Emerging NeurotherapeuticTechnologies

KEY CLINICAL POINTS

1. See source text for full details

FIGURES IN THIS CHAPTER

RAW CONTENT

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Emerging

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Technologies

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CHAPTER

500

FURTHER READING emerging diagnostic and therapeutic approaches that have the poten-

Barabasi A-L et al: Network medicine: A network-based approach to tial to transform the lives of patients with neurologic disorders. These

human disease. Nat Rev Genet 12:56, 2011. include technologies to harness plasticity, neuroimaging, neurostimu-

Cheng F et al: Network-based approach to prediction and population- lation, and brain–machine interfaces.

based validation of in silico drug repurposing. Nat Commun 9:2691,

2018. NONINVASIVE TECHNOLOGIES TO

Liu X et al: Robustness and lethality in multilayer biological networks. HARNESS PLASTICITY

Nat Commun 11:6043, 2020. Neurologic rehabilitation aims to harness activity-dependent plasticity

Loscalzo J et al (eds): Network Medicine: Complex Systems in Human mechanisms to maximize functional restoration. This principle can

Disease and Therapeutics. Cambridge, MA, Harvard University Press. be applied to a diverse range of functional domains such as move-

 ment control, sensory processing, language, pain, and cognition. For

 example, recent randomized controlled clinical trials for motor recov-

Loscalzo J et al: Human disease classification in the postgenomic era: ery after stroke have suggested that intensity of training may be par-

A complex systems approach to human pathobiology. Mol Syst Biol ticularly important for sustained long-term improvements. Moreover,

3:124, 2007. studies of the effects of such training in rodent and nonhuman primate

Maiorino E, Loscalzo J: Phenomics and robust multiomics data models further suggest that plasticity of cortical "motor maps" as well

for cardiovascular disease subtyping. Arterioscl Thromb Vasc Biol as the coordinated firing of neurons in remaining networks underlie

43:1111, 2023. observed functional improvements with rehabilitation. The incorpora-

Menche J et al: Disease networks. Uncovering disease-disease rela- tion of technology for neurologic rehabilitation has the great potential

tionships through the incomplete interactome. Science 347:1257601, to revolutionize the delivery of care by significantly increasing access,

2015. reducing the burden for adherence to high-intensity regimens, and

Oldham WM et al: Network analysis to risk stratify patients with exer- maximizing engagement. Below are three examples of how emerging

cise intolerance. Circ Res 122:864, 2018. technology can be used to harness neural plasticity and maximize

Paci P et al: Gene co-expression in the interactome: Moving from functional restoration.

correlation toward causation via an integrated approach to disease

module discovery. NPJ Syst Biol App 7:3, 2021. ROBOTICS

Wang R et al: Multiomics network medicine approaches to precision Rehabilitation robotics for both the upper and the lower limb have

medicine and therapeutics in cardiovascular diseases Arterioscl the potential to improve motor outcomes after stroke or other forms

Thromb Vasc Biol 43:493, 2023. 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 per-

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spective of the health care system and each patient. Outside of clinical

Technologies trials, such a training program can be quite difficult to implement and

maintain. It can also be costly and require significant effort.

Motor rehabilitation protocols using robotics have been developed

Jyoti Mishra, Karunesh Ganguly

and tested for both the upper limb and the lower limb. Such robotic

therapies have often focused on the delivery of high-intensity move-

ment practice that can surpass what is possible via existing standards

Neurotherapeutic technologies represent a diverse group of very of care. Moreover, robotic systems are capable of precisely measuring

promising treatment approaches with a common purpose of improving movement parameters (e.g., the kinematics of the movements) and

neurologic function. Decades of basic science research have paved the providing quantitative feedback regarding the changes in performance

path for these novel technologies that have the potential to transform during the training period. A particular focus has been on maximizing

the lives of patients with neurologic diseases. A key goal is to minimize patient engagement and recruitment of attentional and reward path-

the consequences of lost abilities, whether they are motor, sensory, or ways, both of which are increasingly recognized to drive neural plastic-

cognitive. A common objective is to also harness the inherent plastic- ity. Ongoing advances in design and the user interface will continue to

ity of the nervous system, regardless of age, and even in the face of a improve comfort and support sustained effort. For example, via close

degenerative process. monitoring of performance and movement parameters, the system

The technologies described below are the culmination of both an can aid at key points in order to minimize fatigue and ensure maximal

increased understanding of neural plasticity mechanisms in both the engagement. Moreover, antigravity support of the upper limb can allow

intact and the injured nervous system as well as advances in technol- practice and task engagement even in the presence of severe weakness;

ogy and computational power. While it is also clear that there may be this would be extremely challenging and labor intensive under current

fundamental limits on plasticity and repair mechanisms (the closing of standards of care. Recent analysis also suggests that robotic devices

developmental windows and/or loss of the ability of a network to com- may at least match outcomes realized with existing standards of care.

pensate), the brain remains highly plastic regardless of age and even in However, rehabilitation robotics may also provide more precise feed-

the face of ongoing injury and/or degenerative processes. Collectively, back and permit novel quantitative rehabilitation approaches.

there is now growing evidence to support neurologic restorative efforts Figure 500-1 shows one example of an upper-limb robotic exoskel-

for both “static” (e.g., stroke) and progressive neurologic disorders. eton device that is currently being evaluated for training after stroke.

These technologies may not appear, at first glance, directly relevant A randomized, multicenter trial compared treatment with this exo-

to traditional medical care, but it is worth noting that clinicians have skeleton system against conventional therapy provided by physical and

the most knowledge and experience about specific disease processes, occupational therapists. Participants were enrolled in the chronic phase

available treatments, and the expected course of illnesses affecting and all had moderate-to-severe deficits; the groups underwent three

the nervous system. It is thus critical that neurologic specialists and sessions per week over an 8-week period. For robotic training, subjects

other clinicians play an important role in the future adoption of these trained with games to improve mobilization and to practice activities of

technologies for neurologic rehabilitation. The sections below outline daily living. This study provided evidence that both conventional and

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PART

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Emerging

Topics

in

Clinical

Medicine

enhanced view of the world around. AR is being tested in a diverse

group of patients with neurologic impairments in the motor,

FIGURES & ILLUSTRATIONS — FROM HARRISON'S

■ 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 population-based validation of in silico drug repurposing. Nat Commun 9:2691, 2018.

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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.

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500 Emerging Neurotherapeutic Technologies

Jyoti Mishra, Karunesh Ganguly

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 plasticity 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

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

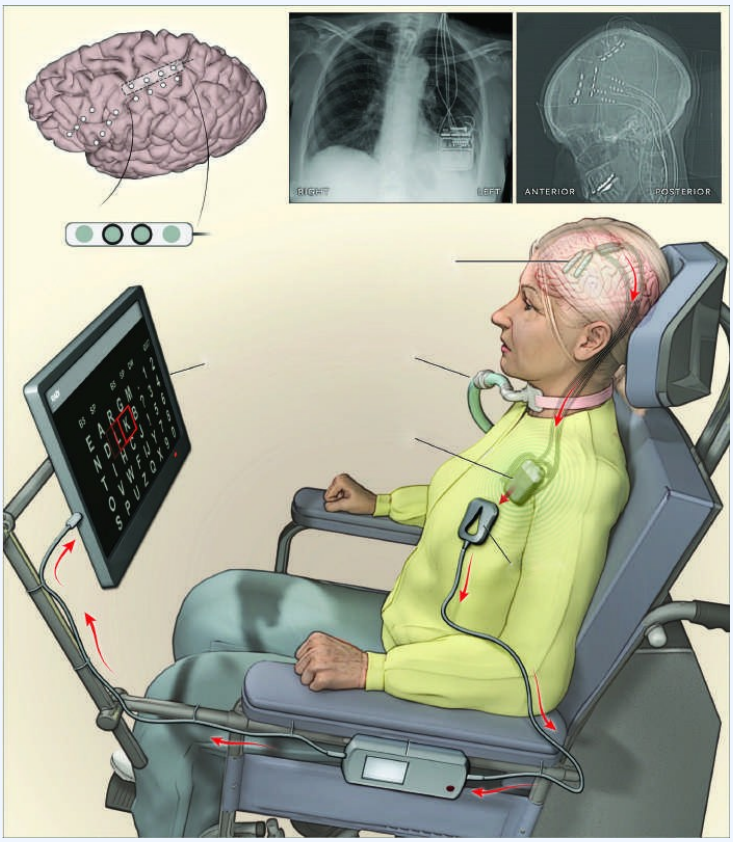
Rehabilitation robotics for both the upper and the lower limb have the potential to improve motor outcomes after stroke or other forms of brain injury. There is a growing recognition that focused training involving a range of tasks might be important for improved functional outcomes. While there is a 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.

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 feedback 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

Harrison's 22e · Figure 1

Figure 500-1 shows one example of an upper-limb robotic exoskel- eton device that is currently being evaluated for training after stroke. A randomized, multicenter trial compared treatment with this exo- skeleton 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

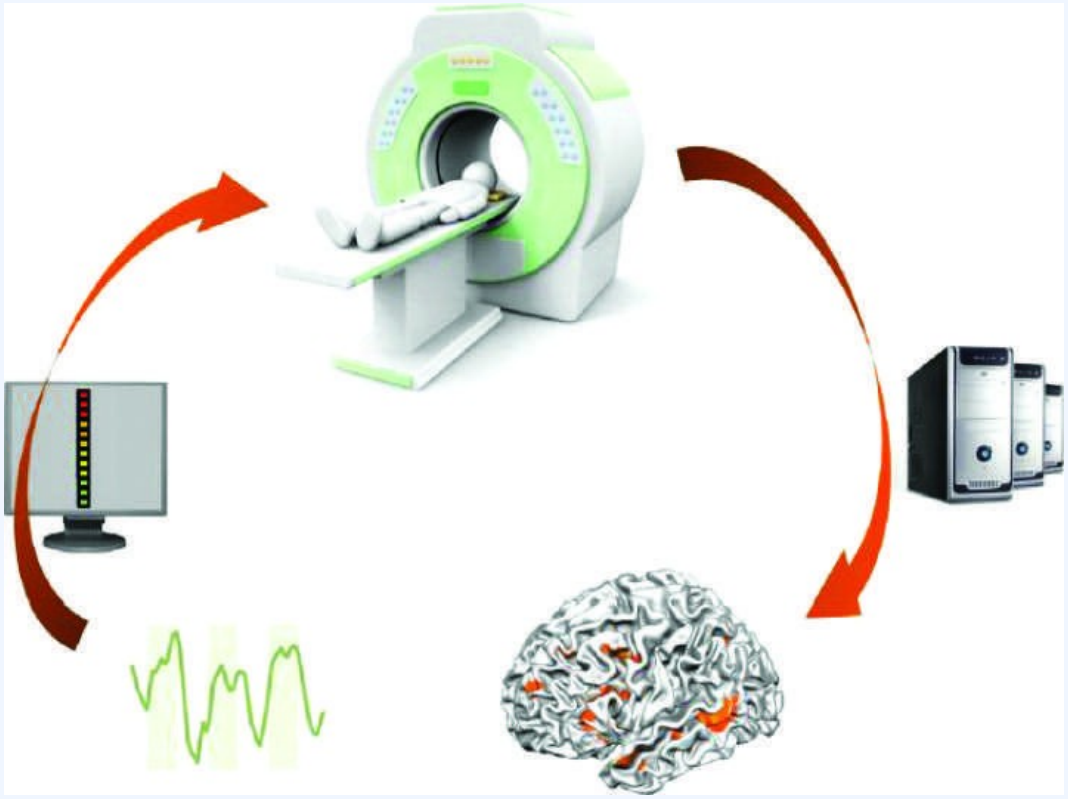


Harrison's 22e · Figure 2

FIGURE 500-6 Illustration of an amyotrophic lateral sclerosis (ALS) patient with a fully the brain. B. X-ray of chest showing the wireless module. C. X-ray of leads and wire et al: Fully implanted brain–computer interface in a locked-in patient with ALS. N Engl J with permission from Massachusetts Medical Society.)

Harrison's 22e · Figure 3

FIGURE 500-2 Augmented reality (AR) for phantom limb pain. A. A patient is shown a live activation during training. C. The patient matches target postures during rehabilitation. (M Ortiz-Catalan et al: Phantom motor execution facilitated by machine learning and patients with chronic intractable phantom limb pain. Lancet 388:2885, 2016.)



Harrison's 22e · Figure 4

FIGURE 500-3 Neurofeedback using functional magnetic resonance imaging (fMRI). neurocognitive models of auditory-visual hallucinations into therapy. Front Psychiatry

Harrison's 22e · Figure 5

FIGURE 500-2 Augmented reality (AR) for phantom limb pain. A. A patient is shown a live activation during training. C. The patient matches target postures during rehabilitation. (M Ortiz-Catalan et al: Phantom motor execution facilitated by machine learning and patients with chronic intractable phantom limb pain. Lancet 388:2885, 2016.)

Harrison's 22e · Figure 6

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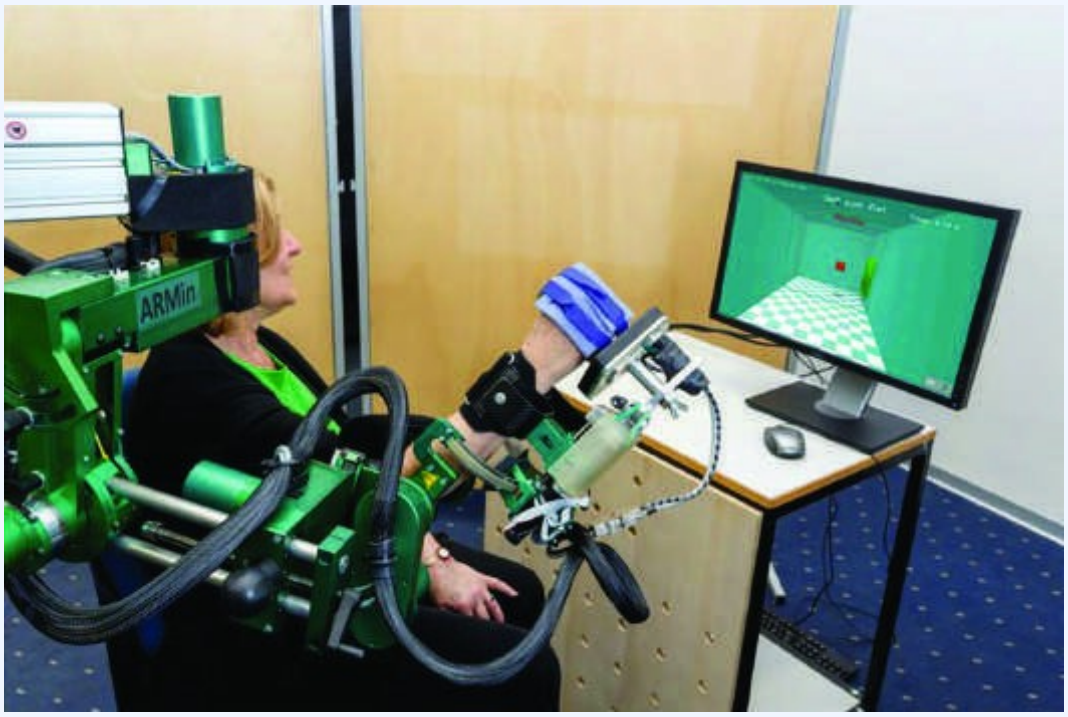
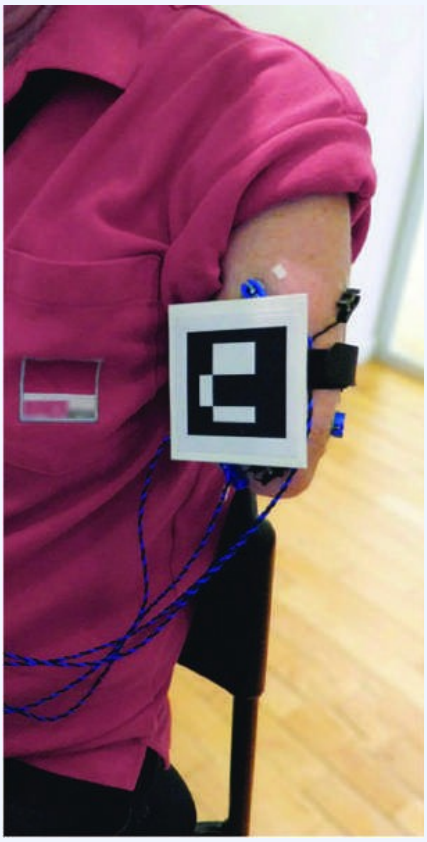


Harrison's 22e · Figure 7

FIGURE 500-1 Photograph of a subject interacting with a complex upper-limb to enhance visual feedback during gait training. 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 Figure 500-2 shows an innovative application of AR for the treat- One 10:e0126948, 2015.) ment of "phantom limb" pain. A subset of both upper-limb and lower- limb amputees experience painful sensations that appear to originate from the missing limb. Past research has suggested that mirror therapy robotic therapy could improve function in patients with chronic stroke. can be an effective treatment for phantom limb pain. During mir- Multiple studies have also found similar gains when using either con- ror therapy treatments, patients move their healthy arm in front of ventional or traditional approaches. Thus, a growing body of research a mirror to produce a perception of movements of the missing limb.



Harrison's 22e · Figure 8

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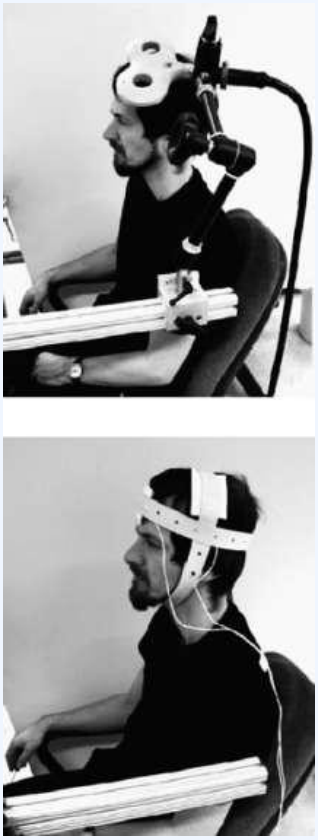

Harrison's 22e · Figure 9

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.)

Harrison's 22e · Figure 10

a FIGURE 500-5 Components of a brain–machine interface (BMI). (Reproduced with A Tsu et al: Cortical neuroprosthetics from a clinical perspective. Neurobiol Dis 83:154, to each individual are lacking. BCIs offer a promising means to restore through patient groups described above, while the pathways for Recent studies of signals to muscles are disrupted, the brain itself is largely patterns of net- Thus, BCIs can restore function by communicating how the patient brain. For example, in a "motor" BCI, a subject's intention studies that aim translated in real time to control a device. As illustrated in the components of a motor BCI include the following: (1)