Introduction

Worldwide, stroke is one of the leading causes of death, and for those who survive, it carries significant morbidity. Approximately 16 million people worldwide are affected by stroke each year, and the estimated prevalence of stroke survivors is over 60 million [1]. With great implications for independence and functional recovery, stroke carries significant repercussions for quality of life, health care, and costs. Currently, preventative approaches and selective treatment, with physical and occupational rehabilitation as the main modalities for recovery of motor abilities, cognitive function, and resolution of pain syndromes post-stroke. Neuromodulation therapies hold great promise for stroke survivors and are beginning to gain traction as the next frontier in regards to post-stroke rehabilitation. It is the aim of this review to explore current beliefs regarding post-acute stroke recovery through neuroplasticity of surviving brain tissue and the impact of neuromodulation through non-invasive and invasive interventions. By understanding the scope of these interventions, the areas in which neuromodulation may be most effective, and the types of recovery they may help constitute, the impact of neuromodulation as a budding area in neurological care and therapy can be better characterized and outlined for future study.

Keywords: Ischemic Stroke; Recovery; Neuromodulation; Plasticity

Abstract

Strokes continue to be a leading cause of death and carries significant morbidity impacting the quality of life for survivors. Although there are preventative measures and growing hyperacute treatments, physical and occupational rehabilitation continue to be the main modalities for recovery of motor abilities, cognitive function, and resolution of pain syndromes post-stroke. Neuromodulation therapies hold great promise for stroke survivors and are beginning to gain traction as the next frontier in regards to post-stroke rehabilitation. It is the aim of this review to explore current beliefs regarding post-acute stroke recovery through neuroplasticity of surviving brain tissue and the impact of neuromodulation through non-invasive and invasive interventions. By understanding the scope of these interventions, the areas in which neuromodulation may be most effective, and the types of recovery they may help constitute, the impact of neuromodulation as a budding area in neurological care and therapy can be better characterized and outlined for future study.

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Introduction

Worldwide, stroke is one of the leading causes of death, and for those who survive, it carries significant morbidity. Approximately 16 million people worldwide are affected by stroke each year, and the estimated prevalence of stroke survivors is over 60 million [1]. With great implications for independence and functional recovery, stroke carries significant repercussions for quality of life, health care, and costs. Currently, preventative approaches and selective hyperacute treatment strategies are the main modes of stroke treatment, with physical and occupational rehabilitation as the mainstay of functional recovery after stroke. Most rehabilitative therapies are centered around improving the functional outcomes in regards to deficits post-acute stroke; the most common of which are: motor function, cognitive decline, and pain syndromes [2,3].

In 2008, the estimated costs for cerebrovascular accidents, the most common of which is stroke, was $34.3 billion in the United States, and, when coupled with projected costs for lost productivity and premature mortality, the expense is enormous [4]. Stroke is also a major cause of severe disability in the United States, with over half of older stroke survivors experiencing moderate to severe long-term disability [5]. The American Heart Association’s report on the sequelae of older ischemic stroke survivors were: 50% had hemiparesis, 30% were unable to ambulate without assistance, 26% were dependent on activities of daily living, 35% had depressive symptoms, and 26% were institutionalized in a nursing facility [3]. Other studies have produced similar findings with one third of survivors suffering from motor dysfunction, and approximately half experiencing musculoskeletal pain, one third having a motor dysfunction, and half of the survivors experiencing some form of psychosocial complications, including anxiety and depression [6]. Cognitive decline may affect up to 65% of post-stroke survivors [2]. Strokes not only dramatically impact the quality of life for patients and families, but healthcare in general, from a cost perspective. Recent research in the post-acute stroke recovery phase has started to focus on the role of neuronal plasticity. This refers to the innate ability of neurons to morphologically change their synaptic connections [7]. Neuromodulation is the general term used when referring to a technique that attempts to excite neurons within the surviving brain tissue in order to use plasticity to induce their reorganization. After a stroke, the damage to the surviving neurons may cause aberrant connections, and by inducing functional reorganization and changes in excitation of spared cortical areas, functional recovery can be augmented [7]. Currently there are two general categories of neuromodulation: non-invasive and invasive, both of which aim at stimulating various areas of brain structures to enhance cortical connections. Much of the research in this emerging field is oriented towards the electrical stimulation of populations of neurons which can cause either Long-Term Potentiation (LTP) or Depression (LTD), both of which are underlying mechanisms for neuronal plasticity [8]. Although the exact pathways have not been elucidated, it has been proposed that balances between LTP/LTD are the most probable mechanisms underlying motor learning [9].

The role of neuromodulation in motor recovery after stroke holds great potential. Several recent studies have explored the connection between the role of excitability changes in perilesional cortex and neuronal plasticity, as well as functional motor outcomes [10,11]. Moreover, neuromodulation also has neuroprotective properties, by reducing toxic substances to neurons which subsequently lead to improvements in cognitive impairments, such as working memory and executive abilities, in patients with dementia [12,13]. With such strides in cognition and psychosocial applications of neuromodulation, perhaps these treatment modalities may be applicable to stroke patients. Lastly, neuromodulation has been shown to be efficacious in the management of pain syndromes, including post-stroke pain. Due to the complexity of pain pathways, there is no panaacea, instead therapies are dictated by the type of pain experienced by the patient. For instance, surface motor cortex stimulation has been effective for neuropathic pain by activating descending intrinsic pain control systems, whereas peripheral nerve stimulation of large myelinated afferent neurons has been effective for peripheral neuropathies by inhibiting spinalthalamic transmission of signals [13].

With the growing wealth of evidence behind neuromodulation, it is the aim of this review to explore current beliefs regarding post-acute stroke recovery through neuroplasticity of surviving brain tissue and the impact of neuromodulation through non-invasive and invasive interventions. Neuromodulation holds the potential to impact motor function, in addition to cognition and pain syndromes post-stroke, underscoring the possibility of improving quality of life and functional outcomes for these patients and their families. Not
only providing promise and hope for better outcomes, these new strides may hold broader implications for health care resources and costs long term if proven to be optimal.

**Non-invasive Neuromodulation**

The brain architecture communicates via highly interconnected neuronal arrays with set characteristics per area delineated by neuronal membrane capacitance and voltage-gated currents, creating the property of neurons to resonate at specific frequencies to transmit specific information to other parts of the brain [14].

The aim of transcranial brain stimulation is to utilize various tools that can induce long-lasting neuromodulation, via manipulation of intrinsic neural activity and redirect cortical neurons to adapt to frequency-specific oscillatory input [8]. Due to the many aspects of neuromodulation, different protocols have been created to either facilitate or inhibit neuronal activity. This can modify expression of neuronal proteins, such as neurotransmitters and neurotrophins, which then activate the long-term potentiation pathway [15].

Furthermore, cortical stimulation can influence contralateral and downstream pathways rather than being confined to monosynaptic connections, so high-frequency stimulation in the motor cortex can lead to decreased stretch reflexes in the leg of patients with multiple sclerosis, thereby decreasing spasticity [16]. This theory, along with extrapolations of this concept, led to the generation of transcranial direct current stimulation, transcranial alternating current stimulation, transcranial random noise stimulation, and transcranial magnetic stimulation, various mechanisms of neural oscillations evoking excitation of varying frequencies in selectively targeted areas.

**Transcranial Magnetic Stimulation/Transcranial Direct Current Stimulation**

A frequently utilized tool for non-invasive stimulation is transcranial magnetic stimulation (TMS) [3]. This process uses different configured coils to create an extracranial magnetic field that is powerful enough to influence neuronal activity in a pulse-like manner. The effect that these coils will have directly relates to the frequency of impulses, types of coils, their geometric orientation in relation to the brain, and the distance between the coils themselves and the brain [15]. One method that has been well documented is the use of low-frequency pulses, defined as less than one hertz, to reduce the excitability of neurons and higher frequencies, defined as more than 5 hertz, to increase excitability of neurons [15]. Another common protocol uses brief bursts of low-intensity theta frequency stimuli in a continuous pattern to decrease motor cortex excitability and high-frequencies to increase it [15].

Transcranial Direct Stimulation (tDCS) is another non-invasive technique that uses surface electrodes to apply weak electrical currents through the scalp. This physical current is presumed to cause neuronal membrane depolarization or hyperpolarization, depending on the orientation of the electrodes. tDCS has been shown to improve motor function in stroke patients, when coupled with motor training, due to cortical reorganization [4] via ipsilateral and peri-lesional cortex stimulation and modulation of interhemispheric inhibition [15]. It is thought that cathodal stimulation of the unaffected hemisphere will cause a suppression of activity locally, allowing for the transcallosal disinhibition of the affected hemisphere, thereby increasing neauronal response to repair itself [17]. This same mechanism has been proposed for the improvement of neurocognitive deficits in stroke patients; specifically in task related functions [10], as well as memory and affective complications [19–21]. These results, though minimal, are statistically significant in demonstrating that modulation of ipsilesional activity can improve motor recovery, likely by promoting plastic reorganization of spared cortex.

A recent study, aimed to assess the efficacy of high-frequency brain stimulation on lower limb motor function in patients with chronic subcortical stroke, examined repetitive TMS, targeting deeper and larger brains regions, demonstrated that three weeks of treatment could induce long-term improvements in lower limb function, lasting beyond the end of the treatment [19]. Furthermore, a recent meta-analysis studied the effects of TMS on neuropathic pain, including post-stroke supra-spinal related pain, and concluded that TMS provides a significant reduction invarious neuropathic pain conditions [21–25]. There are three main proposed mechanisms for this: 1) induction of neuroplasticity can allow for the brain to simply reorganize itself in a way that reverses the plasticity induced with neuropathic pain, 2) direct stimulation of descending inhibitory pathways to decrease the response to painful stimuli, 3) direct stimulation of endogenous opioid secretions [19]. With promising results in the recovery of motor function, cognition, and pain management, TMS may be a fruitful option in post-acute stroke recovery for certain patients.

**Visual and Auditory Brain Stimulation**

In addition to transcranial mechanisms of stimulation, procedures using audio, visual, and auditory stimulation are a noninvasive means of stimulation. The mechanism of action is via the incorporation of different portions of the brain associated with a functional task by using sensory stimuli to reinforce the connections and therefore improve the performance of that task [19]. Increasing the activity of a neuron can strengthen the connections it makes with other neurons. However, this task proves difficult in patients with degenerative neurons that are harder to stimulate, therefore, researchers have postulated that audiovisual stimulation can use different pathways to stimulate mirror neurons, activating the degenerative ones [22]. A study examining this concept in patients with left hemiparesis secondary to stroke found that in-person demonstration of the required task resulted in improved ability to perform the task, reduced execution time to perform the task, and increased EEG activity, perhaps correlating to neuronal recruitment during task performance [11]. Audio and visual stimulation has also been shown to increase cognitive performance. Researchers were successful in stimulating the areas of the frontal lobe that perceive language to use it to improve speech production in non fluent aphasic stroke participants, who seldom improve in the chronic stroke phase [25]. There is a myriad of potential that this noninvasive therapy holds for stroke patients when coupled with physical therapy rehabilitation and other mechanisms of therapy.

**Functional Electrical Stimulation (FES)**

Functional electrical stimulation peripherally delivers triggered electrical impulses to the muscles and has been shown to induce motor function recovery [21]. The electrical stimulation of the muscles, which causes forced movement, is believed to induce cortical reorganization and strengthening of the ipsilateral pathways [26]. This is due to the fact that FES activates both sensory and motor neurons. Activation of motor neurons causes both orthodromic and antidromic impulses. Using hebbian theory of neuronal activity, the combination of presynaptic stimulation, which is induced through the patient's voluntary effort, and the postsynaptic stimulation, induced through the antidromic impulses, can strengthen synapses [26]. FES devices are usually integrated into neuroprostheses and are typically made for the upper extremity. There are new variations using FES which can be triggered or controlled with electromyography (EMG), and
have been shown to augment muscle contraction in proportion to voluntary EMG signals. There is evidence to suggest that this form of therapy not only helps lower motor neuron recovery function but they also seem to play a role in somatosensory recovery, and may possibly induce brain reorganization [20]. Furthermore, FES has been shown to be significantly effective in reducing the severity of shoulder subluxation and pain [22], further underscoring its potential significance in post-stroke rehabilitation. With these strides in peripheral stimulation for motor recovery, non-invasive modes of neuromodulation may hold a multitude of possibilities for rewiring brain circuitry.

**Invasive Neuromodulation: Deep Brain Stimulation**

Invasive mechanisms of neuromodulation are aimed at accessing deeper brain structures and involves the surgical implantation of electrodes in close proximity to the tissue which is to be modulated, which are then coupled with neurostimulators that can be programmed to manage the activity of the electrodes [28–29]. These neurostimulators, implantable pulse generators, can then be accessed by physicians to make certain adjustments to the treatment, such as the amplitude, frequency, and pulse width that the electrodes generate [30]. Deep brain stimulation (DBS), the mainstay of invasive neuromodulation, has been widely used for over 25 years as a non-lesional method to modulate brain circuits locally or remotely [31]. It is the standard of care for the management of advanced Parkinson’s disease, yielding reliable and significant results of enhanced motor function, and demonstrating improvement when used to treat movement disorders of both neural and non-neural origin [32]. DBS, like all surgeries, carries associated risks. However, the technological equipment has been applied and approved in numerous medical devices in the past several decades, and DBS technology has long been profiled for safety in terms of implantable materials and charge concentration, of course varying by target location and voltage used. The mechanism by which DBS is thought to improve symptoms in these diseases is via disruption of abnormal neural synchrony between affected brain regions [33]. The effects of DBS are highly dependent on the location of the implantable electrodes, along with their timing and frequency [34]. Therefore, the ongoing study of this technology for the treatment of other neurological diseases, including stroke for motor recovery and function as well as pain syndromes post-stroke are an expanding field. It is only a matter of time before this equipment, verified safe through other diseases, is applied for neuromodulation in stroke if consistently demonstrated to be beneficial.

**Deep Brain Stimulation for Improvement in Motor Function**

DBS of various movement control tracts in the cerebral circuitry present diverse interventions for post-stroke interventions for potential motor function recovery. One such example is presented by Machado et al. who argues for the role of DBS in the dentatothalamocortical pathway as a novel approach for enhancing motor rehabilitation following stroke, as this pathway terminates with projections to premotor and posterior parietal terminations, where such areas represent the common perilesional zone that survives following a middle cerebral artery ischemic stroke, presenting the possibility to use this pathway to enhance excitability in the perilesional tissue undergoing plastic reorganization after an MCA stroke [4]. In a small prospective multicenter study, using DBS in conjunction with standard rehabilitation demonstrated a significant improvement in the participants Upper Extremity Fugl-Meyer score and hand function score of the Stroke Impact Scale [35]. These improvements continued to be seen at the 12-week follow up assessment. The existence of functional enhancement after withdrawal of cortical stimulation has been suggested to be due to the induction of neural plasticity and not only direct enhancement caused by the stimulation [36]. Therefore, in the future this treatment could be a transient form of therapy to enhance recovery rather than a life-long implantation of a device. Now that this procedure has been shown to be safe in patients experiencing cerebrovascular disease, large randomized clinical trials will be needed to uncover the extent to which DBS can stimulate motor recovery throughout different neural pathways.

**Deep Brain Stimulation for Inhibiting Involuntary Movements**

Conversely, DBS can have a role in alternative pathways aimed at inhibitory control of motor function. Katayama et al. [37] explored the role of DBS and motor cortex stimulation in patients with post-stroke movement disorders and post-stroke pain. In regards to movement disorders post-stroke, they identified the thalamic nuclei ventralis oralis posterior et intermedius as a DBS target useful in more than 70% of patients with post-stroke involuntary movements, including hemiballismus, hemichorea-athetosis, and tremors. It has been known that using high-frequency stimulation can decrease neuronal firing rates substantially [39]. The general postulated mechanisms of this inhibition include the activation of presynaptic inhibitory interneurons, induction of LTD, and depolarization-induced blockade of somatic ion channels [37]. Regardless of tract intervened upon by DBS, of key importance in post-stroke treatment for motor rehabilitation, is the fact that DBS is a reversible procedure that can be modified in frequency and amount of stimulation as well as location if need be.

**Implications in Cognition**

While the impact of DBS in motor dysfunction is most well studied, the role of DBS in cognition is not yet clear, and most specifically, in terms of DBS for those suffering from stroke, the impact on cognition is even further obscure. Although not specifically identified in the literature, the understanding of electrical stimulation in terms of cognition can be extrapolated from other recent studies. Electrical stimulation of the temporal lobe was discovered to influence the perception of memories and feelings by Dr. Wilder Penfield, and more recent studies have demonstrated that stimulation of the entorhinal cortex can enhance spatial memory [33]. Furthermore, recent studies have even shown that DBS could be used to increase hippocampal volume in patients with Alzheimer’s disease [39]. Most studies using DBS to enhance memory have used epileptic patients but small clinical trials stimulating the nucleus basalis of Meynert in Alzheimer’s patients indicated an increase in glucose metabolism in the medial temporal lobe, suggesting enhanced activity [33]. There has been variability with regards to the assessment of patients, with studies using either visual or spatial tasks but not both, with some of these assessments including the MMSE, Wisconsin Card Sorting Test, and Alzheimer’s Disease Assessment Scale cognitive subscale [33]. The lack of standardization across studies makes it difficult to generalize the effects of DBS to other neurocognitive impairments. Additionally, the finer details of the DBS procedure, including electrode size and position, stimulation frequency, pulse width, and current amplitude, among others, need to be further investigated to elucidate the exact mechanisms of how DBS can enhance memory in post-stroke patients.

**Implications in Pain Management**

In addition to a potential role in motor and cognitive recovery via neuromodulation, DBS holds promise in post-stroke pain syndromes [39]. In the aforementioned Katayama et al. [37] study, they demonstrated excellent pain control achieved by motor cortex stimulation in approximately 50% of patients with post-stroke...
pain, underscoring the neuronal renetworking occurring after stroke, or other neurological insult, causing focal reorganization and plasticity of surviving brain tissue linked to excitability changes in perilesional cortex. Central post-stroke pain (CSPS) is the classification of pain resulting from a primary lesion or dysfunction of the central nervous system secondary to stroke, which occurs in 8-14% of all stroke patients and presents with unique manifestations in each patient [40]. With pathophysiology linked to neurotransmitter modulation, DBS has been applied in this chronic pain syndrome, targeting the periventricular gray region (PVG) and nucleus accumbens (NAC), with stimulation of the NAC and PVG providing substantial improvement in pain rating after one year [41]. The mechanism of analgesia via stimulation of the NAC was first observed with septal stimulation, an area in close proximity to the NAC, providing intense reward and relieving chronic pain [42]. The mechanism in PVG stimulation is thought to be due to endogenous opioid release and activation of descending pain inhibitory pathways [43].

Neuropathic pain refers to pain caused by a somatosensory system lesion or disease [44], with symptoms often the most debilitating and duration often the longest of chronic pain diseases. A review examining DBS with motor and sensory cortical stimulation examines all recent prospective studies examining long-term outcomes in patients and advocate that DBS is superior to motor cortical stimulation for refractory pain syndromes and may be more appropriate than sensory cortical stimulation for certain pain etiologies, including phantom pain after amputation [45]. In regards to pain after stroke, DBS reveals greatest efficacy for stroke patients complaining of burning hyperesthesia [18].

Tractography is a growing technique of identifying specific neuronal tracts and pathways of eloquence and importance after imaging for surgical planning. Of the many instances where this technology is proving useful, thalamic pain is of particular interest in the context of post-stroke pain. Thalamic pain, a result of a thalamic insult such a lacunar stroke, is often debilitating in nature and resistant to medical therapy [46]. The role of imaging-based tractography in the stereotactic trajectory planning for the placement of a spinothalamiccortical tract (STC) DBS in thalamic pain has the potential to literally color the field currently obscured by limitations of low contrast in MR imaging of the posterior limb of the internal capsule or thalamus, targets for DBS. A study examining this technology yielded results demonstrating a reduction in pain by 40% in 75% of patients studied, lasting for greater than one year [47]. While invasive neuromodulation may hold a role in pain management post-stroke, studies also affirm the role of non-invasive treatments in cases of stroke-induced thalamic pain syndromes via gamma knife radiosurgery of the centromedian nucleus, resulting in improved symptom control and quality of life [48].

**Discussion**

This review identified a number of noninvasive and invasive methods of using neuromodulation to treat ischemic stroke. One thing that is increasingly apparent in reviewing this literature is that each method of neuromodulation has a varying mechanism of action that is dependent on the location and purpose of the treatment. In stroke, often our treatment is to protect normal brain tissue or promote function of surviving tissue after the ischemic event. The function of the neuromodulation to accomplish this is quite different from the purpose of other mechanisms of neuromodulation that work to inhibit disinhibiting lesions or aberrant architecture.

The role of neuromodulation in post-stroke recovery has been evolving quite rapidly. Pending the location of the stroke, the specific brain regions involved, and subsequent deficits, varying mechanisms of neuromodulation may prove more effective than others. While the literature highlights the promise of these multiple techniques in many areas of post-ischemic stroke treatment, no clear consensus is evident at this time. Given the variability within one modality alone and the dearth of comparative research, it is difficult to say what the most effective parameters are within those mechanisms of neuromodulation. Without understanding whether these methods have been optimized, it would be difficult to prove that any specific method, non-invasive or invasive, may be superior or inferior to others. Once we start to isolate and identify the best parameters for each invasive and noninvasive method, to identify where each mechanism yields the greatest results, the next step would be to have clinical trials directly comparing the effectiveness between these methods, not only comparing invasive and noninvasive methods, but also juxtaposing various methods within each category.

The main purpose of this review was to explore current beliefs regarding post-acute stroke recovery through neuroplasticity of surviving brain tissue and the impact of neuromodulation through non-invasive and invasive interventions. In addition to understanding how these interventions work, it is important to understand the potential impact they may hold for patients, science, and health care. In order to characterize what studies are currently being conducted to examine the effectiveness of these interventions and underscore the future trends of this field, a review of all registered clinical trials involving neuromodulation and stroke on the worldwide registry ClinicalTrials.gov was completed. This search yielded 16 ongoing clinical trials using neuromodulation to treat post-stroke patients, with only three of these studies looking specifically at acute-stroke patients. What was of particular interest in this search was the variety of the trials enrolled. There are a few trials that look at neuromodulation as an additive measure via combination of various techniques, such as DCS and FES together, while other trials examined neuromodulation in conjunction with other treatments such as stem cell transplantation or pharmacological agents. Two studies compare non-invasive treatments; DCS versus TMS and continuous versus intermittent impulses in TMS. What we can extrapolate from this search of ongoing clinical trials is that current and future research strives to further expand upon and develop a clear front runner in the field of non-invasive neuromodulation, identify the ideal protocols for administration of each type of non-invasive neuromodulation, and compare various techniques to highlight which may be most effective in which scenarios. What is currently evident is that whether used in isolation or in combination with other treatments, neuromodulation as a field holds tremendous potential.

**Summary**

In sum, the field of neuromodulation is a growing one, with many implications for the common and morbid disease of stroke. It provides many proven benefits to patients via non-invasive, or minimally invasive, interventions aimed at altering the post-stroke excitableness of brain architecture to remodel circuits affected by the event. This review concludes that neuromodulation holds the potential to impact motor function, cognition, and pain syndromes post-stroke, with the possibility of greatly impacting and improving quality of life and functional outcomes. It is the potential these interventions have to truly change the lives of stroke patients, the possible impact this therapy could have on patient outcomes as well as the healthcare system, and the plethora of options in treatment that these techniques provide that identify the field of neuromodulation as a budding area in neurological care and therapy.


