Published in final edited form as:

Exp Brain Res. 2009 April ; 194(4): 587–596. doi:10.1007/s00221-009-1736-2.

Dopaminergic influence on rat tongue function and limb movement initiation

Michelle R Ciucci, PhD [Post-Doctoral Fellow] and

Department of Surgery Division of Otolaryngology University of Wisconsin 600 Highland Avenue
K4/709 Madison, WI 53792 (608) 263-0192 ciucci@surgey.wisc.edu

Nadine P Connor, PhD [Assistant Professor]

Department of Surgery Division of Otolaryngology University of Wisconsin 600 Highland Avenue
K4/709 Madison, WI 53792 (608) 265-8711 connor@surgey.wisc.edu

Abstract

Altering dopamine synaptic transmission can affect both cranial and limb sensorimotor function, but often to a different degree of severity. We hypothesized that haloperidol has dose-dependent but differential effects on lingual forces, lingual movement rates, and limb movement initiation. We measured average and maximal lingual force, tongue press rate and cataleptic descent time in 9 Fischer 344/Brown Norway rats in varied doses of haloperidol. Decreases in lingual force and temporal parameters and increases in cataleptic descent time were related to haloperidol dose. However, they were related to a different degree as the relationships were strong between average force and tongue press rate, moderate between maximal force and tongue press rate, moderate between average force and cataleptic descent time, and weak between maximal force and cataleptic descent time. Elucidating the relationships between the cranial and limb sensorimotor systems in the context of altered dopamine synaptic transmission may assist in developing therapies for conditions such as Parkinson's disease.

Keywords

tongue; haloperidol; dopamine; rat

Introduction

The cardinal signs leading to a diagnosis of Parkinson's disease (PD) are tremor, bradykinesia, and rigidity (DeLong & Wichmann, 2007), although it is widely understood that PD encompasses deficits in the cognitive, affective, gastrointestinal, sensory, communication, and swallowing domains (Cheon et al., 2008; Dubois & Pilon, 1997; Farley & Koshland, 2005; Horak, Frank & Nutt, 1996; Marras, et al., 2008; Miller, et al., 2008; Nilsson, Ekberg, Olsson, Hindfelt, 1996; Miller, Noble, Jones & Burn 2006; Owen et al., 1992; Potulska, Friedman, Krolicki, Spychala, 2003; Schneider, Diamond & Markham, 1986). It is estimated that between 50 to 90% of patients with PD experience some form of disordered swallowing (dysphagia) (Eadie & Tyrer, 1965; Hunter, Crameri, Austin, Woodward & Hughes, 1997) and the consequences range from mild difficulty with certain foods to death caused by aspiration pneumonia (Wang et al., 2002). Recent evidence has shown that the disease process begins in the lower brainstem, in the dorsal motor nucleus of the vagus, and progresses rostrally affecting gain setting nuclei in the brainstem, nigrostriatal pathways, allocortex, mesocortex, and

eventually the neocortex (Braak, et al., 2004). Accordingly, it is not surprising that cranial sensorimotor systems are affected by the disease.

The diagnosis of PD, which relies primarily on symptoms found in the limbs, generally does not occur until Braak stages III-IV when the degeneration has progressed to the midbrain, basal forebrain and transition zone between allocortex and neocortex (Braak et al., 2004). Cranial sensorimotor systems may already be affected during preclinical early stages (Stages I-II), given that brainstem degeneration has been found in Stages I-II within the gigantocellular nucleus (Braak et al., 2004), which innervates the caudal hypoglossal nucleus. These areas also receive projections from the periaqueductal gray, the paraventricular hypothalamic nucleus, central nucleus of the amygdala, lateral hypothalamic area, and parvocellular reticular nucleus (Yang et al., 2005). Thus, there is clear potential for early disruption in critical cranial sensorimotor functions, such as voice and swallowing, due to the reliance on complex integration of all of these systems for proper function (Jurgens, 2002). However, it is unclear when or to what degree cranial deficits appear in relation to the emergence of other general sensorimotor deficits, such as those frequently observed in limb movement initiation.

Although PD involves multiple sensory and motor functions, many clinical signs of dysphagia are associated with lingual dysfunction, such as aberrant movements (Leopold & Kagel, 1996), increased number of swallows per bolus (Bird, Woodward, Gibson, Phyland & Fonda, 1992; Nagaya, Kachi, Yamata & Igata, 1998), tongue pumping (festinated lingual movements) (Bird, et al., 1992; Leopold & Kagel, 1996; Nagaya, et al., 1998), premature or uncontrolled loss of bolus from the oral cavity (Nagaya, et al., 1998), and residue on the tongue (Nagaya, et al., 1998). Similarly, neuroleptic therapies, which interfere with dopaminergic synaptic transmission, have been linked with 'extrapyramidal' signs that affect both the oral and pharyngeal phases of swallowing (Dziewas, et al., 2007; Hayashi et al., 1997; Sokoloff & Pavlakovic, 1997) and can lead to airway compromise (Fioritti, Giaccotto, Melega, 1997). Of the subtypes, neuroleptic-induced bradykinetic dysphagia and dyskinetic dysphagia share features of Parkinsonian dysphagia, including aberrant tongue movements (Gregory, Smith, Rudge, 1992), tongue pumping (Sokoloff & Pavlakovic, 1997; Bashford & Bradd, 1996), reduced base of tongue movement (Sokoloff & Pavlakovic, 1997; Leopold & Kagel, 1996), poor bolus control (Stewart, 2003), and disorganized oral movements (Bashford & Bradd, 1996). Clearly, dopaminergic synaptic transmission plays a role in swallowing and interruption of normal lingual function can contribute to dysphagia. It is unclear if these deficits are related to issues of tongue force generation, timing, or both.

There may be differences in the manifestations of dopamine loss across general/limb and cranial sensorimotor systems. For instance, as previously discussed, limb and cranial deficits in patients with PD do not always follow the same time-course in terms of their emergence (Miller et al., 2008). Further, pharmaceutical and surgical therapies aimed at improving sensorimotor function in PD do not reliably improve all aspects of swallowing, while benefiting limb sensorimotor control (Ciucci, Barkmeier-Kraemer & Sherman, 2008; Fuh, Lee, Wang, et al. 1997; Hunter, Crameri, Austin, Woodward & Hughes, 1997; Potulska, Friedman, Krolicki, Jedrzejaowski & Sychala, 2002). Studies aimed at examination of sensorimotor functions solely within the limbs or within cranial structures cannot address issues of differential impairment in relation to magnitude of dopamine dysfunction (Connor, Abbs, Cole & Gracco, 1989). Accordingly, it appears necessary to study the effects of dopamine loss in more than one muscle group or movement type in a given experimental subject to gain a global understanding of the influence of dopamine on sensorimotor function.

Previous research has shown that haloperidol (a D2 dopamine receptor antagonist) administration leads to a dose-dependent decrease in peak tongue force, movement duration, and number of licks per session (Das & Fowler, 1995; Fowler & Das 1993). These deficits

were reversible with anticholinergic therapy, suggesting that this paradigm represents a good model for neuroleptic-induced deficits and PD. However, the nature of these deficits and how they potentially relate to both oral and general/limb sensorimotor impairments have not been examined. Additionally, the relationships among temporal and force characteristics and general/limb sensorimotor impairment have not been adequately studied. Our hypotheses were that interfering with dopaminergic synaptic transmission will: a) decrease lingual force and movement rate parameters as well as limb movement initiation, and, b) will differentially affect lingual and general/limb sensorimotor systems. To test these hypotheses, we employed a rat model of complex protrusive tongue behaviors and behavioral measures of upper limb movement initiation (i.e. cataleptic descent) (Alvarez-Cervera, Villaneuva-Toledo, Moo-Puc, et al., 2006; Sanberg, Bunsey, Giordano, & Norman, 1988).

Methods

Subjects

Nine male 9-month-old Fischer 344/Brown Norway rats were used in this study with 3 different levels of haloperidol-induced dopaminergic dysfunction and a control condition. Animals were housed in pairs in standard polycarbonate cages on a 12:12 light-dark reversed light cycle. Rats were obtained from Charles River (Raleigh, NC) 8 weeks prior to the start of the tongue exercise program to allow acclimation to the animal care facility, reversal of light cycle, water restriction, and familiarization to the operandum. Food was given ad libitum. Water was restricted to 3 hours per day after training to press a disk for water reward (described below). All experiments were approved by the University of Wisconsin Institutional Animal Care and Use Committee (IACUC).

Measurement

Lingual Force and Temporal Measurement—A custom instrument was designed, based on previous research on rodent models of licking behavior (Figure 1) (Fowler & Mortell, 1992; Moss *et al.*, 2001; Moss, Birkestrand & Fowler, 2002; Smittkamp, Brown & Stanford, 2008; Stanford *et al.*, 2003), that allowed us to modify and acquire tongue force and temporal measures during complex protrusive tongue movements. This set-up involved a traditional learning paradigm in which rats were trained to press a disk with their tongue by gradually restricting their access to water. The paradigm gradually restricted water access from 8 hours on day 1 to 3 hours on day 5. Three hours of water exposure was determined by our IACUC to be the least restrictive program for rats that allowed water to be useful as a reinforcer in our behavioral studies, but did not present a substantial compromise to animal health or well being. (Toth and Gardiner, 2000) To familiarize the animals with the testing room and set-up, subjects had been receiving their water from an affixed water dish placed in a cage and at a location within the cage that resembles the test enclosure for 6 days prior to force training.

The experiment involved an introductory period, a training period, and increment testing. Throughout the experiment, animals were placed individually into a polycarbonate cage resembling the homecage, but equipped with a 1 × 1 centimeter (cm) aperture and force operandum disk (force transducer) that delivered aliquots of water based on tongue press behaviors (Figure 1). During the introductory period, which lasted 6 days, water was manually dispensed when the animal approached the force operandum disk for the first 3 days. On and after day 4, the animal was required to press the operandum disk with a minimum of .2 g of force to obtain an automatically-dispensed water reward. Rats then received daily (10 minutes per day), individualized training for 4 weeks until they successfully learned to push the disk habitually for a water reward. Animals were monitored by direct visual observation for all training and data collection sessions to ensure that disk presses occurred only with the tongue and not with the teeth, which can artificially elevate tongue forces.

Increment testing immediately followed the training period. Progressively increased force targets within one session were created by rapidly increasing force thresholds for obtaining a water reward. Performance of the desired behavior (i.e. pressing the tongue against the disk) was then rewarded with an aliquot of water on a variable ratio 5 (VR5) schedule. Increment testing (10 minute sessions) allowed us to record the maximum voluntary tongue press forces and temporal measures for a control condition and also following 3 haloperidol injections of increasing dose. Specifically, rats were first given an intraperitoneal (IP) injection of saline (vehicle) on the first 3 days of testing to establish baselines for tongue force and temporal measures and to constitute a control condition. Following these 3 days of baseline testing, IP injections of .05, .1 or .2 mg/kg of the dopamine-antagonist haloperidol were given to each of the 9 rats, with a 3 day wash-out in between dose conditions. The 10-minute training sessions, as described above, were performed during the wash-out days. As such, increment testing was completed in 12 days (3 days of baseline testing; .05 mg./kg day, 3 day wash-out; .1 mg/kg day, 3 day wash-out, .2 mg/kg day) and the animals were then euthanized. All testing occurred 45 minutes after injection. Lingual force and temporal measures during tongue presses and cataleptic descent times were obtained in the 4 experimental conditions.

General/Limb Sensorimotor Impairment Measurement—*Cataleptic descent*, a well-established behavioral measure, was used to test the effect of dopaminergic antagonism on the initiation of forelimb movement as an index of general/limb motor impairment (Alvarez-Cervera, et al., 2005; Sanberg et al., 1988). Cataleptic descent time was defined as the duration in seconds from initial forelimb placement on a bar (2 cm diameter, situated 9 cm off of homecage floor) to bilateral release. Rats were given 300 second trials over a period of 15 minutes, as detailed by Alvarez-Cervera, et al., (2005). Cataleptic descent duration was collected in each of the 4 conditions discussed previously. The descent time was measured as the difference in seconds between pre and post injection.

Data Recording and Analysis

For tongue presses, output of the force transducer was sampled at 40 Hz with a precision of 0.2 g using custom designed computer data acquisition software (Matrix Product Development, Cottage Grove, Wis.). This sampling rate was adequate for the 6 Hz tongue press movements recorded and did not interfere with VR5 delivery of the water reward that we experienced with higher sampling rates. Parameters sampled by the device included number of tongue presses during the data collection period and the peak force of each tongue press. Using this paradigm, the following variables were collected:

1. *Total Number of Tongue Presses* was the total amount of tongue presses that occurred during the 10 minute data acquisition period.
2. *Tongue Press Rate* was the average number of tongue presses per minute during the first three minutes of training. Tongue press rate (presses/min) was calculated for the first 3 minutes because animals produced the greatest number of tongue presses during this time period, with a peak occurring at 2 minutes across all conditions.
3. *Average force per tongue press (g)* was calculated by averaging the forces produced per tongue press across all presses.
4. *Maximal force (g)* was the highest observed force in the data collection session.

For cataleptic descent, the value used in analysis was average change in seconds from baseline time (pre-injection) to 45 minutes after injection.

A One-Way Analysis of Variance (ANOVA) was used for the 5 dependent variables in the Control and 3 Haloperidol Conditions. Post-hoc testing was performed with Fisher's Protected Least Significant Differences. We examined the association among tongue press rate, average

force, maximal force, and cataleptic descent using a Mixed model repeated measures with one dependent variable, one independent variable, and a random rat effect. For those variables that had a significant relationship, we also calculated Spearman's correlations to determine the degree and directionality of the relationship. In order to meet the assumptions for correlation analysis, we posit that each condition (control and haloperidol doses) can be considered independent based on our results from the Mixed model. All analyses were performed with SAS statistical software (SAS Institute Inc., Cary, N.C.). The critical value for obtaining statistical significance was set at the $\alpha=.05$ level.

Results

Total Number of Tongue Presses

The number of tongue presses was significantly decreased following haloperidol administration and as a function of increasing haloperidol dose ($F(2,23)=25.0; p<.0001$). The total number of tongue presses was reduced to the greatest degree at the higher doses of haloperidol (Figure 2). Specifically, the .1 mg/kg and .2 mg/kg doses resulted in significantly reduced numbers of tongue presses relative to the 0.05 mg/kg dose condition ($p=.0028$ and $p<.0001$, respectively). However, the .1 and .2 mg/kg doses were not significantly different from each other ($p=.09$).

Tongue Press Rate

Tongue press rate was significantly reduced following haloperidol injection and with increasing doses of haloperidol ($F(2,23)=21.55; p<.0001$). As shown in Figures 3a and 3b, tongue press rate was reduced to the greatest degree at the higher doses of haloperidol. Specifically, the .1 mg/kg and .2 mg/kg doses resulted in reduced tongue press rates relative to the 0.05 mg/kg dose condition ($p=.0023$ and $p<.0001$, respectively). However, the .1 and .2 mg/kg doses were not different from each other ($p=.09$). In Figure 3b, note that the peak rate of tongue pressing tended to occur at 2 minutes into the testing session and then tapered off throughout the 10 minute testing session.

Average Force

As shown in Figure 4, average force was lower in the higher haloperidol dose conditions and a significant main effect was found ($F(2,23)=41.04; p<.0001$). However, there was not a significant difference between the control vs. .05 mg/kg haloperidol conditions ($p=.73$). Average force was significantly lower in the .2 mg/kg versus .1 mg/kg ($p<.0001$) and the .2 vs. .05 mg/kg ($p<.0001$). Additionally, the .1 mg/kg average force was significantly lower than the .05 mg/kg average force ($p=.004$).

Maximal Force

Maximal force was significantly reduced in the highest haloperidol dose condition (Figure 5) and a significant main effect for maximal force was found ($F(2,23)=25.83; p<.0001$). That is, low levels of dopamine antagonism did not significantly affect the rats' ability to generate a maximal force as this effect was only observed at higher doses. Specifically, significantly reduced maximal force was observed in the .2 mg/kg condition vs. control ($p<.0001$), the .05 mg/kg ($p<.0001$), and the .1 mg/kg conditions ($p<.0001$). The lowest doses of haloperidol (i.e., .05 and .1) were not different from each other ($p=.19$) or from the control condition ($p=.8$ for control vs. .05 mg/kg and $p=.14$ for control versus .1 mg/kg).

Cataleptic Descent

There was a significant main effect for cataleptic descent time ($F(2,23)=16.29; p<.0001$), with significantly longer descent times at the highest dose of haloperidol (Figure 6). The .2mg/kg

condition duration was significantly longer than the .1 mg/kg duration ($p=.04$), .05 mg/kg duration ($p=.004$), and the control duration ($p=.004$). There were no other significant relationships observed.

Motor Impairment Relationships

Average force and maximal force were significantly related ($F(1, 25)=261.73; p<.0001$) and strongly positively correlated ($r=.87, p<.0001$), suggesting that animals with the highest average tongue forces also obtained the highest maximal forces. Tongue press rate and average force were also significantly related ($F(1, 25)=37.78; p<.0001$) and strongly positively correlated ($r=.79, p<.0001$), while tongue press rate and maximal force were significantly related ($F(1, 25)=20.44; p=.0001$) but only moderately positively correlated ($r=.63, p<.0001$).

Across all conditions, forelimb movement initiation (cataleptic descent) appeared to be related to both temporal and force measures of tongue press actions (Figure 8), however the strength of these relationships was variable depending on the task. For tongue press rate and cataleptic descent, the relationship was significant ($F(1, 25)=17.55; p<.0003$) and the correlation was $r=-.69$ ($p<.0001$). Average force and cataleptic descent were significantly related ($F(1, 25)=19.5; p=.0002$) and moderately negatively correlated ($r=-.61, p<.0001$). These negative relationships indicated that a progressive decline in forelimb sensorimotor function (manifested as an increase in cataleptic descent time) tended to accompany a decrease in tongue force and tongue press rate. Maximal force and cataleptic descent were also significantly related ($F(1, 25)=15.94; p<.0005$) and negatively correlated, but to a lesser degree ($r=-.42, p=.01$).

Discussion

The purpose of this study was to examine the effects of altering dopaminergic synaptic transmission with the dopamine antagonist haloperidol on temporal and force measures of tongue function and forelimb movement initiation. Results may support that both cranial (lingual) and general/limb motor impairment (forelimb movement initiation as measured by cataleptic descent) are related to dopamine function but demonstrate distinct deficit patterns. We found that lingual temporal and force deficits and forelimb movement initiation deficits have dose-dependent responses to dopamine antagonism, but in distinct ways.

With regard to temporal measures, the total number of tongue presses produced in a training session was sensitive to all doses of haloperidol, including the lowest dose (.05 mg/kg) when compared to the control condition. However, the 2 highest doses of haloperidol (.1 and .2 mg/kg) were not different from each other. Similarly, tongue press rate was reduced in all haloperidol conditions when compared to the control condition. However, only the .05 mg/kg dose was different from the higher doses (.1 and .2 mg/kg were not different from each other). This suggests that temporal characteristics of tongue movement are vulnerable to even small alterations of dopaminergic synaptic transmission but this affect is not dose-dependent at higher levels of dopamine antagonism.

Haloperidol appeared to affect tongue force production differently than it affected temporal characteristics of tongue movement. Average force per tongue press was vulnerable to changes in levels of dopamine depletion, except for the lowest dose (.05 mg/kg haloperidol) condition. At higher doses, there was a progressive decline in the ability of the rat to generate the typical tongue forces observed in the control condition (as measured by average force per tongue press). In contrast, only the highest haloperidol dose (.2 mg/kg) appeared to affect maximal force levels, which suggests that rats in this study were capable of generating adequate maximal forces in the face of dopamine depletion, except with extreme interruption in dopaminergic synaptic transmission. However, these animals were unable to generate sufficient and sustained typical force levels over periods of tongue pressing.

Similar to maximal force generation, cataleptic descent was vulnerable to only the highest dose of haloperidol as the only significant differences were found between the .2 mg/kg dose and other conditions. That is, lower doses were not different from the control condition or from each other. Thus, the vulnerability of the cranial motor system (in terms of maximal force generation) is comparable to the limb motor system in the face of dopamine antagonism. But in terms of timing, the tongue was impaired even at lower doses while the limb was not. In light of Braak's findings that degeneration commences in the lower brainstem (Braak, et al., 2004), this finding supports the idea that bulbar deficits may present differently than limb deficits that emerge in later stages of the disease process.

Average tongue force and tongue press rate were strongly correlated with each other, while maximal force was only moderately correlated with tongue press rate. These findings suggest that deficits in tongue sensorimotor control are likely associated with both force and timing issues. When relationships among tongue movement measures and cataleptic descent of the forelimb were examined, only weak to moderate relationships were discovered, particularly for measures of maximum tongue force. As discussed above, the ability to generate a maximal force may not be a predictor of overall sensorimotor performance and is less sensitive to smaller amounts of dopamine depletion.

The relatively large range of correlation values among measures of lingual sensorimotor control and forelimb movement initiation impairment due to dopamine antagonism suggest that forelimb movement impairments and cranial dysfunction have distinct manifestations. These distinctions may be most apparent in the dose-response characteristics of deficit emergence. Specifically, lingual deficits appeared with smaller doses of dopamine antagonism than limb initiation deficits and thus may appear earlier in a chronic model of neurodegeneration. As such, it would be interesting to examine this relationship in a chronic model of PD, when early cranial deficits may emerge before limb deficits are apparent and to test hypotheses regarding treatment strategies and medications related to tongue function.

We do not assume that haloperidol is the best model for PD, as it has widespread effects on dopamine-mediated brain pathways other than nigrostriatal. We were cautious in interpreting our cataleptic descent findings in regard to limb deficits, as the reduced cataleptic descent times may reflect motivation and cognition as well as a more general sensorimotor deficit. Additionally, we were interested in testing 'gross' motor function as reflected by the catalepsy and tongue press paradigms vs. skilled or fine motor control. A more specific measure of forelimb use, such as the 'Vermicelli Handling Test' (Allred, et al., 2008) could have been used as an alternative and will be explored in future work. Likewise, a sensorimotor task that requires more fine control, such as vocalization, will be considered in future studies. Further, it would be interesting to examine limb force generation abilities and compare them to lingual force generation abilities. Our study included 9 animals, a sample size that was based on previous work from our laboratory (Connor, Russell, Wang, Jackson, Mann & Kluender, in press) and on power calculations. Although this sample size may appear small, we detected both statistically significant and biologically meaningful differences among groups with 9 animals.

We designed this study to control several factors, including timing of the behavioral task, time elapsed in between testing, drug tolerance, and drug sensitization. Because our prior work has shown that task performance degrades with time elapsed in between trials and also that tongue forces can be modified (e.g. increased) with repeated trials across days and weeks, we needed to balance these factors to maximize equality of our conditions. Accordingly, 3 days was the maximum amount of time justifiable between testing days. Therefore, we did not randomize drug conditions, but began with the lowest dose of haloperidol to ensure wash-out between conditions and ended with the highest dose. Because there was a consistent decline in

behavioral function with increasing dose across animals, it is unlikely that drug tolerance contributed to the results meaningfully. While dopamine receptor antagonism with haloperidol has been shown to lead to context-dependent sensitization (Amtage & Schmidt, 2003; Lanis & Schmidt, 2001), daily doses of .25mg/kg haloperidol were necessary. In contrast, our study used a three day wash-out and lower doses (.05, .1, and .2mg/kg), which likely prevented context-dependent sensitization. However, it is interesting to speculate that the haloperidol effects shown in our study could be associated with a sensitization mechanism because it has been suggested that failure to move in Parkinsonism as the disease progresses may be a sensitization mechanism (Amtage & Schmidt, 2003; Bergman & Deuschl, 2002; Schmidt, Tzschentke & Kretschmer, 1999). Further research specifically designed to address this issue is necessary to examine the possibility of sensitization.

There are potential human research and clinical implications from this study. In studies of oromotor control for lip and jaw movements Gentil and colleagues found that generating maximal force during lip and jaw movements was not affected by PD, but the ability to finely grade and sustain forces was (Gentil, Garcia-Ruiz, Pollak & Benabid, 1999). Similarly, in our study, the ability to generate a maximal force for a task was not as affected as sustaining the movement over time. A similar finding was noted during swallowing in patients with PD, who showed a progressive decline in dynamic aspects of swallow function, but maintained adequate timing of passing the bolus through the pharynx (Ciucci, Barkmeier-Kraemer & Sherman, 2008). Specifically, maximal forces (implied from timing bolus clearance abilities) needed to generate adequate pressure to drive the bolus through the pharynx in a timely manner were relatively stable, while excursion of structures, such as the hyoid bone, were highly variable and progressively declined. It would be interesting to investigate the ability to sustain adequate forces across consecutive swallows versus training maximal force generation during a swallow as a potential treatment strategy for Parkinsonian dysphagia.

Our findings of a decline in force and temporal measures of tongue function were similar to those found in other research (Das & Fowler, 1996; Fowler & Das, 1994). However, this study took the paradigm a step further by specifically examining the dose-dependent response of the temporal and force characteristics as well as examined them in relation to each other and in the context of general/limb sensorimotor impairment. Our data suggest that temporal characteristics of tongue movement are more vulnerable to lower levels of dopamine synaptic transmission alteration, while force impairment requires higher levels. This has implications for studying the nature of onset and progression of swallowing dysfunction within the context of PD. One would expect that in examining characteristics of dysphagia in early PD (with less alteration of dopaminergic synaptic transmission), a degradation of temporal characteristics may be a more salient feature of the disorder. Further, we would expect that generating an appropriate sustained force over repetitions may be problematic while generating a maximal force may not until later stages of PD. These findings are relevant to the development of hypotheses regarding the discrepancy between limb and cranial motor deficits observed in PD and in developing behavioral treatments designed to ameliorate these deficits.

Acknowledgements

We would like to thank Hao Wang, John Russel, Aaron Johnson, Allison Schaser, and Lisa Vinney for assisting with animal training, Glen Leverson for statistical consulting, Kelsey Anderson for editing, Dr. Timothy Schallert for consultation, and Dr. Timothy McCulloch for artwork. This study was supported by grants from the National Institute of Deafness and Other Communication Disorders (R01DC005935 and R01DC008149).

References

- Allred RP, Adkins DL, Woodlee MT, et al. The Vermicelli Handling Test: A simple quantitative measure of dexterous forepaw function in rats. *J Neurosci Methods* 2008;170:229–244. [PubMed: 18325597]

- Alvarez-Cervera FJ, Villaneuva-Toledo J, Moo-Puc RE, et al. A novel automated rat catalepsy bar test system based on a RISC microcontroller. *J of Neurosci Methods* 2005;146:76–83. [PubMed: 15935223]
- Amtage J, Schmidt WJ. Context-dependent catalepsy intensification is due to classical conditioning and sensitization. *Behav Pharmacol* 2003;12(2):143–149.
- Bashford G, Bradd P. Drug-induced Parkinsonism associated with dysphagia and aspiration: a brief report. *Geriatr Psychiatry Neurol* 1996;9:133–5.
- Bergman H, Deuschl G. Pathophysiology of Parkinson's disease: from clinical neurology to basic neuroscience and back. *Mov Disord* 2002;17(suppl 3):S28–S40. [PubMed: 11948753]
- Bird MR, Woodward MC, Gibson EM, et al. Asymptomatic swallowing disorders in elderly patients with Parkinson's disease: a description of findings on clinical examination and videofluoroscopy in sixteen patients. *Age Ageing* 1994;23:251–254. [PubMed: 8085513]
- Braak H, Ghebremedhin E, Rub U, et al. Stages in the development of Parkinson's disease-related pathology. *Cell Tissue Res* 2004;318:121–134. [PubMed: 15338272]
- Cheon SM, Ha MS, Park MJ, et al. Nonmotor symptoms of Parkinson's disease: Prevalence and awareness of patients and families. *Parkinsonism Relat Disord* 2008;14:286–90. [PubMed: 18042421]
- Connor NP, Russell JA, Wang H, Jackson MA, Mann L, Kluender KR. Effect of tongue exercise and protrusive force and muscle fiber area in aging rats. *J Speech Lang Hear Res*. in press
- Ciucci MR, Barkmeier-Kraemer JM, Sherman SJ. Subthalamic stimulation improves deglutition in Parkinson's disease. *Mov Disord* 2008;23:676–83. [PubMed: 18163451]
- Connor NP, Abbs JH, Cole KJ, et al. Parkinsonian deficits in serial multiarticulate movements for speech. *Brain* 1989;112:997–1009. [PubMed: 2775998]
- Das S, Fowler SC. An update of Fowler and Das: anticholinergic reversal of haloperidol-induced, within-session decrements in rats' lapping behavior. *Pharmacol Biochem Behav* 1996;53:853–5.
- DeLong MR, Wichmann T. Circuits and circuit disorders of the basal ganglia. *Arch Neurol* 2007;64:20–4. [PubMed: 17210805]
- Dubois B, Pillon B. Cognitive deficits in Parkinson's disease. *J Neurol* 1997;244:2e8. [PubMed: 9007738]
- Dziewas R, Warnecke T, Schnabel M, et al. Neuroleptic-induced dysphagia: case report and literature review. *Dysphagia* 2007;22:63–7. [PubMed: 17024549]
- Eadie MJ, Tyrer JH. Alimentary disorder in Parkinsonism. *Australas Ann Med* 1965;14:13–22. [PubMed: 14271784]
- Farley BG, Koshland GF. Training BIG to move faster: the application of the speed-amplitude relation as a rehabilitation strategy for people with Parkinson Disease. *Exp Brain Res* 2005;167(3):462–7. [PubMed: 16283401]
- Fioritti A, Giaccotto L, Melega V. Choking incidents among psychiatric patients: retrospective analysis of thirty-one cases from the west Bologna psychiatric wards. *Can J Psychiatry* 1997;42(5):515–20. [PubMed: 9220116]
- Fowler SC, Das S. Haloperidol-induced decrements in force and duration of rats' tongue movements during tongue pressing are attenuated by concomitant anticholinergic treatment. *Pharma Biochem Behav*. 1994
- Fowler SC, Mortell C. Low doses of haloperidol interfere with rat tongue extensions during licking: a quantitative analysis. *Behav Neurosci* 1992;106(2):386–95. [PubMed: 1590957]
- Fuh JL, Lee RC, Wang SJ, et al. Swallowing difficulty in Parkinson's disease. *Clin Neurol Neurosurg* 1997;99:106–112. [PubMed: 9213054]
- Gentil M, Garcia-Ruiz P, Pollak P, et al. The effect of stimulation of the subthalamic nucleus on oral control of patients with Parkinsonism. *J Neurol Neurosurg Psychiatry* 1999;67:329–333. [PubMed: 10449555]
- Gregory RP, Smith PT, Rudge P. Tardive dyskinesia presenting as severe dysphagia. *J Neurol Neurosurg Psychiatry* 1992;55(12):1203–4. [PubMed: 1479401]
- Hayashi T, Nishikawa T, Koga I, et al. Life-threatening dysphagia following prolonged neuroleptic therapy. *Clin Neuropharmacol* 1997;20(1):77–81. [PubMed: 9037576]
- Horak FB, Frank J, Nutt J. Effects of dopamine of postural control in Parkinsonian subjects: scaling, set, and tone. *J Neurophys* 1996;75:2380–2396.

- Hunter PC, Crameri J, Austin S, et al. Response of parkinsonian swallowing dysfunction to dopaminergic stimulation. *J Neurol Neurosurg Psychiatry* 1997;63:579–583. [PubMed: 9408096]
- Jurgens U. Neural pathways underlying vocal control. *Neurosci Biobehav Rev* 2002;26:235–258. [PubMed: 11856561]
- Lanis A, Schmidt WJ. NMDA receptor antagonists do not block the development of sensitization of catalepsy, but make its expression state-dependent. *Behav Pharmacol* 2001;12(2):143–149. [PubMed: 11396519]
- Leopold NA, Kagel MA. Pharyngo-esophageal dysphagia in Parkinson disease. *Dysphagia* 1997;12:11–18. [PubMed: 8997827]
- Marras C, McDermott MP, Rochon PA, et al. Parkinson Study Group DATATOP Investigators. Predictors of deterioration in health-related quality of life in Parkinson's disease: results from the DATATOP trial 2008;23(5):653–9.
- Miller N, Noble E, Jones D, et al. to swallow: dysphagia in Parkinson's disease 2006;235:614–8.
- Monte FS, DaSilva-Junior FP, Braga-Neto P, et al. Swallowing abnormalities and dyskinesia in Parkinson's disease. *Mov Disord* 2005;204:457–462. [PubMed: 15625689]
- Moss SJ, Wang G, Chen R, et al. 3-acetylpyridine reduces tongue protrusion force but does not abolish lick rhythm in the rat. *Brain Res* 2001;920:1–9. [PubMed: 11716805]
- Moss SJ, Birkestrand B, Fowler SC. The neuroimmunophilin GPI-1046 partially protects against 3-acetylpyridine toxicity in the rat. *Neurosci Lett* 2002;321:53–6. [PubMed: 11872255]
- Nagaya M, Kachi T, Yamada T, et al. Videofluorographic study of swallowing in Parkinson disease. *Dysphagia* 1998;13:95–100. [PubMed: 9513304]
- Nilsson H, Ekberg O, Olsson R, et al. Quantitative assessment of oral and pharyngeal function in Parkinson's disease. *Dysphagia* 1996;11:144–50. [PubMed: 8721074]
- Owen AM, James M, Leigh PN, et al. Fronto-striatal cognitive deficits at different stages of Parkinson's disease. *Brain* 1992;115(Pt 6):1727–51. [PubMed: 1486458]
- Potulska A, Friedman A, Krolicki L, et al. Swallowing disorders in Parkinson's disease. *Parkinsonism Relat Disord* 2003;9:349–53. [PubMed: 12853234]
- Potulska A, Friedman A, Krolicki L, et al. Swallowing disorders in Parkinson's disease. *Neurol Neurochir Pol* 2002;26:449–456. [PubMed: 12185801]
- Robbins J, Levine R, Wood J, et al. Age effects on lingual pressure generation as a risk factor for dysphagia. *J Gerontol A Bio Sci Med Sci* 1995;50:M257–62. [PubMed: 7671027]
- Sanberg PR, Bunsey MD, Giordano M, et al. The catalepsy test: Its ups and downs. *Behav Neurosci* 1988;102(5):784–59.
- Schmidt WJ, Tzschentke TM, Kretschmer BD. State-dependent blockade of haloperidol-induced sensitization of catalepsy by MK-801. *Eur J Neurosci* 1999;11:3365–3368. [PubMed: 10510204]
- Schneider JS, Diamond SG, Markham CH. Deficits in orofacial sensorimotor function in Parkinson's disease. *Ann Neurol* 1986;19(3):275–282. [PubMed: 3963772]
- Smittkamp SE, Brown JW, Stanford JA. Time-course and characterization of orolingual motor deficits in B6SJL-Tg(SOD1-G93A)1Gur/J mice. *Neuroscience* 2008;151(2):613–21. [PubMed: 18061359]
- Sokoloff LG, Pavlakovic R. Neuroleptic-induced dysphagia. *Dysphagia* 1997;12(4):177–9. [PubMed: 9294935]
- Stanford JA, Vorontsova E, Surgener SP, et al. Aged Fischer 344 rats exhibit altered orolingual motor function: relationships with nigrostriatal neurochemical measures. *Neurobiol Aging* 2003;24(2):259–66. [PubMed: 12498959]
- Stewart JT. Dysphagia associated with risperidone therapy. *Dysphagia* 2003;18(4):274–5. [PubMed: 14571332]
- Toth LA, Gardiner GW. Food and water restriction protocols: physiological and behavioral considerations. *Contemp Top Lab Anim Sci* 2000;2039(6):9–17. [PubMed: 11487246]
- Wang XD, You GF, Chen HB, et al. Clinical course and cause of death in elderly patients with idiopathic Parkinson's disease. *Chin Med J* 2002;115:1409–11. [PubMed: 12411124]
- Yang CC, et al. Excitatory innervation of caudal hypoglossal nucleus from nucleus reticularis gigantocellularis in the rat. *Neuroscience* 1995;65(2):365–74. [PubMed: 7539895]

Fig. 1.
Schematic design of experimental set-up

Fig. 2.

Total number of tongue presses (mean and standard error of the mean) that occurred in the 10-min training session for the control and three varying doses of haloperidol conditions. All haloperidol conditions were significantly different from the control condition ($P < 0.01$), and the 0.1 and 0.2 mg/kg were significantly different from the 0.05 mg/kg condition ($P = 0.0028$ and $P < 0.0001$, respectively), but not from each other. Higher levels of dopamine antagonism did not appear to affect the total number of tongue presses differentially.

Fig. 3.

Tongue press rate. **a** Average tongue presses per minute over 10-min training session in the control and varying doses of haloperidol conditions. **b** Average tongue press rate (mean and standard error of the mean) of the first 3 min, group comparisons. All haloperidol conditions were significantly different from the control condition ($P < 0.01$), and the 0.1 and 0.2 mg/kg were significantly different from the 0.05 mg/kg condition ($P = 0.0023$ and $P < 0.0001$, respectively), but not from each other. Higher levels of dopamine antagonism did not appear to affect tongue press rate differentially

Fig. 4.

Average force (mean and standard error of the mean) produced across all tongue presses for the control and three varying doses of haloperidol conditions. Average force was not significantly different between the control and 0.05 mg/kg condition, but was for the 0.1 and 0.2 mg/kg conditions ($P < 0.0001$). Low levels of dopamine antagonism do not appear to affect average force. However, there were significant differences between the 0.05 and 0.01 mg/kg conditions ($P = 0.004$) and the 0.05 and 0.2 mg/kg conditions ($P < 0.0001$). Additionally, the 0.1 and 0.2 mg/kg conditions were significantly different from each other ($P < 0.0001$).

Fig. 5. Maximal force (mean and standard error of the mean) produced for the control and three varying doses of haloperidol conditions. Maximal force was only affected at the highest dose of haloperidol (0.2 mg/kg), as this was significantly different from the control ($P < 0.0001$), 0.05 ($P < 0.0001$) and 0.1 ($P < 0.0001$) mg/kg conditions

Fig. 6.

Cataleptic descent times (mean and standard error of the mean) for the control and three varying doses of haloperidol conditions. The animals maintained bilateral forelimb contact with the bar for a longer time period in the 0.2 mg/kg condition than the other haloperidol conditions ($P = 0.004$ for 0.05 and $P = 0.04$ for 0.1 mg/kg) and in the control condition ($P = 0.004$). Cataleptic descent was only affected significantly at the highest level of dopamine antagonism

Fig. 7.

Correlations of force and temporal parameters of tongue press. **a** Average force versus maximal force ($r = 0.87$, $P < 0.0001$). **b** Tongue press rate (at 2 min) versus average force ($r = 0.79$, $P < 0.0001$). **c** Tongue press rate (at 2 min) versus maximal force ($r = 0.63$, $P < 0.0001$). Average force and maximal force were strongly positively correlated. Tongue press rate correlated strongly with average force, but only moderately with maximal force, indicating some aspects of force measures have a weaker relationship to temporal measures

Fig. 8.

Correlations of movement initiation deficits and parameters of tongue press. **a** Tongue press rate versus cataleptic descent ($r = -0.69$, $P < 0.0001$). **b** Average force versus cataleptic descent ($r = -0.61$, $P < 0.0001$). **c** Maximal force versus cataleptic descent ($r = -0.42$, $P = 0.01$). The relationship of cataleptic descent to temporal and force measures depended on the task. As cataleptic times increased (showing impairment) tongue press rate decreased to a moderate extent. Similarly, descent times and average force were moderately negatively correlated. Maximal force and cataleptic descent were also negatively correlated, but to a lesser degree, indicating that movement initiation impairment has a weaker relationship with generating a maximal lingual force than average force or temporal parameters