Published in final edited form as:

J Commun Disord. 2011 ; 44(5): 549–556. doi:10.1016/j.jcomdis.2011.04.008.

Behavioral and neurophysiological correlates of striatal dopamine depletion: A rodent model of Parkinson's disease

Emily K. Plowman^{a,*} and Jeffrey A. Kleim^b

Emily K. Plowman: plowman@usf.edu

^aDepartment of Communication Sciences and Disorders, University of South Florida, Tampa, FL 33620, USA

^bSchool of Biological and Health Systems Engineering, Arizona State University, Tempe, AZ, USA

Abstract

Both limb and cranial motor functions are adversely impacted by Parkinson's disease (PD). While current pharmacological and surgical interventions are effective in alleviating general limb motor symptoms of PD, they have failed to provide significant benefit for cranial motor functions. This suggests that the neuropathologies mediating limb and cranial motor impairments in PD may differ. Animal models provide a mechanism by which the potential neural dysfunctions underlying these different motor impairments may be characterized. Central goals to our laboratory have been to (a) determine the differential responses of cranial motor and limb motor function to striatal dopamine depletion and (b) determine the differential effects of striatal dopamine depletion on the integrity of cranial motor and limb motor neural circuits. This paper details the use of a comprehensive battery of limb and cranial motor behavioral tasks and the application of intracortical microstimulation to assess corticospinal and corticobulbar circuits in a rodent model of PD. Our work suggests that striatal dopamine depletion does differentially affect cranial and limb motor function and corticospinal and corticobulbar circuits. Further, we propose that cranial motor impairments in PD may be mediated by pathology both within and outside nigrostriatal dopamine system.

Learning outcomes—Readers will be able to (a) describe a set of motor tests used to assess limb motor and cranial motor function in an animal model of Parkinson's disease, (b) understand the application of intracortical microstimulation to assess corticospinal and corticobulbar circuits, (c) describe the differential effects of dopamine depletion on limb motor and cranial motor function in a rodent model of PD, and (d) understand the potential role of dysfunction outside the nigrostriatal system mediating cranial motor impairments in Parkinson's disease.

Keywords

Parkinson's disease; Cranial motor; Limb motor; Corticobulbar; Corticospinal; Intracortical microstimulation; Rodent; Translational

*Corresponding author. Tel.: +1 813 974 2397; fax: +1 813 974 0822.

1. Introduction

Parkinson's disease (PD) is a chronic, progressive and currently non-curable neurodegenerative disease associated with substantial morbidity, increased mortality, and high economic burden. Approximately 1.5 million Americans are currently diagnosed with PD at a cost of \$23 billion dollars annually (Weintraub, Comella, & Horn, 2008) with a three to four fold increase in disease rate expected to occur over the next ten years (Tanner & Ben-Shlomo, 1999). Although PD is classically defined by the presence of general motor symptoms that include resting tremor, bradykinesia, rigidity, and postural instability, cranial motor deficits in the form of a hypokinetic dysarthria and dysphagia are reported to occur in 90% of PD patients (Sapir, Ramig, & Fox, 2008). These impairments have been documented to be associated with significant reductions in quality of life, social interactions and mental well-being (Plowman-Prine, Sapienza, et al., 2009). Alarming, aspiration pneumonia constitutes the leading cause of death in PD, resulting in a life expectancy ten years below the general population (Hely, Reid, Adena, Halliday, & Morris, 2008).

Speech and voice subsystems significantly affected in PD may include respiration, phonation, articulation, resonance, and prosody (Schulz & Grant, 2000). Hallmark perceptual characteristics of Parkinsonian speech include reduced loudness, monotony of pitch and loudness, reduced stress, variable rate, short rushes of speech, imprecise consonants, and a harsh and breathy voice (Darley, Aronson, & Brown, 1969; Plowman-Prine, Okun, et al., 2009; Ramig, Fox, & Sapir, 2008).

Swallowing impairments in PD are usually attributed to movement dysfunction of affected bulbar structures and include: lingual tremor, repetitive lingual pumping, anterior bolus leakage, slow or impaired mastication, mandible rigidity, reduced and delayed pharyngeal constrictor contraction, slow and reduced laryngeal excursion, slowing of true vocal fold closure, reduced epiglottic range of movement, reduced and delayed opening of the esophageal sphincter's, abnormal esophageal motility, and esophageal bolus redirection (Chou, Evatt, Hinson, & Kompoliti, 2007; Durham, Hodges, Henry, Geasland, & Straub, 1993; Leopold & Kagel, 1996, 1997; Nagaya, Kachi, Yamada, & Igata, 1998). These bulbar movement abnormalities may contribute to functional swallowing deficits that include: poor oral bolus control, ineffective oral transit, increased oral transit time, oral buccal residue, premature spillage of the bolus into the valleculae, delay in the execution of the swallow reflex, stasis in the valleculae or pyriforms, penetration and/or aspiration, and gastroesophageal reflux (Pitts, Bolser, Rosenbek, Troche, & Sapienza, 2008; Troche, Sapienza, & Rosenbek, 2008; Troche, Huebner, Rosenbek, Okun, & Sapienza, 2010; Troche, Okun, et al., 2010).

2. Cranial motor vs. limb motor dysfunction in Parkinson's disease

Current medical interventions for PD include levodopa replacement therapy and deep brain stimulation (DBS) of basal ganglia structures. We have recently examined the differential effects of levodopa medications on speech motor vs. limb motor function in sixteen individuals with idiopathic PD (Plowman-Prine, Okun, et al., 2009). Specific aims were to: (a) examine the effects of levodopa on 35 perceptual speech dimensions grouped into seven

speech-sign clusters and (b) compare the relative effectiveness of levodopa on global motor functioning vs. speech production. Patients read the “Grandfather Passage” both “on” and “off” levodopa medications and three blinded speech-language pathologists performed perceptual speech analyses using a seven-point ordinal scale. A movement disorders neurologist administered the Unified Parkinson's disease Rating Scale (UPDRS) to rate general motor performance across medication cycles. In this study, administration of levodopa medications was observed to have no effect on any of the 35 speech dimensions or on any of the seven speech sign clusters (see Fig. 1). In contrast to speech production, general motor performance was observed to improve on average by 33% with administration of levodopa, a finding that was both clinically and statistically significant. Interestingly, closer inspection of the UPDRS revealed significant improvements with levodopa medications for all subscales except for the two cranial motor components (speech and face subscales, see Fig. 2). Our results confirmed differential responsiveness across cranial motor and limb motor systems to dopamine replacement therapy and we hypothesized at this time that either (a) the somatotopic representation and segregated processing circuits of the basal ganglia might provide a framework to explain the noted discrepant improvements across speech motor and non-speech motor modalities or (b) speech motor function in PD relies on the operations of non-dopaminergic circuitry and/or neurotransmitters (Plowman-Prine, Okun, et al., 2009).

Other investigators have also reported a lack of change or improvement in cranial motor symptoms following treatments directed at the nigrostriatal dopaminergic system (Goberman, Coelho, & Robb, 2002; Louis, Winfield, Fahn, & Ford, 2001; Skodda, Flasskamp, & Schlegel, 2010; Solomon & Hixon, 1993) or DBS implantation of the subthalamic nucleus (Farrell, Theodoros, Ward, Hall, & Silburn, 2005; Moretti et al., 2003; Dromey, Kumar, Lang, & Lozano, 2000; Rousseaux et al., 2004; Zibetti et al., 2007) or globus pallidus (Volkmann et al., 1998). Together these results suggest that cranial motor impairments are due to neural pathologies independent or secondary to those mediating impairments in upper extremity and gait and highlight the need for the development of alternative, effective, and neurobiologically driven treatments that specifically target cranial motor deficits in PD.

3. Dissociating cranial motor vs. limb motor dysfunction in an animal model of striatal dopamine depletion

Human clinical data suggests that cranial motor and limb motor dysfunction in PD may be mediated by different underlying neural pathologies, however the precise nature of these differences are not currently well understood. Although PD has historically been thought of a disease of the basal ganglia resulting from the loss of dopaminergic neurons within the substantia nigra, there is good reason to believe that not all clinical manifestations of PD result solely from dopamine loss within the nigrostriatal pathway. Indeed, PD has now come to be recognized as a multi-system neurodegenerative disease (Braak & Del Tredici, 2008) that includes the widespread loss of cholinergic, serotonergic, and noradrenergic neurons within the brainstem, spinal cord, and peripheral nervous system (Olanow & Prusiner, 2009).

Animal models provide a platform for investigating how dysfunction within specific neural systems known to be affected in PD manifest as impairments in specific classes of behavior. Using a variety of neurochemical and behavioral manipulations basic scientists can attempt to dissect out the specific behavioral effects of selectively disrupting different systems in laboratory animals. Because PD is associated, in part, with a loss of dopamine within the striatum, striatal dopamine depletion has become the primary animal model of PD. We have applied this model to specifically examine the effects of striatal dopamine depletion on cranial vs. limb motor function. The long-term goal is to use this information to develop neurobiologically informed therapies that specifically target oral motor impairment to be translated to the human patient population. More effective treatment strategies of oral motor dysfunction in PD will improve patient quality of life, reduce individual health care cost and ultimately reduce PD related mortality.

3.1. Rodent model of striatal dopamine depletion

Although there are number of different techniques for depleting dopamine, the two most common involve either injecting the neurotoxin 6-hydroxydopamine (6-OHDA) directly into the striatum or into the fibers of the medial forebrain bundle that carry dopamine to the striatum from the substantia nigra. Intrastratial injections involve four infusions of 6-OHDA spanning the entire length of the striatum. This induces direct toxic damage to the dopaminergic terminal axons and gradual dopamine depletion occurs over approximately four weeks (Kirik, Rosenblad, & Bjorklund, 1998). Injections into the medial forebrain bundle involve one infusion into the dopaminergic axons from the substantia nigra and dopamine depletion and Parkinson's symptoms occur more rapidly and usually within 48 h. The degree of dopamine depletion can then be verified using standard immunohistochemistry techniques that assay the levels of the dopamine synthesizing enzyme tyrosine hydroxylase (Fig. 3).

3.2. Motor testing battery

We have employed a sensitive behavioral testing assay that utilizes existing and well-established behavioral tests that differentially assess limb and cranial motor function. Fig. 4 depicts this motor testing battery along a spectrum with limb motor tasks to the left (green) and cranial motor tasks to the right (red).

3.2.1. Cylinder task—Animals are placed into a transparent cylinder (20 cm × 30 cm) and spontaneous forelimb placement during vertical exploration of the novel environment is observed (Shallert & Woodlee, 2005). The number of independent wall placements of the dominant and the non-dominant forelimb are recorded as well as the number of times the animal shifts its weight using rapid alternating wall-stepping movements (counted as “both limbs”). An asymmetry ratio is then calculated as an index of voluntary forelimb use $[(\# \text{ non-dominant} + 1/2 \text{ both}) \div (\# \text{ non-dominant} + \# \text{ dominant} + \# \text{ both}) \times 100]$ (Schallert, Kozlowski, Humm, & Cocke, 1997). In our work with unilaterally depleted 6-OHDA rodents, this variable has correlated with degree of dopamine depletion and is a useful indicator of PD severity of a particular animal during the experiment.

3.2.2. Single pellet reaching—Animals are trained to reach through a 1 cm slot with a preferred limb for a small food pellet. This is a learned behavior that requires daily training and the acquisition of a skilled reaching movement from a small well over several weeks. A successful reach is scored when the animal grasps the food pellet and brings it into the cage and to its mouth without dropping the pellet (Whishaw, Pellis, Gorny, & Pellis, 1991). Although in depth biomechanical analyses can be performed on this task, basic measures used in our laboratory include: (a) percentage of successful reaches, (b) number of sensory errors, and (c) total number of reach attempts.

3.2.3. Vermicelli pasta handling—This eating task is a simple quantitative measure of forepaw dexterity (Tennant et al., 2010). Animals are given five strands of 7 cm uncooked vermicelli strands in their home cage and video recorded for subsequent analyses. Following the protocol of Allred et al. (2008), the following measures are made: (a) time to eat each strand, (b) number of forepaw adjustments, and (b) asymmetry ratio (%) of forepaw adjustments (# non-dominant adjustments/total # adjustments).

3.2.4. Sunflower seed opening—Animals are placed into a clear plastic arena with five sunflower seeds located in the upper right hand corner. A mirror is placed at a 120 degree angle at the back of the enclosure to allow visualization of sunflower manipulation in the instance that the rat faced away from the experimenter and towards the back of the enclosure. The experimenter makes two measurements online: (a) total time spent manipulating, opening, and placing the seed into the mouth across all five trials and (b) the total number of shell pieces produced to open the five seeds (Whishaw & Coles, 1996).

3.2.5. Vermicelli pasta biting acoustics—Tim Schallert's laboratory pioneered the novel idea of recording acoustic properties of rodent chewing and biting patterns (see Kane et al., this issue). Animals are placed in a plexiglass arena set up inside a sound-proof chamber and presented 5 uncooked vermicelli pasta strands. Audio recordings of chewing sounds are obtained using an AudioTechnica Model ATM73a unidirectional microphone digitized directly to a Marantz PMD670 recorder equipped with a built in pre-amplifier. Acoustic waveforms are digitized and high pass filtered at 3000 kHz for subsequent analysis of frequency, time and amplitude components using Adobe Audition version 3.

3.2.6. Lick-force task—Rats are placed in a lick-force recording chamber previously described by Fowler and Wang (1998). Briefly, this enclosure contains a lick disk (18 mm in diameter) attached to the shaft of a force transducer with a computer controlled peristaltic pump that delivers water to the center of the lick disk through a 0.5 mm diameter hole. The force transducer is capable of resolving force measurements to 0.2 g equivalent weights. Through a Labmaster interface (Scientific Solutions, Mentor, OH) a computer program records session force–time data at a rate of 100 samples per second, allowing for force–time waveforms of each individual lick. During training, the force requirement for a water bolus reward is set at 2 g and continuous licking behavior is reinforced by delivery of 0.06 ml of water to the lick disk surface after every 12th lick (fixed-ratio of FR12 schedule). Training occurs for fourteen continuous days and lick-force waveforms from the final two days of training are averaged to represent lingual performance at a particular time point (pre-lesion

or post-lesion). The Labmaster interface program quantifies the following lingual parameters: (a) total number of licks, (b) average lick peak force, (c) maximal lick force, and (d) lick rhythm.

We have used this motor testing battery to obtain comprehensive profiles of limb motor vs. cranial motor dysfunction following dopamine depletion. Our recent work has shown that while unilateral striatal dopamine depletion significantly impairs both limb and cranial motor function, limb motor impairments are more severe than cranial motor impairments. Further, only limb motor impairments have been significantly correlated to degree of dopamine depletion (see Fig. 6).

4. Investigating corticospinal and corticobulbar circuits in a rodent model of Parkinson's disease

Although the finding that striatal dopamine depletion appears to differentially affect cranial vs. limb motor function, these data do not provide us with any direct insight into the specific mechanisms mediating these differences. Identifying the specific neuropathologies mediating any neurological impairment is not trivial, however animal models provide the opportunity to examine the specific neurophysiological and neuroanatomical consequences of disrupting those neural systems affected in PD. We have employed intracortical microstimulation (ICMS) to begin to investigate how striatal dopamine depletion differentially affects corticobulbar (cranial motor) and corticospinal (limb motor) neural circuits by examining movement representations across the different classes of movement.

During ICMS, animals are anesthetized under sterile conditions and a craniotomy is performed to expose the motor cortex. A glass microelectrode is then systematically lowered 1550 μ m to cortical layer V where small amounts of current are passed to transynaptically activate corticospinal and corticobulbar neurons. Animals are in a prone position and, at each stimulation site, movement thresholds for the shoulder, wrist, jaw and tongue are recorded. A detailed motor map is then created for limb motor and cranial motor circuits and total motor map area (mm²) and mean threshold (μ A) for each body region of interest calculated. Our work has shown that while both limb and cranial motor maps are significantly reduced following striatal dopamine depletion, limb motor maps are more dramatically reduced. Further, only limb motor maps are significantly correlated with degree of dopamine depletion. An example of a representative motor map for control and unilateral 6-OHDA animals are shown in Fig. 5A and B respectively.

5. Why would cranial motor and limb motor functions be differentially affected by striatal dopamine depletion?

As described above, the neuropathology of PD is complex and involves dysfunction within multiple neural systems, including the nigrostriatal dopamine pathway (Braak & Del Tredici, 2008). Results from our preliminary animal studies suggest that striatal dopamine depletion significantly impairs both limb and cranial motor function, and this is reflected as a loss in cortical movement representations. However, limb motor impairments are more severe than cranial motor impairments, are associated with a more dramatic loss in motor

maps, and are more highly correlated with degree of dopamine depletion than cranial motor function and circuits. This is consistent with the clinical observation that therapies targeting the nigrostriatal dopaminergic system are more effective for limb motor symptoms than cranial motor impairments in PD. There are several possible explanations and important considerations when interpreting these animal data. First, the results may be biased by the specific animal model we have chosen. This is an important concern when attempting to translate preclinical studies to human patient populations. Intrastriatal injections of 6-OHDA may have behavioral effects different from other models of dopamine depletion. Second, this animal model depletes dopamine over several weeks whereas human PD patients lose dopamine over several decades. The resulting behavioral and neural dysfunctions may therefore differ. Further, most animal models of PD involve manipulations that deplete dopamine unilaterally whereas individuals with PD experience loss that progresses bilaterally. This is particularly important given that cranial motor function and corticobulbar tracts are much less lateralized than limb motor and corticospinal projections.

If we assume that our animal models are at least in part reflecting the human PD condition, an alternative explanation may be that cranial motor impairments are mediated by pathologies outside of the nigrostriatal dopaminergic system. An interesting hypothesis is that axial motor (including cranial motor) impairments in PD are due to degeneration of neurons within the locus coeruleus (LC) (Grimbergen, Langston, Roos, & Bloem, 2009). The LC is a small brainstem nucleus situated bilaterally in the pontine tegmentum and represents the primary source of norepinephrine (NE) for much of the CNS (Mann & Yates, 1983). Post-mortem studies of PD patients have demonstrated profound cell loss within the LC, particularly in the caudal region (Chan-Palay & Asan, 1989) known to project to the cerebellum (Mason & Corcoran, 1979) that is integrally involved in a number of cranial motor functions including speech (Ackermann, 2008), swallow (Mosier & Bereznya, 2001), and respiration (Xu & Frazier, 2000). Indeed, the proportion of neural degeneration in the LC has been reported to be greater than that observed within the substantia nigra in individuals with PD (Zarow, Lyness, Mortimer, & Chui, 2003). Consistent with the reported cell loss in the LC of PD patients, cerebrospinal fluid analysis and postmortem studies have demonstrated reduced levels of NE and its metabolites (Kish, Shannak, Rajput, Gilbert, & Hornykiewicz, 1984; Maruyama, Naoi, & Narabayashi, 1996).

6. Conclusions

Parkinson's disease significantly impairs cranial motor function and while current medical interventions alleviate general motor dysfunction, they fail to consistently benefit cranial motor impairments in this disease population. This paper has detailed the use of a rodent model to investigate the potential different neuropathologies mediating cranial motor vs. limb motor dysfunction in PD. Our work demonstrates that (a) striatal dopamine depletion significantly impairs both limb and cranial motor function and this is reflected as a loss in cortical motor representations and (b) limb motor impairments are more severe than cranial motor impairments, are related to degree of dopamine depletion, and are associated with a more dramatic loss in movement representations. These results suggest that limb motor function and circuits are more sensitive to dopamine transmission and that cranial motor function may be due to dysfunction within other neurotransmitter systems and

structures in PD. Future work will explore this possibility and use this model as a platform to develop and test neurobiologically based therapies for cranial motor function in PD.

Appendix A: Continuing education

1. Pharmacological and surgical treatments used in Parkinson's disease have been shown to be:
 - a. consistently effective for both limb and cranial motor function
 - b. consistently effective for cranial motor but not limb motor function
 - c. consistently effective for limb motor but not cranial motor function
2. Parkinson disease can be modeled in a rodent by injecting a neurotoxin 6-hydroxydopamine into two specific targets in the brain. They are:
 - a. medial forebrain bundle and cerebellum
 - b. medial forebrain bundle and thalamus
 - c. striatum and medial forebrain bundle
 - d. striatum and cerebellum
3. Behavioral tests for cranial motor function in rodents include:
 - a. cylinder task
 - b. lick-force task
 - c. pasta biting
 - d. skilled reaching
 - e. both b and c
4. One method of assessing the integrity of corticospinal and corticobulbar neural circuits in animal models is:
 - a. intracortical microstimulation
 - b. acoustic analysis
 - c. sunflower seed test
 - d. ultrasound
5. Dopamine appears to be the most important neurotransmitter for speech and swallowing in Parkinson's disease:
 - a. true
 - b. false

References

- Ackermann H. Cerebellar contributions to speech production and speech perception: Psycholinguistic and neurobiological perspectives. *Trends in Neurosciences*. 2008; 31(6):265–272. [PubMed: 18471906]
- Allred RP, Adkins DL, Woodlee MT, Husbands LC, Maldonado MA, Kane JR, et al. The vermicelli handling test: A simple quantitative measure of dexterous forepaw function in rats. *Journal of Neuroscience Methods*. 2008; 170(2):229–244. [PubMed: 18325597]
- Braak H, Del Tredici K. Cortico-basal ganglia-cortical circuitry in Parkinson's disease reconsidered. *Experimental Neurology*. 2008; 212(1):226–229. [PubMed: 18501351]
- Chan-Palay V, Asan E. Quantitation of catecholamine neurons in the locus coeruleus in human brains of normal young and older adults and in depression. *Journal of Comparative Neurology*. 1989; 287(3):357–372. [PubMed: 2570793]
- Chou KL, Evatt M, Hinson V, Kompoliti K. Sialorrhea in Parkinson's disease: A review. *Movement Disorders*. 2007; 22(16):2306–2313. [PubMed: 17659637]
- Darley FL, Aronson AE, Brown JR. Differential diagnostic patterns of dysarthria. *Journal of Speech, Language, and Hearing Research*. 1969; 12(2):246–269.
- Dromey C, Kumar R, Lang AE, Lozano AM. An investigation of the effects of subthalamic nucleus stimulation on acoustic measures of voice. *Movement Disorders*. 2000; 15(6):1132–1138. [PubMed: 11104196]
- Durham TM, Hodges ED, Henry MJ, Geasland J, Straub P. Management of orofacial manifestations of Parkinson's disease with splint therapy: A case report. *Special Care in Dentistry*. 1993; 13(4):155–158. [PubMed: 8303510]
- Farrell A, Theodoros D, Ward E, Hall B, Silburn P. Effects of neurosurgical management of Parkinson's disease on speech characteristics and oromotor function. *Journal of Speech, Language, and Hearing Research*. 2005; 48(1):5–20.
- Fowler SC, Wang G. Chronic haloperidol produces a time- and dose-related slowing of lick rhythm in rats: Implications for rodent models of tardive dyskinesia and neuroleptic-induced parkinsonism. *Psychopharmacology (Berl)*. 1998; 137(1):50–60. [PubMed: 9631956]
- Goberman A, Coelho C, Robb M. Phonatory characteristics of parkinsonian speech before and after morning medication: The ON and OFF states. *Journal of Communication Disorders*. 2002; 35(3):217–239. [PubMed: 12064785]
- Grimbergen YA, Langston JW, Roos RA, Bloem BR. Postural instability in Parkinson's disease: The adrenergic hypothesis and the locus coeruleus. *Expert Review of Neurotherapeutics*. 2009; 9(2):279–290. [PubMed: 19210201]
- Hely MA, Reid WG, Adena MA, Halliday GM, Morris JG. The Sydney multicenter study of Parkinson's disease: The inevitability of dementia at 20 years. *Movement Disorders*. 2008; 23(6):837–844. [PubMed: 18307261]
- Kane JR, Ciucci MR, Jacobs AN, Tews N, Russell JA, Ahrens AM, et al. Assessing the role of dopamine in limb and cranial oromotor control in a rat model of Parkinson's disease. *Journal of Communication Disorders*. this issue.
- Kirik D, Rosenblad C, Bjorklund A. Characterization of behavioral and neurodegenerative changes following partial lesions of the nigrostriatal dopamine system induced by intrastriatal 6-hydroxydopamine in the rat. *Experimental Neurology*. 1998; 152(2):259–277. [PubMed: 9710526]
- Kish SJ, Shannak KS, Rajput AH, Gilbert JJ, Hornykiewicz O. Cerebellar norepinephrine in patients with Parkinson's disease and control subjects. *Archives of Neurology*. 1984; 41(6):612–614. [PubMed: 6721735]
- Leopold NA, Kagel MC. Prepharyngeal dysphagia in Parkinson's disease. *Dysphagia*. 1996; 11(1):14–22. [PubMed: 8556872]
- Leopold NA, Kagel MC. Pharyngo-esophageal dysphagia in Parkinson's disease. *Dysphagia*. 1997; 12(1):11–20. [PubMed: 8997827]
- Louis ED, Winfield L, Fahn S, Ford B. Speech dysfluency exacerbated by levodopa in Parkinson's disease. *Movement Disorders*. 2001; 16(3):562–565. [PubMed: 11391759]

- Mann DM, Yates PO. Pathological basis for neurotransmitter changes in Parkinson's disease. *Neuropathology and Applied Neurobiology*. 1983; 9(1):3–19. [PubMed: 6133229]
- Maruyama W, Naoi M, Narabayashi H. The metabolism of L-DOPA and L-threo-3,4-dihydroxyphenylserine and their effects on monoamines in the human brain: Analysis of the intraventricular fluid from parkinsonian patients. *Journal of the Neurological Sciences*. 1996; 139(1):141–148. [PubMed: 8836986]
- Mason ST, Corcoran ME. Seizure susceptibility after depletion of spinal or cerebellar noradrenaline with 6-OHDA. *Brain Research*. 1979; 166(2):418–421. [PubMed: 427596]
- Moretti R, Torre P, Antonello RM, Capus L, Gioulis M, Zambito Marsala S, et al. 'Speech initiation hesitation' following subthalamic nucleus stimulation in a patient with Parkinson's disease. *European Neurology*. 2003; 49(4):251–253. [PubMed: 12736547]
- Mosier K, Bereznaya I. Parallel cortical networks for volitional control of swallowing in humans. *Experimental Brain Research*. 2001; 140(3):280–289. [PubMed: 11681303]
- Nagaya M, Kachi T, Yamada T, Igata A. Videofluorographic study of swallowing in Parkinson's disease. *Dysphagia*. 1998; 13(2):95–100. [PubMed: 9513304]
- Olanow CW, Prusiner SB. Is Parkinson's disease a prion disorder? *Proceedings of the National Academy of Sciences of the United States of America*. 2009; 106(31):12571–12572. [PubMed: 19666621]
- Pitts T, Bolser D, Rosenbek J, Troche M, Sapienza C. Voluntary cough production and swallow dysfunction in Parkinson's disease. *Dysphagia*. 2008; 23(3):297–301. [PubMed: 18483823]
- Plowman-Prine EK, Okun MS, Sapienza CM, Shrivastav R, Fernandez HH, Foote KD, et al. Perceptual characteristics of Parkinsonian speech: A comparison of the pharmacological effects of levodopa across speech and non-speech motor systems. *NeuroRehabilitation*. 2009; 24(2):131–144. [PubMed: 19339752]
- Plowman-Prine EK, Sapienza CM, Okun MS, Pollock SL, Jacobson C, Wu SS, et al. The relationship between quality of life and swallowing in Parkinson's disease. *Movement Disorders*. 2009; 24(9):1352–1358. [PubMed: 19425089]
- Ramig LO, Fox C, Sapis S. Speech treatment for Parkinson's disease. *Expert Review of Neurotherapeutics*. 2008; 8(2):297–309. [PubMed: 18271714]
- Rousseaux M, Krystkowiak P, Kozłowski O, Ozsancak C, Blond S, Destee A. Effects of subthalamic nucleus stimulation on parkinsonian dysarthria and speech intelligibility. *Journal of Neurology*. 2004; 251(3):327–334. [PubMed: 15015014]
- Sapis S, Ramig L, Fox C. Speech and swallowing disorders in Parkinson disease. *Current Opinion in Otolaryngology & Head and Neck Surgery*. 2008; 16(3):205–210. [PubMed: 18475072]
- Schallert T, Kozłowski DA, Humm JL, Cocke RR. Use-dependent structural events in recovery of function. *Advances in Neurology*. 1997; 73:229–238. [PubMed: 8959217]
- Schulz GM, Grant MK. Effects of speech therapy and pharmacologic and surgical treatments on voice and speech in Parkinson's disease: A review of the literature. *Journal of Communication Disorders*. 2000; 33(1):59–88. [PubMed: 10665513]
- Shallert, T.; Woodlee, MT. Orienting and placing. In: Whishaw, IQ.; Kolb, B., editors. *The behavior of the laboratory rat: A handbook with tests*. Oxford: Oxford University Press; 2005. p. 129-140.
- Skodda S, Flasskamp A, Schlegel U. Instability of syllable repetition in Parkinson's disease-Influence of levodopa and deep brain stimulation [Electronic version]. *Movement Disorders*. 2010; 25(10):1002/1002.23439
- Solomon NP, Hixon TJ. Speech breathing in Parkinson's disease. *Journal of Speech, Language, and Hearing Research*. 1993; 36(2):294–310.
- Tanner CM, Ben-Shlomo Y. Epidemiology of Parkinson's disease. *Advances in Neurology*. 1999; 80:153–159. [PubMed: 10410715]
- Tennant KA, Asay AL, Allred RP, Ozburn AR, Kleim JA, Jones TA. The vermicelli and capellini handling tests: Simple quantitative measures of dexterous forepaw function in rats and mice [Electronic version]. *Journal of Visualized Experiments*. 2010; 4110.3791/2076
- Troche MS, Huebner I, Rosenbek JC, Okun MS, Sapienza CM. Respiratory-swallowing coordination and swallowing safety in patients with Parkinson's disease [Electronic version]. *Dysphagia*. 2010

- Troche MS, Okun MS, Rosenbek JC, Musson N, Fernandez HH, Rodriguez R, et al. Aspiration and swallowing in Parkinson disease and rehabilitation with EMST: A randomized trial. *Neurology*. 2010; 75(21):1912–1919. [PubMed: 21098406]
- Troche MS, Sapienza CM, Rosenbek JC. Effects of bolus consistency on timing and safety of swallow in patients with Parkinson's disease. *Dysphagia*. 2008; 23(1):26–32. [PubMed: 17551793]
- Volkman J, Sturm V, Weiss P, Kappler J, Voges J, Koulousakis A, et al. Bilateral high-frequency stimulation of the internal globus pallidus in advanced Parkinson's disease. *Annals of Neurology*. 1998; 44(6):953–961. [PubMed: 9851441]
- Weintraub D, Comella CL, Horn S. Parkinson's disease—Part 1: Pathophysiology, symptoms, burden, diagnosis, and assessment. *American Journal of Managed Care*. 2008; 14(Suppl. 2):40–48.
- Whishaw IQ, Coles BL. Varieties of paw and digit movement during spontaneous food handling in rats: Postures, bimanual coordination, preferences, and the effect of forelimb cortex lesions. *Behavioural Brain Research*. 1996; 77(1–2):135–148. [PubMed: 8762164]
- Whishaw IQ, Pellis SM, Gorny BP, Pellis VC. The impairments in reaching and the movements of compensation in rats with motor cortex lesions: An endpoint, videorecording, and movement notation analysis. *Behavioural Brain Research*. 1991; 42(1):77–91. [PubMed: 2029348]
- Xu F, Frazier DT. Modulation of respiratory motor output by cerebellar deep nuclei in the rat. *Journal of Applied Physiology*. 2000; 89(3):996–1004. [PubMed: 10956343]
- Zarow C, Lyness SA, Mortimer JA, Chui HC. Neuronal loss is greater in the locus coeruleus than nucleus basalis and substantia nigra in Alzheimer and Parkinson diseases. *Archives of Neurology*. 2003; 60(3):337–341. [PubMed: 12633144]
- Zibetti M, Torre E, Cinquepalmi A, Rosso M, Ducati A, Bergamasco B, et al. Motor and nonmotor symptom follow-up in parkinsonian patients after deep brain stimulation of the subthalamic nucleus. *European Neurology*. 2007; 58(4):218–223. [PubMed: 17823535]

Fig. 1. Mean Unified Parkinson's disease Rating Scale (UPDRS) subscale scores. All subscales significantly improved (decreased) following administration of levodopa medications except the two cranial motor subscales (speech and face).

Fig. 2. Mean speech-sign cluster perceptual ratings “on” and “off levodopa medications showing no significant improvements/changes following administration of medication.

Fig. 3.

Representative coronal sections through the striatum of a control (A) and a unilateral depleted 6-OHDA rat (B). Using a stain with a near infrared fluorescent tag for tyrosine hydroxylase, dopamine depletion can be calculated using standard densitometry techniques. Note that an artificial cut has been made in the left hemisphere for identification purposes.

Fig. 4. Behavioral testing battery of tasks relying differentially on the limb motor vs. the cranial motor functions. Using this battery of tests we have been able to dissociate limb and cranial motor function following unilateral and bilateral dopamine depletion.

Fig. 5. Representative ICMS motor maps for a control (A) and unilateral 6-OHDA rat (B). Tongue = red, jaw= orange; wrist=green; elbow= blue; pink =whisker; yellow= neck and black=no response. Forelimb and oral motor maps are reduced in the 6-OHDA animal; however forelimb motor maps are more dramatically reduced. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of the article.)

Fig. 6. Summary of Pearson's R correlation values for each behavioral task and motor maps with TH depletion showing significant relationships between limb motor tasks and map (black) with TH depletion but not with cranial motor tasks and cranial maps (white) and TH depletion. Significant correlations are denoted with an asterisk (*).