2019 Marmoset Community White Paper

I. Executive Summary

A. Marmosets are a rapidly emerging Biomedical Model System

The common marmoset (*Callithrix jacchus*) has experienced unprecedented growth in research across the United States and is rapidly emerging as a likely keystone biomedical model system in the next chapter of scientific discovery. Over the past decade, the number of colonies in the country has **quadrupled**. *There are now at least 28 research colonies serving over 40 Principal Investigators (PIs) in the United States.* In contrast to institutional investments in other countries for marmoset research – most notably in Japan – the emergence of marmosets in the US has been driven almost entirely by Investigator Initiated projects. Although these grassroot efforts have been successful, several crucial bottlenecks have emerged which threaten to thwart the continued growth of this powerful biomedical model system. At this juncture, crucial strategic investment is needed by the NIH to address these issues and allow the marmoset model to realize its full potential as a cornerstone species able to accelerate the rate of discovery in biomedical research and better understand human disease.

This White Paper both highlights the advantages of marmoset monkeys for accomplishing the stated mission of the NIH and identifies the crucial, strategic investments needed to elevate and expand the impact of this model system for biomedical research.

B. Past NIH Investment in Marmoset Research

Over the past 5 fiscal years [2014-2018] the NIH has invested ~$117,000,000 in research involving marmosets. In FY2018, the NIH supported 41 grants with over $21,000,000 in funding from 10 different Institutes and the Office of the Director. The FY2018 total, however, was a significant decline from previous years. In FY2015, for example, the NIH invested nearly $30,000,000 in marmoset research. Notably, the ~40% decrease in funding was negatively correlated with the increasing number of marmoset colonies in the US. Over the same period of time [2014-2018] the number of marmoset colonies increased by over 60%. This negative correlation indicates that past NIH funding is not keeping pace with the growth of the field and requires immediate financial investment by the NIH to support the burgeoning community.

Notably, the Office of the Director is the first at NIH to support projects aimed at developing transgenic gene-editing technologies in marmosets. The OD funded 3 new grants totaling $2,240,000 of support in FY2018. These next-generation molecular approaches are crucial keystone to the long-term success of the marmoset model, requiring continued and increased support by the NIH.

C. Recommendations & Priorities for Future NIH investment in Marmoset Research

The marmoset model has enjoyed substantial growth over the past decade largely through grass-roots, researcher-initiated projects. While these ventures have been remarkably productive, several bottlenecks must be addressed in order for the model to reach its full potential as a keystone system for addressing NIH's stated goal to enhance health, lengthen life and reduce illness and disability in humans. As a nonhuman primate species with several unique reproductive, physiological and behavioral advantages, marmosets are uniquely positioned to accelerate progress to this end. We are presently at a crucial juncture in the development of the model; substantial investment by the NIH is needed to the core resources and infrastructure required to support the rapidly growing community and facilitate an accelerated rate of discovery for human diseases.

The marmoset community met for the first PI meeting in September 2018 in Boulder, CO to identify key bottlenecks facing the field and the crucial resources needed to overcome these challenges. Based on input and feedback from the community, we have identified the following 4 resource and infrastructure priorities that require immediate investment from the NIH.

1. Expansion of the U.S. Marmoset Population.
2. Management of Genetic Diversity in the U.S. Marmoset Population
3. Investment in Developing Gene-Editing Technologies in Marmosets
4. Support for Marmoset Training and Meetings

To address these issues, we recommend the NIH support a number of crucial RFA/PAR within the next year to support the development of the foundational infrastructure and resources for marmoset research to flourish in the United States.

D. Marmoset Community Initiatives

In addition to the above recommendations for the NIH, the community also recognized the continued benefits of grass-roots initiatives from across the collective of marmoset Investigators to strengthen the field. During the Marmoset PI meeting, the community identified two new initiatives that will be implemented.

1. Collective Marmoset Pool for New Investigators
2. Resource Sharing

E. Marmosets are a Model of Human Disease.

The principal long-term goal of the marmoset research community is to expand the use of this model organism in order to accelerate our rate of discovery for understanding human disease. The recommendations in this White Paper for immediate strategic investments by the NIH supporting crucial resources and infrastructure are needed to maximize the impact of marmosets as a cornerstone model organism to study human diseases. Marmosets offer unique opportunities to study and understand biomedical processes that have not been feasible to model in other nonhuman primates. The species' rapid development and aging, for example, make it possible to longitudinally examine diseases that afflict humans at specific times in life, both during ontogeny and senescence. Likewise, the small size and high fecundity provide logistical advantages for the development and implementation of next-generation gene-editing technologies. Furthermore - because of notable similarities in their social behavior, cognition and communication with humans, as well as the shared functional brain architecture of all primates - this nonhuman primate species is uniquely suited to model the neuropsychological disorders that afflict humans. The marmoset model has the potential to transform our understanding of the myriad of genetic, physiological and environmental factors affecting human disease as a keystone biomedical model in the next chapter of scientific inquiry.

II. Introduction

Marmosets are an emerging model system for biomedical research

The common marmoset (*Callithrix jacchus*) is a New World monkey that has been used as a model system in biomedical research for several decades. Although marmosets had been used in diverse areas of research, until recently only a handful of investigators actively used the species, which was generally regarded as a niche model system. In less than a decade, however, this landscape has dramatically changed in the United States. Whereas there were 7 marmoset colonies in the US in 2008, there are now 28. This represents a 4-fold increase, with most of the increase occurring in the past 6 years (Figure 1). Notably, several of these colonies serve multiple Investigators and we have identified over 40 Principal Investigators currently using marmosets in biomedical research in the United States. This rate of expansion for a nonhuman primate model is unprecedented and reflects the central role that marmosets will play in the next chapter of biomedical research in the United States. To support the rapidly growing demands for marmosets, it is imperative that significant, strategic investments be made so that the model is able to realize its vast potential to transform biomedical research in the decades to come.

Several physiological and logistical advantages of marmosets have been crucial to the species rapid emergence over the past few years. For example, marmosets have a gestation of only ~150 days and typically birth fraternal twins, which establishes marmosets as having amongst the highest fertility of any primate (1). Likewise, marmoset development is notably rapid – reaching adulthood in ~14-18months and becoming aged at ~8yo (2, 3) Like rodents, marmosets are small – weighing ~300-400g – and large populations can be housed in smaller facilities than larger primates. However, unlike rodents, marmosets exhibit the shared physiological, behavioral and cognitive characteristics that are unique to primates, including the core functional architecture and organization of our nervous system (4). This unique complement of characteristics affords the exciting opportunity

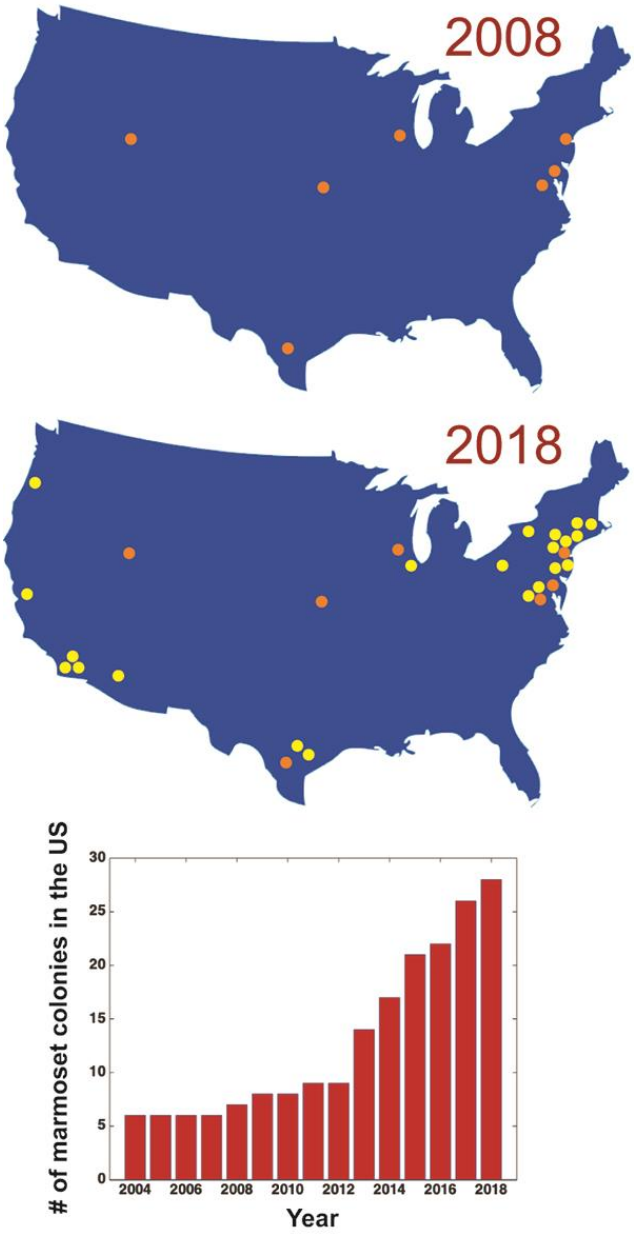

Figure 1. Growth of Marmoset Colonies in the United States. [Top] The schematic maps of the US show the marmoset research colonies [above] in 2008 in orange dots, while [Middle] plots the new colonies in yellow dots that have been established through 2018. [Bottom] Bar graph plots the # of marmoset colonies by year for the past 15 years. Notably, most of the growth in has occurred since 2013.

to feasibly utilize a primate species to model many of the diseases that afflict humans, ranging from those that affect humans at specific times in life – including both developmentally and during aging – to neuropsychiatric disorders that impact uniquely primate properties of our brain.

A pivotal cornerstone in the emergence of the marmoset model has been the realization that these characteristics could be feasibly leveraged with the species advantages for next-generation molecular technologies to make unprecedented advances in human disease. Much of the growth in marmosets occurred following the first report of germline transmission of a green fluorescence protein transgene in marmosets by Erika Sasaki and colleagues (5). Further development of viral and transgenic technologies in marmosets has cemented marmosets at the center of this transformative research enterprise (6-14)

Advantages of Marmosets for Biomedical Research.

Marmosets have been used as animal models in biomedical research across a diversity of disciplines for several decades (Figure 2). Although the most common use today is in studies of molecular and systems neuroscience, their widespread use historically reflects the numerous advantages that the species offers for research programs, ranging from infectious disease to reproduction to neuropsychiatric disorders. Here we discuss some of the key advantages that marmosets have for further utilization in biomedical research.

High Reproductive Power. Common marmosets produce 2-3 offspring every 5-6 months – the highest fertility of any anthropoid primate (1). This high fertility is a major advantage over any other nonhuman primate species typically used in research, enabling high-speed population expansion, within 3-5 years in comparison to decades. It is a specific advantage for technologies, such as transgenics, in which rapid establishment of genetically defined lines is essential. As an example, 10 macaque breeding females will, in two years' time, have produced a maximum of 20 offspring, all of which will be immature; i.e, the reproductive population will not have increased during that time. In contrast, in the same 2-year period, 10 marmoset breeding females will have produced an average of 60 offspring and the reproductive population will have tripled, as marmosets reach reproductive maturity by 14-18 months of age. While application of transgenic technologies to nonhuman primates will likely remain an expensive enterprise when compared to rodents, the use of marmosets brings this technology within an acceptable financial range for applications in which the nonhuman primate is a particularly compelling model, such as Alzheimer's disease (AD),

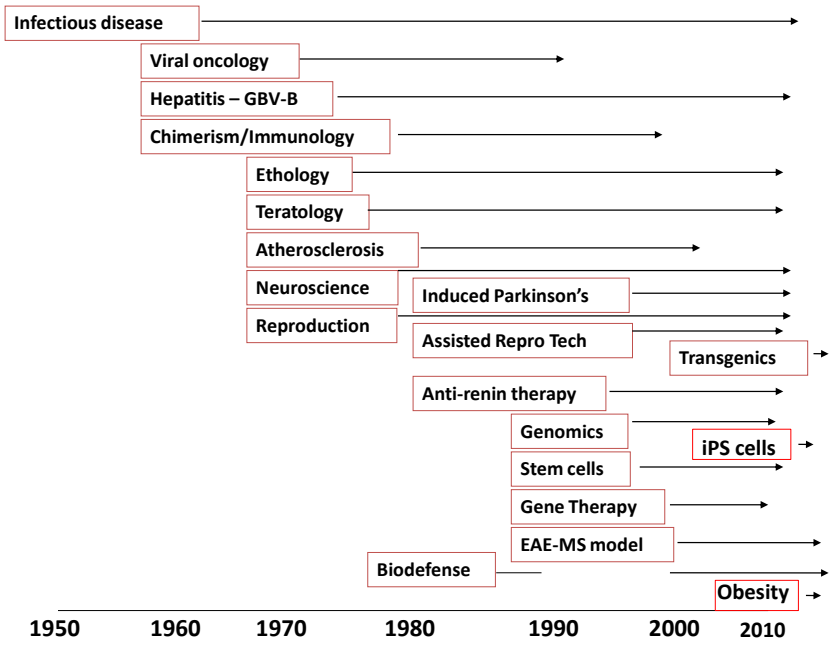

Figure 2. Timeline of when different areas of biomedical research began using marmosets.

Parkinson's disease (PD), and other neurodegenerative diseases. Furthermore, the efficiency of *in vitro* fertilization of oocytes (100/collection/animal) is very high (>50%), making marmosets highly economical and scalable for generating the number of genetically modified marmosets needed for preclinical evaluation.

Small Size. Adult common marmosets weigh 300-400 grams – meaning they are about the size of a laboratory rat. Their small size makes them easier to handle than large-bodied monkeys and allows for spacious, social housing in a relatively small laboratory space. Owing to their small size, marmosets require limited amounts of test compounds when used to study vaccines, therapeutics or other interventions – a decided advantage when test material is in limited quantities.

Fast Maturation and Short Life Span. Many of the most pressing U.S. human health concerns involve diseases that emerge early in development, are chronic or for which aging is a strong risk factor. The fast maturation and relatively short life span of marmosets makes them a valuable resource to study developmental, chronic and aging related diseases. Marmosets are sexually mature at 14-18 months of age and display signs of age-related pathologies – such as β-amyloid accumulation in the brain (15), impaired cochlear function and lean mass loss - by 8-13 years of age. Most importantly, the time period required to move from early to late life – i.e. to advance through the stages of development, aging or chronic disease - is within the range of a typical, NIH-funded project (i.e. 5 year R01 grant). Furthermore, like humans, marmosets are typically group-housed with pair-bonded parents and 2 generations of offspring, making it possible to observe the process of aging across three generations of animals in the same cage. This is a particularly attractive feature for transgenic models in which disease onset may depend on aging factors, such as neurodegenerative disorders like AD and PD (16, 17).

Brain Architecture and Function. The marmoset brain comprises the core brain architecture unique to – and shared by - all primates, including humans (18, 19). This includes a large neocortex, granular prefrontal cortex – a substrate unique to the primate brain (20) – reduced olfactory regions and an expansion of the visual and auditory cortical fields. Furthermore, marmoset cortex is lissencephalic (smooth) which offers a significant logistical advantage to neuroscientific inquiry as the entirety of the neocortical fields are accessible directly below the skull, rather than within sulci. While marmosets have a rat-like body size, they have a primate-typical brain size of 2% of body weight. The rat brain, in contrast, is 0.5% of their body weight.

Social Behavior, Cognition and Communication. Primates are distinguished from other animals by the breadth and sophistication of our sociality, including the dynamic models we develop for social decision-making to effectively navigate the complexities of these social landscapes. While marmosets share these attributes with other primates, their societies also exhibit characteristics that are typical of humans yet rare in other primates (4). Marmosets, for example, pair-bond and cooperatively care for their offspring (3). Cooperation occurs frequently in marmoset society and the species displays high levels of prosociality (21). Several experiments show that marmosets also utilize imitation, a distinct social learning mechanism that is rare amongst primates as it has only been reported in humans and chimpanzees (22). Marmosets are also highly vocal, engaging in near tonic levels of conversational exchanges with conspecifics by utilizing turn-taking mechanisms that are learned during development (23). While vocal communication is critical to mediating their social interactions, marmosets also utilize a diverse corpus of visual signals – including facial expressions – as a parallel social signaling system, similarly to humans (4).

Current Uses of Marmosets in Biomedical Research

Marmosets are currently used as model organisms across numerous biomedical disciplines, ranging from infectious disease to reproductive biology to neuroscience. The increasing interest in marmosets is also reflected in the notable rise in marmoset publications. Using 'marmoset' as a keyword search in PubMed for each of the past 15 years shows a steady increase in number of marmoset publications (Figure 3). Since 2012, over 200 peer-reviewed manuscripts involving marmosets have been published annually.

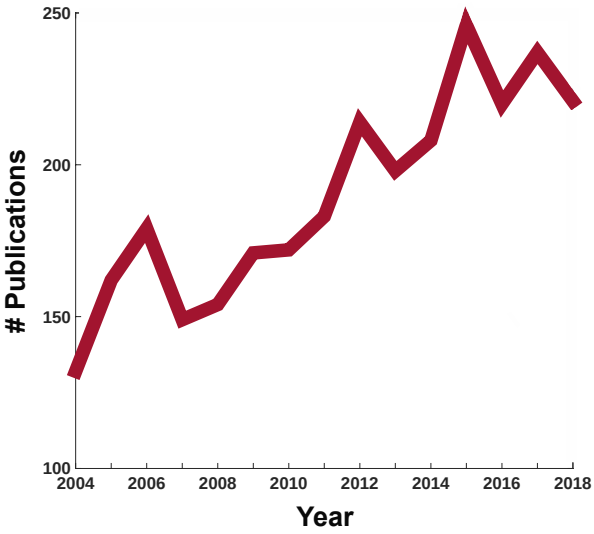

Figure 3. Plots the total number [#] of peer-reviewed publications with marmosets listed on PubMed each year for the past 15 years.

Recent Representative Publications.

- Iwano et al. 2018. Single-cell bioluminescence imaging of deep tissue in freely moving animals. *Science*, 359, 935**–**939
- Samonds J, et al. 2018. Natural image and receptive field statistics predict saccade sizes. *Nature Neuroscience*, 21, 1591- 1599.
- Leibovitch E. et al. 2018. Herpesvirus trigger accelerates neuroinflammation in a nonhuman primate model of multiple sclerosis. *PNAS,* 115, 11292-11297.
- Mucker E, et al. 2018. Intranasal monkeypox marmoset model: Prophylactic antibody treatment provides benefit against sever monkeypox virus disease. *PLoS Neglected Tropical Disease*, 12, e0006581.
- Knoll J, et al. 2018. Lawful tracking of visual motion in humans, macaques and marmosets in a naturalistic continuous, and untrained behavioral context. *PNAS*, 115, E10486-E10494.
- Lum et al. 2018. Multimodal assessments of Zika virus immune pathophysiology responses in marmosets. *Scientific Reports*, 8, 17125.
- Kondo T, et al. 2018. Calcium transient dynamics of neural ensembles in the primary motor cortex of naturally behaving monkeys. *Cell Reports*, 24, 2191-2195.
- Eliades S & Tsunada J. 2018. Auditory cortical activity drives feedback-dependent control in marmosets. *Nature Communications*, 9, 2540
- Gultekin Y & Hage S. 2018. Limiting parental interaction during vocal development affects acoustic call structure in marmoset monkeys. *Scientific Reports*, 4, eaar4012.
- Mundinano I. et al. 2018. Transient visual pathway critical for normal development of primate grasping behavior. *PNAS*, 115, 1364-1369.
- Feng L & Wang X. 2017. Harmonic template neurons in primate auditory cortex underlying complex sound processing. *PNAS*, 114, E840-E848.

Here we detail the current use and advantages of marmosets for NIH Institutes, Centers, and Initiatives that support nonhuman primate research in order to further highlight the broad potential of this species in the next chapter of biomedical research.

- Appendix 1 | NIH BRAIN Initiative
- Appendix 2 | NIH Office of Research Infrastructure Programs
- Appendix 3 | National Institute of Mental Health
- Appendix 4 | National Institute Neurological Disorders and Stroke
- Appendix 5 | National Institute Deafness and other Communication Disorders
- Appendix 6 | National Institute of Aging
- Appendix 7 | National Institute Child Health and Human Development
- Appendix 8 | National Eye Institute

III. Past NIH Investment in Marmoset Research

The NIH has increasingly invested in marmoset research over the past decade. A December 2018 search of NIH RePORT database using the term 'Marmoset' for 'Project Title' and 'Project Abstracts' revealed that in FY2018 the NIH supported 41 projects with $21,000,000 in funding. Over the past 5 years [2014-2018], the NIH has invested $117,000,000 in research involving marmosets. Funding for marmoset research from the NIH, however, has declined since 2015 (Figure 4) despite the accelerated increase in the number of marmoset colonies across the nation (Figure 1). **Whereas the number of marmoset colonies in the US has increased by ~60% since 2015, NIH funding for marmoset research has decreased ~40% during the same period of time.** NIH support for marmoset research is, therefore, negatively correlated with the burgeoning field; a discrepancy that requires immediate investment to foster the continued expansion of the marmoset model throughout the biomedical sciences in the United States.

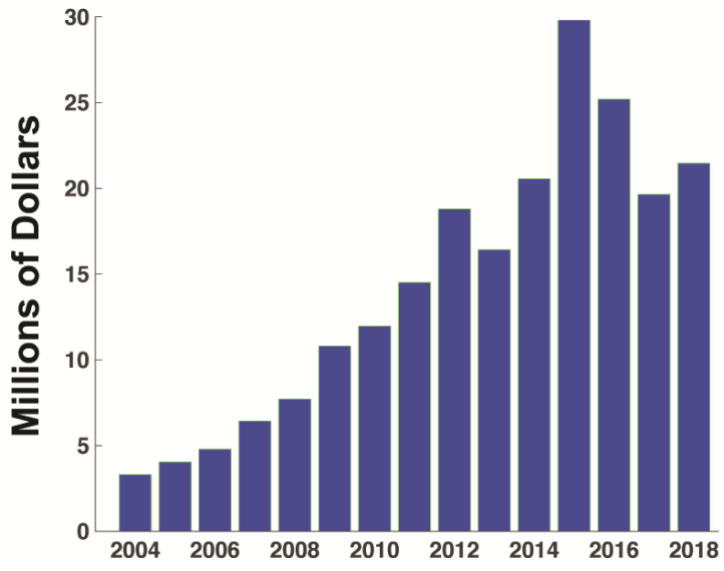

Figure 4. NIH funding for marmosets over the past 15 years, from FY2004-2018

Despite their clear significance for understanding human disease, biomedical research involving nonhuman primates accounts for only ~3% of the NIH budget. The majority of these funds support biomedical research in rhesus macaques. In FY2018, for example, the NIH supported 535 projects with rhesus macaques with over $339,000,000 in funding from 19 Institutes and the Office of the Director. Notably, the NIAID provided almost half of the funding for rhesus macaques, yet this Institute did not support any research in marmosets.

One notable advance in NIH funding for marmosets occurred in the past year. The Office of the Director awarded the first 3 grants for developing transgenic gene-editing technologies in the marmosets totaling $2,240,000 in FY2018 funding. Continued and increased support for this dimension of marmoset research is crucial, as the development of next-generation molecular technologies is a likely cornerstone of this model system in the years to come.

IV. Recommendations & Priorities for future NIH Investment in Marmoset Research.

The first Marmoset Principal Investigators meeting took place in Boulder, Colorado on September 26th & 27th, 2018. As a rapidly growing community, the principal aim of this workshop was to [1] identify key bottlenecks facing the field and [2] establish the strategic plans to address these issues. We initiated a survey amongst the 30 meeting attendees and distributed it to the remaining marmoset researchers based in the United States who were unable to attend to give us a more quantitative basis for our recommendations. Listed below are the most critical priorities along with recommendations that should factor heavily for strategic plans in the next phase of marmoset research. Notably, the highest priorities for the community pertain to a significant need for resource and infrastructure investment to curtail the existing challenges facing marmoset users.

1. Expansion of the U.S. Marmoset Population.

The most commonly cited bottleneck for research from our survey was the availability of animals for research. This crucial bottleneck has occurred because **there are currently no reliable distributors of marmosets for biomedical research in the country.** There are presently ~1900 marmosets in the country across 28 identified research colonies in the United States. However, nearly every investigator polled noted that their colony was smaller than they ideally needed for their research. The sum of the ideal colony sizes for research across the existing marmoset researchers was nearly 4400 animals, as most PIs felt their colony would ideally be about double its current size. These suggests that at present that over a **2000 animal deficit** exists for the needs of marmoset researchers in the United States. Importantly, this total represents only current marmoset users. Given the growth of marmoset labs throughout the country, this number will surely increase accordingly. Furthermore, whereas most existing labs currently perform neuroscience research and require relatively small colonies (~25-50 animals), marmosets are only beginning to bridge into areas of research that traditionally require large numbers of animals, such as the development of genetic models, infectious disease, and drug addiction. In order to facilitate the use of marmosets in these areas, significantly larger populations available for sale are needed. We recommend an immediate and significant investment to rapidly expand strategic marmoset populations for use in US biomedical research. In addition, we recommend support devoted to the maintenance of aging colonies, as the development of aging research in this model depends on the availability of older animals. Furthermore, we recommend that national breeding centers be strategically placed along the East and West coasts of the US in close proximity to the Universities and Institutes that currently support marmoset research (Figure 1), or are likely to in the near future, in order to reduce the substantial shipping costs associated with transporting nonhuman primates across the country.

Solution. A Resource PAR/RFA is needed to establish an interconnected network of breeding centers strategically placed to serve the rapidly expanding community. The dearth of available marmosets in the US remains the most significant bottleneck for research and will need to be resolved for the model system to continue to expand.

2. Management of Genetic Diversity Marmoset Populations.

The existing marmoset populations in the US come from unknown origins, but it is speculated based on limited genealogical records that many are from a single source in Europe. This presents challenges because it necessitates that a more concrete strategic plan be implemented

to both expanding marmoset populations and managing existing populations over time in order to increase the genetic diversity in the U.S. marmoset population. To this end, we recommend strategically genotyping portions the current marmoset population for at least the two following reasons:

- To identify the existing sources of greatest genetic diversity in the populations and initiate a breeding program to increase this diversity.
- To identify naturally existing gene mutations in marmosets that may be valuable for human disease models.

Given the current size of the US population (~1900 animals), it will be necessary to both optimize diversity amongst these animals as well as seek out avenues to introduce new genes into the population. We recommend pursuing actions to introduce entirely different genetic stock from that currently in the US marmoset population, either through physically adding new animals into the population or through artificial insemination methods from those other populations.

Solution. A Resource PAR/RFA is needed to fund large-scale genotyping of the existing marmoset population, as well as for options to increase genetic diversity across the nation. This investment will likely be an invaluable cornerstone to a diversity of research areas in the coming years.

3. Investment in Advancing Genetic Technologies for Marmosets.

Next-generation molecular technologies have revolutionized biomedical research in the past decade and fueled a remarkable path of scientific discovery. A cornerstone of the rapid marmoset emergence is the amenability of the species to these technologies and the prospect of leveraging their benefits in a primate model. The rapid advances in these technologies have almost entirely been made in non-primate model organisms, typically in mice, but it is evident that each technique must be further developed for implementation in primates. As discussed above, mice have poor predictive power for human disease and primate models are needed to accelerate discoveries most pertinent to humans. We recommend that significant investments in the development of molecular technologies for marmosets be made.

Solution. A Resource PAR/RFA is needed to directly fund the development and expansion of the molecular tool kit available for use in marmosets. This includes efforts to establish transgenic lines as well as further optimization of viral based methods that can be utilized in this primate species.

4. Support for Marmoset Training and Meetings.

The marmoset community has expanded rapidly in recent years. Because of the scarcity of marmoset laboratories a decade ago, the vast majority of researchers who have adopted marmosets as a model organism in the past half-decade did not receive formal training during graduate school or post-doctoral periods. Instead, many new researchers previously gained their primary training either in rodents or macaque monkey and have faced considerable challenges adapting their research program to marmosets. To address this issue, we propose immediate investments supporting training of new researchers by the leaders of the field as well as scholarly meetings to facilitate dissemination of knowledge in a more public forum.

Solution. A Resource PAR/RFA is needed to directly fund training of new marmoset researchers for management, surgical approaches, and experimental techniques. Funding would be needed to support training at Institutions with established marmoset laboratories and scientific leaders

of different cutting-edge technologies would accelerate research efforts and reduce the need for single labs to develop approaches in isolation.

V. Marmoset Community Initiatives

During the PI meeting, the Community also identified initiatives that could be undertaken by the Investigators to further strengthen marmoset research. The following two projects were determined to address the most pressing concerns for the community.

1. Collective Marmoset Pool for New Investigators.

Concerns were raised that the current shortage of available marmosets could dampen enthusiasm of Institutions to continue hiring new marmoset investigators. While the first recommendation for NIH investment in marmoset research was to expand the marmoset population, it is likely that this will require a transition period of ~1-3 years before animals are readily available. In order to more immediately address this pressing issue, we proposed that established investigators would commit 10% of their population annually to seed the laboratory of new marmoset investigators. The first priority will be to provide new Assistant Professor hires with sufficient numbers of animals to begin their lab, followed by Investigators currently working with other animal models but wishing to establish a marmoset research program.

2. Resource Sharing Forum.

Because the emergence of marmoset research in the U.S. has been driven primarily by Investigator Initiated projects, researchers have approached this model system from different backgrounds. Many Investigators had little to no experience working with marmosets. Furthermore, several labs have worked on similar problems in parallel without knowledge of the other research effort. To expedite the transition to marmoset and avoid unnecessary redundancy in technology development between laboratories, it was suggested that we establish a research sharing forum for the community. This online forum will serve as both a repository of existing knowledge – ranging from best practices for husbandry to behavioral training approaches – and as a place for community members to share experiences, ask questions and coordinate efforts across the country.

VI. Marmosets are a Model of Human Disease.

The collective objective of the Marmoset research community to leverage the benefits of this NHP model system in order to accelerate our knowledge of the genetic, physiological and environmental factors underlying human disease. While a diversity of animal models has significantly contributed to our general knowledge of the cellular and molecular basis of disease in biological systems, precisely how these processes unfold within the uniquely primate physiology remains sorely under studied. All of the Community Priorities and Recommendations focus on establishing essential resources and infrastructure necessary for marmosets to bridge this considerable gap and realize the model's potential as a keystone organism in biomedical research for the next generation.

The mouse system is a powerful tool for medical research due to the ability to manipulate the mouse genome. Yet considerable anatomical, physiological, cognitive, and behavioral differences between mice and humans limit the degree to which insights from mouse models

shed light on human diseases. This is reflected in the high number of failed clinical trials for drugs that were effective in treating mouse models of human disease.

The non-human primate of choice for studying mechanisms of brain function has traditionally been the macaque. However, the common marmoset represents a complementary species with advantageous characteristics for studying a range of human disease. First, the marmoset has strong reproductive power. Macaques reach sexual maturity after ~5 years and give birth once a year to a single offspring. Rhesus and cynomolgus macaques typically live 25 years and can live up to 30 and 40 years in captivity, respectively. This lifespan presents a number of logistical challenges for longitudinal studies of age-related disorders, including neurodegenerative diseases. In contrast, marmosets reach sexual maturity at 18 months of age, and females give birth twice a year, usually to non-identical twins or triplets. Figure 5 demonstrates the reproductive power of marmosets. In order to obtain 400 offspring from 50 breeding females, it takes 6 and 20 years from marmosets and rhesus macaques, respectively. Furthermore, the efficiency of *in vitro* fertilization of oocytes (100/collection/animal) is very high (>50%), making marmosets highly economical and scalable for generating the number of genetically modified marmosets needed for preclinical evaluation. Second, because of marmosets' small body size, they can be housed in social groups consistent with the size and composition of groups in the wild. This is particularly important because the range of sophisticated social and cognitive behaviors that emerge naturally within social groups – and that are shared with humans (4, 24) - can be effectively studied under more controlled laboratory conditions. This makes them ideal for modeling human aging, neurodegenerative and psychiatric disorders. Furthermore, since marmosets can be housed in their natural social group, the anxiety, depression, and social withdrawal common amongst laboratory housed rhesus macaques (25) does not emerge. Because these behaviors are atypical of marmosets in laboratories, genetic models of psychiatric disorders will not be confounded by these environmental factors. Third, in contrast to rhesus macaques, marmosets are free of Herpes B viruses, making the species safer to work with. Finally, technologies for generating transgenic marmosets have already been developed, and their short generation time represents a distinct advantage for creating and expanding transgenic lines over larger nonhuman primate species.

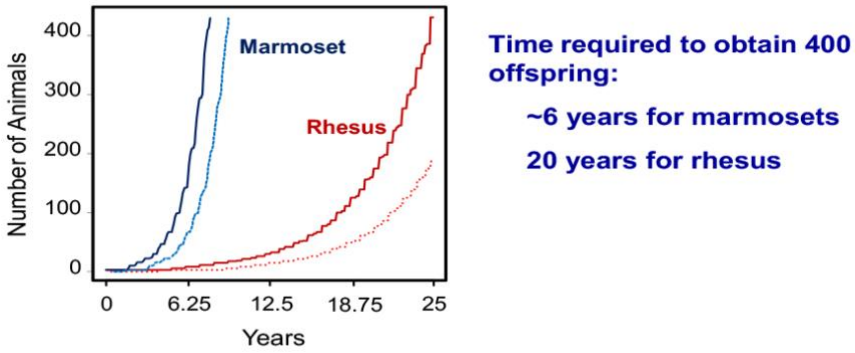

Figure 5. Comparison of time required to produce 400 offspring from 50 breeding females in marmosets versus rhesus macaques. Darker lines represent expansion of total population while lighter lines represent expansion of breeder population.

VII. Contributors.

Primary Authors.
Cory Miller
Kuo-Fen Lee

Contributing Authors.
Alessandra Angelucci
Diego Contreras
Yogita Chudasama
Ricki Colman
Diego Contreras
Steven Eliades
Veronica Gayan
Keren Haroush
Elias Issa
Agnes Lacreuse
Rogier Landman
Kuo-Fen Lee
David Leopold
Partha Mitra
Kim Phillips
John Reynolds
Cory Ross
Afonso Silva
Suzette Tardif
Yi Zhou

Appendix 1

National Institute of Health BRAIN Initiative

2019 Marmoset Community White Paper

Central to the mission of the BRAIN initiative is the creation of innovative technologies and gathering of information for understanding how individual cell types and complex neural circuits interact in space and time to generate normal brain function and dysfunction in the diseased brain. Priority research areas of the BRAIN Initiative include the generation of a census of cell types, and understanding circuit wiring, the function of specific cell types and circuits via causal manipulations, and large scale multi-area interactions. Current research towards these goals is still largely centered on the mouse model, due to this species' small brain size and amenability to genetic manipulations. However, this animal model is proving inadequate to understand the full complexity of the human brain and behavior. Marmosets offer unique advantages for both developing new technologies and expanding our knowledge of the brain. As non-human primates, this New World species is within the same taxonomic family as humans (Order: Primates) and share the core brain architecture and broad behavioral repertoire. For example, marmosets have an extensively developed prefrontal cortex, and their motor control, sensory perception and social cognition is very similar to those of humans. In contrast to the more commonly used macaque monkey, however, they offer the advantage of a much smaller body (300-400gr in weight), a small lissencephalic brain, a shorter gestational period (5-6 months) and life span (8-12 yrs of age), a faster maturational period (sexual maturity is reached around 1.5 yrs of age), and high fecundity (producing litters of 2-3 offspring). These advantages make marmosets an ideal non-human primate species to address the goals of the BRAIN Initiative. For example, the fast maturation and high fecundity of the marmoset is a great advantage for the generation of transgenic lines. Indeed, recent advances in genetic engineering in marmosets have opened new pathways to study the brain, allowing modeling of disorders with a genetic component, such as Alzheimer's disease, Schizophrenia, Autism and Huntington's disease, in which mouse models have so far been unsuccessful in translation to humans. Moreover, the marmoset small brain size is ideal for studying circuit wiring and connectomics in a complex non-human primate brain that is several orders of magnitudes smaller than the macaque brain, whose large brain size still poses a big data challenge for computational tools. Additionally, in contrast to the large and convoluted macaque brain, the marmoset's small lissencephalic brain allows the accessibility needed for brain-wide, high resolution *in vivo* imaging techniques, such as two-photon microscopy.

Breadth of Current Research. There are several research questions within the BRAIN Initiative mission currently being addressed using the marmoset as a model species. A group of studies have developed calcium imaging in the marmoset brain (10, 26). Other studies have developed *in vivo* optogenetics in the marmoset, using simple optical fibers and surface photostimulation (12), and applied it to investigate the function of feedback connections between visual cortical areas (14). Studies are currently underway to produce a spatially specific catalog of cell types in the marmoset brain, using single-cell RNA sequencing, to pave the way for future studies of primate genetics and circuits. BRAIN Initiative funds have been, and continue to be, used successfully for the development of new viral tools for targeting specific cell types in the non-human primate brain. For example, novel recombinant adeno-associated virus (rAAV) vectors that restrict gene expression to GABAergic interneurons in many vertebrate species including

marmosets using the mDlx enhancer (11) have recently been developed. Studies of the auditory system have successfully leveraged the aforementioned advantages of marmosets to pioneer numerous neural recording and behavioral techniques to make new discoveries about the physiological mechanisms underlying sensory perception and social communication in the primate brain (27-40). More recently, researchers have also begun to take advantage of the marmoset natural tendency to orient towards visual stimuli, and the accessibility of the middle temporal (MT) visual area and frontal eye field on the cortical surface of this species, to study a diverse range of visual behaviors in marmosets (41-45).

The Future. The marmoset is a unique model to investigate the non-human primate brain in ways that are not allowed by other primate species. Promising future research areas are briefly discussed below. First, the marmoset small lissencephalic brain is ideally suited for the development of wide-field calcium imaging to enable imaging of millions of neurons across cortical layers and multiple brain areas. Future efforts are directed towards increasing the width and depth capabilities of imaging in this primate species Second, the marmoset small brain size is also ideal for the development of large-scale manipulations of cortical circuit activity, to understand interareal interactions. Future efforts are directed towards developing large-area manipulations throughout the cortical depth, and performing spatiotemporally patterned photostimulation to mimic the spatiotemporal patterns of neuronal activity. Third, efforts are under way to couple single-cell RNA sequencing with behavioral studies in marmoset (as previously done in mouse (46)), to establish computational tools that allow linking gene expression in specific cell types to behaviorally relevant circuits in a primate. Fourth, current and future efforts are under way for further development of viral tools for cell specific targeting in non-human primate brains; for example, rAAV vectors that can specifically infect subtypes of inhibitory neurons in marmoset cortex. Finally, a revolution in understanding the human brain in health and disease will require non-invasive real-time mapping of neurotransmitter and calcium signaling. New vasoactive imaging probes with high sensitivity and resolution have been developed in rodents (47, 48) and are currently being developed for marmosets.

Authors.
Alessandra Angelucci
Rogier Landman
John Reynolds

Appendix 2

National Institutes Office of Research Infrastructure Programs

2019 Marmoset Community White Paper

The core mission of the Office of Research Infrastructure Programs (ORIP) within the Office of Director (OD) is to advance the NIH mission by supporting research infrastructure and research-related resource programs and by coordinating NIH's science education efforts. Specifically, ORIP's Strategic Plan supports the NIH-Wide Strategic Plan by funding the "scientific human and physical resources that will help to ensure the Nation's capability to prevent disease." ORIP awards grants to support research resources, such as animal models of human disease and state-of-the-art biomedical instrumentation. ORIP plans, organizes, and conducts workshops, both independently and in collaboration with NIH Institutes and Centers, to identify and pursue scientific opportunities. ORIP supports research-training opportunities for veterinary scientists to capitalize on their distinct perspective and expertise based in a deep understanding of comparative medicine and insight into animal models of human diseases. In the last several decades, the mouse system has been a powerful model for medical research due to, in large part, an array of sophisticated gene-editing techniques to manipulate the mouse genome and strategies for cell-type specific, inducible, or spatiotemporal regulation. However, considerable anatomical, physiological, cognitive, and behavioral differences between mice and humans limit the degree to which insights from mouse models shed light on human diseases. This is reflected in the high number of failed clinical trials for drugs that were effective in treating mouse models of human disease. Thus, non-human primates (NHPs) may serve as better models for studying human disease with the macaque being the traditional choice. However, the common marmoset (*Callithrix jacchus*) has emerged recently as a complementary species with advantageous characteristics that expand the types of studies that can be performed in a nonhuman primate. First, marmosets share with other primates, including humans, many aspects of physiology, a complex brain organization, and sophisticated social and cognitive behaviors. For example, like humans, marmosets are diurnal and housed in social groups consistent with the size and composition of groups in the wild. This is particularly important because the range of sophisticated social and cognitive behaviors that emerge naturally within social groups can be effectively studied under more controlled laboratory conditions. Second, marmosets are among the shortest-lived NHPs with small body size and strong reproductive power, making them highly economical and scalable for housing and generating the number of marmosets needed for preclinical evaluation. Third, in contrast to rhesus macaques, marmosets are free of Herpes B viruses, making the species safer to work with. Finally, technologies for generating genetically modified marmosets have already been developed, and their short generation time represents a distinct advantage for creating and expanding transgenic lines over larger nonhuman primate species.

Breadth of Current Research. Ongoing research in the marmoset is focused on modeling various human diseases and investigating in a wide range of systems and multiple levels of analysis, including aging, Alzheimer's disease, Parkinson disease, Huntington's disease and multiple sclerosis. Furthermore, the marmoset has been used to develop a model system to evaluate various gene-editing approaches and strategies for therapy. Efforts are also ongoing to characterize the effects of pharmacological and life-style interventions on health span in the marmoset.

The Future. ORIP can play an essential role in addressing numerous resources issues that impede the progress in using marmosets as a biomedical model. Here are some examples. First, one of major bottlenecks in using marmosets to model human disease is the extreme short supply of marmosets available for sale to research community. Second, the genetic diversity of marmoset population in this country is largely unknown. The information is critical in better maintaining high population diversity and modeling human disease. For example, it will be extremely informative to know the divergence and frequency of marmoset alleles relevant to human mutations such as major risk factors ApoE and Trem2 for AD. Third, it is not known if immunological reagents and protocols for analytic experiments in the marmoset are available. Database for these reagents and, if needed, developing these reagents will become critical for the success of modeling human disease. Fourth, it is critical to develop genetic viral tools that work in the marmoset. Finally, ORIP can offer workshop to advance above endeavors and disseminate the resulting resources.

Author
Kuo-Fen Lee

Appendix 3

National Institute of Mental Health

2019 Marmoset Community White Paper

The core mission of the National Institute of Mental Health (NIMH) is to transform the understanding and treatment of mental illness through basic and clinical research. Traditionally, research funded by the NIMH has taken advantage of three main species – namely the mouse, the macaque monkey, and the human. This combination has led to a series of important discoveries that has gradually expanded our understanding of how the brain supports a range of higher cognitive processes. However, progress towards understanding and treating mental health and behavioral disorders has slowed, marking the need for a substantial paradigm shift in the scientific approach toward more human-relevant experimental-models. The common marmoset (*Callithrix jacchus)* has emerged as a powerful nonhuman primate model for neuroscience, owing to several advantages for research related the goals of the NIMH. Research with marmosets, for example, has broadened the range of experimental paradigms used to study primate brain mechanisms of cognition, including those whose failure underlies common mental disorders. Furthermore, marmosets retain highly complex primate behavior and prefrontal cortex functions, rendering them a promising model of human brain function. In addition, with the relative ease of breeding marmosets in captivity, they are an ideal primate in which to develop and implement modern gene-editing technologies. The combination of these factors underlies the enormous promise of marmosets for bridging the gap between molecular and genetic approaches, systems neuroscience, and drug discovery for mental health diseases.

The marmoset brain shares many of the unique primate specializations evident in humans, thus offering the opportunity to expand our understanding of brain function relevant to human mental health and disease. Furthermore, new experimental opportunities are rooted in marmosets' gregarious social behavior, which, together with their relative ease in handling and breeding, invite investigation into interactive and developmental aspects of primate cognition. Marmosets are particularly well suited for studying the brain in paradigms involving interactive social behavior. Several aspects of their behavior resemble that of humans, including their cooperative foraging and defense, reciprocal communication, and biparental rearing of offspring. The marmoset's brain shares many of its primate features with the human brain, including specializations for social perception and vocal communication. These scientific factors – together with practical considerations such as the relative ease in breeding and handling marmosets compared to macaques – opens the door to a range of naturalistic experimental paradigms. Recent advances in miniaturization and telemetry make it possible to measure and manipulate brain circuits during natural social exchanges, such as affiliative, competitive, and reproductive behaviors. Further, the marmoset is an ideal species for studying mechanisms of prenatal and postnatal brain development relevant to mental illness. Similar to other primates, marmoset brain development diverges from other mammals by the inclusion of additional zones of neural progenitors, the preservation of neural stem cells after birth, and an unusually protracted childhood during which the brain matures slowly amid abundant social experience. The systematic investigation into the anatomy and physiology of primate brain development and its bearing on cognition – from the cellular and molecular processes in the embryo to the brain's circuit development during critical periods in early life – requires high level control over a species' reproductive biology, breeding, rearing, and weaning. Marmosets breed easily in captivity and can be housed in multigenerational families that cooperate in the rearing of infants. Moreover,

marmosets exhibit routine twinning, typically with two reproductive cycles each year and offspring reaching sexual maturity at the age of eighteen months. Together, these factors provide a much needed opportunity to study unique features of primate brain development whose failure is suspected to be at the core of psychiatric disorders.

More generally, marmosets' complex behavior and inquisitive nature make them a model of interest for a broader set of questions in high level cognition. As such, marmosets allow for studying the interplay between cognitive, emotional, and motivational processes as well as their modulation by internal state factors, such as stress, and how these may fall apart in mental health disorders. Taken together, the marmoset affords unique opportunities to investigate new dimensions of primate brain function relevant to mental health and disease.

Breadth of Current Research. In the past several decades, marmosets have been used in a few experimental neuropsychology programs to study aspects of executive function (49, 50) and emotion (51, 52). This work has demonstrated that the organization of the prefrontal cortex is similar to that found in macaques and humans. In parallel, systematic mapping studies of the sensory systems have illustrated that the cortical blueprint of the marmoset is fundamentally similar to that of the macaque and human (18). More recent work has demonstrated specializations in the marmoset brain for the perception of faces (53) as well as the production and perception of vocal behavior (23, 37, 39). Technological advances in optical imaging using genetically encoded calcium indicators (10, 13, 54) have rapidly begun to import technology developed in the mouse into the marmoset. This, together with emerging transgenic methods and interactive behavioral paradigms, have changed conceptions of the types of experiments currently feasible in nonhuman primates.

The Future. The next phase of marmoset research holds great promise, both for increasingly precise basic science research into cognitive circuits as well as the production of primate models of neuropsychiatric disease. In both cases, the creation of transgenic animals is likely to figure prominently into the research. For basic scientific research, the use of viral and transgenic gene-editing technologies will serve as basic tools for experiments in the domains of both neurodevelopment and social interaction, providing, for example, cell type specific reporters indicating activity level or maturation state. The recent generation of transgenic marmosets expressing genetically encoded calcium indicators at the NIH (7) is an important step in enabling chronic in vivo monitoring of neural activity using high resolution optical imaging. In the creation of disease models, transgenic animals will enable translational studies aimed at understanding the complex neural mechanisms of human brain function with the ultimate goal of molecular targeting for pharmacotherapy.

Authors.
David Leopold
Yogita Chudasama
Keren Haroush

Appendix 4

National Institute of Neurological Disorders and Stroke

2019 Marmoset Community White Paper

The core mission of National Institute of Neurological Disorders and Stroke (NINDS) is twofold. First, NINDS seeks fundamental knowledge about the brain and nervous system. Second, NINDS aims to use that knowledge to reduce the burden of neurological diseases. In support of its mission, NINDS performs and funds basic, translational, and clinical neuroscience research on more than 600 neurological diseases, including genetic diseases (e.g. Huntington's disease; muscular dystrophy), developmental disorders (e.g. cerebral palsy), neurodegenerative diseases (e.g. Parkinson's disease; Alzheimer's disease; multiple sclerosis), metabolic diseases (e.g. Gaucher's disease), cerebrovascular diseases (e.g. stroke; vascular dementia), trauma (e.g. spinal cord and head injury), convulsive disorders (e.g. epilepsy), infectious diseases (e.g. AIDS dementia) and brain tumors. Common marmosets (*Callithrix jacchus*) offer unique, powerful advantages to both components of the NINDS mission. In support of the first component, marmosets are particularly well suited for neuroanatomical and functional brain studies, as their brains retain the typical anatomical and functional organization of the primate brain. A major advantage is that the marmoset is a lissencephalic primate, which greatly facilitates the mapping of functional brain areas by neuroimaging techniques, such as fMRI and optical imaging, as well as by electrophysiology, with high spatial resolution. In support of the second component, marmosets are excellent models of neurological disorders. Unlike rodents, marmosets are outbred and every individual is genetically different. Further, the marmoset brain has a gray-to-white matter ratio comparable to humans, which strongly facilitates modeling diseases such as multiple sclerosis and small vessel disease. The species also exhibits the breadth of cognitive sophistication that distinguishes primates from other taxonomic groups. Finally, gene-edited marmosets can be generated with an intergeneration time and establishment of transgenic lines 2-3 times faster than other primate species, which makes marmosets be the ideal primate species for the development of genetically engineered lines. For all of the above reasons, marmosets are poised to be a central player to advance the core mission of the NINDS.

Breadth of Current Research. Marmosets are currently being used to elucidate pathogenetic mechanisms of multiple sclerosis (55, 56), as marmoset models of MS have clinicopathologic correlation patterns, lesion heterogeneity, immunologic mechanisms, and disease markers that more closely mimic the human disease. Marmoset models of stroke (57, 58) and Alzheimer's (59, 60) have been developed as the marmoset brain features cell types and behavioral deficits that most closely mimic human stroke. And transgenic marmoset models of stroke (61), polyglutamine diseases (62) and severe combined immunodefficiency (63) have been developed to allow better modelling of neurological disorders. Meanwhile, we know more about the organization of the primate brain thanks to the very high resolution anatomical, neurophysiological, and functional imaging efforts being made in marmosets, with the development of brain atlases based on MRI (64, 65), gene-expression (66), cortical connections (67), and the use of high-resolution fMRI for mapping sensory regions (53, 68, 69) as well as

neurophysiological and calcium imaging studies of motor control in freely-moving marmosets (54, 70).

The Future. There's a bright future for biomedical research, as marmosets are poised to make a tremendous, potentially revolutionary contribution both to our current understanding of brain anatomy and function and to the causes and mechanisms of neurological disorders. The small marmoset brain allows, for the first time in a primate species, the integration of whole-brain morphological (MRI, fMRI, and neuronal tracing) studies performed at the microscale with cell-specific gene expression. This will enable the construction of a comprehensive atlas/database that will contain completely novel knowledge about the primate brain. The development of genetic-engineering techniques in marmosets will enable the study of a broad range of neurological and neuropsychiatric disorders as well as spur the development of precision medicine and gene-therapy approaches to manage and treat these diseases. In particular, being among the shortest-lived primate species, marmosets are uniquely suited to provide crucial information about primate brain development and about the mechanisms of neurodegenerative diseases in which aging is a major comorbidity and contributing factor.

Author.
Afonso Silva

Appendix 5

National Institute of Deafness and Other Communication Disorders

2019 Marmoset Community White Paper

The core mission of the National Institute of Deafness and Other Communication Disorders (NIDCD) to understand normal and disordered processes of hearing, balance, taste, smell, voice, speech and language as well as to improve the treatment of communication impairment and other sensory disorders. The common marmoset (*Callithrix jacchus*) has contributed significantly to research designed to address these key issues for several decades and will remain a cornerstone model to significantly advance the core missions of the NIDCD in the years to come. With their complex and human-like social behavior and brain organization, marmosets are an ideal model for studies of normal and disordered hearing. As a non-human primate with perceptual hearing ranges and auditory brain structures similar to that of humans, marmosets can provide greater insight into basic mechanisms of hearing than studies in more evolutionarily distant rodent models can. Moreover, because they can be easily bred and raised in laboratory conditions, have an average lifespan of 10 years, and exhibit age-related hearing loss, marmosets provide a unique opportunity to longitudinally study the effects of development and aging upon hearing over the entire lifespan. Because they are amenable to genetic manipulation as well as more genetically similar to humans than other species, marmosets may provide better understanding of genetic causes of hearing loss and their rehabilitation. Marmosets are also one of the few non-human mammalian models of vocal communication. Even in the laboratory colony, marmosets are highly social primates in constant interactive vocal contact with each other facilitated by the ability to be kept in natural social and family groups. As a result, marmosets can provide critical insight into normal mechanisms of communication, the evolutionary origins of speech, and disorders in communication that can arise from deafness, neurologic disease, or social isolation. Thus marmosets have substantial potential to understand the critical interplay between hearing and vocal communication and the development of novel strategies to prevent and treat disorders stemming from hearing loss. Notably, work in the marmoset auditory system was the first to leverage the many advantages of this model organism to explore core questions of systems neuroscience research with nonhuman primates, such as sensory coding in neocortex (71) and the cortical basis of vocal communication (32, 72, 73). The potential of the marmoset model also extends beyond hearing, but includes less well investigated facets of the NIDCD mission. As prolific scent markers, marmosets are amenable to studying the neural mechanisms of olfaction in a non-human primate. As a species that naturally moves rapidly in three dimensions and relies more heavily on head than eye movements, marmosets are potentially useful in studying both the peripheral and central aspects of the vestibular system, in particular less-well understood encoding of gravity and tilt.

Breadth of Current Research. Recent work in marmosets has begun to address many fundamental questions central to the mission of the NIDCD. In basic hearing research, neural recordings in the marmoset auditory cortex by Bendor and Wang (35) have localized a pitch-selective brain area, answering a long-standing question in auditory perception and physiology. Marmosets also exhibit human-like pitch perceptual patterns (27). Marmosets are beginning to be used to understand therapies for hearing loss, having recently become a model species for studying the neural effects of Cochlear Implants, revealing critical similarities and differences from normal sensory processing (28). Marmosets have also shown recent advances in our

understanding of hearing loss genetics, with recent studies of the marmoset cochlea showing patterns of hearing-related gene expression that are distinct from that in mice and more similar to humans (74), thus suggesting marmosets may be a better model for genetic hearing loss. Marmosets are also proving themselves to be an excellent model for vocal communication and its disorders (23, 32). Marmosets engage in cooperative, turn-taking vocal conversations with rules similar to that of human communication (75, 76). Some evidence also suggests that infant marmosets babble, similarly to human babies, and their vocal development may be dependent, in part, on interactions with their parents (77-79). Finally, the breadth of current work is not limited to the auditory-vocal domain, with recent anatomic studies of marmoset olfaction showing human-like connections between the olfactory bulb and cortex (80).

The Future. Marmosets are uniquely suited for future advances in our understanding of critical open questions in disordered hearing and communication. For example, what are the long-term effects of hearing loss and hearing restoration on the brain and what are the mechanisms by which this can contribute to cognitive decline? This association has garnered significant recent interest and attention, but the underlying mechanisms remain uncertain. Because of marmosets' lifespan, reproductive patterns, and social behavior, they are an ideal model for studying age-related hearing loss and its consequences on cognitive decline and social isolation that have been revealed as critically important in humans. Furthermore, marmosets would be amenable to more rapid testing of hearing or other rehabilitation to determine its effects on future age-related changes. Second line of critical forthcoming research pertains to genetic and neuroanatomical origins of speech and other vocal communication disorders. Although marmosets do not possess human language, their vocalizations exhibit many similarities and they are the only non-human primate species in which vocal communication can readily be studied in the laboratory, including greater homology with humans than other non-primate research models. When combined with the potential for genetic manipulations and longitudinal studies during development, marmosets are an ideal model for understanding these disorders and potential therapies.

Authors.
Steven Eliades
Yi Zhou

Appendix 6

National Institute of Aging

2019 Marmoset Community White Paper

The core mission of the National Institute of Aging (NIA) is to support and conduct genetic, biological, clinical, behavioral, and social research on aging. Common marmosets (*Callithrix jacchus*) share with other primates, including humans, many aspects of physiology, a complex brain organization, and sophisticated social and cognitive behaviors, facilitating translational research on human conditions. With an average lifespan of about 10 years and a maximum lifespan of 21, marmosets are also among the shortest-lived anthropoid primates. This characteristic makes them uniquely suited for studies of aging, as the dynamics of the aging process can be studied longitudinally throughout the entire lifespan, an approach not feasible in more long-lived primates. Thus, developing the marmoset as a model for human aging has the potential to advance the NIA mission in a number of areas. First, the short lifespan of the marmoset provides the opportunity to track the progression of normal aging and age-related disorders and study their underlying mechanisms in order to achieve better prevention and prognosis. Interestingly, marmosets develop a number of age-related changes of specific relevance to human late-life phenotypes. For example, they exhibit age-related declines in basic biological markers, such as a decrease in lean muscle mass, that are similar to those observed in humans. They also show a marked age-related increase in cancers, amyloidosis, pathogenic tau accumulation, diabetes and renal diseases, typical of human late-life disorders. Many aspects of functional decline during normative aging in marmosets are also similar to those of humans, with marmosets exhibiting hearing loss as well as declines in cognitive and motor function with increased age. Aging is the greatest risk factor for many diseases including Alzheimer's Disease (AD), and understanding how age-related changes at both the system and cellular levels predispose the brain to these diseases will be critical to developing effective prevention and treatment strategies. Of particular interest, aged marmosets spontaneously develop β-amyloid deposition and an increase in abnormally phosphorylated tau, both implicated in the pathogenesis of AD. Because the high rate of failure in AD clinical trials has been ascribed, in part, to the inadequacy of rodent models that recapitulate only limited aspects of AD pathology, these aspects of marmoset biology position the species as an excellent primate model for advancing our understanding of AD. In addition, the development of genetically modified marmosets may lead to new models for AD and other age-related neurodegenerative conditions such as Parkinson's disease. Thus, the marmoset has substantial potential for the development of novel strategies to prevent and treat neurological diseases of aging including, but not limited to, AD. Moreover, because the marmoset is a highly social primate who forms long-lasting bonds and can be maintained in a social group in the laboratory, it should also prove particularly valuable as a model to study social influences on the aging process and their impact on the pathogenesis of age-associated diseases. Finally, this short-lived primate offers the opportunity to test the safety and efficacy of interventions against age-related burden in a compressed time-frame relative to long-term studies in macaques or humans, thus allowing for the evaluation of specific interventions to extend human health span. The advantages of marmosets for studies of age-related diseases have positioned this emerging model system to advance the core mission of the NIA.

Breadth of Current Research. Ongoing research in the marmoset investigates age-related changes in a wide range of systems and multiple levels of analysis (81). Several studies examine age-related physiological and structural changes in this species to understand how aging of the metabolome may increase diabetes and cardiovascular diseases risk (82) or to identify factors promoting osteoporosis resistance in females (83), for example. At the CNS level, much work is focused on characterizing normal age-related changes in the brain (15), perception, cognition, and motor function (84, 85) as well as the neuroendocrinology of these processes (81). A rapidly growing area of research focuses on establishing marmoset models for age-related brain disorders, including for AD, Parkinson's disease, Huntington's disease, multiple sclerosis, and stroke (86). Efforts are also ongoing to characterize the effects of pharmacological (e.g, rapamycin; (87)) and life-style (e.g., exercise;(88)) interventions on health span in this species.

The Future. Offering key advantages for aging research, the marmoset provides unique tools to advance our understanding of aging at multiple levels of analysis. Studies focused on the basic biology of aging will help elucidate how age-related changes in immune function, mitochondrial function, DNA damage repair and epigenetic processes may increase the brain's vulnerability to neurodegeneration. At the system level, advances in neuroscience techniques applicable to behaving marmosets, such as chemogenetics, optogenetics, 2-photon imaging, and high field functional MRI will be critical to identify the neural changes that underlie perceptual and cognitive deficits in healthy and pathological aging. In addition, the development of genetically modified models for neurodegenerative diseases that apply recent revolutionary approaches such as CRISP/Cas9 gene editing will provide new tools for understanding the mechanisms underlying neurodegeneration and designing new treatment strategies with high translational potential to humans. Due to its short lifespan, the marmoset will also be an ideal animal model to study the effects of early life interventions (e.g., diet, caloric restriction) on the development of late-life diseases. Finally, the rich social behavior of the marmoset will offer the opportunity study the mechanisms by which social influences impact the aging process.

Authors.
Agnès Lacreuse
Ricki Colman
Veronica Galvan
Kim Phillips
John Reynolds
Cory Ross

Appendix 7

National Institute of Child Health and Human Development

2019 Marmoset Community White Paper

The principle mission of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) is to ensure that every person is born healthy, that women suffer no harmful effects from the reproductive process, that children have the chance to fulfill their potential to live healthy and productive lives free from disease, and the well-being of all people through optimal rehabilitation. Animal models of disease have significantly contributed to the quests meeting the NICHD mission. The common marmoset (*Callithrix jacchus*) – a small monmorphic New World monkey – has a number of critical advantages to accelerate the rate of discovery in this research area. Like other primates, marmosets share the core physiological properties and brain architecture with humans. However, it is the species small size, short life span, high fecundity, and human-like social structure that distinguish them from other primates and make them a particularly powerful biomedical model of child health and human development. Adult common marmosets average 300-450 grams, about the size of a rat. They are reproductively competent at approximately 1.5 years of age, produce litters of 2-3 offspring every 5-6 months, and are considered aged at 8-12 years of age. The small size and fast life history of marmosets represents an advantage in many types of studies, including those involving reproduction, child-rearing, child health, impact of early life interventions, chronic disease effects, and testing compounds for which only small volumes may be affordably available. In particular, within a 5-year grant period, a marmoset can be followed from its own conception through to adulthood and reproduction in its offspring. Furthermore, the frequent production of twins and triplets enables study designs that can effectively control for genetic contribution by using siblings in different study groups. In addition, common marmosets are cooperative breeders with shared parenting responsibilities, a social structure very similar to humans. This similarity facilitates use of the common marmoset to model parenting and family effects on child development. Tools that further enhance the value of this species include complete sequencing, assembly, and annotation of the marmoset genome, generation of iPS cells, and production of transgenic marmosets – the first successful production of a transgenic nonhuman primate with germline transmission. For transgenic production, the fast maturation and high fecundity of the marmoset is a great advantage. The use of marmosets may bring transgenic line production within an acceptable financial range for areas of interest to NICHD in which the primate is a particularly compelling model such as autism spectrum disorder, Fragile X syndrome, and osteogenesis imperfecta.

Breadth of Current Research. Ongoing common marmoset research covers many areas of interest to NICHD. Several studies (89, 90) have documented a greatly diminished role for ovarian estradiol in metabolism and have established the relationship between estradiol depletion and diminished negative feedback in the development of polycystic ovarian syndrome (PCOS). A group of studies (91-94) have described marmoset pediatric obesity and its metabolic consequences as well as the role of both developmental programming and the establishment of feeding phenotypes during weaning on the development of pediatric obesity. Rutherford and colleagues (95, 96) have taken advantage of litter size variation in marmosets to model the effects of varying intrauterine environments on developmental programming on a female's future reproductive success. Ongoing studies are investigating the role of dietary fat, puberty, and

metabolism in the development of adolescent mood disorders. Pryce and colleagues established a model for examining the impact of separation on infant attachment and affective behavior during early development (97). This work has led to the further development of the model by French and colleagues (98, 99), who have examined the role of oxytocin in modulating mate-guarding behavior and reunion affiliation following social separation in an attempt to understand the critical behavioral processes that contribute to the preservation of long-lasting relationships. Marmosets are a well-established model for vocal development. Their cooperative breeding system has been a major asset in research showing the crucial role of social interaction in vocal development (77-79). Importantly, there is evidence that marmosets are appropriate models for both autism (100) and Zika virus infection (101).

The Future. The marmoset is a unique and valuable nonhuman primate model to investigate human development throughout the entire life process. Given their short lifespan and their short generation time, they may be particularly important for evaluating the impact of developmental processes and programming on future generations. The development of tools allowing assessment of neurobehavioral developmental milestones (102) and brain development from infancy to adulthood (103) will greatly facilitate this work, as will the ability to create transgenic models. In particular, there is great potential for the development of genetically modified models for diseases that have dramatic impacts on child health and development, such as autism spectrum disorder and Fragile X syndrome. Given the emergence of devastating neotropical diseases, such as Zika, we also anticipate increasing interest in marmoset disease models, particularly for diseases endemic to marmoset natural habitats and that may have prolonged latencies or unexpected later life effects. Finally, there is increasing appreciation for the role of social interactions in disease development and this is an area in which marmosets are a particularly valuable model over other potential models due to their human-like family structure.

Authors.
Cory N. Ross
Ricki J. Colman

Appendix 8

National Eye Institute

2019 Marmoset Community White Paper

The core mission of the National Eye Institute (NEI) is to support research on the mechanisms underlying visual perception, from the early stages of processing in the eye to downstream processes in the lateral geniculate nucleus, primary visual and extrastriate cortex, and including areas involved in higher order visual processes such as visual attention and the control of eye movements. Natural selection has endowed primates, including humans, with specializations that affect visual processing in all these areas such as, critically, the fovea, which has an outsized impact on the way visual information is processed, not simply because it yields higher acuity than any other mammal, leading to fine spatial form (shape) processing (104), but because it fundamentally changes how primates use their eyes to acquire information about the world. The primate brain has a network of oculomotor areas (105) and efficient strategies for moving the eyes so that the fovea is rapidly positioned over targets of interest. Rapid eye movements (saccades), are made two to three times every second as the brain samples the visual scene, and these signals are smoothly integrated across time so that it looks to the observer as though a wide visual field is seen crisply during a period of viewing. The areas governing the planning of saccades also play a critical role in the deployment of visuospatial attention, which strongly influences visual processing (106). Eye movements are also critical for visuo-motor manipulations during tool use and face recognition during social interactions. Relative to other mammals, primate vision is defined by these specializations along the full extent of the visual pathway from enhanced low-level retinal processing through high-level visual abilities. Thus vision research in non-human primates affords clear advantages over rodents. Both Old- and New-world monkeys have critical roles to play in the study of primate vision, but marmosets have several practical advantages: they are economical to house and easy to handle, and lack B-virus. Further, as detailed below, the marmoset has additional advantages over other primate models for vision research in multiple areas:

Development **-** Their short developmental timescale (reaching sexual maturity ~3x faster than macaques) allows study of postnatal development in the early visual system, and they offer interesting opportunities for developmental studies of color vision, as they exhibit genetic polymorphisms that affect the long-wavelength sensitive cones, yielding both dichromats (all males, some females) and some trichromats (some females) (107).

Mapping - The lissencephalic brain of the marmoset places multiple areas (such as V2, MT, face patches in IT, FEF) on the surface of the brain, where they are readily accessible for laminar recordings, array recordings, intrinsic imaging, fluorescent calcium imaging, and surface-based optogenetics (10, 12-14, 54, 108). The smaller brain of the marmoset makes large-scale mapping more efficient. Studies in Japan have already shown the promise of large-scale mapping techniques such as diffusion tensor imaging and widefield imaging.

Behavior – Like macaques, marmosets readily accept head restraint, a prerequisite for some approaches to electrophysiology and imaging (24) and can readily perform tasks requiring sensory discrimination (43). Marmosets make saccadic and smooth pursuit eye movements (41, 42) and preserve the use of eye movements to explore visual scenes and the relationship

between saccadic velocity and displacement (43-45). Marmosets naturally exhibit a rich visuo-social behavior that in many respects parallels human.

Disease – Treatments for debilitating diseases like blindness and retinal degeneration benefit from studying animals whose retinae are similar to those of humans. Marmosets, macaques, and humans have very similar foveal cone densities though marmosets have higher cone density in the visual periphery (109). The rapid reproductive cycle of the marmoset and lower cost of housing relative to the macaque is an advantage when testing novel treatments such as gene therapy and neuroprosthetics where costs may be prohibitive in a macaque.

Breadth of Current Research. The breadth of research related to the mission of NEI Eye currently underway in marmosets is notable, ranging from disease modeling of the visual periphery to higher level visual processing. For example, myopia (nearsightedness) is a prevalent disease of the eye that affects >20% of the human and can develop throughout life. Work has been done in marmosets studying how corrective optics early in development can affect the evolution of nearsightedness (Troilo & Judge, *Vision Research* 1993). Ongoing work in marmoset is studying the genetic markers and the molecular signaling pathways involved in myopia so that potential therapeutic targets can be identified (110). Recent work in marmosets has also begun to show how interactions between cortical areas affect visual processing elucidating the long debated role of cortical feedback in vision. Using novel optogenetic techniques for circuit dissection, the specific effects of long-range projections from V2 on V1 function were demonstrated advancing on work using more classical techniques in macaques (14). Moreover, visual face processing is important in primate social interactions and developmental prosopagnosia and autism are examples of specific disorders of face recognition afflicting a large fraction of the human population. Marmosets are highly social (4) and, like humans, are highly attentive to faces (43, 45) because they convey meaningful social information (111) and exhibit specialized regions for face processing in high-level visual cortex (53). Studies of this face-patch network are poised to expand with ongoing efforts to developed transgenic marmoset models of autism disorder.

The Future. As a rapidly emerging model system, marmosets are likely to play a critical role in elucidating the intricacies of the primate visual system for decades to come and increase the range of studies for which the species is employed. Marmosets, for example, are an attractive species for studying diseases with a developmental component because of a fast life cycle and high reproduction rates. The rapid sexual maturation of marmosets (18 months) will be critical for studying schizophrenia, autism-spectrum disorders, and attention-deficit hyperactivity disorder in which psychopathology is manifest in childhood. Furthermore, visual deficits, particularly in the M pathway of early vision are well documented in schizophrenia and can be studied in marmosets as well as studying oculomotor, face processing, and visual attention deficits in autism. Marmosets are the shortest-lived anthropoid primates, with a typical lifespan of 9–12 years as compared with 25–40 years for rhesus macaques. Their shorter lifespan makes them better suited to longitudinal studies of age-related vision loss. Finally, an acute need exists throughout neuroscience for means of targeting the elements of cortical circuits in the non-human primate. The benefits of the development of these capacities, both through the establishment of genetically engineered Cre and Flp lines and through the development of enhanced viral targeting capacities (11) will be particularly impactful in the visual system due to the over 50 years of foundational research on visual circuits.

Authors
John Reynolds

Alessandra Angelucci
Diego Contreras
Elias Issa

Literature Cited

1. Tardif SD, Smucny DA, Abbott DH, Mansfield K, Schultz-Darken N, Yamamoto ME. Reproduction in captive common marmosets (Callithrix jacchus). Comparative Medicine. 2003;53:364-8.
2. Yamamoto M. From dependence to sexual maturity: the behavioural ontogeny of Callitrichidae. In: Rylands AB, editor. Marmosets and Tamarins: Systematics, Behavior and Ecology. London: Oxford University Press; 1993. p. 235-54.
3. Schiel N, Souto A. The common marmoset: An overview of its natural history, ecology and behavior. Developmental Neurobiology. 2017;77:244-62.
4. Miller CT, Freiwald W, Leopold DA, Mitchell JF, Silva AC, Wang X. Marmosets: A Neuroscientific Model of Human Social Behavior. Neuron. 2016;90:219-33.
5. Sasaki E, Suemizu H, Shimada A, Hanazawa K, Oiwa R, Kamioka M, Tomioka I, Sotomaru Y, Hirakawa R, Eto R, Siozawa S, Maeda T, Ito M, Ito R, Kito C, Yagihashi C, Kawai K, Miyoshi H, Tanioka Y, Tamaoki N, Habu S, Okano H, Nomura T. Generation of transgenic non-human primates with germline transmission. Nature. 2009;459:523-7.
6. Sato K, Oiwa R, Kumita W, Henry R, Sakuma T, Ryoji I, Nozu R, Inoue T, Katano I, Sato K, Okahara N, Okahara J, Shimizu Y, Yamamoto M, Hanazawa K, Kawakami T, Kametani Y, Suzuki R, Takahashi TT, Weinstein E, Yamamoto T, Sakakibara Y, Habu S, Hata J, Okano H, Sasaki E. Generation of a nonhuman primate model of severe combined immunodeficiency using highly efficient genome editing. Cell stem cell. 2016;19:127-38.
7. Park JE, Zhang XF, Choi S, Okahara J, Sasaki E, Silva AC. Generation of transgenic marmosets expressing genetically encoded calcium indicators. Scientific Reports. 2016;6:34931.
8. Watakabe A, Sadakane O, Hata K, Ohtsuka M, Takaji M, Yamamori T. Application of viral vectors to the study of neural connectivities and neural circuits in the marmoset brain. Developmental Neurobiology. 2017.
9. Watakabe A, Ohtsuka M, Kinoshita M, Takaji M, Isa K, Mizukami H, Ozawa K, Isa T, Yamamori T. Comparative analyses of adeno-associated viral vector serotypes 1,2,5,8, and 9 in marmoset, mouse and macaque cerebral cortex. . Neuroscience Research. 2015;93:144-57.
10. Sadakane O, Masamizu Y, Watakabe A, Terada S, Ohtsuka M, Takaji M, Mizukami H, Ozawa K, Kawasaki H, Matsuzaki M, Yamamori T. Long-term Two-photon Calcium Imaging of neuronal populations with subcellular resolution in adult non-human primates. . Cell reports. 2015;13:1989-99.
11. Dimidschtein J, Chen Q, Temblay R, Rogers SL, Saldi G, Guo L, Xu Q, Liu RC, Lu C, Chu J, Avery M, Rashid M, Baek M, Jacob A, Smith G, Wilson D, Kosche G, Kuglikov I, Rusielwicz T, Kotak V, Mowery T, Anderson S, Callaway EM, Dasen J, Fitzpatrick D, Fossati V, Long MA, Noggle S, Reynolds JH, Sanes DH, Rudy B, Feng G, Fishell G. A viral strategy for targeting and manipulating interneurons across vertebrate species. . Nature Neuroscience. 2016;19:1743-9.
12. MacDougall M, Nummela SU, Coop S, Disney AA, Mitchell JF, Miller CT. Optogenetic photostimulation of neural circuits in awake marmosets. J Neurophys. 2016;116:1286-94.
13. Santisakultarm TP, Kresbergen CJ, Bandy DK, Ide DC, Choi S, Silva AC. Two-photon imaging of cerebral hemodynamics and neural activity in awake and anesthetized marmosets. . Journal of Neuroscience Methods. 2016;271:55-64.
14. Nurminen L, Merlin S, Bijanzadeh M, Federer F, Angelucci A. Top-down feedback controls spatial summation and response amplitude in primate visual cortex. Nature Communications. 2018;9(1):2281. doi: 10.1038/s41467-018-04500-5.
15. Rodriguez-Callejas JD, Fuchs E, Perez-Cruz C. Evidence of Tau Hyperphosphorylation and Dystrophic Microglia in the Common Marmoset2016;8(315). doi: 10.3389/fnagi.2016.00315.
16. Colman RJ. Non-human primates as a model for aging. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease. 2018;1864(9, Part A):2733-41. doi: https://doi.org/10.1016/j.bbadis.2017.07.008.

17. Tardif SD, Mansfield KG, Ratnam R, Ross CN, Ziegler TE. The marmoset as a model of aging and age-related disease. ILAR journal/ National Research Council, Institute of Laboratory Animal Resources. 2011;52:54-65.
18. Solomon SG, Rosa MGP. A simpler primate brain: The visual system of the marmoset monkey. Frontiers in Neural Circuits. 2014;8(96):1-24.
19. Chaplin T, Yu H, Soares J, Gattass R, Rosa MGP. A conserved pattern of differential expansion of cortical areaas in simian primates. J Neurosci. 2013;18:15120-5.
20. Laubach M, Amarante LM, Swanson K, White SR. What, If Anything, Is Rodent Prefrontal Cortex? eneuro. 2018;5(5):ENEURO.0315-18.2018. doi: 10.1523/eneuro.0315-18.2018.
21. Burkart JM, Hrdy SB, van Schaik CP. Cooperative breeding and human cognitive evolution. . Evolutionary Anthropology. 2009;18:175-86.
22. Voelkl B, Huber L. Imitation as faithful copying of a novel technique in marmoset monkeys. PLoS ONE. 2007;2(7):e611.
23. Eliades SJ, Miller CT. Marmoset vocal communication: Neurobiology and behavior. Developmental Neurobiology. 2017;In Press:286-99.
24. Mitchell JF, Leopold DA. The marmoset monkey as a model for visual neuroscience. Neuroscience Research. 2015;93:20-46.
25. Camus SMJ, Blois-Heulin C, Li Q, Hausberger M, Bezard E. Behavioural Profiles in Captive-Bred Cynomolgus Macaques: Towards Monkey Models of Mental Disorders? PLoS ONE. 2013;8(4):e62141. doi: 10.1371/journal.pone.0062141.
26. Ding R, Liao X, Li J, Zhang J, Wang M, Guang Y, Qin H, Li X, Zhang K, Liang S, Guan J, Lou J, Jia H, Chen B, Shen H, Chen X. Targeted Patching and Dendritic Ca2+ Imaging in Nonhuman Primate Brain in vivo. Scientific Reports. 2017;7(1):2873. doi: 10.1038/s41598-017-03105-0.
27. Song X, Osmanski MS, Guo Y, Wang X. Complex pitch perception mechanisms are shared by humans and a New World monkey. PNAS. 2016;113:781-6.
28. Johnson LA, Della Santina CC, Wang X. Selective Neuronal Activation by Cochlear Implant Stimulation in Auditory Cortex of Awake Primate. The Journal of Neuroscience. 2016;36:12468-84.
29. Zhou Y, Wang XW. Spatially extended forward suppression in primate auditory cortex. European Journal of Neuroscience. 2014;39:919-33.
30. Issa EB, Wang X. Altered neural responses to sounds in primate primary auditory cortex. J Neurosci. 2011;31:2965-73.
31. Bendor DA, Wang X. Neural coding of periodicity in marmoset auditory cortex. J Neurophys. 2010;103:1809-22.
32. Eliades SJ, Wang X. Neural substrates of vocalization feedback monitoring in primate auditory cortex. Nature. 2008;453:1102-6.
33. Bendor DA, Wang X. Neural response properties of the primary, rostral and rostrotemporal core fields in the auditory cortex of marmoset monkeys. J Neurophys. 2008;100:888-906.
34. Wang X, Lu T, Snider RK, Liang L. Sustained firing in auditory cortex evoked by preferred stimuli. Nature. 2005;435:341-6.
35. Bendor DA, Wang X. The neuronal representation of pitch in primate auditory cortex. Nature. 2005;436:1161-5.
36. Gao L, Kostlan K, Wang Y, Wang X. Distinct Subthreshold Mechanisms Underlying Rate-Coding Principles in Primate Auditory Cortex. Neuron. 2016;91(4):905-19. doi: https://doi.org/10.1016/j.neuron.2016.07.004.
37. Roy S, Zhao L, Wang X. Distinct neural activities in premotor cortex during natural vocal behaviors in a New World primate, the common marmoset (Callithrix jacchus). J Neurosci. 2016;36:12168-79.
38. Toarmino CR, Yen CC, Papoti D, Bock NA, Leopold D, Miller CT, Silva AC. Functional magnetic resonance imaging of auditory cortical fields in awake marmosets. Neuroimage. 2017;162:86-92.
39. Nummela S, Jovanovic V, de la Mothe LA, Miller CT. Social context-dependent activity in marmoset frontal cortex populations during natural conversations. . J Neurosci. 2017;37:7036-47.
40. Miller CT, Thomas AW, Nummela S, de la Mothe LA. Responses of primate frontal cortex neurons during natural vocal communication. J Neurophys. 2015;114:1158-71.
41. Mitchell J, Priebe N, Miller CT. Motion dependence of smooth eye movements in the marmoset. J Neurophys. 2015;113:3954-60.

42. Samonds JM, Geisler WS, Priebe NJ. Natural image and receptive field statistics predict saccade sizes. Nature Neuroscience. 2018;21(11):1591-9. doi: 10.1038/s41593-018-0255-5.
43. Mitchell J, Reynolds J, Miller CT. Active vision in marmosets: A model for visual neuroscience. J Neurosci. 2014;34:1183-94.
44. Knöll J, Pillow JW, Huk AC. Lawful tracking of visual motion in humans, macaques, and marmosets in a naturalistic, continuous, and untrained behavioral context2018;115(44):E10486-E94. doi: 10.1073/pnas.1807192115 %J Proceedings of the National Academy of Sciences.
45. Nummela SU, Jutras MJ, Wixted JT, Buffalo EA, Miller CT. Recognition Memory in Marmoset and Macaque Monkeys: A Comparison of Active Vision. J Cog Neurosci. 2019;In Press.
46. Moffitt JR, Bambah-Mukku D, Eichhorn SW, Vaughn E, Shekhar K, Perez JD, Rubinstein ND, Hao J, Regev A, Dulac C, Zhuang X. Molecular, spatial and functional single-cell profiling of the hypothalamic preoptic region2018:eaau5324. doi: 10.1126/science.aau5324 %J Science.
47. Okada S, Bartelle BB, Li N, Breton-Provencher V, Lee JJ, Rodriguez E, Melican J, Sur M, Jasanoff A. Calcium-dependent molecular fMRI using a magnetic nanosensor. Nature Nanotechnology. 2018;13(6):473-7. doi: 10.1038/s41565-018-0092-4.
48. Hai A, Cai LX, Lee T, Lelyveld VS, Jasanoff A. Molecular fMRI of Serotonin Transport. Neuron. 2016;92(4):754-65. doi: https://doi.org/10.1016/j.neuron.2016.09.048.
49. Dias R, Robbins TW, Roberts AC. Dissociation in prefrontal cortex of affective and attentional shifts. Nature. 1996;380:69-72.
50. Clarke HF, Walker SC, Dalley JW, Robbins TW, Roberts AC. Cognitive Inflexibility after Prefrontal Serotonin Depletion Is Behaviorally and Neurochemically Specific. Cerebral Cortex. 2007;17(1):18-27. doi: 10.1093/cercor/bhj120.
51. Roberts AC, Wallis JD. Inhibitory control and affective processing in the prefrontal cortex: Neuropsychological studies in the marmoset. Cerebral Cortex. 2000;10:252-62.
52. Roberts AC. Primate orbitofrontal cortex and adaptive behaviour. Trends in Cognitive Sciences. 2006;10(2):83-90. doi: https://doi.org/10.1016/j.tics.2005.12.002.
53. Hung CC, Yen CC, Ciuchta JL, Papoti D, Bock NA, Leopold DA, Silva AC. Functional mapping of face-selective regions in the extrastriate visual cortex of the marmoset. The Journal of neuroscience : the official journal of the Society for Neuroscience. 2015;35(3):1160-72. doi: 10.1523/JNEUROSCI.2659-14.2015. PubMed PMID: 25609630; PMCID: 4300322.
54. Kondo T, Saito R, Otaka M, Yoshino-Saito K, Yamanaka A, Yamamori T, Watakabe A, Mizukami H, Schnitzer MJ, Tanaka KF, Ushiba J, Okano H. Calcium Transient Dynamics of Neural Ensembles in the Primary Motor Cortex of Naturally Behaving Monkeys. Cell reports. 2018;24(8):2191-5.e4. doi: 10.1016/j.celrep.2018.07.057.
55. Lee NJ, Ha SK, Sati P, Absinta M, Luciano NJ, Lefeuvre JA, Schindler MK, Leibovitch EC, Ryu JK, Petersen MA, Silva AC, Jacobson S, Akassoglou K, Reich DS. Spatiotemporal distribution of fibrinogen in marmoset and human inflammatory demyelination. Brain. 2018;141(6):1637-49. Epub 2018/04/25. doi: 10.1093/brain/awy082. PubMed PMID: 29688408; PMCID: PMC5972667.
56. Leibovitch EC, Caruso B, Ha SK, Schindler MK, Lee NJ, Luciano NJ, Billioux BJ, Guy JR, Yen C, Sati P, Silva AC, Reich DS, Jacobson S. Herpesvirus trigger accelerates neuroinflammation in a nonhuman primate model of multiple sclerosis. Proc Natl Acad Sci U S A. 2018;115(44):11292-7. Epub 2018/10/17. doi: 10.1073/pnas.1811974115. PubMed PMID: 30322946; PMCID: PMC6217390.
57. Teo L, Boghdadi AG, de Souza M, Bourne JA. Reduced post-stroke glial scarring in the infant primate brain reflects age-related differences in the regulation of astrogliosis. Neurobiol Dis. 2018;111:1-11. Epub 2017/12/06. doi: 10.1016/j.nbd.2017.11.016. PubMed PMID: 29203280.
58. Le Gal R, Bernaudin M, Toutain J, Touzani O. Assessment of behavioural deficits following ischaemic stroke in the marmoset. Behav Brain Res. 2018;352:151-60. Epub 2017/08/02. doi: 10.1016/j.bbr.2017.07.042. PubMed PMID: 28760698.
59. Rodriguez-Callejas JD, Fuchs E, Perez-Cruz C. Evidence of Tau Hyperphosphorylation and Dystrophic Microglia in the Common Marmoset. Front Aging Neurosci. 2016;8:315. Epub 2017/01/10. doi: 10.3389/fnagi.2016.00315. PubMed PMID: 28066237; PMCID: PMC5177639.
60. Philippens IH, Ormel PR, Baarends G, Johansson M, Remarque EJ, Doverskog M. Acceleration of Amyloidosis by Inflammation in the Amyloid-Beta Marmoset Monkey Model of Alzheimer's Disease. J

Alzheimers Dis. 2017;55(1):101-13. Epub 2016/11/02. doi: 10.3233/JAD-160673. PubMed PMID: 27662314; PMCID: PMC5115608.
61. Park JE, Silva AC. Generation of Genetically Engineered Non-Human Primate Models of Brain Function and Neurological Disorders. Am J Primatol. 2019.
62. Tomioka I, Ishibashi H, Minakawa EN, Motohashi HH, Takayama O, Saito Y, Popiel HA, Puentes S, Owari K, Nakatani T, Nogami N, Yamamoto K, Noguchi S, Yonekawa T, Tanaka Y, Fujita N, Suzuki H, Kikuchi H, Aizawa S, Nagano S, Yamada D, Nishino I, Ichinohe N, Wada K, Kohsaka S, Nagai Y, Seki K. Transgenic Monkey Model of the Polyglutamine Diseases Recapitulating Progressive Neurological Symptoms. eNeuro. 2017;4(2). Epub 2017/04/05. doi: 10.1523/ENEURO.0250-16.2017. PubMed PMID: 28374014; PMCID: PMC5368386.
63. Sato K, Oiwa R, Kumita W, Henry R, Sakuma T, Ito R, Nozu R, Inoue T, Katano I, Sato K, Okahara N, Okahara J, Shimizu Y, Yamamoto M, Hanazawa K, Kawakami T, Kametani Y, Suzuki R, Takahashi T, Weinstein EJ, Yamamoto T, Sakakibara Y, Habu S, Hata J, Okano H, Sasaki E. Generation of a Nonhuman Primate Model of Severe Combined Immunodeficiency Using Highly Efficient Genome Editing. Cell Stem Cell. 2016;19(1):127-38. Epub 2016/07/05. doi: 10.1016/j.stem.2016.06.003. PubMed PMID: 27374787.
64. Liu C, Ye FQ, Yen CC, Newman JD, Glen D, Leopold DA, Silva AC. A digital 3D atlas of the marmoset brain based on multi-modal MRI. Neuroimage. 2018;169:106-16. Epub 2017/12/07. doi: 10.1016/j.neuroimage.2017.12.004. PubMed PMID: 29208569; PMCID: PMC5856608.
65. Woodward A, Hashikawa T, Maeda M, Kaneko T, Hikishima K, Iriki A, Okano H, Yamaguchi Y. The Brain/MINDS 3D digital marmoset brain atlas. Sci Data. 2018;5:180009. Epub 2018/02/14. doi: 10.1038/sdata.2018.9. PubMed PMID: 29437168; PMCID: PMC5810420.
66. Shimogori T, Abe A, Go Y, Hashikawa T, Kishi N, Kikuchi SS, Kita Y, Niimi K, Nishibe H, Okuno M, Saga K, Sakurai M, Sato M, Serizawa T, Suzuki S, Takahashi E, Tanaka M, Tatsumoto S, Toki M, U M, Wang Y, Windak KJ, Yamagishi H, Yamashita K, Yoda T, Yoshida AC, Yoshida C, Yoshimoto T, Okano H. Digital gene atlas of neonate common marmoset brain. Neurosci Res. 2018;128:1-13. Epub 2017/11/08. doi: 10.1016/j.neures.2017.10.009. PubMed PMID: 29111135.
67. Majka P, Chaplin TA, Yu HH, Tolpygo A, Mitra PP, Wojcik DK, Rosa MG. Towards a comprehensive atlas of cortical connections in a primate brain: Mapping tracer injection studies of the common marmoset into a reference digital template. J Comp Neurol. 2016;524(11):2161-81. Epub 2016/04/22. doi: 10.1002/cne.24023. PubMed PMID: 27099164; PMCID: PMC4892968.
68. Yen CC, Papoti D, Silva AC. Investigating the spatiotemporal characteristics of the deoxyhemoglobin-related and deoxyhemoglobin-unrelated functional hemodynamic response across cortical layers in awake marmosets. Neuroimage. 2018;164:121-30. Epub 2017/03/10. doi: 10.1016/j.neuroimage.2017.03.005. PubMed PMID: 28274833; PMCID: PMC5587354.
69. Toarmino CR, Yen CCC, Papoti D, Bock NA, Leopold DA, Miller CT, Silva AC. Functional magnetic resonance imaging of auditory cortical fields in awake marmosets. Neuroimage. 2017;162:86-92. Epub 2017/08/24. doi: 10.1016/j.neuroimage.2017.08.052. PubMed PMID: 28830766; PMCID: PMC5705576.
70. Walker J, MacLean J, Hatsopoulos NG. The marmoset as a model system for studying voluntary motor control. Developmental Neurobiology. 2017;In Press.
71. Wang X. Cortical Coding of Auditory Features2018;41(1):527-52. doi: 10.1146/annurev-neuro-072116-031302. PubMed PMID: 29986161.
72. DiMattina C, Wang X. Virtual vocalization stimuli for investigating neural representations of species-specific vocalizations. J Neurophys. 2006;95:1244-62.
73. Wang X, Merzenich MM, Beitel R, Schreiner CE. Representations of species-specific vocalizations in the primary auditory cortex of the common marmoset: temporal and spectral characteristics. J Neurophys. 1995;74:2685-706.
74. Hosoya M, Fujioka M, Ogawa K, Okano H. Distinct Expression Patterns Of Causative Genes Responsible For Hereditary Progressive Hearing Loss In Non-Human Primate Cochlea. Scientific Reports. 2016;6:22250. doi: 10.1038/srep22250
https://www.nature.com/articles/srep22250#supplementary-information.
75. Takahashi D, Narayanan D, Ghazanfar AA. Coupled oscillator dynamics of vocal turn-taking in monkeys. Current Biology. 2013;23:2162-8.

76. Miller CT, Wang X. Sensory-motor interactions modulate a primate vocal behavior: antiphonal calling in common marmosets. Journal of Comparative Physiology A. 2006;192:27-38.
77. Gultekin YB, Hage SR. Limiting parental feedback disrupts vocal development in marmoset monkeys. Nature Communications. 2017;8:14046. doi: 10.1038/ncomms14046.
78. Gultekin YB, Hage SR. Limiting parental interaction during vocal development affects acoustic call structure in marmoset monkeys. Science Advances. 2018;4.
79. Chow C, Mitchell J, Miller CT. Vocal turn-taking in a nonhuman primate is learned during ontogeny. Proceedings of the Royal Society, B. 2015;282:210150069.
80. Liebetanz D, Nitsche MA, Fromm C, Reyher CKH. Central Olfactory Connections in the Microsmatic Marmoset Monkey (Callithrix jacchus). Cells Tissues Organs. 2002;172(1):53-69. doi: 10.1159/000064386.
81. Gervais NJ, Remage-Healey L, Starrett JE, Pollack DJ, Mong JA, Lacreuse A. Adverse effects of aromatase inhibition on the brain and behavior in a non-human primate. . J Neurosci. 2019;In Press.
82. Hoffman JM, Tran V, Wachtman LM, Green CL, Jones DP, Promislow DEL. A longitudinal analysis of the effects of age on the blood plasma metabolome in the common marmoset, Callithrix jacchus. Experimental Gerontology. 2016;76:17-24. doi: https://doi.org/10.1016/j.exger.2016.01.007.
83. Saltzman W, Abbott DH, Binkley N, Colman RJ. Maintenance of bone mass despite estrogen depletion in female common marmoset monkeys (Callithrix jacchus);0(0):e22905. doi: doi:10.1002/ajp.22905.
84. Workman KP, Healey B, Carlotto A, Lacreuse A. One-year change in cognitive flexibility and fine motor function in middle-aged male and female marmosets (Callithrix jacchus);0(0):e22924. doi: doi:10.1002/ajp.22924.
85. Sadoun A, Rosito M, Fonta C, Girard P. Key periods of cognitive decline in a nonhuman primate model of cognitive aging, the common marmoset (Callithrix jacchus). Neurobiology of Aging. 2019;74:1-14. doi: https://doi.org/10.1016/j.neurobiolaging.2018.10.003.
86. Jennings GC, Landman R, Zhou Y, Sharma J, Hyman J, Movschon JA, Qiu Z, Roberts AC, Roe AW, Wang X, Zhou H, Wang L, Zhang F, Desimone R, Feng G. Opportunities and challenges in modeling human brain disorders in transgenic primates. . Nature Neuroscience. 2016;19:1123-30.
87. Tardif S, Ross C, Bergman P, Fernandez E, Javors M, Salmon A, Spross J, Strong R, Richardson A. Testing Efficacy of Administration of the Antiaging Drug Rapamycin in a Nonhuman Primate, the Common Marmoset. The Journals of Gerontology: Series A. 2015;70(5):577-88. doi: 10.1093/gerona/glu101.
88. Phillips KA, Hambright MK, Hewes K, Schilder BM, Ross CN, Tardif SD. Take the monkey and run. Journal of Neuroscience Methods. 2015;248:27-31. doi: https://doi.org/10.1016/j.jneumeth.2015.03.023.
89. Bethea CL, Reddy AP, Flowers M, Shapiro RA, Colman RJ, Abbott DH, Levine JE. High fat diet decreases beneficial effects of estrogen on serotonin-related gene expression in marmosets. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2015;58:71-80. doi: https://doi.org/10.1016/j.pnpbp.2014.11.008.
90. Kraynak M, Flowers MT, Shapiro RA, Kapoor A, Levine JE, Abbott DH. Extraovarian gonadotropin negative feedback revealed by aromatase inhibition in female marmoset monkeys2017;313(5):E507-E14. doi: 10.1152/ajpendo.00058.2017. PubMed PMID: 28679622.
91. Power ML, Ross CN, Schulkin J, Ziegler TE, Tardif SD. Metabolic consequences of the early onset of obesity in common marmoset monkeys2013;21(12):E592-E8. doi: doi:10.1002/oby.20462.
92. Riesche L, Tardif SD, Ross CN, deMartelly VA, Ziegler T, Rutherford JN. The common marmoset monkey: avenues for exploring the prenatal, placental, and postnatal mechanisms in developmental programming of pediatric obesity2018;314(5):R684-R92. doi: 10.1152/ajpregu.00164.2017. PubMed PMID: 29412686.
93. Ross CN, Power ML, Artavia JM, Tardif SD. Relation of Food Intake Behaviors and Obesity Development in Young Common Marmoset Monkeys2013;21(9):1891-9. doi: doi:10.1002/oby.20432.
94. Tardif SD, Power ML, Ross CN, Rutherford JN. Body mass growth in common marmosets: Toward a model of pediatric obesity2013;150(1):21-8. doi: doi:10.1002/ajpa.22110.

95. Rutherford JN, deMartelly VA, Layne Colon DG, Ross CN, Tardif SD. Developmental Origins of Pregnancy Loss in the Adult Female Common Marmoset Monkey (Callithrix jacchus). PLOS ONE. 2014;9(5):e96845. doi: 10.1371/journal.pone.0096845.
96. Rutherford JN, Tardif SD. Developmental Plasticity of the Microscopic Placental Architecture in Relation to Litter Size Variation in the Common Marmoset Monkey (Callithrix jacchus). Placenta. 2009;30(1):105-10. doi: https://doi.org/10.1016/j.placenta.2008.10.010.
97. Dettling AC, Feldon J, Pryce CR. Repeated parental deprivation in the infant common marmoset (callithrix jacchus, primates) and analysis of its effects on early development. Biological Psychiatry. 2002;52(11):1037-46. doi: https://doi.org/10.1016/S0006-3223(02)01460-9.
98. Cavanaugh J, Mustoe A, French JA. Oxytocin regulates reunion affiliation with a pairmate following social separation in marmosets2018;80(10):e22750. doi: doi:10.1002/ajp.22750.
99. Cavanaugh J, Mustoe A, Womack SL, French JA. Oxytocin modulates mate-guarding behavior in marmoset monkeys. Horm Behav. 2018;106:150-61. doi: https://doi.org/10.1016/j.yhbeh.2018.10.009.
100. Nakako T, Murai T, Ikejiri M, Hashimoto T, Kotani M, Matsumoto K, Manabe S, Ogi Y, Konoike N, Nakamura K, Ikeda K. Effects of lurasidone on ketamine-induced joint visual attention dysfunction as a possible disease model of autism spectrum disorders in common marmosets. Behav Brain Res. 2014;274:349-54. doi: https://doi.org/10.1016/j.bbr.2014.08.032.
101. C.Y. C, C. S-SM, J. B, T. L, S. Y, M. T, V. H, L. P, S. S, G. Y, L. G, S. T, J. P. Experimental zika virus inoculation in a new world monkey model reproduces key features of the human infection. Scientific Reports. 2017;7(1):17126.
102. Ausderau KK, Dammann C, McManus K, Schneider M, Emborg ME, Schultz-Darken N. Cross-species comparison of behavioral neurodevelopmental milestones in the common marmoset monkey and human child2017;59(7):807-21. doi: doi:10.1002/dev.21545.
103. Sawiak SJ, Shiba Y, Oikonomidis L, Windle CP, Santangelo AM, Grydeland H, Cockcroft G, Bullmore ET, Roberts AC. Trajectories and Milestones of Cortical and Subcortical Development of the Marmoset Brain From Infancy to Adulthood. Cerebral Cortex. 2018;28(12):4440-53. doi: 10.1093/cercor/bhy256.
104. Kirk EC, Kay RF. The Evolution of High Visual Acuity in the Anthropoidea. In: Ross CF, Kay RF, editors. Anthropoid Origins: New Visions. Boston, MA: Springer US; 2004. p. 539-602.
105. Krauzlis RJ. The Control of Voluntary Eye Movements: New Perspectives2005;11(2):124-37. doi: 10.1177/1073858404271196. PubMed PMID: 15746381.
106. Reynolds JH, Chelazzi L. ATTENTIONAL MODULATION OF VISUAL PROCESSING2004;27(1):611-47. doi: 10.1146/annurev.neuro.26.041002.131039. PubMed PMID: 15217345.
107. Jacobs GH, Neitz J, Crognale M. Color vision polymorphism and its photopigment basis in a callitrichid monkey (Saguinus fuscicollis). Vision Res. 1987;27(12):2089-100. doi: https://doi.org/10.1016/0042-6989(87)90123-4.
108. Nassi Jonathan J, Avery Michael C, Cetin Ali H, Roe Anna W, Reynolds John H. Optogenetic Activation of Normalization in Alert Macaque Visual Cortex. Neuron. 2015;86(6):1504-17. doi: https://doi.org/10.1016/j.neuron.2015.05.040.
109. Troilo D, Rowland HC, Judge SJ. Visual optics and retinal cone topography in the common marmoset (Callithrix jacchus). Vision Res. 1993;33(10):1301-10. doi: https://doi.org/10.1016/0042-6989(93)90038-X.
110. Tkatchenko TV, Troilo D, Benavente-Perez A, Tkatchenko AV. Gene expression in response to optical defocus of opposite signs reveals bidirectional mechanism of visually guided eye growth. PLOS Biology. 2018;16(10):e2006021. doi: 10.1371/journal.pbio.2006021.
111. Kemp C, Kaplan G. Facial expressions in common marmosets (Callithrix jacchus) and their use by conspecifics. Animal Cognition. 2013;16:773-88.