Published in final edited form as:

Semin Neurol. 2021 April ; 41(2): 206–216. doi:10.1055/s-0041-1725137.

Brain-computer interfaces in neurorecovery and neurorehabilitation

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Abstract

Recent advances in brain-computer interface technology to restore and rehabilitate neurologic function aim to enable persons with disabling neurologic conditions to communicate, interact with the environment, and achieve other key activities of daily living and personal goals. Here we evaluate the principles, benefits, challenges and future directions of brain-computer interfaces in the context of neurorehabilitation. We then explore the clinical translation of these technologies and propose an approach to facilitating implementation of brain-computer interfaces for persons with neurologic disease.

Keywords

Brain-computer interface; neurorecovery; neurorehabilitation; neurotechnology; brain-machine interface

I. Introduction

The co-evolution of computer technology, bioengineering and neuroscience over the past two decades has enabled the potential for unprecedented advances in facilitating neurorecovery through brain-computer interfaces (BCI). The rapidly expanding BCI technology field and its implications for clinical research and practice is of growing importance for clinicians who seek to deliver optimal care to persons with lasting functional deficits resulting from neurologic disease or neurotrauma.[1,2] By enabling restoration or replacement of lost function, BCIs have the potential to improve quality of life by enhancing the autonomy and agency of users, ameliorating isolation, and promoting societal re-integration.[3,4] Here, after reviewing the principles, benefits, challenges and opportunities of BCIs in the context of neurorecovery, clinical translation of these technologies is explored,

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and a practical approach to facilitating access to BCIs for people with neurologic disease in different phases of care is proposed. Here, we use the term “neurorestoration” to refer to the restored function that results immediately from use of a technology (in this case, a BCI). “Neurorehabilitation” is used to refer to the process by which the remaining/intact neural system regains the ability to perform a function. “Neurorecovery” is our more general term for the goal, which is agnostic to approach.

What is a Brain-Computer Interface?

A brain-computer interface (BCI) is a system that translates central nervous system (CNS) signals into command signals for an external or internal device. The historical groundwork for BCI technology was set in the 1800s by the pioneering research of Richard Caton, Adolf Beck and Hans Berger whose discoveries surrounding continuous electrical activity in the brain provided a substrate for the measurement and manipulation of nervous system signals.[5,6] These discoveries paved the way for the key non-human primate research and later development and deployment of EEG neurofeedback and the first BCI prototypes.[7–12] The term BCI has since come to encompass a broad array of technologies that interface with the nervous system, from cochlear implants to restore hearing to the NeuroPace device, a responsive neurostimulator for the treatment of medically refractory epilepsy.[13,14] Broadly construed, BCIs serve to restore or rehabilitate function, with the ultimate aim of improving users’ capacities to communicate, interact with the environment, and achieve other personal goals.[15]

Restoration of lost function typically entails bypassing a lesion incurred by disease or trauma, with the aim of directly supplanting the function lost. Examples of this include BCI-enabled prosthetic arm control to supplant lost limb function[16–22] or BCI-enabled typing or speech to supplant impaired verbal communication capability.[23–31] In so doing, such technologies facilitate novel means to perform an activity in a manner that bypasses the lesioned area that is ordinarily engaged in performing that function.

Rehabilitation of function through BCIs typically involves the use of neurofeedback with or without neural stimulation, with the goal of promoting plasticity and enabling re-learning of a lost function.[32] Instead of bypassing a deficit-producing lesion, rehabilitative BCIs aim to promote the nervous system’s ability to re-learn previously lost or deteriorated function.[33] One example is training on a BCI orthosis system with the goal of ultimately restoring *native* upper extremity function for patients with hemiparesis after stroke.[34–36] Rehabilitative BCI techniques that aim to shape or engage cortical/subcortical/spinal plasticity to facilitate neural re-learning and re-mapping may be coupled with restorative BCI systems and operate synergistically.[37]

Another emerging role of BCIs is to improve diagnostic precision in disorders of consciousness, thereby illuminating opportunities for neurorehabilitation. BCIs may foreseeably aid in assessing covert responsiveness (i.e., responsiveness that is not detectable on bedside neurologic exam) in persons with disorders of consciousness; such persons are often misdiagnosed with traditional behavioral assessments that rely heavily on intact motor systems or higher-order cognitive abilities to infer level of awareness.[38–41] For example, one BCI system has been used to complement assessment of visual fixation;[42] by coupling a computer-based visual fixation task with EEG to detect event-related potentials occurring with visual fixation, the system aims to aid in detection of awareness that can sometimes evade bedside behavioral assessment.[42,43]

Populations commonly cared for by neurologists who may benefit from BCIs include people with syndromes resulting from disconnection of the pathways to peripheral neuromotor targets with resulting severe speech and motor impairments. This includes those who have sustained functional deficits due to stroke, spinal cord injury, traumatic brain injury, motor neuron disease, multiple sclerosis, locked in syndrome, cerebral palsy, and disorders of consciousness.[44–46]

II. The Components of a BCI: Actuating Cognition

The components of BCIs include the trio of sensor, decoder and effector.[47] The BCI sensor serves to detect and record neural data, and a decoder then processes and converts this data into a command signal that is transmitted to an effector to carry out relevant function. Critically, sensory feedback is provided to the user, traditionally in the form of visual feedback.[48,49] Auditory[50] and haptic feedback approaches[51,52] are also being explored.

BCI Sensors: Capturing Intention

BCI sensors primarily detect electrical, hemodynamic or magnetic signals from the central nervous system. Sensors designed to detect electrical signals utilize methods such as scalp-based electroencephalography (EEG), brain surface-based electrocorticography (ECoG), and intracortical microelectrodes. Sensors designed to detect hemodynamic signals utilize methods such as functional magnetic resonance imaging (fMRI) and functional near-infrared spectroscopy (fNIR), which rely on changes in blood oxygenation to localize neural activity of interest.[53,54] Magnetoencephalography (MEG) is the primary modality used to sense magnetic brain signals induced by synchronized neural currents.[55] Multimodal sensors may combine detection of different signals to enhance performance. Examples of multimodal sensors include combinations of MEG and EEG[56], or of EEG and fMRI.[57] Sensors can be distinguished by their location (e.g., implanted within deep brain structures, or within cortex, or subdural, epidural, intra- or epicranial, on the scalp, or external to the head), temporal resolution (i.e., sensing speed), spatial resolution (i.e., sensing detail), signal-to-noise ratio, sensor size, and ability to record signals for an extended period of time.[58] Electrical sensors, and specifically EEG and MEGs, are the two most common types of BCI sensors used toward the restoration of movement and communication for people with neurologic disease.

Neural Decoding: Translating Neural Information

After neural activity or its proxy is captured and recorded by a sensor, a BCI decoder uses an algorithm to process this information and produce a signal that can be transmitted to an effector to actuate a helpful output. Neural decoding algorithms associate patterns of neural activity with intended user behavior.[47,59] While initial neural decoding algorithms relied on linear statistical analyses (such as the Kalman filter, also known as linear quadratic estimation), advances in computational power and artificial intelligence are leading to improvements in BCI performance through machine learning techniques.[60,61]

These advances in neural decoding hold promise for improved BCI performance by accounting for the variability in neural activity that has historically proved to be a challenge to some BCI's consistency in inferring intended user action.[29]

Neural effector and Feedback: Bringing Intention to Action

BCI effectors process signals received by a neural decoder to produce a desired output. Examples of BCI effectors include computer cursors[62], robotic orthoses,[63–67] exoskeletons[68–70], wheelchairs[71–73], virtual reality environments (i.e., computer-generated simulations that allow users to interactively practice activities)[74–76], artificial voice[77,78], flash spellers[79–83], or reanimation of one's own limb.[84,85 86–88]

Neurofeedback is a critical component of both restoration of function (closed-loop control) as well as rehabilitation of function. The most common neurofeedback strategy has been audiovisual (AV) feedback.[89] Real-time AV feedback to subjects has been studied in aiding task-specific training and recovery.[90] Neurofeedback strategies also include neuromodulation techniques, such as adaptive deep brain stimulation, and non-invasive brain stimulation, directed at changing the nervous system to achieve improved motor/cognitive/mood aims.[91] For example, through haptic or behavioral feedback techniques, persons with limb weakness resulting from stroke may learn to improve ipsilesional mu-rhythm activation and upregulate ipsilesional sensorimotor networks.[91–93]

A critical component of BCIs is the feedback provided, which "closes the loop" between the device and user. This could come in the form of pure visual feedback, for example a 2-dimensional cursor control on a computer screen or multidimensional robot arm movement, or through visual and sensory feedback during functional electrical stimulation (FES)-induced movement of one's own arm and wrist.[94] This feedback has been shown to influence the tuning properties of individual neurons and cortical networks involved in BCI control, a concept called *closed-loop neural adaptation*.[95] BCI neurofeedback has been shown to change properties of the neurons and groups of neurons involved in BCI control[96,97], and the implications of these changes for closed-loop BCI control are being further explored.[98] Systems-neuroscience level neurofeedback paradigms are currently being explored to enhance neurorehabilitation.[99]

III. BCIs in Neurorecovery and Neurorehabilitation

In the context of neurorecovery and neurorehabilitation, a BCI may aim to restore a capacity lost due to injury or disease. Capacities that BCIs may serve to restore include communication, motor function, mobility, autonomic functions (bowel, bladder and sexual functions), hearing (through cochlear implants), and vision (retinal prostheses).

BCIs may alternatively serve to induce plasticity in neural circuits in order to regain *native* function after neural injury. The brain's capacity for structural reorganization was studied and codified by neuropsychologist Donald Hebb, who proposed that "[w]hen an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased…any two cells or systems of cells that are repeatedly active at the same time will tend to become 'associated,' so that activity in one facilitates activity in the other."[100] The notion that co-active cells could form stronger synaptic connections in rich learning environments is a principle now known as Hebbian plasticity. The short mantra is that "neurons that fire together wire together."[101] In line with this principle, some BCIs aim to induce patterned recruitment of neurons to strengthen synaptic connections sub-serving functions that have been impaired due to neural damage. Approaches to inducing neural plasticity include repetitive stimulation of a neural pathway, paired stimulation of multiple points in a neural pathway, or closed-loop stimulation, a technique that uses endogenous activity at one point in a pathway to trigger activation of a second point in a neural pathway.[102]

IV. BCIs in Clinical Translation

How may clinicians prescribe a BCI to a person who might benefit?

In order for a BCI system to enter into clinical use in the field of neurorehabilitation, a series of complex development phases and checkpoints must be met.[103,104] The bench to bedside costs of medical device development are substantial.[105] From its nascent stages of research design and development, a BCI system must pass through clinical trials to demonstrate safety and, hopefully, efficacy, attain clearance from relevant regulatory bodies (such as the FDA in the United States), and succeed in manufacturing and marketing before finally arriving at clinical implementation. This complex landscape may prove challenging to navigate not only for researchers but also for clinicians interested in providing BCIs to patients in clinical practice.

The FDA has taken a leading role in crafting a roadmap for the regulatory assessment of BCIs, releasing draft guidance in February 2019 on "Implanted Brain-Computer Interface (BCI) Devices for Patients with Paralysis or Amputation – Non-Clinical Testing and Clinical Considerations."[106] The NeuroTech Network (http://www.neurotechnetwork.org) is a non-profit organization that promotes advocacy for, access to, and awareness of neurotechnology products including BCIs for persons with impairments, and provides resources for learning about available categories of neurotechnologies for patients and providers. While clinicaltrials.gov captures most ongoing BCI research in the US, to date there is no unified, routinely updated repository of clinically actionable knowledge of available BCIs for clinicians, patients or surrogates to reference and utilize. Such a resource could serve to increase access to the latest in BCI technology. The emergence of consumer applications may be valuable in their ability to gather considerable capital to advance technology development, but may also confuse consumers regarding the ability of these devices to provide efficacy in a medical context.

Clinicians interested in providing BCIs to persons who might benefit from them should be aware of the following three categories of products, stratified according to stage of development: (1) BCIs approved for clinical use and available through manufacturers (2) BCIs under clinical study and available through active clinical trials (3) BCIs in pre-clinical development.

BCIs approved for clinical use

The category of BCIs approved for clinical use includes deep brain stimulation systems for persons with movement disorders or epilepsy (including NeuroPace, which relies on an implanted ECoG strip electrode to detect epileptogenic activity and responsively deliver electric pulses to preempt impending seizures). While open-loop DBS is FDA-approved, closed-loop DBS systems whose neuromodulatory outputs are determined in part by brain-recorded and decoded signals, are still investigational. The NeuroPace system is estimated to cost 30,000–40,000 USD and is covered by major insurance companies for patients with refractory focal epilepsy who are not candidates for epilepsy surgery.[107] The costs of BCIs are inclusive of materials, surgical placement (when required) and support services; there is no uniform policy of reimbursement for BCIs among insurers and government programs.[108]

Neurotechnologies for neurorecovery that have been approved for clinical use span beyond the class of BCIs, and include myoelectric orthoses for persons who have lost limb function due to amputation or spinal cord injury, wearable robotic exoskeletons, and cochlear implants. While not the primary focus of this review, clinicians should be aware of several of these neurotechnologies given their clinical availability and utility in neurorecovery. The first FDA-approved neuroprosthesis was the NeuroControl Freehand System, which restored hand function in patients with spinal cord injuries; unfortunately, manufacturing of this system is no longer ongoing, despite the technical success of the product and satisfaction of its users.[104,109] The DARPA-funded DEKA LUKE arm system was FDA-approved for clinical use is 2014. It uses EMG electrodes to sense user-intended movement and translates these signals into complex movements with multiple degrees of freedom. The cost of the LUKE arm is around 150,000 USD and may be a covered service by the Veterans Affairs (VA) but is not by most insurance companies.[110] Other neuromuscular prostheses, including a bone-anchored robotic arm with implanted electrodes in nerves and muscles of the upper arm allowing for bidirectional sensorimotor communication with a prosthetic hand, are in active development and have been integrated into daily use for some patients.[111] The ReWalk robotic exoskeleton, manufactured by ARGO Medical Technologies (Israel), Ekso GT, by Ekso Robotics (California), and Indego, by Parker Hannifin (Ohio), are FDA-approved devices that enable user-initiated lower extremity motion through wearable robotic support systems.[112,113] The cost of ReWalk is around 80,000 USD and is covered through the VA Choice program for eligible veterans but is not covered by most insurance companies.[114] Prerequisites for its use include spinal cord injury; height between 160 cm and 190 cm (5’3– 6’2); weight below 100 kg (220 lbs); healthy bone density; absence of severe spasticity, cognitive conditions that could interfere with the operation of the device, significant contractures, or history of severe neurologic illness other than spinal cord injury.[115] Ekso GT was the first exoskeleton FDA-approved for stroke patients.[116,117] These products are available through their respective manufacturers and distributors, and through networks of training centers listed online.[112,113,115]

BCIs under clinical investigation

Most patients using clinical-grade BCIs today are doing so as part of clinical trials. As of May 2019, there are currently 93 brain-computer interface projects with registered clinical trials. Clinicians can visit www.clinicaltrials.gov and search by eligibility criteria, study type and location to find which trial(s) a patient might be suitable for, and contact information for study coordinators to determine patient eligibility and coordinate enrollment. Once eligibility has been determined, study coordinators work with patients and families to orchestrate necessary steps in enrolling.

The category of BCIs under development contains a broad array of investigational technologies. In the context of neurorehabilitation, these include technologies to restore communication, motor function and mobility; to enhance sleep, awareness and cognition; and to restore autonomic functions including bowel, bladder and sexual functions. Patients, families and clinicians should be made aware of BCIs on the horizon which may bear on future approaches to neurorecovery while reinforcing realistic expectations. Knowledge of available and emerging BCIs that may aid in restoration or rehabilitation of function may serve to counter therapeutic nihilism sometimes encountered in settings of acute devastating neurologic injury, and aid in optimally informing decision-making for patients, families and clinicians.[118]

There are a variety of research groups actively investigating and improving BCI technology in both animal and human research. A milestone in restorative BCI for communication was recently achieved with the application of deep-learning methods to reconstruct neural signals detected by implanted electrocorticography (ECoG) devices into audible language in human subjects.[77,78]

V. Challenges and Potential Solutions for BCI Translation

Despite significant promise, a variety of scientific, technical, clinical, ethical, and economic steps have limited the clinical translation of BCIs.

From an engineering standpoint, the ability of implanted sensors to reliably detect and record signals[119] may depreciate with time, for a variety of reasons that have been attributed to reactive gliosis[120] and inflammation[121], micromovement, mechanical breakdown[122], or changes in impedance that may progress as a device remains implanted.[123–128] The relative contributions of these factors to the decline (which can occur slowly, over many months to years) are not clear. Recent advances in materials chemistry, computational modeling, and nanotechnology, however, enable construction of more durable sensors to withstand the challenges faced by earlier materials.[129–131] Coupled with developments in sensor calibration and signal decoding utilizing machine learning techniques, these advances portend more robust, reliable and accurate BCIs in coming years.

Even if an efficacious, safe and beneficial technology is devised, if the target patient population is small or economically disenfranchised, deployment can prove unsustainably expensive, especially given the multidisciplinary team required for implementation and support. The NeuroControl Freehand System, which restored hand function in patients with spinal cord injuries but was discontinued in 1998 despite technical success, is an example of this.[104] These barriers are especially high in the case of implanted BCIs. Recognizing these factors and the unmet public health needs that BCIs promise to meet, the FDA's Center for Devices and Radiological Health (CDRH) has introduced new mechanisms for expedited access, efficient review (including a joint-review mechanism with CMS), and pre-submission assessments to streamline the development cycle and catalyze clinical translation while maintaining safeguards on patient protection.[104,106]

From a clinical standpoint, many patients and clinicians lack actionable knowledge about BCIs and how they can be applied toward care.[132] For clinicians actively caring for patients with BCIs, relevant outcome measures and methods for evaluating performance and patient satisfaction may be opaque. Closer collaboration among engineers, clinicians, patient advocates, and other stakeholders will be instrumental in ensuring that clinical outcome measures are clear, patient priorities are met, risk-benefit balance is optimized, and public-health impact is maximized. Before prescribing a BCI, which might entail referral to a specialty center or consultation with an expert in the relevant domain, clinicians and researchers should ensure realistic expectations among users and caregivers. This should include detailed discussions of the risks, benefits and potential shortcomings of the relevant BCI.[133]

In the absence of a uniform policy of reimbursement for BCIs among insurers and government programs, the current costs of BCIs may affect their adoption.[108,134] In the event that a BCI is not paid for by insurance, patients may be responsible for the costs; some have turned to medical crowdfunding for this purpose, a trend that has raised ethical and social issues.[135] Recognizing these obstacles, more uniform reimbursement policies are needed to help ensure that BCIs are affordable and equitably accessible to those in need. Such policies will undoubtedly be easier to develop once BCIs demonstrate a consistent and reliable benefit to even a small group of people, as portrayed for example in the development and deployment of the NeuroPace BCI.[136]

As BCIs continue to advance in sophistication, ethical questions relating to user agency and responsibility[137], decision-making capacity[138], shaping of personal identity[139], privacy[132,140,141], storage and sharing of recorded neural data[142], bio-enhancement applications[143], access disparities[144], and research ethics[133,145] are anticipated to grow increasingly prevalent and pertinent. Careful anticipation and evaluation of these issues can help to ensure bioethical resilience across the BCI development lifecycle and foster successful clinical translation into neurorehabilitation practice.[146–148]

Conclusions

Brain-computer interfaces offer immense potential for neurorecovery and neurorehabilitation for patients with neurologic disease. BCIs may serve to measure and restore capacities lost due to neurologic injury or disease, or to induce plasticity to improve learning and remapping after neural injury. A variety of obstacles and opportunities in successful clinical translation can be identified across the lifecycle of BCI development, from early design and discovery, to clinical trials, regulatory approval and clinical implementation. Clinicians caring for persons with neurologic impairments should be aware of the current landscape of BCIs across various stages of the development lifecycle and understand how to match BCI technologies with eligible patients. Ongoing collaboration between researchers, engineers, clinicians, patient advocates, regulatory bodies, bioethicists, payers and other stakeholders will be essential to ensure that the promises of BCIs for neurorecovery are captured and sustained in this evolving era of novel neurotechnologies.

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Figure 1.
Lifecycle of BCI Development

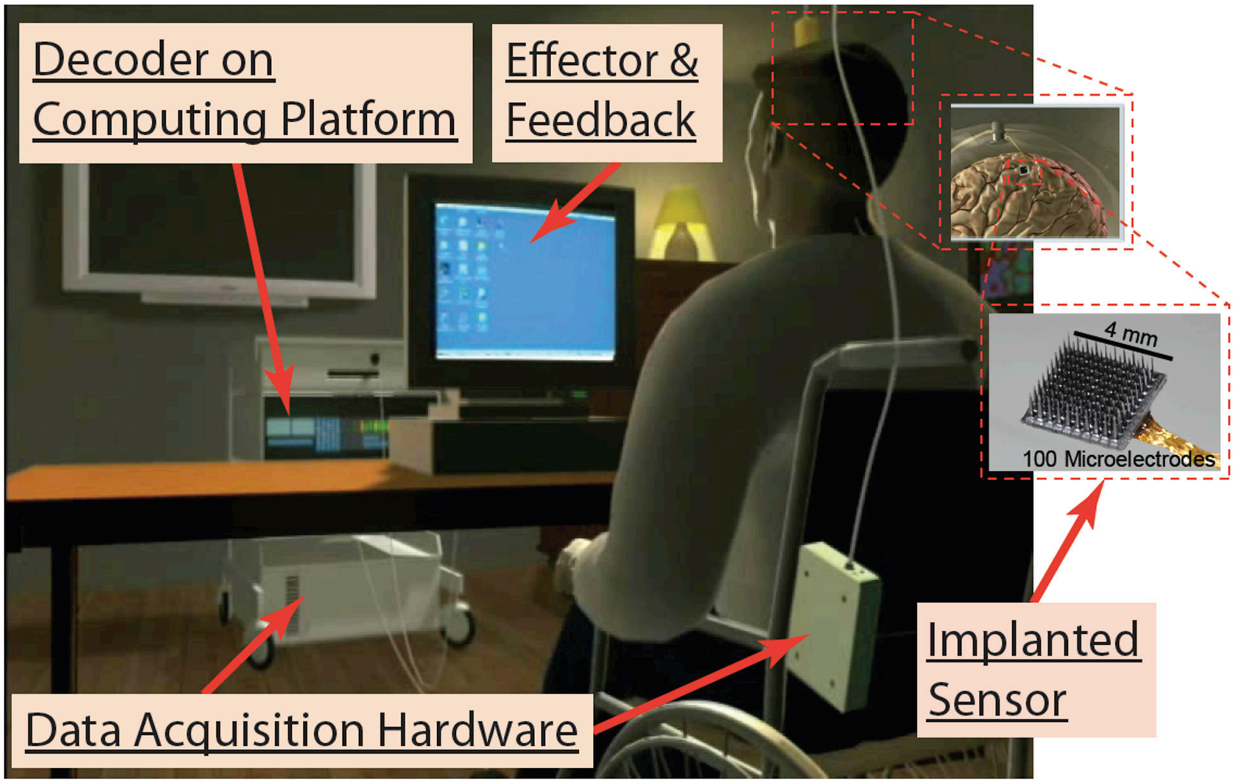

Figure 2.

Schematic of BrainGate BCI Setup. This figure depicts the percutaneous and cable-connected system used currently. Percutaneous wireless systems are in clinical testing, and fully implanted systems are in development.

Table 1.

Brain-Computer Interface (BCI) clinical trials actively recruiting.

Neurologic Condition	**BCI Intervention**	**Location**	**ClinicalTrials.gov Identifier**
Communication			
Locked in syndrome Tetraplegia	Assistive communication device that enables users to control a text-entry interface using EEG signals to compose messages.	University of Geneva, Campus Biotech Geneva, Switzerland	NCT03213561
Persons with ALS and locked-in syndrome	EEG and/or near-infrared spectroscopy (NIRS) based BCI. NIRS will be used train a classifier to predict "yes" and "no" answering patterns; for patients who can still open eyes, an EEG-controlled BCI for communication will be used.	University of Tuebingen Tubingen, Baden Wuerttemberg, Germany	NCT02980380
Tetraplegia Locked-in Syndrome Brainstem Stroke ALS	CortiCom system of high-channel ECoG grids to investigate motor imagery and imagined speech as sources for brain-computer interactions	Johns Hopkins Medicine Baltimore, Maryland, United States	NCT03567213
Tetraplegia Locked-in Syndrome ALS	Placement of BrainGate2 Neural Interface System into motor-related cortex to identify methods and features that could allow for recovery a host of abilities that normally rely on the hands.	Stanford; MGH; Case Western; Providence VA, United States	NCT00912041
Movement Control			
Traumatic Tetraplegia With Cervical Cord Injury	ECoG-enabled motorized exoskeleton	CLINATEC Grenoble, France	NCT02550522
Quadriplegia	Wireless EEG headset to control a virtual keyboard using P300 evoked related potentials (ERPs).	Hopital Raymond Poincare Garches, France	NCT01707498
Chronic Stroke Hemiparesis	Ipsihand EEG headset designed to use EEG signals from the non-lesioned hemisphere to control a motorized glove worn on the affected hand that moves the according to the type of signal detected.	Washington University in St. Louis Saint Louis, Missouri, United States	NCT03611855
Acute stroke with severe unilateral motor upper extremity hemiparesis	Neuromuscular electrical stimulation (NMES) applied contingent to voluntary activation of primary motor cortex, as detected by a subject-specific EEG patterns extracted with machine learning techniques.	Division of Neurorehabilitation, University Hospital of Geneva Geneva, GE, Switzerland	NCT03379532
Incomplete tetraplegia with injury at level C4–C8	FES-BCI: Functional electrical stimulation (FES) applied contingent to EEG patterns arising from patient thinking to move hand.	Queen Elizabeth National Spinal Injuries Unit Glasgow, United Kingdom	NCT01852279
Locked in syndrome	ECoG sensing device to control assistive technology with switch signals (such as operating home apparatus or writing text)	University Medical Center Utrecht, Netherlands	NCT02224469
Tetraplegia Spinal Cord Injury	Blackrock Microsystems NeuroPort Arrays implanted in the motor cortex for long-term neural recording and control of external devices.	University of Pittsburgh Pittsburgh, Pennsylvania, United States	NCT01364480
Spinal Cord Injuries Tetraplegia Quadriplegia	Neuroport cortical recording array to determine desired grasp patterns for FES; users will be asked to think about holding different shaped objects and corresponding cortical signal patterns will be decoded to match grasp patterns.	Louis Stokes VA Medical Center, Cleveland, OH Cleveland, Ohio, United States	NCT03482310
ALS SCI Stroke Multiple sclerosis Muscular dystrophies	ECoG-based wearable hand robotic exoskelaton	University of California San Francisco San Francisco, California, United States	NCT03698149
Stroke Upper limb impairment	FES-BCI: Functional electrical stimulation (FES) applied contingent to EEG patterns arising from user thinking to move	Centro de Referencia Estatal de Atención al Daño Cerebral	NCT03508037

Neurologic Condition	**BCI Intervention**	**Location**	**ClinicalTrials.gov Identifier**
		(CEADAC) Madrid, Spain	
ALS Shoulder trauma	EEG-based neurofeedback based on motor imaging in therapeutic videogames	Hopital PITIE SALPETRIERE Paris, France	NCT03545451
Tetraplegia Spinal Cord Injury Brainstem Stroke	Blackrock Microsystems CRS Arrays will be implanted in the motor cortex and sensory cortex and trained to send user-driven neural signals to devices or displays; microstimulation used to mimic sensory input.	University of Pittsburgh Pittsburgh, Pennsylvania, United States	NCT01894802
Spinal cord injury, brainstem stroke, muscular dystrophy, amyotrophic lateral sclerosis or other motor neuron disorder with complete or incomplete tetraplegia	Placement of BrainGate2 Neural Interface System into motor-related cortex to identify methods and features that could allow for recovery a host of abilities that normally rely on the hands.	Stanford; MGH; Case Western; Providence VA, United States	NCT00912041
Quadriplegia	Neural Communication System - Placement of Neuroport arrays into posterior parietal cortex with brain-control training of simplified computer or tablet computer environments	University of California Los Angeles Los Angeles, California, United States	NCT01958086
Quadriplegia	Neural Prosthetic System 2 (NPS2) - Placement of Neuroport arrays into posterior parietal and somatosensory cortexes with brain-control training to perform reach and grasp tasks with sensory feedback via intracortical microstimulation.	Rancho Los Amigos National Rehabilitation Center Downey, California, United States	NCT01964261
Stroke Arm paralysis	Cortimo Neuromotor Prosthetic to Treat Stroke-Related Paresis - Placement of Blackrock Microsystems Multiport to decode signals to drive activity of wearable arm orthosis	Thomas Jefferson University Philadelphia, Pennsylvania, United States	NCT03913286
Stroke with upper limb deficit	Neurofeedback for Upper-limb Recovery After Stroke (NeuroFB-AVC) - Coupled EEG-fMRI neurofeedback	Rennes University Hospital Rennes, France	NCT03766113
Pain			
Chronic Musculoskeletal Pain Tennis Elbow Lateral Epicondylitis	Neurofeedback Treatment for Chronic Musculoskeletal Pain - EEG-based neurofeedback of pain-related neuronal oscillation power as a training paradigm for controlling chronic musculoskeletal pain	Center For Sensory-Motor Interaction Aalborg, Denmark	NCT03863847
Cognitive			
Brain Injury	EEG/SSEP evaluation of attentional modulation in different conditions	Hospices Civils de Lyon Lyon, France	NCT02567201
Mild TBI PTSD	IASIS System - Transcutaneous electrical stimulation (TES) paired with resting state MEG neurofeedback	VA San Diego Healthcare System, San Diego, CA San Diego, California, United States	NCT03244475
Attention Deficit Hyperactivity Disorder (ADHD) Autism Spectrum Disorders	Computer game that uses eye-tracking and EEG to train attention and emotional recognition	Institute of Mental Health Singapore, Singapore	NCT02618135
ADHD	BCI-based cognitive training through P300-based controlled games	Hospices Civils de Lyon Bron, France	NCT03289793
Alzheimer’s disease	EEG-based neurofeedback involving intermittent audiovisual cues to adjust attentional engagement.	Oregon Health & Science University Portland, Oregon, United States	NCT03790774
Mild Cognitive Impairment	Auditory stimulation during slow wave sleep detected by polysomnography	Northwestern University Chicago, Illinois, United States	NCT02608840