National Institute of Mental Health

2021 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 recent emphasis on the common marmoset as a promising model for neuroscience heralds a broadening of experimental paradigms to study brain mechanisms of cognition, including those whose failure underlies prevalent mental disorders. Traditionally, research in cognitive neuroscience has also taken advantage of the three aforementioned main species: the mouse, the macaque monkey, and the human. This has led to a series of important discoveries, gradually transforming our understanding of how the brain supports a range of higher cognitive processes. The marmoset adds new and important dimensions to our understanding of brain function, with great relevance to mental health and disease within an animal model whose brain shares many of its primate specializations with the human. Importantly, new experimental opportunities are rooted in marmosets' gregarious social behavior, which, together with their relative ease in breeding and handling, 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 closely resemble that of humans, including their cooperative foraging and defense, reciprocal communication, and allomaternal rearing of offspring. The marmoset 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 a high degree of 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, with 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.

Breadth of research. In the past several decades, marmosets have been used in experimental neuropsychology programs to study aspects of executive function (99, 100) and emotion (101, 102). 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 also fundamentally similar to that of the macaque and human (103-106). Additional work has demonstrated specializations in the marmoset brain for the perception of faces (33, 107, 108), the production and perception of vocal behavior (78, 83, 85, 86, 109-111), and more recently begun to uncover circuits underlying curiosity driven behavior (112). Technological advances in optical imaging using genetically encoded calcium indicators (25, 113), as well as viral based optogenetic approaches (18-20) have rapidly begun to import technology developed in the mouse into the marmoset. This, together with emerging transgenic methods (5-7), chronic wireless recordings (114, 115) and interactive behavioral paradigms (116, 117), have expanded conceptions of the types of experiments currently feasible in nonhuman primates.

Future. Future marmoset research holds great promise both for increasingly precise basic science research into cognitive circuits, as well as the generation 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, transgenic animals will serve as valuable 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. Regarding translational neuropsychiatric research, preclinical models are beginning to yield deeper understanding into underlying mechanisms and potential treatments for autism spectrum disorder (118), depression (52), stress response (119), and fear memory relevant for PTSD in humans (120). 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 and brain stimulation. Taken together, the remarkable similarities between marmosets' brain architecture and cognitive and social capacities with humans, as well as the species wide array of cutting-edge molecular and genetic tools, this primate model provides a promising bridge between basic science research and clinical psychiatry.

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