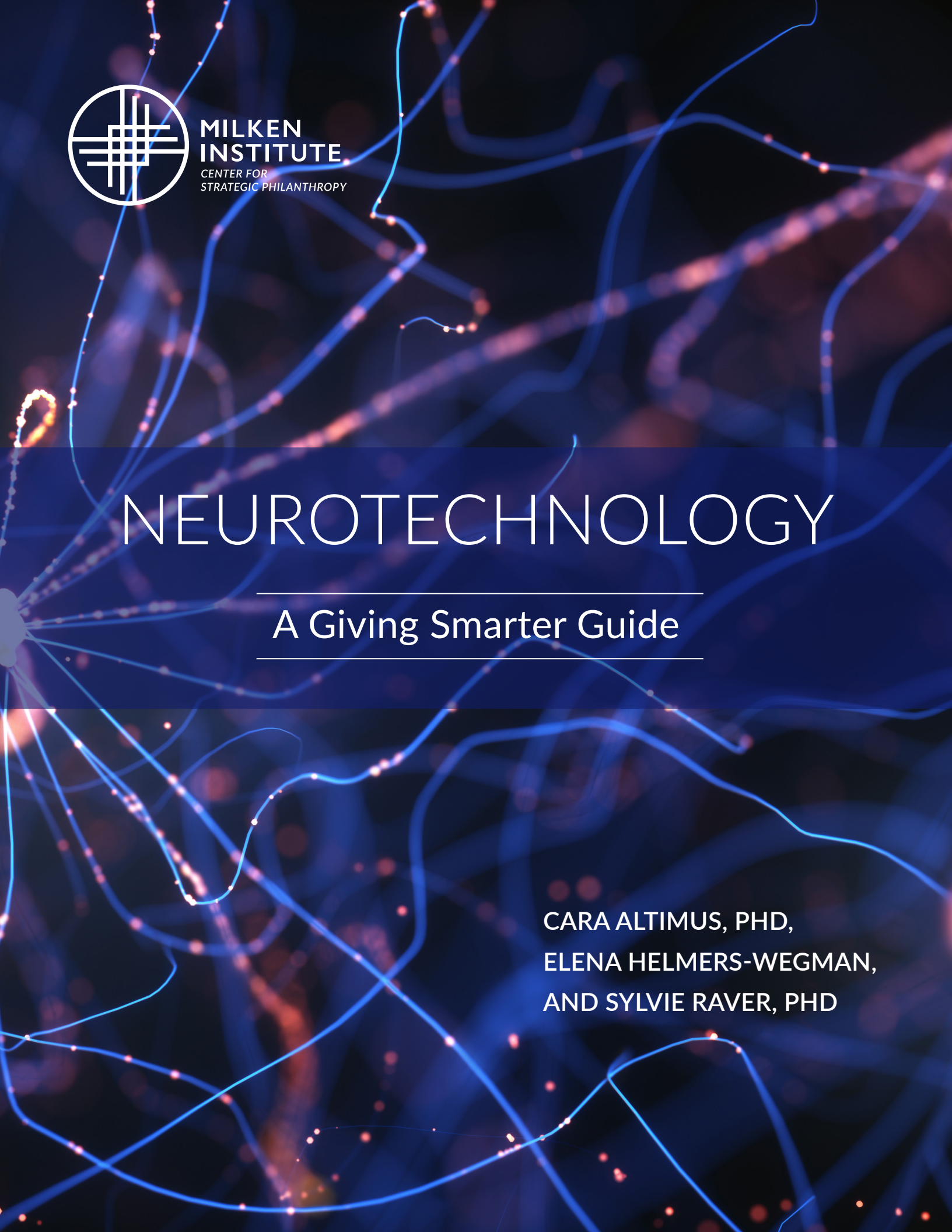

NEUROTECHNOLOGY

A Giving Smarter Guide

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ABOUT US

About the Milken Institute

The Milken Institute is a nonprofit, nonpartisan think tank.

For the past three decades, the Milken Institute has served as a catalyst for practical, scalable solutions to global challenges by connecting human, financial, and educational resources to those who need them. Guided by a conviction that the best ideas, under-resourced, cannot succeed, we conduct research and analysis and convene top experts, innovators, and influencers from different backgrounds and competing viewpoints. We leverage this expertise and insight to construct programs and policy initiatives.

These activities are designed to help people build meaningful lives in which they can experience health and well-being, pursue effective education and gainful employment, and access the resources required to create ever-expanding opportunities for themselves and their broader communities.

About the Center for Strategic Philanthropy

The Milken Institute Center for Strategic Philanthropy advises philanthropists and foundations seeking to develop and implement transformative giving strategies.

FOREWORD

There has never been a more exciting time for science and technology to enhance quality of life and longevity for humans across the globe. Yet critical gaps and roadblocks stand in the way of our fully realizing the potential of 21st-century neurotechnology innovations. It is at the troughs and barriers of realizing viable new technologies where philanthropy can serve a pivotal role.

Strong federal, state, and foreign government investment through the Brain Research Through Advancing Innovative Neurotechnologies initiative, Defense Advanced Research Projects Agency, and elsewhere has significantly grown the foundational, basic research on neurotechnology. But holes in the science funding pipeline—most notably in the so-called funding Valley of Death—are limiting our ability to leverage these new advancements. The Valley of Death can delay and even prevent neurotech breakthroughs from reaching patient care settings.

Health and science philanthropy can fill specific voids through funding translational research by making targeted investments that help catapult laboratory progress into new medical tools and treatments. It is this chasm between federal basic research and corporate product development—first-in-human trials, for example, or in assembling and sustaining the interdisciplinary teams needed—where philanthropy can have the greatest impact. Other sectors lack the incentive systems, risk tolerance, and charitable mission to fill this gap the way philanthropy can.

Philanthropists and philanthropic organizations like BrightFocus Foundation are well-equipped to help lead and drive a new, expanded role for philanthropy in neurotech. We are pleased to have partnered with the Milken Institute for this Giving Smarter Guide. This guide is a starting point for philanthropic investment—and through it, we hope that by collaborating with philanthropists, new and effective neurotech tools will become available to patients. It is our vision that funders across the research ecosystem can pave the way for bold technological and scientific ideas to become medical realities. Science, particularly neurotech, holds great power and promise to transform aging from something feared to something filled with joy and potential.

Stacy Pagos Haller
President and CEO
BrightFocus Foundation
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EXECUTIVE SUMMARY

When most people think about advances in medicine, drug development is the first thing that comes to mind. However, technology and devices are proving to be valuable options for treating intractable illnesses. Technological solutions in the field of neurology are exploding because they hold the potential to specifically target the biology of illness in ways that drugs cannot.

Neurotechnology is broadly understood as any technology designed to improve and repair nervous system function, as well as to enable researchers and clinicians to visualize the brain. Examples of neurotech in popular culture include Elon Musk's announcement of a brain-machine interface and the brain scanner that Stephen Hawking used to speak, but dozens of other devices are in use today. Neurotech devices help with pain relief, provide physicians with insight into brain function, and stimulate the brain to treat Parkinson's disease.

Although this rapidly changing technology class offers enormous promise for people living with a broad range of diseases, navigating investments in neurotechnology is complex. Success depends on biology, engineering, device regulation, and macro trends in the device market. This report breaks down the landscape and explores potential applications, opportunities, and barriers to help guide philanthropy's pivotal role in moving the field forward.

State of the Field

Advancing the understanding of how the brain drives thought, emotion, and action, coupled with leaps in engineering and computation, could greatly impact people suffering from neurological diseases. However, scientists and device developers have struggled to navigate funding, pass regulatory reviews, or establish a sustainable marketplace for neural devices. Without strategic and sustained momentum focused on moving ideas into the marketplace, these factors will continue to hold back technology applications to neural-based illnesses.

Public funders' substantial investments in neuroscience and neuro-engineering have focused on the early research phases, leaving many ideas and potential technologies underdeveloped and inaccessible to patients. Philanthropic investors can take a targeted approach to realize the potential of neurotechnology. In this Giving Smarter Guide, the Center for Strategic Philanthropy (CSP) explores the landscape of neurotechnology to better understand the definition, application, development, and funding models underlying the concept of neurotechnology. Through this analysis, CSP has identified six opportunities where philanthropic investment can be the lever that changes the lives of people living with neural-based illnesses.

Opportunity 1: Develop the understanding of neural circuits that underlie diseases of the brain
Opportunity 2: Support early-stage human trials
Opportunity 3: Support the development of noninvasive and less invasive technologies
Opportunity 4: Facilitate the inclusion of industry and business experts in translational programs
Opportunity 5: Fund an open-science platform to broaden the scope of clinical trials
Opportunity 6: Foster scientific and entrepreneurial collaboration

THE NERVOUS SYSTEM: AN OVERVIEW

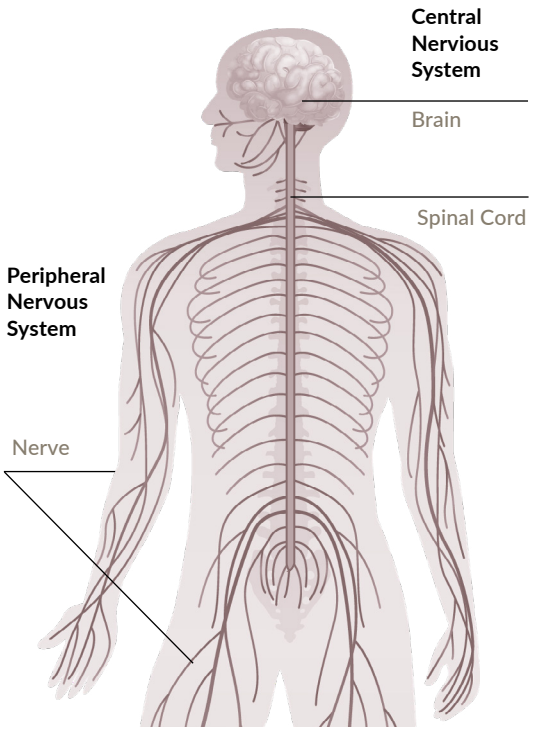
Philanthropists who wish to impact neurotech should have a basic understanding of the biology of the brain.

From Neurons to Networks

The nervous system consists of many types of cells, but the fundamental functional unit is the nerve cell, or **neuron**. Neurons communicate with each other and other cells through electrical and chemical signals.

Neurons are organized into interconnected functional and anatomical networks, known as **neural circuits**, that process information. In turn, circuits that serve similar roles are grouped into **neural systems** to perform basic functions such as sensation (e.g., vision and hearing) and movement, or complex brain functions such as consciousness and decision-making.

FIGURE 1: BASIC CENTRAL NERVOUS SYSTEM/ PERIPHERAL NERVOUS SYSTEM DIAGRAM



Source: *Adapted from Brain Made Simple (2021)*

Functional Organization of Neural Systems

The nervous system has two main components: the central nervous system (**CNS**) and the peripheral nervous system (**PNS**). The CNS consists of the brain and spinal cord, while the PNS consists of **nerves** that branch out from the brain or spinal cord to contact organs and peripheral tissues. The PNS functions primarily to connect the CNS to the body's limbs and organs and consists of nerves distributed throughout the body.

The brain is divided into three broad regions that perform specific functions: the hindbrain, the midbrain, and the forebrain.

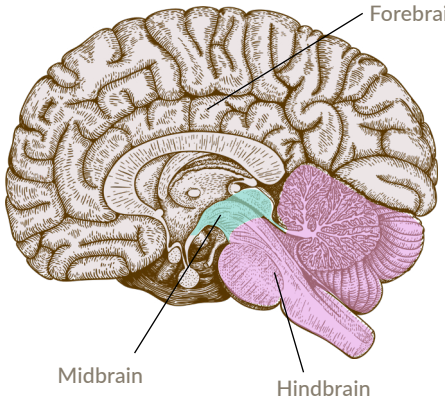
The **hindbrain** includes the upper portion of the spinal cord, most of the brainstem, and the cerebellum and is responsible for vital functions. This region controls digestion, breathing, and heart rate and coordinates facial movements and voluntary body movements such as balance and posture. The **midbrain** lies just above the hindbrain. This region controls visual and auditory reflexes and controls many sensory and motor functions, including eye movements. The **forebrain** is the largest part of the brain. The forebrain consists of the **cerebrum**, which is divided down the midline into two hemispheres (the right and left hemisphere), each of which controls the opposite side of the body.

The forebrain also includes many deeper structures that serve vital and complex functions. Some interior forebrain structures of particular relevance to neurotechnology include the following:

- the **hypothalamus**, which lies deep in the brain and regulates autonomic, endocrine, and visceral functions such as sleep and food intake;
- the **hippocampus**, which is involved in the storage of long-term memories;
- the **amygdala**, which is integral to the perception of emotions in ourselves and others; and,
- the **basal ganglia**, a large cluster of nerve cells that lie deep in the brain and are critical for voluntary control of movement.

The **spinal cord** receives and processes sensory information from throughout the body and controls movements of the limbs and trunk of the body. Damage to any part of the spinal cord can result in loss of sensation and/or function below the site of injury.

FIGURE 2: SIMPLE BRAIN DIAGRAM



Source: *Adapted from Lumen (2021)*

NEURAL-BASED DISEASES

Neural-based diseases and disorders have a devastating impact on individuals and communities, and pose major scientific, medical, and societal challenges. Symptoms of a disease or features of a disorder are referred to as "indications" for a particular therapeutic approach or treatment.

Neurological Disorders: Diseases that affect the CNS and PNS are broadly categorized as neurological disorders. This category includes diseases that affect the brain, spinal cord, peripheral nerves, and bodily tissues that are innervated by nerves.

Mental Disorders: Mental health conditions or mental illnesses are generally characterized by abnormal thoughts, perceptions, emotions, behaviors, and/or relationships with others. These illnesses affect hundreds of millions of individuals across the world (World Health Organization 2021a).

Aging-Related Diseases: Aging has widespread effects on the brain and cognition and can contribute to disease progression as well as aging-related cognitive and memory impairments. Alzheimer's disease is the most common cause of dementia among older adults, although other types of dementias are prevalent (Centers for Disease Control and Prevention 2021).

Blindness and Visual Disorders: More than 2 billion people worldwide are estimated to experience some form of visual impairment or blindness (World Health Organization 2021b). Vision and eye disorders can arise from damage to or degeneration of tissues at multiple levels in the complex and intricate visual system, including the eye, retina, nerves (such as the optic nerve), and brain.

Deafness and Auditory Disorders: Approximately 500 million people around the world experience disabling hearing loss due to congenital (present at birth) or acquired causes. Similar to disorders of the visual system, deafness and communication disorders can result from damage or deterioration at multiple points along the auditory pathway, including the outer, middle, and inner ear structures, auditory nerve, and multiple brain structures.

Neurotechnological devices serve as powerful tools to not only treat such diseases and disorders but also enhance functions, such as memory or attention, in otherwise healthy brains.

GLOSSARY			
DISEASE – underlying etiology is known; highest level of understanding; distinct and measurable	**DISORDER** – cluster of symptoms not accounted for by a more pervasive condition (i.e., unknown etiology); functional abnormality, but not enough clinical evidence for a distinct diagnosis	**CONDITION** – broad term encompassing all diseases, illnesses, disorders, etc.	**INDICATION** – symptom or feature of a disease or disorder

TABLE 1: EXAMPLES OF NEURAL-BASED DISEASES AND DISORDERS

Neurological	Mental	Neurodegenerative	Blindness and Visual	Deafness and Auditory
Epilepsy	Anxiety disorders	Parkinson's disease	Glaucoma	Noise-induced hearing loss
Stroke	Depression	Huntington's disease	Macular degeneration	Tinnitus (ringing in the ears)
Migraine and other headache disorders	Bipolar disorder	Amyotrophic lateral sclerosis	Diabetic retinopathy	Age-related hearing loss
Brain and spinal cord injury due to trauma or infection	Obsessive-compulsive disorder	Alzheimer's disease and other dementias	Retinitis pigmentosa	Auditory neuropathy
Chronic pain conditions	Post-traumatic stress disorder	Lewy body dementia	Cataract	Sudden deafness caused by trauma or infection
Multiple sclerosis	Schizophrenia	Frontotemporal disorders		
Sleep disorders	Suicidal thoughts			

Source: Milken Institute (2021)

NEUROTECHNOLOGY: TECHNICAL OVERVIEW AND EXAMPLES

The term neurotechnology refers to any technology that fundamentally influences how people understand the nervous system and various aspects of consciousness, thought, and higher order activities generated and executed by the nervous system. It also includes technologies designed to improve and repair nervous system function and allow researchers and clinicians to visualize the brain. CSP has grouped neurotechnologies into three broad categories that describe the broad function of the technology:

- **Record:** capture signals from the brain such as electrical activity or blood flow to understand the brain's activity and/or function,
- **Map:** understand how biological components of the brain—including molecules, cells, circuits, and systems—interact with each other, and
- **Influence:** provide electrical, magnetic, chemical, or sensory input to the nervous system to alter function predictably.

Defining Features of Neurotechnologies

An array of devices serving many different functions fall under the all-encompassing neurotechnology umbrella. Consequently, the field tends to divide established and emerging technologies based on three defining features:

- the invasiveness and complexity of a procedure to implant the device,
- the configuration of the device's recording and stimulation systems, and
- the location in the nervous system where the device primarily exerts its effects.

Degrees of Invasiveness

A fundamental, defining feature of neurotechnology is its degree of invasiveness—not only of the device itself but also of the procedure required to implant it successfully.

The degree of invasiveness is critical because it affects medical expenses, the recovery period, the device's permanency and stability once implanted, and the method in which the device engages its biological target. The research and clinical community broadly defines invasiveness in three categories:

Invasive: Invasive devices make direct contact with the brain or nervous system tissues (Cervera et al. 2018). Examples include a deep brain stimulator to treat symptoms of Parkinson's disease or a brain-computer interface to control a prosthetic arm. Invasive devices are surgically implanted under the skin or into neural tissue. The depth of the implant varies, but these devices are most often implanted in the brain and spinal cord. A device's proximity to its target tissue enables fine-tuned delivery of stimulation or recording, thereby increasing its efficacy. Invasive devices have experienced the most headway in the neurotechnology field—mostly because of their improved efficacy compared to other types of devices.

Because invasive devices are, by definition, inside the body, they can pose relatively high risks over the short-, medium-, and long-term. These risks include tissue inflammation, infection, and deterioration of device components. In addition, implanting a device such as a deep brain stimulator requires a complex surgery under anesthesia and is therefore available only within specialty clinical settings, which sharply limits patient access. Because of these features, invasive devices tend to be the most expensive neurotechnologies for patients to access. These devices are also relatively permanent because removal requires additional surgery and follow-up, which can lead to further complications.

Minimally Invasive: Because of the risks and barriers associated with invasive devices, neurotech developers seek less invasive methods to manipulate neural tissue. Minimally invasive devices still require some type of surgical procedure for device implantation or integration, but these surgeries are less involved. For instance, while an electrode array implanted directly into the cortex would be labeled as invasive, the use of flexible electrodes that can access the cortex through blood vessels to the brain would be labeled as minimally invasive (Jeong et al. 2021).

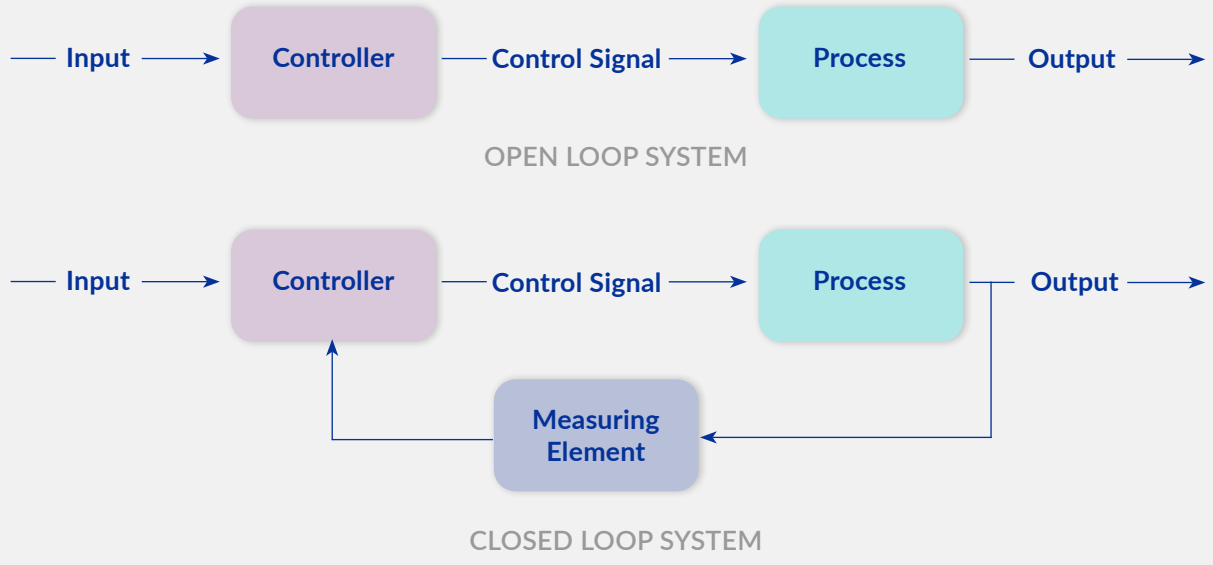
Structural design and materials can also determine the degree of invasiveness. Technology that integrates with the nervous system without mechanical disruption to tissues is deemed to be minimally invasive (US Department of Health and Human Services et al. 2015). Therefore, biocompatibility, or the ability of the body to adapt to a device, plays a role in this designation as well. Overall, minimally invasive approaches are intended to decrease the surgical burden while enabling chronic implantation. Dramatic innovation is expected for this emerging space.

Noninvasive: Noninvasive devices work by sending impulses or recording activity through the skin (Cervera et al. 2018). Noninvasive devices are generally believed to pose the lowest risk because surgical procedures are usually not needed. An example of noninvasive technology is transcranial magnetic stimulation (TMS), in which magnetic stimulating impulses are delivered to certain areas of the brain through a device applied to the head (Rosen et al. 2009). Recent developments in noninvasive techniques have improved accuracy in the clinical setting, leading to consideration of noninvasive brain stimulation as a therapeutic option (Belda-Lois et al. 2011). These types of devices constitute the low-risk category but are currently underdeveloped compared to other approaches.

Stimulation Systems

A second defining feature of neurotechnology relates to how the device stimulates the brain and records information. Stimulation and recording processes may operate independently of each other, as in an open loop configuration, or may be integrated and influence each other, as in a closed loop configuration. Multiple factors determine the system parameters, including our understanding of the underlying disease biology and pathophysiology, and engineering and technical computing

FIGURE 3: OPEN LOOP AND CLOSED LOOP SYSTEMS



Source: Adapted from ResearchGate (2021)

capabilities. In turn, stimulation system configurations inform the efficacy of devices, stimulation side effects, the longevity of device components, the frequency and nature of clinical follow-up, and related medical expenses (Ghasemi, Sahraee, and Mohammadi 2018).

Open Loop Systems: In this configuration, stimulation parameters such as duration, frequency, and intensity of electrical pulses are pre-programmed and delivered on a scheduled basis (Ghasemi, Sahraee, and Mohammadi 2018). Therefore, open loop devices do not automatically respond to changes in a patient's clinical symptoms, physiology, or the underlying disease. Users of these technologies undergo a repeated process of stimulation, evaluation of symptom progression and disease efficacy, and readjustment of device parameters by a clinician.

This "one-size-fits-all" approach is less adaptable for certain disorders, such as epilepsy and depression, because a time lag occurs between delivery of stimulation and adjustment of stimulation features (Ghasemi, Sahraee, and Mohammadi 2018). However, in movement disorders such as Parkinson's disease, the open-loop systems can be highly effective.

Closed Loop Systems: Although the effectiveness of open loop systems in treating a variety of diseases has been shown, the use of closed loop systems is growing. In a closed loop system, also known as adaptive technologies or "read-write" systems, the device essentially acts as an internal feedback loop to mirror the brain's native neural circuitry. Closed loop systems are dynamic and respond in real time to physiological signals recorded from neural tissues via preset algorithms embedded within the technology. Therefore, stimulation parameters (e.g., duration, frequency, amplitude) adapt in response to physiological signals recorded and analyzed by the device itself (Advisory Committee to the NIH Director BRAIN Initiative Working Group 2.0, n.d.).

To be effective, adaptive devices require an understanding of physiological hallmarks, or biomarkers, of a neural disease or disorder so that the device can detect these hallmarks ("read") and adjust its stimulation parameters in real time ("write") (Hoang et al. 2017). These devices also rely on sophisticated engineering, data processing, and computer algorithms. Closed loop neurotechnologies will require further development and clinical testing to fully realize their benefits, which include improved device efficacy, reduced side effects of stimulation, extended device battery life, and fewer in-person medical assessments.

Location-Based Definitions

A third defining feature of neurotechnology relates to the area of the nervous system in which the device is implanted and/or primarily exerts its function. Devices can affect the CNS, PNS, or both. Examples of devices that interface exclusively with the CNS are deep brain stimulators to treat symptoms of Parkinson's disease or spinal cord stimulation systems to address paralysis (Ghasemi, Sahraee, and Mohammadi 2018; Kawala-Sterniuk et al. 2021).

Examples of PNS-targeted devices include vagus nerve stimulators and nerve cuffs (Cervera et al. 2018; Günter, Delbeke, and Ortiz-Catalan 2019). PNS-targeted devices have shown promise in

treating disorders such as neuropathic pain, which results from damage to the PNS (DosSantos et al. 2016). The vagus nerve is also an increasingly popular target for such devices because it innervates multiple organs and the brain, serves both sensory and motor functions, and is critical for voluntary and involuntary bodily functions (Günter, Delbeke, and Ortiz-Catalan 2019).

Finally, neurotechnology devices may engage with both the CNS and PNS to reconnect damaged or impaired connections between components of the nervous system. Brain-computer interfaces to control neuroprosthetics are examples of these devices because they directly connect a patient's brain and some form of external hardware, such as a prosthetic hand, to complete various functions (Kawala-Sterniuk et al. 2021).

Classifying Current Neural Technologies

The following tables detail the classification of current technologies within the relevant categories and the most common use of those technologies.

TABLE 2: RECORDING AND MAPPING TECHNOLOGIES

Electroence-phalography (EEG)	Magnetoence-phalography (MEG)	Magnetic Resonance Imaging (MRI) Scanning	Positron Emission Technology (PET) Scanning
Noninvasive	**Noninvasive**	**Noninvasive**	**Noninvasive**
CNS	CNS	CNS or PNS	CNS
Electrical Activity	**Electrical Activity**	**Imaging Technique**	**Imaging Technique**
An EEG is a noninvasive recording that reflects the collective electrical activity of neuron populations. EEG signals are recorded by multiple electrodes arranged on the scalp and predominantly reflect the activity of neurons in the cortex. EEGs show activity patterns that correlate with different stages of sleep and wakefulness, as well as activity characteristic of disease states, such as seizures.	An MEG recording is a noninvasive measurement of the magnetic field generated by the electrical activity of neurons that are recorded by sensors (magnetometers) located outside the head in a helmet. MEG recordings can detect brain activity on a millisecond-by-millisecond basis and indicate where in the brain the activity is produced, resulting in precise temporal and spatial resolution.	An MRI scan is a noninvasive imaging technology that uses strong magnets to produce three-dimensional images of organs such as the brain and spinal cord. MRI technology can reveal structural abnormalities such as brain tumors. A functional (fMRI) scan can be used to examine the brain's activity by showing which brain regions consume more oxygen than others under certain conditions.	A PET scan is a noninvasive imaging technique that uses a radioactive drug, called a tracer, to measure metabolic activity and reveal brain or organ functioning. PET scans are often used in the diagnosis of disorders that interfere with brain functioning including dementias, neurodegenerative diseases, epilepsy, brain trauma, and cancer.

Source: *Milken Institute (2021)*

TABLE 3: TECHNOLOGIES THAT INFLUENCE BRAIN ACTIVITY

Electrical Stimulation	Transcranial Magnetic Stimulation (TMS)	Transcranial Direct Current Stimulation (tDCS)	Ultrasound Neuromodulation
Invasive	**Noninvasive**	**Noninvasive**	**Noninvasive**
CNS or PNS	CNS	CNS or PNS	CNS
Electrical Activity	**Electrical Activity**	**Electrical Activity**	**Various**
Researchers and clinicians can stimulate cells in the brain, spinal cord, and peripheral nerves with electrodes. Electrical stimulators have been approved for use in humans to treat a variety of neurological conditions and mental health disorders including Parkinson's disease, depression, spinal cord injuries, and epilepsy. Examples of electrical stimulators include deep brain stimulation, spinal cord stimulation, and vagus nerve stimulation.	TMS pulses are targeted to specific brain sites and are delivered through a magnetic coil held against one particular part of the head. TMS has been approved as a treatment for severe forms of major depression.	tDCS noninvasively delivers direct electrical currents to specific parts of the brain. This stimulation method involves passing a constant, low-intensity current across two electrodes positioned on the head. tDCS can excite neuronal activity (anodal stimulation) or reduce neuronal activity (cathodal stimulation). No tDCS treatment is currently approved for clinical use.	An emerging, noninvasive technique known as focused ultrasound neuromodulation delivers ultrasound waves to nervous system tissue. Focused ultrasounds can transiently modulate neural activity with relatively high special resolution and reach structures deep in the brain. This technique could be used to map and investigate brain function as well as to modulate brain activity for therapeutic purposes.

Source: Milken Institute (2021)

THE NEUROTECHNOLOGY DEVELOPMENT LANDSCAPE: A MACRO VIEW

Over the past century, pharmaceutical products (drugs) have dominated medical innovation. However, neural devices have substantial potential to revolutionize the treatment of neural-based illnesses. Advances in engineering and our fundamental understanding of the brain have enhanced the applicability of devices to brain-based illness. These devices are increasingly able to engage specific neural tissue through greater spatial and temporal resolution.

Major public investment in neuroscience is improving our understanding of the brain, which will eventually enable more targeted application of these technologies. This opportunity is not without challenges—the complexity of the brain and neural-based illnesses renders this class of illness one of the most difficult to develop treatments for, and the pathway to neurotechnology commercialization is largely unpaved. Nonetheless, engineering advances and the promise of life-changing solutions drive continued progress in the space.

Innovation Pipeline

Application of Existing Technologies

Several neurological disease-modifying devices are in use today. They include deep brain stimulators, brain-machine interface technology, spinal cord stimulators, and vagus nerve stimulation (Stieglitz 2021). These technologies were optimized for specific physiology but could be modified for new applications. This type of adaptation of existing devices, which have already been studied and have known safety profiles, can accelerate development of new treatments for different diseases. With this approach, researchers and clinicians can leverage current market devices based on improved fundamental understanding of the neural circuits underlying the disease and thereby skip the engineering process required to develop an entirely new device.

However, such adaptation requires substantial study and innovation. Researchers must determine which neural targets are most influenced by stimulation for any new disease application and how to optimize stimulator parameters to achieve the necessary change in neural activity. In some cases, the device itself must be modified to provide a better "fit" for the physical location.

Further, the invasive neural device industry is dominated by three major companies: Medtronic, Boston Scientific, and Abbott. To develop new protocols for "off the shelf" use of neural devices for new indications or applications, clinician researchers must partner with one of these companies. This need creates a bottleneck to accessing Food and Drug Administration (FDA)-approved technologies for experimental use because the companies must evaluate the risk associated with experimental treatments against the potential impact on their existing marketed products ("BRAIN Initiative 2.0: From Cells to Circuits, Toward Cures," n.d.). These barriers limit the application of existing devices to new indications, which is fundamentally problematic because neurotechnology is indication-agnostic by nature.

Engineering Advances

Material and manufacturing improvements are leading to dramatic innovation in neural technologies. Devices are becoming smaller and less invasive, and researchers are experimenting with new approaches to modifying neural activity. These advances are important because miniaturization of neural devices can both increase the precision of neural engagement and decrease the auxiliary damage to neural tissue and burden to the user (Cho et al. 2021).

However, for these advances to realize the greatest impact, interdisciplinary collaboration among engineers, neuroscientists, and surgeons is needed to identify the materials and design most suitable for neural tissue ("BRAIN Initiative 2.0: From Cells to Circuits, Toward Cures," n.d.). Few research centers in the world have the ability to bring together these partnerships, let alone sustain them in a meaningful or productive way.

Regulatory and Access Pathways

Marketing Approval: Like all medical products in the United States, neural devices are regulated by the FDA. Within the FDA, the Center for Devices and Radiological Health (CDRH) is responsible for reviewing and monitoring all neural devices that are generally considered medium- to high-risk and thus require extensive study. An early step in the review process is "first in human" testing, which requires researchers to obtain an Investigational Device Exemption. This early step toward commercialization is critical because it engages the FDA in discussions about safety and provides a pathway for in-human study and, if needed, iterative device improvements (Mallis, n.d.; Holmes et al. 2016). Results from an early study in humans will dictate the appropriate regulatory pathway, which considers the potential risk, the similarity of the new device to others already approved, and the number of people with the disease or condition that the device is intended to treat. The specific pathway impacts the timeline for review as well as the evidence needed to receive FDA approval.

Reimbursement: Importantly, FDA approval rarely ensures the commercial viability of a neural device. Manufacturers generally seek insurance coverage that is predominantly governed by the Centers for Medicare & Medicaid Services (CMS). CMS determines reimbursement based on clinical data obtained through randomized control trials. The FDA and CMS often place different emphases on the requirements for either medical device approval or clearance (FDA) and device coverage and reimbursement (CMS). More specifically, the FDA stresses safety and efficacy, while CMS stresses the superiority of a product relative to the "gold standard" of care or treatment. The differences in FDA and CMS assessment are often cited as a key barrier to bringing devices to the commercial market (Diage 2019).

Clinical Access: FDA and CMS approval does not guarantee patient access to a neurological device. Few clinicians or medical centers possess the expertise to assess whether a neurological device could help a patient. Patients report traveling long distances to a handful of major neurological centers to access these treatments, which complicates follow-up care (Dall et al. 2013). Finally, the American Academy of Neurology has reported a worsening global shortage of neurologists for nearly a decade—leading to physician burnout and long wait times for new and existing patient visits (Majersik et al. 2021).

Funding

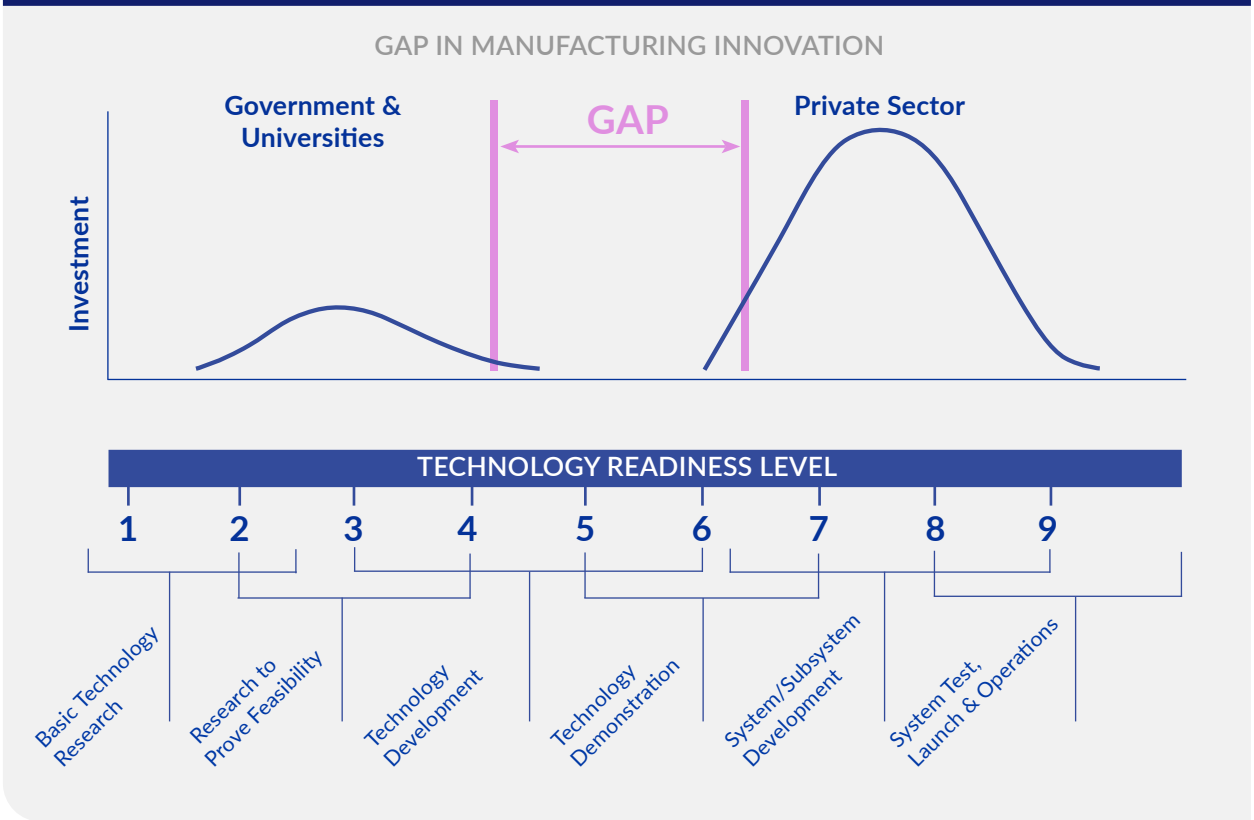
Brain science is arguably experiencing a funding heyday globally, with substantial new investments focused on several game-changing projects. These projects include mapping the human brain, developing new technology for neural devices, and developing new research tools to study the brain (an effort led by the National Institutes of Health, or NIH).

Further, venture capital firms have reported record investments in neuro-relevant technologies, creating a landscape that is flush with private funding (Munro and Dowden 2018). However, innovators report stalled projects resulting from big influxes of funding at the basic stage, then no funding for translational research or clinical trials.

Steep Valley of Death: Medical product development tends to suffer from insufficient funding in the translational research phase, which is where many medical research projects falter. This phenomenon is often referred to as the Valley of Death. Neurological devices, and medical devices in general, experience some of the same challenges to funding and development as pharmaceutical products—but with important differences in how the funding gaps manifest and, therefore, how funders might overcome these shortcomings.

Because of increased federal funding for neuroscience research, most researchers report sufficient and easy access to basic and foundational work that underlies the hypothesis-building phases of initial neural device development and application. In addition, NIH has emphasized funding for small business programs that facilitate early commercialization efforts ("BRAIN Initiative 2.0: From Cells to Circuits, Toward Cures," n.d.). However, device manufacturers note that these funds are ill-suited for the necessary iterative development of devices and are better suited for pharmaceutical development (Holmes et al. 2016).

FIGURE 4: RESEARCH-TO-INDUSTRY VALLEY OF DEATH



Source: Adapted from the Global Federation of Competitiveness Councils (2021)

Competition with the Direct-to-Consumer Market: A unique characteristic of the medical device industry is that there is currently a proliferation of neuro-relevant devices built upon the fundamental technology and knowledge necessary for the development of therapeutic devices. The challenge, however, is that devices in development seek to address symptomatic domains such as improving cognition, accelerating learning, improving focus, or promoting a feeling of calmness, rather than treating a specific disorder. These devices leverage the same technology and knowledge as devices that could address important neural-based illnesses. Still, as long as they do not claim to *treat* a medical illness, they remain outside of the FDA's purview. The FDA classifies these products as promoting a healthy lifestyle unrelated to the diagnosis, cure, mitigation, prevention, or treatment of a disease or condition. Importantly, this distinction applies to only low-risk devices (US Food and Drug Administration 2019). This guidance may accelerate the development of wellness-focused devices, but neurotechnology device developers believe this trend to be a potential risk to the neural device industry. This belief is based on the facts that direct-to-consumer devices, such as apps to treat mental health conditions, can be developed at substantially lower cost, do not require regulatory review or study of comparative efficacy necessitated by CMS, and could erode the public's confidence in the application of neurotechnology to treat illness (Whitcomb 2021).

A ROLE FOR PHILANTHROPY IN CATALYZING A NEUROTECHNOLOGY REVOLUTION

Mental and neurological conditions account for 13 percent of the global burden of disease (World Health Organization 2011). However, most people living with brain-based disorders endure ineffective treatments and limited success in managing symptoms. For example, few therapies exist for neurodegenerative illnesses including Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS). Neurological devices that directly engage neural circuits that underlie disease could dramatically change the range of treatments available for brain-based illnesses. Although the past decade has seen banner public funding for neuroscience, this investment has not translated to dramatic changes in the availability or application of neurological devices in patient communities. CSP's analysis of the landscape reveals that critical funding gaps have contributed to this stagnation. CSP has identified six key ways that philanthropic funders can overcome these barriers to bring neural technologies into the mainstream and fundamentally alter the interventions available for neural-based illness.

Opportunity 1: Develop Fundamental Understanding of Neural Circuits Underlying Disease

The past decade has seen dramatic advances in science's understanding of the brain and the circuits that underlie perception, cognition, and emotion. In addition, dramatic investment by governments around the globe, including the US government, to develop new tools to query the brain will likely inform understanding of the human nervous system. However, the field's current mechanistic understanding of the underlying neural circuits and biological targets prevents informed adaptation of technologies.

More broadly, the neuroscience field lacks a consolidated model of how neural tissue drives perception, cognition, and consciousness, which remains a critical barrier to developing new therapeutic strategies for neuroscience. Fundamental discovery and descriptive science will drive progress toward this vision. As scientists learn how to describe and predict neural function, they will better adapt neural technologies to the biology more efficiently.

Funders focused on developing neural technologies for a specific disease or disorder can benefit from a long-term program to elucidate the neural circuits that underlie or drive the condition. Generally, studying circuits rather than individual cells or molecules will be more helpful for guiding neural technology application. This is because the current resolution of neural technologies is equivalent to small brain regions, rather than effecting changes specific to a single neuron. Investment to improve foundational knowledge is an important long-term approach toward building a greater pipeline of therapeutic strategies but will likely not lead to immediate changes to patient care for any specific disorder.

Opportunity 2: Support Early-Stage Human Trials

Federal agencies in the United States have committed substantial funding to discovery science and initial device development, which has led to a proliferation of early-stage technologies and potential applications. However, the translation of these concepts to clinic-ready devices has largely stalled.

Philanthropy could intervene by providing expertise and financial support at pivotal points in translating device design to human studies. Although a few foundations focused on a specific technology or indication have successfully moved technologies into clinical study, much of the field struggles to access similar funding. The result is a bottleneck of first in human studies necessary to optimize device use for a specific indication.

Philanthropic attention to this specific barrier will likely have the most immediate impact on both device development and patient outcomes because funding levels drop during this critical stage. Early phase human studies (consisting of fewer than six participants) should be focused on assessing safety and initial signals of efficacy in the experimental design. These findings will inform further device refinement and larger-scale clinical study. Many studies at this stage will require fewer than three years of support to cover study planning, subject recruitment, and experimentation.

Opportunity 3: Support the Development of Noninvasive and Less Invasive Technologies

Based on technologies currently available for therapeutic use, scientists and clinicians generally find that invasive technologies are more effective because they act directly on the target tissue and thus more robustly engage biological targets. However, invasive approaches, such as deep brain stimulation, pose a higher risk and are therefore only used after less invasive approaches have been attempted and failed. In addition, implanting a device such as a deep brain stimulator requires a complex surgery under anesthesia and is therefore available only within specialty clinical settings, which sharply limits patient access. Importantly, clinicians have found that anesthesia can irreversibly accelerate neurodegenerative disease symptom development, making invasive devices a particularly difficult choice for individuals with a neurodegenerative disease, such as Alzheimer's or Parkinson's.

Although these risks and barriers highlight the need for less invasive approaches, researchers and clinicians have noted that current less invasive technologies are not as effective, likely due to poor engagement of biological targets. Further, researchers and clinicians have pointed out that many studies of noninvasive devices have been poorly controlled or show high placebo effects that make results difficult to interpret. However, many promising, less invasive technologies are in development and undergoing refinement. Because these technologies carry lower patient risk, human trials are easier to initiate because of a simplified regulatory review process and greater traction in patient communities.

Philanthropic support will be critical to promoting the rigorous science necessary to bring less invasive technologies into clinical practice; foundations can direct capital to specific bottlenecks while prioritizing impartial scientific vetting. Without rigorous scientific practices at every step of the development process, these devices are less likely to meet the regulatory and reimbursement requirements necessary for introduction to the clinical setting.

Returns on investment in noninvasive and less invasive technology development have longer timelines than investment in studying new applications of existing devices because these technologies tend to be in the earlier stages of development and study. However, because these classes carry lower risk, they will likely move through regulatory review more quickly and exhibit improved utility within clinical settings. Funders of less invasive technologies should consider fostering the development of devices that could impact an array of potential indications and of methods to assess target engagement quantitatively. Finally, as noninvasive and less invasive approaches reach clinical study, specific attention should be paid to the inclusion of true control conditions to compare efficacy to a meaningful placebo control.

Opportunity 4: Create an Ecosystem of Navigational Support

Much of the innovation in device development and application is occurring in academic settings and early-stage biotech companies. Unlike pharmaceutical development, where early-stage academic discoveries are typically advanced by industry and biotech partners, neurotechnology development often relies on academic expertise and support through later phases of clinical study.

Device development teams encounter complex challenges. Academic institutions rarely possess the manufacturing, business, financing, regulation, and legal expertise necessary for later developmental phases. Although this knowledge can be attained via university resources or consultants, neural device innovators report that missteps can sideline a scientifically sound project and thus add complexity to these hurdles.

Philanthropists and foundations can play a key role in facilitating device development by helping research teams access quality expertise for regulatory and market navigation. Private funders have developed programmatic offerings around this concept in adjacent fields that can be adapted to a new program focused on neurotechnology. Models to consider include:

- identifying and providing access to regulatory consultants,
- partnering with contract research laboratories to guarantee that grant funding supports quality manufacturing and consistent regulatory guidance, and
- supporting project time for individuals with regulatory and/or business expertise within grant agreements.

Opportunity 5: Support an Open-Science Platform to Accelerate the Experimental Application of Neurotechnology

The medical device industry is small and risk-averse, with only three established industry players. Clinician researchers report severe restrictions in accessing implantable devices from the manufacturers, which limits expanded use of devices to new disease areas.

To address this issue, a group of researchers is pursuing an open technology platform (The Open Platform Initiative) in which a nonprofit organization would develop a suite of neural devices that have FDA approval and a manufacturing partnership. The nonprofit could therefore mediate the access and manufacturing of recording and stimulation neurotechnology devices. This effort will likely require philanthropic backing but could profoundly influence the application of neural devices to disease. In addition, the democratization of these technologies would likely lead to greater iteration of device use (such as stimulation paradigms) and, in turn, substantial improvements in existing device protocols.

Opportunity 6: Grow the Landscape of Innovators Working on Neurotechnology

A central theme in accelerating scientific innovation is the importance of diverse ideas and perspectives, particularly when developing solutions across multiple scientific disciplines. However, interdisciplinary science is inherently difficult because experts in any discipline develop field-specific definitions, journals struggle to review findings that cross disciplines, and funders must vet proposals across a range of expertise.

Interestingly, neurotechnology has emerged as a research area at the nexus of already disparate scientific ecosystems, namely, neuroscience, engineering, and clinical neurology. However, the challenges that are common for interdisciplinary science also exist for neurotechnology. Any funder of neurotechnology must consider how to assemble and retain diverse and functional teams. To this end, funders should use all tools at their disposal including, but not limited to, grant agreements that specify team requirements and existing meetings to codify and promote teaming.

CONCLUSION

From implanted devices, such as deep brain stimulation to newer, noninvasive approaches, neurotechnology has the potential to radically shift treatment and outcomes for neurological patients. Currently, however, the complexity of the brain paired with a difficult landscape for commercial development have made it difficult for scientists, entrepreneurs, and other innovators to see their ideas through to fruition. With targeted investment in a few key areas, individual and family philanthropists, foundations, and other private funders can dramatically improve the lives of millions. These investments could range from building out the anatomical and circuitry understanding for a specific neural-based illness to funding early-stage clinical trials in an effort to focus new development on a particular disease or disorder. Broader foundational investments such as developing the workforce, establishing an open-source platform technology, and supporting navigation of regulatory, reimbursement, and business aspects of device development will advance the field. Finally, investments in the development of less invasive approaches that can engage the brain with efficacy similar to that of more invasive approaches will likely unfold over longer time periods but promise game-changing benefits for the patient communities.

The scale and scope of neurotechnology make this an effort that requires coordinated, collective action among many funders, but one that can shape the future of device application to many diseases.

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