Commentary

The Future of Nonhuman Primate Neuroscience: Peril or Possibilities?

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COVID-19 and polio vaccines, HIV/AIDS treatments, blood transfusions, and organ transplantation are just a few of the medical advances made possible by research involving nonhuman primates, specifically monkeys. In neuroscience, we have monkeys to thank for deep brain stimulation therapy, a neurosurgical treatment for Parkinson's disease, and now also for dystonia, depression, and obsessive–compulsive disorder. We have monkeys to thank for brain computer interfaces, which are used to help people suffering with spinal cord injury and stroke to grab objects and speak to loved ones again. Cochlear implants also emerged from research involving monkeys, as will the development of retinal implants restoring sight for people with blinding diseases. Virtually everything we know about the human visual system in health and disease has its roots in foundational science involving monkeys. Indeed, the promise of treatments and a cure for blinding diseases such as macular degeneration require studies in monkeys as they, and not rodents or other mammals, have a feature of their retina called a macula that provides the high acuity vision characteristic of humans and other primates. According to the Alzheimer's association (Alzheimer's Association, 2024), ∼7 million people are living with Alzheimer's and related dementias. In 2024, Alzheimer's and other dementias (multiple system atrophy, frontotemporal dementia, progressive supranuclear palsy, and Lewy body dementia) will cost the United States (US) $360B. Although rodent models have led to significant progress in our understanding of signaling pathways and molecular processes underlying neurodegeneration, monkeys with their complex brain circuits especially in the prefrontal cortex hold the key for developing effective treatments and cures (Beckman et al., 2021).

In 2022, ∼30% of young adults 18–25 years old in the US experienced some form of mental illness such as bipolar disorder, depression, anxiety, schizophrenia, or addiction (National Alliance on Mental Illness, 2024). In 2022, the lost revenue to the US economy resulting from mental illness was ∼$200B (The White House, 2024). The cost to the US to treat the breadth of neurological and neuropsychiatric disorders is $1T each year, as 1 in 4 individuals are estimated to be affected at some point in their lifetime. Monkeys will be necessary for the discovery, development, and testing of disease-modifying treatments for neuropsychiatric disorders and autism spectrum disorder too, because monkeys share with humans sophisticated social cognitive faculties and the supporting brain mechanisms that other mammals either lack or developed mechanisms that are too far divergent from humans. Increasing our investment and support for neuroscience research involving monkeys remains critical to realize our hope for turning these numbers around and alleviating the suffering of millions of individuals and families.

Perhaps surprisingly, the monumentally powerful impact of research involving monkeys comes from a small fraction of all biomedical and behavioral research ongoing in the US. Only 0.5% of scientific work involves monkeys—with the rest, ∼95.5%, involving rats and mice and other species, yet the impact is disproportionately large. The proportion of research in neuroscience involving monkeys is similarly small, with estimates ranging from the hundreds to <1,000 total animals annually. With ratios of impact to use so high, there must be strong and unanimous support for nonhuman primate neuroscience, correct?

Incorrect. The future of nonhuman primate neuroscience in the US is in jeopardy. At the direction of the US Congress, the National Institutes of Health (NIH) commissioned the National Academy of Sciences, Engineering, and Medicine (NASEM) to perform an independent study on the state of the science and needs of research involving monkeys. Over 1 year ago in May 2023, NASEM released their study report titled, "Nonhuman primate models in biomedical research - State of the science and future needs" (Ramos et al., 2023). The report contains vital, and at times sobering, information relevant to neuroscientific discovery in the US. A key conclusion in the report is that there is a shortage of macaque monkeys available for research in the US. Currently, US scientists who involve macaque monkeys in their research programs are unable to obtain the animals required to advance scientific understanding and treatments

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for diseases affecting millions of people. If purpose-bred macaques can be found, the costs are becoming prohibitive—running ~$25,000 or higher per animal, an ~150% increase in cost per animal. The cost of housing and caring for monkeys is also increasing, nearing $40 per day per animal in some institutions. Further limiting access is that virtually all domestic and international air carriers no longer transport research animals, having succumbed to pressure from special interest groups opposed to animal research.

Reports from the US Department of Agriculture indicate that ~70,000 monkeys are involved in research annually (USDA, 2024). Prior to 2020, ~30,000 of these animals came from China. In 2020, China abruptly ceased exporting monkeys. The cessation of exports, combined with the need for macaques for vaccine testing resulting from the COVID-19 pandemic, and the preexisting and insufficient level of federal funding for domestic breeding programs led to the current national crisis, highlighting how our reliance on a foreign power can cripple biomedical research in our country. The current state jeopardizes our ability to advance neuroscience and risks our standing as global leaders in neuroscience and biomedical research. To ensure a sustainable resource of nonhuman primates for biomedical research, including and especially in neuroscience, the US must engage in domestic capacity building. The report from NASEM stated clearly in Conclusion 3-2: "Without decisive action and a national commitment to a comprehensive plan for nonhuman primate (NHP) availability, the ability of the National Institutes of Health (NIH) – supported extramural program investigators to conduct studies requiring the use of an NHP model will become a function more of access to NHPs than of a concerted response to national public health priorities. The core tenet of NIH that only the most meritorious research should receive the highest priority will thereby be threatened."

It is incontrovertible that studies involving humans, rodents, and other species phylogenetically removed from primates are vital and continue to shed light on foundational mechanisms that give rise to healthy and diseased brain function. However, developing treatments and cures for Alzheimer's disease and related neurodegenerative diseases, and the many neuropsychiatric illnesses, will all ultimately require an understanding of the brains of primates and perhaps the immune system, which, like the brain, is significantly more like humans in monkeys than in rodents. Moreover, it remains unclear if the mapping between brain circuits and brain cell types are preserved or differentially mapped between primate and other mammalian species. Neurological and neuropsychiatric disorders and many other disorders of brain function result not only from an interplay of genetics, social environmental interactions, and diet but also from how genes and experience contribute to the development and function of complex brain circuits. It is the dissection of complex brain circuits, the unraveling of the functional wiring diagram of the brain in different contexts in primates that will lead to scientific breakthroughs in our understanding of these disorders and clinical impact for patients. It is in this arena—unraveling of complex, functional, and flexible neuronal circuits—where monkeys are essential. Realizing the tremendous promise of novel gene therapy approaches such as CRISPR-CAS9, ZFN, and TALENs to unravel these circuits, as well as ultimately treat or cure neurological and neuropsychiatric disorders, will also require research involving monkeys.

Acknowledging the essential need for research involving monkeys does not preclude the value and the need to develop and validate complementary, novel approach models that do not rely on animals such as in silico approaches. However, such models will likely always fall short of capturing the richness and complexity of the primate brain and behavior. And they will not allow us to circumvent the challenging ethical questions. If we get to a stage where we can replicate a human on a chip, we simply transfer all the ethical issues associated with animal research to the chip: Is it sentient? Does it have autonomy and rights? Can it be held responsible? With the astronomical advances in technologies developed to study brain function resulting from the BRAIN initiative, a groundbreaking program at NIH, we are now well-positioned to take nonhuman primate neuroscience to the next level and realize tangible and lasting impact on our understanding of complex brain circuit function toward alleviating suffering for all living beings, especially in the areas of mental health, aging, and neurodegeneration. Funding from the BRAIN initiative led to unprecedented, accelerated rates of discovery, ranging from the advances in artificial intelligence and imaging technologies to the application of gene therapy techniques to map circuits, the development of high-density electrophysiological methods that allow large-scale brain activity monitoring, and the development of these technologies in freely moving animals performing ecologically relevant tasks. It is an exciting and important time to be a neuroscientist and especially one who works with monkeys. It is also a terrifying and sobering time to be a neuroscientist working with monkeys as we bear witness to the steady onslaught of threats to this critical area of research.

There remain several significant impediments to realizing the full potential of nonhuman primate neuroscience beyond the shortage of animals. First, society's relationship with animals has changed. Rather than companions, many people now view their pets as family members. In 2023, the pet industry contributed over $200B to the economy of the US (Pet Advocacy Network, 2023). The change in relationship to animals extends to the people who work with laboratory animals in neuroscience. In our many years working with monkeys at multiple institutions including NIH, we are increasingly aware that not all in academia, including even neuroscientists and laboratory veterinary medicine providers, are comfortable with research that involves monkeys, even if they appreciate its value, impact, and significance. Arguably, people are uncomfortable with nonhuman primate research because of the similarity between us and monkeys. Indeed, it is precisely because of the similarities between monkeys and humans in so many areas—genetics, physiology, susceptibility to infection and immune system function, female reproductive system function, motor behavior, cognitive behavior, social behavior and communication, and brain anatomy among other things—that makes monkeys such powerful models of human health and disease. However, we as scientists must connect with people on an emotional level and must remind people that we too have changed our relationship with animals and we too care deeply about our pets and our laboratory animals. Second, likely due to increased regulatory burden, higher costs, and concerns about public relations, more institutions are closing their doors to research involving monkeys. In some cases, animal welfare guidelines are being weaponized resulting in laboratory closures and institutions retreating in fear of antiscience extremists. Work involving animal models is fraught with moral complexities and especially work involving monkeys. We believe the moral quandaries must be addressed, and they must be addressed first by the scientific community. Unless and until we learn to communicate with the public, our colleagues, and leadership

of our home institutions about the essentiality as well as our deep understanding of the moral and emotional complexities of our work, our ability to advance this area of neuroscience is doomed.

Perhaps the least acknowledged threat to this field is the lack of support for nonhuman primate neuroscientists who come under attack by members of special interest groups opposed to animal research. We witnessed the activity of special interest group wax and wane over the decades, but what remains constant is the meager or nonexistent support and protection from our own institutions, including NIH. There should be no hesitation in acknowledging the impact and importance of this work and the value of the scientists and the animals necessary to perform it. The current stance must change if the field is to continue. Students and trainees no longer want to begin a career in this field out of fear as they see their mentors dealing with the constant onslaught of harassment and even violence. Scientists in public institutions are particularly vulnerable as all information that filters through a public institution is subject to public records requests—state laws that are weaponized by antiscience extremists to spread disinformation, disparage, and threaten scientists. This too must stop, and we need to engage lawmakers and law enforcement officers to help us in this effort. The expert members of the NASEM panel identified the threats to this work and the potential demise of our field as a matter of national security. We must prevent that from happening.

We encourage everyone who cares about people and other animals to speak up, speak out, and take action to ensure that this vital area of neuroscience continues in the US and, in turn, enables us to fulfill our responsibility as global leaders in neuroscience health discovery toward the improvement of lives everywhere. Now is the time to speak to your congresspersons, organize and participate in Capitol Hill visits, advocate for research involving monkeys at your own institutions, hire junior faculty who work with monkeys, partner with your professional societies especially Society for Neuroscience (SfN) on outreach and governmental affairs efforts, raise awareness of the importance of nonhuman primate research in the popular media, speak to your colleagues and your institutional leadership, include discussions of the importance of this area of neuroscience and its ethics in the classes you teach, and write and publish opinion pieces like this one, to name a few ways that you can get involved and help.

We applaud the recent statement made by the SfN (Society for Neuroscience, 2024) acknowledging the critical role that monkeys play in our mission to advance and advocate scientific exchange, to support diversity and career training, and to educate the public about the importance of our work. We encourage every neuroscientist to amplify this statement. We also invite researchers to join the Simian Collective (Simian Collective, 2024), the group who authored this piece and who have the goal of bringing together the community of neuroscientists whose work involves monkeys to learn about science, ethics, and advocacy, as well as create a lasting and supportive community of peers across career stages. Join us in our national efforts to educate and inform our universities and institutional leadership, our veterinarians and other laboratory animal care professionals, our federal and state government and elected officials, as well as each other. Only by joining together can we fulfill our shared mission to end the suffering of all beings, humans as well as other animals, through advancing science.

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