Neuron
Perspective

Brains, Genes, and Primates

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One of the great strengths of the mouse model is the wide array of genetic tools that have been developed. Striking examples include methods for directed modification of the genome, and for regulated expression or inactivation of genes. Within neuroscience, it is now routine to express reporter genes, neuronal activity indicators, and opsins in specific neuronal types in the mouse. However, there are considerable anatomical, physiological, cognitive, and behavioral differences between the mouse and the human that, in some areas of inquiry, limit the degree to which insights derived from the mouse can be applied to understanding human neurobiology. Several recent advances have now brought into reach the goal of applying these tools to understanding the primate brain. Here we describe these advances, consider their potential to advance our understanding of the human brain and brain disorders, discuss bioethical considerations, and describe what will be needed to move forward.

Introduction

Science lacks a full understanding of how the brain works in health and how it fails in disease. As a consequence, medical researchers do not have a well-defined long-term strategy for the development of new and effective treatments for mental disorders. The size of the problem cannot be overstated. The cost of

neurological diseases to society is enormous. Dementias alone, for example, cost more than heart disease and cancer, exceeding $160 billion in the United States alone (Hurd et al., 2013), equivalent to $500 per United States citizen per year. The toll in human suffering is immense, both to the patients and to their families. Progress on treatment for psychiatric conditions, such as schizophrenia, is comparably stalled. Schizophrenia is a life sentence, and at best current drug therapy is palliative, with severe side effects. The etiology of autism, though intensively explored, remains frustratingly baffling, and neither amelioration of symptoms nor a cure seems imminent. For autism, too, human misery takes a truly staggering toll. We now know of 600 diseases of the nervous system, with a high likelihood that each of us will suffer from one of them in our lifetime. At this stage, there is no effective treatment, and little if anything to assist with prevention. With increases in the size of the aging population, the human and economic costs will certainly increase in step, possibly to crushing proportions.

One of the major obstacles to progress in understanding and developing treatments for these diseases is the relatively limited set of genetic tools currently available to systematically study and test relevant neural circuits in primates, the mammalian order of which we are members. Rodent models play an essential role in neurobiology, where a powerful array of modern genetic tools has been successfully applied. Striking examples include methods for targeted inactivation of endogenous genes and for regulated expression of transgenes, yielding cell-type-specific expression of opsins, fluorescent markers, and neuronal activity indicators. These tools have enabled major advances in neurobiology, and they will continue to be used to great effect in rodents. There are, however, considerable anatomical, physiological and behavioral differences between the rodent and the human. This means that for many disorders, especially those involving high-level cognitive functions, studies of rodents may not reveal the mechanisms at work in the human brain. The development of primate models for human diseases also addresses a major concern articulated in 2011 by a British independent panel chaired by Sir Patrick Bateson ("the Bateson report"), which is that while much nonhuman primate work is of high quality, its impact on our understanding of human disease and its treatment has been limited (http://www.wellcome.ac.uk/stellent/groups/corporatesite/@policy_communications/documents/web_document/wtvm052279.pdf). Arguably this limitation arises in part because the lack of genetic tools for cell-type-specific targeting of protein expression has limited our understanding of neural circuits in the primate brain. Without these tools, primate models of genetically based diseases cannot be created and studied. Equally important, the lack of tools to cause cell-type-specific expression of proteins such as opsins and genetically encoded neuronal activity indicators severely limits basic scientific understanding of the primate brain.

Concern over these critical limitations led to a recent symposium at the Salk Institute for Biological Studies, in which world leaders in multiple disciplines met to consider how to bring modern genetic tools to bear directly on understanding the primate brain. The purpose of this Perspective is to describe the findings of this symposium and to motivate its conclusion that the goal of developing genetically modified primates for use in studying the primate brain is both necessary and within reach. Advances in methods of gene editing and stem cell technology, coupled with successes in germline transmission of transgenes in the common marmoset (*Callithrix jacchus*), position researchers to make critical advances in our fundamental scientific understanding of the primate brain. At the same time, we acknowledge and discuss the ethical considerations of engaging in work with transgenic nonhuman primates.

This new line of research promises to significantly accelerate progress in understanding the fundamental organizing principles of the primate brain and the etiology of human neurological and psychiatric disorders, progress on which so many victims and their families have pinned their hopes.

The Need for Nonhuman Primates as a Model for Studying the Human Brain

Rodents serve as important animal models in many domains of biomedical research. Within neuroscience, powerful genetic tools are being used to probe the functions of different components of the murine brain. This work is highly relevant to understanding the workings of the human brain because mouse and human brains share many of the same circuit components and there are important similarities in the ways these components are wired together (Figure 1). Further, the social, cognitive, and perceptual abilities of rodents are more impressive than at first assumed, which has enabled researchers to study neural mechanisms underlying some of these functions in the behaving mouse. As we come to understand these mechanisms in mice, it is likely that this will enhance our understanding of the human brain, shedding light on its disorders.

These advantages notwithstanding, rodents do differ in important ways from humans. Brain circuitry, cognitive capacities, and behavioral repertoires have evolved over the 83 million years that have passed since the rodent and primate lineages separated (Meredith et al., 2011). Over this time, natural selection has endowed primates with specialized brain structures that give rise to our particular motor, perceptual, and cognitive capacities (Kaas, 2013). These specializations include prominent expansion of the frontal cortex, parts of which are implicated in psychiatric disorders and have no homolog in other mammals (Wise, 2008).

To take a simple concrete example, humans and nonhuman primates differ from rodents in how they explore the visual environment. The primate oculomotor system serves to move the eyes to align the high-resolution fovea with objects of interest in a scene. The fovea has a huge impact on the way visual information is processed, not simply because it yields higher acuity, but because it changes in a fundamental way how primates use their eyes to acquire information about their world. Evolution has endowed primates with efficient strategies for moving their eyes so 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 in a remarkable computational feat, 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. Primates also have stereoscopic vision across the majority of the visual field, and the computational capacity to construct a three-dimensional representation of the visual world. They possess the ability to smoothly track objects moving through that world, a capacity that is associated with