08 - 500 Emerging Neurotherapeutic Technologies

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■ ■FURTHER READING Barabasi A-L et al: Network medicine: A network-based approach to human disease. Nat Rev Genet 12:56, 2011. Cheng F et al: Network-based approach to prediction and populationbased validation of in silico drug repurposing. Nat Commun 9:2691, 2018. Liu X et al: Robustness and lethality in multilayer biological networks. Nat Commun 11:6043, 2020. Loscalzo J et al (eds): Network Medicine: Complex Systems in Human Disease and Therapeutics. Cambridge, MA, Harvard University Press. Copyright 2017 by the President and Fellows of Harvard College. All rights reserved. Loscalzo J et al: Human disease classification in the postgenomic era: A complex systems approach to human pathobiology. Mol Syst Biol 3:124, 2007. Maiorino E, Loscalzo J: Phenomics and robust multiomics data for cardiovascular disease subtyping. Arterioscl Thromb Vasc Biol 43:1111, 2023. Menche J et al: Disease networks. Uncovering disease-disease relationships through the incomplete interactome. Science 347:1257601, 2015. Oldham WM et al: Network analysis to risk stratify patients with exer cise intolerance. Circ Res 122:864, 2018. Paci P et al: Gene co-expression in the interactome: Moving from correlation toward causation via an integrated approach to disease module discovery. NPJ Syst Biol App 7:3, 2021. Wang R et al: Multiomics network medicine approaches to precision medicine and therapeutics in cardiovascular diseases Arterioscl Thromb Vasc Biol 43:493, 2023. Jyoti Mishra, Karunesh Ganguly

Emerging Neurotherapeutic Technologies Neurotherapeutic technologies represent a diverse group of very promising treatment approaches with a common purpose of improving neurologic function. Decades of basic science research have paved the path for these novel technologies that have the potential to transform the lives of patients with neurologic diseases. A key goal is to minimize the consequences of lost abilities, whether they are motor, sensory, or cognitive. A common objective is to also harness the inherent plastic ity of the nervous system, regardless of age, and even in the face of a degenerative process. The technologies described below are the culmination of both an increased understanding of neural plasticity mechanisms in both the intact and the injured nervous system as well as advances in technology and computational power. While it is also clear that there may be fundamental limits on plasticity and repair mechanisms (the closing of developmental windows and/or loss of the ability of a network to compensate), the brain remains highly plastic regardless of age and even in the face of ongoing injury and/or degenerative processes. Collectively, there is now growing evidence to support neurologic restorative efforts for both “static” (e.g., stroke) and progressive neurologic disorders. These technologies may not appear, at first glance, directly relevant to traditional medical care, but it is worth noting that clinicians have the most knowledge and experience about specific disease processes, available treatments, and the expected course of illnesses affecting the nervous system. It is thus critical that neurologic specialists and other clinicians play an important role in the future adoption of these technologies for neurologic rehabilitation. The sections below outline

emerging diagnostic and therapeutic approaches that have the potential to transform the lives of patients with neurologic disorders. These include technologies to harness plasticity, neuroimaging, neurostimulation, and brain–machine interfaces.

NONINVASIVE TECHNOLOGIES TO HARNESS PLASTICITY Neurologic rehabilitation aims to harness activity-dependent plasticity mechanisms to maximize functional restoration. This principle can be applied to a diverse range of functional domains such as movement control, sensory processing, language, pain, and cognition. For example, recent randomized controlled clinical trials for motor recovery after stroke have suggested that intensity of training may be particularly important for sustained long-term improvements. Moreover, studies of the effects of such training in rodent and nonhuman primate models further suggest that plasticity of cortical “motor maps” as well as the coordinated firing of neurons in remaining networks underlie observed functional improvements with rehabilitation. The incorporation of technology for neurologic rehabilitation has the great potential to revolutionize the delivery of care by significantly increasing access, reducing the burden for adherence to high-intensity regimens, and maximizing engagement. Below are three examples of how emerging technology can be used to harness neural plasticity and maximize functional restoration. ■ ■ROBOTICS Rehabilitation robotics for both the upper and the lower limb have the potential to improve motor outcomes after stroke or other forms of brain injury. There is a growing recognition that focused training involving a range of tasks might be important for improved functional outcomes. While there is a growing recognition of “sensitive periods” that might represent optimal windows for rehabilitation after injury (e.g., perhaps the first several months after a stroke), such training likely has a role in the chronic period as well (e.g., maintenance therapy may also guard against known declines in function over time). Notably, the delivery of intensive training is a great challenge from both the perspective of the health care system and each patient. Outside of clinical trials, such a training program can be quite difficult to implement and maintain. It can also be costly and require significant effort. CHAPTER 500 Emerging Neurotherapeutic Technologies Motor rehabilitation protocols using robotics have been developed and tested for both the upper limb and the lower limb. Such robotic therapies have often focused on the delivery of high-intensity movement practice that can surpass what is possible via existing standards of care. Moreover, robotic systems are capable of precisely measuring movement parameters (e.g., the kinematics of the movements) and providing quantitative feedback regarding the changes in performance during the training period. A particular focus has been on maximizing patient engagement and recruitment of attentional and reward pathways, both of which are increasingly recognized to drive neural plasticity. Ongoing advances in design and the user interface will continue to improve comfort and support sustained effort. For example, via close monitoring of performance and movement parameters, the system can aid at key points in order to minimize fatigue and ensure maximal engagement. Moreover, antigravity support of the upper limb can allow practice and task engagement even in the presence of severe weakness; this would be extremely challenging and labor intensive under current standards of care. Recent analysis also suggests that robotic devices may at least match outcomes realized with existing standards of care. However, rehabilitation robotics may also provide more precise feed back and permit novel quantitative rehabilitation approaches. Figure 500-1 shows one example of an upper-limb robotic exoskeleton device that is currently being evaluated for training after stroke. A randomized, multicenter trial compared treatment with this exoskeleton system against conventional therapy provided by physical and occupational therapists. Participants were enrolled in the chronic phase and all had moderate-to-severe deficits; the groups underwent three sessions per week over an 8-week period. For robotic training, subjects trained with games to improve mobilization and to practice activities of daily living. This study provided evidence that both conventional and robotic therapy could improve function in patients with chronic stroke. Multiple studies have also found similar gains when using either conventional or traditional approaches. Thus, a growing body of research supports the idea that such devices might complement conventional approaches to rehabilitation. Future work will need to define how rehabilitation robotics can optimally use adaptive and quantitative methods to further augment the recovery process.

FIGURE 500-1 Photograph of a subject interacting with a complex upper-limb exoskeleton and a virtual reality system. (From U Keller et al: Robot-assisted arm assessments in spinal cord injured patients: A consideration of concept study. PLoS One 10:e0126948, 2015.)

■ ■VIRTUAL AND AUGMENTED REALITY

Therapeutic approaches using virtual reality (VR) and augmented reality (AR) aim to treat neurologic illnesses by specifically and quantitatively altering a patient’s subjective experiences and interactions with the environment. Core components of both are advanced hardware and computational methods to generate simulated, yet realistic, perceptions. While some applications permit users to dynamically change the viewed perspective, other applications are designed to allow interactions among multiple users. Visual feedback is often a key component; this can include simple computer monitors or more immersive “head-mounted” viewers that modify the simulation based on changes in perspective. Tracking of movements (e.g., hand and head position) is often included. Multiple methods are used to allow a user to interact with the environment; interactions can be guided by straightforward means such as a keyboard, mouse, or even a joystick. More immersive methods are also frequently used. For example, gloves with embedded sensors and haptic inputs can allow the user’s hand to be represented in real time in the simulated environment. Moreover, haptic interfaces can provide sensory feedback, allowing patients to interact with and “feel” virtual objects through multiple sensory modalities. A particular strength of these approaches is that therapeutic interventions can be studied in very controlled environments. VR enables a user to interact with a simulated reality that can be precisely and quantitatively controlled. In addition to allowing patients to dynamically experience an altered reality, it can simultaneously monitor a subject’s behaviors and responses. Such monitoring can allow precise measurements of clinically relevant parameters (e.g., motor actions, perception, cognitive processing) and can also be applied in specific rehabilitation training to achieve functionally meaningful goals. A growing body of literature indicates that VR environments can be tailored to individual needs and preferences, thereby maximizing engagement, motivation, and adaptation to ensure sufficient difficulty of tasks. VR environments can be designed to create powerful “gam ing” platforms that are actually targeting clinically relevant parameters. For example, the upper-limb robotic systems described previously are frequently combined with VR environments that allow interaction with virtual objects. In contrast to VR, AR overlays an artificial filter over a subject’s view of the actual physical world, thus providing an “augmented” or

enhanced view of the world around. AR is being tested in a diverse group of patients with neurologic impairments in the motor, sensory, or cognitive domains. AR may offer a particularly unique rehabilitation intervention for stroke patients. It is widely known that brain injuries limit patients’ physical interaction with their environments. Further more, physical and cognitive impairments may limit social interac tions. Such impoverished experiences are likely to be present during both the acute and the chronic phases. Importantly, there is clear basic scientific evidence that environmental enrichment can be a key com ponent of rehabilitation; such enrichment may offer additive benefits to the often-limited formal rehabilitation sessions per week. Consistent with this are clinical studies suggesting that motor and cognitive out comes may suffer when interactions with the environment are reduced; AR may be capable of increasing enrichment. For example, in the case of spatial neglect after stroke, the impaired modality may be accounted for using AR methods. Similarly, physical impairments that limit walk ing speeds can also limit visual feedback; both AR and VR can be used to enhance visual feedback during gait training. Figure 500-2 shows an innovative application of AR for the treat ment of “phantom limb” pain. A subset of both upper-limb and lowerlimb amputees experience painful sensations that appear to originate from the missing limb. Past research has suggested that mirror therapy can be an effective treatment for phantom limb pain. During mir ror therapy treatments, patients move their healthy arm in front of a mirror to produce a perception of movements of the missing limb. Previous studies have suggested that maladaptive plasticity of affected sensory cortices may be treated with mirror therapy. Importantly, in comparison to mirror therapy, AR-based therapy for phantom limb pain can be based on movements of the affected limb, i.e., using the remaining portion of the limb as opposed to the unaffected contra lateral limb. This study demonstrated a novel treatment in which “phantom motor execution” is enabled using sophisticated machinelearning algorithms. More specifically, the study “decoded” phantom limb movements by measuring electromyogram (EMG) activity at the stump. Importantly, while the distal muscles responsible for move ments were lost as a result of amputation, the remaining EMG activity could be used to predict presumed distal limb movements. As shown in Fig. 500-2, these inferred movements were projected onto an AR screen to create the perception of limb movements. The study showed that a subset of patients with long-term refractory phantom limb pain could experience a significant reduction in pain levels after using the AR system. ■ ■NEUROGAMING Computerized programs that harness the power of video games have shown some evidence for ameliorating deficits in visual perception, age-related degeneration, and neuropsychiatric disorders. An essential feature of effective video game training is the progressive adjustment of the level of difficulty in line with the cognitive improvement of the patient. Important areas of active research include ways to enhance sus tainability of neurogame training over long time periods and improv ing training transfer, i.e., the generalizability of task-specific training in one cognitive domain to more broad-based functional improvements. By leveraging video game technology, neurogames allow for dynamic user interaction and maintain user engagement across multiple ses sions over several days of training. Important game mechanics include repetitive practice, performance-adaptive challenges, and several lay ers of reward feedback—from moment-to-moment point rewards to reward milestones over multiple sessions. Notably, neurogames have therapeutic potential as they can be targeted to specific neurocognitive deficits. For instance, games have shown significant benefits in aging, by targeting speed of processing and training the abilities to multitask and suppress distractions. In each case, selective targeting is achieved by focusing the adaptive challenges to the neurocognitive domain of interest. Duration of response time windows available to the user or the level of interference are selectively targeted in the case of speed of processing training and interference training, respectively. More recent research demonstrated that it is possible to engender focused circuit neuroplasticity using such selective targeting in neurogaming. For example, older adults learned to adaptively perform within progressively more challenging distractor environments. Neuroplasticity selective to distractor processing was evidenced in this study at both the microscale, i.e., at the resolution of single neuron spiking in sensory cortex, as well as macroscale, i.e., electroencephalography (EEG)-based event-related potential recordings. Video games have also shown promise in the treatment of visual deficits such as amblyopia, and in cognitive remediation in neuropsychiatric disorders such as schizophrenia. However, while the evidence base has been encouraging in small-sample randomized controlled trials (RCTs), larger RCTs are needed to demonstrate definitive therapeutic benefit. This is especially necessary as the commercial brain training industry continues to make unsubstantiated claims of the benefits of neurogaming; such claims have been formally dismissed by the scientific community. Like any other pharmacologic or device-based therapy, neurogames need to be systematically validated in multiphase RCTs establishing neural target engagement and documenting cognitive and behavioral outcomes in specific disorder populations. Generalizability of training benefits from task-specific cognitive outcomes to more broad-based functional improvements remains the holy grail of neurogaming. Next-generation neurogames will aim to integrate physiologic measures such as heart rate variability (an index of physical exertion), galvanic skin responses, and respiration rate (indices of stress response), and even EEG-based neural measures. The objectives of such multimodal biosensor integration are to enhance the “closed-loop mechanics” that drive game adaptation and hence improve therapeutic outcomes and perhaps result in greater generalizability. These complex, yet potentially more effective, neurogames of the future will need rigorous clinical study for demonstration of validity and efficacy.

A B C D FIGURE 500-2 Augmented reality (AR) for phantom limb pain. A. A patient is shown a live AR video. B. Electromyography electrodes placed over the stump record muscle activation during training. C. The patient matches target postures during rehabilitation. D. Patient playing a game in which a car is controlled by “phantom movements.” (M Ortiz-Catalan et al: Phantom motor execution facilitated by machine learning and augmented reality as treatment for phantom limb pain: A single group, clinical trial in patients with chronic intractable phantom limb pain. Lancet 388:2885, 2016.)

NEUROIMAGING Feedback display (e.g., thermometer)

■ ■NEUROIMAGING OF CONNECTIVITY

Multimodal neuroimaging methods including functional magnetic resonance imaging (fMRI), EEG, and magnetoencephalography (MEG) are now being investigated as tools to study functional connectivity between brain regions, i.e., extent of correlated activity between brain regions of interest. Snapshots of func tional connectivity can be analyzed while an individual is engaged in specific cog nitive tasks or during rest. Resting-state functional connectivity (rsFC) is espe cially attractive as a robust, task-indepen dent measure of brain function that can be evaluated in diverse neurologic and neuropsychiatric disorders. In fact, meth odologic research has shown that rs-fMRI can provide more reliable brain signals of energy consumption than specific task-based fMRI approaches. FIGURE 500-3 Neurofeedback using functional magnetic resonance imaging (fMRI). (From T Fovet et al: Translating neurocognitive models of auditory-visual hallucinations into therapy. Front Psychiatry 7:103, 2016.) PART 20 Emerging Topics in Clinical Medicine In recent years, there has been a surge of research to identify robust rsFC-based biomarkers for specific neurologic and neuropsychiatric disorders and thereby inform diagnoses and even predict specific treatment outcomes. For many such disorders, the network-level neurobiologic substrates that correspond to the clinical symptoms are not known. Furthermore, many are not unitary diseases, but rather heterogeneous syndromes composed of varied co-occurring symptoms. Hence, the quest for robust network biomarkers corresponding to com plex neuropsychologic disorders is challenging and still in its infancy; yet some studies have made significant headway in this domain. For example, in a large multisite cohort of ~1000 depressed patients, Drys dale et al. (2017) showed that rsFC measures can subdivide patients into four neurophysiologic “biotypes” with distinct patterns of dysfunctional connectivity in limbic and frontostriatal networks. These biotypes were associated with different clinical-symptom profiles (combinations of anhedonia, anxiety, insomnia, anergia, etc.) and had high (>80%) diagnostic sensitivity and specificity. Moreover, these biotypes could also predict responsiveness to transcranial magnetic stimulation (TMS) therapy. Another recent study demonstrated utility of rsFC measures to predict diagnosis of mild traumatic brain injury (mTBI), which is clini cally challenging by conventional means. Apart from fMRI-based measures of rsFC, EEG- and MEG-based rsFC measures are also being actively investigated, as these provide a relatively lower-cost alternative to fMRI. While EEG is of lowest cost, it compromises on spatial resolution. The major strength of MEG is its ability to provide more accurate source-space estimates of functional oscillatory coupling than EEG, as well as provide measures at various physiologically relevant frequencies (up to 50 Hz shown to be clinically useful). In this regard, EEG and MEG are complementary to fMRI, which can only be used to study slow activity fluctuations (i.e., <0.1 Hz); the potential for EEG/MEG modalities to provide valid diagnostic bio markers is currently underexploited and requires further study. ■ ■CLOSED-LOOP NEUROIMAGING Neuroscientific studies to date are predominantly designed as “openloop experiments,” interpreting the neurobiologic substrates of human behavior via correlation with simultaneously occurring neu ral activity. In recent years, advances in real-time signal processing have paved the way for “closed-loop neuroimaging,” wherein humans

3T MRI acquisition Image reconstruction The task of the subject is to lower the temperature display Real-time fMRI can directly manipulate experiment parameters in real-time based on specific brain signals (Fig. 500-3). Closed-loop imaging methods can not only advance our understanding of dynamic brain function but also have therapeutic potential. Humans can learn to modulate their neural dynamics in specific ways when they are able to perceive (i.e., see/hear) their brain signals in real-time using closed-loop neuroim aging-based neurofeedback. Early studies showed that such neuro feedback learning and resulting neuromodulation could be applied as therapy for patients suffering from chronic pain, motor rehabilitation in Parkinson’s and stroke patients, modulation of aberrant oscillatory activity in epilepsy, and improvement of cognitive abilities such as sustained attention in healthy individuals and patients with attentiondeficit hyperactivity disorder (ADHD).

These approaches have also shown potential for deciphering state-of-consciousness in comatose patients, wherein a proportion of vegetative/minimally conscious patients can communicate awareness via neuroimaging-based mental imagery. Closed-loop neuroimaging therapeutic studies have utilized realtime fMRI, EEG, and MEG methods. It is common for neural signals to be extracted from specific target brain regions for neuromodulation. However, given that distributed neural networks underlie behavioral deficits, new studies have also explored neurofeedback on combinatorial brain signals from multiple brain regions extracted using multivariate pattern analysis (MVPA). While early studies indicate therapeutic potential, clinical RCTs of closed-loop neuroimaging neu rofeedback have shown mixed results. This may largely be because of the individual heterogeneity in neuropsychiatric disorders such that there is no one-size-fits-all therapy. Closed-loop neuroimaging-based therapies need to be more personalized to the preintervention cogni tive and neurophysiologic states of the individual, and a better under standing developed regarding learning principles and mechanisms of self-regulation underlying neurofeedback. Clinical practitioners applying these methods also need to be well-educated on the hardware/ software capabilities of these brain–computer interfaces to maximize patient outcomes. NONINVASIVE BRAIN STIMULATION Noninvasive brain stimulation (NIBS) is widely recognized as having great potential to modulate brain networks in a range of neurologic and psychiatric diseases; it is currently approved by the U.S. Food and Drug

TMS coil Magnetic field TMS coil (µs) tDCS electrodes tDCS electrode Current flow – + + + + + + – – – – – – – – + + + (min) Anode Cathode FIGURE 500-4 Illustration of transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) setups. The upper panels show a TMS setup. Coils generate magnetic fields that can in turn generate electrical fields in the cortical tissue. The lower panels show a tDCS setup. The electrical current is believed to flow from the anode (+) to the cathode (–) through the superficial cortical areas leading to polarization. (Reproduced with permission from R Sparing, FM Mottaghy: Noninvasive brain stimulation with transcranial magnetic or direct current stimulation [TMS/tDCS]—From insights into human memory to therapy of its dysfunction. Methods 44:329, 2008.) Administration (FDA) as a treatment for depression. Importantly, there is a very large body of basic research indicating that neuromodulation of the nervous system with electrical stimulation can have both shortterm and long-term effects. While TMS uses magnetic fields to gener ate electrical currents, transcranial direct current stimulation (tDCS), in contrast, is based on direct stimulation using electrical currents applied at the scalp (Fig. 500-4). TMS induces small electrical currents in the brain by magnetic fields that pass through the skull; it is known to be painless and therefore widely used for NIBS. Animal research suggests that anodal tDCS causes a generalized reduction in resting membrane potential over large cortical areas, whereas cathodal stimu lation causes hyperpolarization. Prolonged stimulation with tDCS can cause an enduring change in cortical excitability under the stimulated regions. Further, changes in resting-state fMRI-based activity and functional connectivity have also been observed after tDCS. Notably, there is uncertainty regarding precisely how much electrical current is able to penetrate through the skull and modulate neural networks. Indeed, recent work has found that typical stimulation paradigms may not generate sufficient electrical fields to modulate neural activity; an alternate possibility is that peripheral nerves may be modulated and thus affect neural activity. Neuromodulation via stimulation techniques such as tDCS and TMS have shown promise as methods to improve motor function after stroke; there are a growing number of studies demonstrating functional benefits of combining physical therapy with brain stimulation. Two commonly utilized TMS paradigms include low-frequency “inhibitory” stimulation of the healthy cortex or high-frequency “excitatory” stimulation of the injured hemisphere. Each aims to modify the balance of reciprocal inhibition between the two hemispheres after stroke. A meta-analysis of RCTs published over the past decade found a significant beneficial effect on motor outcomes. Unfortunately, a recent large multicenter trial to assess the long-term benefits of TMS

on motor recovery after stroke (NICHE trial) did not find a benefit at the population level. Ongoing research aims to better understand how stimulation can directly affect neural patterns and thus allow more customization of stimulation—past trials did not record the neural responses to stimulation.

TMS and tDCS interventions are also being applied in psychiatric disorders. A substantial body of evidence supports the use of TMS as an antidepressant in major depressive disorder (MDD). TMS is also being investigated for its potential efficacy in posttraumatic stress disorder (PTSD), obsessive compulsive disorder (OCD), and treatment of auditory hallucinations in schizophrenia. Various repetitive TMS (rTMS) protocols have shown efficacy in major depression. These include both low-frequency (≤1 Hz) and high-frequency (10–20 Hz) rTMS stimulation over the dorsolateral prefrontal cortex (DLPFC). Mechanistically, low-frequency rTMS is associated with decreased regional cerebral blood flow while high-frequency rTMS elicits increased blood flow, not only over the prefrontal region where the TMS is applied but also in associated basal ganglia and amygdala circuits. Notably, the differential mechanisms of low- versus high-frequency rTMS protocols are associated with mood improvements in different sets of MDD patients, and patients showing benefits with one protocol may even show worsening with the other, again pointing to individual heterogeneity in network function. EEG-guided TMS is also being investigated in psychiatric disorders, for instance, the individual resting alpha-band (8–12 Hz) peak frequency to determine TMS stimulation rates. With respect to transcranial electrical stimulation in psychiatry, tDCS is the most commonly used protocol. In major depression, there is a documented imbalance in left versus right DLPFC activity; hence, differential anodal versus cathodal tDCS in the left versus right prefrontal cortex may be a potentially efficacious approach. Interestingly while metaanalysis shows promise for NIBS methods in psychiatric illness, large RCTs have failed to generate benefits compared to placebo treatment. Future success may require careful personalized targeting based on network dynamics and refinement of protocols to accommodate combinatorial treatments. CHAPTER 500 Emerging Neurotherapeutic Technologies IMPLANTABLE NEURAL INTERFACES Fully implantable neural interfaces that can improve clinical function already exist. Cochlear implants, for example, are sensory prostheses that can restore hearing in deaf patients. Environmental sounds are processed in real-time and then converted into patterned stimulation delivered to the cochlear nerve. Importantly, even while the patterned stimulation remains the same, there are gradual improvements in the perception of speech and other complex sounds over a period of several months after device implantation. Activity-dependent sculpting of neural circuits is hypothesized to underlie the observed perceptual improvements. Similarly, the development of deep-brain stimulation (DBS) was based on decades of work showing that surgical lesions to specific nuclei could alleviate tremor and bradykinesia in animal models. DBS involves chronic implantation of a stimulating electrode that targets specific neural structures (e.g., subthalamic nuclei or the globus pallidus in Parkinson’s disease). At least for movement disorders, it is commonly thought that targeted areas are functionally inhibited by the chronic electrical stimulation. ■ ■IMPLANTABLE DEVICES FOR NEUROMODULATION There has been recent progress in the development of implantable neural interfaces to treat neurologic and psychiatric illnesses. For example, for patients with refractory focal epilepsy and clearly identified seizure foci, invasive “responsive stimulation” is FDA approved. Responsive stimulation is grounded on principles of closed-loop stimulation based on real-time monitoring of brain oscillations; specifically, the device aims to detect the earliest signatures of the onset of a seizure, usually at a stage that is not symptomatic, and then deliver focused electrical stimulation to prevent further progression and generalization. A large RCT of this device was performed in patients with intractable focal epilepsy; they were assigned to either sham or active stimulation in response to seizure detection. There was a significant reduction in seizure frequency in the stimulation group, but it was rare for patients to become seizure-free. There were also modest improvements in quality of life. Notably, there was a small increased risk of hemorrhage associated with the device. In addition to providing clinicians with another treatment option, this device has offered important avenues for research and further optimization. For example, it is now possible to monitor subclinical and clinical seizures and intracranial EEG in patients with chronic epilepsy. This has resulted in new knowledge about the association of seizures with circadian rhythms and sleep. It is also anticipated that a better understanding of the triggers of seizures and the development of better stimulation algorithms, based on real-world data, can ultimately lead to more effective treatments.

Signal processing Neural signals

Action potentials Field potentials There is also great interest in the development of treatments for refractory depression. One area of focus has been on the development of DBS to treat depression. While early smaller studies were promising, a larger study failed to find benefits at the population level. Subsequent analysis has suggested the possibility that more precise tailoring of stimulation parameters to each individual is warranted, both at the level of specific pathways identified through neuroimaging as well as network activity biomarkers. Recent studies have, in fact, supported the notion that individualized patterns of network activity are predictive of a patient’s symptoms and how the patient might respond to stimulation. There are now planned studies that aim to tailor stimulation to each individual with severe depression.

FIGURE 500-5 Components of a brain–machine interface (BMI). (Reproduced with permission from A Tsu et al: Cortical neuroprosthetics from a clinical perspective. Neurobiol Dis 83:154, 2015.) PART 20 Emerging Topics in Clinical Medicine ■ ■VAGUS NERVE STIMULATION TO IMPROVE RECOVERY AFTER STROKE Vagal nerve stimulation (VNS) has recently been approved by the FDA as a therapy to enhance motor recovery after stroke. Animal studies first provided clear evidence that VNS is safe and can enhance plasticity in both intact animals as well as in models of injury. Importantly, these studies indicated that precise timing of movements is important for efficacy. For example, in animal models of stroke, stimulation of the vagus nerve was timed to the end of successful movement repetitions; these studies further indicated that the precise timing of VNS during rehabilitation is essential. VNS appears to result in rapid activation of cholinergic and noradrenergic systems; the activation of these neuromodulators may enhance attentional effects and improve “signal to noise,” thus facilitating the encoding of relevant task features. This basic research culminated in smaller clinical trials and a subsequent pivotal randomized trial of VNS in stroke. In this trial, after 6 weeks of therapy paired with VNS, participants randomized to the VNS group (n = 53) had a significant increase in forelimb function compared to the control group. In addition, 90 days after the study was completed, a higher percentage of patients in the VNS group maintained clinically meaningful responses. Together, this indicates that VNS is a promising new therapy to augment rehabilitation after stroke. However, given the variability of effects for single patients, additional research is required to determine which stroke patients are the most likely to benefit. Future advances that allow VNS to be delivered in the home setting should also lead to greater use of this approach. ■ ■BRAIN–COMPUTER INTERFACES FOR PARALYSIS Brain–computer interfaces (BCIs) represent a more advanced neural interface that aims to restore motor function. Multiple neurologic disor ders (e.g., traumatic and nontraumatic spinal cord injury, motor neuron disease, neuromuscular disorders, stroke) can result in severe and dev astating paralysis. Patients cannot perform simple activities, and they remain fully dependent for care. In patients with high cervical injuries, advanced amyotrophic lateral sclerosis (ALS), or brainstem strokes, the effects are especially devastating and often leave patients unable to com municate. While there has been extensive research into each disorder, clinically effective approaches for rehabilitation of long-term disability

Device control

Neural signals Control signals a Electrodes Computer cursor b Prosthetic limb Feedback are lacking. BCIs offer a promising means to restore function. In the patient groups described above, while the pathways for transmission of signals to muscles are disrupted, the brain itself is largely functional. Thus, BCIs can restore function by communicating directly with the brain. For example, in a “motor” BCI, a subject’s intention to move is translated in real time to control a device. As illustrated in Fig. 500-5, the components of a motor BCI include the following: (1) recordings of neural activity, (2) algorithms to transform the neural activity into control signals, (3) an external device driven by these control signals, and (4) feedback regarding the current state of the device. Many sources of neural signals can be used in a BCI. While EEG signals can be obtained noninvasively, other neural signals require invasive placement of electrodes. Three invasive sources of neural sig nals include electrocorticography (ECoG), action potentials or spikes, and local field potentials (LFPs). Spikes and LFPs are recorded with electrodes that penetrate the cortex. “Spikes” represent high-bandwidth signals (300–25,000 Hz) that are recorded from either single neu rons or multiple neurons (“multiunit”). LFPs are the low-frequency (~0.1–300 Hz) components. In contrast, ECoG is recorded from elec trodes that are placed on the cortical surface. ECoG signals may be viewed as an intermediate-resolution signal in comparison with spikes/ LFPs and EEG. While it is worth noting that there is still considerable ongoing research into the specific neural underpinning of each signal source, there has been great progress in the ability to decode a user’s intention. A central goal of the field of BCIs is to improve function in patients with severe disability. This can consist of a range of communication and assistive devices such as a computer cursor, keyboard control, wheelchair, or robotic limb. In the ideal scenario, the least invasive method of recording neural signals would allow the most complex level of control. Decades of research in nonhuman primates and early-phase clinical trials have demonstrated the feasibility of direct neural control of assistive technology based on recording of neural signals at multiple resolutions. There have been numerous examples of human subjects with a range of neurologic illnesses (e.g., brainstem stroke, ALS, spinal cord injury) who have demonstrated the actual use of implantable neu ral interfaces. This includes demonstrations of both the control of com munication interfaces as well as robotic limbs. Early pilot clinical trials of BCIs based on invasive recordings of neural signals showed that relatively high rates of brain-controlled typing are possible (e.g., >30 characters per minute). A past case study additionally demonstrated that a fully implantable BCI system could allow communication in a locked-in ALS patient (Fig. 500-6). At the time of the study, the patient required mechanical ventilation and could only communicate using eye movements. She was implanted with multiple subdural cortical electrodes; the neural signals were then processed and sent wirelessly to an external augmentative alternative communication (AAC) device.

A Posterior Anterior e1 e2 e3 e4 Electrode strip D Tablet Transmitter (implanted device) FIGURE 500-6 Illustration of an amyotrophic lateral sclerosis (ALS) patient with a fully implanted communication interface. A. Illustration of the location of electrodes on the brain. B. X-ray of chest showing the wireless module. C. X-ray of leads and wire routing. D. Schematic of the subject performing a typing task. (From MJ Vansteensel et al: Fully implanted brain–computer interface in a locked-in patient with ALS. N Engl J Med 375:2060, 2016. Copyright © 2016 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.) Importantly, she could use the interface with no supervision from research staff, albeit with a relatively low communication rate. Over the past 5 years, there has been tremendous progress toward the goal of restoring much higher rates of communication in partici pants with severe impairments. These studies have used either ECoG or spike-based decoding. One of the first studies indicated that a participant with a brainstem stroke and anarthria could communicate using a set of 50 words. Two subsequent studies showed that decoding a significantly larger set of words is possible, using either spiking or ECoG. For example, one study, using spike-based recordings, indicated that decoding of a large vocabulary was possible using phoneme-based decoding; that is, an arbitrary and a remarkably large set of words could be decoded by decomposing into its set of phonemes. Together, these studies indicate the real possibility of a clinically viable speech neuroprosthetic to restore fast communication in those with anarthria or severe dysarthria. Overall, there has been tremendous progress recently in the transla tion of BCIs. There are now also multiple commercial efforts to take these findings from pilot studies and to scale them to a commercially viable device. In fact, there is already a single participant with tetraple gia implanted with a first-in-class commercial device that can record spiking activity. While there are still challenges with long-term stability, this participant appears to be using this implanted device to control a computer (e.g., to control a cursor and to play video games) in the home setting. Additional work will be required to fully quantify how stable neural interfaces are and the level of performance that can be reliably achieved. As these characteristics become increasingly clear,

B C Electrodes (implanted) Ventilator Antenna CHAPTER 500 Receiver Emerging Neurotherapeutic Technologies it should allow targeted clinical translational efforts that are geared toward specific patient needs and preferences (e.g., extent of disability, medical condition, noninvasive vs invasive). For example, patients with high cervical injuries (i.e., above C4, where the arm and the hand are affected) have rehabilitation needs different from patients with lower cervical injuries (i.e., below C5–C6, where the primary deficits are the hand and fingers). Moreover, interfaces to restore communication may be different from those aimed toward movement control. We fully anticipate that over the next decade there will be larger scale clinical studies to demonstrate how BCIs allow participants with severe impair ments to experience the ability to communicate and to control assistive technology. ■ ■FURTHER READING Baniqued PDE et al: Brain-computer interface robotics for hand rehabilitation after stroke: A systematic review. J Neuroeng Rehabil 18:15, 2021. Bassett DS et al: Emerging frontiers of neuroengineering: A network science of brain connectivity.

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