PERSPECTIVE

COLLOQUIUM PAPER

The neurology clinic needs monkey research

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This report discusses how a number of currently incurable diseases might be treated by advances developed as the result of current ongoing research on monkeys. The diseases discussed include Parkinson's disease, amyotrophic lateral sclerosis, spinal cord injury, peripheral neuropathy, and stroke. Finally, the report discusses the devastating effect the animal rights movement and adverse publicity can have on basic neurobiological research on monkeys.

neurological diseases | monkey research | needed therapies

Neurological and psychiatric diseases present an immense public health burden in the United States and throughout the world. One estimate is that they comprise 19% of all disability-adjusted life years (1). In neurology, although our diagnostic capacity has grown significantly in the past 50 y, therapeutic strategies lag far beyond diagnosis and are still limited to very narrow niches, such as the first 4.5 h after a stroke begins (2). Medical diseases, like heart or kidney failure, have a number of treatment modalities, like drugs, surgery, or, when all else fails, transplant. Unfortunately, the brain or even the spinal cord cannot be transplanted. In this review, I will describe a number of neurological diseases and discuss how basic research on nonhuman primates could help develop useful therapeutic approaches.

Parkinson's Disease

Parkinson's disease, a neurodegenerative disease that attacks an area of the brain known as the basal ganglia, is perhaps the most successful therapeutic triumph arising from research on monkeys. It is a disease characterized by motor tremor, slowness, and rigidity, and is typified by the degeneration of a particular class of neurons that contain dopamine and project from the substantia nigra pars compacta to the caudate nucleus, two structures within the basal ganglia. As reviewed by Jerrold Vitek in his chapter, the current state-of-the-art treatment is electrical stimulation of the subthalamic nucleus. This approach was developed as the result of years of basic neurophysiological research by Mahlon DeLong and his colleagues, who sought to understand the role of the basal ganglia in the generation of normal movement. DeLong began by studying the normal physiology of the basal ganglia, including the substantia nigra (3), the globus pallidus, and subthalamic nuclei (4).

In 1976, a chemistry graduate, trying to synthesize desmethylprodine (MPPP), an opioid, injected himself with his product and suddenly developed a parkinsonian syndrome. His MPPP had been contaminated with *N*-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which the Kopin laboratory at the National Institute of Mental Health showed caused a similar parkinsonian syndrome in rhesus monkeys (5). Delong's group (6) studied the activity of the subthalamic nucleus in rhesus monkeys who had been treated with MPTP, showing that subthalamic neurons were hyperactive in the MPTP monkeys. They then discovered that stimulation of the subthalamic nucleus ameliorated the symptoms of MPTP-induced parkinsonism in the monkeys (6). Although there are a number of successful drug

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therapies for Parkinson's disease, such as L-DOPA, which work by augmenting the activity of dopamine in the basal ganglia, deep brain stimulation of the subthalamic nucleus is the best treatment modality when drugs fail (7).

However, there are nonmotor symptoms of Parkinson's disease as well. Patients with Parkinson's disease develop apathy, sleep disorders, impulse control disorders, and ultimately dementia. These symptoms do not respond to current treatment modalities for Parkinson's disease but are equally devastating. Patients with Parkinson's disease often have degeneration of cells in the frontal cortex, and it is not known whether the nonmotor symptoms arise from frontal degeneration, from degeneration of nonnigral dopamine neurons [for example, neurons in the ventral tegmental area, which also degenerate in MPTP monkeys (8)], or from dysfunction of the projection of the substantia nigra pars compacta to the nonmotor regions of the caudate nucleus. Studies on parkinsonian and normal monkeys may well provide a key to these disorders and enable successful therapies. More importantly, the current therapies for Parkinson's disease are network therapies: Rather than attacking the cause of the disease, they help the damaged network perform better. The real cure for Parkinson's disease will arrive after we understand why the dopaminergic cells in the substantia nigra pars compacta that project to the caudate nucleus degenerate. Monkey models of Parkinson's disease that have the same mechanism for cell degeneration as human Parkinson's disease will have to be used to screen candidate treatments.

Amyotrophic Lateral Sclerosis (or "Lou Gehrig's Disease")

Amyotrophic lateral sclerosis (ALS) is a disease that destroys spinal motor neurons, the neurons in the spinal cord that directly control the action of muscles, and the cortical neurons that directly control the spinal motor neurons (9). It is called Lou Gehrig's disease because it killed the famous Columbia University and New York Yankee baseball player at the age of 38. ALS begins insidiously, as the patients begin to notice slight weakness of their arms or legs, or slight difficulty with swallowing. As the disease progresses, they become weaker and weaker, until they can no longer breathe. Lou Gehrig died 2 y after he first noticed that he was becoming weak.

There is currently no known mechanism for the neuronal degeneration in the disease. There are a number of genetic causes of ALS, which make up a total of 5–10% of the cases, the most common of which are a hexanucleotide repeat in gene C90RF72, and mutations in the enzyme superoxide dismutase (SOD1). However, most ALS patients have normal SOD1 levels.

This incurable disease presents a terrible ethical problem. Patients with ALS die of respiratory distress or starvation. They cannot breathe, and they cannot cough or swallow effectively, so food can travel from their mouth into their trachea, leading to repetitive bouts of pneumonia. Respiratory distress can be treated with a tracheotomy (trach) to protect their airways and enable artificial respiration. The nutritional problems associated with poor swallowing can be treated with percutaneous endoscopic gastrostomy (PEG), a feeding tube through which nutrients can be instilled into their intestinal system. Many patients reject this option, preferring to die, like my last ALS patient, who died while I was supervising the Columbia University Medical Center neurology ward service. He chose to die rather than live with a trach and a PEG.

Others choose to continue living, entirely dependent upon a trach and a PEG. Dr. Wayne Wickelgren, a famous mathematical psychologist, developed ALS. He chose to live in his living room, on a respirator, with a trach and a PEG. For much of that time, he was able to communicate with lip and eye movements. His wife and children could understand him. When New York City had a blackout that lasted for a day, Wayne's backup batteries lasted until the lights came back on. He lived for 5 y with a trach and a PEG, but ultimately, the process of ALS invades much more of the brain than the motor system, and he died. He and his daughter Ingrid wrote a book together while Wayne was on the respirator, *Math Coach*, a guide to teaching your children math. It is still in print and available from Amazon.

Monkey research can help patients with ALS in a number of ways. A prosthetic arm can help a patient do some of the activities of daily living, like typing on a keyboard and, for patients who do not need the PEG, feed themselves. The chapters by Richard Andersen and Andrew Schwartz describe how several laboratories have developed prosthetic arms and even hands that quadriplegic humans can control with their own brain activity, recorded by multielectrode arrays implanted in their brains. The dramatic success of brain–machine interfaces came about because of work on the activity of neurons in the cerebral cortex of rhesus monkeys, which began with the pioneering work of Edward Evarts (10), who developed the techniques for studying the activity of neurons in the brain of awake, behaving monkeys. He then studied the activity of neurons in the motor cortex of monkeys who were performing conditioned voluntary movements (11). After years of research on the neurophysiology of the normal cerebral cortex of awake, behaving monkeys by many laboratories (12–16), it became possible to develop brain–machine interfaces. In order to show that a human prosthesis was possible, it was necessary to show that a monkey could control a cursor on a screen (17, 18) and ultimately a robotic arm with thought alone, monitored by multiple electrodes implanted in its brain (18–20). The monkeys could control the robots with thought alone, without actually making movements. Research on the basic science of movement control in monkeys has enabled the idea of a prosthetic arm to move from a dream to an engineering problem.

Although most ALS patients are cognitively normal, they can communicate only with great difficulty. A first step has been to use the knowledge accumulated from monkey neurophysiology to allow paralyzed humans to communicate by typing through a brain–machine interface (21). Recently, Nima Mesgarani and coworkers (22) have shown that it is possible to decode activity from the brain of human patients speaking numbers with electrodes implanted prior to epilepsy surgery and to train a speech synthesizer to say those numbers. The recording techniques were developed by scientists doing basic brain research on monkeys. Because monkeys have a number of language-like calls which they make and to which they respond (a call for hawk to which they respond by getting out of the trees; a call for ocilla, a small cat to which they respond by climbing higher into the trees), it is possible to use the monkey call as a model for speech decoding, and work out the techniques for building a language prosthesis.

Spinal Cord Injury

Christopher Reeve, Superman in the movies, fell off a horse and destroyed the spinal cord in his neck. After the accident, he had difficulty breathing on his own, or moving his arms and legs, although he could shrug his shoulders. His brain was unharmed, as were his motor neurons and muscles, but the accident destroyed the communication between his brain and the motor neurons that controlled the muscles, and caused his almost total paralysis.

Car crashes, athletic injuries, bicycle accidents, and diseases like abscesses that affect the spinal cord, fill hospital wards with quadriplegics. Spinal cord damage affects not only limb movement and posture, but bladder, bowel, and sexual function.

Just as a robotic arm can be triggered by brain signals for arm movement, a robotic exoskeleton could be triggered by brain signals from the neural network that controls walking (23), or even the patient's own muscles could be controlled (24)—but this system is not as well understood as reaching and grasping, and will require basic research, in monkeys, on the brain mechanisms of walking.

Peripheral Neuropathy

The first step in sensation and the last step in the generation of movement require peripheral nerves to carry signals to and from the spinal cord or brainstem (25, 26). These are the longest single nerve cells in the body, traveling, in the case of certain sensory nerves, from the toe to the brainstem, and in the case of motor nerves from the spinal cord to the muscles in the foot that control toe movements. As such, they are vulnerable to damage and disease processes like infection, diabetes, toxins, and vitamin deficiencies. There are a number of hereditary peripheral neuropathies that can develop at any time from infancy to adulthood. The longer the nerves are, the more vulnerable they are—so peripheral neuropathies often first present as leg weakness or the inability to sense pain, light touch, joint position.

Pain is a particularly important sensory function because of its protective nature. Patients with small unmyelinated fiber peripheral neuropathy, most dramatically, have congenital absence of pain, but also patients with types of diabetic, toxic, and infectious neuropathies (for example, leprosy) cannot feel pain, so injure themselves by not being able to activate pain-induced withdrawal circuits. The terrible face, arm, and leg degeneration of patients with leprosy arises because the bacteria destroy the peripheral nerves that sense pain. The patients burn themselves because they cannot feel heat and pain, and do not know to remove their hand from a fire unless they see it or smell the burning flesh. They destroy their joints because they cannot feel when they overextend them. Luckily, leprosy is now curable, but hereditary peripheral neuropathies, like congenital insensitivity to pain (27), are not.

Motor peripheral neuropathies could be assisted by robotic exoskeletons driven by brain signals, just like stroke. Sensory peripheral neuropathies could be helped by sensors that could tell the cerebral cortex or the spinal cord that the external hand temperature is above the temperature at which tissue damage occurs, and stimulate withdrawal circuits. The Andersen group has demonstrated the feasibility of a brain–machine interface for perceptual localization of a tactile stimulus. Brain–machine interfaces for sensation are as possible as brain–machine sensation for movement (28) and will require preliminary work in monkeys in a similar way. For this to be realized, we will need to know much more about the spinal, brainstem, thalamic, and cortical processing of pain. We could only learn this from basic research in monkeys.

Stroke and Plasticity

Stroke results from the occlusion of a cerebral or brainstem artery, either from an arteriosclerotic plaque or an embolus that originated in a clot somewhere else in the body and migrated in the bloodstream to the brain. The deficit from a stroke depends upon the tissue destroyed. The classical left middle cerebral artery stroke affects motor control, sensory perception, and speech, leaving the patient unable to move the right arm or leg, speak, or understand speech.

The best way to treat stroke is to prevent it, by treating hypertension, and diabetes, and lowering blood cholesterol. Once a stroke occurs, it can be treated by dissolving the clot using intravenous tissue plasminogen activator (TPA), but TPA must be given within 4.5 h of the onset the stroke or the hemorrhagic complications of TPA outweigh the therapeutic effect. Another, more invasive therapy is catheter thrombectomy, in which a drill is threaded up through a catheter to the clot, and the clot removed. Thrombectomy can be done up to 24 h after the result. Often TPA and thrombectomy do not work, and the stroke becomes untreatable. A mystery is why do some patients improve in the months after a stroke, and others, with a similar lesion, never get better. To understand this, we need a good monkey stroke model that reproduces this spectrum of recovery. Basic research into neural plasticity and reorganization of networks has the potential ultimately to facilitate stroke recovery. A hint of the nature of the problem is that the limbic system, important in emotion and motivation, rather than the sensorimotor system controlling sensation and movement, may be the key to recovery from stroke.

Does recovery from stroke involve motivation? Sir Charles Sherrington showed that a monkey whose ability to sense its arm was surgically impaired (by an operation called dorsal rhizotomy) did not use the sensation-free arm, even though its motor system was intact. Dr. Edward Taub, at the Institute for Behavioral Research in Silver Spring, Maryland, showed that monkeys with bilateral intrauterine dorsal rhizotomies used both arms reasonably well, even though they could not sense where their limbs were. Monkeys with unilateral dorsal rhizotomies only used the deafferented arm when the arm with an intact sensory system was constrained (29). Constraint therapy, which was developed because of Dr. Taub's basic research, is now a useful rehabilitative tool, forcing patients to use the weakened limb and recover its function (30). Understanding how motivation drives recovery from neurological injury will enable the development of more effective methods for stroke rehabilitation. This too will require monkey research.

Basic Animal Research and the Public, a Cautionary Tale

In 1980, Alex Pacheco volunteered to work in the Taub laboratory. Dr. Taub went on a week's vacation. While Dr. Taub was on vacation, Pacheco let the husbandry in the laboratory become neglected and took inflammatory pictures. Pacheco then reported Dr. Taub for violations of animal cruelty laws based on the monkeys' living conditions. Police raided the laboratory, seized the monkeys, and charged Dr. Taub with 119 counts of animal cruelty and failure to provide adequate veterinary care, the first such charges to be brought in the United States against a research scientist. The NIH stopped his grants. The Institute for Behavioral Research closed down. Ultimately, Dr. Taub was entirely exonerated, but he never restarted his monkey laboratory. He is now a university professor of psychology at the medical school of University of Alabama at Birmingham.

Ironically, Dr. Taub's research led to two important therapeutic advances. The idea of increasing motivation by constraining the good limb has become a useful technique in stroke rehabilitation (31). The technique of fetal surgery has led to the successful treatment of fetal hydrocephalus (32). The threat to

monkey research continues today. Recently, the laboratory of Nikos Logothetis at the Max Planck Institute for Biological Cybernetics in Tübingen, Germany, was invaded by an animal activist who worked undercover in the laboratory, with results as devastating as the Silver Spring episode. The scientific community must bring the battle to preserve basic neuroscience in monkeys to the public, or we will all end up like Dr. Taub—great science, no laboratories.

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1 D. V. Vigo, D. Kestel, K. Pendakur, G. Thornicroft, R. Atun, Disease burden and government spending on mental, neurological, and substance use disorders, and self-harm: Cross-sectional, ecological study of health system response in the Americas. *Lancet Public Health* **4**, e89–e96 (2019).
2 C. Jin *et al.*, Intravenous tPA (tissue-type plasminogen activator) in patients with acute ischemic stroke taking non-vitamin K antagonist oral anticoagulants preceding stroke. *Stroke* **49**, 2237–2240 (2018).
3 M. R. DeLong, M. D. Crutcher, A. P. Georgopoulos, Relations between movement and single cell discharge in the substantia nigra of the behaving monkey. *J. Neurosci.* **3**, 1599–1606 (1983).
4 M. R. DeLong, M. D. Crutcher, A. P. Georgopoulos, Primate globus pallidus and subthalamic nucleus: Functional organization. *J. Neurophysiol.* **53**, 530–543 (1985).
5 R. S. Burns *et al.*, A primate model of parkinsonism: Selective destruction of dopaminergic neurons in the pars compacta of the substantia nigra by *N*-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. *Proc. Natl. Acad. Sci. U.S.A.* **80**, 4546–4550 (1983).
6 H. Bergman, T. Wichmann, B. Karmon, M. R. DeLong, The primate subthalamic nucleus. II. Neuronal activity in the MPTP model of parkinsonism. *J. Neurophysiol.* **72**, 507–520 (1994).
7 M. C. Rodriguez-Oroz *et al.*, The subthalamic nucleus in Parkinson's disease: Somatotopic organization and physiological characteristics. *Brain* **124**, 1777–1790 (2001).
8 C. A. Brown *et al.*, Dopamine pathway loss in nucleus accumbens and ventral tegmental area predicts apathetic behavior in MPTP-lesioned monkeys. *Exp. Neurol.* **236**, 190–197 (2012).
9 R. Traub, H. Mitsumoto, "Amyotrophic lateral sclerosis and motor neuron diseases" in *Merritt's Textbook of Neurology*, E. D. Louis, S. A. Mayer, L. P. Rowland, Eds. (Wolters Kluwer, Phildelphia, ed. 13, 2016), pp. 731–739.
10 E. V. Evarts, "Methods for recording activity of individual neurons in moving animals" in *Methods in Medical Research*, R. F. Rushmer, Ed. (Year Book, Chicago, 1966), pp. 241–250.
11 E. V. Evarts, Relation of pyramidal tract activity to force exerted during voluntary movement. *J. Neurophysiol.* **31**, 14–27 (1968).
12 A. P. Georgopoulos, J. F. Kalaska, R. Caminiti, J. T. Massey, On the relations between the direction of two-dimensional arm movements and cell discharge in primate motor cortex. *J. Neurosci.* **2**, 1527–1537 (1982).
13 A. P. Georgopoulos, R. E. Kettner, A. B. Schwartz, Primate motor cortex and free arm movements to visual targets in three-dimensional space. II. Coding of the direction of movement by a neuronal population. *J. Neurosci.* **8**, 2928–2937 (1988).
14 A. B. Schwartz, Direct cortical representation of drawing. *Science* **265**, 540–542 (1994).
15 L. Paninski, S. Shoham, M. R. Fellows, N. G. Hatsopoulos, J. P. Donoghue, Superlinear population encoding of dynamic hand trajectory in primary motor cortex. *J. Neurosci.* **24**, 8551–8561 (2004).
16 J. C. Kao *et al.*, Single-trial dynamics of motor cortex and their applications to brain-machine interfaces. *Nat. Commun.* **6**, 7759 (2015).
17 M. D. Serruya, N. G. Hatsopoulos, L. Paninski, M. R. Fellows, J. P. Donoghue, Instant neural control of a movement signal. *Nature* **416**, 141–142 (2002).
18 D. M. Taylor, S. I. H. Tillery, A. B. Schwartz, Direct cortical control of 3D neuroprosthetic devices. *Science* **296**, 1829–1832 (2002).
19 J. E. O'Doherty *et al.*, Active tactile exploration using a brain-machine-brain interface. *Nature* **479**, 228–231 (2011).
20 M. A. Lebedev, M. A. Nicolelis, Brain-machine interfaces: Past, present and future. *Trends Neurosci.* **29**, 536–546 (2006).
21 C. Pandarinath *et al.*, High performance communication by people with paralysis using an intracortical brain-computer interface. *Elife* **6**, e18554 (2017).
22 H. Akbari, B. Khalighinejad, J. L. Herrero, A. D. Mehta, N. Mesgarani, Towards reconstructing intelligible speech from the human auditory cortex. *Sci. Rep.* **9**, 874 (2019).
23 T. Vouga *et al.*, EXiO-A brain-controlled lower limb exoskeleton for rhesus macaques. *IEEE Trans. Neural Syst. Rehabil. Eng.* **25**, 131–141 (2017).
24 C. T. Moritz, S. I. Perlmutter, E. E. Fetz, Direct control of paralysed muscles by cortical neurons. *Nature* **456**, 639–642 (2008).
25 C. Pisciotta, M. E. Shy, "Inherited peripheral neuropathies" in *Merritt's Textbook of Neurology*, E. D. Louis, S. A. Mayer, L. P. Rowland, Eds. (Wolters Kluwer, Philadelphia, 2016), pp. 775–784.
26 T. H. Brannagan, , III, K. Tanji, "Acquired peripheral neuropathies" in *Merritt's Textbook of Neurology*, E. D. Louis, S. A. Mayer, L. P. Rowland, Eds. (Wolters Kluwer, Phildelphia, 2016), pp. 750–774.
27 D. P. Ashwin *et al.*, Hereditary sensory and autosomal peripheral neuropathy-type IV: Case series and review of literature. *Oral Maxillofac. Surg.* **19**, 117–123 (2015).
28 B. Lee *et al.*, Engineering artificial somatosensation through cortical stimulation in humans. *Front. Syst. Neurosci.* **12**, 24 (2018).
29 H. D. Knapp, E. Taub, A. J. Berman, Movements in monkeys with deafferented forelimbs. *Exp. Neurol.* **7**, 305–315 (1963).
30 S. L. Wolf *et al.*; EXCITE Investigators, Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: The EXCITE randomized clinical trial. *JAMA* **296**, 2095–2104 (2006).
31 G. Uswatte *et al.*, Rehabilitation of stroke patients with plegic hands: Randomized controlled trial of expanded constraint-induced movement therapy. *Restor. Neurol. Neurosci.* **36**, 225–244 (2018).
32 S. Cavalheiro, A. F. Moron, S. T. Zymberg, P. Dastoli, Fetal hydrocephalus—prenatal treatment. *Child's Nerv. Syst.* **19**, 561–573 (2003).