Vocal Deficits in Parkinson's Disease

Subjects: Genetics & Heredity

Contributor: Michelle R. Ciucci

This reviews vocalization deficits in models of Parkinson disease.

Parkinson's disease | ultrasonic vocalization | alpha-synuclein | 6-OHDA | Pink1 | DJ1

1. Introduction

Parkinson's disease (PD) is a progressive, degenerative disorder that affects 10 million people worldwide [1][2]. While the disease is known for hallmark motor signs including a resting tremor, bradykinesia, and rigidity that arise as a result of nigrostriatal dopamine depletion, other signs of disease appear years prior to diagnosis, including changes to voice [3][4][5][6]. More than 90% of individuals with PD develop hypokinetic dysarthria, a motor speech disorder that greatly impairs vocal communication [7][8]. Vocal deficits include decreased loudness, monotone pitch, imprecise articulation, and overall decreased intelligibility [9][10][11][12]. This negatively impacts vocal quality and overall quality of life [12]. Pharmacological treatments for PD typically target dopamine pathways by increasing neurotransmitter levels or as dopamine receptor agonists [13][14]. These treatments, however, are not effective in alleviating voice dysfunction, suggesting pathology for voice differs in important ways from classical limb motor alterations [13][14]. Similarly, surgical treatments, like deep brain stimulation, improve limb motor signs, yet do not improve vocal communication and may in fact worsen deficits [15][16][17][18][19][20][21]. Despite the prevalence of hypokinetic dysarthria in PD, pharmacological and surgical treatment options remain limited. Behavioral therapies continue to be the gold standard in treating voice disorders in this population [22]. While research investigating the efficacy of speech-language interventions for PD-related voice dysfunction has grown, a robust understanding of the underlying biological mechanisms responsible for the onset, progression, and treatment-related improvement in vocal dysfunction is limited. Furthermore, while about 10% of PD cases are familial in nature, a vast majority are deemed idiopathic [23]. There are differences among patients with regard to phenotypic expression of PD, including but not limited to akinetic (freezing), tremor-predominant, young onset, etc. Variability is also noted regarding the presence and severity of signs and symptoms, age of onset, and rate of progression of the disease [24]. This extends to vocal deficits, which often present variably. As such, optimizing treatment remains a universal challenge.

The study of ultrasonic vocalizations (USVs) in rat models of PD has increased understanding of vocal communication changes that occur with PD. Similar to humans, rats are highly social animals, generate sound within the larynx, and produce vocalizations that are semiotic in nature [25][26][27][28][29]. USVs are typically categorized by two call types—22-kilohertz (kHz) alarm calls and 50-kHz calls [30][31][32][33][34][35]. 22-kHz calls occur in response to aversive conditions or in negative affective states and are initiated via activation of the ascending cholinergic system [30][34][36][37][38]. 50-kHz calls occur in response to activity in the mesolimbic dopaminergic

system originating in the ventral tegmental area, and are produced in social, nonaggressive, positive affective states [30][31][32][33][34][35]. They represent purposeful affiliative vocalizations, are highly relevant to human communication, and as such, are commonly studied and will be the focus of this review. 50-kHz calls are also more complex, varying by acoustic parameters, such as duration (ms), intensity (dB), bandwidth (Hz), and peak frequency (Hz), as well as non-acoustic parameters, such as complexity (%), call rate (calls/s), latency to call (s), and call type (categorical). There are many different approaches to categorizing call type and categories should correspond to the research question [39][40][41][42][43]. Generally, 50-kHz calls are defined as simple or complex and, depending on the research group, can have sub-categories. Simple calls have constant, non-modulating frequency, and complex calls contain two or more directional changes in frequency of at least 3 kHz each [39][40]. Commonly described complex calls include frequency modulated (FM) calls (frequency changes within a call) and harmonic calls (calls with a fundamental frequency near 30 kHz with a visible harmonic one octave above) [40]. In contrast to human voice, 50-kHz USV production does not involve the vibration of vocal folds [44][45]. USV production shares characteristics with human vocalization including the generation of airflow via buildup of lung pressure, the activation of intrinsic laryngeal muscles, and the modulation of the vocal tract during egressive airflow [28][29]. As such, USVs are used to study vocal sensorimotor control in models of PD.

2. Vocal Deficits in Parkinson's Disease

2.1Neurotoxin Models

Oxidopamine, or 6-hydroxydopamine (6-OHDA), is a catecholaminergic neurotoxin classically used to model PD by inducing significant neurodegeneration of the nigrostriatal dopamine system by unilateral or bilateral infusion to the medical forebrain bundle or the striatum [46][47][48][49][50][51][52][53]. The well-established 6-OHDA rat model has been used to study behavioral changes, mechanisms of cell death, and therapies that could potentially improve PD signs [48][54][55][56][57][58]. Deficits in this model are widespread. In addition to affecting limb movements [59][60][61][62][63], unilateral lesions to the medial forebrain bundle or the striatum have been shown to reduce tongue force, lick force, and lick frequency [64][65][66], as well as chewing behaviors [67], suggesting that nigrostriatal dopaminergic systems may contribute, at least in part, to oral sensorimotor dysfunction.

Nigrostriatal dopamine depletion via unilateral 6-OHDA infusion into the medial forebrain bundle leads to significant changes in USV production. Rat 50-kHz USVs show decreased call intensity, amplitude, and bandwidth [25][68][69]. Additionally, call complexity degrades as a result of the unilateral 6-OHDA lesion. Of all call types (simple, FM, and harmonic), harmonic calls were produced the least frequently; however, this was observed regardless of dopamine depletion [68]. Subsequent work has largely supported these findings, and further showed decreases in call rate, call duration, and bandwidth when tested in a novel cage environment, suggesting that environment can have a significant impact on behavioral outcomes [69]. Observed decreases in complexity and intensity of calls are analogous to hypophonia noted in individuals with PD, thereby demonstrating utility of USVs in assessing phonatory deficits [70]. The effect of time post-lesion on USV production was also studied at acute (72 h) and chronic (4 weeks) timepoints. Results show that after 72 h, call complexity, bandwidth, and intensity of FM calls correlate with striatal dopamine loss. After 4 weeks, bandwidth, intensity of simple calls, and duration of FM calls

were correlated with measures of dopamine depletion. Call complexity was less affected at 4 weeks and was only significantly correlated with percent of tyrosine hydroxylase loss [71]. The 6-OHDA model itself does not fully embody the progressive nature of PD. While dopamine loss may play a role in vocal dysfunction, particularly around the time of diagnosis when dopamine has significantly depleted in the substantia nigra pars compacta (SNpc), other systems may be implicated earlier in disease progression that cannot be fully captured with a 6-OHDA model.

The control of vocalization is complex, involving multiple sensorimotor, cognitive, and limbic brain regions [72][73]. The basal ganglia are certainly implicated in the initiation and modulation of vocalizations. Disrupting nigrostriatal pathways disrupts the quality of vocalization because of altered input to the striatum and consequently the complex circuitry of the basal ganglia and related brain areas. The 6-OHDA lesion to nigrostriatal pathways models one aspect of this complex disease.

2.2. Alpha-Synuclein Overexpression Models

Overexpressing alpha-synuclein using viral vectors models nigrostriatal pathology by injecting within or near the SNpc. In contrast to transgenic models, overexpression via viral vector allows for induction at different timepoints, allows for the targeting of a defined region of the brain, and results in rapid degeneration of nigrostriatal neurons [74]. Furthermore, viral-vector mediated models also show the presence of limb motor deficits [75][76][77][78]. Until recently, vocal deficits were not studied in alpha-synuclein overexpressing models. This is still a largely understudied area, with only two articles discussing vocal deficits in viral-vector-mediated rat models.

Mouse models overexpressing alpha-synuclein [79] have also shown relationships between nigrostriatal alpha-synuclein overexpression and early and progressive decline in behavior. Although not widely studied in the context of vocalization, one additional study characterized vocal deficits in mice overexpressing human wild-type alpha-synuclein under a broad neuronal promoter (Thy1-aSyn) [80]. Grant (2014) found call profile of Thy1-aSyn mice to be significantly different compared to wildtype (WT; healthy) controls. The percent of two-cycle calls and jump down calls was significantly reduced in the Thy1-aSyn model at 2–3 months and 6–7 months, respectively. Furthermore, at 2–3 months, the average duration of calls was significantly decreased (for harmonic, jump down, half cycle, and cycle calls) and at 6–7 months, intensity was significantly reduced in the Thy1-aSyn group. Immunohistochemical findings also revealed alpha-synuclein aggregates in the periaqueductal gray at 5 months in the Thy1-aSyn mice [80]. These deficits coincided with previously reported early sensorimotor deficits, deficits in olfaction, circadian rhythm, and gastrointestinal functioning, and high extracellular striatal dopamine levels [80][81]. Similar to alpha-synuclein overexpressing rat models, mice show early and progressive vocal deficits compared to WTs, suggesting similar underlying mechanisms between both species. Results from these studies indicate that vocal deficits can be induced by alpha-synuclein overexpression, in the absence of dopamine depletion.

2.3. Genetic Models

The *DJ1* knockout (*DJ1-/-)* model demonstrates early onset and progressive limb motor, oromotor, and cranial sensorimotor deficits, including decreased limb, tongue/chewing, and vocalization functions. Yang and colleagues (2018) assessed vocalization abilities in the *DJ1-/-* rat model in prodromal to early timepoints of disease (2–8 months of age) and correlated findings to noradrenergic cell loss within the locus coeruleus. Compared to WT controls, *DJ1-/-* rats were found to develop early and progressive ultrasonic vocalization deficits. Specifically, *DJ1-/-* rats produced longer average and maximum calls, and a greater overall percentage of complex calls. At 8 months of age, *DJ1-/-* rats showed a lower average intensity of calls, a deficit analogous to the decreased vocal loudness (i.e., hypophonia) PD patients typically experience. Findings also revealed that at 8 months of age, *DJ1-/-* rats demonstrated loss of tyrosine hydroxylase-immunoprotective cells in the locus coeruleus, a brainstem region responsible for the synthesis and regulation of noradrenaline. With widespread connections to the central nervous system, including projections into the prefrontal cortex, striatum, hippocampus, and thalamus, the locus coeruleus has a large impact on PD pathology. Disruptions in the central noradrenergic system are associated with motor and non-motor signs of PD, including vocalization [82]. Tyrosine hydroxylase-positive cells in the locus coeruleus were also found to be negatively correlated with tongue force, suggesting that the greater the loss of neurons within the locus coeruleus, the greater the disruption to oromotor functioning [83]. Whether the loss of these neurons is progressive, however, is still unknown. Overall, noradrenaline has been shown to have widespread implications for PD pathology, including vocalization deficits.

3. Conclusions

While hallmark motor deficits are relatively well-understood, certain signs of PD, including vocal deficits, remain poorly understood due to their prodromal onset and complex pathology. As such, multiple complementary models are necessary to provide insights into the progression and pathophysiological underpinnings of communication deficits.

Each of the different models of PD have unique advantages and limitations. Neurotoxin models such as 6-OHDA are useful for the study of mid- to late-stage PD associated with nigrostriatal dopamine depletion, and demonstrate widespread deficits; however, this model shows minimal alpha-synuclein aggregation and does not account for the progressive nature of the disease. In contrast, genetic models like DJ1-/- and Pink1-/- allow for the study of disease progression, as well as the study of intervention at early, prodromal, and later timepoints. However, genetic mutations make up only a small subset of PD cases and may not capture the subtle differences associated with the pathogenesis of other forms of PD.

References

1. Brogley, J.E. DaTQUANT: The Future of Diagnosing Parkinson Disease. J. Nucl. Med. Technol. 2019, 47, 21–26.
2. Kowal, S.L.; Dall, T.M.; Chakrabarti, R.; Storm, M.V.; Jain, A. The current and projected economic burden of Parkinson's disease in the United States. Mov. Disord. 2013, 28, 311–318.

3. Pfeiffer, R.F. Non-motor symptoms in Parkinson's disease. Park. Relat. Disord. 2016, 22, S119–S122.
4. Hlavnika, J.; Cmejla, R.; Tykalová, T.; Šonka, K.; Ruzicka, E.; Rusz, J. Automated analysis of connected speech reveals early biomarkers of Parkinson's disease in patients with rapid eye movement sleep behaviour disorder. Sci. Rep. 2017, 7, 1–13.
5. Postuma, R.B.; Lang, A.E.; Gagnon, J.F.; Pelletier, A.; Montplaisir, J.Y. How does parkinsonism start? Prodromal parkinsonism motor changes in idiopathic REM sleep behaviour disorder. Brain 2012, 135, 1860–1870.
6. Harel, B.T.; Cannizzaro, M.S.; Cohen, H.; Reilly, N.; Snyder, P.J. Acoustic characteristics of Parkinsonian speech: A potential biomarker of early disease progression and treatment. J. Neurolinguistics 2004, 17, 439–453.
7. Ramig, L.O.; Countryman, S.; Thompson, L.L.; Horii, Y. Comparison of two forms of intensive speech treatment for Parkinson disease. J. Speech Hear. Res. 1995, 38, 1232–1251.
8. Ho, A.K.; Iansek, R.; Marigliani, C.; Bradshaw, J.L.; Gates, S. Speech impairment in a large sample of patients with Parkinson's disease. Behav. Neurol. 1998, 11, 131–137.
9. Plowman-Prine, E.K.; Okun, M.S.; Sapienza, C.M.; Shrivastav, R.; Fernandez, H.H.; Foote, K.D.; Ellis, C.; Rodriguez, A.D.; Burkhead, L.M.; Rosenbek, J.C. Perceptual characteristics of parkinsonian speech: A comparison of the pharmacological effects of levodopa across speech and non-speech motor systems. NeuroRehabilitation 2009, 24, 131–144.
10. Darley, F.L.; Aronson, A.E.; Brown, J.R. Differential diagnostic patterns of dysarthria. J. Speech Hear. Res. 1969, 12, 246–269.
11. Ramig, L.O.; Fox, C.; Sapir, S. Speech treatment for Parkinson's disease. Expert Rev. Neurother. 2008, 8, 297–309.
12. Sapir, S.; Ramig, L.; Fox, C. Speech and swallowing disorders in Parkinson disease. Curr. Opin. Otolaryngol. Head Neck Surg. 2008, 16, 205–210.
13. Wang, E.; Kompoliti, K.; Jiang, J.J.; Goetz, C.G. An instrumental analysis of laryngeal responses to apomorphine stimulation in Parkinson disease. J. Med. Speech Lang. Pathol. 2000, 8, 175–186.
14. Kompoliti, K.; Wang, Q.E.; Goetz, C.G.; Leurgans, S.; Raman, R. Effects of central dopaminergic stimulation by apomorphine on speech in Parkinson's disease. Neurology 2000, 54, 458–462.
15. Taha, J.M.; Janszen, M.A.; Favre, J. Thalamic deep brain stimulation for the treatment of head, voice, and bilateral limb tremor. J. Neurosurg. 1999, 91, 68–72.
16. Ghika, J.; Villemure, J.G.; Fankhauser, H.; Favre, J.; Assal, G.; Ghika-Schmid, F. Efficiency and safety of bilateral contemporaneous pallidal stimulation (deep brain stimulation) in levodopa-

responsive patients with parkinson’s disease with severe motor fluctuations: A 2-year follow-up review. J. Neurosurg. 1998, 89, 713–718.

17. Putzke, J.D.; Wharen, R.E.; Wszolek, Z.K.; Turk, M.F.; Strongosky, A.J.; Uitti, R.J. Thalamic deep brain stimulation for tremor-predominant Parkinson’s disease. Park. Relat. Disord. 2003, 10, 81–88.
18. Krack, P.; Batir, A.; Van Blercom, N.; Chabardes, S.; Fraix, V.; Ardouin, C.; Koudsie, A.; Limousin, P.D.; Benazzouz, A.; LeBas, J.F.; et al. Five-Year Follow-up of Bilateral Stimulation of the Subthalamic Nucleus in Advanced Parkinson’s Disease. N. Engl. J. Med. 2003, 349, 1925–1934.
19. Romito, L.M.; Scerrati, M.; Contarino, M.F.; Iacoangeli, M.; Bentivoglio, A.R.; Albanese, A. Bilateral high frequency subthalamic stimulation in Parkinson’s disease: Long-term neurological follow-up. J. Neurosurg. Sci. 2003, 47, 119–128.
20. Hariz, M.I.; Johansson, F.; Shamsgovara, P.; Johansson, E.; Hariz, G.M.; Fagerlund, M. Bilateral subthalamic nucleus stimulation in a parkinsonian patient with preoperative deficits in speech and cognition: Persistent improvement in mobility but increased dependency: A case study. Mov. Disord. 2000, 15, 136–139.
21. Kleiner-Fisman, G.; Herzog, J.; Fisman, D.N.; Tamma, F.; Lyons, K.E.; Pahwa, R.; Lang, A.E.; Deuschl, G. Subthalamic nucleus deep brain stimulation: Summary and meta-analysis of outcomes. Mov. Disord. 2006, 21, S290–S304.
22. Schulz, G.M.; Grant, M.K. Effects of speech therapy and pharmacologic and surgical treatments on voice and speech in Parkinson’s disease: A review of the literature. J. Commun. Disord. 2000, 33, 59–88.
23. Klein, C.; Westenberger, A. Genetics of Parkinson’s disease. Cold Spring Harb. Perspect. Med. 2012, 2, a008888.
24. Foltynie, T.; Brayne, C.; Barker, R.A. The heterogeneity of idiopathic Parkinson’s disease. J. Neurol. 2002, 249, 138–145.
25. Ciucci, M.R.; Ma, S.T.; Kane, J.R.; Ahrens, A.M.; Schallert, T. Limb use and complex ultrasonic vocalization in a rat model of Parkinson’s disease: Deficit-targeted training. Park. Relat. Disord. 2008, 14, S172–S175.
26. Brudzynski, S.M.; Pniak, A. Social contacts and production of 50-kHz short ultrasonic calls in adult rats. J. Comp. Psychol. 2002, 116, 73–82.
27. Brudzynski, S.M. Principles of rat communication: Quantitative parameters of ultrasonic calls in rats. Behav. Genet. 2005, 35, 85–92.
28. Riede, T. Subglottal pressure, tracheal airflow, and intrinsic laryngeal muscle activity during rat ultrasound vocalization. J. Neurophysiol. 2011, 106, 2580–2592.

29. Johnson, A.M.; Ciucci, M.R.; Russell, J.A.; Hammer, M.J.; Connor, N.P. Ultrasonic output from the excised rat larynx. J. Acoust. Soc. Am. 2010, 128, EL75–EL79.
30. Brudzynski, S.M. Communication of adult rats by ultrasonic vocalization: Biological, sociobiological, and neuroscience approaches. ILAR J. 2009, 50, 43–50.
31. Portfors, C.V. Types and functions of ultrasonic vocalizations in laboratory rats and mice. J. Am. Assoc. Lab. Anim. Sci. 2007, 46, 28–34.
32. Schwarting, R.K.W.; Wöhr, M. On the relationships between ultrasonic calling and anxiety-related behavior in rats. Braz. J. Med. Biol. Res. 2012, 45, 337–348.
33. Wöhr, M.; Schwarting, R.K.W. Affective communication in rodents: Ultrasonic vocalizations as a tool for research on emotion and motivation. Cell Tissue Res. 2013, 354, 81–97.
34. Brudzynski, S.M. Ethotransmission: Communication of emotional states through ultrasonic vocalization in rats. Curr. Opin. Neurobiol. 2013, 23, 310–317.
35. Brudzynski, S. Pharmacology of Ultrasonic Vocalizations in adult Rats: Significance, Call Classification and Neural Substrate. Curr. Neuropharmacol. 2015, 13, 180–192.
36. Knutson, B.; Burgdorf, J.; Panksepp, J. Ultrasonic vocalizations as indices of affective states in rats. Psychol. Bull. 2002, 128, 961–977.
37. Blanchard, R.J.; Agullana, R.; McGee, L.; Weiss, S.; Blanchard, D.C. Sex differences in the incidence and sonographic characteristics of antipredator ultrasonic cries in the laboratory rat (Rattus norvegicus). J. Comp. Psychol. 1992, 106, 270–277.
38. Inagaki, H. Sex Differences in Ultrasonic Vocal Expression of Negative Emotional States in Rats. In Handbook of Behavioral Neuroscience; Elsevier B.V.: Amsterdam, The Netherlands, 2018; Volume 25, pp. 337–344. ISBN 9780128096000.
39. Wright, J.M.; Gourdon, J.C.; Clarke, P.B.S. Identification of multiple call categories within the rich repertoire of adult rat 50-kHz ultrasonic vocalizations: Effects of amphetamine and social context. Psychopharmacology 2010, 211, 1–13.
40. Johnson, A.M.; Ciucci, M.R.; Connor, N.P. Vocal training mitigates age-related changes within the vocal mechanism in old rats. J. Gerontol. Ser. A Biol. Sci. Med. Sci. 2013, 68, 1458–1468.
41. Simola, N.; Costa, G. Emission of categorized 50-kHz ultrasonic vocalizations in rats repeatedly treated with amphetamine or apomorphine: Possible relevance to drug-induced modifications in the emotional state. Behav. Brain Res. 2018, 347, 88–98.
42. Barker, D.J.; Root, D.H.; Ma, S.; Jha, S.; Megehee, L.; Pawlak, A.P.; West, M.O. Dose-dependent differences in short ultrasonic vocalizations emitted by rats during cocaine self-administration. Psychopharmacology 2010, 211, 435–442.

43. Ahrens, A.M.; Ma, S.T.; Maier, E.Y.; Duvauchelle, C.L.; Schallert, T. Repeated intravenous amphetamine exposure: Rapid and persistent sensitization of 50-kHz ultrasonic trill calls in rats. Behav. Brain Res. 2009, 197, 205–209.
44. Roberts, L.H. The rodent ultrasound production mechanism. Ultrasonics 1975, 13, 83–88.
45. Roberts, L.H. Evidence for the laryngeal source of ultrasonic and audible cries of rodents. J. Zool. 1975, 175, 243–257.
46. Berger, K.; Przedborski, S.; Cadet, J.L. Retrograde degeneration of nigrostriatal neurons induced by intrastriatal 6-hydroxydopamine injection in rats. Brain Res. Bull. 1991, 26, 301–307.
47. Ichitani, Y.; Okamura, H.; Matsumoto, Y.; Nagatsu, I.; Ibata, Y. Degeneration of the nigral dopamine neurons after 6-hydroxydopamine injection into the rat striatum. Brain Res. 1991, 549, 350–353.
48. Lee, C.S.; Sauer, H.; Björklund, A. Dopaminergic neuronal degeneration and motor impairments following axon terminal lesion by intrastriatal 6-hydroxydopamine in the rat. Neuroscience 1996, 72, 641–653.
49. Przedbroski, S.; Leviver, M.; Jiang, H.; Ferreira, M.; Jackson-Lewis, V.; Donaldson, D.; Togasaki, D.M. Dose-dependent lesions of the dopaminergic nigrostriatal pathway induced by instrastriatal injection of 6-hydroxydopamine. Neuroscience 1995, 67, 631–647.
50. Sauer, H.; Oertel, W.H. Progressive degeneration of nigrostriatal dopamine neurons following intrastriatal terminal lesions with 6-hydroxydopamine: A combined retrograde tracing and immunocytochemical study in the rat. Neuroscience 1994, 59, 401–415.
51. Barata-Antunes, S.; Teixeira, F.G.; Mendes-Pinheiro, B.; Domingues, A.V.; Vilaça-Faria, H.; Marote, A.; Silva, D.; Sousa, R.A.; Salgado, A.J. Impact of aging on the 6-OHDA-induced rat model of Parkinson’s disease. Int. J. Mol. Sci. 2020, 21, 3459.
52. Ungerstedt, U. 6-hydroxy-dopamine induced degeneration of central monoamine neurons. Eur. J. Pharmacol. 1968, 5, 107–110.
53. Johnston, R.E.; Schallert, T.; Becker, J.B. Akinesia and postural abnormality after unilateral dopamine depletion. Behav. Brain Res. 1999, 104, 189–196.
54. Blesa, J.; Phani, S.; Jackson-Lewis, V.; Przedborski, S. Classic and new animal models of Parkinson’s disease. J. Biomed. Biotechnol. 2012, 2012, 845618.
55. Lindner, M.D.; Plone, M.A.; Francis, J.M.; Blaney, T.J.; Salamone, J.D.; Emerich, D.F. Rats with partial striatal dopamine depletions exhibit robust and long-lasting behavioral deficits in a simple fixed-ratio bar-pressing task. Behav. Brain Res. 1997, 86, 25–40.
56. Barnéoud, P.; Parmentier, S.; Mazadier, M.; Miquet, J.M.; Boireau, A.; Dubédat, P.; Blanchard, J.C. Effects of complete and partial lesions of the dopaminergic mesotelencephalic system on

skilled forelimb use in the rat. Neuroscience 1995, 67, 837–848.

57. Winkler, C.; Sauer, H.; Lee, C.S.; Björklund, A. Short-term GDNF treatment provides long-term rescue of lesioned nigral dopaminergic neurons in a rat model of Parkinson’s disease. J. Neurosci. 1996, 16, 7206–7215.
58. Cousins, M.S.; Salamone, J.D. Involvement of ventrolateral striatal dopamine in movement initiation and execution: A microdialysis and behavioral investigation. Neuroscience 1996, 70, 849–859.
59. Olsson, M.; Nikkhah, G.; Bentlage, C.; Björklund, A. Forelimb akinesia in the rat Parkinson model: Differential effects of dopamine agonists and nigral transplants as assessed by a new stepping test. J. Neurosci. 1995, 15, 3863–3875.
60. Schallert, T.; Norton, D.; Jones, T.A. A Clinically Relevant Unilateral Rat Model of Parkinsonian Akinesia. J. Neural Transplant. Plast. 1992, 3, 332–333.
61. Klein, A.; Metz, G.A.; Papazoglou, A.; Nikkhah, G. Differential effects on forelimb grasping behavior induced by fetal dopaminergic grafts in hemiparkinsonian rats. Neurobiol. Dis. 2007, 27, 24–35.
62. Klein, A.; Wessolleck, J.; Papazoglou, A.; Metz, G.A.; Nikkhah, G. Walking pattern analysis after unilateral 6-OHDA lesion and transplantation of foetal dopaminergic progenitor cells in rats. Behav. Brain Res. 2009, 199, 317–325.
63. Whishaw, I.Q.; O’connor, W.T.; Dunnett, S.B. The contributions of motor cortex, nigrostriatal dopamine and caudate-putamen to skilled forelimb use in the rat. Brain 1986, 109, 805–843.
64. Ciucci, M.R.; Russell, J.A.; Schaser, A.J.; Doll, E.J.; Vinney, L.M.; Connor, N.P. Tongue force and timing deficits in a rat model of Parkinson disease. Behav. Brain Res. 2011, 222, 315–320.
65. Plowman, E.K.; Maling, N.; Rivera, B.J.; Larson, K.; Thomas, N.J.; Fowler, S.C.; Manfredsson, F.P.; Shrivastav, R.; Kleim, J.A. Differential sensitivity of cranial and limb motor function to nigrostriatal dopamine depletion. Behav. Brain Res. 2013, 237, 157–163.
66. Plowman, E.K.; Maling, N.; Thomas, N.J.; Fowler, S.C.; Kleim, J.A. Targeted motor rehabilitation dissociates corticobulbar versus corticospinal dysfunction in an animal model of parkinson’s disease. Neurorehabil. Neural Repair 2014, 28, 85–95.
67. Kane, J.R.; Ciucci, M.R.; Jacobs, A.N.; Tews, N.; Russell, J.A.; Ahrens, A.M.; Ma, S.T.; Britt, J.M.; Cormack, L.K.; Schallert, T. Assessing the role of dopamine in limb and cranial-oromotor control in a rat model of Parkinson’s disease. J. Commun. Disord. 2011, 44, 529–537.
68. Ciucci, M.R.; Ahrens, A.M.; Ma, S.T.; Kane, J.R.; Windham, E.B.; Woodlee, M.T.; Schallert, T. Reduction of Dopamine Synaptic Activity: Degradation of 50-kHz Ultrasonic Vocalization in Rats. Behav. Neurosci. 2009, 123, 328–336.

69. Kelm-Nelson, C.A.; Brauer, A.F.L.; Ciucci, M.R. Vocal training, levodopa, and environment effects on ultrasonic vocalizations in a rat neurotoxin model of Parkinson disease. Behav. Brain Res. 2016, 307, 54–64.

70. Fleming, S.M.; Schallert, T.; Ciucci, M.R. Cranial and related sensorimotor impairments in rodent models of Parkinson’s disease. Behav. Brain Res. 2012, 231, 317–322.

71. Grant, L.M.; Barnett, D.G.; Doll, E.J.; Leverson, G.; Ciucci, M. Relationships among rat ultrasonic vocalizations, behavioral measures of striatal dopamine loss, and striatal tyrosine hydroxylase immunoreactivity at acute and chronic time points following unilateral 6-hydroxydopamine-induced dopamine depletion. Behav. Brain Res. 2015, 291, 361–371.

72. Li-Jessen, N.Y.K.; Ridgway, C. Neuroanatomy of Voice and Swallowing. In Neurologic and Neurodegenerative Diseases of the Larynx; Springer International Publishing: Berlin/Heidelberg, Germany, 2020; pp. 21–40.

73. Jean, A. Brain stem control of swallowing: Neuronal network and cellular mechanisms. Physiol. Rev. 2001, 81, 929–969.

74. Kirik, D.; Björklund, A. Modeling CNS neurodegeneration by overexpression of disease-causing proteins using viral vectors. Trends Neurosci. 2003, 26, 386–392.

75. Kirik, D.; Rosenblad, C.; Burger, C.; Lundberg, C.; Johansen, T.E.; Muzyczka, N.; Mandel, R.J.; Björklund, A. Parkinson-Like Neurodegeneration Induced by Targeted Overexpression of α-Synuclein in the Nigrostriatal System. J. Neurosci. 2002, 22, 2780–2791.

76. Kirik, D.; Annett, L.E.; Burger, C.; Muzyczka, N.; Mandel, R.J.; Björklund, A. Nigrostriatal α-synucleinopathy induced by viral vector-mediated overexpression of human α-synuclein: A new primate model of Parkinson’s disease. Proc. Natl. Acad. Sci. USA 2003, 100, 2884–2889.

77. Lo Bianco, C.; Ridet, J.L.; Schneider, B.L.; Déglon, N.; Aebischer, P. α-synucleinopathy and selective dopaminergic neuron loss in a rat lentiviral-based model of Parkinson’s disease. Proc. Natl. Acad. Sci. USA 2002, 99, 10813–10818.

78. Decressac, M.; Mattsson, B.; Lundblad, M.; Weikop, P.; Björklund, A. Progressive neurodegenerative and behavioural changes induced by AAV-mediated overexpression of α-synuclein in midbrain dopamine neurons. Neurobiol. Dis. 2012, 45, 939–953.

79. Fleming, S.M.; Salcedo, J.; Fernagut, P.O.; Rockenstein, E.; Masliah, E.; Levine, M.S.; Chesselet, M.F. Early and progressive sensorimotor anomalies in mice overexpressing wild-type human α-synuclein. J. Neurosci. 2004, 24, 9434–9440.

80. Grant, L.M.; Richter, F.; Miller, J.E.; White, S.A.; Fox, C.M.; Zhu, C.; Chesselet, M.F.; Ciucci, M.R. Vocalization deficits in mice over-expressing alpha-synuclein, a model of pre-manifest parkinson’s disease. Behav. Neurosci. 2014, 128, 110–121.

81. Chesselet, M.F.; Richter, F.; Zhu, C.; Magen, I.; Watson, M.B.; Subramaniam, S.R. A Progressive Mouse Model of Parkinson’s Disease: The Thy1-aSyn (“Line 61”) Mice. Neurotherapeutics 2012, 9, 297–314.
82. Espay, A.J.; Lewitt, P.A.; Kaufmann, H. Norepinephrine deficiency in Parkinson’s disease: The case for noradrenergic enhancement. Mov. Disord. 2014, 29, 1710–1719.
83. Yang, K.M.; Blue, K.V.; Mulholland, H.M.; Kurup, M.P.; Kelm-Nelson, C.A.; Ciucci, M.R. Characterization of oromotor and limb motor dysfunction in the DJ1 -/- model of Parkinson disease. Behav. Brain Res. 2018, 339, 47–56.