



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

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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.

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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

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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,

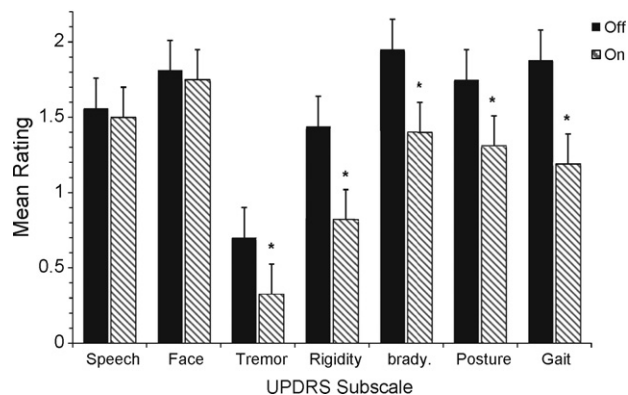


Fig. 1. Mean Unified Parkinson's disease Rating Scale (UPDRS) subscale scores. All subscales significantly improved (decreased) following administration of levodopa medications except the two cranial motor subscales (speech and face).

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