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. <u>Marmosets are particularly well suited for studying the brain in paradigms involving interactive social behavior</u>. 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, <u>the marmoset is an ideal species for studying mechanisms of prenatal and postnatal brain development relevant to mental illness.</u> 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.

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