Neural Circuits Catch Fire

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Circuits comprise the functional architecture of the nervous system, and to identify neural circuits is to uncover its wiring diagram. Progress toward this goal has accelerated in recent years, largely owing to technical advances in imaging, physiology, and circuit modeling. Unraveling brain circuitry has become a goal not just of neuroscience, but also of society at large. In the USA, the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative seeks to use new technologies to understand “how individual cells and complex neural circuits interact in both time and space” [1]. Similar programs in Europe (Human Brain Project) and Japan (Brain/MINDS) attempt to bring us closer to understanding the structure and function of the nervous system. The goal of this issue of *Neurotherapeutics* is to demonstrate how neural circuits can be manipulated for therapy of nervous system disease or injury. The ultimate goal is to use new

understanding about circuits derived from these large neuroscience initiatives to restore neurological function.

What is a neural circuit? In its simplest form, a neural circuit is a neuron and its connection to another neuron. Normally, this occurs in groups, with a nucleus, or collection of neurons, being connected by axons to another group of neurons; however, alternative kinds of connections (e.g., gap junctions) and even cell types (e.g., astrocytes) can participate in neural circuits. What defines the therapies discussed in this issue is that they are directed toward this functional unit. In some cases therapies are directed at connections that are perturbed by injury or disease. Others target intact neural connections in order to subsume the lost function of a damaged circuit. Implicit in this approach is the idea that individual circuits function together to create a network that can be manipulated to adapt to injury or disease. When one or more nodes of the network are perturbed, functions can shift within the network.

How might one target a neural circuit? We have divided this issue into 4 general strategies. The first section describes applications of electrical stimulation. Stimulation uses a fundamental characteristic of neural circuits, their dependence on electrical signals, to manipulate them. This is a strategy currently in clinical practice; electrical stimulation has already produced large-scale benefits to people with Parkinson’s disease and other movement disorders, as well as other neurological and psychiatric diseases. A second strategy in development is the use of genetic tools to modify circuits. By inserting a gene that can increase or decrease the excitability of neurons, the function of a circuit can be augmented or depressed. Third, promoting axon

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growth can strengthen circuits. As loss of circuit function is often due to injury of the axons that connect them, either regenerating lost axons or promoting sprouting of intact axons can help restore circuit function. Each of these first 3 approaches directs a manipulation specifically at a circuit by placing an electrode, a virus, or a growth factor at or near the circuit. In contrast, the fourth approach raises overall plasticity in the brain, and generates circuit specificity by engaging circuits that underlie certain trained tasks.

Section 1 focuses on electrical stimulation to manipulate circuit function up or down. Neural activity is crucial for the proper formation of neural circuits during development, and repetitive use of circuits is the basis of experiential learning. Whether electrical stimulation can cause similar changes in circuit function as endogenous activity is a crucial question for the field of “electroceuticals”, application of electrical stimulation as therapy. Electrical stimulation can also be used to inhibit function of deranged circuits. This approach is best exemplified by the first article in this section by Drs. Thomas Wichmann and Mahlon DeLong [2], which details how the fundamental understanding of neural circuits can be used to target a single node of the basal ganglia circuits with a “jamming frequency” in order to restore function. In the second paper, Dr. Minassian and colleagues [3] discuss how understanding of spinal circuits responsible for motor control has been used to apply spinal cord stimulation as therapy to restore walking and other motor functions. This section concludes with a paper by Dr. Tessa Gordon [4], who highlights the ease of targeting the peripheral nervous system, making it well-suited to a circuit-specific approach. Thus, the discussion of electrical stimulation progresses from the brain to more centripetal locations of the nervous system. Importantly, the efficacy of deep brain stimulation for movement disorders underscores the idea that clinical success has been largely driven by our understanding of the circuits, and not just by the accessibility of the circuit being targeted.

While electrical stimulation has a long-standing history of research and clinical success, new genetic tools to manipulate circuit excitability are gaining momentum. These tools are particularly exciting as they offer the potential for unprecedented specificity in their targeting. Section 2 begins with a chapter by Drs. HongGeun Park and Jason Carmel [5], which discusses how precision of circuit manipulation can be achieved by genetic tools, based on the circuit location and/or its genetic identity. The second paper in this section, from Drs. Michelle

Cheng, Markus Aswendt, and Gary Steinberg [6], discusses the innovative use of optogenetic tools to map and promote recovery of function following stroke. An attractive early target for these new tools is the retina, which possesses the advantages of accessibility and immune privilege. In the final chapter in this section, Dr. Botir Sagdullaev and colleagues [7] show how optogenetic-based approaches can be used to restore light sensitivity after the loss of photoreceptors, demonstrating how close to clinical application these new tools have come.

As a circuit is largely defined by its axon connections, manipulation of axons is a critical strategy for restoring circuit function. Section 3 of this issue focuses on therapies that promote growth and functional connections of axons. In the first paper, Dr. S. Thomas Carmichael [8] discusses the derangement of neural circuits caused by stroke. This understanding is then used first to identify factors that promote spontaneous axon sprouting and then to apply these factors exogenously to repair neural circuits and restore function. Neural development, the formation of neural circuits, offers a key paradigm for reformation of neural circuits after injury or disease. In the second paper, Dr. Edmund Hollis [9] discusses how our understanding of the specific molecular cues that guide axons during development can be used to enhance repair or remodeling of circuits in the injured spinal cord. In the last paper in this section, Drs. Kathren Fink and William Cafferty [10] discuss the inherent plasticity of neuronal connections to reorganize after injury and restore motor control connections from the brain to the spinal cord. As spontaneous recovery of function outstrips any current therapeutic intervention, enhancing plasticity of intact circuits after injury offers an attractive target for therapy.

The therapeutic strategies discussed in the first three sections achieve circuit specificity by directly manipulating circuits. Section 4 presents an alternative approach—create a heightened state of plasticity generally and then use task-specific training to target select circuits. In the first paper in this section, Dr. Seth Hays [11] discusses combining vagus nerve stimulation, which alters cortical plasticity, with task-specific rehabilitation of motor skill for recovery of movement or auditory experience to treat tinnitus. Finally, this issue ends with a discussion by Dr. Dale Corbett and colleagues [12] on how environmental enrichment and exercise enhance many of the changes associated with spontaneous recovery. These articles detail how these

interventions change the efficacy of activity-dependent plasticity within the trained circuits.

What might the future of circuit specific therapy look like? For diseases that produce stereotypical patterns of circuit derangement, such as Parkinson's, a very standard approach could be used for each patient, similar to current application of deep brain stimulation; however, rather than using loss-of-function electrical stimulation, therapies are likely to try to replace lost nigrostriatal function. This could be achieved in many different ways: electrical stimulation of remaining axons of the nigrostriatal bundle, activation of striatal targets with optogenetics, or systemic delivery of a drug that controls dopamine output of engineered endogenous cells or grafted cells. The application of these technologies will be safer and offer many advantages over current techniques: electrodes might be no thicker than a hair, light to stimulate optogenetics may be delivered on the skull using long-wavelength light that can penetrate the brain, and cells may be engineered with tight control over their function and survival.

The circuit-specific approach allows a much greater degree of personalized medicine. Diseases or injuries that produce diverse lesions, such as stroke, leave a particular set of spared circuits that is unique to each patient. The end goal of regenerative medicine would be to replace the lost circuits. But a more practical medium-term goal would be to coax spared neural circuits to subsume the lost function of damaged ones. Here, the changes that occur normally in response to injury could be instructive, as endogenous plasticity can often restore large amounts of function. Therapy directed at the substitute circuits, whether electrical stimulation, genetic manipulations, or growth factors, could further improve recovery. Finally, these targeted therapies would likely be performed under a state of heightened general plasticity. This would allow the targeted therapies and the rehabilitation that would accompany them to have the greatest effect. Rehabilitation is necessary to ensure that new or strengthened circuits are incorporated into the functions that the patient wants to recover most.

The nervous system offers a unique way of achieving precision medicine by targeting of specific circuits, the fundamental unit of nervous system function. Like molecular precision medicine, this approach promises improved efficacy and fewer off-target effects than most current neurotherapeutics. Similarly, our understanding of the therapeutic targets will drive subsequent improvements in the therapy. Indeed, the explosion of information about how neural circuits develop and how they control behavior in maturity directly informs the proper application of therapy directed at circuits. The new technologies being developed by the Brain Research through Advancing Innovative Neurotechnologies Initiative and other large-scale efforts promise to provide tools for circuit manipulation that are more precise and safer than those currently in use. Thus, we are entering an era of unprecedented discovery both about neural circuits and

about how to target them for the benefit of people who suffer from neurological impairments.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

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