Published in final edited form as:

Neurol Res. 2018 April ; 40(4): 303–311. doi:10.1080/01616412.2018.1438226.

Vocalization Development in Common Marmosets for Neurodegenerative Translational Modeling

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Abstract

Objectives—In order to facilitate the study of vocalizations in emerging genetic common marmoset models of neurodegenerative disorders, we aimed to analyze call type changes across age in a translational research environment. We hypothesized that acoustic parameters of vocalizations would change with age, reflecting growth of the vocal apparatus and a maturation of control needed to make adult-like calls.

Methods—Nineteen developing common marmosets were longitudinally video- and audio-recorded between the ages of 1–149 days in a naturalistic setting without any vocalization elicitation protocol. Vocalizations were coded for call type (cry, tsik, trill, phoe, and trill-phoe) and analyzed for duration (sec), minimum & maximum frequency (Hz), and bandwidth (Hz). Mixed model linear regressions were performed to assess the effects of age on call parameters listed above for each call type.

Results—Cries decreased in duration ($p=0.038$), maximum frequency ($p=0.047$), and bandwidth ($p=0.023$) with age. Tsik calls decreased in duration ($p=0.002$) and increased in minimum frequency ($p=0.004$) and maximum frequency ($p=0.005$) with age. Trill calls increased in duration ($p=0.003$), and trillphoe bandwidth ($p=0.031$) decreased with age.

Discussion—Our results demonstrate that development of common marmoset vocalizations is call type-dependent and that changes in acoustic parameters can be detected without complex vocalization elicitation paradigms or specialized audio recording equipment. Thus, we demonstrate the feasibility of a naturalistic protocol to collect and objectively analyze marmoset vocalizations longitudinally. This approach may be useful for studying vocal communication deficits in genetic models of neurodegenerative disorders.

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Disclosure Statement

The authors have no other relevant conflicts of interest associated with this project.

Keywords

Callithrix jacchus; common marmosets; neurodevelopment; vocalizations; models

INTRODUCTION

Changes in communication are common in neurodegenerative disorders, impacting social well-being and quality of life for millions of patients and their families. These changes can occur early in disease progression, especially in Parkinson's disease (PD) and Alzheimer's disease (AD) [1, 2], in some cases even before diagnosis [3, 4]. Animal models of these diseases are important for translational medicine, including development and testing of new drug and behavioral treatments [5, 6, 7, 8]. However, communication is overlooked in these animal models, thus missing a critical life function.

Modeling neurodegenerative diseases through transgenesis and genomic editing is emerging as a common methodology, particularly in PD and AD. Non-human primates (NHPs) are commonly used to model human diseases due to their close evolutionary relationship to humans. Relative to larger NHP species, common marmoset monkeys (*Callithrix jacchus*) are favored due to their small size (300–500 g at adult weight), short lifespan (16 years), reproductive productivity (onset of puberty at 18 months, multiple litters of twins or triplets per year), and ease of housing in a captive colony [8, 9, 10]. Their efficient reproductive behavior makes marmosets ideal for genetic modification [11], especially in the context of rapidly-developing technology in genomic engineering [12]. Genetic models of neurodegenerative diseases can shed light on early, sub-clinical signs of disease processes that are not feasible in human patients. Thus, a thorough understanding of typical marmoset development is warranted in order to make comparisons to genetically modified animals. Understanding early functional changes may lead to the discovery of biomarkers for earlier diagnoses and better treatment options, which are both urgently needed [13].

Many neurodegenerative diseases have negative impacts on vocal communication [14, 15]. For example, PD affects voice and speech in up to 90% of patients [16], compromising health, employment, social engagement, and quality of life [17, 18, 19]. These voice and speech deficits are mostly refractory to standard of care medical treatment (levodopa) [20] or surgical treatment (deep brain stimulation) [21, 22]. Although voice and speech changes are not commonly reported by patients with PD until the later stages of the disease [23], there is recent evidence of preclinical communication changes, both in humans [3] and in animal models [24, 25]. Study of vocal changes early in neurodegenerative diseases can result in greater understanding of disease pathology, progression, and identification of behavioral biomarkers, that could improve diagnosis and treatment.

Marmosets are becoming a model NHP species for studies on vocal communication. They have a complex social system with an abundant vocal repertoire in the wild [26, 27]. The range of vocalizations is well-conserved in monkeys raised in captive colonies bred for research purposes and can be evaluated without complex elicitation protocols [e.g., 28, 29, 30, 31, 32]. Vocalizations develop in common marmosets with modeling from parental feedback [33, 34], and call acoustic parameters develop differently based on call type [31].

Most published evaluations of marmoset vocalization development are performed using specialized audio recording equipment, and call analysis requires specific training. This can be prohibitive for more general translational research groups. Presently, simpler methods to assess vocalizations that are still sensitive to subtle changes are limited. The main goal of this study was to analyze call type changes across age in a translational research environment. We hypothesized that acoustic parameters of vocalizations would change with age, reflecting growth of the vocal apparatus and a maturation of control needed to make adult-like calls.

METHODS

Subjects

Nineteen common marmoset monkeys from 13 family units were evaluated in this study (Table 1). Twin pairs were evaluated simultaneously and were grouped together for statistical analysis. The subjects were part of a previous study assessing early motor development in marmosets [35]. Subjects were housed with their family in cages ($0.6 \times 0.9 \times 1.8$ m), maintained on a 12-hour light/dark cycle with a temperature range of 24–30 °C and relative humidity of 30–70%. Animals were fed twice daily (Mazuri Callitrichid High Fiber Diet, Land O Lakes, Mazuri, Brentwood, MO), with daily supplements of fruit, vegetables, or mealworms. Water was continuously available. Animals were monitored for general appearance, condition, food intake, feces output, and weight. The present study was performed in strict accordance with the recommendations in the National Research Council Guide for the Care and Use of Laboratory Animals (2011) and the American Society of Primatologists principles for the ethical treatment of nonhuman primates in an AAALAC accredited facility (Wisconsin National Primate Research Center, Graduate School, University of Wisconsin-Madison). The Institutional Animal Care and Use Committee at the University of Wisconsin-Madison approved the experimental protocol (permit G00679). All efforts were made to minimize the number of animals used and to ameliorate any distress.

Data Collection and Analysis

After several habituation sessions, ten minute videos were recorded twice a week with a hand-held camera with a built-in microphone (HDRCX440, Sony Corporation, Tokyo, Japan) by one of the authors (KMB), to better follow the individual subjects. The built-in microphone records at a frequency of 48 kHz with a 16-bit resolution. Videos were collected during weeks 1–21 of age. During video recording, the animal was visualized in the video frame and was allowed to move freely about the cage to interact with his/her family in a naturalistic way. Recordings were obtained in the late morning and early afternoon in a counter-balanced manner. Videos for evaluation were selected based on presence of visually-identifiable calls. Audio was extracted from the videos using QuickTime software (Apple Inc., Cupertino California) and analyzed using Praat software (Pratt, Amsterdam, The Netherlands). Samples were bandpass filtered from 1 to 20 kHz to eliminate extraneous noise. Calls were selected for analysis when the animal was visibly calling in the video frame and coded into call types as outlined by Pistorio and colleagues [31].

Call types included in the present study (Figure 1) were: 1) cry: a call with multiple harmonics with a duration up to 1 second, used only by infant monkeys to get attention from other monkeys; 2) tsik: a short call (0.02–0.1 seconds) with pitch slightly rising and then falling to a lower frequency, typically used as an alarm call; 3) phee: a monosyllabic call up to 1 second in duration with a steady frequency, used as a within-group contact call; 4) trill: a monosyllabic call up to 0.75 seconds in duration with a cyclical frequency modulation, also used as a within-group contact call; 5) trillphee: a call starting off trill-like and ending phee-like; and 6) cry-combination: a call typically starting with a cry and ending with another call type, such as a phee or trill [27, 31, 36]. Twitter calls have also been described as polysyllabic calls with brief sweeps from low frequency to high frequency, used as a between-group territorial call or to communicate agitation [27, 31, 36]; however, no twitter calls were observed in the present study.

For each call type, extracted acoustic parameters were average call duration (seconds-sec), minimum frequency (Hertz-Hz), maximum frequency (Hz), and call bandwidth (maximum frequency – minimum frequency; Hz). Intensity parameters were not considered in the present study, as we could control distance to the microphone in the naturalistic setting. Calls were excluded from analysis if they coincided with another animal's call, they were obscured by environmental noise (e.g., the door to the room opening), or if the animal was not clearly in the video frame facing the camera. Two undergraduate researchers (MKD, SAH) extracted acoustic parameters after training to at least 80% reliability. Outlier call parameters were reassessed by a different investigator (CJ).

Statistical Analysis

SPSS software (IBM Analytics, Armonk, New York) was used for statistical analysis. Intraclass correlation coefficients (ICC) were used to determine inter-rater reliability for analyzing calls. To assess the effects of age (in days) on acoustic parameters (listed above), mixed model linear regressions were performed. Sex was not considered as a variable due to difficulty differentiating individuals from a mixed sex twin pair, and sexual dimorphism is not evident in marmosets [10]. Separate models were created for each call parameter. Each model was evaluated with a fixed effect for age and a random effect with separate slopes for subject. Assumptions of linearity, normality, homoscedasticity, and collinearity were assessed prior to running the models. A criterion reference of $\alpha < 0.05$ was used to represent statistical significance.

RESULTS

All marmosets, including infants and other monkeys in the home cage, tolerated being videotaped. On average, the marmosets adjusted to having a study team member in front of the home cage with a video camera after three 10-minute habituation sessions.

Intraclass correlation values were between 0.95–0.98 for all call parameters following 2 or 3 training sessions. With the study team member in the room, young marmosets produced a variety of call types, including cries, cry combinations, tsiks, trills, phees, and trill-phees (Figure 1). Tsiks were the most frequently identified call type, and emerged before 1 week of age. Cries were also common, and persisted through 20 weeks. Trills, phees, and trill-

phes were observed within the first 4 weeks and became relatively more common as time progressed. In general, during the first 4–6 weeks, the marmosets clung to a member of the family unit, which made identification of vocalizations more difficult than when the animal was on its own, and may have prevented the identification of additional calls. Call profiles captured during each week are in Figure 2.

In all, 3748 calls were analyzed (1256 cry, 1572 tsik, 80 phee, 448 trill, 203 trillphee, and 189 cry combination calls). Mean acoustic parameters from each animal at each time point were entered into statistical modeling. Parameters in cry, tsik, trill, and trillphee calls changed significantly during the 21 weeks of observation (Table 2, Figure 3). Cries decreased in duration ($F(1,46) = 4.57$; $p = 0.038$), maximum frequency ($F(1,46) = 4.16$; $p = 0.047$), and bandwidth ($F(1,46) = 5.50$; $p = 0.023$) over time. Tsik calls decreased in duration ($F(1,59) = 10.84$; $p = 0.002$) and increased in minimum frequency ($F(1,59) = 8.86$; $p = 0.004$) and maximum frequency ($F(1,59) = 8.64$; $p = 0.005$) over time. Trill calls increased in duration ($F(1,40) = 10.30$; $p = 0.003$) and trillphee bandwidth decreased ($F(1,33) = 5.08$; $p = 0.031$) with age. No phee call parameters changed significantly over the 20 weeks of development. Due to increased inter- and intra-individual variability in cry combination call types, these were excluded from statistical analysis.

DISCUSSION

Our results in developing marmoset monkeys demonstrate that the early changes in acoustic parameters are call-type dependent. We also established the feasibility of a naturalistic protocol to collect and objectively analyze marmoset vocalizations longitudinally without complex vocalization elicitation paradigms or specialized audio recording equipment.

Changes in acoustic parameters during the first 21 weeks of life may reflect development of communicative sensorimotor control in addition to changes due to growth. For example, if acoustic changes were solely related to increased vocal tract size, then frequency (pitch), including minimum, maximum, and bandwidth values, should decrease for all call types. However, the only frequency decrease observed was in cry maximum frequency, and tsik minimum and maximum frequency actually increased. This frequency increase, as well as decreases in cry and tsik duration and decreases in cry and trillphee bandwidth, may represent a change in sensorimotor control and a shift towards more adult-like calls [31, 35]. For example, adult marmosets produce tsik calls with 0.06 second durations, with minimum frequencies of approximately 5200 Hz and maximum frequencies of 18300 Hz [32], and the maturing marmoset is approximating it. Increases in call duration, seen in trill calls, may be indicative of increased breath support or ability to sustain vocal output. Adult marmosets produce trill calls of approximately 0.46 seconds in length [32].

It is important to consider vocal changes in context with the overall development of marmoset sensorimotor and social behavior [37]. Marmosets become more independent as fine motor skills and self-calming behaviors emerge between 4–8 weeks of age. They begin to eat solid food unaided and engage in tree gouging and social play at around 12–16 weeks. Female sex hormones set in and social grooming behaviors emerge at 16–18 weeks [37].

Call rate decreases as marmosets reach adulthood [31]. It is likely that some of the observed changes in the present study are due to social-emotional development and vocal practice.

Of additional interest are the parameters that did *not* change with age. In contrast to Pistorio and colleagues [31] who reported a decrease in most frequency parameters and an increase in duration of phee calls, we found no duration, frequency, or bandwidth change. Their paradigm, however, involved placing the monkey alone in a cage in a room away from other family members. This isolating environment may have increased the relative frequency of phee calls, which are generally considered to be long-distance contact calls [38]. Call parameters that do not change with age may be better candidate calls for comparison to vocalizations in genetic models of neurodegenerative disease, as statistical comparison may be simpler.

Our results highlight the feasibility for recording marmoset vocalizations in a naturalistic setting. The call distribution may have been impacted by a human observer in close proximity to the marmoset's cage, resulting in more tsik calls [32], and also by sampling bias for call selection based on the animal's position. However, it is important to note that regular vocalization recording was possible without the need for transporting the animals to specialized soundproof rooms, thus separating them from the family unit for extended periods of time. Although we used video recordings and not a specialized sound system, the recordings were robust enough to detect subtle changes in acoustic parameters over time. Additionally, data analysis reached high reliability with a few training sessions with undergraduate lab personnel. This paradigm would thus be ideal for translational research labs interested in studying vocalization as one of many component outcomes of neurological disease modeling.

This study presented several limitations. With a naturalistic approach, there was no certainty that each monkey would make every call type during each recording session. Vocalizations from twin pairs were evaluated together statistically, as animals were not able to be differentiated on video. Additionally, we only analyzed vocalizations that were visibly made on camera, which may preclude analysis of more covert calls, such as twitter. These limitations might be addressed by placing multiple cameras at different angles, which would also assist in analyzing vocal behavior in context. Finally, we did not standardize the distance of the camera to the cage, so we cannot make accurate measurements of call intensity (loudness), an important vocal parameter that may be impacted by neurological disease.

In humans, neurodegenerative disease affects several aspects of communication [14, 15]. In the case of PD, patients have reduced vocal quality (e.g., breathiness or roughness), intensity (loudness), inflection, and articulation [19, 39, 40], even in the early stages of disease progression [1]. Changes in vocalizations in animal models of PD have been demonstrated in several model species. Common findings in rodents with parkinsonism induced by neurotoxin or transgenesis are reduced number of calls, reduced intensity of calls, and reduced call-complexity [24, 41, 42], most of which are improved with behavioral therapy (vocal exercise) [25, 43] but not with levodopa [44]. Studies in common marmosets with neurotoxin-induced parkinsonism have only reported a reduced number of vocalizations,

without performing any further acoustic analyses [45, 46, 47, 48, 49]. Employing detailed acoustic analysis, such as that used in the current study, may reveal changes to vocal communication analogous to those found in humans and rodent models.

Marmoset vocalizations change with age, but this change is call-type dependent. This dataset, captured in healthy developing marmosets, can serve as a comparison group for future studies involving transgenic models of neurological diseases, with the capability for investigation into early changes to vocal function associated with neuropathology.

Acknowledgments

This work was supported by NIH P51OD011106, NIH R24OD019803; NIH T32 GM007507, NIH F31 DC015709, NIH DC011130, and NIH R01DC014358. We would like to acknowledge biostatisticians Drs. Dou-Yan Yang and Yue Ma for their consultation on statistical analysis.

Biographies

Corinne Jones is a PhD Candidate at the University of Wisconsin-Madison in the Department of Communication Sciences & Disorders and the Neuroscience Training Program. Ms. Jones is a licensed and certified speech-language pathologist. Her research focuses on sensorimotor control of voice and swallowing in Parkinson's disease.

Mary Duffy is a BS graduate of UW-Madison and plans to apply to PA school.

Sarah Hoffman is a BS graduate of UW-Madison and plans to apply to PA school

Nancy Schultz-Darken is an Associate Scientist and Scientific Head of the Scientific Protocol Implementation Unit with the Wisconsin National Primate Research Center. Dr. Schultz-Darken specializes in behavior, neuroendocrinology, and neuroscience in non-human primates.

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Michelle Ciucci is an Associate Professor of Communication Sciences & Disorders, Department of Surgery-Division of Otolaryngology, and Neuroscience Training Program at UW-Madison. Dr. Ciucci's research interests focus on the neurobiological and behavioral underpinnings of cranial sensorimotor control in health and disease states.

Marina Emborg is an Associate Professor of Medical Physics and the director of the Preclinical Parkinson's Research Program in the Wisconsin National Primate Research Center, at UW-Madison. Dr. Emborg's research explores strategies to prevent, slow, or stop neurodegeneration.

References

1. Ciucci MR, Grant LM, Rajamanickam ES, et al. Early identification and treatment of communication and swallowing deficits in Parkinson disease. *Seminars in Speech and Language*.

- 2013 Aug; 34(3):185–202. PubMed PMID: 24166192; PubMed Central PMCID: PMC4477682. DOI: 10.1055/s-0033-1358367 [PubMed: 24166192]
2. Verma M, Howard RJ. Semantic memory and language dysfunction in early Alzheimer's disease: a review. *International journal of geriatric psychiatry*. 2012 Dec; 27(12):1209–17. PubMed PMID: 22298328. DOI: 10.1002/gps.3766 [PubMed: 22298328]
 3. Harel BT, Cannizzaro MS, Cohen H, et al. Acoustic characteristics of Parkinsonian speech: a potential biomarker of early disease progression and treatment. *Journal of Neurolinguistics*. 2004 Nov; 17(6):439–453. PubMed PMID: WOS: 000225277700003. DOI: 10.1016/j.jneuroling.2004.06.001
 4. Hirni DI, Kivisaari SL, Krumm S, et al. Neuropsychological Markers of Medial Perirhinal and Entorhinal Cortex Functioning are Impaired Twelve Years Preceding Diagnosis of Alzheimer's Dementia. *Journal of Alzheimer's disease : JAD*. 2016 Mar 26; 52(2):573–80. PubMed PMID: 27031465. DOI: 10.3233/jad-150158 [PubMed: 27031465]
 5. Carrion R, Patterson JL. An animal model that reflects human disease: the common marmoset (*Callithrix jacchus*). 2012 Jun; 2(3):357–362. 2012. DOI: 10.1016/j.coviro.2012.02.007
 6. Eslamboli A. Marmoset monkey models of Parkinson's disease: which model, when and why? *Brain research bulletin*. 2005 Dec 30; 68(3):140–9. PubMed PMID: 16325013. DOI: 10.1016/j.brainresbull.2005.08.005 [PubMed: 16325013]
 7. Okano H, Hikishima K, Iriki A, et al. The common marmoset as a novel animal model system for biomedical and neuroscience research applications. *Seminars in fetal & neonatal medicine*. 2012 Dec; 17(6):336–40. PubMed PMID: 22871417. DOI: 10.1016/j.siny.2012.07.002 [PubMed: 22871417]
 8. Tardif SD, Mansfield KG, Ratnam R, et al. The marmoset as a model of aging and age-related diseases. *ILAR journal / National Research Council, Institute of Laboratory Animal Resources*. 2011; 52(1):54–65. PubMed PMID: 21411858; PubMed Central PMCID: PMCPMC3775658.
 9. Abbott DH, Barnett DK, Colman RJ, et al. Aspects of common marmoset basic biology and life history important for biomedical research. *Comparative medicine*. 2003 Aug; 53(4):339–50. PubMed PMID: 14524409. [PubMed: 14524409]
 10. Schultz-Darken N, Braun KM, Emborg ME. Neurobehavioral development of common marmoset monkeys. *Developmental psychobiology*. 2016 Mar; 58(2):141–58. PubMed PMID: 26502294; PubMed Central PMCID: PMCPMC4829073. DOI: 10.1002/dev.21360 [PubMed: 26502294]
 11. Sasaki E, Suemizu H, Shimada A, et al. Generation of transgenic non-human primates with germline transmission. *Nature*. 2009 May 28; 459(7246):523–7. PubMed PMID: 19478777. DOI: 10.1038/nature08090 [PubMed: 19478777]
 12. Qiu Z, Li X. Non-human Primate Models for Brain Disorders - Towards Genetic Manipulations via Innovative Technology. *Neuroscience bulletin*. 2017 Apr; 33(2):247–250. PubMed PMID: 28251519; PubMed Central PMCID: PMCPMC5360846. DOI: 10.1007/s12264-017-0115-4 [PubMed: 28251519]
 13. Miller DB, O'Callaghan JP. Biomarkers of Parkinson's disease: present and future. *Metabolism: clinical and experimental*. 2015 Mar; 64(3 Suppl 1):S40–6. PubMed PMID: 25510818; PubMed Central PMCID: PMCPMC4721253. DOI: 10.1016/j.metabol.2014.10.030 [PubMed: 25510818]
 14. Mahler LA, Ramig LO, Fox C. Evidence-based treatment of voice and speech disorders in Parkinson disease. *Current opinion in otolaryngology & head and neck surgery*. 2015 Jun; 23(3):209–15. PubMed PMID: 25943966; eng. DOI: 10.1097/moo.0000000000000151 [PubMed: 25943966]
 15. Woodward M. Aspects of communication in Alzheimer's disease: clinical features and treatment options. *International psychogeriatrics*. 2013 Jun; 25(6):877–85. PubMed PMID: 23522497; eng. DOI: 10.1017/s1041610213000318 [PubMed: 23522497]
 16. Robbins JA, Logemann JA, Kirshner HS. Swallowing and speech production in Parkinson's disease. *Annals of Neurology*. 1986 Mar; 19(3):283–7. PubMed PMID: 3963773; eng. DOI: 10.1002/ana.410190310 [PubMed: 3963773]
 17. Ho AK, Ianssek R, Marigliani C, et al. Speech impairment in a large sample of patients with Parkinson's disease. *Behavioural neurology*. 1998; 11(3):131–137. PubMed PMID: 11568413; eng. [PubMed: 11568413]

18. van Hooren MR, Baijens LW, Vos R, et al. Voice- and swallow-related quality of life in idiopathic Parkinson's disease. *Laryngoscope*. 2016 Feb; 126(2):408–14. PubMed PMID: 26153234; eng. DOI: 10.1002/lary.25481 [PubMed: 26153234]
19. Sapir S, Ramig L, Fox C. Speech and swallowing disorders in Parkinson disease. Current opinion in otolaryngology & head and neck surgery. 2008 Jun; 16(3):205–10. PubMed PMID: 18475072; eng. DOI: 10.1097/MOO.0b013e3282febd3a [PubMed: 18475072]
20. Fabbri M, Guimaraes I, Cardoso R, et al. Speech and Voice Response to a Levodopa Challenge in Late-Stage Parkinson's Disease. *Frontiers in neurology*. 2017; 8:432. PubMed PMID: 28878734; PubMed Central PMCID: PMC5572389. eng. doi: 10.3389/fneur.2017.00432 [PubMed: 28878734]
21. D'Alatri L, Paludetti G, Contarino MF, et al. Effects of bilateral subthalamic nucleus stimulation and medication on parkinsonian speech impairment. *J Voice*. 2008 May; 22(3):365–72. PubMed PMID: 17368837; eng. DOI: 10.1016/j.jvoice.2006.10.010 [PubMed: 17368837]
22. Xie Y, Zhang Y, Zheng Z, et al. Changes in speech characters of patients with Parkinson's disease after bilateral subthalamic nucleus stimulation. *J Voice*. 2011 Nov; 25(6):751–8. PubMed PMID: 21227642; eng. DOI: 10.1016/j.jvoice.2010.08.002 [PubMed: 21227642]
23. Dickson JM, Grunewald RA. Somatic symptom progression in idiopathic Parkinson's disease. *Parkinsonism & related disorders*. 2004 Dec; 10(8):487–92. PubMed PMID: 15542009; eng. DOI: 10.1016/j.parkreldis.2004.05.005 [PubMed: 15542009]
24. Grant LM, Kelm-Nelson CA, Hilby BL, et al. Evidence for early and progressive ultrasonic vocalization and oromotor deficits in a PINK1 gene knockout rat model of Parkinson's disease. *Journal of neuroscience research*. 2015 Nov; 93(11):1713–27. PubMed PMID: 26234713; PubMed Central PMCID: PMC4575652. eng. DOI: 10.1002/jnr.23625 [PubMed: 26234713]
25. Kelm-Nelson CA, Yang KM, Ciucci MR. Exercise Effects on Early Vocal Ultrasonic Communication Dysfunction in a PINK1 Knockout Model of Parkinson's Disease. *Journal of Parkinson's disease*. 2015; 5(4):749–63. PubMed PMID: 26577653; PubMed Central PMCID: PMC4869531. Eng. DOI: 10.3233/jpd-150688
26. Stevenson MF, Poole TB. An ethogram of the common marmoset (*Callithrix jacchus jacchus*): general behavioural repertoire. *Animal behaviour*. 1976 May; 24(2):428–51. PubMed PMID: 820223. [PubMed: 820223]
27. Epplé G. Comparative studies on vocalization in marmoset monkeys (*Hapalidae*). *Folia primatologica; international journal of primatology*. 1968; 8(1):1–40. PubMed PMID: 4966050. [PubMed: 4966050]
28. Norcross JL, Newman JD. Social context affects phoe call production by nonreproductive common marmosets (*Callithrix jacchus*). *American journal of primatology*. 1997; 43(2):135–46. PubMed PMID: 9327096. DOI: 10.1002/(sici)1098-2345(1997)43:2<135::aid-ajp3>3.0.co;2-y [PubMed: 9327096]
29. Norcross JL, Newman JD. Effects of separation and novelty on distress vocalizations and cortisol in the common marmoset (*Callithrix jacchus*). *American journal of primatology*. 1999; 47(3):209–22. PubMed PMID: 10075435. DOI: 10.1002/(sici)1098-2345(1999)47:3<209::aid-ajp3>3.0.co;2-0 [PubMed: 10075435]
30. Norcross JL, Newman JD. Context and Gender-Specific Differences in the Acoustic Structure of Common Marmoset (*Callithrixjacchus*) Phee Calls. *American journal of primatology*. 1993; 30:37–54.
31. Pistorio AL, Vintch B, Wang X. Acoustic analysis of vocal development in a New World primate, the common marmoset (*Callithrix jacchus*). *Journal of the Acoustical Society of America*. 2006 Sep; 120(3):1655–70. PubMed PMID: 17004487. [PubMed: 17004487]
32. Agamaite JA, Chang CJ, Osmanski MS, et al. A quantitative acoustic analysis of the vocal repertoire of the common marmoset (*Callithrix jacchus*). *Journal of the Acoustical Society of America*. 2015 Nov; 138(5):2906–28. PubMed PMID: 26627765; PubMed Central PMCID: PMC4644241. DOI: 10.1121/1.4934268 [PubMed: 26627765]
33. Gultekin YB, Hage SR. Limiting parental feedback disrupts vocal development in marmoset monkeys. *Nature communications*. 2017 Jan 16; 8:14046. PubMed PMID: 28090084; PubMed Central PMCID: PMC5241798. eng. doi: 10.1038/ncomms14046

34. Takahashi DY, Liao DA, Ghazanfar AA. Vocal Learning via Social Reinforcement by Infant Marmoset Monkeys. *Current biology : CB*. 2017 May 24. PubMed PMID: 28552359; eng. doi: 10.1016/j.cub.2017.05.004
35. Braun K, Schultz-Darken N, Schneider M, et al. Development of a novel postnatal neurobehavioral scale for evaluation of common marmoset monkeys. *American journal of primatology*. 2015 Apr; 77(4):401–17. PubMed PMID: 25676438; PubMed Central PMCID: PMC4374045. DOI: 10.1002/ajp.22356 [PubMed: 25676438]
36. Sterling Uo. [cited 2017 October 22, 2017] Understanding behavior: Calls. Available from: <http://www.marmosetcare.com/understanding-behaviour/calls.html>
37. Ausderau KK, Dammann C, McManus K, et al. Cross-species comparison of behavioral neurodevelopmental milestones in the common marmoset monkey and human child. *Developmental psychobiology*. 2017 Aug 01. PubMed PMID: 28763098; eng. doi: 10.1002/dev.21545
38. Miller CT, Beck K, Meade B, et al. Antiphonal call timing in marmosets is behaviorally significant: interactive playback experiments. *Journal of comparative physiology A, Neuroethology, sensory, neural, and behavioral physiology*. 2009 Aug; 195(8):783–9. PubMed PMID: 19597736; PubMed Central PMCID: PMC3787898. eng. DOI: 10.1007/s00359-009-0456-1
39. Ramig LO, Fox C, Sapir S. Parkinson's disease: speech and voice disorders and their treatment with the Lee Silverman Voice Treatment. *Seminars in Speech and Language*. 2004 May; 25(2): 169–80. PubMed PMID: 15118943; eng. DOI: 10.1055/s-2004-825653 [PubMed: 15118943]
40. Sapir S. Multiple factors are involved in the dysarthria associated with Parkinson's disease: a review with implications for clinical practice and research. *Journal of Speech, Language, and Hearing Research*. 2014 Aug; 57(4):1330–43. PubMed PMID: 24686571; eng. DOI: 10.1044/2014_jslhr-s-13-0039
41. Kane JR, Ciucci MR, Jacobs AN, 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*. 2011 Sep-Oct;44(5):529–537. PubMed PMID: WOS:000294699400004. DOI: 10.1016/j.jcomdis.2011.04.005 [PubMed: 21820129]
42. Paumier KL, Luk KC, Manfredsson FP, et al. Intrastriatal injection of pre-formed mouse alpha-synuclein fibrils into rats triggers alpha-synuclein pathology and bilateral nigrostriatal degeneration. *Neurobiology of disease*. 2015 Oct.82:185–199. PubMed PMID: 26093169; PubMed Central PMCID: PMC4640952. eng. DOI: 10.1016/j.nbd.2015.06.003 [PubMed: 26093169]
43. Kelm-Nelson CA, Brauer AF, Ciucci MR. Vocal training, levodopa, and environment effects on ultrasonic vocalizations in a rat neurotoxin model of Parkinson disease. *Behavioral Brain Research*. 2016 Mar 26.307:54–64. PubMed PMID: 27025445; Eng. DOI: 10.1016/j.bbr.2016.03.006
44. Kelm-Nelson C, Ciucci M. Levodopa improves a subset of motor function associated with nigrostriatal deficits in a Pink1 $-/-$ rat model of Parkinson disease. *Neuroscience*. 2018 In publication.
45. Ando K, Obayashi S, Nagai Y, et al. PET analysis of dopaminergic neurodegeneration in relation to immobility in the MPTP-treated common marmoset, a model for Parkinson's disease. *PloS one*. 2012; 7(10):e46371. PubMed PMID: 23056291; PubMed Central PMCID: PMC3466292. Eng. doi: 10.1371/journal.pone.0046371 [PubMed: 23056291]
46. Albanese A, Granata R, Gregori B, et al. Chronic administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine to monkeys: behavioural, morphological and biochemical correlates. *Neuroscience*. 1993 Aug; 55(3):823–32. PubMed PMID: 8105418; Eng. [PubMed: 8105418]
47. Allen JM, Cross AJ, Yeats JC, et al. Neuropeptides and dopamine in the marmoset. Effect of treatment with 1-methyl-4-phenyl-1, 2, 3, 6 tetrahydropyridine (MPTP): an animal model for Parkinson's disease? *Brain*. 1986 Feb; 109(Pt 1):143–57. PubMed PMID: 2417654; Eng. [PubMed: 2417654]
48. Gibb WR, Terruli M, Lees AJ, et al. The evolution and distribution of morphological changes in the nervous system of the common marmoset following the acute administration of 1-methyl-4-

phenyl-1,2,3,6-tetrahydropyridine. *Mov Disord.* 1989; 4(1):53–74. PubMed PMID: 2494438; Eng. DOI: 10.1002/mds.870040109 [PubMed: 2494438]

49. Jenner P, Rose S, Nomoto M, et al. MPTP-induced parkinsonism in the common marmoset: behavioral and biochemical effects. *Advances in neurology.* 1987; 45:183–6. PubMed PMID: 2881443; Eng. [PubMed: 2881443]

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Figure 1.
Example spectrograms of call types analyzed.

Figure 2.

Call profiles by week, representing the percentage of each call type produced.

Figure 3.

Acoustic parameters by age and animal family. Red points indicate single or twin pairs of female monkeys, blue points indicate single or twin pairs of male monkeys, and purple points indicate twin pairs with one male and one female. In the plots displaying minimum and maximum frequency, lighter colored symbols represent minimum frequency and darker colored symbols represent maximum frequency. Parameters that significantly change are marked with an asterisk.

Table 1

Demographics of common marmoset monkey subjects

Monkey # Family Letter	Sex	Age Range (days/weeks)	Number of Videos with Vocalizations	Call Types Produced
1A	M	33–72 / 4–10	8	Cry, Tsik, Phee, Trill, Trillphee
2B	F	81–143 / 11–20	7	Cry, Tsik, Phee, Trill, Trillphee
3C	F	24–83 / 3–11	8	Cry, Tsik, Phee, Trill, Trillphee
4D / 5D	F / F	23–146 / 3–20	9	Cry, Tsik, Trill, Trillphee
6E	M	91–147 / 13–21	16	Cry, Tsik, Phee, Trill, Trillphee
7F / 8F	M / M	8–56 / 2–8	8	Cry, Tsik, Phee, Trill, Trillphee
9G / 10G	M / M	20–123 / 2–17	6	Cry, Tsik, Phee, Trill, Trillphee
11H / 12H	M / F	1–38 / 0–5	4	Cry, Tsik, Phee, Trill, Trillphee
13I / 14I	F / M	1–35 / 0–5	5	Cry, Tsik, Phee, Trill, Trillphee
15J / 16J	M / F	28–149 / 4–21	3	Cry, Tsik, Trill
17K	F	16–49 / 2–7	4	Cry, Tsik, Phee, Trill, Trillphee
18L	M	59–71 / 8–10	2	Tsik, Phee, Trill, Trillphee
19M	F	25–81 / 3–11	5	Tsik, Phee, Trillphee

Table 2

Summary of mixed effects models. Intercept parameters reflect the y-intercept of the overall regression line and age parameters reflect the slope of the regression line.

Model	Parameter	Estimate (Standard Error)	Significance
Cry Duration*	intercept	0.59 (0.04)	t(46) = 15.71, p < 0.001
	age	-0.0013 (0.0006)	t(46) = -2.14, p = 0.038
Cry Minimum Frequency	intercept	4552.07 (183.80)	t(46) = 24.77, p < 0.001
	age	5.00 (3.08)	t(46) = -1.20, p = 0.11
Cry Maximum Frequency*	intercept	16855.94 (287.79)	t(46) = 58.57, p < 0.001
	age	-9.84 (4.83)	t(46) = -2.04, p = 0.047
Cry Bandwidth*	intercept	12303.82 (377.64)	t(46) = 32.58, p < 0.001
	age	-14.85 (6.33)	t(46) = -2.35, p = 0.023
Tsik Duration*	intercept	0.053 (0.003)	t(59) = 16.88, p < 0.001
	age	-0.00014 (0.00004)	t(59) = -3.29, p = 0.002
Tsik Minimum Frequency*	intercept	5272.75 (357.17)	t(59) = 14.76, p < 0.001
	age	14.34 (4.82)	t(59) = 2.98, p = 0.004
Tsik Maximum Frequency*	intercept	11705.26 (328.95)	t(59) = 35.58, p < 0.001
	age	13.04 (4.44)	t(59) = 2.94, p = 0.005
Tsik Bandwidth	intercept	6434.34 (374.93)	t(59) = 17.16, p < 0.001
	age	14.34 (4.82)	t(59) = -0.24, p = 0.80
Phee Duration	intercept	0.55 (0.089)	t(28) = 6.17, p < 0.001
	age	-0.00028 (0.001)	t(28) = -0.27, p = 0.79
Phee Minimum Frequency	intercept	7642.14 (280.50)	t(28) = 27.25, p < 0.001
	age	1.46 (3.21)	t(28) = 0.46, p = 0.65
Phee Maximum Frequency	intercept	9696.18 (262.72)	t(28) = 36.91, p < 0.001
	age	-4.46 (3.00)	t(28) = -1.49, p = 0.15
Phee Bandwidth	intercept	2054.04 (270.10)	t(28) = 7.61, p < 0.001
	age	-5.92 (3.09)	t(28) = -1.92, p = 0.065
Trill Duration*	intercept	0.28 (0.022)	t(40) = 12.34, p < 0.001
	age	0.001 (0.0003)	t(40) = 3.21, p = 0.003
Trill Minimum Frequency	intercept	7274.09 (235.47)	t(40) = 30.89, p < 0.001
	age	4.12 (3.49)	t(40) = 1.18, p = 0.25
Trill Maximum Frequency	intercept	10396.91 (195.31)	t(40) = 53.23, p < 0.001
	age	0.26 (2.90)	t(40) = 0.089, p = 0.93

Model	Parameter	Estimate (Standard Error)	Significance
Trill Bandwidth	intercept	3122.82 (237.33)	t(40) = 13.16, p < 0.001
	age	-3.86 (3.52)	t(40) = -1.10, p = 0.28
Trillphee Duration	intercept	0.35 (0.06)	t(33) = 6.24, p < 0.001
	age	0.001 (0.0008)	t(33) = 1.19, p = 0.24
Trillphee Minimum Frequency	intercept	7602.48 (274.69)	t(33) = 27.68, p < 0.001
	age	3.30 (4.14)	t(33) = 0.80, p = 0.43
Trillphee Maximum Frequency	intercept	10308.85 (273.55)	t(33) = 37.69, p < 0.001
	age	-5.87 (4.12)	t(33) = -1.42, p = 0.16
Trillphee Bandwidth*	intercept	2706.37 (270.06)	t(33) = 10.02, p < 0.001
	age	-9.18 (4.07)	t(33) = -2.25, p = 0.031