Brain Stimulation 11 (2018) 3–28

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

Deep brain stimulation for stroke: Current uses and future directions

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ARTICLE INFO

Article history:
Received 11 September 2017
Accepted 7 October 2017
Available online 12 October 2017

Keywords:
Deep brain stimulation
Stroke
Pain
Movement disorder
Paresis
Neuroplasticity

ABSTRACT

Background: Survivors of stroke often experience significant disability and impaired quality of life related to ongoing maladaptive responses and persistent neurologic deficits. Novel therapeutic options are urgently needed to augment current approaches. One way to promote recovery and ameliorate symptoms may be to electrically stimulate the surviving brain. Various forms of brain stimulation have been investigated for use in stroke, including deep brain stimulation (DBS).

Objective/Methods: We conducted a comprehensive literature review in order to 1) review the use of DBS to treat post-stroke maladaptive responses including pain, dystonia, dyskinesias, and tremor and 2) assess the use and potential utility of DBS for enhancing plasticity and recovery from post-stroke neurologic deficits.

Results/Conclusions: A large variety of brain structures have been targeted in post-stroke patients, including motor thalamus, sensory thalamus, basal ganglia nuclei, internal capsule, and periventricular/periaqueductal grey. Overall, the reviewed clinical literature suggests a role for DBS in the management of several post-stroke maladaptive responses. More limited evidence was identified regarding DBS for post-stroke motor deficits, although existing work tentatively suggests DBS—particularly DBS targeting the posterior limb of the internal capsule—may improve paresis in certain circumstances. Substantial future work is required both to establish optimal targets and parameters for treatment of maladapative responses and to further investigate the effectiveness of DBS for post-stroke paresis.

Introduction

Broadly defined as any rapidly developing neurological deficit(s) attributable to an acute and focal central nervous system (CNS) injury of vascular origin [1], stroke is a leading cause of mortality [2,3] and disability [4,5] worldwide. Stroke can engender a large number of sensorimotor sequelae including motor weakness and impairment of voluntary motor control (paresis), spasticity, incoordination (ataxia), apraxia, sensory loss/numbness, dysarthria, and dysphagia [6], and can also lead to various cognitive and psychiatric deficits such as neglect, aphasia, and depression [7,8]. In addition to these impairments, stroke can produce maladaptive 'positive' symptoms including central neuropathic pain [9], movement disorders (e.g., tremor, dystonia, or dyskinesias) [10], and epilepsy [11], which develop in the months or years following stroke. For many patients, both the deficits and the maladaptive responses prove refractory to medical therapy.

Current interventions for the management of acute stroke emphasize reperfusion and must be initiated within hours of symptom onset to ensure benefit [12]. Treatment options beyond this time window are largely rehabilitation-based; these depend largely on augmenting spontaneous motor recovery, which predominantly occurs within the 'critical period' 3–6 months post-stroke [13] and reflects enhanced neuroplasticity—and consequent structural and functional reorganization of surviving neural circuitry—within the brain [14–16]. Despite these interventions, many stroke patients undergo incomplete recovery and suffer from impaired quality of life due to residual functional deficits and disturbances [17,18]. This unmet need has driven the examination of several novel treatment modalities, including the application of electrical stimulation to the nervous system as a means to further engage post-stroke neuroplasticity and enhance functional recovery. Neuromodulation modalities currently under investigation for use in stroke include transcranial direct current stimulation (tDCS), repetitive transcranial magnetic stimulation (rTMS), motor cortex

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https://doi.org/10.1016/j.brs.2017.10.005
1935-861X/

stimulation (MCS), and deep brain stimulation (DBS) [19]. Here we focus on deep brain stimulation (DBS), examining its use as a treatment for post-stroke maladaptive sequelae and exploring its therapeutic potential for post-stroke paretic deficits.

DBS for stroke

An invasive form of neuromodulation, DBS entails implanting stimulating electrodes in the brain parenchyma, connecting them to an implantable pulse generator (IPG), and using them to chronically deliver electrical pulses to targeted brain structures. The delivery of electrical stimulation with DBS is reversible and programmable; stimulation may be delivered either continuously or intermittently and stimulation parameters (frequency, pulse width, voltage) and contact settings can be readily adjusted. DBS is used to modulate dysfunctional brain circuitry both locally and remotely and may be administered anywhere in the brain [20].

DBS is well-established as a safe and effective treatment for movement disorders such as Parkinson's disease, essential tremor, and dystonia [21,22] and in recent years has shown promise for management of several circuit-based neuropsychiatric conditions, including obsessive-compulsive disorder [16,17], major depression [23,24], anorexia nervosa [25], Tourette's syndrome [26,27], and Alzheimer's disease [28–30]. The mechanisms underpinning DBS remain incompletely understood, but likely involve modulation of local neuronal cell bodies and concurrent induction of action potentials in nearby axons [31–33]. DBS may also interact with diseased circuitry at the network level, disrupting or overriding pathological oscillatory activity (e.g., aberrant beta-band oscillations within basal ganglia circuits in Parkinson's disease) via alteration of neuronal firing patterns and timing at both local and remote nodes within targeted neural circuits and thereby improving overall network function [34–38].

In keeping with the widespread clinical effects and therapeutic latency (between weeks to months) that characterizes the response to DBS in many conditions [39], recent neuroimaging work indicates that DBS can produce both early and delayed changes within targeted neural circuits, suggesting an effect on network plasticity. Subcallosal cingulate cortex DBS in depression patients, for example, produces lasting regional cerebral blood flow changes within depression-implicated circuits [23]. Similarly, DBS of the columns of the fornix appears to increase cortical glucose metabolism and functional connectivity in Alzheimer's patients [29,40], reversing the characteristic course of changes in this disease. Additional work indicates fornix DBS may also have direct effects on brain structure in Alzheimer's, slowing or in certain patients even reversing hippocampal atrophy [41]. Studies examining Papez circuit DBS in rodent models suggest these changes may be driven by the release of neurotrophic factors like brain-derived neurotrophic factor and vascular endothelial growth factor [42–44]. Paired-pulse TMS studies measuring motor cortical excitability also attest to DBS's ability to reshape aberrant neurocircuitry [45]. Subthalamic nucleus (STN) DBS for example, has been shown to restore deficient intracortical inhibition (ICI) in Parkinson's disease patients in a manner similar to dopaminergic drugs [46–49], perhaps by normalizing activity of excitatory cortical neurons via activation of cortico-basal ganglia-thalamo-cortical loops [50]. STN DBS may also modulate ICI by activating descending CST fibres in the cerebral peduncle [49,51], and by antidromically stimulating the CST [52].

Literature search

To evaluate how DBS has been employed for treatment of post-stroke conditions and to determine the targets, parameters, and outcomes of this intervention, we conducted a systematic literature review of all published original research involving DBS in stroke patients. Both reports involving treatment for maladaptive post-stroke disorders and those focusing on ameliorating post-stroke paretic motor deficits, spasticity, or upper motor neuron syndrome (UMNS) were included. To improve the sensitivity of our analysis, cases involving traumatic brain injury that caused presumed cardiovascular lesions or hemorrhage were also examined.

The literature search, conducted in July 2016, began with an initial search of the NCBI Pubmed database using the following search terms: '((((((deep brain stimulation[MeSH Major Topic]) OR DBS[MeSH Major Topic]) OR transcranial magnetic stimulation [MeSH Major Topic]) OR epidural stimulation[MeSH Major Topic]) OR motor cortex stimulation[MeSH Major Topic]) OR electrical stimulation[MeSH Major Topic]) AND stroke[MeSH Major Topic]'. This was supplemented by a second search of the same database using the following search terms: '(((((((deep brain stimulation [MeSH Terms]) OR transcranial magnetic stimulation[MeSH Terms]) OR epidural stimulation[MeSH Terms]) OR motor cortex stimulation[MeSH Terms]) OR electrical stimulation[MeSH Terms]) AND stroke[MeSH Major Topic]) AND brain[MeSH Terms]))' to ensure relevant papers were not missed. Additional spot check searches stemming from key references in identified works were also carried out to further strengthen the literature review's reliability. Only English language articles published in peer-reviewed journals were included. In total, our literature search identified 95 unique papers relating to either paresis, spasticity, UMNS or 'positive' post-stroke disorders (pain, tremor, dystonia, dyskinesias), which were included for further analysis.

DBS for maladaptive 'positive' post-stroke disorders

As summarized in Table 1 through 4, the literature search established that DBS has been examined for treatment of several kinds of maladaptive 'positive' post-stroke disorders, including neuropathic pain (43 papers - Table 1), tremor (33 papers - Table 2), dystonia (16 papers - Table 3), and dyskinesias (9 papers - Table 4). DBS for these conditions has involved a variety of different structural targets (Table 5, Table 6). Targets chosen for DBS therapy in post-stroke positive disorders proved largely to be the same as those used for equivalent disorders of non-stroke etiology. Accordingly, the posterior limb of the internal capsule (PLIC), sensory thalamus, and periventricular/periaqueductal grey (PVG/PAG) has been targeted for intractable pain, motor thalamus targeted for tremor, and globus pallidus internus (GPi) targeted for post-stroke dystonia [53]. Dyskinesia proved an exception; while dyskinesia in the context of Parkinson's disease is traditionally managed with STN or GPi DBS [54], post-stroke dyskinesia has mainly been treated with DBS of motor thalamus.

DBS for post-stroke pain

Post-stroke pain is the most common form of central neuropathic pain, affecting between 1% and 12% of stroke patients [55–58]. Often extremely debilitating, it is frequently accompanied by evoked pain (allodynia or hyperalgesia), sensory abnormalities (including hyposensitivity or dysaesthesias), and crippling emotional distress [56]. In contast to early theories that held that pain originates strictly from lesions of the somatosensory thalamus (especially the ventroposterolateral (VPL) and ventroposteromedial (VPM) nuclei) [59–61], which constitutes a termination point of the spinothalamic tract [62], it is now understood that the disorder can arise from any lesions affecting pain processing pathways within the brain, including the brainstem [63], posterior limb of internal capsule (PLIC) or corona radiata [64,65], insula [66], and