From basic brain research to treating human brain disorders

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The human brain is the most complex entity we know. Disorders of the human brain are embedded in this complexity. Potential advances in treating these disorders result from the growing understanding of this complex organization. The brains of monkeys have some important similarities to the human brain in structure and organization, and monkeys have therefore been extensively studied to help us to understand human brain disorders. With this in mind, the National Academy of Sciences (NAS) convened a colloquium, "Using Monkey Models to Understand and Develop Treatments for Human Brain Disorders," in Irvine, California on January 7th and 8th, 2019. The colloquium articles in this issue of PNAS offer a glimpse into the relationship of scientific discovery to the treatment of brain disorders. We begin by considering how this kind of scientific discovery works.

The Essential Role of Basic Research

The better we know how a machine works, the more likely we are able to fix it when it breaks. When our automobile needs repair, we take it to someone we think understands how it works and therefore is likely to be able to fix it. We do the same thing when we have a brain disorder; we go to the doctor we think understands the brain system underlying the specific disorder and hope that she can provide a treatment. It is the understanding of the brain system that comes first; without that understanding the treatment is likely to be a hit or miss guess or an expensive failure. The understanding is not all or none, it is continually developing, often over many years. Anyone who has close experience with a brain disease knows that current medicine is mostly groping in the dark with these disorders. It is the job of basic science to turn on some lights.

Consider an example of the contribution to clinical treatment of basic research. Suppose you have difficulty reading. Your eye doctor measures the smallest letters you can see, and then how steady your eyes are during reading. She finds that your eyes are normal, but that they are not stable; it is this instability that makes you unable to see well. She then needs to find exactly what the eye movement problem is. Knowing that, she can then turn to the results of basic research—done primarily on monkeys over the last 50 y—on the series of neurons in the brain (brain circuits) that are essential for seeing and those that are essential for moving the eyes. She can concentrate on the brain circuits for eye movements and on the part of the circuit that would produce the eye movement error in the patient. Knowing that, she might be able to use a specific medication or other intervention to increase or decrease brain activity at a particular point in the circuit, to reduce the eye movement error, and improve your reading.

The point of this illustration is that treating a complaint as simple as "Doc, I can't read" depends on knowing about the brain circuits that underlie the task of reading. These circuits were not investigated to answer the question, "Why can't I see?" but rather "How can we understand the brain circuits required for seeing and how are they organized?" Developing this essential knowledge has taken the work of hundreds of scientists over at least half a century.

All of science depends on basic research, research that has the goal of understanding a system rather than the goal of fixing or building it. Brain research is

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relatively new. Detailed studies of brain function have only been made in the last 150 y. Contrast this with the recent and rightly celebrated 50th anniversary of the moon landing, which is based on the knowledge gained over many hundreds of years, roughly since the acceptance of the Copernican view of a sun-centered solar system. The challenge of brain research is also great; a conservative estimate of the number of neurons in the brain is 80 billion, more than 10 times the population of the world; the number of possible connections among those neurons is at least 100 trillion, many thousands of times the number of stars in our galaxy.

Understanding Depends on Animal Models

There are many questions about human biology that researchers hope to answer, from how our bowels work to how our brains work. Experience shows that it is always most profitable to study a biological system in an animal in which the system is well developed and in which it is relatively easy to study. For example, for many years the study of transmission of nerve impulses along the axon of a neuron was studied in the squid, a marine invertebrate. The axon connects one neuron to another neuron or to a muscle. The squid was studied because it has a giant axon that quickly activates a muscle that expels water to rapidly push the squid away from a predator. Because the axon is large, it was possible to do recordings from inside as well as outside the axon. This convenience made it the animal of choice for studying axon transmission and led to a Nobel Prize for Alan Hodgkin and Andrew Huxley in 1963. The invasive experiments that were essential for understanding could be performed in these animals, but would not have been ethically possible in humans, even if they had a giant axon (which they do not). Animals used to study a particular system are referred to as animal models of that system. Advances in most areas of medicine depend on research on animal models.

It is important to distinguish between animal models and mathematical models. Mathematical (or computational) models are built on the data derived from experiments, including the data from animal models. Such models build a mathematical representation of the experimental observations made in the animal models that not only summarize the findings of the experiments but also make predictions that can be tested in future experiments. In a sense, the goal of all experiments is to provide sufficient data to build a mathematical model of the system being studied. To return to the squid, Hodgkin and Huxley's Nobel Prize was based as much on their mathematical model as on their animal model.

The animal model is used during experiments and the mathematical models are constructed after experiments. The occasional argument that such mathematical models can replace experimental models is specious; computer models are derived from the experimental data and guide future experiments, but they cannot generate the data themselves. And at a given moment in time, it is common for several models to explain the available data available. Further experiments must be done to determine which model best captures the fundamentals of the system, and should thus guide development of therapeutics.

Selecting the Best Animal Model

A fundamental principle of biological research is that to answer a biological question, one must pick the best animal model, as in the case of the squid for transmission of nerve impulses. Our goal is to pick an animal model that is appropriate for the study of the human brain and its disorders. Considering some examples illustrates the range of models used and how the answers they provide depend on the fit to the questions asked.

Fruit flies have provided key links between genetics and human disease beginning with Thomas Hunt Morgan's discovery that genes are carried on chromosomes. It was subsequently realized that over half the genes responsible for human disease are conserved (remain the same) across many species. A clinically specific example is Friedreich's ataxia, an inherited disease that confines patients to wheelchairs and usually leads to early death. The disease results from a defective gene (FXN) and since this gene is conserved across species, basic research can be performed in fruit flies, which carry the gene and are easy to use. Ways to correct the genetic deficit can be found in fruit flies, then tested in humans.

Mice and humans are mammals, and thus share vastly more features of brain structure and function than do fruit flies and humans. Thus, the mouse has been used in many cases where a genetic alteration in a mouse can produce a disease similar to one in humans. This has been done for a number of neurological diseases. For example, Rett syndrome is an autism spectrum disorder that affects only girls. Huda Zoghbi discovered in 1999 that its primary cause is mutation of a specific gene, MECP2. When this gene is absent in mice, they display neurological symptoms similar to Rett syndrome. Restoration of the absent gene reverses the neurological disorder. This and other examples demonstrate the relative ease with which a disease with a specific genetic deficit can be replicated in the mouse, which in turn facilitates the search for genetic or other treatments in humans. In addition, the ability to use genetic tools in the mouse has greatly expanded its importance for understanding its brain function.

Monkeys (both Old World monkeys, macaques, and New World monkeys, marmosets) have the major advantage of brains whose organization and function most closely matches the brains of humans. The advantage of such similarities between monkeys and humans is dramatically illustrated by one of the triumphs of science: the conquest of polio, a now almost-forgotten disorder.

Polio is a devastating disease that paralyzed many, forcing them to use respiratory maintenance in iron lungs. It also changed daily life; it postponed events and closed swimming pools around the world for many summers. The virus that causes polio was first identified in 1910 by Karl Landsteiner and Erwin Popper. They had failed to identify the virus using rabbits, mice, and guinea pigs, but finally succeeded in monkeys, and demonstrated transmission between humans and monkeys. In 1935, 25 y later, tests of a trial vaccine were carried out on humans after limited preliminary tests on monkeys. Immunity was not always produced, but some cases of polio probably were produced. The problem was the lack of sufficient understanding of both the virus and the vaccine. The next vaccine trials were 20 y later, in 1955, when knowledge had expanded, and the vaccine developed by Jonas Salk was successful. A scourge of the world has been almost completely eradicated. The basic understanding of the virus and the vaccine took over half century to achieve, and was possible only after discovering that the best animal model for the disease was the monkey.

Considering just these three animal models illustrates a major characteristic of animal models for brain research. In many cases a specific model is a critical tool for answering the questions needed for expanding basic understanding and developing a treatment for a brain disorder. The treatment of polio relied on the monkey model, and there are a variety of human brain disorders that will almost certainly require the understanding of brain

systems in monkeys because of the similarity of brain organization and function between these two primates, monkeys and humans.

Current Research on Monkeys and Prospects for Treatment of Human Brain Disorders

In this Colloquium the articles concentrate on the benefits of the monkey model for developing the basic understanding required before treatment of a human disease is possible. It will become evident that many of these disorders result from the failure of circuits of neurons in the brain. Some research already shows applications to humans; others show how the advances will lead to treatments of human disorders. Here we do not attempt a comprehensive summary, but instead highlight a few striking examples that have already led to treatment of brain disorders, are being tested in human trials, or are being refined for such testing. We also point out what understanding of brain function was required before treatments for human brain disorders could even be envisioned, and what the consequences for such treatment would be if basic research on monkeys were reduced. We consider investigations in five sections and below provide an introduction to each. The first is a comparison of the brains and behaviors of mice, monkeys, and humans. The following four sections are on brain disorders and are introduced by a Perspective written by a clinician. In the following research descriptions some articles refer to "monkeys" and others to "nonhuman primates"; in all cases the references are to macaque monkeys or marmoset monkeys.

Brains and Behavior: Mice, Monkeys, and Humans

The first section considers the fundamental issues in evaluating mice and monkeys as models for human brain disorders. While all of the animals considered in this colloquium are mammals, there are major differences among them simply because there are substantial differences in their brains. This section provides examples of the differences across the species considered in the colloquium: Mice, marmoset monkeys, macaque monkeys, and humans.

A major difference is the number of anatomical areas in the highest region of the brain, the cerebral cortex, and the connections between them. These cortical areas are the fundamental units of the cerebral cortex and the basis for complex cognition. According to Van Essen et al. (1), mice have 43 different areas in each hemisphere, marmosets as many as 117, macaque monkeys as many as 161, and humans as many as 180. This increase in number of cortical areas is consistent with the increase in brain size and behavioral ability across the species. Moreover there are obvious parallels in the organization of these areas across the three primate species that cannot be readily discerned in mice.

Disney and Robert (2) consider species differences in brain transmitters, the chemicals that nerve cells use to communicate with each other. They report that a transmitter in mice that acts on a particular type of cortical neuron may not act on that neuron in the same way in macaque monkeys. Drugs that act on the brain usually work through neurotransmitter systems. So while in some cases a drug may act similarly in mice, monkeys, and humans, in other cases a drug developed for mice may not work for primates, including humans.

Luo and Maunsell (3) consider a complex behavioral function, attention, which is a component of many brain disorders. Their review of attention studies in monkeys shows that, while attention may seem to be a unitary system, it can be better understood as multiple distinct brain processes, often cooccurring and frequently involving different brain pathways.

One of the great advantages of fly and mouse models is that genes can be easily manipulated. Arranging for nerve cells to express particular genes has been a useful tool for neurobiology, notably the creation of light sensitivity in neurons through optogenetics. The activity of such neurons can be controlled by light. Even though optogenetic access is more difficult to achieve in monkeys, a variety of molecular techniques is under active development in these animals. El-Shamayleh and Horwitz (4) summarize the state of this particular art, and show that for many purposes, optogenetic control of brain activity in monkeys can be readily achieved.

The message of all these studies is that the brains from mice to monkeys to humans show substantial differences in anatomical structure, neuronal transmitters, and behavioral ability. This is hardly surprising given that the brain is a major distinguishing feature between these mammals, but it has profound consequences for developing treatments for human brain disorders.

Disorders of Development

Damage during development affects the brain in a qualitatively different manner than does damage during adulthood. Adult brain injury often results in severe and selective cognitive impairments, with loss of ability in one function against a background of otherwise spared cognition. Examples include amnesia (selective impairment in forming new memories), aphasia (selective loss of the ability to understand or express speech), and agnosia (inability to recognize and identify familiar objects or people). In contrast, cognitive impairments due to brain damage sustained during development are typically less severe but more general, affecting a wider range of cognition. One possibility for these differences is that focal damage sustained early in life can impact the function of other brain regions that are connected with the damaged area during the processes of maturation. However, we don't currently have a full understanding of all of the factors that contribute to the differential effects on cognition of damage acquired at different points during development. The nonhuman primate model is critical for advancing our understanding of developmental disorders because it allows prospective and longitudinal studies in a system—unlike the mouse—where the course and specificity of cortical development is much the same as it is in humans.

The articles in this section highlight the contribution of the nonhuman primate model to our current understanding of developmental disorders of cognition. The clinical perspective by Cacucci and Vargha-Khadem (5) provides a theoretical and clinical framework for understanding the cognitive effects of brain injury in children. The article by Bachevalier (6) describes a series of developmental studies in monkeys that have informed our understanding of the development of the hippocampus and its unique role in the primate memory system. The hippocampus is particularly vulnerable to periods of low oxygen, and early damage to the hippocampus is observed in children who have experienced hypoxic or ischemic events, epilepsy, and even stress. The studies using the nonhuman primate model have provided important information about the time course of the emergence of hippocampal-dependent cognitive functions, how memory is affected with early damage to the hippocampus, and the clinical implications of damage to this part of the brain in developmental neuropsychiatric disorders. None of this information can be obtained from work with other models, such as the mouse. The article by Kiorpes (7) describes the childhood developmental disorder of amblyopia, which disrupts vision in a large population

of children around the world. Kiorpes describes work with the nonhuman primate model that recapitulates the human disease in ways that other models like the mouse do not. This model has provided insight into the brain mechanisms that underlie amblyopia, as well as new understanding of its origins and sensitive periods. This research has led to important changes in clinical practice both by enhancing understanding of the importance of early interventions in children with conditions that predispose them to amblyopia, and also in guiding novel therapies for affected children based on monkey experiments on brain plasticity. Experiments in nonhuman primate models of brain damage sustained early in life has been, and will continue to be, critical for advancing our understanding of the potential for compensatory processes and reorganization of function. These studies are instrumental to the goal of developing novel therapeutic interventions to improve human health and outcomes for children, adolescents, and adults affected by developmental disorders.

Disorders of Aging

Advances in medicine have strikingly increased life expectancy, and the group of individuals aged 65 and older represents the fastest growing sector of our population. Age-related changes in cognition, both as a result of neurodegenerative disease and in the course of "healthy" aging, impact a large proportion of our population and present a major public health concern. The articles in this section describe the clinical need for increased understanding of changes in brain health that occur during aging and describe exciting insights gained through experiments using the nonhuman primate model. Haque and Levey (8) offer a clinical perspective, with a focus on Alzheimer's disease, which is the most common cause of dementia and accounts for over 60% of all cases. While research over the past few decades has provided insights into the pathological processes associated with Alzheimer's disease, there is still currently no disease-modifying treatment or cure. This article describes the gap in our understanding and the value of the nonhuman primate model for bridging between rodent and human studies to advance our ability to rapidly test novel therapeutic candidates. The articles by Arnsten et al. (9) and Beckman et al. (10) describe exciting advances in nonhuman primate models for Alzheimer's disease. Arnsten et al. (9) show that aging rhesus monkeys naturally develop cognitive deficits, along with neuropathology that is similar to that seen in humans with Alzheimer's disease, including amyloid plaques and tau tangles; mice show none of these age-related changes. The findings presented in this article use electron microscopy to examine early changes in tau phosphorylation, which identifies how and where degeneration occurs in the course of aging. Beckman et al. (10) describe the development of a rhesus monkey model of Alzheimer's disease, with increases in forms of the Aβ peptide, a component of the amyloid plaques, producing markers of Alzheimer's disease in monkeys that are similar to those observed in human patients. Together, these exciting developments in the monkey model of Alzheimer's provide important new platforms to develop effective treatments for Alzheimer's and other dementias.

The article by Gray and Barnes (11) makes the important point that changes in cognition associated with "normal" aging—changes that are not associated with a specific neurodegenerative disease—are not well-understood. This article reviews research with animal models and highlights the value of the nonhuman primate. Macaque monkeys have striking similarities to humans in behavior, sensory processing, and neural architecture, and Gray and Barnes demonstrate the fundamental insights into age-related memory decline and hearing loss that have been gained through the use of the monkey model of human aging. Together, these articles (8–11) point to the exciting potential and the critical need for the nonhuman primate model—the only animal model that recapitulates the human disease—in accelerating our understanding of the processes associated with brain aging as well as the development of novel therapeutic approaches to treat age-related changes in cognition.

Restoring Motor and Sensory Function

Growing knowledge about the neuronal circuits in the brain of monkeys that underlie the control of movement and the registration of sensory input make it possible to compensate for losses of these functions in humans. The articles in this section provide illustrations of the restorations of motor and sensory functions in humans. The clinical perspective by Goldberg (12) introduces this section by reiterating the immense public health burden of neurological and psychiatric diseases. Goldberg goes on to summarize the challenges in combatting Parkinson's disease, amyotrophic lateral sclerosis ("Lou Gehrig's disease"), spinal cord injury, peripheral neuropathy, and stroke, and he points out that progress in understanding each of these disorders depends on fundamental research on monkeys.

The article by Vitek and Johnson (13) summarizes the success in reducing the tremor in many Parkinson's patients by using stimulation of specific sites deep within the brain. They trace the course of basic research on monkeys that identified the brain circuits underlying limb movement, and identified the brain location where stimulation should reduce tremor, and did. The next two articles by Kennedy and Schwartz (14) and by Andersen, Aflalo, and Kellis (15) provide dramatic examples, showing how understanding the organization of the monkey brain's control of limb movements led to the development of prosthetic devices that enable paralyzed human patients to control artificial arms with activity from their own brains. This is possible because of the similarity of the functional anatomy of the parts of monkey and human brain that control of limb movement; these structures are strikingly different in rodents. In the tests of the prosthesis, neurons in regions of the cerebral cortex that control limb movements were recorded while the patient imagined the goal of the movement. The patterns of neuronal activity were then fed into a computer that used the information—derived from monkeys—to translate human neuronal responses into instructions to move a mechanical arm. In the tests by Kennedy and Schwartz (14) the recorded neurons were in the primary motor region of the cortex, and in the tests by Andersen et al. (15) the brain signals were derived from neurons in other areas that project to the motor cortex. Both articles show that patients who cannot move their own arms can control a mechanical arm to carry out their wishes, to their almost unbelievable joy.

Some patients cannot move, but others cannot see. Picaud et al. (16) consider methods by which sensory information can be translated into neuronal activity to produce visual sensations where normal signals have been disrupted by degenerative diseases of the retina. These diseases are major causes of irreversible blindness in humans. This blindness is especially devastating when it invades the central retina, the macula, because this disrupts the vision of fine detail, needed for many everyday tasks, including reading. Primates are the only mammals that have a macula, so research in the monkey is essential for developing therapies for human degenerative retinal diseases that affect the macula. Picaud et al. also show that monkeys, but not mice,

possess a complement of retinal neurons with human-like molecular specificity, required to engineer cell-type–specific molecular solutions to recreate light sensitivity in diseased retinas.

Disorders of Mood

Mood disorders include all types of depression that disrupt life's activities. Studying humans with depression has provided insight into the widespread changes in brain activity associated with the condition, but we are still a long way from providing effective treatments. Separating out cause from compensation with respect to the brain changes observed, understanding what underlies the widespread variation in the symptoms of depression, and why individuals are responsive to some treatments but not others or are unresponsive to all available treatments, are some of the core questions that need to be addressed. The articles in this section expand our knowledge of some of the core brain areas involved.

The human prefrontal cortex is implicated in depression as it is in nearly every psychiatric disorder. The prefrontal cortex exhibits an enormous expansion and becomes highly differentiated in humans. Nonhuman primates, including the well-studied macaque and the more recently introduced marmoset, also have a well-developed frontal lobe with similar structure to that found in humans. In contrast, rodents are entirely missing some areas in their much smaller, less differentiated frontal cortex. The clinical perspective by Rudebeck et al. (17) review the attempt to locate regions in the human brain where deep brain stimulation might reduce depression, using what is known from the monkey brain as a guide. Roberts and Clarke (18) focus on one particular brain region implicated in depression, the ventromedial prefrontal cortex. They dissect its contribution to the specific symptoms of anxiety and anhedonia, and its sensitivity to antidepressants in marmosets, providing a critical bridge between studies in rodents and humans. Bernardi and Salzman (19) provide insight into the interactions between cognition and emotion which, when dysregulated, underlie common psychiatric disorders. Using multisite recordings of neuronal activity in macaques, the authors investigate these interactions within the amygdala and frontal cortex. Hikosaka et al. (20) have studied multiple relevant neuronal circuits in another subcortical area, the basal ganglia. They show how different circuits control different behaviors, many of which are related to psychiatric symptoms in humans. Dum et al. (21) answer the long-standing question of how the primate brain controls brain and body states by finding multisynaptic connections from motor, cognitive, and affective networks in monkey cerebral cortex to the adrenal medulla, the source of the adrenal hormones that prepare us under stress to fight or flee. In contrast, the rat medulla is many more synapses away from cognitive and affective cortical areas, and there is no direct input from motor areas that do not even exist in the rat. The theme that runs through all of these reports reflects the opportunities for understanding and treatment provided by the similarities between humans and monkeys in brain organization and cognitive function.

Preserving Future Treatments for Human Brain Disorders

This sample of advances in research on monkeys clarifies the challenges in developing a basic understanding of human brain disorders, and the likelihood of progress in treating them. Equally clear is that ending advances in understanding of the brain will end progress in treatment of brain disorders. Predicting the future of brain research is a fool's errand, but there is little reason to believe that techniques will be devised that will make animal models unnecessary. In some cases, including those we have highlighted here, monkeys will be the best and often the only suitable model. Continuing research with monkeys does not guarantee that cures will result, but when it is our best approach, it must continue. Monkey research will lead to further understanding of brain function, will enable the development of treatments for debilitating human disorders, and will relieve the suffering of countless patients for whom treatments will not otherwise be developed.

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