamen seed

and left STG cluster, illustrating that there is no difference between OHC vs. PDN subjects, but that connectivity is significantly lower in PDSI compared to both OHC and PDN.

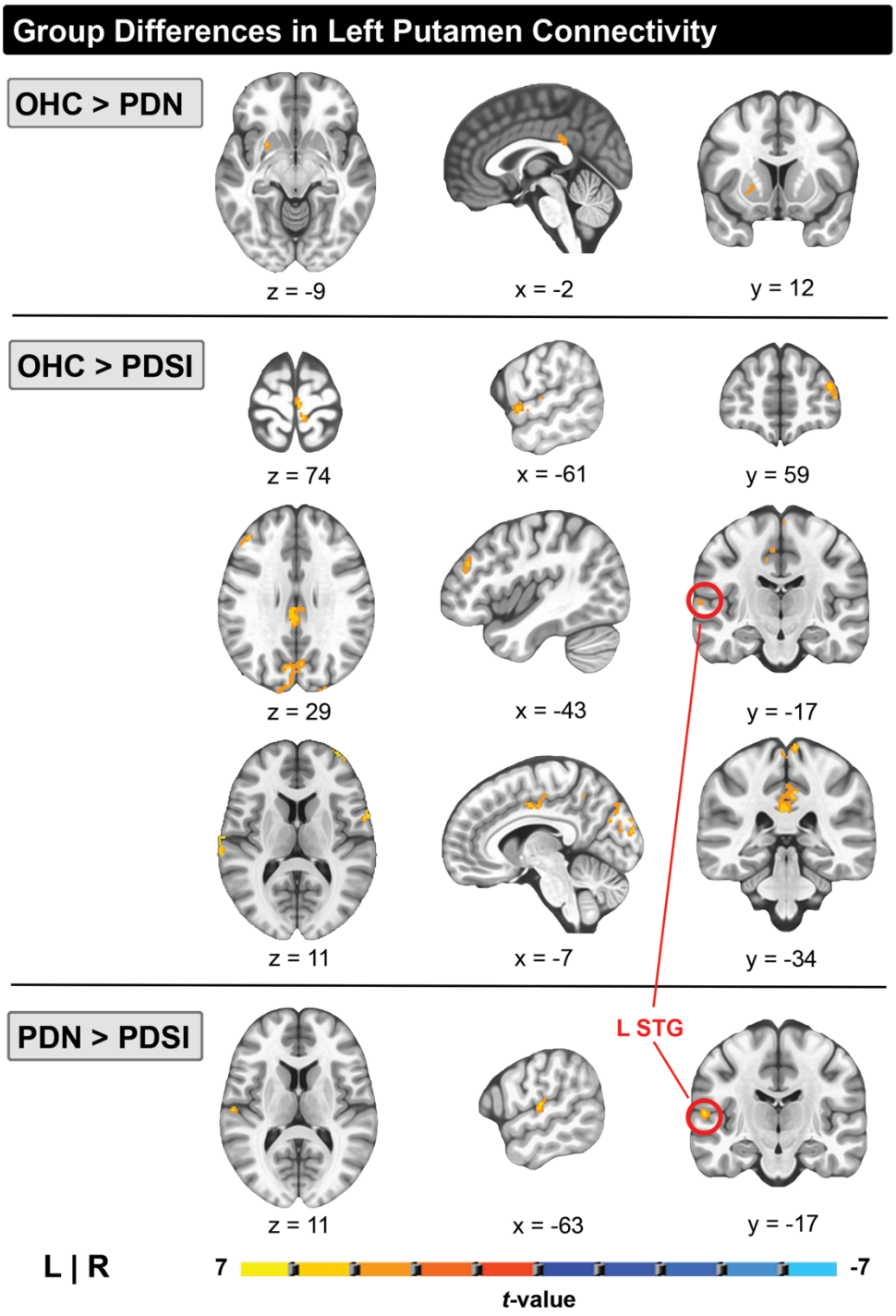

Figure 2. Pairwise group differences in whole brain resting-state functional connectivity of the left putamen (p<0.001, cluster size >272 mm^3, FWE<0.05). Top row: Areas of reduced left putamen connectivity in PD versus HC. Middle row: Areas of reduced left putamen connectivity in PDSI versus HC. Bottom row: Areas of reduced left putamen connectivity in PDSI versus PD. The red circle indicates a region in the left posterior STG with reduced connectivity in PDSI compared to both HC and PD groups. Abbreviations: superior temporal gyrus (STG)

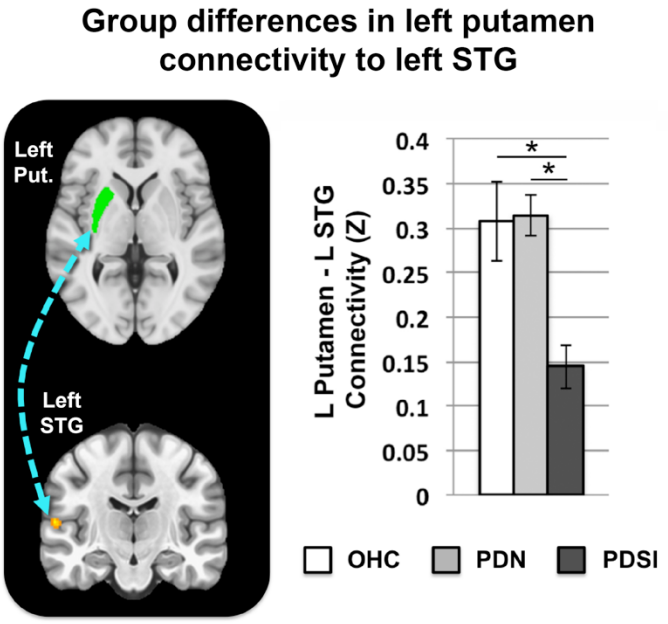

Figure 3. Mean functional connectivity between left putamen and left STG across OHC, PDN, and PDSI groups. The connectivity values for each group represent the mean *Z*-score within a cluster-derived mask of left STG (OHC: $Z = 0.307$, PDN: $Z = 0.315$, PDSI: $Z = 0.144$). Significance was derived from our voxel-wise analysis (*$p<0.001$, cluster size >272 mm^3, FWE<0.05). Abbreviations: putamen (Put.), superior temporal gyrus (STG)

2.4.2 Right putamen

A significant group effect was identified for the right putamen. Differences in right putamen connectivity were observed in two of the three pairwise comparisons (OHC vs. PDN and OHC vs. PDSI). PDN subjects had lower connectivity between the right putamen and the right middle cingulate compared to OHC subjects. When compared to OHC subjects, the PDSI group demonstrated widespread reductions in right putamen connectivity to cortical regions, including left cingulate motor area, left SMA and right sensorimotor cortex. However, there were no statistically significant differences in right putamen connectivity between subjects in the PDN and PDSI groups, **Table IV**.

2.4.3 Left caudate

No significant group effects were found for the left caudate seed.

2.4.4 Right caudate

A significant group effect was found for the right caudate seed. Differences in right caudate connectivity were observed in two of the three pairwise comparisons (OHC vs. PDN and OHC vs. PDSI). Compared to the OHC group, PDN subjects had lower connectivity of the right caudate to left SMA. Differences were also observed between OHC and PDSI groups, with the PDSI subjects demonstrating reduced connectivity of the right caudate with left SMA and right inferior temporal gyrus. There were no statistically significant differences in right caudate connectivity between PDN and PDSI groups.

2.4.5 Left GPe

A significant group effect was found for the left GPe seed. Differences in left GPe connectivity were observed in two of the three pairwise comparisons (OHC vs. PDN and OHC vs. PDSI). Compared to the OHC group, PDN subjects had lower connectivity between the left GPe and the right cuneus. The PDSI group had lower left GPe connectivity to left middle occipital gyrus and left SMA compared to OHC subjects. No differences were found between PDN and PDSI groups.

2.4.6 Right GPe

A significant group effect was found for the right GPe seed. Differences in right GPe connectivity were observed in two of the three pairwise comparisons (OHC vs. PDN and OHC vs. PDSI). PDN subjects had lower connectivity between right GPe and right precuneus compared to OHC subjects. In addition, the PDSI group demonstrated lower right GPe connectivity to right paracentral lobule, left SMA, and left cuneus compared to the OHC group. No differences in right GPe connectivity were observed between PDN and PDSI groups.

2.4.7 Left GPi

A significant group effect was found for the left GPi seed. Differences in left GPi connectivity were observed in one of the three pairwise comparisons (PDN vs. PDSI) as shown in **Table IV**. When compared to the PDN group, our analysis revealed that the PDSI group had stronger left GPi connectivity with a region of the left precentral gyrus, corresponding to left dorsal premotor cortex (PMd) and dorsolateral laryngeal motor cortex (LMC; **Figure 4**, left and middle columns) as well as stronger left GPi connectivity with left and right angular gyrus (**Figure 4**, right column). No significant differences were observed between the OHC and PDN group or between the OHC and PDSI group. **Figures 5 and 6** summarize the mean functional connectivity (*Z*) of left GPi connectivity to left PMd/LMC (**Figure 5**) and bilateral angular gyrus (**Figure 6**), illustrating that connectivity is no different between OHC vs. PDN subjects or OHC vs. PDSI subjects, but that it is significantly higher in PDSI compared to PDN. It is important to point out that although statistically significant differences were not found for the OHC vs. PDN and the OHC vs. PDSI comparisons, **Figure 5** and **Figure 6** (top and bottom panels) show that the mean Z score of the OHC subjects does look different when compared to PDN and PDSI. This raises the possibility that we did not have the sensitivity to detect a significant difference. For the two connections between left GPi and angular gyrus, a post-hoc seed to seed analysis showed that the mean connectivity

values approached significance for the comparison of OHC and PDN subjects (left GPi – left angular gyrus: $t = 1.742$, $p = 0.098$; left GPi – right angular gyrus: $t = 1.753$, $p = 0.099$). A post-hoc sample size estimate demonstrated that we would need the following sample sizes to detect significant differences for these connections: 114 subjects per group (OHC vs. PDN) and 70 subjects per group (OHC vs. PDSI) for the left PMd/LMC connection; 70 subjects per group (OHC vs. PDN) and 109 subjects per group (OHC vs. PDSI) for the left angular gyrus connection; and 44 subjects per group (OHC vs. PDN) and 237 subjects per group (OHC vs. PDSI) for the right angular gyrus connection. We address this point in the discussion**.**

2.4.8 Right GPi

No significant group effects were found for the right GPi seed.

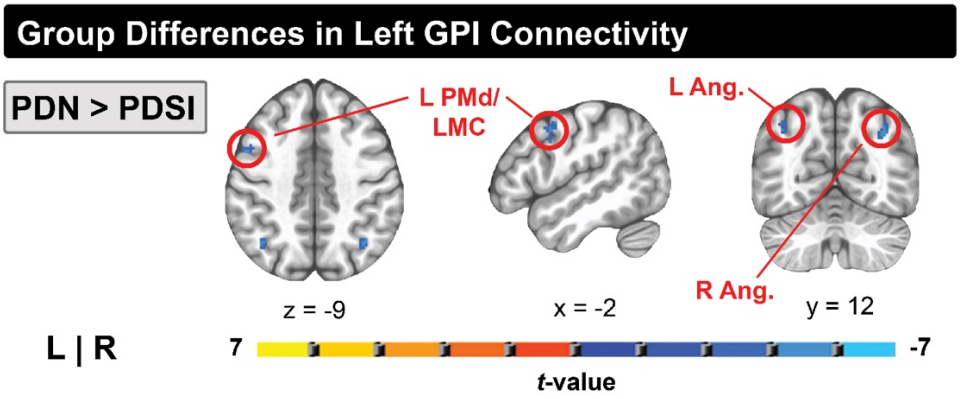

Figure 4. Pairwise group differences in whole brain resting-state functional connectivity of the left GPi (p<0.001, cluster size >272 mm^3, FWE<0.05). Shown in blue are regions of increased functional connectivity of left GPi in PDSI versus PD. The red circle indicates a region on the precentral gyrus corresponding to the dorsal premotor cortex. Abbreviations: dorsal premotor cortex (PMd), laryngeal motor cortex (LMC), internal globus pallidus (GPi)

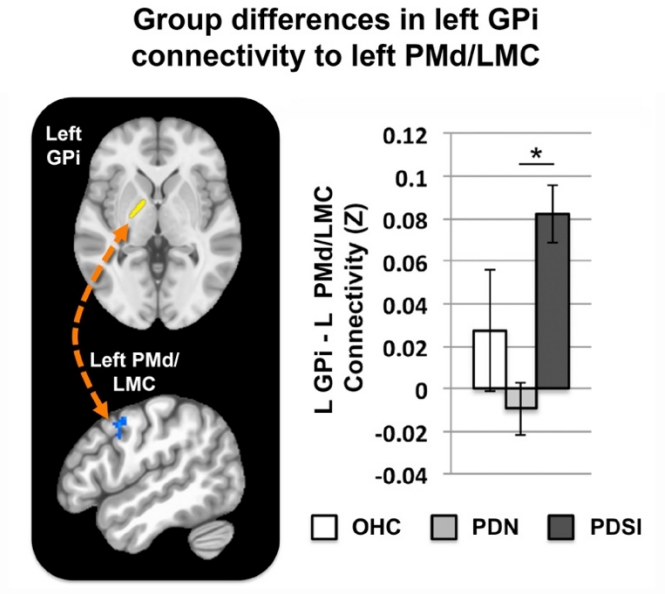

Figure 5. Mean functional connectivity between left GPi and left PMd across OHC, PDN, and PDSI groups. The connectivity values for each group represent the mean *Z*-score within a cluster-derived mask of left PMd (OHC: $Z = 0.028$, PDN: $Z = -0.009$, PDSI: $Z = 0.082$). Significance was derived from our voxel-wise analysis (*$p<0.001$, cluster size >272 mm^3, FWE<0.05). Abbreviations: dorsal premotor cortex (PMd), laryngeal motor cortex (LMC)

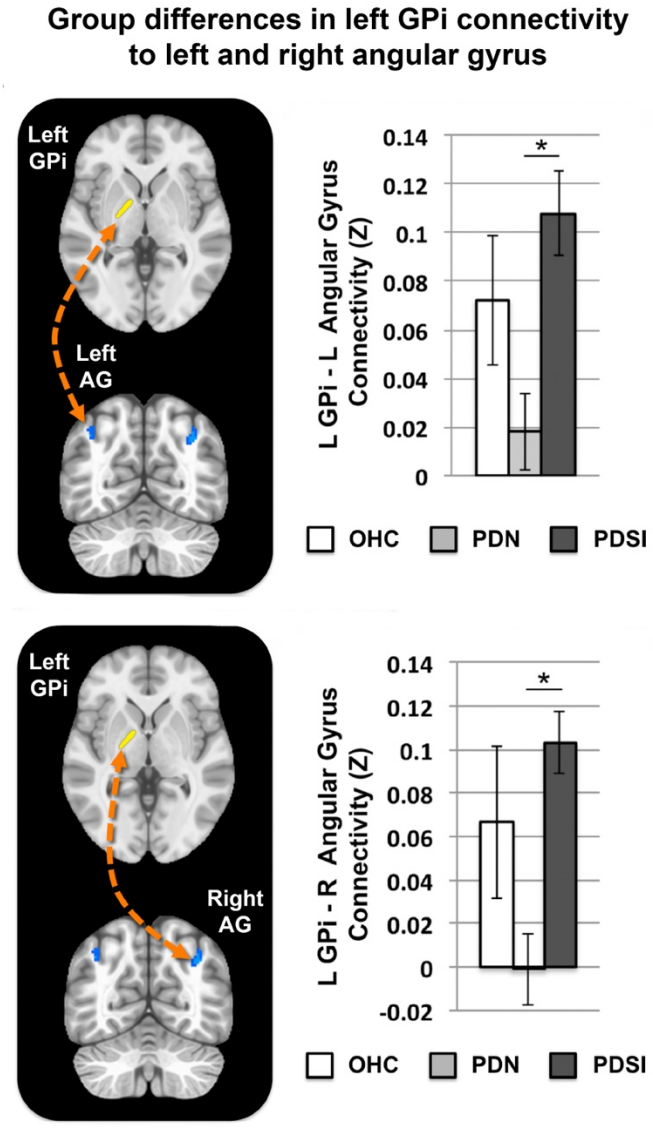

Figure 6. Group differences in left GPi connectivity to the left and right angular gyrus (AG). Top: Mean functional connectivity between left GPi and left AG across OHC, PDN, and PDSI groups. The connectivity values for each group represent the mean *Z*-score within a cluster-derived mask of left angular gyrus (OHC: $Z = 0.072$, PDN: $Z = 0.018$, PDSI: $Z = 0.108$). Bottom: Mean functional connectivity between left GPi and right AG. The connectivity values for each group represent the mean *Z*-score within a cluster-derived mask of right angular gyrus (OHC: $Z = 0.067$, PDN: $Z = -0.001$, PDSI: $Z = 0.103$). Significance was derived from our voxel-wise analysis (*$p<0.001$, cluster size >272 mm^3, FWE<0.05).

Table IV. Pairwise group differences in basal ganglia connectivity

	Comparison	Brain region(s)	Size (mm^3)	MNI coordinates (peak)			*t*-value
				x	y	z	
Seed	**Between-group differences**						
Left Putamen	OHC > PDN	L Putamen	288	-25	+9	-9	4.229
		L Posterior Cingulate	272	-1	-35	+27	4.118
	OHC > PDSI	L Posterior Cingulate	4240	-1	-31	+27	5.116
		R Cuneus	2800	+7	-71	+27	4.727
		R Middle Frontal Gyrus	1056	+41	+61	+7	5.090
		R Paracentral Lobule	1032	+7	-33	+77	4.617
		L Middle Cingulate Cortex	632	-7	-3	+41	5.152
		L Superior Temporal Gyrus	592	-63	-7	-1	4.857
		L Middle Frontal Gyrus	464	-41	+41	+27	4.587
		R Precuneus	456	+7	-59	+53	8.586
		L Superior Temporal Gyrus	312	-69	-25	+13	4.659
		R Superior Occipital Gyrus	304	+25	-95	+27	4.894
	PDN > PDSI	L Superior Temporal Gyrus	272	-59	-17	+11	5.643
Right Putamen	OHC > PDN	R Middle Cingulate	824	+1	-31	+33	4.271
	OHC > PDSI	L Middle Cingulate	2440	+1	-41	+45	5.507
		L Superior Frontal Gyrus	984	-33	+65	+13	5.508
		R Paracentral Lobule	776	+3	-25	+75	5.373
		R Superior Frontal Gyrus	752	+35	+65	+9	7.446
		L Cuneus	688	-5	-93	+21	4.468
		R Lingual Gyrus	632	+15	-41	-5	4.894
		L SMA	544	-11	-15	+49	4.809
		R Superior Medial Gyrus	392	+7	+27	+59	4.244
		R Cuneus	384	+19	-83	+43	4.036
		L Parahippocampal Gyrus	336	-27	-43	-9	4.588
		L Middle Temporal Gyrus	312	-69	-25	-5	4.825
	PDN > PDSI	-	-	-	-	-	-
Left Caudate	OHC > PDN	-	-	-	-	-	-
	OHC > PDSI	-	-	-	-	-	-
	PDN > PDSI	-	-	-	-	-	-
Right Caudate	OHC > PDN	L SMA	416	-7	+15	+61	4.871
	OHC > PDSI	L SMA	1432	-9	+15	+55	5.592
		R Inferior Temporal Gyrus	392	+57	-59	-11	4.931
	PDN > PDSI	-	-	-	-	-	-
Left GPe	OHC > PDN	R Cuneus	312	+5	-77	+35	4.469
	OHC > PDSI	L Middle Occipital Gyrus	2376	-25	-85	+17	5.261
		L SMA	472	-9	-15	+49	5.412
	PDN > PDSI	-	-	-	-	-	-

$p<0.001$, cluster extent >$272mm^3$ (34 voxels)
FWE=0.05
Abbreviations: SMA, Supplemental motor area; PMd, dorsal premotor cortex; LMC, laryngeal motor cortex

Table IV (cont.). Pairwise group differences in basal ganglia connectivity

	Comparison	Brain region(s)	Size (mm^3)	MNI coordinates (peak)			*t*-value
				x	y	z	
Seed	**Between-group differences**						
Right GPe	OHC > PDN	R Precuneus	576	+3	-77	+37	4.965
	OHC > PDSI	R Paracentral Lobule	408	+3	-37	+71	5.194
		L SMA	392	-11	-15	+51	5.403
		R Cuneus	272	+1	-77	+35	4.305
	PDN > PDSI	-	-	-	-	-	-
Left GPi	OHC > PD	-	-	-	-	-	-
	OHC > PDSI	-	-	-	-	-	-
	PDN > PDSI	L Angular Gyrus	488	-39	-63	+41	-4.492
		L Precentral Gyrus (PMd/LMC)	464	-51	+7	+43	-4.573
		R Angular Gyrus	352	+37	-63	+41	-4.878
Right GPi	OHC > PDN	-	-	-	-	-	-
	OHC > PDSI	-	-	-	-	-	-
	PDN > PDSI	-	-	-	-	-	-

$p<0.001$, cluster extent >272mm^3 (34 voxels)
FWE=0.05
Abbreviations: SMA, Supplemental motor area; PMd, dorsal premotor cortex; LMC, laryngeal motor cortex

2.4.9 Correlation with motor severity and PD medication

The comparison of PDN and PDSI subjects revealed group differences in four distinct functional connections: 1) left putamen-left STG, 2) left GPi-left PMd/LMC, 3) left GPi-left angular gyrus, 4) left GPi-right angular gyrus. To determine whether the strength of these connections was related to motor symptom severity, we first extracted the mean connectivity scores for each of these four seed-cluster pairs, as described above. We then used a Pearson's *r* calculation to correlate mean connectivity values with MDS-UPDRS Part III scores within PDN and PDSI groups, applying a statistical threshold of $p < 0.05$. MDS-UPDRS Part III motor scores did not correlate significantly with the connectivity of left putamen – left STG (PDN: $r = 0.093$, $p = 0.560$; PDSI: $r = -0.3044$, $p = 0.076$), left GPi – left PMd /LMC

(PDN: $r = 0.075$, $p = 0.639$; PDSI: $r = 0.012$, $p = 0.944$), left GPi – left angular gyrus (PDN: $r = -0.071$, $p = 0.655$; PDSI: $r = -0.065$, $p = 0.711$), or left GPi – right angular gyrus (PDN: $r = -0.014$, $p = 0.930$; PDSI: $r = -0.1518$, $p = 0.384$). **Figure 7** depicts the mean seed to cluster connectivity (Z) plotted against MDS-UPDRS Part III scores for each or the four seed-cluster pairs

To determine whether group differences in connectivity strength were related to medication effects, we further correlated LEDD with the strength of the same four functional connections within medicated PDN and PDSI groups. This analysis revealed that the connectivity strength between left GPi and left PMd/LMC was inversely correlated with LEDD within the PDN group ($r = -0.403$, $p = 0.046$*, **Figure 8** – top right corner), but not within the PDSI group ($r = -0.213$, $p = 0.317$). LEDD did not correlate significantly with the connectivity of left putamen – left STG (PDN: $r = 0.367$, $p = 0.072$; PDSI: $r = -0.024$, $p = 0.911$), left GPi - left angular gyrus (PDN: $r = -0.240$, $p = 0.249$; PDSI: $r = -0.076$, $p = 0.724$), or left GPi – right angular gyrus (PDN: $r = 0.025$, $p = 0.905$; PDSI: $r = -0.166$, $p = 0.439$).

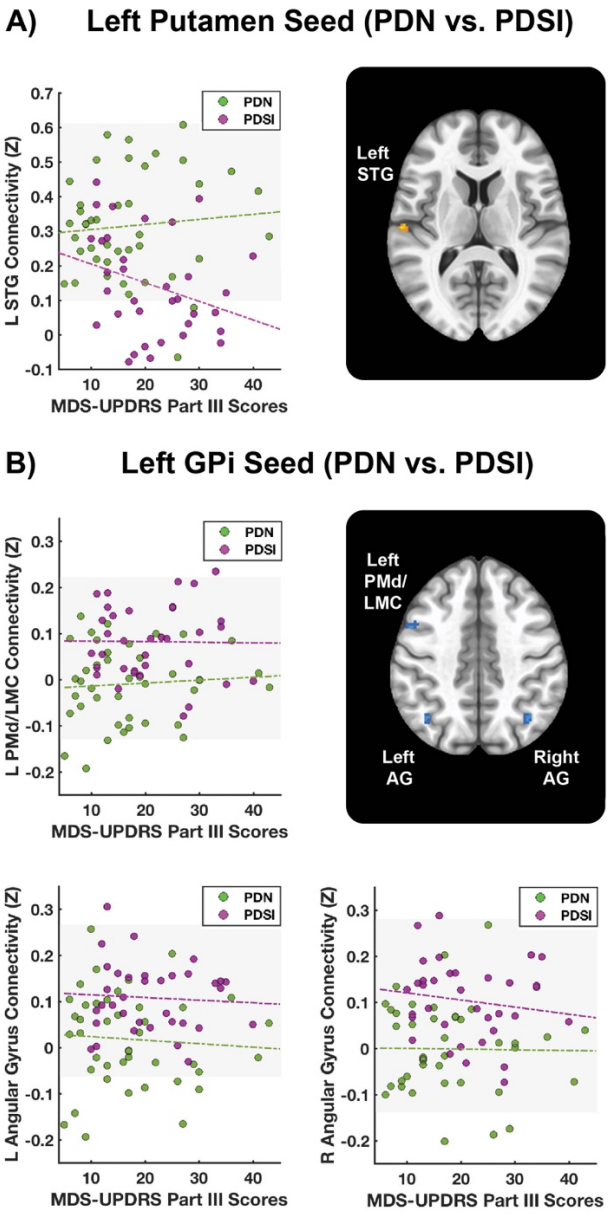

Figure 7. Functional connectivity and motor severity scores. Scatter plots depict functional connectivity scores (*Z*) plotted against motor severity scores (MDS-UPDRS Part III). Green dashed lines represent a linear fit of the data for PDN subjects. Purple dashed lines represent a linear fit of the data for PDSI subjects. A) Motor severity correlations for left putamen – left STG connection. B) Motor severity correlations for left GPi – left PMd/LMC, left GPi – left angular gyrus, and left GPi –right angular gyrus connections. Abbreviations: superior temporal gyrus (STG), internal globus pallidus (GPi), dorsal premotor cortex (PMd), laryngeal motor cortex (LMC), Movement Disorders Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS).

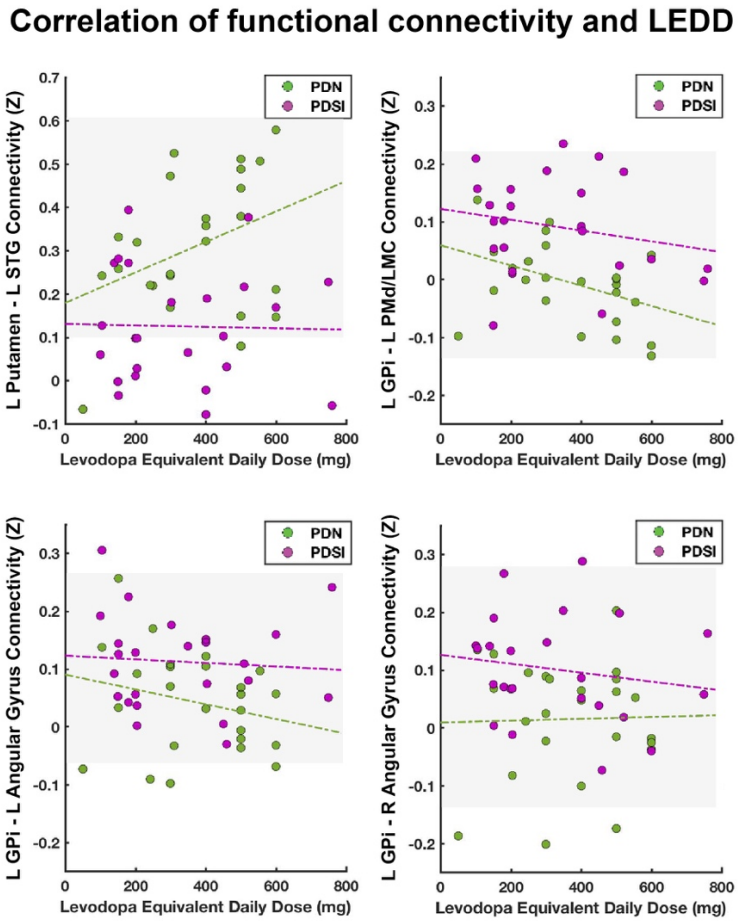

Figure 8. Functional connectivity and levodopa equivalent daily dose (LEDD). Scatter plots depict functional connectivity scores (*Z*) plotted against LEDD (mg). Green dashed lines represent a linear fit of the data for PDN subjects. Purple dashed lines represent a linear fit of the data for PDSI subjects.

2.5 DISCUSSION

This study identified differences in functional basal ganglia connections between OHC, PDN, and PDSI subjects, which furthers our understanding of the neural processes contributing to speech production difficulties in PD. These differences can be summarized by five key findings. First, our seed to whole-brain analyses identified a connection between left putamen and left STG that was significantly reduced in PDSI compared to both OHC and PDN groups (**Figures 2 and 3**). Second, our analyses identified three connections between left GPi and cortex in which PDSI subjects had increased connectivity compared to the PDN group (**Figures 4 - 6**). Third, the results of our PDN vs. PDSI comparisons were not related to severity of motor impairments (**Figure 7**). Fourth, functional connectivity between left GPi and left PMd/LMC was inversely correlated with LEDD in the PDN, but not the PDSI group (**Figure 8**). Finally, we observed that group differences between PDN and PDSI groups were found only for left hemisphere basal ganglia seeds (**Table IV**), suggesting that the mechanisms of speech impairment in PD may arise primarily from disruption of left hemisphere basal ganglia connectivity.

2.5.1 Abnormal left putamen connectivity in PDSI.

We confirmed the prediction that compared to OHCs the PDSI subjects would have abnormal left-hemisphere striatal connectivity to cortical regions involved in speech production. Although we found no differences in the connectivity of left putamen to SMA or premotor cortex, our results do show that left putamen connectivity with sensorimotor cortex and STG is indeed lower in PDSI relative to OHC (**Figure 2**). We also confirmed the prediction that when compared to PDN, PDSI subjects would have

abnormal striatal connectivity to STG, but not motor cortices (**Figures 2 & 3**). This finding is consistent with a study by Simonyan et al. (2013) who found that BOLD activity in the left anterior putamen was positively correlated with activity in left STG during sentence production. The results of these comparisons suggest that, while PDSI subjects have widespread reductions in connectivity between the left putamen and cerebral cortex (including cortical areas involved in speech production), reduced functional connectivity between the putamen and left STG may be uniquely linked to speech impairments in PD.

It is possible that reduced connectivity of the left putamen with left STG reflects a mechanism of impaired speech error detection and correction in PD. STG serves as functional integration area with partial overlap between speech perception and production mechanisms (C. J. Price, 2012). This functional overlap makes STG uniquely suited to detect and integrate auditory feedback during speech production (Behroozmand et al., 2016; Behroozmand et al., 2015; Hickok & Poeppel, 2007; Parkinson et al., 2012; Paus, Perry, Zatorre, Worsley, & Evans, 1996; Tourville & Guenther, 2011; Tourville, Reilly, & Guenther, 2008). The STG cluster identified in the present study corresponds closely to an anterolateral region of Heschl's gyrus that electrocorticography data has linked to online voice error correction following rapid perturbations in auditory feedback (Behroozmand et al., 2016). Compared to healthy individuals, those with PD respond to rapid perturbations in auditory feedback with an exaggerated compensation in vocal output compared to healthy controls (Chen et al., 2013; Huang et al., 2016; Liu, Wang, Metman, & Larson, 2012). It has thus been suggested that people with PD have impaired feedforward control of speech production and, as a result, rely more heavily on sensory feedback integration (Liu et al., 2012). Our findings suggest that in addition to impaired feedforward control, there may be impaired auditory feedback integration mediated by decreased connectivity between left putamen and left STG. For example, not only do people with PD respond to rapid auditory perturbations with exaggerated vocal responses (Chen et al., 2013; Huang et al., 2016; Liu et al., 2012), they also appear to

compensate less than controls when adapting to long-term alterations in auditory feedback (Mollaei, Shiller, & Gracco, 2013). Decreased coupling of left putamen and left STG may thus be indicative of difficulties in integrating sensory information during speech production in PD.

It is also interesting to note that, in addition to articulatory models of speech production such as DIVA, models of pre-articulatory error monitoring suggest that STG may also utilize perceptual feedback in the detection of phonological errors (Indefrey & Levelt, 2004), which research has shown to be abnormal in PD (Gauvin et al., 2017; McNamara, Obler, Au, Durso, & Albert, 1992). This raises another possibility that our observed reductions in left putamen – left STG connectivity in PDSI may be linked to broader changes in the online detection and correction of speech errors in PD. Whether this finding is in fact related to changes in auditory-motor integration or an even more global effect of impaired speech error monitoring can be tested in the future using direct behavioral probes of speech error detection.

2.5.2 Abnormal left GPi connectivity in PDSI.

The present study also identified group differences in cortical connectivity with left GPi. Compared to the PDN group, PDSI subjects exhibited stronger functional connectivity between left GPi and three cortical regions – the left PMd/LMC, the left angular gyrus, and the right angular gyrus. However, there were no statistically significant differences when comparing either PDN or PDSI groups to older healthy controls (**Figures 3 & 4**). As shown in **Figures 5 and 6**, the means of the OHC group appear to be different from both PDN and PDSI groups, which raises the question of whether our study was adequately powered to detect the differences. The standard error of the connectivity for all three GPi connections was higher in healthy controls compared to the PDN and PDSI groups. Our sample size analysis showed that we may have been able to detect a difference with a much larger sample size. However, as we did find statistical significance for several comparisons with our OHC group, another contributory factor in failing

to detect statistically significant results could be the quality of the signal in the GPi. With this in mind, it is interesting to note that rather than observing progressively increased functional connectivity from OHC to PDN to PDSI groups, we observed the lowest levels of functional connectivity in the PDN group and the highest levels of functional connectivity in the PDSI group. This same pattern was observed for each of the three left GPi connections (left PMd/LMC, left angular gyrus, and right angular gyrus). One possible explanation is that these three pathways undergo initial disease-related decreases in functional connectivity followed by an increase in compensatory functional connectivity once speech symptoms emerge. These three cortical connections with left GPi may thus represent pathways that compensate for functional losses in speech production. As most individuals with PD will eventually develop some form of speech impairment, this could be assessed in the future by analyzing resting-state data for the same PDN subjects once they begin to present with speech symptoms. Below we address our findings in the context of compensatory reorganization. However, in doing so, we acknowledge that our discussion is speculative and that elevated GPi connectivity in PDSI could be related to disease pathology rather than compensation.

The discovery of increased left GPi connectivity to left PMd/LMC is particularly intriguing given that it is located on the anterior bank of the precentral gyrus. While this area falls within the functional boundaries of the dorsal premotor cortex, it also corresponds closely with the dorsolateral laryngeal motor cortex defined by Brown et al. (2009). In light of this, we discuss two interpretations of this finding based on whether this cluster is interpreted as a premotor or primary motor region. When considered as a premotor region, increased left GPi - left PMd/LMC connectivity in PDSI subjects could be related to a greater reliance on external cues to compensate for internal cueing deficits during speech production. Problems with internal cueing have been well documented in PD (Jahanshahi et al., 1995; Siegert, Harper, Cameron, & Abernethy, 2002) and are thought to play a role in PD dysarthria (Sapir, 2014). Compared to habitual (internally cued) speech, measures of speech function and intelligibility improve when PD

subjects are prompted (externally cued) to speak more loudly, clearly, or slowly (Dromey & Ramig, 1998; Ho, Bradshaw, Iansek, & Alfredson, 1999; Sapir, 2014; Tjaden, Sussman, & Wilding, 2014). As motor preparatory activity in PMd is biased towards the planning and execution of movements that are externally cued (Halsband, Matsuzaka, & Tanji, 1994; Halsband & Passingham, 1982; Lu, Arai, Tsai, & Ziemann, 2012; Mushiake, Inase, & Tanji, 1991), increased connectivity with GPi could reflect a mechanism for compensatory reliance on external cues during speech production in PD.

The second interpretation considers this cluster to be a primary motor region for laryngeal control – specifically, the dorsolateral laryngeal motor cortex (Brown et al., 2009; Brown, Ngan, & Liotti, 2008). Although the dorsolateral laryngeal cortex is located within the bounds of the premotor cortex, it is considered one of two primary motor regions for voluntary vocalization in humans (Brown et al., 2009; Brown et al., 2008; Simonyan, 2014) and is homologous to laryngeal motor cortex in non-human primates (Simonyan, 2014). Voice abnormalities are prominent in PD (Logemann, Fisher, Boshes, & Blonsky, 1978; Sapir, 2014), with perceptual characteristics including reduced loudness, reduced pitch and intensity variability, harshness, and breathiness (Darley et al., 1969; Duffy, 2013). It is therefore not surprising that we observed differences in basal ganglia connectivity with laryngeal motor cortex when comparing PDSI subjects to PDN subjects. One possibility is that increased connectivity between the two structures is in fact related to the disease process, similar to the observed hyperconnectivity of the subthalamic nucleus to motor cortices in PD (Baudrexel et al., 2011; Kurani et al., 2015). However, in the context of compensatory effects, it is also possible that PDSI subjects require greater coupling between left GPi and left laryngeal motor cortex in order to overcome disease related changes in voice production (e.g., hypophonia). In either case, our finding that PDSI subjects have abnormal connectivity between left GPi and left PMd/LMC lays the foundation for new hypotheses about the role of GPi connectivity in voice and speech production in PD.

The prospect of a compensatory increase in connectivity between left GPi and bilateral angular gyrus

in PDSI is consistent with the current literature on resting-state connectivity in PD (Tahmasian et al., 2017). Located in the inferior parietal lobule, the angular gyrus serves as a multimodal association area, facilitating mental processes such as arithmetic (Arsalidou & Taylor, 2011), visuospatial attention (Nobre et al., 1997), memory (Kim, 2010; Spaniol et al., 2009; Vilberg & Rugg, 2008) sequence learning (Rosenthal, Roche-Kelly, Husain, & Kennard, 2009), and semantic processing (Benson et al., 2001; Obleser, Wise, Dresner, & Scott, 2007; A. R. Price, Peelle, Bonner, Grossman, & Hamilton, 2016; C. J. Price, 2012). Further, the posterior aspect of the angular gyrus serves as part of the default mode network (DMN), which is most active during rest or fixation and becomes deactivated when performing cognitive tasks. A recent meta-analysis of whole-brain resting-state connectivity in PD found converging evidence for elevated functional connectivity of bilateral angular gyrus in PD compared to healthy controls (Tahmasian et al., 2017). The authors similarly proposed that the elevated functional connectivity in PD was due to a compensatory reorganization of intrinsic resting-state networks following the loss of dopaminergic neurons. In line with this idea is a separate meta-analysis of task fMRI data showing that PD patients off medication have greater activity in superior and inferior parietal cortex than controls when performing externally cued (but not internally cued) motor tasks (Herz, Eickhoff, Lokkegaard, & Siebner, 2014). If stronger left GPi – angular gyrus connectivity in PDSI subjects is in fact compensatory, it could indicate that these individuals have a greater reliance on cortical regions involved in multisensory integration or higher level associative processing.

Still, given the diversity of behavioral functions supported by the angular gyrus, it is challenging to generate hypotheses about its role in PDSI based on resting-state data alone. While it seems reasonable to suggest that our observations reflect the compensatory recruitment of bilateral angular gyrus, it is possible that these findings are related to group differences in semantic processing. The dorsal angular gyrus, which corresponds to our present findings, has been proposed as a functional subdivision involved in searching for semantic information (Seghier, Fagan, & Price, 2010) and bottom-up semantic processing

(Whitney, Grossman, & Kircher, 2009). Semantic processing difficulties have been documented in PD, even in the absence of dementia or cognitive impairment (Boulenger et al., 2008; Roberts et al., 2017; Rodriguez-Ferreiro, Menendez, Ribacoba, & Cuetos, 2009; Signorini & Volpato, 2006). As longitudinal changes in UPDRS Part III speech impairment scores have been shown to correlate with impaired semantic verbal fluency in PD (Gago et al., 2009), it is possible that elevated connectivity between left GPi and bilateral angular gyrus reflects differences in semantic processing between PDN and PDSI groups. Future studies will be needed to examine whether elevated left GPi – angular gyrus connectivity in PDSI is related to disease mechanisms, compensatory recruitment of multisensory integration cortices, or group differences in semantic processing.

2.5.3 Correlation with motor severity

As this was the first study of resting-state basal ganglia connectivity to systematically disentangle PD speech impairment from more generalizable motor impairments, it was important to establish whether differences in PDN and PDSI groups might be related to global motor severity. Of the four resting-state connections that differed between PDN and PDSI subjects, none were found to correlate with MDS-UPDRS Part III scores (**Figure 7**). While there is likely a strong degree of overlap between the mechanisms of speech impairments and general motor impairments in PD, the findings of this study suggest that there may be additional neural processes at play that are speech specific. One might easily predict that abnormal basal ganglia connectivity to STG and angular gyrus would not be correlated with motor severity, as these regions are not directly involved in motor output. However, it is intriguing that there was also no correlation between motor severity and left GPi - left PMd/LMC connectivity, as this could be indicative of speech specific changes in motor cortices. That these connections did not correlate with our measure of motor severity suggests that group differences observed in those basal ganglia

connections are indeed independent of overall motor impairment and may be specific to speech impairments in PD. However, it remains to be seen whether correlations will emerge at more advanced stages of PD.

2.5.4 Correlation with PD medication dosage

Consistent with the motor severity scores, the connectivity of left putamen – left STG, left GPi – left angular gyrus, and left GPI – right angular gyrus were not correlated with LEDD. However, the functional connectivity between left GPi and left PMd/LMC was inversely correlated with LEDD within the PDN group alone (**Figure 8**). This finding is in line with prior work showing that levodopa can reduce striatal hyperconnectivity with motor cortices in PD (Kwak et al., 2010). It also suggests that antiparkinsonian medication reduces connectivity between left GPi and left PMd/LMC in PDN subjects, but not in PDSI subjects. Although levodopa provides effective treatment for motor symptoms in the early to moderate disease stages (Jankovic & Aguilar, 2008), the effect of levodopa on speech production is less consistent (Schulz & Grant, 2000, Pinto et al., 2004). If we consider hyperconnectivity of left-GPi and left PMd/LMC to be a disease-related phenomenon, it is possible that this pathological increase in connectivity contributes to speech impairments in PDSI subjects and is not responsive to levodopa in these individuals. Alternatively, if we consider hyperconnectivity to be a compensatory phenomenon, those who are levodopa responsive may no longer have a need for increased coupling between left GPi and left PMd/LMC due to treatment effects elsewhere in the brain. Further study is needed on the effects of PD medication on left GPi – left PMd/LMC connectivity during speech production. Assessment of basal ganglia connectivity on both OFF and ON medication states will provide additional insight into the differential effect of levodopa on PDN and PDSI individuals.

2.5.5 Lateralization effects

It is interesting to note that differences between PDN and PDSI groups were found only for left hemisphere basal ganglia seeds. Given that the cortical representation of speech and language is predominantly left-sided and that speech production involves the left-lateralized dopamine release in the striatum (Simonyan et al., 2013), it is not surprising that speech impairments in PD would be linked to changes in left hemisphere basal ganglia function. The hemisphere-specific findings of the present study may correspond to differences in disease lateralization between the two groups. While the PDN group had an equivalent number of subjects with left lateralized versus right lateralized motor symptoms, nearly 75% of the PDSI group had symptoms that were right lateralized (**Table II**), indicating degeneration of left hemisphere basal ganglia pathways. It is possible that earlier dopamine depletion in left hemisphere basal ganglia pathways causes PD patients with right lateralized motor symptoms to develop speech impairments earlier in the disease process compared to those with left lateralized symptoms. However, further research into speech function and disease lateralization is required before any firm conclusions can be made. If confirmed, our left lateralized findings provide insight into previously observed treatment-related shifts in cortical activity from the left to right hemisphere following successful speech treatment in PD (Narayana et al., 2010). Future work could address the hypothesis that speech impairments in PD arise primarily from changes in left cortico-basal ganglia pathways and that treatment facilitates a functional shift of cortical activity to the right hemisphere. While intriguing, support for this hypothesis is tempered by the fact that speech impairment in PD has also been linked to reduced functional connectivity of right striatal seeds when comparing PD subjects to healthy controls (Elfmarkova et al., 2016; New et al., 2015). However, as previously mentioned, these right lateralized findings involved comparing a single heterogeneous group of PD subjects (including those with and without speech impairment) to OHCs. Therefore, it may be the case that while the disease impacts both left and right striatal seeds, PD patients

with speech impairment experience significantly greater changes in left hemisphere basal ganglia function.

2.5.6 Limitations and future directions

The current study provides new insights into the roles of left putamen and left GPi in PD speech impairment; however, there are a few limitations to address. First, the sample size of our OHC group was relatively small compared to the sample sizes of our PDN and PDSI groups. This is due to the smaller pool of resting-state scans available from the PPMI Control Cohort (n = 21) compared to the PD Cohort (n = 90), which resulted in a smaller sample size once our inclusion criteria were applied (OHC: n = 12; PDN: n = 42; PDSI: n = 35). As a result, we may have had insufficient power to detect more subtle differences between the PD and OHC groups. Second, the MDS-UPDRS Part III Speech Impairment score is a course metric of overall speech function in PD and cannot provide fine-grained information about the nature of the speech impairment (i.e., articulation, voice, prosody etc.). Future studies will focus on collecting prospective fMRI data alongside acoustic and perceptual measures of speech in order to link abnormal basal ganglia connectivity with specific speech symptoms in PD. Moving forward, it will be important to conduct task-based connectivity analysis of putamen and GPi seeds to confirm whether these connections are in fact functioning abnormally during active speech production. By corroborating our findings in both resting-state and task fMRI, we will be able to establish a more complete understanding of the role that functional basal ganglia connections play in the emergence of speech impairments in PD.

2.6 CONCLUSION

The present study demonstrates that there are distinct functional connections between the basal ganglia and cortex that differentiate PD patients with and without speech impairment. These findings point to abnormal resting-state connectivity of left putamen – left STG, left GPi – left PMd, left GPi – left angular gyrus, and left GPi – right angular gyrus connections as potential mechanisms for speech impairment in PD.

CHAPTER 3

The effects of a simulated fMRI environment on voice intensity in individuals with Parkinson's disease hypophonia and older healthy adults

Jordan L. Manes[1], Ellen Herschel[1], Kris Tjaden[2], Todd Parrish[3], Tanya Simuni[4,5], Daniel M. Corcos[1], Angela Roberts[6]

[1] Department of Physical Therapy and Human Movement Sciences, Northwestern University, Chicago, IL

[2] Department of Communication Disorders and Sciences, University at Buffalo, Buffalo, NY

[3] Department of Radiology, Northwestern University, Chicago, IL

[4] Ken and Ruth Davee Department of Neurology, Northwestern University, Chicago, IL

[5] The Parkinson's Disease and Movement Disorders Clinic, Northwestern University, Chicago, IL

[6] Roxelyn and Richard Pepper Department of Communication Sciences and Disorders, Northwestern University, Evanston, IL

3.1 ABSTRACT

Functional magnetic resonance imaging (fMRI) has great promise for understanding neural mechanisms associated with neurogenic speech and language disorders. However, performance of speech tasks within the fMRI environment may not always be analogous to performance outside of the scanner. Using a mock MRI scanner, this study examines the effects of a simulated scanning environment on vowel intensity in individuals with Parkinson's disease and hypophonia (PD) and older healthy control participants (OHC). Thirty participants (15 PD, 15 OHC) performed a sustained /a/ vowel production task in three conditions: 1) Upright, 2) Mock Scanner + No Noise, and 3) Mock Scanner + MRI noise. We performed a 2-way (group*condition) analysis of covariance, adjusting for age and hearing threshold. A second 2-way ANCOVA (medication*condition) was also performed within the PD group to examine the effects of PD medication status (On vs. Off). A significant main effect of group showed that vowel intensity was significantly lower for PD participants compared to the OHC group. A significant main effect of recording condition showed that voice intensity was significantly greater in the Mock Scanner + MRI Noise condition compared to both Upright and Mock Scanner + No Noise conditions. The difference in vowel intensity between Upright and Mock Scanner + No Noise conditions was not significant. There was no significant group*condition interaction. A separate analysis conducted within the PD group showed no main effect of antiparkinsonian medication or medication*condition interaction on vowel intensity. Our findings show that noise within the fMRI environment leads to increased voice intensity during sustained vowel production. These effects seem to be comparable between PD and OHC populations.

3.2 INTRODUCTION

Functional magnetic resonance imaging (fMRI) can be a powerful tool for examining brain activity during speech and voice production. However, performing a task during fMRI may not always be analogous to performance outside of the scanner. Differences between the fMRI and out-of-scanner testing environments typically include a change in body position (laying supine vs. sitting upright) and the presence of loud background noise. While these differences may have little consequence to tasks such as visual discrimination, performance during speech and voice production tasks may be critically impacted by this change in environment. Furthermore, the effects of scanning environment on speech and voice production may differentially impact those with communication disorders compared to healthy individuals. As fMRI studies of speech production are important for understanding the neural mechanisms of neurogenic speech disorders, it is important to not only consider the effects of scanning environment on healthy individuals, but also the effect that scanning environment may have on the clinical populations under investigation.

In this study, we focus on the effects of the scanning environment on voice intensity among individuals with hypophonia resulting from Parkinson's disease (PD) and older healthy adults. Individuals with PD hypophonia speak with a lower voice intensity than healthy adults of the same age and may present with other dysarthric speech characteristics (Duffy, 2013). The neural mechanisms of speech changes in PD are not well characterized and fMRI provides a promising approach for understanding the neural underpinnings of hypophonic speech in PD. However, in order to accurately interpret the results of fMRI studies using speech production tasks in this population, it is important to consider whether or not the effects of scanning environment differ for individuals with PD hypophonia compared to older healthy controls. Further, as fMRI studies of speech in PD may also seek to examine participants both on and off of their antiparkinsonian medication, it is worth considering whether any effects of scanning environment

on this population might be dependent on medication status.

The acoustic noise generated during fMRI is a major limiting factor when conducting speech studies in the scanner. The sound exposure during echo-planar imaging (EPI; the standard approach for fMRI studies) has been estimated to range from 122-138 dB sound pressure level (SPL) inside the head coil (Foster, Hall, Summerfield, Palmer, & Bowtell, 2000; Ravicz, Melcher, & Kiang, 2000). This is attenuated by the use of hearing protection during fMRI scanning. Combined, the use of earplugs and earmuffs can reduce the sound exposure by 39-41 dB SPL (Ravicz & Melcher, 2001). Thus, sound exposure during echo planar imaging should range between 81-99 dB SPL when this combined hearing protection is used. During a typical task fMRI scan, the data is collected in a continuous manner, with the scanner actively collecting data and producing acoustic noise while the participant simultaneously performs the task of interest. To combat the effects of background noise, many neuroimaging studies of speech production have opted to collect sparsely sampled fMRI data (Perrachione & Ghosh, 2013). Using this approach, the task is executed by the participant during an acoustically silent period (when the gradient is off) and followed immediately after by the collection of fMRI data (Hall et al., 1999). The slow nature of the blood-oxygen level dependent (BOLD) response measured by fMRI allows researchers to capture the peak of the BOLD response 4-5 seconds after the task begins, thereby giving the participant a short window to perform the task without the interference of loud background noise. However, the sparse sampling approach can also come at the cost of longer scan times or reduced statistical power (Nebel et al., 2005).

When continuous scanning protocols are used, it is almost certain that the acoustic background noise will impact the participant's voice intensity. It is well established that speaking in the presence of background noise prompts healthy individuals to systematically increase voice intensity (Lane & Tranel, 1971; Lombard, 1911; Zollinger & Brumm, 2011a, 2011b). This phenomenon, known as the "Lombard effect" has been demonstrated in the presence of several different noise types and intensities (Egan, 1971;

Garnier, Henrich, & Dubois, 2010). The Lombard effect is preserved in individuals with PD and hypophonia (Scott G Adams et al., 2006; Scott G Adams et al., 2005; S. G. Adams & Lang, 1992; S. G. Adams et al., 2006; Dykstra, Adams, & Jog, 2012b). Although those with PD and hypophonia speak with a reduced vocal intensity, they are able to systematically increase vocal intensity when speaking in the presence of background noise in a way that parallels that of older healthy adults (Scott G Adams et al., 2006; Scott G Adams et al., 2005; S. G. Adams et al., 2006; Dykstra et al., 2012b). These parallel Lombard responses occur across multiple types of background noise stimuli, including conditions of pink noise, music, and multi-talker babble (Scott G Adams et al., 2006). Thus, it stands to reason that during continuous fMRI scanning, voice intensity will increase similarly for both groups in response to acoustic scanner noise.

In addition to scanner noise, participant position is another important consideration in fMRI speech task designs. In fMRI experiments, participants are performing speech tasks while laying supine, which differs from the upright posture typically used in natural speech production. The effect of body position on voice intensity has not been systematically studied in healthy adults or in individuals with PD hypophonia. However, the mechanics of speech breathing (Hoit, 1995) are known to differ between the upright and supine positions, which may affect one's ability achieve the desired vocal intensity while lying supine. Compared to upright posture, laying supine decreases the size of the respiratory apparatus, resulting in a diminished ability to utilize passive reoil forces. The rib cage muscles take a more active role in expiration, while the abdominal muscles remain largely inactive (Hoit, 1995). Supine speech breathing may be exceptionally effortful in PD due to rigidity and weakness of the rib cage (Hovestadt et al., 1989; Sabate et al., 1996; Solomon & Hixon, 1993), increased reliance on abdominal muscles for expiration (Huber & Darling-White, 2017; Huber et al., 2003; Solomon & Hixon, 1993), and lower lung volume initiations for generating passive recoil forces (Huber & Darling-White, 2017). In the context of Lombard speech, individuals with PD rely on a combination of both respiratory and laryngeal strategies to

achieve greater voice intensity when speaking in the presence of background noise (Stathopoulos et al., 2014). However, different respiratory-laryngeal strategies might be needed in the supine position during fMRI scanning.

Another factor for consideration is whether medication state has any effect on speech performance in the scanning environment. In the fMRI literature, studies of PD speech can be found both in the on medication and off medication states (Maillet et al., 2012; Pinto et al., 2011; Rektorova et al., 2007). Testing individuals with PD on their typical antiparkinsonian medication can help to reduce tremor and head movement artifacts during fMRI; however, some research questions may require testing after medication withdrawal or a comparison of on versus off medication states. In general, dopaminergic therapy does not appear to have a robust or consistent effect on voice intensity (Fabbri et al., 2017; Ho et al., 2008; Jiang, Lin, et al., 1999; Kompoliti et al., 2000; Skodda et al., 2010), thus it seems unlikely to have a meaningful impact on voice intensity during fMRI. Still, there are a few reasons to test this empirically. First, medication can improve some aspects of respiratory function in PD, including vital capacity (De Letter et al., 2007; De Letter et al., 2010; Monteiro, Souza-Machado, Valderramas, & Melo, 2012) and peak expiratory flow (de Bruin, de Bruin, Lees, & Pride, 1993; Monteiro et al., 2012). If speech breathing in PD indeed becomes more effortful in the supine position, it is possible that medication related improvements in respiratory function could enable target voice intensities to be more easily reached when the individual is lying down. Second, the tasks previously used to evaluate the effects of dopaminergic medication on voice intensity include only a small number of trials (Fabbri et al., 2017; Ho et al., 2008; Jiang, Lin, et al., 1999; Kompoliti et al., 2000; Skodda et al., 2010). The length of time and number of trials required for fMRI tasks is substantially greater than what is used in a typical acoustic speech experiment, making it more likely that the participants will experience fatigue of the speech motor systems. As there is some evidence to suggests that levodopa can reduce motor fatigue in individuals with PD (Lou et al., 2003), it is worth examining the effects of PD medication on voice intensity using a task

more typical of an fMRI experiment. By doing so, we can instill greater confidence that fMRI experiments of PD speech may be accurately interpreted across and between medication states.

The purpose of this study is to examine the effects of a simulated fMRI environment on the voice intensity of individuals with PD and hypophonia and older healthy controls (OHC). To accomplish this, we utilize a mock MRI scanner and ask participants to perform a sustained vowel production task in three conditions: 1) seated upright outside of the mock scanner ("Upright"), 2) laying supine inside the mock scanner with no MRI sounds ("Mock Scanner + No Noise"), and 3) laying supine inside the mock scanner with MRI sounds played over headphones ("Mock Scanner + MRI Noise"). The Upright condition is used to represent a typical recording setup for acoustic speech analysis. The Mock Scanner + No Noise condition is used to simulate the environment of a sparsely sampled fMRI experiment, in which the participant is supine and wearing headphones, but no MRI sounds are present. Finally, the Mock Scanner + MRI Noise condition is used to simulate the environment of a continuously sampled fMRI experiment. With respect to group effects, we expect that vowel intensity in the PD group will be lower than that in the OHC group across all recording conditions. With respect to recording conditions, we predict that vowel intensity for both groups will be significantly higher in the Mock Scanner + MRI Noise condition compared to both the Upright and Mock Scanner + No Noise conditions, in line with prior studies of Lombard effect in older healthy adults and those with PD hypophonia (Scott G Adams et al., 2006; Scott G Adams et al., 2005; S. G. Adams & Lang, 1992; S. G. Adams et al., 2006; Dykstra et al., 2012b). Given the higher respiratory demands during supine speech breathing (Hoit, 1995) and the known respiratory changes in PD (Hovestadt et al., 1989; Huber & Darling-White, 2017; Huber et al., 2003; Sabate et al., 1996; Solomon & Hixon, 1993), we predict a group*condition interaction in which group differences in vowel intensity will be more pronounced in the Mock Scanner conditions compared to the Upright condition. Within the PD group, we further examine the effects of medication state (on medication vs. 12-hour withdrawal) on vowel SPL across each of the three recording conditions. As there is not strong

evidence to suggest that PD medication leads to meaningful improvements in voice intensity (Daniels, Oates, Phyland, Feiglin, & Hughes, 1996; Fabbri et al., 2017; Kompoliti et al., 2000; Skodda et al., 2010), we predict that PD participants will produce vowels at a comparable voice intensity when on versus off medication.

3.3 MATERIALS AND METHODS

3.3.1 Participants

We recruited 15 participants who presented with PD hypophonia and 15 older healthy controls (OHC). All participants were right-handed, native English speakers between 40-80 years old with a score of either ≥26 on the Montreal Cognitive Assessment (MoCA) or ≥18 on the MoCA-Blind (if screened over the phone). PD participants were either referred by a movement disorders neurologist at Northwestern Memorial Hospital, recruited from a laboratory participant registry, or recruited through PD community events. All participants with PD were judged to have hypophonia by their referring neurologist or by a trained member of the study team.

3.3.2 Procedure

All testing was performed at Northwestern University's Center for Translational Imaging. Informed consent was obtained in accordance with Northwestern University's guidelines. Participants in both groups were given a hearing test (Oscilla SM910-B), so that a measure of hearing threshold could be used as a covariate in the final statistical analysis. Hearing threshold was calculated using a bilateral pure tone average threshold of 0.5, 1, and 2 kHz. In addition, both groups completed a demographics survey and the Mattis Dementia Rating Scale (DRS-2) (Matteau et al., 2011; Matteau, Dupre, Langlois, Provencher, & Simard, 2012). Participants practiced the sustained vowel production task for 1-2 blocks before performing the task in the three different recording environments: 1) Upright, 2) Mock Scanner + No Noise, and 3) Mock Scanner + MRI Noise. Recording during the Upright condition took place after the

practice task, but before the mock scanner conditions. This was done in an effort to alleviate the discomfort of PD participants repeatedly going in and out of the mock scanner. Once inside the mock scanner, the order of the conditions (Mock Scanner + No Noise vs. Mock Scanner + MRI Noise) was counterbalanced.

Testing for PD participants took place on two consecutive days. Day 1 testing was conducted in the afternoon while participants were on their regular antiparkinsonian medication, while Day 2 testing was conducted the next morning following 12-hour medication withdrawal. Voice recordings for the three conditions were collected on both days to capture performance both on and off medication. In addition, participants in the PD group were administered the Communicative Participation Item Bank (CPIB) (Baylor et al., 2013) as well as the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS), with Part III motor testing completed on Day 2 (off medication).

3.3.3 Sustained vowel production task

We collected voice recordings while participants performed a sustained vowel production task. The task consisted of ten vowel production blocks (30s each) and ten rest blocks (30s each). During the task, participants were presented with either a "+" symbol (rest) or "Ah" (vowel production). During the "Ah" blocks, subjects were instructed to produce an /a/ vowel for approximately 3-5 seconds at their normal conversational loudness and repeat for the duration of the block. As individuals with PD hypophonia can increase vocal loudness when provided with external cues to do so (Darling & Huber, 2011; Sadagopan & Huber, 2007; Tjaden, Lam, & Wilding, 2013; Tjaden & Wilding, 2004), this self-paced paradigm was designed so that participants would rely primarily on internal, rather than external cueing mechanisms for vowel initiation and production. **Figure 9** illustrates the task design.

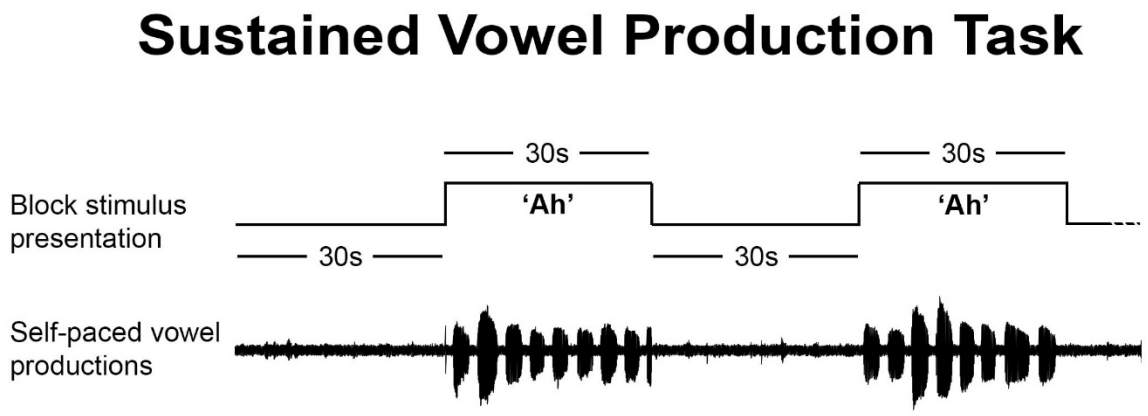

Figure 9. Sustained vowel production task. Above: block stimulus presentation consisting of 30s sustained vowel blocks ('Ah') alternated with 30s rest blocks. Below: head microphone recordings of self-paced /a/ vowels produced during the 30s sustained vowel blocks.

3.3.4 Recording of speech and voice samples

Speech and voice samples were recorded using a head mounted, unidirectional microphone (Shure SM10A) positioned 3 cm from the lower lip. The distance of 3 cm was chosen in order to accommodate the head coil in the mock MRI scanner while maintaining a consistent recording setup when the participant was seated upright. The microphone was channeled through a pre-amplifier (ART Project Series USB Dual Pre) and then relayed onto a laptop computer for recording in Audacity. Speech samples were recorded at a sampling frequency of 44.1kHz. In order to estimate voice SPL, a sound level meter (SLM; Extech 407736) was positioned 30cm from the lower lip. In the Upright condition, the SLM was used for calibration and remained fixed throughout recording. In the mock scanner conditions, the SLM was used only for calibration due to the space limitations inside the bore.

3.3.5 fMRI simulation

To create a simulated fMRI environment, we utilized a mock MRI scanner with the bore and internal dimensions identical to those of a Siemens 3T TIM-TRIO MRI scanner. Visual and auditory stimuli for the sustained vowel task were presented using E-Prime software (https://pstnet.com/products/e-prime/). The mock head coil was affixed with an angled mirror so that task instructions and stimuli could be viewed on a display monitor placed outside of the mock scanner. MRI sounds were delivered via over-the-ear headphones. The volume of the MRI sounds was held constant across sessions and subjects (90 dB) and specifically simulated the EPI noise generated during an fMRI experiment. The intensity of 90 dB was chosen to approximate the mid-range of noise exposure experienced during fMRI when both ear plugs and earmuffs are used (Foster et al., 2000; Ravicz & Melcher, 2001; Ravicz et al., 2000). Vowel production in the mock scanner conditions was recorded using the same head mounted microphone and recording setup as in the Upright condition.

3.3.6 SPL Calibration

To achieve accurate SPL measurements, we applied a two-step calibration procedure as described in Method 6 in Svec and Granqvist (2018). As the bore of the mock MRI scanner was too small to take SLM measurements at 30 cm, calibration recordings for the mock scanner conditions were taken outside of the bore while the participant was positioned supine on the table with the microphone at its fixed 3cm distance. The table was then immediately rolled into the bore of the mock MRI scanner and the task was started.

3.3.7 Analysis of acoustic voice measures

We extracted voice SPL from the vowel production recordings collected in the three recording environments. Any vowel production that lasted less than 0.5 seconds was excluded from analysis. Voice intensity measures were analyzed using Praat (Boersma, 2017). The raw voice intensity was extracted from each vowel production and adjusted by the calibration factor. The calibrated voice intensity was then averaged across all 10 blocks. To examine the effects of group and recording condition on SPL, we performed a two-way analysis of covariance (ANCOVA) using SPSS Version 26.0 for Mac (IBM Corp., Armonk, N.Y., USA). Included in our two-way ANCOVA were the main factors of group (PD vs OHC) and recording condition (Upright vs. Mock Scanner + No Noise vs. Mock Scanner + MRI Noise) as well as the covariates of age and hearing threshold. For this analysis, we specifically used PD participants after 12-hour medication withdrawal. This was done in order to estimate their baseline disease state as well as well as to extend the prior literature of the Lombard effect into the off-medication PD state. A second analysis was performed within the PD group determine whether voice intensity during fMRI simulation differed between on- and off-medication states. For 2 of the 15 PD participants, recordings conducted during the on-medication conditions were discarded due to poor data quality. Using the remaining 13 participants, we performed a two-way medication*condition ANCOVA, which included the main factors of medication status (On vs. Off medication) and recording condition (Upright vs. Mock Scanner + No Noise vs. Mock Scanner + MRI Noise) as well as the covariates of age and hearing threshold.

3.4 RESULTS

3.4.1 Participant Characteristics

Characteristics of the PD and OHC groups are shown in **Table V**. There were no statistically significant group differences in age, sex, DRS-2 score, or hearing threshold. Parkinson's disease characteristics for the PD group are reported in **Table VI**.

Table V. Participant characteristics for PD and OHC groups.

Variable	PD (N = 15)	OHC (N = 15)	p-value (OHC vs. PD)
Age			0.366
Mean	63.13	61.47	
(Min, Max)	(49, 78)	(42, 71)	
Sex			1.000†
Male	10 (66.7%)	10 (66.7%)	
Female	5 (33.3%)	5 (33.3%)	
DRS-2			0.190
Mean	140.47	141.40	
(Min, Max)	(137, 144)	(138, 144)	
Hearing Threshold			0.100
Mean db SPL	21.39	17.33	
(Min, Max)	(10.0, 31.7)	(7.5, 35.0)	

**p < 0.05, two-tailed, two sample t-test*
† Chi-squared test for independence
Abbreviations: DRS-2, Mattis Dementia Rating Scale 2, SPL, sound pressure level

Table VI. Parkinson's disease characteristics for PD participants

MDS-UPDRS	
MDS-UPDRS Total Score	58.2
MDS-UPDRS Part I	9.07
MDS-UPDRS Part II	12.20
MDS-UPDRS Part III (Motor Exam)	34.93
Item 3.1 (Speech)	1.23
MDS-UPDRS Part IV	2.00
Hoehn & Yahr	
Stage 0	0 (0.0%)
Stage 1	1 (6.7%)
Stage 2	13 (86.7%)
Stage 3-5	1 (6.7%)
TD/PIGD Classification	
TD	6 (40.0%)
PIGD	7(46.7%)
Indeterminate	2 (13.3%)
Side Most Affected	
Left	8 (53.3%)
Right	7 (46.7%)
Symmetric	0 (0.0%)
Levodopa Equivalent Daily Dose	
Mean (mg)	730.00
(Min, Max)	(120, 1563)
CPIB	
Mean	22.53
(Min, Max)	(14, 30)

Abbreviations: MDS-UPDRS, Movement Disorders Society - Unified Parkinson's Disease Rating Scale, TD, tremor dominant, PIGD, postural instability & gait disturbance, CPIB, Communication Participation Item Bank

3.4.2 Group*condition ANCOVA

A two-way group*condition ANCOVA indicated a significant main effect for group ($F(1,82) = 16.836$; $p = 0.0001$*) as well as a significant main effect for condition ($F(2,82) = 10.096$, $p = 0.0001$*). However, there was no statistically significant group*condition interaction ($F(2,82) = 0.287$, $p = 0.7516$). A simple main effects analysis revealed that participants in the PD group produced vowels at a lower SPL compared to OHCs (Mean difference = -4.734, 95% CI [-7.029, -2439], $p = 0.0010$***, Figure 10**). The observed and adjusted SPL means by group are reported in **Table VII**. In our post-hoc analysis of condition effects, participants produced vowels at a significantly higher SPL in the Mock Scanner + MRI Noise condition compared to both the Upright condition (Mean difference = 5.994, 95% CI [3.321, 8.668], $p = 0.0001$*) and the Mock Scanner + No Noise condition (Mean difference = 3.635, 95% CI [0.961, 6.308], $p = 0.008$*). The difference in vowel intensity between Upright and Mock Scanner + No Noise conditions did not reach statistical significance (Mean difference = 2.360, 95% CI [-0.314, 5.034], $p = 0.0829$, **Figure 11**). The observed and adjusted SPL means by condition are reported in **Table VIII**.

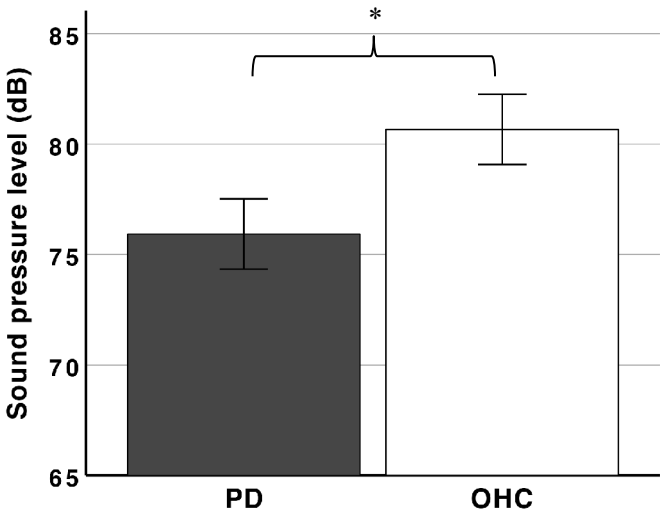

Figure 10. Comparison of vowel intensity (voice dB SPL) between OHC and PD groups, collapsed across conditions. Sound pressure level reflects the estimated marginal means, adjusted for age (centered at 62.30) and hearing threshold (centered at 19.36). Error bars represent +/-2 standard error. *$p < 0.05$

Table VII. ANCOVA Results and Descriptive Statistics for Sound Pressure Level by Group, Collapsed Across Conditions

Group	Sound Pressure Level (dB)				
	Observed mean	SD	Adjusted mean	SE	n
Parkinson's disease + hypophonia	75.978	5.503	75.930	0.796	45
Older healthy controls	80.615	5.786	80.663	0.796	45

Adjustments based on age mean 62.30 and hearing threshold mean 19.36.

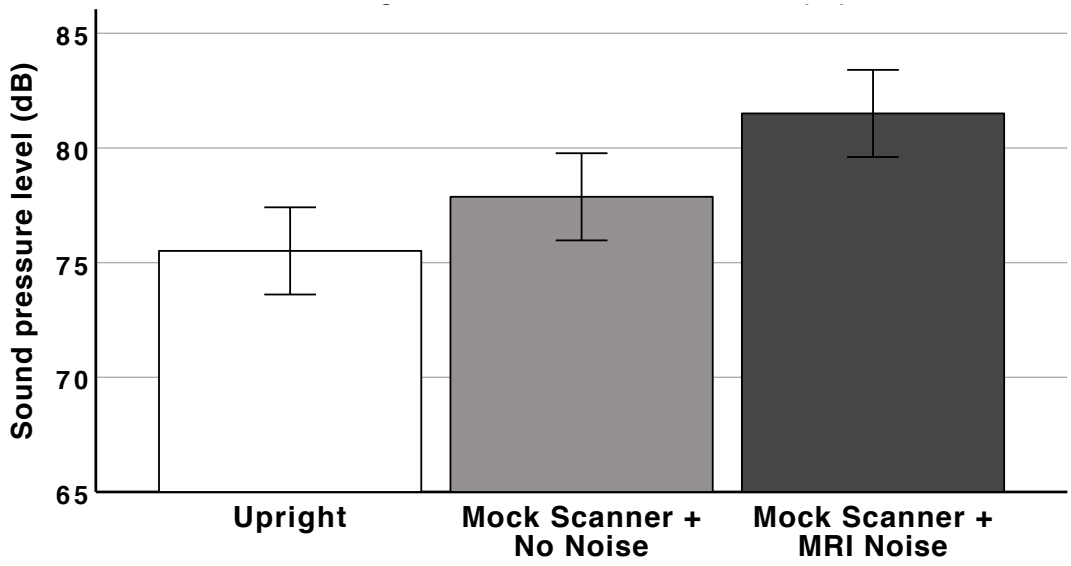

Figure 11. Comparison of vowel intensity (voice dB SPL) between recording conditions, collapsed across PD and OHC groups. Sound pressure level reflects the estimated marginal means, adjusted for age (centered at 62.30) and hearing threshold (centered at 19.36). Error bars represent +/-2 standard error. *$p < 0.05$

Table VIII. ANCOVA Results and Descriptive Statistics for Sound Pressure Level by Condition, Collapsed Across PD and OHC Groups

Recording Condition	Sound Pressure Level (dB)				
	Observed mean	SD	Adjusted mean	SE	n
Upright	75.512	5.817	75.512	0.950	30
Mock Scanner + No Noise	77.872	5.197	77.872	0.950	30
Mock Scanner + MRI Noise	81.506	5.806	81.506	0.950	30

Adjustments based on age mean 62.30 and hearing threshold mean 19.36

3.4.3 Medication*condition ANCOVA

A two-way medication*condition ANCOVA within the PD group again revealed a main effect for condition (F(2,70) = 12.963, $p = 0.00002$*), but no significant main effect of medication ($F(1,70) = 0.107$, $p = 0.7443$) and no condition*medication interactions ($F(2,70) = 0.218$, $p = 0.8044$) on vowel SPL (**Figure 12**). The observed and adjusted SPL means by medication state are reported in **Table IX**. Within the PD group, participants again produced vowels at a significantly higher SPL in the Mock Scanner + MRI Noise condition compared to both the Upright condition (Mean difference = 8.086, 95% CI [4.914, 11.258], $p = 0.000003$*) and the Mock Scanner + No Noise condition (Mean difference = 4.417, 95% CI [1.245, 7.589], $p = 0.007$*). However, in this case, voice SPL during the Mock Scanner + No Noise condition was significantly greater than voice SPL during the Upright condition (Mean difference = 3.669, 95% CI [4.97, 11.258], $p = 0.024$*, **Figure 13**). The observed and adjusted SPL means by medication state are reported in **Table X**.

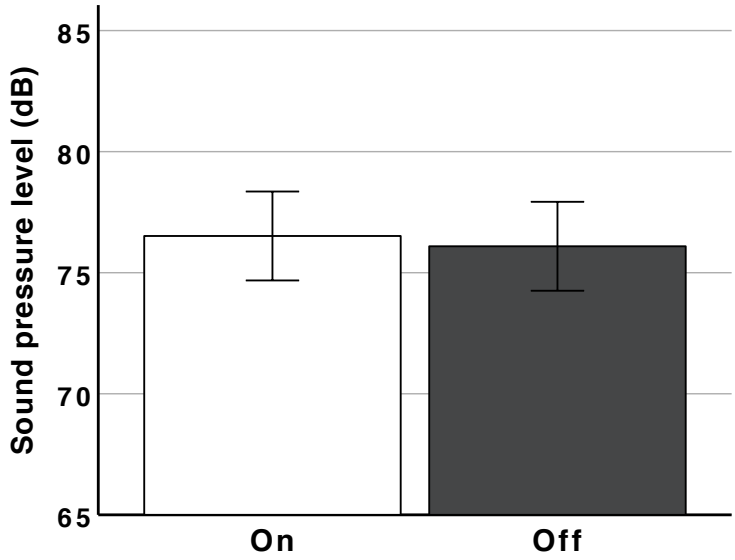

Figure 12. Comparison of vowel intensity (voice dB SPL) between ON and OFF medication status, collapsed across recording conditions. Sound pressure level reflects the estimated marginal means, adjusted for age (centered at 63.69) and hearing threshold (centered at 22.18). Error bars represent +/- 2 standard error. *$p < 0.05$

Table IX. ANCOVA Results and Descriptive Statistics for Sound Pressure Level by Medication, Collapsed Across Recording Conditions

Group	Sound Pressure Level (dB)				
	Observed mean	SD	Adjusted mean	SE	n
On medication	76.517	7.179	76.517	0.918	39
Off medication	76.092	5.811	76.092	0.918	39

Adjustments based on age mean 63.69 and hearing threshold mean 22.18.

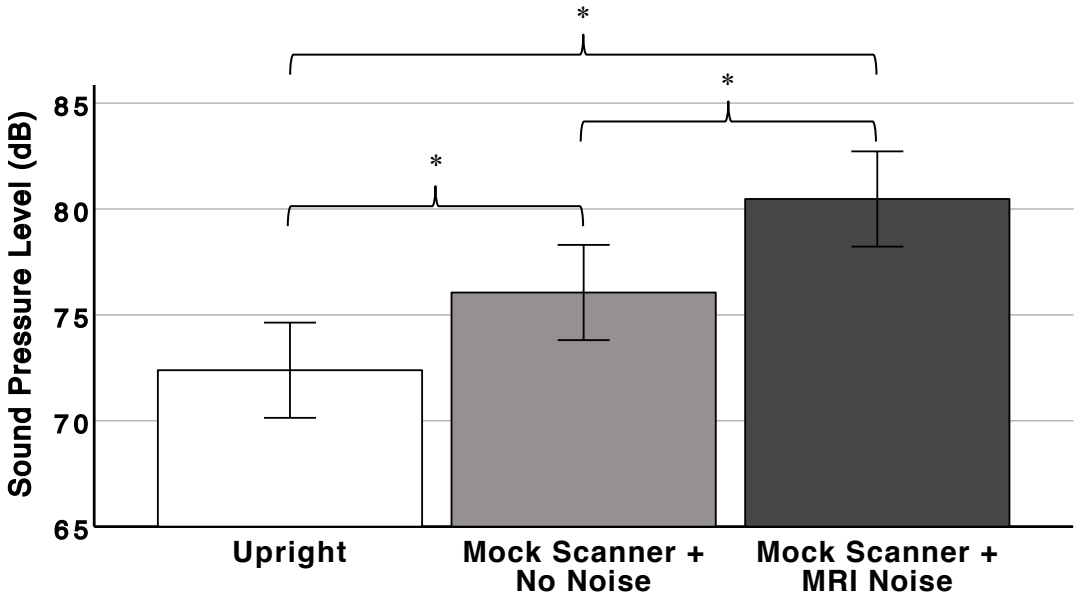

Figure 13. Comparison of vowel intensity (voice dB SPL) between recording conditions (within the PD group). Sound pressure level reflects the estimated marginal means, adjusted for age (centered at 63.69) and hearing threshold (centered at 22.18). Error bars represent +/-2 standard error. *$p < 0.05$

Table X. ANCOVA Results and Descriptive Statistics for Sound Pressure Level by Condition, Within the PD Group

Recording Condition	Sound Pressure Level (dB)				
	Observed mean	SD	Adjusted mean	SE	n
Upright	72.386	4.688	72.386	1.125	26
Mock Scanner + No Noise	76.055	5.829	76.055	1.125	26
Mock Scanner + MRI Noise	80.472	6.305	80.472	1.125	26

Adjustments based on age mean 63.69 and hearing threshold mean 22.18.

3.5 DISCUSSION

There were four major findings in this study. First, we found a significant main effect for group, which demonstrated that the sustained vowel intensity produced by the PD group was significantly lower than that of the OHC group. Second, we found a significant main effect for recording condition, which demonstrated that sustained vowel intensity was significantly louder in the Mock Scanner + MRI Noise condition compared to both the Upright and Mock Scanner + No Noise Conditions. Third, we did not observe any group*condition interaction effects, suggesting that the effects of different scanning environments were consistent across both groups. Fourth, there were no differences in voice intensity across the three recording conditions when PD participants were tested on- versus off-medication.

With respect to our first finding, we observed lower voice intensity in the PD group, as expected. While differences between PD and OHC voice intensity have been demonstrated using loud sustained vowels (De Keyser et al., 2016), sustained vowels tasks performed at a habitual volume have not been widely used for differentiating voice intensity between these two groups. The ability to detect such differences in intensity using this type of simple, quasi-speech task is encouraging for fMRI studies as it requires minimal movement of the lips and jaw, thereby reducing the likelihood of excessive head motion in the scanner.

Regarding our second finding, this study is the first to explicitly examine how the Lombard effect impacts voice intensity when translated into the fMRI environment. Our findings mirror those observed in the traditional upright recording environment, with the addition of fMRI background noise leading to increased voice intensity in both PD and OHC populations (Scott G Adams et al., 2006; Scott G Adams et al., 2005; S. G. Adams et al., 2006; Dykstra et al., 2012b). The effects observed during our fMRI simulation suggest that performing speech tasks during continuous fMRI scanning will cause individuals to vocalize at a significantly greater intensity compared to performance during sparsely sampled fMRI

scans or performance outside of the scanner. The effects of background noise during continuous scanning could have implications for the interpretation of fMRI results, as one may observe neural processes related to this adaptation in addition to any effects of interest. Sparsely sampled fMRI experiments may help alleviate these effects and presumably provide a more ecologically valid representation of vocal performance. However, it is important to note that we did observe a significant difference in voice intensity between the Mock Scanner + No Noise condition and Upright condition in our medication*condition analysis within the PD group. These differences could reflect the change in body position or possible dampening effects of over-the-ear headphones. It therefore merits some degree of caution when inferring whether voice production during sparsely-sampled fMRI is an accurate representation of typical voice production outside of the scanner, particularly in clinical populations.

With respect to our third finding, absence of a significant group*condition interaction effect demonstrates that the fMRI simulation conditions had similar effects on our PD and OHC groups. The absence of an interaction effect is somewhat surprising given the known respiratory deficits in PD (Hovestadt et al., 1989; Huber & Darling-White, 2017; Huber et al., 2003; Sabate et al., 1996; Solomon & Hixon, 1993) and higher respiratory demand required for supine speech breathing (Hoit, 1995). One possible reason for this is that the PD participants in this study were largely in the early-mid stages of the disease and may have experienced less rigidity and weakness within the respiratory apparatus. In a longitudinal study of speech breathing, Huber and Darling-White (2017) found that individuals with PD had comparable lung volume initiations and terminations to controls at baseline, but later deviated as the disease progressed. It is therefore possible that group*condition interactions would be found when examining individuals with PD at later stages of the disease. Another possibility is that individuals with PD are able to successfully adapt to the change in body position by employing additional respiratory or laryngeal strategies to achieve the desired vocal intensity (Stathopoulos et al., 2014). By contrast, the comparable response to MRI noise between PD and OHC groups is consistent with prior studies of the

Lombard effect, which showed parallel responses to background noise in PD and OHC groups (Scott G Adams et al., 2006; Scott G Adams et al., 2005; S. G. Adams et al., 2006; Dykstra et al., 2012b). While continuous fMRI scanning may influence vocal intensity during voice production tasks, the effects appear to be comparable between OHC and PD groups. Based on the present findings, the effects of the fMRI environment do not appear to have a meaningful influence on the interpretation of between-group comparisons in these populations. However, it will be important to extend these findings to individuals who are in the later stages of PD and to directly examine respiratory as well as laryngeal strategies for supine speech production.

Regarding our fourth finding, we did not find a main effect of PD medication on vowel intensity in the PD group. This is consistent with prior studies showing that voice intensity is unresponsive to dopaminergic stimulation (Daniels et al., 1996; Fabbri et al., 2017; Kompoliti et al., 2000; Skodda et al., 2010). There was also no interaction effect between medication status and recording condition. Thus, any effects of the fMRI recording environment on vowel intensity were comparable regardless of medication status. It should be noted that the results of our medication analysis come with two important limitations. First, the Day 1 speech measures were collected during the afternoon, while Day 2 measures were collected in the morning after overnight medication withdrawal. Thus, there is a possibility of diurnal differences between the two testing sessions. Second, we did not evaluate MDS-UPDRS Part III scores during both on and off medication states, so we could not confirm whether motor function did in fact decrease after medication withdrawal.

This study provides an intriguing look into changes in voice production within an analogous fMRI environment. Still, it is important to note the degree to which these findings may or may not generalize to other studies. For instance, this study specifically focused on measures of voice intensity. It is possible that other acoustic measures might respond differently to changes in background noise or body position. Further, the study focused exclusively on voice intensity during vowel production and did not

examine the effects of fMRI on voice intensity during connected speech tasks (e.g., reading or conversational tasks). As studies observing the Lombard effect have been conducted using overt word production (Junqua, 1993; Van Summers, Pisoni, Bernacki, Pedlow, & Stokes, 1988), sentence reading (Arciuli, Simpson, Vogel, & Ballard, 2014; Castellanos, Benedí, & Casacuberta, 1996; Darling & Huber, 2011), passage reading (Sadagopan & Huber, 2007; Vogel, Fletcher, & Maruff, 2014), and conversational interactions (Garnier et al., 2010; Patel & Schell, 2008; Stathopoulos et al., 2014; Vogel et al., 2014) it is likely that the presence of MRI noise would lead to increased voice intensity during these tasks as well. Finally, the present study focused on two specific populations of interest – individuals with PD and hypophonia and older healthy adults. The documentation of Lombard effect in younger healthy adults would suggest that comparable effects would be seen in typical speakers of a younger age (Garnier et al., 2010; Lane & Tranel, 1971). However, it is unknown whether the effects of scanning environment may have a different effect on other clinical populations. This may be especially important in populations, such as stuttering, in which altered auditory feedback is known to impact behavior (M. R. Adams & Hutchinson, 1974; M. R. Adams & Moore, 1972; Wingate, 1970). Investigating the influence of fMRI scanning environment across different acoustic measures, tasks, and populations would be a useful extension of the present research.

In sum, the present study suggests that the effects of scanning environment should be taken into consideration when conducting speech or voice production tasks during fMRI experiments, as such conditions can lead to increased voice intensity in the scanner. Collecting voice recordings in a simulated fMRI environment could provide a more ecologically valid estimate of speech behavior during fMRI experiments and provide information as to whether behavioral performance in the scanner is comparable to an individual's typical performance when upright and out of the scanner. Quantification of these effects may prove to be useful covariates for later fMRI analyses, particularly when continuous scanning protocols are used. The use of sparsely sampled fMRI experiments could help to mitigate the confounding

effects of scanner noise on vocal intensity. However, we suggest that researchers use caution when interpreting behavior during sparsely sampled scans as analogous to performance outside of the scanner, as elevated voice intensity may also be present within a sparsely sampled fMRI environment. Taken together, our results stress the importance of understanding how behavior during out-of-scanner tasks translates to behavior within the fMRI scanning environment.

CHAPTER 4

Motor cortical activity during sustained vowel production in individuals with Parkinson's disease who have hypophonia

Jordan L. Manes[1], Ajay S. Kurani[2], Ellen Herschel[1], Angela Roberts[3], Todd Parrish[2], Kris Tjaden[4], Tanya Simuni[5,6], Daniel M. Corcos[1]

[1]Department of Physical Therapy and Human Movement Sciences, Northwestern University, Chicago, IL, USA

[3]Department of Radiology, Northwestern University, Chicago, IL

[3]Roxelyn and Richard Pepper Department of Communication Sciences and Disorders, Northwestern University, Evanston, IL

[4]Department of Communication Disorders and Sciences, University at Buffalo, Buffalo, NY

[5]Ken and Ruth Davee Department of Neurology, Northwestern University, Chicago, IL

[6] The Parkinson's Disease and Movement Disorders Clinic, Northwestern University, Chicago, IL

4.1 ABSTRACT

Hypophonia, or “soft speech”, is a common feature of Parkinson’s disease (PD) and is characterized by reduced vocal intensity. The contribution of the motor cortical activity to reduced vocal intensity in PD is not clear. Functional imaging studies of speech production in PD have mixed results when using word and sentence production tasks – with some reporting hypoactivation in the motor cortices and others reporting hyperactivation. In this study, we employed a sustained vowel production task during functional magnetic resonance imaging to compare brain activity between individuals with PD and hypophonia and older healthy controls (OHC). When comparing active vowel production (/a/) versus fixation rest, the PD group showed fewer active brain regions compared to the OHC group. With respect to motor cortical activity, both OHC and PD groups showed bilateral activation of the laryngeal/phonatory area of the primary motor cortex (LPA) as well as activation of the supplementary motor area. Of note, the OHC group recruited activity in the bilateral trunk motor area and right dorsal premotor cortex (PMd), which was not found in the PD group. Further, activity in the right PMd was significantly lower in the PD group compared to OHC ($p < 0.001$, uncorrected). We then correlated right PMd activity with maximum phonation time, as well as voice sound pressure level measures taken from the same sustained vowel production task performed in a simulated fMRI environment. Right PMd was not significantly correlated with sound pressure level in either the OHC or PD group. However, maximum phonation time was positively correlated with right PMd activity in the PD group ($r = 0.612$, $p = 0.026$). While there were no statistically significant group differences in the activity of the LPA, the peak regions of LPA activity in OHC and PD groups were spatially localized to different areas of the precentral gyrus. A cluster extent analysis showed that the cluster size was not significantly different between the two groups, despite the difference in peak location. Together, these results suggest that sustained vowel production in PD hypophonia involves functional changes in the right LPA and dorsal premotor cortices.

4.2 INTRODUCTION

The majority of individuals with Parkinson's disease (PD) experience adverse changes to their speech and voice at some point throughout the disease course (Sapir, 2014). The constellation of motor speech symptoms in PD, referred to collectively as "hypokinetic dysarthria", include monopitch, monoloudness, reduced stress, imprecise consonants, inappropriate silences, short rushes of speech, harsh voice, breathy voice, low pitch, and variable rate. Among the most prevalent changes to the parkinsonian voice is the development of hypophonia – a condition characterized by reduced loudness or "soft speech" (Duffy, 2013). The physiology of hypophonia includes deficits in both laryngeal function and respiratory support for speech breathing (Hammer, 2013; Huber & Darling-White, 2017; Huber et al., 2003; Solomon & Hixon, 1993). However, at the cortical level, it is not clear how reduced vocal intensity relates to changes in the activity of the motor cortices (i.e., primary motor cortex, premotor cortex, and SMA). The reduction of vocal intensity in hypophonia appears to mirror the hypokinesia (reduced movement amplitude) observed in PD limb movements, and may reflect scaling deficits seen in PD (Sapir, 2014). According to the classic rate model of PD, hypokinetic and bradykinetic movements arise from reduced thalamocortical excitation of the motor cortices following the degeneration of dopaminergic cells in the substantia nigra pars compacta and subsequent dysregulation of the cortico-basal ganglia pathways. Thus, if the reduced vocal amplitude observed in hypophonia is indeed hypokinetic in nature, it should follow that motor cortical activity is hypoactive during phonation.

Neuroimaging studies of speech production in PD have reported mixed findings with respect to motor cortical activation, making it difficult to discern whether reduced vocal intensity is explicitly linked to reduced activity in the motor cortices. During speech production tasks, studies of PD speech have shown disease related changes in the activity of primary motor cortex, premotor cortex, and supplementary motor area (SMA). However, the directionality of these differences has varied across

studies. Within the primary motor cortex, both instances of hypoactivation (Narayana et al., 2020; Pinto, Thobois, et al., 2004) and hyperactivation (Rektorova et al., 2007) have been observed in PD during overt speech production. Similarly, both hypoactivation (Narayana et al., 2020) and hyperactivation (Arnold et al., 2014; Pinto et al., 2011) has been reported in the left dorsal premotor cortex (PMd). In the supplementary motor area (SMA), some studies of PD speech production have reported hypoactivation of SMA (Baumann et al., 2018; Rektorova et al., 2007), while others have reported no differences in SMA activity between PD and healthy control groups (Arnold et al., 2014; Narayana et al., 2020; Pinto et al., 2011).

Mixed reports of hypoactivity and hyperactivity in the motor cortices are also seen in PD during volitional hand movements, and researchers have provided a few possible explanations for this discrepancy. One hypothesis is that hypoactivation is related to initial deafferentation of the cortex, while hyperactivation acts as a subsequent compensatory mechanism (Tessa et al., 2010). Another hypothesis is that the directionality of change in motor cortical activation is related to specific PD phenotypes. A study by Yu et al. (2007) found that hyperactivity in the sensorimotor cortex during hand movements was positively correlated with rigidity scores in individuals with akinetic-rigid PD. This is in line with other studies suggesting that rigidity is linked to hyperactivity in the primary motor cortex (Cantello et al., 1991; Cantello et al., 1995; Lefaucheur, 2005). By contrast, hypoactivity in the motor cortices (particularly SMA) may be related to hypokinetic and bradykinetic features of PD (Ellaway et al., 1995; Lefaucheur, 2005; Obeso et al., 2008), in line with the classic rate model of PD. Finally, motor cortical activity in PD may depend on the task employed (Catalan, Ishii, Honda, Samii, & Hallett, 1999; Turner, Grafton, McIntosh, DeLong, & Hoffman, 2003) and the degree to which it engages the specific motor features of interest (e.g., using movement speed tasks to probe bradykinesia).

Employing a task that is specifically phonatory in nature may help to establish whether hypophonia is related to hypoactivation in the motor cortices. The existing imaging literature on PD

speech has focused more broadly on speech production using overt sentence reading (Arnold et al., 2014; Rektorova et al., 2007), covert sentence reading (Baumann et al., 2018), and word production (Pinto et al., 2011) tasks. However, speech production tasks in healthy adults have been shown to recruit additional regions of the cortex that are not found during vowel production alone (Ozdemir, Norton, & Schlaug, 2006).While sentence production tasks may provide a more global picture of hypokinetic dysarthria in PD, they may not be sufficient to differentiate speech characteristics with different physiological mechanisms (e.g., speech characteristics related to rigidity versus those related to bradykinesia). Using a phonatory task, such as vowel production, can help to disentangle mechanisms of hypophonia from speech characteristics with other physiological origins.

In healthy adults, fMRI studies of vowel production/phonation have shown activity in primary motor cortex (Brown, Ngan, & Liotti, 2008; Grabski et al., 2013; Ozdemir et al., 2006; Soros et al., 2006), premotor cortex (Brown et al., 2008; Grabski et al., 2013), and SMA (Brown et al., 2008; Grabski et al., 2013; Soros et al., 2006). In the primary motor cortex, phonation is typically linked to the bilateral activation of the laryngeal/phonatory area (LPA). This is located towards the middle/inferior region of the precentral gyrus and includes two peaks of activation - the dorsolateral LPA and the ventromedial LPA (Brown et al., 2008). In addition to the LPA, a study by Correia et al. (2020) found additional bilateral activation in the trunk motor area when comparing voiced versus voiceless utterances. The authors proposed that activation of the trunk motor area was linked to the use of trunk muscles for respiratory control during phonation.

In addition to the height of activation in the motor cortices, it is worth considering whether the spatial representation of the LPA is altered in those with PD hypophonia. A recent article by Chen et al. (2020) found that the severity of dysarthria in PD was predicted by cortical atrophy in right orofacial motor cortex. Changes in the brain morphology of right primary motor cortex could lead to functional reorganization in the LPA. Indeed, changes in the spatial representation of hand motor cortex have been

previously noted in PD using transcranial magnetic stimulation, and the degree of displacement was shown to correlate with severity of PD (Thickbroom, Byrnes, Walters, Stell, & Mastaglia, 2006). It is possible that spatial representation of right LPA is similarly displaced in those with PD hypophonia.

The purpose of this study was to 1) characterize the BOLD responses of older healthy controls (OHC) and PD patients with hypophonia as they perform a sustained vowel task, 2) determine whether activity in the motor cortices is hypoactive during sustained vowel production in PD patients with hypophonia, 3) examine whether changes in motor cortical activity correlate with voice intensity or with maximum phonation time, and 4) examine whether PD hypophonia is linked to changes in the spatial representation of the LPA. To accomplish this, we recruited a group of OHC participants and a group of PD participants with hypophonia to perform a sustained vowel production task while undergoing fMRI. In order to obtain high fidelity measures of voice intensity, participants also performed the same vowel production task outside of the scanner in a simulated MRI environment. We hypothesized individuals with PD and hypophonia would have significantly lower activity in the LPA, SMA, and premotor cortex compared to age-matched healthy controls and that both voice intensity and maximum phonation time would be positively correlated with activation in the LPA. Based on prior work linking dysarthria severity in PD morphological changes in right motor cortex (Y. Chen et al., 2020), we further hypothesized that the spatial representation of right LPA would differ between OHC and PD groups.

4.3 MATERIALS AND METHODS

4.3.1 Participants

The sample of individuals who participated in the study for Chapter 3 of this dissertation also participated in the present imaging experiment. Of the initial 15 OHC and 15 PD participants recruited, 3 were excluded for poor fMRI data quality. One OHC participant was excluded due to the presence of a magnetic susceptibility artifact on the scalp. Two PD participants were excluded due excessive head movement (see quality assurance criteria below). The remaining 14 OHC and 13 PD participants were included in the final analysis. All participants were right-handed, native English speakers between 40-80 years old with a score of either ≥26 on the Montreal Cognitive Assessment (MoCA) or ≥18 on the MoCA-Blind (if screened over the phone). Participants were excluded if they reported moderate to severe hearing loss. Healthy control participants reported no history of neurological disorders or speech disorders. All participants with PD were judged to have hypophonia by their referring movement disorders neurologist or by a trained researcher. None of the PD participants had completed the full Lee Silverman Voice Treatment ® (LSVT) program within the past two years. PD disease severity ranged from mild to moderate (Hoehn and Yahr Stage 1-3), and all PD participants were currently taking antiparkinsonian medication. Characteristics of the OHC and PD groups are shown in **Table XI**. There were no statistically significant group differences in age, sex, hearing threshold (bilateral pure tone average threshold of 0.5, 1, and 2 kHz), or cognition (defined by scores on the Mattis Dementia Rating Scale 2 (DRS-2)). Disease characteristics for the PD group are reported in **Table XII**.

Table XI. Participant characteristics for OHC and PD groups.

Variable	OHC (n = 14)	PDH (n = 13)	p-value (OHC vs. PD)
Age			0.663
Mean	61.07	62.23	
(Min, Max)	(42, 71)	(49, 78)	
Sex			0.861[†]
Male	10 (71.4%)	9 (69.2%)	
Female	4 (28.6%)	4 (30.8%)	
DRS-2			0.881
Mean	141.43	140.62	
(Min, Max)	(138, 144)	(138, 144)	
Hearing Threshold			0.246
Mean db SPL	17.44	21.41	
(Min, Max)	(7, 35)	(10, 31.67)	

[†]*Chi-squared test for independence*
Abbreviations: DRS-2, Mattis Dementia Rating Scale 2, CPIB, Communication Participation Item Bank

Table XII. Parkinson's disease characteristics for PD participants

MDS-UPDRS	
MDS-UPDRS Total Score	57.54
MDS-UPDRS Part I	8.92
MDS-UPDRS Part II	12.69
MDS-UPDRS Part III (Motor Exam)	33.92
MDS-UPDRS Part III (Speech Item)	1.23
MDS-UPDRS Part IV	2.00
Hoehn & Yahr	
Stage 0	0 (0.0%)
Stage 1	1 (7.7%)
Stage 2	11 (84.6%)
Stage 3-5	1 (7.7%)
TD/PIGD Classification	
TD	4 (30.8%)
PIGD	7 (53.8%)
Indeterminate	2 (15.4%)
Side Most Affected	
Left	8 (61.5%)
Right	5 (38.5%)
Symmetric	0 (0.0%)
LEDD (mg)	
Mean	747.92
(Min, Max)	(120,1563)
CPIB	
Mean	22.38
(Min, Max)	(14,30)

Abbreviations: MDS-UPDRS, Movement Disorders Society Unified Parkinson's Disease Rating Scale, TD, tremor dominant, PIGD, postural instability and gait disturbance, LEDD, levodopa equivalent daily dose, CPIB, Communicative Participation Item Bank

4.3.2 Procedure

All testing was performed at Northwestern University's Center for Translational Imaging. Informed consent was obtained in accordance with Northwestern University's guidelines. Participants were given a

hearing test (Oscilla SM910-B), so that a measure of hearing threshold could be used as a covariate in the statistical analysis.

In order to test the hypothesis that motor cortical activity is reduced in PD participants with hypophonia, we collected fMRI data while participants performed a sustained vowel production task.

To test our hypothesis that voice intensity would correlate with fMRI activity in laryngeal motor cortex, participants performed the same sustained vowel production task outside of the scanner in a simulated fMRI environment. This was done in order to obtain high fidelity audio recordings in an ecologically similar environment, which could be used to obtain voice SPL measurements. The order of fMRI and speech testing was counterbalanced to control for the effects of vocal fatigue.

Testing for HC subjects was conducted during a single study visit. Testing for PD participants was broken up into 2 days. Day 1 testing was conducted while participants were on their typical PD medication, while Day 2 testing was conducted following overnight medication withdrawal. On Day 1, PD patients were administered the hearing test, DRS-2, demographics survey, CPIB, and the MDS-UPDRS Parts I, II, and IV. After completing Day 1 testing, PD participants were asked to withhold their medication beginning at 8:30 PM for off-medication testing on Day 2. On Day 2, participants completed the sustained vowel task, MDS-UPDRS Part III motor testing, and fMRI testing while off medication.

4.3.3 Sustained vowel production task

The sustained vowel task was identical to the task used in Chapter 3 of this dissertation. The task was performed both in the scanner during fMRI testing as well as outside of the scanner in a mock MRI

scanner (see below). The task consisted of ten vowel production blocks (30s each) and ten rest blocks (30s each). During the task, participants were presented with either a "+" symbol (Rest) or "Ah" (Vowel Production). During the "Ah" blocks, subjects were instructed to produce an /a/ vowel for approximately 3-5 seconds at their normal conversational loudness and repeat for the duration of the block. We instructed the participants to keep their mouths slightly open through the duration of the task to try to limit movement of the head and jaw when vocalizing. This self-paced paradigm was designed so that participants would rely on internal, rather than external cueing mechanisms for the initiation of each utterance.

4.3.4 Mock MRI Scanner

In order to collect samples of vowel production that would mirror performance in the MRI scanner as closely as possible, participants performed the sustained vowel production task while laying supine in a mock MRI scanner while MRI sounds were delivered via over-the-ear headphones. This reflects a subset of the data previously reported in Chapter 3 of this dissertation - specifically SPL measures collected during the Mock Scanner + MRI Noise condition on Day 2 (off medication). To account for inter-subject differences in Lombard responses during fMRI, we also calculated difference in voice SPL between the Mock Scanner + MRI Noise and Upright conditions reported in Chapter 3. This Lombard response measure was then entered as a covariate in the fMRI analysis.

4.3.5 Statistical analysis of voice SPL and maximum phonation time

Our out-of-scanner behavioral measures included 1) voice SPL during the sustained vowel production task in the mock scanner, and 2) maximum phonation time (seconds). To extract voice SPL during the

sustained vowel production task, we applied the same two-step calibration procedures as reported in Chapter 3 (Svec & Granqvist, 2018). We considered only vowels of 0.5 seconds duration or longer to eliminate any vowels that ended prematurely due the coughing, throat clearing, or the end of the stimulus block. Voice SPL was analyzed using one-way analysis of covariance (ANCOVA), with group defined as a fixed factor and age and hearing threshold defined as covariates. For maximum phonation time, participants were instructed to sustain an /a/ vowel for as long as possible in their normal conversational loudness. Maximum phonation time was also analyzed using a one-way ANCOVA, with group defined as a fixed factor and age and hearing threshold defined as covariates.

4.3.6 Image acquisition

Imaging data were collected on a Siemens 3T PRISMA MRI scanner using a 64-channel head coil. T1-weighted anatomical scans were collected in the sagittal plane using an MPRAGE GRAPPA sequence at a voxel resolution of $0.8mm^3$ (TR = 2000ms, TE = 2.99ms, flip angle = 8°, FOV = 256mm). BOLD T2*-weighted functional scans were collected in 56 interleaved slices using a multiband acceleration factor of 2 and voxel size of 2x2x2 mm (TR = 2000ms, TE = 25 ms, flip angle = 80°, FOV = 208mm). The sustained vowel production task was presented over a computer monitor using E-Prime and viewed through an angled mirror mounted to the head coil. An MRI compatible microphone was mounted to the head coil and positioned ~1 cm from the lower lip. These microphone recordings were collected to monitor task compliance and to record the timing of self-paced vowel productions for later fMRI analysis.

4.3.7 Quality Assurance Criteria

To be included in our statistical analysis, we required that at least 7 minutes (210 time points) of each

fMRI scan had a framewise displacement (FD) < 0.5 and DVARS < 5%.

4.3.8 Preprocessing of fMRI data

All fMRI data was processed and analyzed using a SPM12 and AFNI tools. Functional images underwent initial despiking, B0 distortion correction, and realignment to the first time point. During realignment, 6 motion parameters were extracted. Additional motion correction was applied using the ART Repair Toolbox version 5b in SPM12 (https://cibsr.stanford.edu/tools/human-brain-project/artrepair-software.html). Volumes were censored using linear interpolation if the framewise displacement (FD) was greater than 0.5 mm. Functional images were then smoothed using a gaussian kernel (full-width-half maximum of 6mm).

Subject-level analysis of BOLD fMRI data was conducted in subject-space using a general linear model (GLM) in SPM12 before being normalized to MNI space for group-level statistical analysis. To do this, we extracted the timing and duration of each self-paced vowel-production using noise-attenuated, in-scanner microphone recordings. We then analyzed the data in a block design, with the block onset starting at the initiation of the first vocalization and ending at the end of the last vocalization. The subject-level GLM included the block timing and 6 motion parameters, with global normalization scaling applied. The first-level statistical results (Ah vs. Rest) were then normalized to MNI space. To normalize the functional scans to MNI space, the anatomical scans were segmented into gray matter, white matter, and cerebral spinal fluid masks in SPM12 and co-registered to the first volume of the participant's functional scan. The co-registered anatomical images were normalized to the MNI 2009c symmetric template (Fonov, 2009) using combined affine and nonlinear warp transformations in AFNI. This combined transformation was then applied to the deconvolved fMRI data in order to perform group-level statistical

analysis.

4.3.9 Statistical analysis of fMRI data

Group-level statistical analysis was conducted using SPM12. Our model included the covariates of age, hearing threshold, SPL (within group), and Lombard response. A group EPI mask was created to limit the analysis to voxels which shared 90% overlap across subjects. Within each group, we generated task activation maps (Ah vs. Rest) at a height threshold of $p < 0.001$, uncorrected. We then calculated group contrasts (OHC vs. PD) at a height threshold of $p < 0.001$, uncorrected and cluster threshold of $p < 0.05$, uncorrected.

4.3.10 Cluster extent analysis of M1

M1 clusters were restricted within the M1 and premotor boundaries of the Human Motor Area Template (Mayka, Corcos, Leurgans, & Vaillancourt, 2006). We created left and right M1 boundary masks for each group from clusters showing at least 20% overlap across participants ($n \geq 3$). We then combined the OHC and PD masks to create a boundary area for the between-group cluster analysis of left and right M1. For each participant, we counted the number of voxels present in the M1 activation cluster (within the boundary mask). We then performed a one-way ANCOVA on the voxel count with the fixed factor of group and covariates of age and hearing threshold.

4.4 RESULTS

4.4.1 Sustained vowel dB SPL

A one-way ANCOVA showed a trend to a significant effect of group on voice SPL during the sustained vowel task ($F(27) = 3.959$, $p = 0.059$), **Figure 14a.**

4.4.2 Maximum phonation time

A one-way ANCOVA revealed a significant main effect for group on maximum phonation time ($F(27) = 5.604$, $p = 0.027$). Maximum phonation time was significantly lower in the PD group compared to OHC (difference = 4.239, $p = 0.027$), **Figure 14b**.

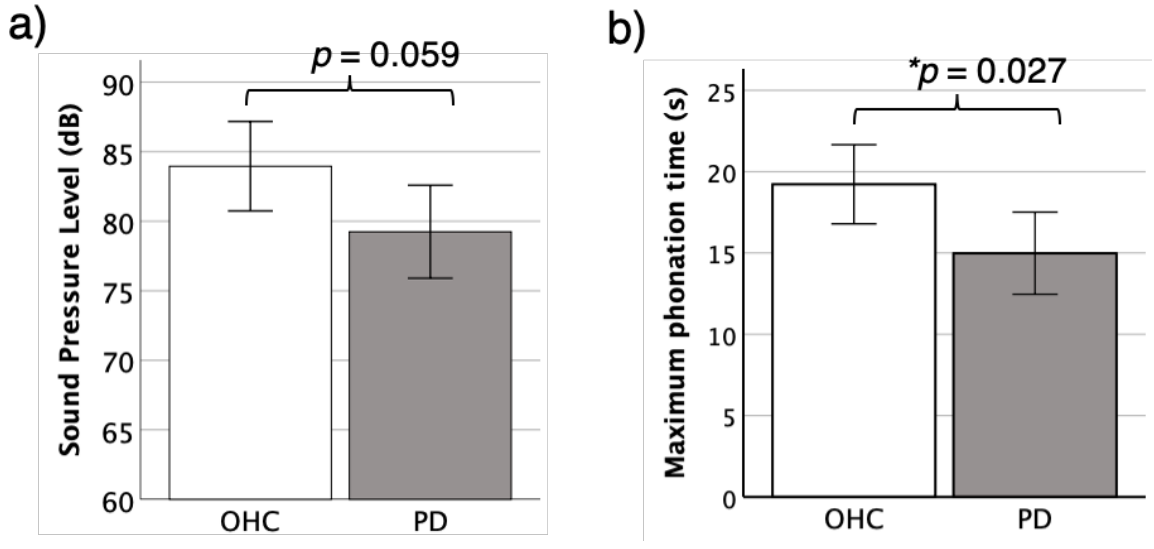

Figure 14. Between-group comparisons of a) sound pressure level during sustained vowel production, and b) maximum phonation time. Error bars represent +/-2 SE. *$p < 0.05$

4.4.3 Task performance inside the scanner

On average, participants in the OHC group sustained /a/ vowels for durations within the target range of 3-5 seconds (mean 3.82 seconds), while participants in the PD group fell short of the target range (mean 2.85 seconds), **Figure 15a**. The duration of vowels produced showed a trend towards a significant difference between the OHC and PD groups ($t = 1.920$, $p = 0.066$). Participants in the PD group produced significantly more vowels than the OHC group (OHC mean: 62.8 vowels, PD mean: 83.2 vowels, $t = -3.71$, $p = 0.026$), **Figure 15b**. Thus, overall, the vowels produced by the PD group tended to be of higher frequency and shorter duration.

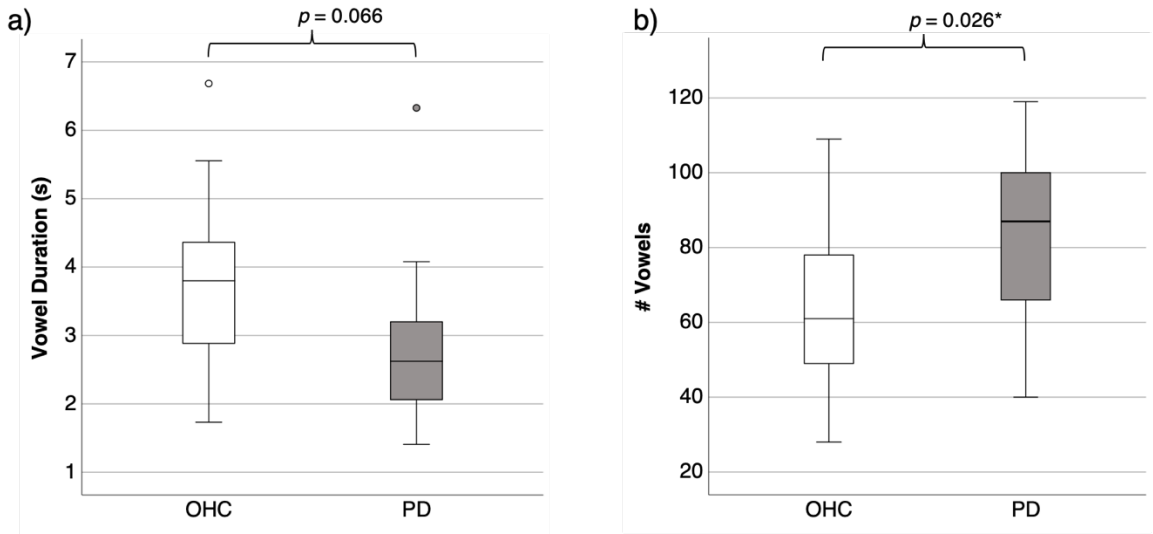

Figure 15. Box plots of vowel durations produced by OHC and PD groups during the fMRI sustained vowel task.

4.4.4 BOLD activity during sustained vowel production

When comparing 'Ah' vs Rest conditions in the OHC group, BOLD activation in the motor cortices was found bilaterally in the LPA of the primary motor cortex (M1) and in the trunk motor area of M1, as well as right SMA and right dorsal premotor cortex (PMd; $p < 0.001$, uncorrected). Activation was also found bilaterally in the cerebellum (VI), caudate, inferior frontal gyrus, and precuneus. In the right hemisphere, BOLD activity was found in superior temporal gyrus, cuneus, medial frontal gyrus, and insula. In the left hemisphere, additional BOLD activations were found in the inferior occipital gyrus and postcentral gyrus. Fewer areas of BOLD activation were in the PD group when comparing 'Ah' vs. Rest conditions. In the motor cortices, BOLD activity for the PD group was found in the bilateral LPA region of M1 and right SMA; however, there was no BOLD activity in the trunk motor area of M1 or in the right PMd ($p < 0.001$, uncorrected). Additional BOLD activations were found in the right cerebellum (VI), right cuneus, left superior temporal gyrus, and left inferior occipital gyrus. Group activation maps for OHC and PD groups are shown in **Figure 16**, and the clusters of activation are reported in **Table XIII**.

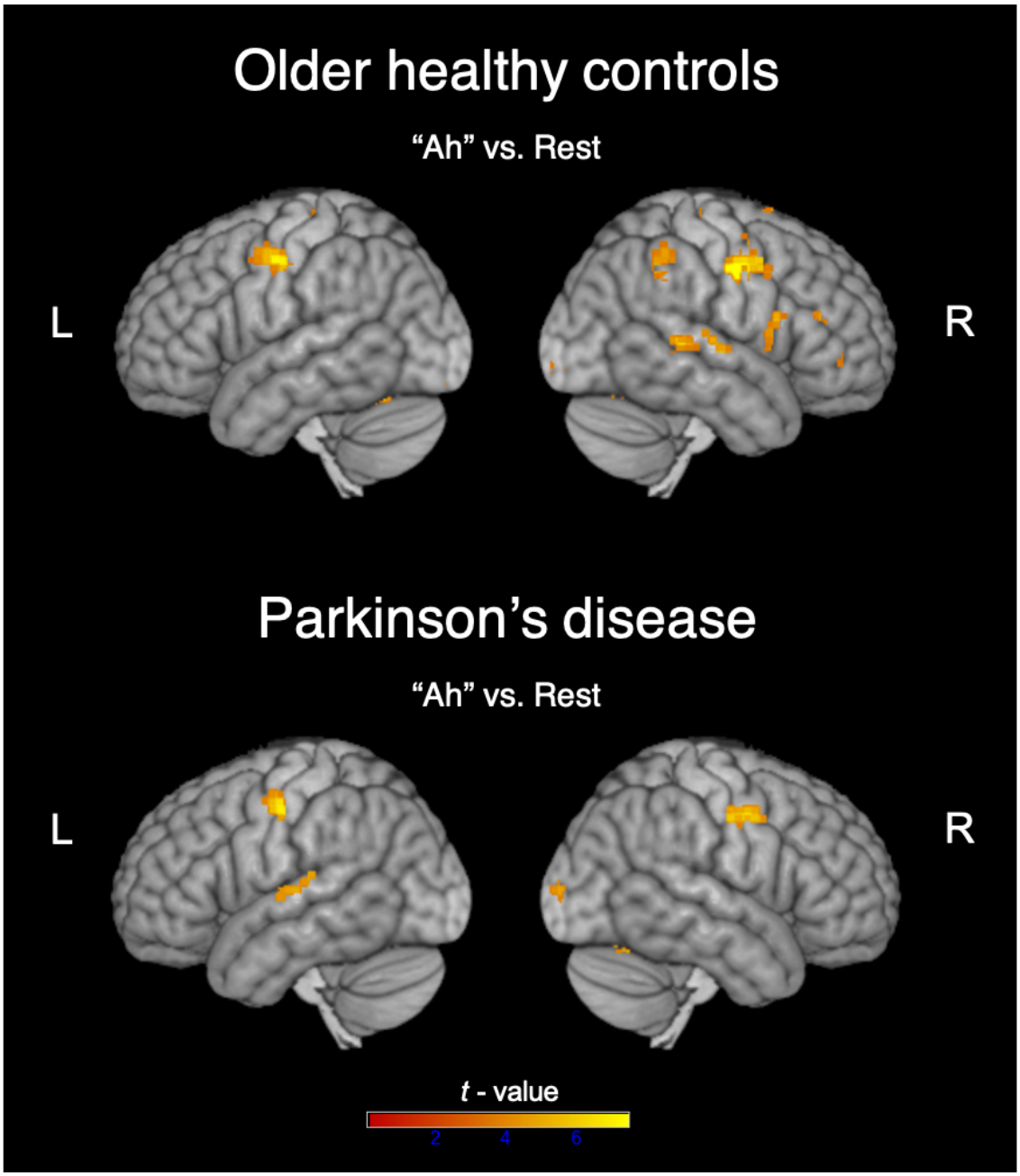

Figure 16. Surface rendering of BOLD activation maps during sustained vowel production for OHC (top) and PD (bottom) groups. ($p < 0.001$, uncorrected).

Table XIII. BOLD activations during sustained vowel production

Comparison	Brain region(s)	BA	Size (voxels)	MNI coordinates (peak)			*t*-value
				x	y	z	
	BOLD activations						
OHC	R Precentral gyrus (M1/LPA)	4/6	215	49	-7	41	8.50
	R Precentral gyrus (M1/TMA)	4/6	80	21	-25	59	7.63
	L Cerebellum VI	-	185	-25	-63	-23	7.55
	L Caudate	-	112	-19	-13	27	7.50
	L Precentral gyrus (M1/LPA)	4/6	182	-51	-9	47	7.22
	R Superior temporal gyrus	22/21	103	65	-35	5	6.56
	R Precuneus	39/7	76	27	-61	35	6.24
	R Cerebellum VI	17/18	205	15	-67	-17	6.13
	R Middle Frontal Gyrus (PMd)	6	101	35	-1	51	5.87
	L Precentral gyrus (M1/TMA)	4	94	-17	-27	59	5.86
	L Inferior occipital gyrus	17/18	62	-17	-91	-13	5.73
	R Caudate	-	70	19	-13	25	5.70
	R Superior temporal gyrus	22/21	55	55	-15	1	5.66
	R Inferior frontal gyrus	44	66	49	13	17	5.63
	R Cuneus	17/18	76	13	-95	-5	5.25
	R Inferior frontal gyrus	46	63	37	33	17	5.19
	R Superior frontal gyrus (SMA)	6	196	7	11	71	5.14
	R Inferior parietal lobule	40	120	49	-47	45	5.06
	R Medial frontal gyrus	8	67	9	17	51	4.59
	R Caudate	-	32	19	31	1	5.31
	L Inferior frontal gyrus	47/45	41	-35	31	5	5.25
	R Insula	13	33	39	19	21	5.16
	L Postcentral gyrus	3	36	-25	-35	57	5.06
	L Precuneus	39	30	-27	-61	35	4.91
PD	R Cerebellum VI	-	56	29	-65	-25	7.39
	L Precentral gyrus (M1/LPA)	4/6	164	-51	-11	47	6.92
	R Precentral gyrus (M1/LPA)	6	156	55	-3	45	6.64
	R Superior frontal gyrus (SMA)	6	91	9	-5	63	5.11
	L Superior temporal gyrus	42	61	-65	-25	13	5.04
	L Inferior occipital gyrus	17/18	53	-17	-91	-11	4.66
	R Cuneus	18	34	21	-97	7	4.82
OHC > PD	R Middle frontal gyrus (PMd)	6	43	37	-1	51	5.28
PD > OHC	-	-	-	-	-	-	-

Height threshold $p < 0.001$, uncorrected; cluster extent threshold $p < 0.05$, uncorrected
Abbreviations: M1, primary motor cortex, LPA, laryngeal/phonatory area, SMA, supplemental motor area; TMA, trunk motor area; PMd, dorsal premotor cortex

4.4.5 Comparison of OHC and PD groups during sustained vowel production

A vowel-wise comparison of OHC and PD groups showed that BOLD activity in right PMd was significantly lower in the PD group ($p < 0.001$, uncorrected), **Figure 17**. There were no regions in which BOLD activity was higher in PD compared to OHC, **Table XIII**.

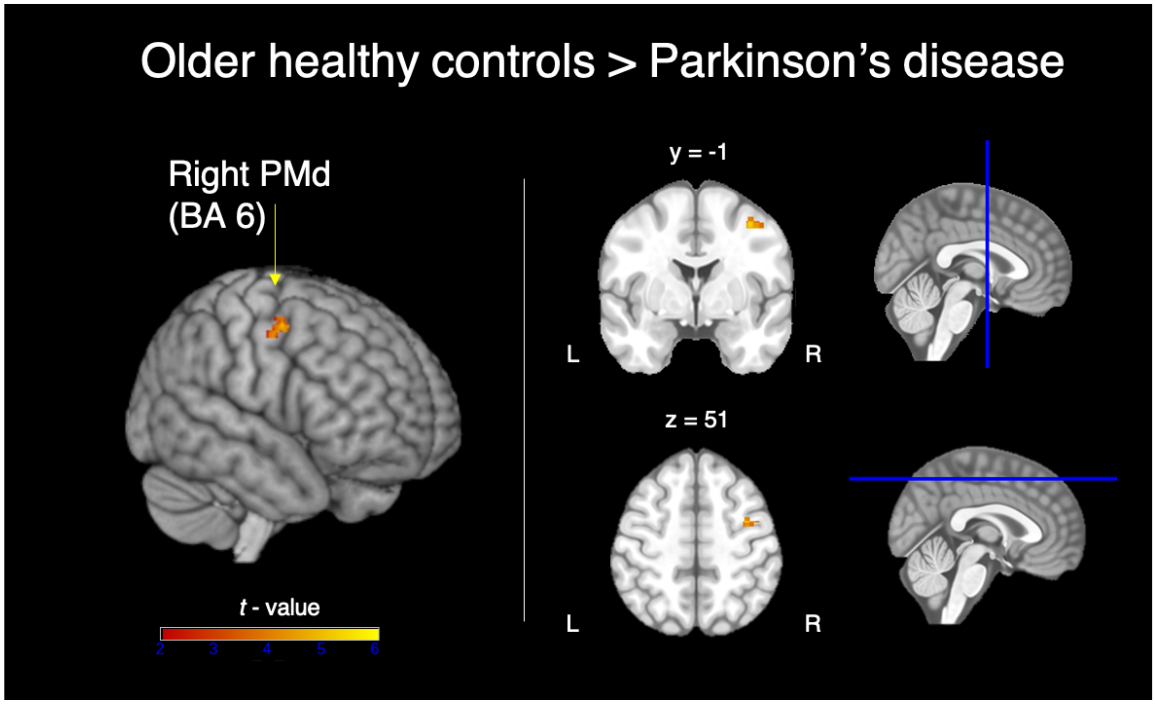

Figure 17. Comparison of BOLD activation maps during sustained vowel production between OHC and PD (height threshold $p < 0.001$, uncorrected; cluster threshold $p < 0.05$, uncorrected). Left: surface rendering of right PMd cluster, search depth of 16mm. Right: right PMd cluster depicted on coronal and axial slices.

4.4.6 PMd correlation with voice SPL and maximum phonation time

We examined behavioral correlations with right PMd by first extracting the mean beta values of right PMd for each participant. Right PMd beta values were then correlated with voice SPL (sustained vowel production in the mock scanner) and with maximum phonation time within each group. We found no significant correlations between right PMd beta values and voice SPL in either the OHC (r = 0.364, p = 0.201) or the PD group (r = -0.409, p = 0.166). Right PMd beta values were not significantly correlated with maximum phonation time in the OHC group (r = 0.181, p = 0.536); however, there was a significant positive correlation between right PMd beta values and maximum phonation time in the PD group (r = 0.612, p = 0.026). Scatter plots depicting the behavioral correlations for OHC and PD groups are depicted in **Figure 18**.

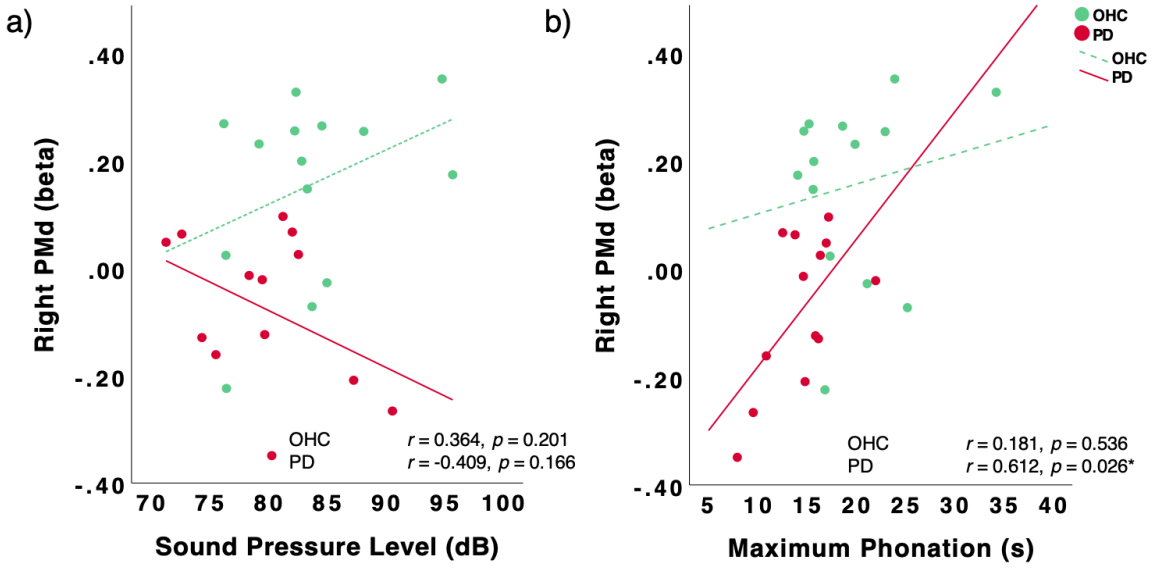

Figure 18. Correlation of right PMd beta values with a) sound pressure level, and b) maximum phonation time. Lines represent the linear fit of data points within each group. Data from the OHC group are plotted in green and data from the PD group are plotted in red. *p < 0.05, uncorrected.

4.4.7 Spatial representation of laryngeal motor cortex

Table XIV depicts the Euclidean distance between OHC and PD peak M1 coordinates as well as the distance between OHC and PD M1 center of mass coordinates. The peak activation coordinates for left M1 were spatially similar between OHC and PD groups. However, in the right M1, the peak activation for the PD group was located more dorsal and anterior compared to the OHC group. The centers of mass for both left and right M1 clusters were relatively similar between the two groups, **Figure 19**.

Table XIV. Distance between OHC and PD peak activation and center of mass coordinates

	OHC	**PD**	**Euclidean distance (mm)**
Peak activation			
Left M1	-51, -9, 47	-51, -11, 47	2.00
Right M1	49, -7, 41	55, -3, 45	8.25
Center of Mass			
Left M1	-50, -10, 44	-49, -9, 46	2.45
Right M1	49, -9, 43	48, -10, 44	1.73

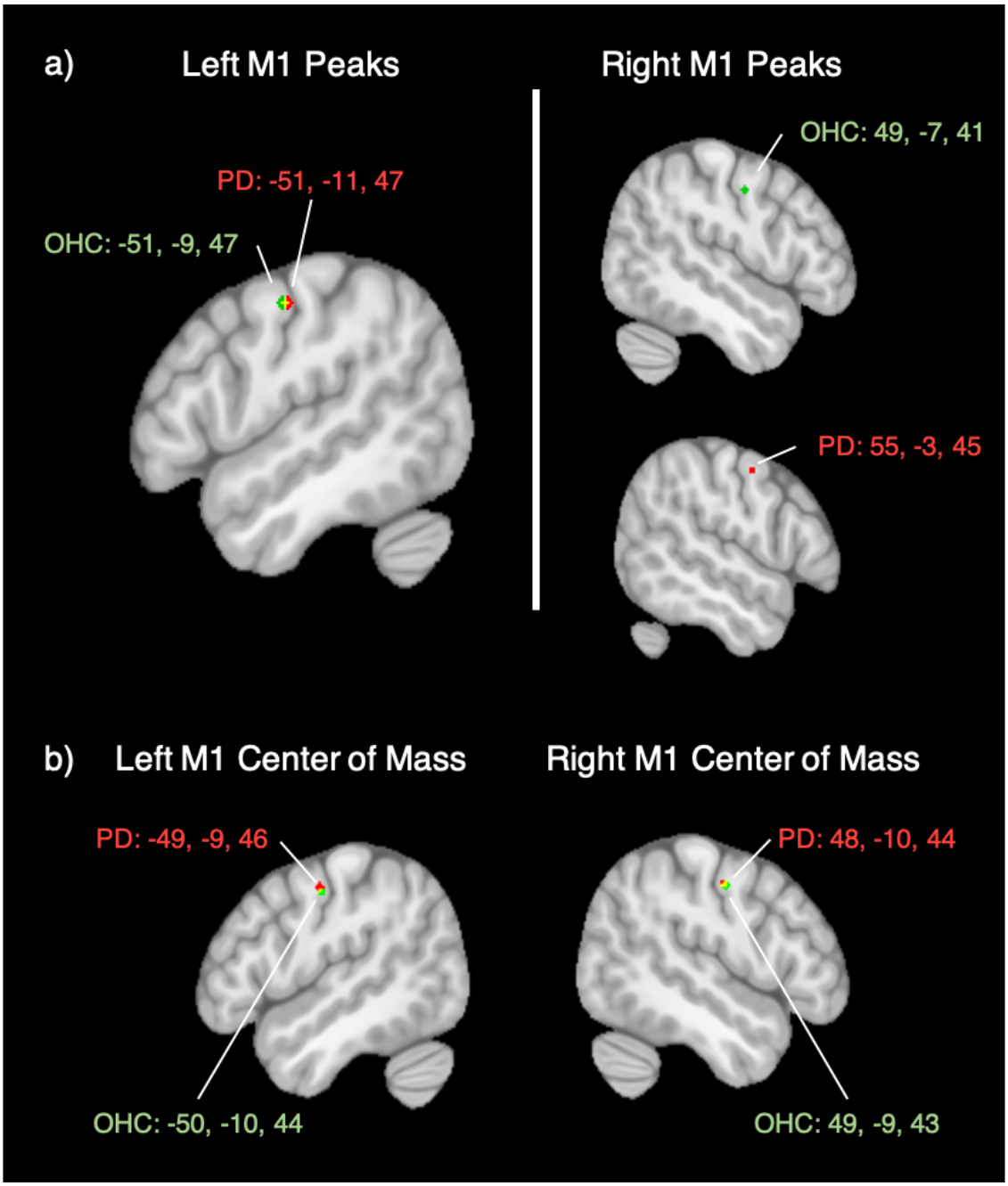

Figure 19. Spatial localization of a) peak left and right M1 coordinates during sustained vowel production, and b) center of mass coordinates of M1 activation during sustained vowel production. Coordinates for the OHC group are depicted in green. Coordinates for the PD group are depicted in red.

4.4.8 Cluster extent analysis of laryngeal motor cortex

Figure 20 depicts the overlap of M1 activation clusters for each participant, at a threshold of $p < 0.05$, FWE corrected. A one-way ANCOVA showed that there was no effect of group on the cluster extent of either left M1 ($F(27) = 0.682$, $p = 0.418$) or right M1 ($F(27) = 0.545$, $p = 0.468$). The comparison of M1 cluster extents are depicted in **Figure 21**.

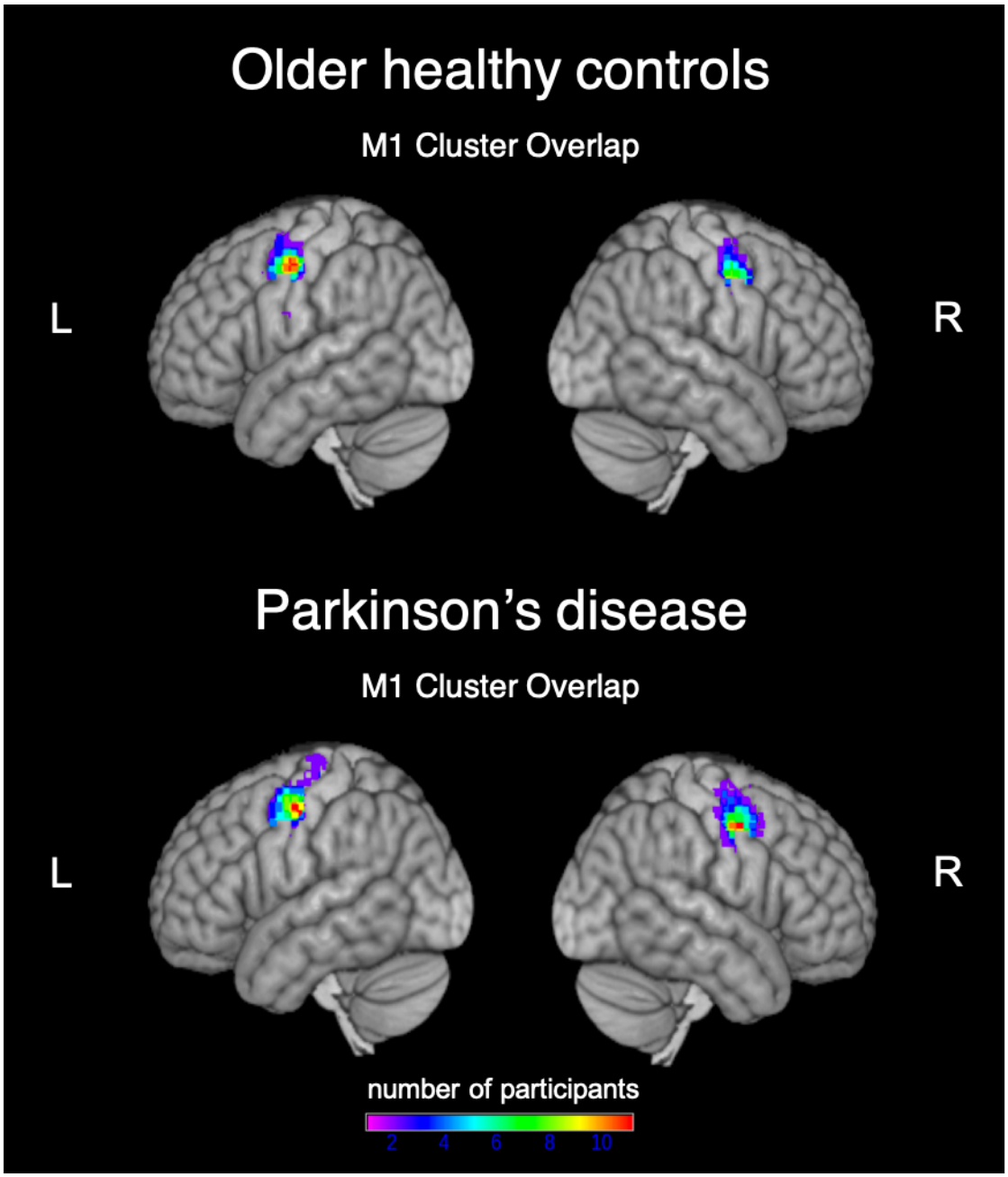

Figure 20. Overlap of M1 activation clusters across participants in OHC and PD groups. Clusters were defined using a height threshold of $p < 0.05$, FWE corrected and restricted to the M1 and premotor boundaries of the HMAT.

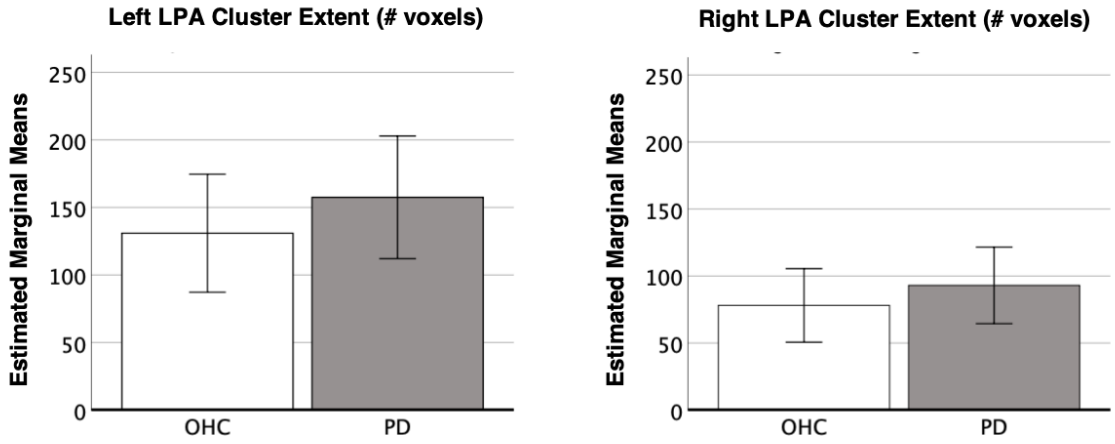

Figure 21. Cluster extent analysis of left and right M1. A one-way ANCOVA revealed no significant group differences in the cluster extent of left M1 or right M1.

4.5 DISCUSSION

The present study can be summarized by four main findings. First, we observed that individuals in the PD group recruited fewer brain regions during the sustained vowel production task compared to the OHC group. Most notably, activations in the bilateral trunk motor area and right PMd were present in the OHC group, but not in PD. Second, we found that BOLD activity in right PMd was significantly lower in the PD group compared to OHC. Third, we observed that BOLD activity in right PMd was positively correlated with maximum phonation time in the PD group. Fourth, we observed differences in the spatial representation of right M1 between OHC and PD groups.

When participants performed the sustained vowel production task in mock scanner environment, the magnitude of the SPL difference between the groups (-4.712 dB SPL) was comparable to that reported in Chapter 3 of this dissertation (-4.734 dB SPL). Even though the finding trended towards statistical significance ($p = 0.059$), we interpret the finding as significant and attribute the higher p-value to lower statistical power arising from fewer overall observations (one condition vs. three) and fewer degrees of freedom, rather than a true lack of effect. We observed significantly lower maximum phonation times in the PD group. The maximum phonation time reported in the OHC group is in line with published norms for older healthy adults (Maslan, Leng, Rees, Blalock, & Butler, 2011). In addition, the observation of lower maximum phonation time in PD is in line with previous studies (Bauer, Aleric, Jancic, & Miholovic, 2011; Midi et al., 2008; Yuceturk, Yilmaz, Egrilmez, & Karaca, 2002) and may reflect reduced respiratory support for phonation and/or reduced glottal efficiency in PD. Together, the observed reductions in voice SPL and maximum phonation time indicate that the PD group experienced phonatory deficits during vowel production.

When participants performed the sustained vowel production task in the scanner, we found that individuals in the PD group tended to produce more vowels of shorter duration compared to the OHC

group. On average, the OHC group produced vowels within the target duration range of 3-5 seconds (mean = 3.82 seconds), while the PD group fell short of the target range (mean = 2.85 seconds). The shorter vowel duration in PD could be the result of the decreased phonatory support, in line with decreased maximum phonation time observed in this group. Individuals with PD may be self-selecting shorter phonation times to conserve respiratory/phonatory effort. The observed duration and number of vowels produced by each group suggest that the performance of self-paced vowel productions is not identical between OHC and PD groups. Thus, we cannot rule out this being the cause for PMd activation differences in the OHC > PD comparison.

Overall, the PD group recruited fewer brain regions than the OHC group during the sustained vowel production task. SMA activity was present in both OHC and PD groups. However, there were differences in the recruitment of primary motor and premotor cortical areas during sustained vowel production. In the OHC group, we found activity bilaterally in two clusters along the precentral gyrus: 1) the dorsal LPA, which controls the intrinsic laryngeal muscles (Brown et al., 2008; Correia et al., 2020; Simonyan, 2014), and 2) the trunk motor area, which is involved in volitional breathing (Ramsay et al., 1993; Takai, Brown, & Liotti, 2010), and phonation (Correia et al., 2020; Olthoff, Baudewig, Kruse, & Dechent, 2008). By contrast, BOLD activation maps for the PD group showed activity in the bilateral dorsal LPA, but no activity in the trunk motor area. This absence of activity in the trunk motor area could be related to weakness or akinesia in the chest wall during speech breathing (Hovestadt et al., 1989; Sabate et al., 1996; Solomon & Hixon, 1993). Reduced respiratory support from the expiratory muscles of the trunk would be consistent with our finding of reduced maximum phonation time in PD.

Activity in right PMd was found in the OHC group, but not in the PD group. Further, the contrast comparison of BOLD activity in OHC vs. PD showed that the PD group had significantly lower activity in right PMd compared to OHC. Hypoactivity of right PMd has not been previously reported during speech production in PD. Studies by Arnold et al., (2014) and Pinto et al., (2011) have reported that

individuals with PD have hyperactivity in the left PMd during speech production tasks. Hyperactivity of left PMd was not observed in the present study and may therefore be related to non-phonatory speech behaviors that were no utilized in the sustained vowel production task. Although hypoactivation in right PMd has not been previously reported, this finding is in line with prior work examining the neural correlates of voice treatment in PD. Narayana et al., (2010) found post-treatment activation in right PMd, which was not present pre-treatment. Further, the activity in right PMd was positively correlated with increased voice intensity (SPL) following successful voice treatment (Narayana et al., 2010). As the participants in our PD group had not completed the LSVT program within the past two years, the absence of right PMd is in line with the findings observed in the pre-treatment group. Interestingly, we found that activity in right PMd was positively correlated with maximum phonation time in PD, but not with voice SPL. Narayana et al. (2010) did not find significant differences maximum phonation time following LSVT; however, increased maximum phonation times following voice therapy have been reported in other studies (Dromey, Ramig, & Johnson, 1995). The correlation between right PMd and voice SPL found by Narayana et al., (2010) may be a function of treatment rather than an intrinsic behavioral link between right PMd and SPL. The absence of a significant correlation between right PMd and SPL in the OHC group would support this notion. Our finding of a positive correlation between right PMd activity and maximum phonation time in PD could point to a link between right PMd and respiratory drive that is not explicitly tied to SPL. However, this would require further study.

In our spatial analysis of LPA representation in PD, we found peak activity in left M1 to be in similar positions for OHC and PD groups. However, peak activity in right M1 was located in a more dorsal, anterior, and lateral position in PD compared to OHC. This finding is intriguing in light of new evidence showing that severity of hypokinetic dysarthria is related to morphological changes in right M1 (Y. Chen et al., 2020). Chen et al., (2020) found that atrophy in the right ventral M1 and right fusiform gyrus were predictive of dysarthria severity, as judged by the Voice Handicap Index (Rosen, Lee,

Osborne, Zullo, & Murry, 2004). Although the area of morphological change in right M1 is located more ventral to the region of functional activity in the present study, it is possible that atrophy of the right M1 could lead to changes in the spatial or functional organization of the dorsal laryngeal M1 area. Despite the group differences in right M1 position, the cluster extent of both left and right M1 clusters were comparable between OHC and PD. Thus, the change in position was not due to the recruitment of additional regions of motor cortex.

This study suggests three lines of additional research. First, most of the participants in our PD group presented with mild speech symptoms (mean MDS-UPDRS Item 3.1 = 1.23), and there was not a broad range of severity across participants. This was, in part, due to the fact that participants in our PD group were in the mild to moderate disease state. The recruitment of individuals in the later stages of PD is particularly challenging as the severity of rest tremor, dystonia, and dyskinesias may prohibit the individual from lying still in an MRI scanner. Still, expanding this research to include participants with a wider range of speech severity would be informative and a useful extension of the present research since the between group differences would be larger. Second, the group level activations seen in the Ah vs. Rest contrasts were relatively weak. This may have been due to the simplicity of the sustained vowel task or the relatively low task demands. Belyk and Brown (2014) similarly found weak group-level activations during a humming phonation task and suggested that it may be related to the softness of the vocalizations. The authors also noted that while all participants demonstrated activity in the dorsolateral and ventrolateral LPA, the activity was weak and spatially variable between participants. An alternative approach could be to use a sustained vowel task with varying degrees of effort (e.g., at 100% and 200% of the participant's normal loudness). Third, future studies could collect more precise respiratory measures to confirm the link between hypoactivity in the PMd and changes in respiratory drive for phonation.

Altogether, our findings suggest that PD hypophonia is associated with functional changes in the right primary motor and premotor cortices during sustained vowel production. Hypoactivation of right

PMd may be related to decreased phonatory support in PD hypophonia. In addition, the spatial representation of right LPA may be altered in PD hypophonia, even when comparable levels of BOLD activity are found with OHCs.

CHAPTER 5

DISCUSSION

The experiments conducted as part of this dissertation have linked speech and voice impairments in PD to both changes in cortico-basal ganglia connectivity (CHAPTER 2) and changes in motor cortical activity (CHAPTER 4). In addition, CHAPTER 3 addressed methodological challenges to conducting speech experiments on PD participants inside the scanner. As the primary goal of this dissertation was to further the understanding of neural processes underlying speech and voice difficulties in PD, the discussion presented here in CHAPTER 5 focuses on the data presented in CHAPTER 2 and CHAPTER 4. It should be noted that CHAPTER 2 and CHAPTER 4 refer to the functional region of laryngeal/phonatory representation in the motor cortex by different names. In CHAPTER 2, this is referred to as the laryngeal motor cortex (LMC) and reflects the terminology in the published manuscript. In CHAPTER 4, this is referred to as the laryngeal phonatory area (LPA). The change in terminology was done to more accurately reflect the function of this region, as it is involved in both laryngeal and respiratory aspects of phonatory control (Belyk & Brown, 2017). However, in order to maintain similar terminology throughout CHAPTER 5, LMC will be used to denote either LMC or LPA.

The discussion below is broken down into 4 sections. The first section summarizes the main findings of CHAPTER 2 and CHAPTER 4. The second section relates the research of this dissertation to the function of specific brain regions in PD speech and voice: a) basal ganglia, b) primary motor cortex, and c) pre-motor cortex. The third section discusses methodological challenges and concerns regarding

the use of fMRI to study speech and voice impairment in PD. The fourth section outlines future lines of research that would build upon the work presented in this dissertation.

5.1 Summary of neuroimaging findings

5.1.1 CHAPTER 2: Altered resting-state functional connectivity of the putamen and internal globus pallidus is related to speech impairment in Parkinson's disease

The study presented in CHAPTER 2 provided the first evidence of resting-state functional connectivity differences between individuals with Parkinson's disease and speech impairment (PDSI) and those with Parkinson's disease and no speech impairment (PDN). In this study, we found decreased functional connectivity between the left putamen and left superior temporal gyrus (STG) in PDSI compared to both OHC and PDN groups. Compared to the PDN group, the PDSI group also had greater connectivity between the left internal globus pallidus (GPi) and the left dorsal premotor cortex/laryngeal motor cortex, the left angular gyrus, and the right angular gyrus. Although functional connectivity of the GPi was different between PDN and PDSI groups, neither group showed significant differences in GPi connectivity with OHCs.

5.1.2 CHAPTER 4: Motor cortical activity during sustained vowel production in individuals with Parkinson's disease who have hypophonia

The study in CHAPTER 4 revealed differences in motor cortical activation between OHC and PD groups during a sustained vowel production task. During vowel production, the OHC group showed

activity in the bilateral dorsal laryngeal motor cortex (dLMC), bilateral trunk motor area, supplementary motor area (SMA), and right dorsal premotor cortex (PMd). By contrast the PD group showed activations only in the bilateral dLMC, and SMA, with no activity in the bilateral trunk motor area or in right PMd. When comparing OHC vs. PD, the statistical analysis showed that the PD group had significantly lower activity in the right PMd compared to OHC. Activity in this region of PMd was positively correlated with maximum phonation time, but not with voice intensity. In addition, it was found that the location of peak dLMC activity was comparable between OHC and PD in the left hemisphere but was spatially different in the right hemisphere. A cluster extent analysis showed that size of the clusters was comparable and that this was due to a spatial shift and not due to the recruitment of additional areas in the motor cortex.

5.2 Brain regions involved in speech and voice impairment in PD

5.2.1 Basal ganglia

The data presented in this dissertation point to specific changes in the striatum and globus pallidus that are involved in speech and voice impairment in PD. The findings within the globus pallidus are particularly insightful as speech related changes in the globus pallidus have not been previously reported in PD. It is worth noting that while changes in the subthalamic nucleus (STN) may also contribute to speech impairments in PD, the connectivity of STN was not explicitly examined in the present research. The STN was excluded from our connectivity analysis in CHAPTER 2 due to the difficulty of accurately localizing the STN using the Basal Ganglia Human Area Template (BGHAT (Prodoehl, Yu, Little, Abraham, & Vaillancourt, 2008)). Upon visual inspection, STN definitions provided by the BGHAT did not line up accurately with the participants T1 and T2 anatomical scans. The

difficulty in localizing the STN was likely due to the presence of geometric distortions, which can be more pronounced near the midbrain (Duzel et al., 2015). As B0 scans were not available for the PPMI database, we were unable to apply distortion corrections to create accurate region of interest masks for the STN using the BGHAT definitions. The discussion of basal ganglia contributions to speech and voice impairment in PD, therefore, focuses on the striatum and globus pallidus, which were investigated as part of this dissertation.

5.2.1.1 Striatum

The striatum consists of both the putamen and the caudate, both of which act as the major input nuclei from the cortex to the basal ganglia and play important roles in speech and voice production (Arnold et al., 2014; Bohland & Guenther, 2006; Brown et al., 2009; Chang et al., 2009; Parkinson et al., 2012; Pichon & Kell, 2013; Robinson et al., 2012; Simonyan et al., 2013; Tourville & Guenther, 2011). The most notable findings in this dissertation regarding striatal function came from the study presented in CHAPTER 2, in which we demonstrated that that the functional connectivity between the left putamen and left superior temporal gyrus was lower in the PDSI group compared to both OHC and PDN groups. It is likely that this reflects a deficit in the integration of sensory cues from the auditory cortex with outgoing motor speech commands. Indeed, evidence from overt reading suggests a mediating role of the putamen for visual-motor integration (Seghier & Price, 2010), and deficits in auditory-motor integration have been documented in PD during voice production (X. Chen et al., 2013; Kiran & Larson, 2001; Liu, Wang, Metman, & Larson, 2012). Of note, neither the left nor right putamen were found to be active during the sustained vowel task presented in CHAPTER 4. In a study by Brown et al., (2008) activity in the putamen was found during lip movements and tongue movements, but not during phonation or glottal stops. Similarly, putamen activity was not noted by Ozdemir et al., (2006) during speaking, singing,

humming, or vowel production compared to baseline. The data from CHAPTER 4 are consistent with these findings. However, other studies have reported activity in the bilateral putamen during vowel production tasks (Grabski et al., 2013; Soros et al., 2006), and humming (Belyk, Johnson, & Kotz, 2018).

Although activity in the putamen was absent in our study of vowel production, we did observe activation in the bilateral caudate in the OHC group which was not present in the PD group. However, our group contrasts did not reveal a significant group difference in this area. The role of the caudate in speech has largely been linked to speech prosody control (Arnold et al., 2014; Kotz et al., 2003; Pichon & Kell, 2013; Robinson et al., 2012) and emotional speech (Kotz, Dengler, & Wittfoth, 2015), both of which are known to be impaired in PD (Frederic L Darley et al., 1969; Duffy, 2013; Pell, Cheang, & Leonard, 2006; Pell & Leonard, 2003; Schroder, Nikolova, & Dengler, 2010). However, it is unclear why an emotionally neutral vowel production task would elicit activity in the caudate as this has not been reported in prior studies of vowel production. One possibility is that the activity in the caudate is related to cognitive preparation for vocalizations, rather than overt vowel production. Arnold et al., (2014) found that the caudate was active during cognitive preparation for overt sentence reading with a neutral intonation. Given that the analysis was conducted in a block design, activity related to the preparation for each vowel production would also be included in the comparison of Ah vs. Rest blocks. Thus, it's possible that the caudate activity observed during the vowel production task is related to cognitive preparation. With respect to functional connectivity, none of our three groups (OHC, PDN, and PDSI) differed in the functional connectivity of the left caudate (Manes et al., 2018). However, the OHC group had significantly greater connectivity with left SMA compared to both PDN and PDSI groups and greater connectivity between right putamen and right inferior temporal gyrus compared to PDSI. Arnold et al. (2014) also found that participants with PD had hypo-connectivity of the caudate and SMA as well as the DLPFC and IFG during cognitive preparation for overt sentence reading. It was proposed that this hypo-connectivity could be related to reduced cognitive "energization" for movement execution and thus a

potential mechanism of hypophonia. Although the connection between the caudate and SMA was lower in the PD group compared to controls, the activity in the caudate during cognitive preparation was not significantly different between groups. If the activity in the caudate found in the CHAPTER 4 is in fact related to cognitive preparation for vowel productions, then the findings presented in this dissertation would be consistent with the data reported by Arnold et al., (2014) – specifically, the observation of PD hypo-connectivity between the caudate and SMA despite no significant group differences in caudate activity.

5.2.1.2 Globus pallidus

The globus pallidus is comprised of two segments – the internal globus pallidus (GPi), which provides a tonic inhibitory signal to thalamocortical neurons, and the external globus pallidus (GPe), which inhibits the STN as part of the "indirect" basal ganglia pathway. The GPi acts as the primary output structure of the basal ganglia. As the GPi provides tonic inhibition to the thalamus, the inhibition of GPi neurons (via the "direct pathway") facilitates movement, while excitation of the GPi (via the "indirect pathway") inhibits movement. The rate model of PD suggests that the hypokinetic and bradykinetic symptoms of PD arise due to an imbalance in the activity of the direct and indirect pathways. In this model, the loss of dopaminergic modulation causes an up-regulation of the indirect pathway and down-regulation of the direct pathway, leading to hyperactivation of the GPi and a subsequent decrease in thalamocortical motor output (Obeso et al., 2008). The hypokinetic speech characteristics of PD are believed to follow this model; however, the role of GPi in PD speech impairment has been largely unaccounted for by neuroimaging literature. This may be in part due to methodological challenges. As the globus pallidus appears very pale on T1-weighted anatomical scans, automated segmentation of white matter and gray matter can misclassify the basal ganglia as white matter and exclude the region from

statistical analysis. This problem was encountered in CHAPTER 2 and additional steps had to be taken to remove the globus pallidus from white matter masks generated by SPM12. Further, the delineation between GPi and GPe can be difficult to detect visually on T1 anatomical scans. Given the small size of the GPi, it is also possible that voxel-wise clusters of activity or connectivity may not meet cluster extent thresholds during statistical analysis of fMRI data.

The study presented in CHAPTER 2 was able to overcome these challenges and provide the first evidence of GPi hyper-connectivity related to PD speech impairment (Manes et al., 2018). Using the BGHAT region of interest definitions (Prodoehl et al., 2008), we were able to successfully separate the GPe and GPi signals and generate resting-state connectivity maps for each region. Our major findings were related to the functional connectivity of the left GPi. The functional connectivity between left GPi to left PMd/LMC was higher in PDSI compared to PDN pointing directly to changes in the cortico-basal ganglia pathways that support motor speech control (See further discussion in sections 5.2.2.1 and 5.2.3). In addition, we found that left GPi connectivity to the bilateral angular gyrus was higher in PDSI compared to PDN, demonstrating altered GPi connectivity to regions outside the motor speech network. Interestingly, left GPi connectivity to all three regions was not statistically different between OHC and either the PDN or PDSI groups. This was due to the fact that the lowest levels of connectivity were found in the PDN group while the highest levels of connectivity were found in the PDSI group. One possible explanation could be the presence of initial deafferentation in PDN followed by a compensatory increase in GPi functional connectivity in PDSI. However, the degree to which these findings are compensatory or related to disease pathology remains to be seen.

5.2.2 Primary motor cortex

5.2.2.1 Laryngeal motor cortex/laryngeal phonatory area

The somatotopic representation of the larynx in the human motor cortex has been a topic of extensive discussion (Bouchard, Mesgarani, Johnson, & Chang, 2013; Brown et al., 2009; Brown et al., 2008; Dichter, Breshears, Leonard, & Chang, 2018; Simonyan, 2014). Humans appear to be unique in that they have two focal points along the precentral gyrus which are involved with phonation. These have been labelled at as the dorsal laryngeal motor cortex (dLMC) and the ventral laryngeal motor cortex (vLMC) (Belyk & Brown, 2017; Bouchard et al., 2013; Dichter et al., 2018). The vLMC is located ventral to the motor representation of the lips, tongue, and jaw, while the dLMC is located dorsal to the motor representation of the speech articulators (Belyk & Brown, 2017; Brown et al., 2008). Brown et al., (2008) originally referred to the dLMC as the "larynx/phonation area" and found two peaks of activity within the dLMC cluster. There were referred to as the "dorsolateral larynx/phonation area" (located in BA 6) and the "ventromedial larynx/phonation area" (located in BA 4). Of note, the PMd/LMC region identified in CHAPTER 2 was located on the anterior bank of the precentral gyrus in BA 6 and corresponded closely to the dorsolateral dLMC area identified by Brown et al., (2008). By contrast the dLMC activity observed during vowel production in CHAPTER 4 was located on the posterior bank of the precentral gyrus and was in line with the dLMC regions reported by Belyk et al., (2020; 2018).

Despite being named for its involvement in the control of laryngeal muscles, the LMC is also involved in controlled expiration (but not inspiration), even in the absence of laryngeal involvement (Belyk et al., 2020; Loucks, Poletto, Simonyan, Reynolds, & Ludlow, 2007; Simonyan, Ostuni, Ludlow, & Horwitz, 2009). Belyk et al., (2020) showed that both the dLMC and vLMC can be activated during whistling, a task which involves respiratory and articulatory control, but not laryngeal movement. Belyk et al., (2020) thus proposed that the two areas of the LMC represent laryngeal/respiratory integration areas. In an ECoG study performed during neurosurgery, Dichter et al. (2018) was able to evoke laryngeal

EMG activity in 18 patients by providing electrical stimulation to the dLMC. In 20/82 patients, he was also able to elicit vocalizations with left dLMC stimulation, presumably requiring engagement of both laryngeal and respiratory mechanisms.

Since both laryngeal and expiratory impairments are related to hypophonia in PD, it would be expected that individuals with PD hypophonia would have decreased activity in the LMC during phonation. However, this is not what was found in our study of vowel production in PD. Although both OHC and PD groups activated the bilateral dLMC, there were no group differences in dLMC activity. Rather, the right PMd was hypoactive in our PD group compared to OHC and dLMC activity was unchanged. In the resting-state functional connectivity study in CHAPTER 2, the connectivity between left GPi and left PMd/LMC was not statistically different between PDSI and OHC groups, however, it was different between PDN and PDSI groups. It could be that individuals with PD speech impairment undergo functional reorganization of speech networks that allows them to maintain the same level of LMC activity during vocalization. Functional connectivity analysis performed during voice production in healthy adults has shown that the LMC is functionally connected to multiple brain regions, including the bilateral putamen, globus pallidus, and caudate (Simonyan et al., 2009). Further investigating these functional connections between LMC and basal ganglia in the context of PD hypophonia could help bridge the gap between our resting state connectivity findings in CHAPTER 2 and task-fMRI findings in CHAPTER 4.

5.2.2.2 Trunk motor area

In CHAPTER 4, we observed that in the comparison of “Ah” vs. rest, the OHC group showed activity in the bilateral trunk motor area (TMA) of the motor cortex, while the PD group did not. Although there was no significant difference in TMA activity in the group comparison, it is worth

considering whether the absence of TMA activation may have contributed to decreased respiratory support for phonation in the PD group. Weakness in the trunk muscles can lead to decreased respiratory support for speech breathing in PD (Hovestadt et al., 1989; Sabate et al., 1996; Solomon & Hixon, 1993) as well as impaired posture. Of the 13 participants in our PD group, 9 were rated as having impaired posture on the MDS-UPDRS Motor Exam (3 participants rated as "1", 3 participants rated as "2", and 3 participants rated as "3"). It is possible that hypokinesia/weakness of the trunk muscles could have contributed to impaired posture, decreased respiratory support, and hypophonia in these 9 participants. However, this relationship would need to be tested using more precise measures of posture and respiratory aerodynamics during speech breathing. Another possibility is that that speaking under the condition of fMRI noise prompted OHC participants to actively engage expiratory trunk muscles to increase vocal loudness, prompting the engagement of the TMA. Meanwhile, the PD group could have relied primarily on laryngeal strategies to increase vocal loudness and therefore not engaging the TMA (Stathopoulos et al., 2014). More detailed measures of posture, voice, and respiratory function could be useful to collect alongside fMRI data when employing respiratory and phonatory tasks in PD.

5.2.3 Premotor cortex

The research reported in both CHAPTER 2 and CHAPTER 4 of this dissertation has pointed to the involvement of PMd in PD speech and voice impairments. The PMd is involved in the programming of movement parameters, such as amplitude and direction (Kurata, 1993; Riehle & Requin, 1989), as well as integrating sensory information to produce the desired motor output (Wise, Boussaoud, Johnson, & Caminiti, 1997). Although there is extensive literature on the role of PMd in the general motor control literature, the role of PMd in speech production is not well established. One study by Zarate and Zatorre (2008) found a link between PMd and vocal responses to altered auditory feedback. The participants

performed a task in which they sang at target frequencies and their pitch auditory feedback was perturbed. When participants were asked to volitionally compensate for the shift so that the auditory feedback matched the target pitch, they activated the left PMd. However, when participants were asked to ignore the shift and try to maintain their current vocal pitch, they activated the right PMd.

Individuals with PD have shown hyperactive compensatory responses to pitch perturbation tasks (Liu et al., 2012), suggesting a greater responsiveness to sensory input for executing vocalizations. Given the role of the left PMd in sensorimotor transformations, the increased reliance on external sensory input could explain observations that left PMd is hyperactive in PD during speech tasks (Arnold et al., 2014; Pinto et al., 2011). In CHAPTER 2, we demonstrated that the PDSI group had hyper-connectivity between left GPi and left PMd/LMC during the resting-state. It is possible that this pathway helps to mediate sensorimotor transformations during speech production and that hyper-connectivity reflects the increased reliance on sensory feedback for speech motor control.

The study presented in CHAPTER 4 showed that PD participants with hypophonia had hypoactivity in the right PMd when performing a sustained vowel task. While participants in the OHC group activated right PMd for vowel production, the PD group did not. Activity in the right PMd has not been previously reported in neuroimaging studies of vowel production. However, it is possible that the recruitment of right PMd is the result of typical age-related changes in brain activity during phonation. A study by Wong et al, (2009) compared brain activity of younger and older adults as they listened to speech under noisy conditions. The results of the study showed that, compared to younger adults, older adults had greater activity in several clusters along the border of the precentral and middle frontal gyri, including regions corresponding to right PMd. The authors interpreted this as an age-related compensatory increase in the recruitment of prefrontal areas. It is possible that older healthy adults also engage in compensatory recruitment the right PMd when performing a voice production task in noise. If this is the case, it would imply that the typical compensatory PMd activity seen in OHCs is reduced or

absent in individuals with PD hypophonia.

The link between right PMd and hypophonia is supported by the work of Narayana et al., (2010) who found that right PMd activity was increased in PD participants after successfully completing the Lee-Silverman Voice Treatment. If activation of right PMd is indeed part of the typical voice production network in OHCs, then voice therapy may help to restore activity in this region and enable more effective vocalization. In the study presented in CHAPTER 4, we showed that right PMd was positively correlated with maximum phonation time. Thus, those with poorer respiratory support for phonation had weaker activity in right PMd. As voice treatment increases both loudness and maximum phonation time (Dromey et al., 1995), increased activity in PMd may be tied to improved respiratory drive for phonation.

5.3 The use of fMRI for studying PD speech: Methodological challenges and considerations

There are a number of methodological challenges to consider when using fMRI to study speech and voice impairment in PD. These include solicitation of the Lombard effect during continuous scanning, interaction of PD subtype and head motion, and correcting for excessive head motion.

CHAPTER 3 of this dissertation addressed the solicitation of the Lombard effect during continuous fMRI scanning and demonstrated that the increased vocal intensity induced by scanner noise was comparable between OHC and PD participants. This is important not only for the development of future studies, but also the interpretation of the existing literature. To date, all fMRI studies of PD overt speech production have been conducted using continuous scanning protocols, thereby engaging Lombard effect (Arnold et al., 2014; Maillet et al., 2012; Narayana et al., 2020; Pinto et al., 2011; Rektorova et al., 2007). Although, CHAPTER 3 showed that increased vocal intensity in fMRI noise is comparable between individuals with mild-moderate PD and OHC, it remains an open question as to whether these groups employ common neural mechanisms for increasing voice intensity when speaking in noise. Within

the PD population, there are individual differences in the respiratory and laryngeal strategies for achieving that increased vocal intensity (Stathopoulos et al., 2014). This by itself may lead to variability in neural responses to background noise during speech production (e.g., those more reliant on respiratory strategies may recruit trunk motor cortex, while those more reliant on laryngeal strategies may only recruit the laryngeal phonatory area). Understanding the neural correlates of the Lombard effect in PD and OHC may help with interpretation of existing fMRI studies that employ continuous scanning protocols during speech production.

Another challenge to studying PD speech using fMRI is the interaction between PD subtype and head motion. Excessive head motion during the scan can lead to poor image quality and the data may need to be discarded if motion correction techniques are unsuccessful. This is particularly relevant for studies of speech and voice production as movement of the speech effectors can cause additional head motion. Due to head motion considerations, acquiring quality fMRI data from PD participants with moderate to severe tremor is typically not feasible. By contrast, those with primarily akinetic-rigid symptoms are able to remain very still during fMRI scanning. The need to limit head motion in the scanner is therefore likely to result in some degree of bias with respect to PD subtypes, favoring those with akinetic-rigid symptoms over those with tremor-dominant symptoms. This can also limit the range of PD severity that can be studied using fMRI, as was the case in CHAPTER 4. Advancements in fMRI motion correction may be able to assist with this moving forward; but, for the time being, the difficulty of collecting quality data on participants with moderate to severe tremor continues to limitation when conducting fMRI studies of PD speech production.

The application of sparse sampling techniques to studying PD speech may help resolve the challenges related to the Lombard effect and challenges related to speech-induced head motion. By eliminating scanner noise during speech production, the Lombard effect may be reduced in participants. However, the presence of ear protection may still lend a degree of auditory masking, prompting increased

vocal intensity. When possible, the addition of real-time auditory feedback may be useful for speech production experiments to overcome the masking effects caused by hearing protection.

5.4 Future directions

The research presented in this dissertation affords many possible avenues for future study. From a methodological perspective, quantifying the interactions between speech behavior and scanning environment will be important for the interpretation of fMRI data across a range of speech tasks and clinical populations. As all fMRI studies of PD speech to date have used continuous fMRI scanning protocols, a systematic investigation into the neural correlates of Lombard responses in OHC and PD populations would inform the existing fMRI literature on PD speech production. Further, the application of sparse-sampling fMRI protocols could help to confirm previous findings in the PD speech literature without the presence of acoustic fMRI noise. Exploring the neural correlates of phonation in healthy aging would be another helpful extension of the present research. An fMRI study comparing vowel production between older and younger adults would shed light on whether the right PMd activity observed in our OHC group was due to age-related changes in cortical activity. Our understanding of hypophonia could be further developed by examining the relationship between motor cortical activity and intensity modulation in PD hypophonia. In CHAPTER 4, our fMRI task only required that participants produce vowels in their normal conversational loudness. Collecting imaging data across a range of vocal intensities would allow us to examine whether motor cortical activity increases with increasing phonatory demand. Further, correlating fMRI activity with more precise respiratory and postural measures may help to further explain the relation between PMd and maximum phonation time as well as the potential role of the trunk motor area in hypophonia. Finally, the findings from CHAPTER 2 and CHAPTER 4 could be bridged by performing a task-driven functional connectivity analysis of vowel production in PD. This

would extend our resting state findings and confirm whether these changes we observed in PDSI functional connectivity are also present during active vocalization.

Vita

Jordan L. Manes

PhD Candidate, Systems and Cognitive Neuroscience
jordanleighmanes@gmail.com

RESEARCH OBJECTIVE:

My long-term research objective is to expand the understanding of brain-behavior interactions contributing to speech and voice difficulties in Parkinson's disease. To accomplish this, my work utilizes non-invasive brain imaging and acoustic speech measures to examine the relationship of speech and voice characteristics with brain activity as well as connectivity within cortico-basal ganglia circuitry.

EDUCATION

2013-2020 **PhD, Systems & Cognitive Neuroscience**, Northwestern University, Evanston, IL
Specialization in Movement and Rehabilitation Sciences
Advisor: Dr. Daniel M. Corcos

2007-2011 **BA, Psychology**, University of Texas at San Antonio, San Antonio, TX
Summa Cum Laude, Highest Honors
Advisor: Dr. Donald A. Robin

TEACHING AND RESEARCH INTERESTS

Human Neuroimaging
Functional Connectivity Mapping
Speech Motor Control
Motor Speech Disorders
Parkinson's Disease

GRANTS & FELLOWSHIPS

2016-2018 Ruth L. Kirschtein National Research Service Award
"fMRI Correlates of Speech and Voice Impairment in Parkinson's Disease" National Institute on Deafness and Other Communication Disorders (F31 DC015717)

2015-2016 Predoctoral appointment to Training Program in the Neurobiology of Movement and Rehabilitation Sciences (NIH T32 HD057845)

RESEARCH EXPERIENCE

2013-2020 **PhD Candidate,** Northwestern University Interdepartmental Neuroscience
Department of Physical Therapy and Human Movement Sciences (PI: Daniel M. Corcos)
Northwestern University

- Compared whole brain, resting state functional connectivity of the basal ganglia between Parkinson's patients with and without speech impairment
- Examined activation of laryngeal motor cortex during vowel production in individuals with Parkinson's disease and hypophonia

2011-2013 **Research Area Specialist Associate & Lab Manager**
Human Performance Lab, Research Imaging Institute (PI: Donald A. Robin)
University of Texas Health Science Center at San Antonio

- Examined the conjunction of basal ganglia functional connectivity networks with functional speech networks using meta-analytic connectivity modeling of archived neuroimaging coordinates.
- Collected fMRI, behavioral, and neuropsychological data from patients with chronic pain syndromes.
- Collected pre/post-treatment speech recordings and PET data from Parkinson's patients undergoing the Lee Silverman Voice Treatment®

2010-2011 **Student Associate**
Human Performance Lab, Research Imaging Institute (PI: Donald A. Robin)
University of Texas Health Science Center at San Antonio

- Collected fMRI and TMS data from healthy individuals as they performed audio-vocal perturbation tasks.

TEACHING EXPERIENCE

2017- 2018 **Walter Payton Lecture: Basal Ganglia, Motor Control, and Parkinson's Disease**
Guest Lecturer, Northwestern University Brain Awareness Outreach

2015-2017 **Neuroscience I, Neuroscience II**
Peer tutor, Northwestern University

2015 **Introduction to Neuroscience**
Teaching Assistant, Northwestern University

2015 **Advanced Neuroanatomy**
Teaching Assistant, Northwestern University

2009 **Introduction to Psychology**
Supplemental Instructor, University of Texas at San Antonio

PUBLICATIONS

(Submitted) **Manes, J. L.,** Herschel, E., Tjaden, K., Parrish, T., Simuni, T. Corcos, D. M., Roberts, A. (Under review). The effects of a simulated fMRI environment on voice intensity in individuals with Parkinson's disease hypophonia and older healthy adults.

2019 Patel, S., Gao, L., Wang, S., Gou, C., **Manes, J.**, Robin, D.A., Larson, C.L., (2019). Comparison of volitional opposing and following responses across speakers with different vocal histories. *Acoustical Society of America*, *146*(6), 4244-4254.

2018 **Manes, J.L.**, Tjaden, K., Parrish, T., Simuni, T., Roberts, A., Greenlee, J., Corcos, D. M., & Kurani, A. S. (2018). Altered resting-state functional connectivity of the putamen and internal globus pallidus is related to speech impairment in Parkinson's disease. *Brain and Behavior*, *8*(9), e01073.

2014 **Manes, J. L.,** Parkinson, A. L., Larson, C. R., Greenlee, J. D., Eickhoff, S. B., Corcos, D. M., & Robin, D. A. (2014). Connectivity of the subthalamic nucleus and globus pallidus pars interna to regions within the speech network: A meta-analytic connectivity study. *Human Brain Mapping*, *35*(7), 3499-516

2014 **Manes, J.,** Maas, E., Robin, D. (2014). Motor Speech Disorders: Apraxia and Dysarthria. In Justice, L.M. and Redle, E.E. (Eds.) *Communication Disorders: A Clinical Evidence-Based Approach.* (3rd Ed.). Upper Saddle River, NJ: Pearson

2012 **Manes, J.L**., Robin, D.A. (2012). A motor learning perspective for optimizing intervention intensity. *International Journal of Speech-Language Pathology*, *14*(5), 447-450.

2012 Parkinson, A.L., Flagmeier, S.G., **Manes, J.L**., Larson, C.R., Rogers, B., Robin, D.A. (2012). Understanding the neural mechanisms involved in the sensory mechanisms of voice production. *Neuroimage*, *61*(1), 314-322

CONFERENCES AND PRESENTATIONS

2020 **Motor Speech Conference, Santa Barbara, CA**
Poster Presentation: Correlating out-of-scanner voice intensity with laryngeal motor cortex activity in older healthy adults and individuals with Parkinson's disease and hypophonia

2019 **Boston Speech Motor Control Symposium, Boston, MA**
Poster Presentation: Laryngeal motor cortex activity during sustained vowel production in Parkinson's disease with hypophonia

2018 **Motor Speech Conference, Savanna, GA**
Oral presentation: Altered resting-state functional connectivity of basal ganglia nuclei related to speech impairment in Parkinson's disease

2017 **MRS Training Day, Chicago, IL**
Oral presentation: Resting-state basal ganglia connectivity and speech impairment in Parkinson's disease.

2015 **Organization for Human Brain Mapping, Honolulu, HI**
Poster Presentation: Resting state functional connectivity associated with speech dysfunction in Parkinson's disease.

2014 **International Conference on Motor Speech, Sarasota, FL**
Poster Presentation: Meta-analytic connectivity of the globus pallidus pars interna to regions within the motor speech network.
Oral Presentation (In place of Amy Parkinson): Effective connectivity associated with auditory error detection in musicians with absolute pitch.

2011 **National Conference on Undergraduate Research, Ithaca, NY**
Oral Presentation: Defining the timing and function of cortical areas involved in the pitch-shift reflex using fMRI and TMS.

CONTINUING EDUCATION

2018 Lessons for Success, American Speech-Language-Hearing Association
2015 Training Course in fMRI, University of Michigan
2014 Advanced Neuroimaging Methods with a Clinical Focus, Northwestern University

COMMUNITY INVOLVEMENT

2016 Teacher's Workshop, Northwestern University Brain Awareness Outreach
2014 Ad hoc reviewer, International Journal of Speech-Language Pathology
2014-2019 Volunteer, Northwestern University Brain Awareness Outreach

TECHNICAL SKILLS:

SPM12, AFNI, MATLAB, E-Prime, SPSS, Audacity, Praat

WEBSITES

https://www.researchgate.net/profile/Jordan_Manes
https://scholar.google.com/citations?user=3uqhrg4AAAAJ&hl=en

References

Adams, M. R., & Hutchinson, J. (1974). The effects of three levels of auditory masking on selected vocal characteristics and the frequency of disfluency of adult stutterers. *J Speech Hear Res, 17*(4), 682-688. doi:10.1044/jshr.1704.682

Adams, M. R., & Moore, W. H., Jr. (1972). The effects of auditory masking on the anxiety level, frequency of dysfluency, and selected vocal characteristics of stutterers. *J Speech Hear Res, 15*(3), 572-578. doi:10.1044/jshr.1503.572

Adams, S. G., Dykstra, A., Abrams, K., Winnell, J., Jenkins, M., & Jog, M. (2006). Conversational speech intensity under different noise conditions in hypophonia and Parkinson's disease. *Canadian Acoustics, 34*(3), 96-97.

Adams, S. G., Haralabous, O., Dykstra, A., Abrams, K., & Jog, M. (2005). Effects of multi-talker background noise on the intensity of spoken sentences in Parkinson's disease. *Canadian Acoustics, 33*(3), 94-95.

Adams, S. G., & Lang, A. E. (1992). Can the Lombard Effect Be Used to Improve Low Voice Intensity in Parkinsons-Disease. *European Journal of Disorders of Communication, 27*(2), 121-127.

Adams, S. G., Moon, B.-H., Dykstra, A., Abrams, K., Jenkins, M., & Jog, M. (2006). Effects of multitalker noise on conversational speech intensity in Parkinson's disease. *Journal of Medical Speech-Language Pathology, 14*(4), 221-229.

Aldridge, D., Theodoros, D., Angwin, A., & Vogel, A. P. (2016). Speech outcomes in Parkinson's disease after subthalamic nucleus deep brain stimulation: A systematic review. *Parkinsonism Relat Disord, 33*, 3-11. doi:10.1016/j.parkreldis.2016.09.022

Arciuli, J., Simpson, B. S., Vogel, A. P., & Ballard, K. J. (2014). Acoustic changes in the production of lexical stress during Lombard speech. *Lang Speech, 57*(Pt 2), 149-162.

doi:10.1177/0023830913495652

Arnold, C., Gehrig, J., Gispert, S., Seifried, C., & Kell, C. A. (2014). Pathomechanisms and compensatory efforts related to Parkinsonian speech. *Neuroimage Clin, 4*, 82-97. doi:10.1016/j.nicl.2013.10.016

Baudrexel, S., Witte, T., Seifried, C., von Wegner, F., Beissner, F., Klein, J. C., . . . Hilker, R. (2011). Resting state fMRI reveals increased subthalamic nucleus-motor cortex connectivity in Parkinson's disease. *Neuroimage, 55*(4), 1728-1738. doi:10.1016/j.neuroimage.2011.01.017

Bauer, V., Aleric, Z., Jancic, E., & Miholovic, V. (2011). Voice quality in Parkinson's disease in the Croatian language speakers. *Coll Antropol, 35 Suppl 2*, 209-212.

Baumann, A., Nebel, A., Granert, O., Giehl, K., Wolff, S., Schmidt, W., . . . van Eimeren, T. (2018). Neural Correlates of Hypokinetic Dysarthria and Mechanisms of Effective Voice Treatment in Parkinson Disease. *Neurorehabil Neural Repair, 32*(12), 1055-1066. doi:10.1177/1545968318812726

Baylor, C., Yorkston, K., Eadie, T., Kim, J., Chung, H., & Amtmann, D. (2013). The Communicative Participation Item Bank (CPIB): item bank calibration and development of a disorder-generic short form. *J Speech Lang Hear Res, 56*(4), 1190-1208. doi:10.1044/1092-4388(2012/12-0140)

Belyk, M., Brown, R., Beal, D. S., Roebroeck, A., McGettigan, C., Guldner, S., & Kotz, S. A. (2020). Human specific neurophenotype integrates laryngeal and respiratory components of voice motor control.

Belyk, M., & Brown, S. (2014). Somatotopy of the extrinsic laryngeal muscles in the human sensorimotor cortex. *Behav Brain Res, 270*, 364-371. doi:10.1016/j.bbr.2014.05.048

Belyk, M., & Brown, S. (2017). The origins of the vocal brain in humans. *Neurosci Biobehav Rev, 77*, 177-193. doi:10.1016/j.neubiorev.2017.03.014

Belyk, M., Johnson, J. F., & Kotz, S. A. (2018). Poor neuro-motor tuning of the human larynx: a

comparison of sung and whistled pitch imitation. *R Soc Open Sci, 5*(4), 171544. doi:10.1098/rsos.171544

Biswal, B., Yetkin, F. Z., Haughton, V. M., & Hyde, J. S. (1995). Functional connectivity in the motor cortex of resting human brain using echo-planar MRI. *Magn Reson Med, 34*(4), 537-541.

Boersma, P., Weenink, D. (2017). Praat: doing phonetics by computer [Computer Program]. Version 6.0.29.

Bohland, J. W., & Guenther, F. H. (2006). An fMRI investigation of syllable sequence production. *Neuroimage, 32*(2), 821-841. doi:10.1016/j.neuroimage.2006.04.173

Bouchard, K. E., Mesgarani, N., Johnson, K., & Chang, E. F. (2013). Functional organization of human sensorimotor cortex for speech articulation. *Nature, 495*(7441), 327-332. doi:10.1038/nature11911

Brown, S., Ingham, R. J., Ingham, J. C., Laird, A. R., & Fox, P. T. (2005). Stuttered and fluent speech production: an ALE meta-analysis of functional neuroimaging studies. *Hum Brain Mapp, 25*(1), 105-117. doi:10.1002/hbm.20140

Brown, S., Laird, A. R., Pfordresher, P. Q., Thelen, S. M., Turkeltaub, P., & Liotti, M. (2009). The somatotopy of speech: phonation and articulation in the human motor cortex. *Brain Cogn, 70*(1), 31-41. doi:10.1016/j.bandc.2008.12.006

Brown, S., Ngan, E., & Liotti, M. (2008). A larynx area in the human motor cortex. *Cereb Cortex, 18*(4), 837-845. doi:10.1093/cercor/bhm131

Caligiuri, M. P. (1987). Labial kinematics during speech in patients with parkinsonian rigidity. *Brain, 110 (Pt 4)*, 1033-1044. doi:10.1093/brain/110.4.1033

Cantello, R., Gianelli, M., Bettucci, D., Civardi, C., De Angelis, M. S., & Mutani, R. (1991). Parkinson's disease rigidity: magnetic motor evoked potentials in a small hand muscle. *Neurology, 41*(9), 1449-1456. doi:10.1212/wnl.41.9.1449

Cantello, R., Gianelli, M., Civardi, C., & Mutani, R. (1995). Parkinson's disease rigidity: EMG in a small hand muscle at "rest". *Electroencephalogr Clin Neurophysiol, 97*(5), 215-222. doi:10.1016/0013-4694(95)93574-q

Castellanos, A., Benedí, J.-M., & Casacuberta, F. (1996). An analysis of general acoustic-phonetic features for Spanish speech produced with the Lombard effect. *Speech Communication, 20*(1-2), 23-35.

Catalan, M. J., Ishii, K., Honda, M., Samii, A., & Hallett, M. (1999). A PET study of sequential finger movements of varying length in patients with Parkinson's disease. *Brain, 122 (Pt 3)*, 483-495. doi:10.1093/brain/122.3.483

Chang, S. E., Kenney, M. K., Loucks, T. M., Poletto, C. J., & Ludlow, C. L. (2009). Common neural substrates support speech and non-speech vocal tract gestures. *Neuroimage, 47*(1), 314-325. doi:10.1016/j.neuroimage.2009.03.032

Chen, X., Zhu, X., Wang, E. Q., Chen, L., Li, W., Chen, Z., & Liu, H. (2013). Sensorimotor control of vocal pitch production in Parkinson's disease. *Brain Res, 1527*, 99-107. doi:10.1016/j.brainres.2013.06.030

Chen, Y., Zhu, G., Liu, D., Liu, Y., Yuan, T., Zhang, X., . . . Zhang, J. (2020). Brain morphological changes in hypokinetic dysarthria of Parkinson's disease and use of machine learning to predict severity. *CNS Neurosci Ther*. doi:10.1111/cns.13304

Connor, N. P., Abbs, J. H., Cole, K. J., & Gracco, V. L. (1989). Parkinsonian deficits in serial multiarticulate movements for speech. *Brain, 112 (Pt 4)*, 997-1009.

Correia, J. M., Caballero-Gaudes, C., Guediche, S., & Carreiras, M. (2020). Phonatory and articulatory representations of speech production in cortical and subcortical fMRI responses. *Sci Rep, 10*(1), 4529. doi:10.1038/s41598-020-61435-y

Daniels, N., Oates, J., Phyland, D., Feiglin, A., & Hughes, A. (1996). Vocal characteristics and response

to levodopa in Parkinson's disease. *Movement Disorders, 11*(Suppl. 1), 117.

Darley, F. L., Aronson, A. E., & Brown, J. R. (1969). Clusters of deviant speech dimensions in the dysarthrias. *Journal of Speech, Language, and Hearing Research, 12*(3), 462-496.

Darley, F. L., Aronson, A. E., & Brown, J. R. (1969). Differential diagnostic patterns of dysarthria. *J Speech Hear Res, 12*(2), 246-269.

Darling, M., & Huber, J. E. (2011). Changes to articulatory kinematics in response to loudness cues in individuals with Parkinson's disease. *J Speech Lang Hear Res, 54*(5), 1247-1259. doi:10.1044/1092-4388(2011/10-0024)

de Bruin, P. F., de Bruin, V. M., Lees, A. J., & Pride, N. B. (1993). Effects of treatment on airway dynamics and respiratory muscle strength in Parkinson's disease. *Am Rev Respir Dis, 148*(6 Pt 1), 1576-1580. doi:10.1164/ajrccm/148.6_Pt_1.1576

De Keyser, K., Santens, P., Bockstael, A., Botteldooren, D., Talsma, D., De Vos, S., . . . De Letter, M. (2016). The Relationship Between Speech Production and Speech Perception Deficits in Parkinson's Disease. *J Speech Lang Hear Res, 59*(5), 915-931. doi:10.1044/2016_JSLHR-S-15-0197

De Letter, M., Santens, P., De Bodt, M., Van Maele, G., Van Borsel, J., & Boon, P. (2007). The effect of levodopa on respiration and word intelligibility in people with advanced Parkinson's disease. *Clin Neurol Neurosurg, 109*(6), 495-500. doi:10.1016/j.clineuro.2007.04.003

De Letter, M., Van Borsel, J., Boon, P., De Bodt, M., Dhooge, I., & Santens, P. (2010). Sequential changes in motor speech across a levodopa cycle in advanced Parkinson's disease. *Int J Speech Lang Pathol, 12*(5), 405-413. doi:10.3109/17549507.2010.491556

Di Martino, A., Scheres, A., Margulies, D. S., Kelly, A. M., Uddin, L. Q., Shehzad, Z., . . . Milham, M. P. (2008). Functional connectivity of human striatum: a resting state FMRI study. *Cereb Cortex, 18*(12), 2735-2747. doi:10.1093/cercor/bhn041

Dichter, B. K., Breshears, J. D., Leonard, M. K., & Chang, E. F. (2018). The Control of Vocal Pitch in Human Laryngeal Motor Cortex. *Cell, 174*(1), 21-31 e29. doi:10.1016/j.cell.2018.05.016

Dromey, C., Ramig, L. O., & Johnson, A. B. (1995). Phonatory and articulatory changes associated with increased vocal intensity in Parkinson disease: a case study. *J Speech Hear Res, 38*(4), 751-764.

Duffy, J. R. (2013). *Motor speech disorders: Substrates, differential diagnosis, and management*: Elsevier Health Sciences.

Dykstra, A. D., Adams, S. G., & Jog, M. (2012a). Examining the conversational speech intelligibility of individuals with hypophonia associated with Parkinson's disease. *Journal of Medical Speech-Language Pathology, 20*(4), 53-59.

Dykstra, A. D., Adams, S. G., & Jog, M. (2012b). The effect of background noise on the speech intensity of individuals with hypophonia associated with Parkinson's disease. *Journal of Medical Speech-Language Pathology, 20*(3), 19-31.

Egan, J. J. (1971). The Lombard reflex. Historical perspective. *Arch Otolaryngol, 94*(4), 310-312. doi:10.1001/archotol.1971.00770070502004

Elfmarkova, N., Gajdos, M., Mrackova, M., Mekyska, J., Mikl, M., & Rektorova, I. (2016). Impact of Parkinson's disease and levodopa on resting state functional connectivity related to speech prosody control. *Parkinsonism Relat Disord, 22 Suppl 1*, S52-55. doi:10.1016/j.parkreldis.2015.09.006

Ellaway, P. H., Davey, N. J., Maskill, D. W., & Dick, J. P. (1995). The relation between bradykinesia and excitability of the motor cortex assessed using transcranial magnetic stimulation in normal and parkinsonian subjects. *Electroencephalogr Clin Neurophysiol, 97*(3), 169-178. doi:10.1016/0924-980x(94)00336-6

Fabbri, M., Guimaraes, I., Cardoso, R., Coelho, M., Guedes, L. C., Rosa, M. M., . . . Ferreira, J. J. (2017). Speech and Voice Response to a Levodopa Challenge in Late-Stage Parkinson's Disease. *Front*

Neurol, 8, 432. doi:10.3389/fneur.2017.00432

Fonov, V. S. E., A. C.; McKinstry, R. C.; Almli, C. R.; Collins, D. L.; Brain Development Cooperative Group. (2009). Unbiased nonlinear average age-appropriate brain templates from birth to adulthood. *NeuroImage, 47*(Supplement 1), S102. doi:http://dx.doi.org/10.1016/S1053-8119(09)70884-5

Forrest, K., Weismer, G., & Turner, G. S. (1989). Kinematic, acoustic, and perceptual analyses of connected speech produced by parkinsonian and normal geriatric adults. *J Acoust Soc Am, 85*(6), 2608-2622. doi:10.1121/1.397755

Foster, J. R., Hall, D. A., Summerfield, A. Q., Palmer, A. R., & Bowtell, R. W. (2000). Sound-level measurements and calculations of safe noise dosage during EPI at 3 T. *J Magn Reson Imaging, 12*(1), 157-163. doi:10.1002/1522-2586(200007)12:1<157::aid-jmri17>3.0.co;2-m

Garnier, M., Henrich, N., & Dubois, D. (2010). Influence of sound immersion and communicative interaction on the Lombard effect. *J Speech Lang Hear Res, 53*(3), 588-608. doi:10.1044/1092-4388(2009/08-0138)

Grabski, K., Schwartz, J.-L., Lamalle, L., Vilain, C., Vallée, N., Baciu, M., . . . Sato, M. (2013). Shared and distinct neural correlates of vowel perception and production. *Journal of Neurolinguistics, 26*(3), 384-408.

Hacker, C. D., Perlmutter, J. S., Criswell, S. R., Ances, B. M., & Snyder, A. Z. (2012). Resting state functional connectivity of the striatum in Parkinson's disease. *Brain, 135*(Pt 12), 3699-3711. doi:10.1093/brain/aws281

Hall, D. A., Haggard, M. P., Akeroyd, M. A., Palmer, A. R., Summerfield, A. Q., Elliott, M. R., . . . Bowtell, R. W. (1999). "Sparse" temporal sampling in auditory fMRI. *Hum Brain Mapp, 7*(3), 213-223. doi:10.1002/(sici)1097-0193(1999)7:3<213::aid-hbm5>3.0.co;2-n

Hammer, M. J. (2013). Aerodynamic assessment of phonatory onset in Parkinson's disease: evidence of

decreased scaling of laryngeal and respiratory control. *J Parkinsons Dis, 3*(2), 173-179. doi:10.3233/JPD-130180

Hanson, D. G., Gerratt, B. R., & Ward, P. H. (1984). Cinegraphic observations of laryngeal function in Parkinson's disease. *Laryngoscope, 94*(3), 348-353. doi:10.1288/00005537-198403000-00011

Helmich, R. C., Derikx, L. C., Bakker, M., Scheeringa, R., Bloem, B. R., & Toni, I. (2010). Spatial remapping of cortico-striatal connectivity in Parkinson's disease. *Cereb Cortex, 20*(5), 1175-1186. doi:10.1093/cercor/bhp178

Hess, C. W., & Hallett, M. (2017). The Phenomenology of Parkinson's Disease. *Semin Neurol, 37*(2), 109-117. doi:10.1055/s-0037-1601869

Ho, A. K., Bradshaw, J. L., & Iansek, R. (2008). For better or worse: The effect of levodopa on speech in Parkinson's disease. *Mov Disord, 23*(4), 574-580. doi:10.1002/mds.21899

Hoit, J. D. (1995). Influence of body position on breathing and its implications for the evaluation and treatment of speech and voice disorders. *J Voice, 9*(4), 341-347.

Holmes, R. J., Oates, J. M., Phyland, D. J., & Hughes, A. J. (2000). Voice characteristics in the progression of Parkinson's disease. *Int J Lang Commun Disord, 35*(3), 407-418.

Hovestadt, A., Bogaard, J. M., Meerwaldt, J. D., van der Meche, F. G., & Stigt, J. (1989). Pulmonary function in Parkinson's disease. *J Neurol Neurosurg Psychiatry, 52*(3), 329-333. doi:10.1136/jnnp.52.3.329

Huber, J. E., & Darling-White, M. (2017). Longitudinal Changes in Speech Breathing in Older Adults with and without Parkinson's Disease. *Semin Speech Lang, 38*(3), 200-209. doi:10.1055/s-0037-1602839

Huber, J. E., Stathopoulos, E. T., Ramig, L. O., & Lancaster, S. L. (2003). Respiratory function and variability in individuals with Parkinson disease: Pre-and post-Lee Silverman Voice Treatment. *Journal of Medical Speech-Language Pathology, 11*(4), 185-202.

Hunker, C. J., Abbs, J. H., & Barlow, S. M. (1982). The relationship between parkinsonian rigidity and hypokinesia in the orofacial system: a quantitative analysis. *Neurology, 32*(7), 749-754.

Jankovic, J. (2008). Parkinson's disease: clinical features and diagnosis. *J Neurol Neurosurg Psychiatry, 79*(4), 368-376. doi:10.1136/jnnp.2007.131045

Jiang, J., Lin, E., Wang, J., & Hanson, D. G. (1999). Glottographic measures before and after levodopa treatment in Parkinson's disease. *Laryngoscope, 109*(8), 1287-1294. doi:10.1097/00005537-199908000-00019

Jiang, J., O'Mara, T., Chen, H. J., Stern, J. I., Vlagos, D., & Hanson, D. (1999). Aerodynamic measurements of patients with Parkinson's disease. *J Voice, 13*(4), 583-591. doi:10.1016/s0892-1997(99)80012-5

Junqua, J. C. (1993). The Lombard reflex and its role on human listeners and automatic speech recognizers. *J Acoust Soc Am, 93*(1), 510-524. doi:10.1121/1.405631

Kiran, S., & Larson, C. R. (2001). Effect of duration of pitch-shifted feedback on vocal responses in patients with Parkinson's disease. *J Speech Lang Hear Res, 44*(5), 975-987. doi:10.1044/1092-4388(2001/076)

Kompoliti, K., Wang, Q. E., Goetz, C. G., Leurgans, S., & Raman, R. (2000). Effects of central dopaminergic stimulation by apomorphine on speech in Parkinson's disease. *Neurology, 54*(2), 458-462. doi:10.1212/wnl.54.2.458

Kotz, S. A., Dengler, R., & Wittfoth, M. (2015). Valence-specific conflict moderation in the dorso-medial PFC and the caudate head in emotional speech. *Soc Cogn Affect Neurosci, 10*(2), 165-171. doi:10.1093/scan/nsu021

Kotz, S. A., Meyer, M., Alter, K., Besson, M., von Cramon, D. Y., & Friederici, A. D. (2003). On the lateralization of emotional prosody: an event-related functional MR investigation. *Brain Lang, 86*(3), 366-376.

Kurani, A. S., Seidler, R. D., Burciu, R. G., Comella, C. L., Corcos, D. M., Okun, M. S., . . . Vaillancourt, D. E. (2015). Subthalamic nucleus--sensorimotor cortex functional connectivity in de novo and moderate Parkinson's disease. *Neurobiol Aging, 36*(1), 462-469. doi:10.1016/j.neurobiolaging.2014.07.004

Kurata, K. (1993). Premotor cortex of monkeys: set- and movement-related activity reflecting amplitude and direction of wrist movements. *J Neurophysiol, 69*(1), 187-200. doi:10.1152/jn.1993.69.1.187

Kwak, Y., Peltier, S., Bohnen, N. I., Muller, M. L., Dayalu, P., & Seidler, R. D. (2010). Altered resting state cortico-striatal connectivity in mild to moderate stage Parkinson's disease. *Front Syst Neurosci, 4*, 143. doi:10.3389/fnsys.2010.00143

Lane, H., & Tranel, B. (1971). The Lombard sign and the role of hearing in speech. *Journal of Speech and Hearing Research, 14*(4), 677-709.

Lefaucheur, J. P. (2005). Motor cortex dysfunction revealed by cortical excitability studies in Parkinson's disease: influence of antiparkinsonian treatment and cortical stimulation. *Clin Neurophysiol, 116*(2), 244-253. doi:10.1016/j.clinph.2004.11.017

Leopold, N. A., & Kagel, M. C. (1996). Prepharyngeal dysphagia in Parkinson's disease. *Dysphagia, 11*(1), 14-22. doi:10.1007/BF00385794

Liotti, M., Ramig, L. O., Vogel, D., New, P., Cook, C. I., Ingham, R. J., . . . Fox, P. T. (2003). Hypophonia in Parkinson's disease: neural correlates of voice treatment revealed by PET. *Neurology, 60*(3), 432-440.

Liu, H., Wang, E. Q., Metman, L. V., & Larson, C. R. (2012). Vocal responses to perturbations in voice auditory feedback in individuals with Parkinson's disease. *PLoS One, 7*(3), e33629. doi:10.1371/journal.pone.0033629

Lombard, E. (1911). Le signe de l'elevation de la voix. *Ann. Mal. de L'Oreille et du Larynx*, 101-119.

Lou, J. S., Kearns, G., Benice, T., Oken, B., Sexton, G., & Nutt, J. (2003). Levodopa improves physical

fatigue in Parkinson's disease: a double-blind, placebo-controlled, crossover study. *Mov Disord, 18*(10), 1108-1114. doi:10.1002/mds.10505

Loucks, T. M., Poletto, C. J., Simonyan, K., Reynolds, C. L., & Ludlow, C. L. (2007). Human brain activation during phonation and exhalation: common volitional control for two upper airway functions. *Neuroimage, 36*(1), 131-143. doi:10.1016/j.neuroimage.2007.01.049

Maillet, A., Krainik, A., Debu, B., Tropres, I., Lagrange, C., Thobois, S., . . . Pinto, S. (2012). Levodopa effects on hand and speech movements in patients with Parkinson's disease: a FMRI study. *PLoS One, 7*(10), e46541. doi:10.1371/journal.pone.0046541

Manes, J. L., Parkinson, A. L., Larson, C. R., Greenlee, J. D., Eickhoff, S. B., Corcos, D. M., & Robin, D. A. (2014). Connectivity of the subthalamic nucleus and globus pallidus pars interna to regions within the speech network: a meta-analytic connectivity study. *Hum Brain Mapp, 35*(7), 3499-3516.

Manes, J. L., Tjaden, K., Parrish, T., Simuni, T., Roberts, A., Greenlee, J. D., . . . Kurani, A. S. (2018). Altered resting-state functional connectivity of the putamen and internal globus pallidus is related to speech impairment in Parkinson's disease. *Brain Behav, 8*(9), e01073. doi:10.1002/brb3.1073

Maslan, J., Leng, X., Rees, C., Blalock, D., & Butler, S. G. (2011). Maximum phonation time in healthy older adults. *J Voice, 25*(6), 709-713. doi:10.1016/j.jvoice.2010.10.002

Matteau, E., Dupre, N., Langlois, M., Jean, L., Thivierge, S., Provencher, P., & Simard, M. (2011). Mattis Dementia Rating Scale 2: screening for MCI and dementia. *Am J Alzheimers Dis Other Demen, 26*(5), 389-398. doi:10.1177/1533317511412046

Matteau, E., Dupre, N., Langlois, M., Provencher, P., & Simard, M. (2012). Clinical validity of the Mattis Dementia Rating Scale-2 in Parkinson disease with MCI and dementia. *J Geriatr Psychiatry Neurol, 25*(2), 100-106. doi:10.1177/0891988712445086

Mayka, M. A., Corcos, D. M., Leurgans, S. E., & Vaillancourt, D. E. (2006). Three-dimensional locations

and boundaries of motor and premotor cortices as defined by functional brain imaging: a meta-analysis. *Neuroimage, 31*(4), 1453-1474. doi:10.1016/j.neuroimage.2006.02.004

Midi, I., Dogan, M., Koseoglu, M., Can, G., Sehitoglu, M. A., & Gunal, D. I. (2008). Voice abnormalities and their relation with motor dysfunction in Parkinson's disease. *Acta Neurol Scand, 117*(1), 26-34. doi:10.1111/j.1600-0404.2007.00965.x

Miller, N., Noble, E., Jones, D., & Burn, D. (2006). Life with communication changes in Parkinson's disease. *Age Ageing, 35*(3), 235-239. doi:10.1093/ageing/afj053

Monteiro, L., Souza-Machado, A., Valderramas, S., & Melo, A. (2012). The effect of levodopa on pulmonary function in Parkinson's disease: a systematic review and meta-analysis. *Clin Ther, 34*(5), 1049-1055. doi:10.1016/j.clinthera.2012.03.001

Narayana, S., Fox, P. T., Zhang, W., Franklin, C., Robin, D. A., Vogel, D., & Ramig, L. O. (2010). Neural correlates of efficacy of voice therapy in Parkinson's disease identified by performance-correlation analysis. *Hum Brain Mapp, 31*(2), 222-236. doi:10.1002/hbm.20859

Narayana, S., Parsons, M. B., Zhang, W., Franklin, C., Schiller, K., Choudhri, A. F., . . . Cannito, M. (2020). Mapping typical and hypokinetic dysarthric speech production network using a connected speech paradigm in functional MRI. *Neuroimage Clin, 27*, 102285. doi:10.1016/j.nicl.2020.102285

Nebel, K., Stude, P., Wiese, H., Muller, B., de Greiff, A., Forsting, M., . . . Keidel, M. (2005). Sparse imaging and continuous event-related fMRI in the visual domain: a systematic comparison. *Hum Brain Mapp, 24*(2), 130-143. doi:10.1002/hbm.20075

New, A. B., Robin, D. A., Parkinson, A. L., Eickhoff, C. R., Reetz, K., Hoffstaedter, F., . . . Eickhoff, S. B. (2015). The intrinsic resting state voice network in Parkinson's disease. *Hum Brain Mapp, 36*(5), 1951-1962. doi:10.1002/hbm.22748

Obeso, J. A., Marin, C., Rodriguez-Oroz, C., Blesa, J., Benitez-Temino, B., Mena-Segovia, J., . . .

Olanow, C. W. (2008). The basal ganglia in Parkinson's disease: current concepts and unexplained observations. *Ann Neurol, 64 Suppl 2*, S30-46. doi:10.1002/ana.21481

Olthoff, A., Baudewig, J., Kruse, E., & Dechent, P. (2008). Cortical sensorimotor control in vocalization: a functional magnetic resonance imaging study. *Laryngoscope, 118*(11), 2091-2096. doi:10.1097/MLG.0b013e31817fd40f

Ozdemir, E., Norton, A., & Schlaug, G. (2006). Shared and distinct neural correlates of singing and speaking. *Neuroimage, 33*(2), 628-635. doi:10.1016/j.neuroimage.2006.07.013

Parkinson, A. L., Flagmeier, S. G., Manes, J. L., Larson, C. R., Rogers, B., & Robin, D. A. (2012). Understanding the neural mechanisms involved in sensory control of voice production. *Neuroimage, 61*(1), 314-322. doi:10.1016/j.neuroimage.2012.02.068

Parkinson Progression Marker, I. (2011). The Parkinson Progression Marker Initiative (PPMI). *Prog Neurobiol, 95*(4), 629-635. doi:10.1016/j.pneurobio.2011.09.005

Patel, R., & Schell, K. W. (2008). The influence of linguistic content on the Lombard effect. *J Speech Lang Hear Res, 51*(1), 209-220. doi:10.1044/1092-4388(2008/016)

Pell, M. D., Cheang, H. S., & Leonard, C. L. (2006). The impact of Parkinson's disease on vocal-prosodic communication from the perspective of listeners. *Brain Lang, 97*(2), 123-134. doi:10.1016/j.bandl.2005.08.010

Pell, M. D., & Leonard, C. L. (2003). Processing emotional tone from speech in Parkinson's disease: a role for the basal ganglia. *Cogn Affect Behav Neurosci, 3*(4), 275-288. doi:10.3758/cabn.3.4.275

Perrachione, T. K., & Ghosh, S. S. (2013). Optimized design and analysis of sparse-sampling FMRI experiments. *Front Neurosci, 7*, 55. doi:10.3389/fnins.2013.00055

Pichon, S., & Kell, C. A. (2013). Affective and sensorimotor components of emotional prosody generation. *J Neurosci, 33*(4), 1640-1650. doi:10.1523/JNEUROSCI.3530-12.2013

Pinto, S., Mancini, L., Jahanshahi, M., Thornton, J. S., Tripoliti, E., Yousry, T. A., & Limousin, P.

(2011). Functional magnetic resonance imaging exploration of combined hand and speech movements in Parkinson's disease. *Mov Disord, 26*(12), 2212-2219. doi:10.1002/mds.23799

Pinto, S., Ozsancak, C., Tripoliti, E., Thobois, S., Limousin-Dowsey, P., & Auzou, P. (2004). Treatments for dysarthria in Parkinson's disease. *Lancet Neurol, 3*(9), 547-556. doi:10.1016/S1474-4422(04)00854-3

Pinto, S., Thobois, S., Costes, N., Le Bars, D., Benabid, A. L., Broussolle, E., . . . Gentil, M. (2004). Subthalamic nucleus stimulation and dysarthria in Parkinson's disease: a PET study. *Brain, 127*(Pt 3), 602-615. doi:10.1093/brain/awh074

Postuma, R. B., Berg, D., Stern, M., Poewe, W., Olanow, C. W., Oertel, W., . . . Deuschl, G. (2015). MDS clinical diagnostic criteria for Parkinson's disease. *Mov Disord, 30*(12), 1591-1601. doi:10.1002/mds.26424

Prodoehl, J., Yu, H., Little, D. M., Abraham, I., & Vaillancourt, D. E. (2008). Region of interest template for the human basal ganglia: comparing EPI and standardized space approaches. *Neuroimage, 39*(3), 956-965. doi:10.1016/j.neuroimage.2007.09.027

Ramig, L. O., Sapir, S., Fox, C., & Countryman, S. (2001). Changes in vocal loudness following intensive voice treatment (LSVT) in individuals with Parkinson's disease: a comparison with untreated patients and normal age-matched controls. *Mov Disord, 16*(1), 79-83.

Ramsay, S. C., Adams, L., Murphy, K., Corfield, D. R., Grootoonk, S., Bailey, D. L., . . . Guz, A. (1993). Regional cerebral blood flow during volitional expiration in man: a comparison with volitional inspiration. *J Physiol, 461*, 85-101. doi:10.1113/jphysiol.1993.sp019503

Ravicz, M. E., & Melcher, J. R. (2001). Isolating the auditory system from acoustic noise during functional magnetic resonance imaging: examination of noise conduction through the ear canal, head, and body. *J Acoust Soc Am, 109*(1), 216-231. doi:10.1121/1.1326083

Ravicz, M. E., Melcher, J. R., & Kiang, N. Y. (2000). Acoustic noise during functional magnetic

resonance imaging. *J Acoust Soc Am, 108*(4), 1683-1696. doi:10.1121/1.1310190

Rektorova, I., Barrett, J., Mikl, M., Rektor, I., & Paus, T. (2007). Functional abnormalities in the primary orofacial sensorimotor cortex during speech in Parkinson's disease. *Mov Disord, 22*(14), 2043-2051. doi:10.1002/mds.21548

Rektorova, I., Mikl, M., Barrett, J., Marecek, R., Rektor, I., & Paus, T. (2012). Functional neuroanatomy of vocalization in patients with Parkinson's disease. *J Neurol Sci, 313*(1-2), 7-12. doi:10.1016/j.jns.2011.10.020

Riehle, A., & Requin, J. (1989). Monkey primary motor and premotor cortex: single-cell activity related to prior information about direction and extent of an intended movement. *J Neurophysiol, 61*(3), 534-549. doi:10.1152/jn.1989.61.3.534

Robinson, J. L., Laird, A. R., Glahn, D. C., Blangero, J., Sanghera, M. K., Pessoa, L., . . . Fox, P. T. (2012). The functional connectivity of the human caudate: an application of meta-analytic connectivity modeling with behavioral filtering. *Neuroimage, 60*(1), 117-129. doi:10.1016/j.neuroimage.2011.12.010

Rosen, C. A., Lee, A. S., Osborne, J., Zullo, T., & Murry, T. (2004). Development and validation of the voice handicap index-10. *Laryngoscope, 114*(9), 1549-1556. doi:10.1097/00005537-200409000-00009

Sabate, M., Rodriguez, M., Mendez, E., Enriquez, E., & Gonzalez, I. (1996). Obstructive and restrictive pulmonary dysfunction increases disability in Parkinson disease. *Arch Phys Med Rehabil, 77*(1), 29-34. doi:10.1016/s0003-9993(96)90216-6

Sadagopan, N., & Huber, J. E. (2007). Effects of loudness cues on respiration in individuals with Parkinson's disease. *Mov Disord, 22*(5), 651-659. doi:10.1002/mds.21375

Sapir, S. (2014). Multiple factors are involved in the dysarthria associated with Parkinson's disease: a review with implications for clinical practice and research. *J Speech Lang Hear Res, 57*(4), 1330-

1343. doi:10.1044/2014_JSLHR-S-13-0039

Schilder, J. C., Overmars, S. S., Marinus, J., van Hilten, J. J., & Koehler, P. J. (2017). The terminology of akinesia, bradykinesia and hypokinesia: Past, present and future. *Parkinsonism Relat Disord, 37*, 27-35. doi:10.1016/j.parkreldis.2017.01.010

Schroder, C., Nikolova, Z. T., & Dengler, R. (2010). Changes of emotional prosody in Parkinson's disease. *J Neurol Sci, 289*(1-2), 32-35. doi:10.1016/j.jns.2009.08.038

Seghier, M. L., & Price, C. J. (2010). Reading aloud boosts connectivity through the putamen. *Cereb Cortex, 20*(3), 570-582. doi:10.1093/cercor/bhp123

Simonyan, K. (2014). The laryngeal motor cortex: its organization and connectivity. *Curr Opin Neurobiol, 28*, 15-21. doi:10.1016/j.conb.2014.05.006

Simonyan, K., Herscovitch, P., & Horwitz, B. (2013). Speech-induced striatal dopamine release is left lateralized and coupled to functional striatal circuits in healthy humans: a combined PET, fMRI and DTI study. *Neuroimage, 70*, 21-32. doi:10.1016/j.neuroimage.2012.12.042

Simonyan, K., Ostuni, J., Ludlow, C. L., & Horwitz, B. (2009). Functional but not structural networks of the human laryngeal motor cortex show left hemispheric lateralization during syllable but not breathing production. *J Neurosci, 29*(47), 14912-14923. doi:10.1523/JNEUROSCI.4897-09.2009

Skodda, S., Visser, W., & Schlegel, U. (2010). Short- and long-term dopaminergic effects on dysarthria in early Parkinson's disease. *J Neural Transm (Vienna), 117*(2), 197-205. doi:10.1007/s00702-009-0351-5

Smith, S. M., Fox, P. T., Miller, K. L., Glahn, D. C., Fox, P. M., Mackay, C. E., . . . Beckmann, C. F. (2009). Correspondence of the brain's functional architecture during activation and rest. *Proc Natl Acad Sci U S A, 106*(31), 13040-13045. doi:10.1073/pnas.0905267106

Solomon, N. P., & Hixon, T. J. (1993). Speech breathing in Parkinson's disease. *J Speech Hear Res, 36*(2), 294-310. doi:10.1044/jshr.3602.294

Soros, P., Sokoloff, L. G., Bose, A., McIntosh, A. R., Graham, S. J., & Stuss, D. T. (2006). Clustered functional MRI of overt speech production. *Neuroimage, 32*(1), 376-387. doi:10.1016/j.neuroimage.2006.02.046

Spaniol, J., Davidson, P. S., Kim, A. S., Han, H., Moscovitch, M., & Grady, C. L. (2009). Event-related fMRI studies of episodic encoding and retrieval: meta-analyses using activation likelihood estimation. *Neuropsychologia, 47*(8-9), 1765-1779. doi:10.1016/j.neuropsychologia.2009.02.028

Stathopoulos, E. T., Huber, J. E., Richardson, K., Kamphaus, J., DeCicco, D., Darling, M., . . . Sussman, J. E. (2014). Increased vocal intensity due to the Lombard effect in speakers with Parkinson's disease: simultaneous laryngeal and respiratory strategies. *J Commun Disord, 48*, 1-17. doi:10.1016/j.jcomdis.2013.12.001

Svec, J. G., & Granqvist, S. (2018). Tutorial and Guidelines on Measurement of Sound Pressure Level in Voice and Speech. *J Speech Lang Hear Res, 61*(3), 441-461. doi:10.1044/2017_JSLHR-S-17-0095

Takai, O., Brown, S., & Liotti, M. (2010). Representation of the speech effectors in the human motor cortex: somatotopy or overlap? *Brain Lang, 113*(1), 39-44. doi:10.1016/j.bandl.2010.01.008

Tessa, C., Lucetti, C., Diciotti, S., Baldacci, F., Paoli, L., Cecchi, P., . . . Mascalchi, M. (2010). Decreased and increased cortical activation coexist in de novo Parkinson's disease. *Exp Neurol, 224*(1), 299-306. doi:10.1016/j.expneurol.2010.04.005

Thickbroom, G. W., Byrnes, M. L., Walters, S., Stell, R., & Mastaglia, F. L. (2006). Motor cortex reorganisation in Parkinson's disease. *J Clin Neurosci, 13*(6), 639-642. doi:10.1016/j.jocn.2005.06.013

Tjaden, K., Lam, J., & Wilding, G. (2013). Vowel acoustics in Parkinson's disease and multiple sclerosis: comparison of clear, loud, and slow speaking conditions. *J Speech Lang Hear Res, 56*(5), 1485-1502. doi:10.1044/1092-4388(2013/12-0259)

Tjaden, K., & Wilding, G. E. (2004). Rate and loudness manipulations in dysarthria: acoustic and perceptual findings. *J Speech Lang Hear Res, 47*(4), 766-783. doi:10.1044/1092-4388(2004/058)

Tourville, J. A., & Guenther, F. H. (2011). The DIVA model: A neural theory of speech acquisition and production. *Lang Cogn Process, 26*(7), 952-981. doi:10.1080/01690960903498424

Turner, R. S., Grafton, S. T., McIntosh, A. R., DeLong, M. R., & Hoffman, J. M. (2003). The functional anatomy of parkinsonian bradykinesia. *Neuroimage, 19*(1), 163-179. doi:10.1016/s1053-8119(03)00059-4

Van Summers, W., Pisoni, D. B., Bernacki, R. H., Pedlow, R. I., & Stokes, M. A. (1988). Effects of noise on speech production: Acoustic and perceptual analyses. *The Journal of the Acoustical Society of America, 84*(3), 917-928.

Vogel, A. P., Fletcher, J., & Maruff, P. (2014). The impact of task automaticity on speech in noise. *Speech Communication, 65*, 1-8.

Walsh, B., & Smith, A. (2012). Basic parameters of articulatory movements and acoustics in individuals with Parkinson's disease. *Mov Disord, 27*(7), 843-850. doi:10.1002/mds.24888

Wingate, M. E. (1970). Effect on stuttering of changes in audition. *J Speech Hear Res, 13*(4), 861-873. doi:10.1044/jshr.1304.861

Wise, S. P., Boussaoud, D., Johnson, P. B., & Caminiti, R. (1997). Premotor and parietal cortex: corticocortical connectivity and combinatorial computations. *Annu Rev Neurosci, 20*, 25-42. doi:10.1146/annurev.neuro.20.1.25

Wong, P. C., Jin, J. X., Gunasekera, G. M., Abel, R., Lee, E. R., & Dhar, S. (2009). Aging and cortical mechanisms of speech perception in noise. *Neuropsychologia, 47*(3), 693-703. doi:10.1016/j.neuropsychologia.2008.11.032

Wu, T., Wang, L., Chen, Y., Zhao, C., Li, K., & Chan, P. (2009). Changes of functional connectivity of the motor network in the resting state in Parkinson's disease. *Neurosci Lett, 460*(1), 6-10.

doi:10.1016/j.neulet.2009.05.046

Yu, H., Sternad, D., Corcos, D. M., & Vaillancourt, D. E. (2007). Role of hyperactive cerebellum and motor cortex in Parkinson's disease. *Neuroimage, 35*(1), 222-233. doi:10.1016/j.neuroimage.2006.11.047

Yuceturk, A. V., Yilmaz, H., Egrilmez, M., & Karaca, S. (2002). Voice analysis and videolaryngostroboscopy in patients with Parkinson's disease. *Eur Arch Otorhinolaryngol, 259*(6), 290-293. doi:10.1007/s00405-002-0462-1

Zarate, J. M., & Zatorre, R. J. (2008). Experience-dependent neural substrates involved in vocal pitch regulation during singing. *Neuroimage, 40*(4), 1871-1887. doi:10.1016/j.neuroimage.2008.01.026

Zollinger, S. A., & Brumm, H. (2011a). The evolution of the Lombard effect: 100 years of psychoacoustic research. *Behaviour, 148*(11-13), 1173-1198.

Zollinger, S. A., & Brumm, H. (2011b). The Lombard effect. *Curr Biol, 21*(16), R614-615. doi:10.1016/j.cub.2011.06.003