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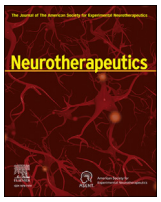

Review

The evolution of neuromodulation for chronic stroke: From neuroplasticity mechanisms to brain-computer interfaces

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ABSTRACT

Stroke is one of the most common and debilitating neurological conditions worldwide. Those who survive experience motor, sensory, speech, vision, and/or cognitive deficits that severely limit remaining quality of life. While rehabilitation programs can help improve patients' symptoms, recovery is often limited, and patients frequently continue to experience impairments in functional status. In this review, invasive neuromodulation techniques to augment the effects of conventional rehabilitation methods are described, including vagus nerve stimulation (VNS), deep brain stimulation (DBS) and brain-computer interfaces (BCIs). In addition, the evidence base for each of these techniques, pivotal trials, and future directions are explored. Finally, emerging technologies such as functional near-infrared spectroscopy (fNIRS) and the shift to artificial intelligence-enabled implants and wearables are examined. While the field of implantable devices for chronic stroke recovery is still in a nascent stage, the data reviewed are suggestive of immense potential for reducing the impact and impairment from this globally prevalent disorder.

Introduction

Due to improving techniques for treating acute stroke, more patients than ever are entering the chronic stroke phase during which motor recovery becomes significantly more challenging [1]. Approximately 34% of the global total healthcare expenditure is spent on stroke, and in the US, the economic burden of chronic stroke increases by approximately $140,000 for treatment, rehabilitation and supportive care over the course of a typical patient's lifetime [2–4]. Furthermore, incidence rates of chronic stroke are projected to grow due to a global increase in population age [2]. These worrisome trends underline the crucial need for effective rehabilitation to improve quality-of-life and enable patients to recover functional ability post-stroke.

The current standard-of-care for post-stroke recovery is physical rehabilitation, which exploits the innate neuroplasticity of the brain to restore function [1,5]. Physical rehabilitation programs, especially when delivered as soon as possible after the onset of stroke, can be highly efficacious [5]. Notwithstanding, the rate of improvement in functional ability regained through physical rehabilitation tends to peak after a few months post-stroke and eventually tapers; minimal improvement is seen after 12 months and many patients remain considerably disabled. Therefore, a critical need exists for interventions that can either increase the rate of functional recovery during the early post-stroke period or that can produce meaningful functional improvement after 12 months. Given that the nature of post-stroke functional recovery is mediated by neuroplastic changes, interventions that increase or prolong neuroplasticity have been the target of recent investigations.

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Abbreviations

BCI	brain-computer interface
CT	computed tomography
DBS	deep brain stimulation
ECoG	electrocorticography
EEG	electroencephalography
EMG	electromyography
FMA-UE	Fugl–Meyer Assessment-Upper Extremity
fMRI	functional magnetic resonance imaging
fNIRS	functional near-infrared spectroscopy
IPG	implantable pulse generator
MEG	magnetoencephalography
MRI	magnetic resonance imaging
tDCS	transcranial direct current stimulation
TMS	transcranial magnetic stimulation
US FDA	US Food and Drug Administration
VNS	vagus nerve stimulation

One such intervention is the application of electromagnetic energy to the brain in the form of neuromodulation, which has been shown to be an effective trigger for neuroplastic processes such as synaptogenesis and functional reorganization [6]. Both invasive and non-invasive modalities exist. Non-invasive modalities such as transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS), have demonstrated improvement of motor function in post-stroke patients [6]. Similarly, invasive modalities such as vagus nerve stimulation (VNS) and deep brain stimulation (DBS) show great promise in improving rehabilitation in stroke patients suffering from disabling symptoms. Moreover, there has been rapid development of therapeutic neurostimulation in the form of brain-computer interfaces (BCIs), which utilizes real-time analysis of brain states to enable automatic adjustment of stimulation parameters [7]. In this paper, we will discuss the landmark trials, current applications, and future directions of the various modalities of invasive neuromodulation for stroke rehabilitation with an emphasis on VNS, DBS and BCI.

Vagus Nerve Stimulation

Vagus nerve stimulation (VNS) is a neurosurgical procedure in which metal contacts are implanted along the proximal segment of the vagus in order to deliver electrical stimulation to the nerve [8]. The proposed mechanism of action of VNS for post-stroke motor recovery has been attributed to activation of ascending neuronal pathways associated with two key nuclei: the nucleus basalis and locus coeruleus [9–12]. Release of acetylcholine from the nucleus basalis and norepinephrine from the locus coeruleus has been shown to play roles in memory consolidation and goal-directed behavior. Studies have also shown that during task performance, brief bursts of acetylcholine and norepinephrine are present and implicated in the modulation of cortical neurons that encode behaviors associated with task performance [9,12–18]. As the vagus nerve projects directly to the nucleus tractus solitarius, which then projects to these critical nuclei (nucleus basalis and locus coeruleus), this established circuitry is what has led to the hypothesis that vagus nerve stimulation may lead to increased plasticity [17,18]. This model was further validated by rodent studies demonstrating reorganization of auditory and motor cortex when VNS is paired with an auditory tone or forelimb movement, respectively [19,20].

Given the promising pre-clinical trial data supporting VNS paired with motor rehabilitation for ischemic stroke, three landmark clinical trials were performed to further assess its efficacy in humans. The first trial by Dawson et al. was a single-blinded, randomized feasibility study evaluating VNS paired with motor rehabilitation [21]. Twenty-one participants with ischemic stroke and moderate to severe upper-limb impairment were randomized to VNS plus rehabilitation or rehabilitation alone. Rehabilitation consisted of three 2-h sessions per week for 6 weeks, and in the VNS group, movements were paired with 0.5-s VNS pulses. In their per-protocol analysis, there was a significant improvement in change in Fugl–Meyer Assessment-Upper Extremity (FMA-UE) score (between-group difference, 6.5 points; 95% confidence interval, 0.4 to 12.6). The second landmark clinical trial consisted of a randomized, multisite, double-blinded, sham-controlled pilot study where all participants were implanted with a VNS device and received 6-week in-clinic rehabilitation followed by a home exercise program [22]. Randomization was to active VNS ($n = 8$) or control VNS ($n = 9$) paired with rehabilitation, and subjects were followed out to 90 days. At day 90, mean FMA-UE scores increased 9.5 points from baseline with active VNS whereas the control scores improved by 3.8 (difference, 5.7 points; CI, −1.4 to 11.5; $P = 0.055$). This three-fold increase mirrored pre-clinical trial findings. A pivotal, randomized, triple-blind, sham-controlled trial, performed in 19 stroke rehabilitation centers was later published. In this trial, 108 participants with moderate-to-severe arm weakness, at least 9 months after ischemic stroke, were randomly assigned to either rehabilitation paired with active vagus nerve stimulation or rehabilitation paired with sham stimulation [23]. At 90 days after in-clinic therapy, a clinically meaningful FMA-UE response was achieved in 23 (47%) of 53 patients in the VNS group versus 13 (24%) of 55 patients in the control group (between group difference 24%, 6–41; $p = 0.0098$). Together, these three pivotal trials demonstrated the safety, feasibility, and efficacy of this intervention and laid the foundation for FDA approval of the Vivistim™ device in 2021, which is now commercially available. With this recent FDA approval, there has been a Medicare National Coverage Decision (NCD 160.18) that confers coverage for Medicare beneficiaries who meet criteria for refractory epilepsy to receive this treatment modality. However, due to the novelty of this therapy, few insurers have yet contemplated coverage for vagus nerve stimulation to treat chronic stroke. Nevertheless, given the recent FDA approval in addition to the girth of evidence supporting the efficacy of this modality, instance coverage will likely expand quickly. A summary of these trials as well as other major clinical trials relating to neuromodulation and chronic stroke can be seen in Table 1.

The future of VNS paired with rehabilitative therapy for stroke has now turned to applications beyond motor recovery. Potential indications include cognitive enhancement, sensory restoration, and possible use in cases of hemorrhagic stroke [24–29]. Interestingly, the ability to modulate the vagus nerve non-invasively (i.e., *trans*-auricularly) to achieve the same motor improvements without surgery is also being intensively explored [30–33]. Altogether, as both the role and mechanism of neuroplasticity in post-stroke recovery has become better understood, the potential for patients suffering from stroke to experience significant recovery with neuromodulation of the vagus nerve has come into sharper focus.

Deep Brain Stimulation for Stroke Recovery

Deep brain stimulation (DBS) is a procedure in which a burr hole is drilled into the skull followed by advancement of a thin electrode through a stereotactic frame to a predetermined target [1]. Correct placement is confirmed with several modalities including clinical examination of the patient, microelectrode recording, macroelectrode stimulation, and intraprocedural Xray, CT or MRI. Though timing varies by institution, some days to weeks after the initial surgery the implantable pulse generator (IPG) for the device is inserted into the chest wall and a subcutaneous wire is tunneled between the IPG and the cranial site to power the lead [34]. Finally, the lead is activated, and stimulation intensity is adjusted to clinical effectiveness. Similar open-loop stimulation technology was used in the Everest trial, which employed epidural cortical stimulation for stroke patients. The pivotal trial did not result in benefit for the stimulation group, and explanations centered on lack of

Table 1
Summary of major clinical trials for neuromodulation and chronic stroke recovery.

Neuromodulation Technique	Author	Year	Study type	Intervention	Number of subjects	Major finding
VNS	Dawson et al. [21]	2016	Randomized controlled clinical pilot study	6 weeks of in-clinic VNS and motor rehab program	21	No serious adverse effects; improved FMA-UE score compared to rehabilitation alone.
VNS	Kimberley et al. [22]	2018	Randomized, double-blinded, sham-controlled pilot study	6 weeks of in-clinic VNS and home exercise program	17	Improved FMA-UE scores; 88% response rate with active VNS compared to 33% for control VNS
VNS	Dawson et al. [23]	2022	Randomized, triple-blind, sham-controlled trial	6 weeks of in-clinic VNS and home exercise program	108	Improved FMA-UE scores; improved wolf motor function scores compared to control.
Cortical epidural stimulation	Levy et al. [35]	2016	Single-blinded RCT	6 weeks of epidural motor cortex stimulation and motor rehab	164	Primary analysis was negative for any significant difference at 4 weeks post-rehabilitation between intervention and control group. Post hoc comparisons indicated treatment effect differences at 24 weeks.
Cerebellar DBS	Baker et al. [44]	2023	Non-randomized; phase I	3 months of motor rehab only followed by 4 months of dentate nucleus stimulation and motor rehab	12	No serious adverse effects; significant FMA-UE score improvement; increased observed ipsilesional metabolism.

motor and sensory evoked potentials to guide lead placement [35,36]. DBS, which incorporates intraoperative microelectrode recording, is currently FDA approved for Parkinson's disease, essential tremor, dystonia, epilepsy, and obsessive-compulsive disorder; as such, all usage for stroke to date has been off-label. Nevertheless, there has been substantial interest in expanding the applications of DBS for stroke, particularly stroke-related motor recovery [37].

DBS for post-stroke movement disorders

Historically, most published case reports for DBS in the setting of stroke recovery have been related to post-stroke development of dystonia, tremor, hemiballismus, and chorea [38–40]. A recent systematic review identified 53 patients with stroke-related movement disorders who improved when targeting the thalamus and basal ganglia as well as internal capsule and zona incerta. The authors concluded that while overall there was reduction in the target symptom for many patients, given the heterogeneity in reports and evaluation methods, the degree of improvement was inconsistent and difficult to correlate with canonical stimulation parameters such as intensity, frequency and pulse width [41]. Interestingly, in some reports, effects were observed long after the index event (median 6.5 years after stroke prior to implantation). Additionally, only two complications were reported (rate of 3.8% of included patients), suggesting that even in severe cases of motor disability, the risk/benefit ratio may be favorable for invasive neuromodulation. An earlier review found similar results and commented on the wide range of stimulation parameters [38]. A recent investigation by Ho et al. evaluating thalamic stimulation for the improvement of motor function after white matter injury has showed promising results [42]. Ho et al. hypothesized that engaging direct excitatory connections to cortico-spinal fibers via deep brain stimulation of the motor thalamus would lead to improvements in motor function in patients suffering from lesions in the white matter, which can occur in patients with ischemic stroke. This hypothesis was tested in a primate model and was followed by further testing in 4 humans. They found electrical stimulation of the motor thalamus enhanced motor cortex excitability at specific stimulation frequencies and consequently potentiated motor output via the CST in human subjects. Moreover, these results also suggest that stimulation of the motor thalamus at optimal stimulation frequencies (50–80 Hz) can improve volitional force control with the absence of noticeable side effects in patients with chronic lesions of the CST [42]. This study provides vital preliminary data supporting further investigation for this therapeutic target.

Overall, the existing literature is limited but suggests that especially in treatment-refractory cases of post-stroke hyperkinetic movement disorders, DBS may be more effective than other treatments given the likelihood of a favorable response with low risk of adverse effects. However, as many authors have noted, this decision should be highly individualized, and the specifics of the patient's stroke burden, motor deficit, and eventual programming parameter choices should be discussed with a team that has expertise in a wide range of treatment options to offer this patient population.

DBS for post-stroke pain

DBS has also demonstrated efficacy for post-stroke pain, which often has substantial negative effects on quality of life and can limit rehabilitation potential [43]. Elias et al. reviewed 218 patients receiving DBS for post-stroke pain, the majority of which targeted thalamus, posterior limb of the internal capsule, and periaqueductal grey [38]. Most patients demonstrated improvement; however, the authors note that caution should be exercised in evaluating these results as analgesia often lessens over time and few patients were followed long-term.

Cerebellar DBS for motor recovery

A large and substantial body of work on the effects of cerebellar stimulation for stroke motor recovery has been published by Machado and colleagues at Cleveland Clinic. Early animal studies focused on establishing functional reorganization of perilesional tissue after stroke as well as effects of stimulation on neurogenesis [44]. Translation to humans culminated in a 2023 open-label Phase I trial on the use of cerebellar DBS targeting the contralateral dentate nucleus for post-stroke recovery, specifically on upper extremity paresis and disability as measured by the Fugl-Meyer assessment [45]. Twelve patients with middle cerebral artery (MCA) infarction within the past one to three years with chronic, moderate to severe upper extremity motor impairment were selected to receive stimulation. Patients were implanted with DBS and then participated in a two-month rehab course with DBS turned OFF. DBS was then turned on and dose titrated for one month, followed by another rehab course with DBS ON. The investigators found that while participants had some mild improvement with rehab alone, the effects of DBS plus rehab enabled higher rates of recovery. Interestingly, time since stroke did not appear to limit treatment-related benefit, with some patients experiencing substantial improvement even three years from the index event. Efficacy was postulated to be related to upregulation of dentatothalamocortical pathway activity, which was supported by functional neuroimaging performed during the study [45]. A summary of this trial as well as other major clinical trials relating to neuromodulation and chronic stroke can be seen in Table 1.

Overall, these results are promising and open the door to the use of DBS for functional recovery post-stroke even in the absence of other

movement disorders. Notably, several studies describe utility of DBS for post-stroke symptoms as well after the acute period of stroke [43,45]. Higher quality evidence is required to fully evaluate the technique's full potential, nevertheless the groundwork for the future of the field has been firmly established.

Brain-Computer Interfaces in Stroke Recovery

Brain-computer interfaces (BCIs) are devices used in individuals with severe neurologic impairment who require computer-assisted restoration, including motor, sensory and/or cognitive functions [46–49]. Historically, most BCIs for stroke rehabilitation have utilized non-invasive approaches (e.g., EEG, MEG, fMRI) to both record from the brain and drive an external actuator for motor rehabilitation, such as a robotic arm [50–54]. These devices primarily sample activity from motor regions (i.e., primary motor cortex, supplementary motor areas) and use decoding of imagined movements (motor-imagery or MI-based BCIs) to drive stimulation of the patient's hemiparetic limb directly (via functional electrical stimulation) or control of an orthotic/prosthesis. Non-invasive BCIs have shown promise for stroke recovery, especially when combined with physical and occupational therapy [54–56]. Nevertheless, low spatial resolution is a known limitation of noninvasive BCIs, which depend on signal separation for robustness of the decoding algorithm.

To improve sample integrity, invasive BCIs using microelectrodes allow for much higher resolution neural recordings and can allow for higher degrees of control over end effectors. Microelectrode arrays were first applied for motor decoding in humans in the early 2000s as part of the BrainGate clinical trials at Brown University [57,58]. Since that time, many other institutions have continued investigating Utah microelectrode arrays for motor decoding and movement restoration [59–61]. Additionally, researchers have begun providing stimulation via these microelectrode arrays to somatosensory cortex to restore sensory feedback for these devices [62–65]. Simulating sensory feedback has been shown to improve robotic arm control, which can lead to better rehabilitation for people with movement limitations [66]. To date, most clinical research for restoring movement with intracortical microelectrodes has focused on quadriparetic participants with amyotrophic lateral sclerosis (ALS) and spinal cord injury, however these devices will soon be used in a similar capacity for patients with stroke.

BCIs for speech restoration

While much previous BCI work has focused on movement recovery, another critical area for BCI development is speech restoration for treatment of aphasia, which is commonly associated with stroke. Similar to work for motor decoding, early literature in speech decoding originated with non-invasive approaches primarily through use of the P300 event-related potential using EEG while the participant focused on a specific letter within a grid of rows and columns [67,68]. In recent years, many groups have also trialed invasive BCIs for speech decoding. In 2017, the BrainGate consortium achieved a decoding rate of 30 characters per second using intracortical microelectrode arrays implanted in cortical motor areas [69]. More recently, a group at UCSF observed that full spoken sentences could be decoded using ECoG grids, demonstrating a strategy to decode words more rapidly than traditional spelling BCIs [70]. Another clever technique was implemented using intracortical electrodes in motor cortex to decode hand-written language, which was able to achieve speeds of 90 characters per minute, a 3-fold improvement over their previous iteration and almost 20 times faster than EEG P300-based decoders [71]. Most recently, ECoG-based decoding in speech cortex reached rates of 78 words per minute, and 62 words per minute was achieved using microelectrode implantation in motor areas [72,73]. While these approaches are still shy of natural language speeds (approximately 160 words per minute), they are beginning to approach these levels using advances in artificial intelligence (AI). The use of invasive BCIs for language recovery has thus shown immense promise and will likely constitute a major effort moving forward for a wide array of neurological injuries and disease, including stroke-induced aphasia.

Bidirectional BCIs

Investigators are beginning to use decoding of brain activity to directly drive brain stimulation for improved motor restoration [46,66]. As described previously, non-invasive modalities, such as transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS), have been shown to improve cortical excitability and plasticity for stroke rehabilitation [53,74,75]. Using invasive microwire technology, previous work in nonhuman primates showed that inducing plasticity through spike-triggered modulation, a form of inter-neuronal bidirectional modulation, is feasible [76,77]. Additionally, microstimulation of motor cortex has been shown to alleviate walking deficits in rodents with spinal cord injury [78]. Thus, a promising future avenue for stroke recovery may be microelectrode-based BCIs for recording/decoding of neural signals with paired-modulation of neural circuits involved in stroke recovery. As described earlier in this review, deep-brain stimulation (DBS) has also proven to be effective in the treatment of different symptoms associated with stroke. Although closed-loop systems that decode activity from one brain area to guide DBS of a separate area have been used successfully in the treatment of Parkinson's disease, depression and epilepsy [79,80], closed-loop invasive systems have not been well-explored for stroke recovery.

Altogether, while much work has been done with BCIs for stroke recovery, the vast majority of this work has occurred either non- or fully invasively. Positioned between these two approaches, a minimally invasive BCI implanted endovascularly has demonstrated promising efficacy in initial clinical trials. The Stentrode device is embedded with transvascular recording electrodes and is advanced through the superior sagittal sinus towards primary motor cortex. In pre-clinical trials, the signal quality of subdural and endovascular arrays were found to be comparable [81–83]. The first in-human trial involved two participants with ALS, while the second trial included 4 participants with ALS and 1 participant with primary lateral sclerosis [84,85]. Neither trial reported any serious adverse events, and both trials demonstrated efficacy in encoding simple motor tasks that allowed for control of a computerized object. The minimally invasive nature of this BCI endovascular implant in addition to its promising efficacy in these early clinical trials call for future larger prospective randomized clinical trials to further determine its efficacy in post-stroke recovery and other motor disorders. Much work remains to be done using BCI technologies along the full spectrum of invasiveness, however the basic engineering solutions for both recording and stimulation of networks underlying stroke deficits have been successfully demonstrated.

Future Directions

The future of neuromodulation is being driven by rapid progress in artificial intelligence (AI), wearables and several other advanced technologies. These promising technologies, while not the topic of this review, have been well described in previously published reviews [86–88]. AI, in particular, has propelled the development of closed-loop systems, aiming to enhance personalization and real-time reactivity of proposed neuromodulatory interventions for stroke recovery. Key to this progress is utilization of a variety of biomarkers as input, which in turn, using complex algorithms, can modify and customize therapeutic output, thereby establishing a responsive and adaptive treatment paradigm [89]. A segment of wearable devices with commercial implications includes virtual (VR) and augmented reality (AR) systems that incorporate haptic and accelerometer data that can be paired with brain physiology to form a more complete picture of movement dynamics [90,91].

Another burgeoning field is the use of neuroimaging data to drive functional restoration. While most of this literature has focused on use of

functional magnetic resonance imaging (fMRI) [92], patient movement and, specifically, stance and ambulation are still not possible to test inside the scanner. Functional Near-Infrared Spectroscopy (fNIRS) has emerged as a solution for these limitations, particularly in the context of stroke recovery. fNIRS is a non-invasive optical technique that measures fluctuations in intracerebral hemodynamics, enabling the monitoring of neuronal activity by way of changes in oxyhemoglobin and deoxyhemoglobin concentration [93,94]. Its portability confers a distinct advantage over fMRI [95]. fNIRS can be deployed at the bedside and has enabled data collection in real-time as patients are asked to complete a motor task, such as walking. This provides personalized data that is especially crucial in patients recovering from stroke, given the high variability of infraction patterns that can lead to similar deficits [92,95]. The limitations of this technology include inferior spatial resolution and an inability to capture subcortical data. Strategies to ameliorate these issues include the incorporation of additional sensors and the integration of supplementary modalities, such as EEG, and increasing the number of fNIRS optodes [93,94]. Early research has already begun to examine the use of robotic devices and exoskeletons that use fNIRS to tailor rehabilitation therapies for post-stroke patients [96]. The integration of AI and innovative technologies like fNIRS paves the way for a new era in personalized neuromodulation for stroke and stroke-related disorders.

Lastly, the current landscape of neuromodulation for chronic stroke has developed from pre-clinical and clinical studies primarily focusing on ischemic stroke. While ischemic stroke has a much higher prevalence, hemorrhagic stroke is a subset of stroke that is more disabling and associated with a higher mortality rate [97]. Thus far, there is a paucity in studies assessing neuromodulation for hemorrhagic stroke. The groundbreaking work that has been established in the field of neuromodulation for ischemic stroke has paved the way for future work in hemorrhagic stroke. While the pathophysiology differs between ischemic and hemorrhagic stroke; the post-stroke recovery paradigms that occur after the initial insult for both pathologies have similarities. Future application and reference of the pre-clinical and clinical study methodology and design for neuromodulation and ischemic stroke should be considered for hemorrhagic stroke in the future.

Author Contributions

All authors have made substantial contributions to the conception or design of the work; the acquisition, analysis, or interpretation of data; and have drafted the work or substantively revised it.

All authors have approved the submitted version (and any substantially modified version that involves the author's contribution to the study).

All authors have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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