REVIEW ARTICLE

Deep Brain Stimulation for Ischemic Stroke Rehabilitation: from Rodents to Human

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Abstract: Ischemic stroke survivWors often suffer from severe disability and impaired quality of life, and the current treatments are inadequate. Deep brain stimulation (DBS) is a promising strategy to enhance recovery and alleviate symptoms, as it can modulate the electrical activity of neural circuits and facilitate neuroprotection and regeneration. In this review, we conducted a comprehensive literature search and summarized the chronic sequelae and mechanisms of ischemic stroke. Then we discuss the common targets and outcomes of DBS in preclinical and clinical studies, as well as the challenges and opportunities of DBS for ischemic stroke treatment.

Keywords: DBS, ischemic stroke; dentate nucleus; motor dysfunction; post-stroke pain.

INTRODUCTION

Ischemic stroke accounts for about 70% of all stroke cases, resulting in significant death and disability (Benjamin *et al.*, 2019). Stroke can cause a wide range of sensory-motor sequelae, including motor weakness, paralysis, spasticity, ataxia, sensory loss/numbness, dysarthria, and dysphagia, as well as a variety of cognitive and psychiatric disorders, such as depression (Guo *et al.*, 2022; Schweizer & Macdonald, 2014).

However, current stroke treatments remain limited, with tPA therapy and mechanical thrombolysis in the acute phase proving to be effective regimens for restoring perfusion (Phipps & Cronin, 2020). Due to the short therapeutic window, only a small number of patients can receive timely intervention (Albers *et al.*, 2018; Powers William *et al.*, 2019). New therapeutic options are constantly being proposed, and attention has been focused on the use of drugs, cell therapies, hydrogels, electrical stimulation, and even ultrasound stimulation to modulate neuroprotection in the acute phase and to promote neuroregeneration in the chronic phase (Baek *et al.*, 2020; Boese *et al.*, 2018; Elias *et al.*, 2018; Griauzde *et al.*, 2019; Jiang *et al.*, 2023).

Various modalities of neuromodulation with electric stimulation are currently being investigated for use in ischemic stroke, such as transcranial direct current stimulation (tDCS), repetitive transcranial magnetic stimulation (rTMS), motor cortex stimulation (MCS), vagus nerve stimulation (VNS) and deep brain stimulation (DBS) (Ananda *et al.*, 2023; Elias *et al.*, 2018). DBS is a well-established treatment for Parkinson's disease, with proven safety and efficacy (Troche *et al.*, 2013). In stroke rehabilitation, DBS is thought to modulate neuroplasticity and enhance functional recovery after stroke (Elias *et al.*, 2018). In this review, we summarize the anatomical and functional aspects of

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DBS targets from pre-clinical and clinical evidence and discuss the potential of DBS as a rehabilitation approach for ischemic stroke.

1. ISCHEMIC STROKE: SITE, MECHANISM, AND SEQUELAE

Much valuable evidence has been accumulated on electrical stimulation for stroke rehabilitation, and it is not our intention to repeat the statements that have been made, but rather to focus on the association between deep brain electrical stimulation and ischemic stroke - particularly ischemic damage triggered by occlusion of the middle cerebral artery - by summarizing and exploring a range of pre-clinical to clinical experience for the reference of colleagues.

1.1. Common occlusion site of stroke

In the 1970s, it was first discovered that the direct cause of ischemic stroke is hypoperfusion in the brain, where vascular occlusion leads to a lack of oxygen and glucose in the brain tissue, which in turn leads to hibernation and even death (Campbell *et al.*, 2019). Depending on the degree of perfusion preservation, the survival of cells in the center and around the ischemic infarct foci varies. Neurons and astrocytes that have temporarily lost their electrophysiological function are present in the region near the ischemic margins, a region known as the ischemic penumbra in nuclear magnetic imaging (Astrup *et al.*, 1981).

The usual cause of ischemic stroke is thromboembolism (Campbell *et al.,* 2019). Thrombus often comes from LARGE artery atherosclerosis and cardiac diseases such as atrial fibrillation (Savoiardo, 1986). The blood supply to the brain comes mainly from the skull base arterial ring, and when one artery embolizes, neighboring arteries may partially provide compensation to maintain the survival of the ischemic penumbra tissue (Table 1). Depending on the embolized vessel, ischemic stroke can cause damage to different regions of brain tissue, corresponding to different clinical symptoms (Mergenthaler *et al.,* 2022). The blood supply to the brain is ensured by four aortas: two internal carotid arteries (ICA) and two vertebral arteries (VA). The ICA ascends vertically from the bifurcation of the common carotid artery to the base of the skull, where it enters the skull through the carotid canal.

(1)The anterior cerebral artery (ACA) supplies the medial surface of the brain and the superior margins of the frontal and parietal lobes (Mergenthaler *et al.,* 2022). (2)The middle cerebral artery (MCA) supplies most of the cerebral hemispheres, including the lateral surface of the cerebral hemispheres and the deep margins of the frontal and parietal lobes. and the deeper structures of the frontal and parietal lobes. (3) The VA circulation, which includes the posterior cerebral artery (PCA), supplies the upper spinal cord, the brainstem, the labyrinth, the cochlea, the cerebellum, the lower thalamus, parts of the thalamus, and the temporo-occipital lobes. The ICA circulation and the VA circulation form the base of the brain in the Willis Circle and provide important collateral circulation to the brain in the event of an obstruction of the ICA.

MCA stroke is the most common stroke group, accounting for half of all stroke incidents (Ng *et al.*, 2007). It affects different brain regions depending on the involved division of the middle cerebral artery. The superior division causes contralateral hemiplegia, hemisensory loss, and non-fluent (Broca's) aphasia on the dominant side, while the inferior division causes contralateral hemianopia and fluent (Wernicke's) aphasia on the left side (S. JX. Murphy & Werring, 2020).

1.2. Permanent sequelae of stroke

Focal ischemic stroke, which may involve cortical and subcortical areas as well as downstream fiber tracts, leads to deficits in neural circuits and may even disturb brain regions distant from the ischemic lesion (Siegel *et al.*, 2016). The impairment of structural and functional connectivity plays a critical role in poststroke deficits and results in multiple sequelae (Egger *et al.,* 2021).

1.2.1. Post-stroke motor dysfunctions

Early damage from blood flow occlusion leads to immediate and irreversible cell death in the ischaemic core, while neurons in the penumbra remain partially perfused but at a reduced rate, and these neurons can be salvaged if blood flow is restored in time (Baron, 2018). Over time, reperfusion, blood-brain barrier (BBB) disruption, and inflammation can bring about a second injury, causing more damage to the remaining tissue (Boese *et al.*, 2018).

Dormancy and loss of neurons are direct contributors to motor deficits, and while a small amount

of neural regeneration and functional compensation exists in the chronic phase, it is often insufficient (Alawieh *et al.,* 2018). Duncan et al.(1992) reported that initial motor impairment as measured by the Fugl-Meyer Upper Extremity (FM-UE) scale accounted for half of the variance in motor score 6 months post ischemic stroke impairment. chronic motor dysfunction can be predicted by assessing the degree of nerve damage in the vulnerable pyramidal tract in patients with acute ischemic stroke. Feng et al. (2015) developed an imaging biomarker (weighted CST lesion load, wCST-LL) to measure corticospinal tract (CST) damage by stroke. wCST-LL in acute stroke predicted motor outcomes (FM-UE scores) at 3 months, especially for severely impaired patients. When patients are above 7.0cc wCST-LL, they had poor motor outcomes (FM-UE < 25) at 3 months. Other preclinical studies have also shown that there is a clear window of time for neuroplasticity and that the ability for brain re-wiring and plasticity is highly correlated with the number of neurons involved after ischemic stroke, thus affecting the recovery of motor function in the chronic phase (Murphy & Corbett, 2009).

1.2.2. Post-stroke pain

Central post-stroke pain (CPSP) is a neuropathic pain syndrome that results from damage in the central nervous system (CNS), for example, ischemic stroke. It is characterized by pain in the body regions that correspond to the injured brain areas. Although the thalamus is the most common site of injury, other brain regions such as the internal capsule, brainstem, and cerebral cortex are also considered candidate targets (Akyuz & Kuru, 2016).

The pathogenesis of CPSP is still not fully elucidated, but it is generally attributed to abnormal nociceptive processing in the damaged brain after a stroke occurs. This may cause alterations in pain perception and hypersensitivity (Betancur *et al.,* 2021). Here are some possible mechanisms:

Head and Holmes (1911) proposed the disinhibition theory to explain the abnormal perception of pain and non-pain stimuli after lateral thalamus injury which can be caused by ischemic stroke. They suggested that the injury would cause loss of cortical control and thalamus hyperactivity. Craig et al. extended this theory and proposed that the imbalance between the thermosensory area in the insula and the limbic network is due to CNS lesion ((Bud) Craig, 1998). They claimed that lesions of the lateral spinothalamocortical pathway, connected to the parieto-insular cortex, would disinhibit the nociceptive activity in the medial spinothalamocortical pathway, connected to the anterior cingulate cortex. This would result in loss of thermo-sensory integration, manifested as burning pain and exaggerated responses to harmless temperatures.

1.2.3. Other post-stroke sequelae

After stroke occurs, other multiple sequelae may persist over time, such as psychosomatic problems and cognitive impairments. Post-stroke depression (PSD) is one of the most common and serious complications following a stroke, with approximately one-third of ischemic stroke patients experiencing depressive symptoms (Guo *et al.,* 2022). PSD has a serious impact on functional recovery and quality of life and is also associated with a high mortality rate. One theory suggests that this phenomenon is primarily related to the dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis, with altered neurotransmitters (e.g., 5-HT and glutamate) contributing to the development of PSD (Juruena *et al.,* 2018). Alternatively, neurotrophic factors, such as insulin-like growth factor-1 (IGF-1) and brain-derived neurotrophic factor (BDNF), are suggested to change serum levels after stroke onset (King *et al.,* 2019).

Cognitive dysfunction is another common stroke complication, affecting approximately one-third of stroke patients (Zhang & Bi, 2020). The pathogenesis of cognitive dysfunction after stroke includes neuronal injury, altered neuronal metabolism, neuroinflammation, and neuroplasticity. Cognitive dysfunction after stroke is commonly assessed in a variety of ways including neuropsychological testing, neuroimaging, and biomarkers.

2. DBS TARGETS FOR CIRCUIT REMODULATION

In this section, we introduce several stimulation targets for DBS implantation. By modulating the electrical balance, neural circuits damaged by stroke can be partially activated or blocked with certain stimulation patterns (Table 2).

2.1. Subthalamic Nucleus

The subthalamus contains the subthalamic nucleus (SNT), which serves to form a loop with the Nucleus reticularis tegmenti projecting back and forth

to form synchronized excitation pulses, from which excitation pulses are delivered to the medial and lateral nuclei of the pallidum and substantia nigra in the main loop of the basal ganglia nerves to provide excitation and temporal control of neural activity in these nuclei, which is then followed by synergistic control of motor actions by the main loop (Obeso *et al.,* 2008). Krämer et al. implanted electrodes into the rat STN and used photothrombosis to inflict ischaemic damage to the cortex (Krämer, Schuhmann, Volkmann, *et al.*, 2022). After 7 days of continuous high-frequency stimulation (130 Hz; 60 μs; monophasic square wave pulses), the forelimb grasping ability of rats with ischemic stroke was significantly improved, while [18F]FDG PET also showed an increase in glucose metabolism in the sensorimotor cortex. More extensive [18F]FDG PET revealed a high glucose uptake in the corticosubthalamic/pallidosubthalamic circuit, particularly ipsilateral to the stimulated side, suggesting that high-frequency electrical stimulation targeting the STN may have remoduled the neuronal network involved in upper limb motor function.

2.2. Mesencephalic locomotor region

The mesencephalic locomotor region (MLR) is a region located in the midbrain that is closely associated with motor evocation. This name originally comes from experiments on electrical stimulation of the cat brain, where electrical stimulation of this region induced locomotor behavior in cats (Shik *et al.*, 1966). The mesencephalic locomotor region is highly conserved evolutionarily and is enriched in glutamatergic MLR neurons expressing vesicular glutamate transporter 2(VGLUT2) in three subregions: the pedunculopontine nucleus (PPN), the cuneiform nucleus (CnF) and the mesencephalic reticular formation (mRT) (Arber & Costa, 2022).

The MLR is considered a target for neuromodulation because of its involvement in the initiation and control of gait. Fluri et al. (2017) implanted stimulating electrodes in the MLR of rats using photothrombosis to trigger stroke in the sensorimotor cortex and initiated electrical stimulation (130 Hz; 60 μs; monophasic square wave pulses) 3-4 days after the stroke occurs. The results showed that high-frequency electrical stimulation targeting the MLR significantly increased walking speed and improved gait in rats with ischemic stroke. Unilateral stimulation of the MLR (ipsilateral to photothrombotic stroke) was sufficient to improve quadrupedal walking. The authors speculate that high-frequency electrical stimulation of the MLR may partially restore normal locomotor behavior in rats by shielding brainstem and spinal locomotor centers from abnormal cortical inputs after ischemic stroke.

2.3. Dentate nucleus

The dentate nucleus (DN) is the largest nucleus in the cerebellum, adjacent to the fourth ventricle. It consists of a dorsal motor area and a ventral non-motor area (Nicholson *et al.,* 2020). The DN projects to the upper cerebral cortex via a dentate synaptic tract (DRT) that crosses the superior peduncle of the cerebellum, whereas the dorsal motor domain of the DN projects to the ventral lateral nucleus of the thalamus, parabasal red nucleus of the lateral ventricles, and the reticular formation, and thus primarily targets the motor and premotor cortex (Tacyildiz *et al.*, 2021). In contrast, the ventral non-motor domain projects to the ventral lateral thalamic nucleus and the dorsomedial paraventricular red nucleus, thus targeting primarily the prefrontal and parietal cortex (Dum & Strick, 2003).

Efferent fibers from the DN to the reticular formation are critical for muscle tone management. Although there is no evidence for a direct link between the right and left DN, they may communicate indirectly through the corpus callosum, the cerebellar junction, and bilateral projections to the mesencephalon and brainstem, and modulate muscle tone during unilateral motor tasks (Hoshi *et al.,* 2005). Thus, the structural and functional specificity of the DN makes it an important target for DBS therapy.

The idea of using electrical stimulation to target DN to modulate movement disorder after ischemic stroke is not new. The first attempt was in 2009, Machado et al. discovered that chronic 30-Hz deep cerebellar stimulation coupled with training enhances post-ischemia motor recovery and peri-infarct synaptophysin expression in rats (Machado *et al.,* 2009, 2013). Then Cooperrider et al. (2015) investigated changes in cortical infarcted rats after receiving lateral cerebellar nucleus (LCN, the rodent analog to the human DN) stimulation in the chronic phase from a neuroplasticity perspective. They found that electrically stimulated treated animals had a twofold increase in synaptic density and exhibited increased long-term potentiation and plasticity, including synaptophysin, NMDAR1,

CaMKII, and PSD95. Recent clinical studies have also shown promising outcomes with solid evidence from a phase I trial, which we shall discuss in the clinical section (Wathen *et al.,* 2018).

3. DBS TARGETS FOR NEUROPROTECTION & NEUROGENESIS

DBS is thought to modulate the inflammatory response in the acute phase and promote neural regeneration in the chronic phase, thus improving post-infarction recovery in terms of regeneration of neurological functions.

3.1. MLR

Recent studies have shown that MLR electrical stimulation 3 days after stroke modulates the level of glucose metabolism in the cerebral cortex and can trigger anti-inflammatory processes within the perilesional area by modulating the cholinergic system (Krämer, Schuhmann, Schadt, *et al.,* 2022; Schuhmann *et al.,* 2019). Another study showed that high-frequency stimulation aimed at the MLR triggers anti-inflammatory processes in the peri-infarct zone by modulating the cholinergic system (Schuhmann *et al.,* 2021). The electrical-stimulated group of rats with cortical infarcts exhibited lower levels of IFN-γ, TNF-α, and IL-1α, and the number of ChAT+ CD4+-cells was significantly elevated, speculating that electrical stimulation may achieve suppression of the inflammatory response through the activation of α7 nicotinic acetylcholine receptor(α7nAchR) (Schuhmann *et al.,* 2021).

3.2. Medial Preoptic Nucleus

In addition, Zhang et al. (2022) found that electrical stimulation of the medial preoptic nucleus (MPNs) could effectively reduce body and brain temperatures in mice, which in turn inhibited the neuroinflammatory response after ischemia, lowered the level of inflammatory factors, and reduced neuronal apoptosis and necrosis, thereby reducing the volume of ischemic cerebral infarction, and improving neurological and cognitive functions.

Lateral Cerebellar Nucleus

Wu et al. placed DBS electrodes in the lateral cerebellar nucleus (LCN) and then created cortical ischemia in the rat cerebral cortex using endothelin-1, and started electrical stimulation 8 days after endothelin-1 injection. The results showed that LCN electrical stimulation could promote the proliferation and differentiation of neural stem cells and the formation of new neurons and synapses by activating cerebellar-cerebral circuits and increasing the expression of neurotrophic factors. The effect of LCN electrical stimulation was affected by parameters such as the frequency, intensity, duration, and timing of stimulation, as well as the severity and location of ischemia (Wu *et al.,* 2020). Chan et al. (2018) found that neurogenesis following motor cortex ischemia could be promoted by electrical stimulation of the LCN in mice, resulting in improved neurological and cognitive function. Cortical ischemia was induced in rats, electrodes were implanted in the contralateral LCN, and then electrical stimulation was started 6 weeks after stroke induction and continued for 4 weeks. The results showed that increased cell proliferation was observed in the peri-injured cortex as well as in bilateral mediodorsal and ventrolateral thalamic subnuclei and that this neurogenic effect at the level of the motor cortex was selective, with more glutamatergic neurogenesis but significantly less GABAergic neurogenesis occurring in rats that had undergone electrical stimulation of the LCN.

3.3. Fastigial Nucleus

The fastigial nucleus(FN) is located at the top of the fourth ventricle and contains adrenergic intrinsic neurons and nerve fibers, which serve as the final integration site and final output of the spinocerebellum and are involved in the regulation of a wide range of whole-body systems including feeding, cardiovascular, respiratory, defecation and urination.(Sathyanesan *et al.,* 2019) Stimulation of the fastigial nucleus is thought to exert neuroprotective effects after stroke through inhibition of apoptosis, inflammatory response, excitotoxic damage on neurons, and electrical activity around the lesion to exert neuroprotective effects after ischemic stroke and to promote reconstruction of neural tissue (Wang *et al.,* 2014).

In addition, several earlier studies have also supported the idea that electrical stimulation promotes increased brain plasticity and enhanced neural regeneration after ischaemic stroke.(Cooperrider *et al.,* 2014; Machado *et al.,* 2013; Morimoto *et al.,* 2011)

4. RECENT CLINICAL APPLICATIONS OF DBS IN POST-STROKE RECOVERY

The literature review reveals two primary indications in recent years for the application of Deep Brain Stimulation (DBS) following an ischemic stroke: the management of post-stroke pain and the intervention for motor dysfunction (Table 3).

4.1. DBS for post-stroke pain

Post-stroke pain can impact up to 50% of stroke survivors, with the majority enduring daily pain (Plecash *et al.*, 2019). The most common forms of chronic post-stroke pain are shoulder pain, central post-stroke pain (CPSP), painful plasticity, and tension-type headache, among which CPSP mainly corresponds to the cerebrovascular lesion (Klit *et al.*, 2009). Initial hypotheses posited that CPSP originated exclusively from a lesion in the somatosensory thalamus (Krause *et al.*, 2012; Paciaroni & Bogousslavsky, 1998). However, contemporary understanding recognizes that the disorder can arise from a lesion impacting any pain processing pathway in the brain, including the brainstem, the posterior limb of the internal capsule (PLIC) or corona retina, and somatosensory cortex emerge as implicated regions in alterations to bursting and oscillatory behavior in diverse areas, such as the somatosensory thalamus and Periaqueductal Gray (PAG) (Elias *et al.*, 2018).

The advancement in our understanding of pain pathways has led to a broadening scope of clinical studies in the past decade, encompassing an expanded array of stimulation sites in research. While the PVG/PAG, somatosensory thalamus (specifically, VPL or VPM thalamus), and PLIC continue to be regarded as commonly used and reliable stimulation sites, new sites such as the nucleus ventrocaudalis parvocellularis internis (VCPCI) and the junction of the Cl and MD (CL/MD) are emerging as potential sources of patient benefit. The anterior cingulate cortex (ACC), in conjunction with the orbitofrontal cortex (OFC) and other pain-related brain regions, is under ongoing investigation in clinical cohorts. As for the evaluation of outcome, The Visual Analog Scale (VAS) remains the most objective measure of pain. However, short-term reductions in objective measures may not necessarily indicate the true efficacy of DBS, as patient analgesia is significantly influenced by the insertion effect (Hamani *et al.*, 2006). Consequently, longer follow-up periods and retrospective studies may be imperative to demonstrate the effectiveness of new stimulation sites.

4.2. DBS for post-stroke motor dysfunctions

The principal motor dysfunctions encompass tremors, dystonia, dyskinesia, and motor deficits. A tremor in stroke patients often stems from thalamic, brainstem, or cerebellar lesions, precipitating either action tremor, resting tremor, or combined Holmes tremor. Recent studies of post-stroke tremor have centered primarily on the Holmes tremor, which is a unique and debilitating movement disorder that usually results from lesions of cerebellothalamic and dento-rubro-olivary connections (Nsengiyumva *et al.*, 2021). The treatment approach for postischemic stroke tremor mirrors that applied to other forms of tremor, with a focus on the motor thalamus, particularly targeting the ventral intermediate nucleus (VIM) and the nucleus ventralis oralis (VO).

Post-stroke dystonia often arises from lesions in the cortico-striato-pallido-thalamic or the cerebello-thalamo-cortical loops (Gonzalez *et al.*, 2015). In post-stroke dystonia, the commonly targeted regions for DBS include the traditional Globus Pallidus Internus (GPi) as well as more recently explored sites such as VIM, Subthalamic Nucleus (STN), and Dentate Nucleus (DN). It is essential to note that the widely used Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS) in DBS trials may lack validation. Disease heterogeneity may explain some of the large differences in BFMDRS improvement, but taken together, stroke-induced dystonia did not respond well enough to DBS (Abdulbaki *et al.*, 2023). Also, this scale does not adequately capture changes relevant to daily functioning and quality of life, therefore, incorporating additional endpoints is crucial for a more comprehensive and accurate assessment of the benefits derived from DBS.

Post-stroke dyskinesias typically include choreiform dyskinesias (ballism, chorea, and athetosis) and non-choreo-dystonic dyskinesias (eg, tremor, asterixis, and myoclonus) (Nakawah & Lai, 2016). Hemiballism is the most common form of dyskinesias that appears in recent research, which is notably better controlled through DBS in clinical cases. The motor nuclei of the thalamus, particularly the VIM and the VO, served as the most frequently targeted areas. However, recent studies have revealed that GPi is also an effective target for treatment.

Upper motor neuron syndrome persists as the predominant consequence of a stroke, and despite contemporary interventions, up to 50% of stroke survivors endure post-stroke disability, often requiring assistance for daily tasksa (Lawrence *et al.*, 2001; Tsao *et al.*, 2022). Empirical data regarding the utility of DBS in addressing paralytic dyskinesia and concomitant Upper Motor Neuron Syndrome (UMNS) is limited. However, recent advancements in cerebellar neuromodulation have exhibited promise in rehabilitation, introducing a potential site selection for patients (Cooperrider *et al.*, 2020). A recent phase I clinical trial has showcased the capacity of Dentate Nucleus (DN) DBS to extend the extent and time window of neuroplasticity after both ischemic and traumatic brain injuries. (Baker *et al.*, 2023). This approach facilitates functional recovery and homologous cortical reorganization, presenting a promising avenue for enhancing patient outcomes.

4.3. Limitation and future direction

The existing clinical literature highlights the pivotal role of DBS in addressing maladaptive phenomena post-stroke. However, the evidence regarding DBS for treating positive post-stroke disorders predominantly originates from case series and case studies rather than blinded, sham-controlled trials. Consequently, there is an imperative need for additional controlled trials to elucidate critical details, such as optimal brain targets and stimulation parameters. While assembling a cohort for post-stroke symptoms with a low probability of occurrence might pose challenges, prospective cohort studies could be incrementally undertaken for high-probability post-stroke pain and hemiparesis. A practical strategy for rare poststroke symptoms would involve systematically documenting patients' symptoms in intricate detail, fostering comparability, and accumulating valuable experience over time.

5. CONCLUSION

From rodents to humans, electrical stimulation of multiple deep brain nuclei as targets can produce a variety of positive effects including neural circuit modulation, inhibition of inflammatory responses, and promotion of neural regeneration. A small number of clinical trials have also demonstrated the safety and efficacy of DBS stimulation, but a great deal of future work is needed to explore the optimal targets and parameters and to further investigate the efficacy of DBS for stroke.

Major Blood Vessels	Secondary Blood Vessels	Support Region	Consequences of Occlusion	Reference
Internal Carotid Arteries(ICA)	Anterior cerebral artery	Medial surface of the brain and the superior margins of the frontal and parietal lobes	Dyskinesia, Emotional numbness, hypobulia, urinary incontinence	(Mergenthaler *et al.,* 2022)
	Middle cerebral artery	Most of the cerebral hemispheres, including the lateral surface of the cerebral hemispheres and the deep margins of the frontal and parietal lobes	Contralateral hemiplegia, hemisensory loss, non-fluent aphasia, contralateral hemianopia, fluent aphasia(Depending on infract division)	(Ng *et al.,* 2007)
Vertebral Arteries(VA)	Posterior cerebral artery	Upper spinal cord, the brainstem, the labyrinth, the cochlea, the cerebellum, the lower thalamus, parts of the thalamus, and the temporo-occipital lobes.	Headache, homonymous hemianopsia	(Mergenthaler *et al.,* 2022)

Table 1. Major blood supply of cerebrum and manifestations after occlusion.

Stimulation Target	Animal	Ischemic Location	Stimulation Time	Stimulation Parameter	Reported Outcome	Observation Time	Year	Reference
MLR	rat	cerebral cortex	7d after photothrombosis	30 Hz, 70 Hz, 130 Hz; 20, 40, 60, 80, 120 μA; 60 μs	Introduce a light-weighted, easily exchangeable stimulating device	not mentioned	2017	(Fluri, Mützel, *et al.*, 2017)
FN	rat	MCA	24h after MCAO	70-μA direct-current square-wave pulse (50 Hz)	Significantly different expressions of miRNAs after FN stimulation	1h	2015	(Pang *et al.*, 2015)
FN	rat	MCA	3d before MCAO	not mentioned	Reduced brain infarct volume and increase Ku70 expression	24h	2014	(Liu *et al.*, 2014)
LCN	rat	cerebral cortex	8d after Endothelin-1-induce	30Hz; 400 μs; Isochronous stimulation	Promoted endogenous neurogenesis	30d	2020	(Wu *et al.*, 2020)
LCN	rat	cerebral cortex	6 weeks after cortical ischemia	not mentioned	Selective motor cortex neurogenesis	4weeks	2018	(Chan *et al.*, 2018)
LCN	rat	cerebral cortex	7d after endothelin-1 injection	isochronal stimulation at 20, 30, 50, and 100 pulses per second	Activation of the DTC pathway increases cortical excitability in post-stroke animals	10min	2015	(Park *et al.*, 2015)
LCN	rat	motor cortex	2weeks after endothelin-1 injection	six charge-balanced square-wave pulses (400 μs pulse-width per phase) with an intraburst frequency of 330 Hz	Enhanced cortical plasticity	5weeks	2014	(Cooperrider *et al.*, 2014)
LCN	rat	cerebral cortex	1weeks after endothelin-1 injection	pulsed, 30-Hz stimulation	Significant improvement in motor function	3 to 5 weeks	2014	(A. G. Machado *et al.*, 2013)
LCN	rat	MCA	not mentioned	50 Hz; frequency band – beta	Modulated cortical excitability in a frequency-dependent fashion	not mentioned	2012	(A. Machado & Baker, 2012)
MLR	rat	sensorimotor cortex	3d after photothrombosis	130 Hz; 60 μs; monophasic square wave pulses	Increased glucose metabolism	24h	2022	(Krämer, Schuhmann, Schadt, *et al.*, 2022)

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Stimulation Target	Animal	Ischemic Location	Stimulation Time	Stimulation Parameter	Reported Outcome	Observation Time	Year	Reference
MLR	rat	cerebral cortex	3h after photothrombosis	130 Hz; 60 μs; monophasic square waves pulses	Trigger anti-inflammatory processes within the perilesional area by modulating the cholinergic system	24h	2021	(Schuhmann *et al.*, 2021)
MLR	rat	sensorimotor cortex	3h after photothrombosis	130 Hz; 60 μs; monophasic square wave pulses	No significant improvement of infarct size and BBB dysfunction	24h	2019	(Schuhmann *et al.*, 2019)
MLR	rat	sensorimotor cortex	3h after photothrombosis	130 Hz; 60 μs; monophasic square wave pulses	Reduces pro-inflammatory mediators near the photothrombotic stroke region	24h	2019	(Schuhmann *et al.*, 2019)
MLR	rat	sensorimotor cortex	3-4d after photothrombotic	130 Hz; 60 μs; monophasic square wave pulses	Higher walking speed and better dynamic gait performance	not mentioned	2017	(Fluri, Malzahn, *et al.*, 2017)
MPNs	mice	MCA	1h after MCAO	100Hz, 1–8V, 90μs pulse duration	DBS produces tolerable hypothermia to promote brain protection and motor function reservation	24h	2022	(S. Zhang *et al.*, 2022)
PPTg	rat	sensorimotor cortex	not mentioned	130 Hz; amplitude 55 $\pm$ 5 μA	No significant improvement of skilled walking	10d	2020	(Bohr *et al.*, 2020)
STN	rat	motor cortex	24h after photothrombosis	130 Hz; 60 μs; monophasic square wave pulses	Improves forelimb use	7d	2022	(Krämer, Schuhmann, Volkmann, *et al.*, 2022)
Straitum	rat	MCA	30d after MCAO	2 Hz; 100 μA	promote neurorestoration by stimulating endogenous neurogenesis and angiogenesis	30d	2011	(Morimoto *et al.*, 2011)

Table 2. Pre-clinical evidence of DBS treatment for ischemic stroke

Indication	Sex/Age (At Surgery)	Ischemic Location	Injury	Stimulation Target	Stimulation Parameter	Reported Outcome	Follow-Up	Reference
Pain	M/50	L Thalamus	(pain) > 2 years	L PLIC	60 Hz, 150 μs, 4.5 V contacts: 3+, 0-, 1-, 2-	40% VAS reduction	12 months	(Hunsche *et al.*, 2013)
	M/74	L Thalamus	(pain) > 2 years	L PLIC	60 Hz, 60 μs, 1 V contacts: G+, 0-	40% VAS reduction	12 months	
	F/71	R Thalamus	(pain) > 2 years	R PLIC	60 Hz, 60 μs, 2 V contacts: 3+, 0-, 1-, 2-	10% VAS reduction initially; relief lost after 3 months	12 months	
Pain thalamic tremor	NR	L posterolateral thalamic area L temporal-occipital area	2 years, 4 months	PVG/PAG, VPL	50 Hz, 210 μs, 1.6 V contact: 2-	Pain reduction significant alleviation of thalamic tremor	>2 months	(Papuć *et al.*, 2013)
Pain	F/69	R MCA	9 years	R VS/VC	60 Hz, 180 μs, 2.5 V contact: case+, 2-, 3-,	Minimal pain relief	1 year	(Morishita *et al.*, 2015)
				R VO	60 Hz, 150 μs, 2.5 V contact: 10+, 9-			
Pain	M/50	R cortical R thalamus	7 years	R VCPCI	40 Hz, 60 μs, 1-3 V contact: case+, 1-	40% VAS reduction	38 months	(Rezaei Haddad *et al.*, 2015)
Pain	M/68	Cerebral atrophy L and R corona radiata R VIM	11 years	L VC	99Hz, 100 μs, 0.1 Ma contact: 3-	Pain intensity was still reduced by approximately 50%	16 months	(Ten Brinke *et al.*, 2020)
				L PVG	Off due to the good effects of Vc DBS			
Pain	F/52	MCA	3 years	CL/MD	1000 Hz, 160 μs, 4.4 Ma contacts: L3-, L4-	< 50% VAS reduction	12 months	(Nowacki *et al.*, 2022)
	M/68	Lateral medulla oblongata	2 years	CL/MD	1000 Hz, 180 μs, 4 mA contacts: L1-, L2+, L3-	> 50% VAS reduction	12 months	
	M/66	Lateral medulla oblongata	18 years	VPL	1000 Hz, 90 μs, 0.9 mA contacts: C3+, C6-	> 50% VAS reduction	12 months	
	F/70	thalamus	3 years	Failed both	NR	NR	12 months	
	M/68	Lateral medulla oblongata	2 years	VPL	20 Hz, 90 μs, 0-1.5 mA contacts: L3-, L4-	< 50% VAS reduction	12 months	
				CL/MD	1000 Hz, 90 μs, 4.1 mA contacts: L3-, L4-			

Indication	Sex/Age (At Surgery)	Ischemic Location	Injury	Stimulation Target	Stimulation Parameter	Reported Outcome	Follow-Up	Reference
Pain	M/59	Lateral medulla oblongata	2 years	VPL	50 Hz, 120 μs, 0-1.4mA contacts: L3-, L4+	> 50% VAS reduction	12 months	(Nowacki *et al.*, 2022)
				CL/MD	1000 Hz, 120 μs, 2 mA contacts: L2-, L3-			
Pain	22-80	Including stroke	—	Bilateral pain-related brain regions	—	VAS	2 years	ClinicalTrials.gov ID NCT04144972
Pain	≥ 21	For stroke: MCA /cavernous malformations	—	ACC and OFC closed-loop stimulation	—	VAS	2 years	ClinicalTrials.gov ID NCT03029884
Pain	18-70	CPSP (Treede-Klit criteria)	—	M1-rTMS/ MCS/ VC-DBS	—	VAS	9 months	ClinicalTrials.gov ID NCT05708729
Pain	18-75	Unilateral ischemic cerebral stroke	>12 months	Thalamus	—	NRS 1-10	2 weeks	ClinicalTrials.gov ID NCT05204472
Holmes tremor	F/45	L thalamic	30 years	Area between L ZI and Voa	185 Hz, 60 μs, 1.8 V contacts: C+, 0-(ZI), 2-(Voa)	73.8% TRS reduction (42 to 11) postural component of right upper limb tremor improved	36 mons	(Grabska *et al.*, 2014)
Holmes tremor	M/67	R superior cerebellar peduncle/cerebellar hemisphere	7 years	L VIM/VO, PSA	135 Hz, 210 μs, variable voltage	100% TRS reduction (17 to 0)	24 months	(Kobayashi *et al.*, 2014)
Holmes tremor	M/50	R thalamic/subthalamic (PCA)	18 years	R GPi	185 Hz, 90 μs, 2 V contacts: 1-	80.0% TRS reduction (45 to 9)	18 months	(Kilbane *et al.*, 2015)

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Indication	Sex/Age (At Surgery)	Ischemic Location	Injury	Stimulation Target	Stimulation Parameter	Reported Outcome	Follow-Up	Reference
Holmes tremor	F/62	R medial cerebral peduncle and bilateral thalamic	2 years	VIM, ZI	140 Hz, 70 μs, 3.5 V contacts: C +, 2 −	UDRS score reduction (26 to 16)	NR	(O'Shea *et al.*, 2020)
Holmes tremor	M/58	R medial thalamic infarction	<1 years	R VIM	150 Hz, 120 μs, 3.5 V	73%TRS reduction (51 to 14)	20 years	(Onder *et al.*, 2023)
Complex tremulous movement	F/62	Bilat ventral posterior thalamus	23 years	R VIM/Czi	185 Hz, 60 μs, 2.5 V contacts: C +, 1-, 3-	TRS score reduction (79 to 54) EQ-5D score (0.238 to 0.394) HADS score (5 to 3)	12 months	(A *et al.*, 2021)
				L VIM/Czi	185 Hz, 60 μs, 3.5 V contacts: C +, 9-, 10-			
Dystonia	M/29	R putamen and frontal periventricular white matter extending to ALIC	23 years	R GPi	160 Hz, 90μs, 3.5 V contacts: Case+, 1-,	BFMDRS-motor improvement at 6 months (42.8%) No BFMDRS-motor improvement at 3 years	3 years	(Witt *et al.*, 2013)
	F/16	L putamen, caudate, ALIC	14 years	R GPi	140 Hz, 60μs, 5.0 V contacts: Case+, 0-, 1-	12.5% BFMDRS-motor improvement subjectively reported symptom improvement	12 months	
	F/10	L MCA	10 years	L GPi	135 Hz, 90μs, 3.5 V contacts: Case+, 2-	4.7% BFMDRS-motor improvement subjectively reported symptom improvement	12 months	

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Indication	Sex/Age (At Surgery)	Ischemic Location	Injury	Stimulation Target	Stimulation Parameter	Reported Outcome	Follow-Up	Reference
Dystonia	F/40	R corona radiata, putamen, insula	4 years	R GPi	180 Hz, 210μs, 3.2 V contacts: 0-, 1-, case+,	No BFMDRS-motor improvement 27% BFMDRS disability improvement	4 years	(Ej *et al.*, 2015)
				R VIM	180 Hz, 60μs, 3.3 V contacts: case+, 5-,			
	M/44	L lentiform	32 years	L GPi	130 Hz, 60μs, 3.8 V contacts: case+, 7-	11% BFMDRS-motor improvement	3 months	
				L VIM	130 Hz, 90μs, 3.8 V contacts: case+, 3-,			
	F/26,28	L caudate, putamen	21 years	L GPi	185 Hz, 60μs, 4.0 V contacts: 1-, 0+, case+	7% BFMDRS-motor improvement 22% BFMDRS-disability improvement	3 years	
				L VIM	185 Hz, 60μs, 4.0 V contacts: 7-, 6+,			
	F/29	L putamen/IC, brainstem	14 years	L GPi	185 Hz, 60μs, 3.7 V contacts: 1-, case+.	86.5% BFMDRS-motor improvement 87.5% BFMDRS-disability improvement	2.5 years	
				L VIM	Switched off (due to lack of efficacy)			
	F/22	L caudate, putamen	21 years	L GPi	60 Hz, 60μs, 3.8 V contacts: 7-, case+,	No BFMDRS-motor improvement 40% BFMDRS-disability improvement	2 years	
				L VIM	60 Hz, 60μs, 2.9 V contacts: 1-, 2+,			
	M/49	Central midbrain, bilateral thalamic, R cerebellar	5 years	R VIM	185 Hz, 60μs, 3.6 V contacts: 3-, case+,	16% BFMDRS-motor improvement	6 years	
Dystonia pain	F/22	L putamen	19 years	L GPi	185 Hz, 120μs, 4.5 V contacts:	25% BFMDRS improvement 59% SF-36 improvement	6 months	(Pj *et al.*, 2015)
				VIM/VOp	185 Hz, 60μs, 4 V contacts:			
Dystonia	M/23	Rt thalamic infarct	15 years	Czi/Voa/Vop	180 Hz, 78 μs, 2.5 mA Contacts: 1-, 4 +	UDRS score (14.5 to 4.5) TRS score (46 to 7) ADL-T24 scale score (19 to 19) QOLS score (49 to 82)	5 years	(Bagatti *et al.*, 2019)

Indication	Sex/Age (At Surgery)	Ischemic Location	Injury	Stimulation Target	Stimulation Parameter	Reported Outcome	Follow-Up	Reference
Dystonia pain	M/21	L caudate, putamen, GP, cortex L cerebral peduncle volume reduction L ICA narrowing	12 years	L STN	2.6 V, 90 μs and 130 Hz contacts: 2+, 3–	64.2% BFMDRS motor score improvement 33.3% disability score improvement improved pain level	3 years	(Tambirajoo *et al.*, 2020)
	F/18	R frontal region R putamen, IC, GPi	11 years	R STN	130 Hz, 90 μs, 3.8 V contacts: case+, 1–	14.3% BFMDRS motor score improvement 11.1% disability scores improvement 100% pain reduction	2 years	
	M/18	R posterior putamen and corona radiata (possible) globus pallidus	14 years	R STN L STN	130 Hz, 60 μs, 1.7 V contacts: case+, 8–, 9– 130 Hz, 60 μs, 0.7 V contacts: case+, 1–	14% BFMDRS motor score improvement 14.3% disability scores improvement pain fully resolved	2 years	
Dystonia	F/37	Brainstem stroke and hypoxic ischemic injury to bilat basal ganglia	32 years	L DN R DN	130 Hz, 60 μs, 2.8 V Contacts: 1-, 2-, 3 + 130 Hz, 60 μs, 1.2 V Contacts: 1-, 2–, 3+	BFMDS score (44 to 18.5) BFMDS disability score (11 to 10)	2 years	(Baker *et al.*, 2023)
Dyskinesia	F/82	Thalamic	2 years	R GPi	180 Hz, 90μs, 3.4 V	Complete control of hemiballismus	12 months	(Franzini *et al.*, 2014)
Dyskinesia	F/53	R thalamic infarct	23 years	R GPi	130 Hz, 90 μs, 3.0 V Contacts: C+, 0–	Near resolution of hemiballism	28 months	(K *et al.*, 2018)
Dyskinesia	M/51	R PCA	5 years	R GPi	NR	Improved hemiballism and functional status	NR	(Ganapa *et al.*, 2019)
Dyskinesia	M/57	Bilat caudate nuclei subsequent to circulatory arrest	16 years	L GPi R GPi	130 Hz, 90 μs, 2.2 V contacts: C+, 1– 130 Hz, 90 μs, 2.2 V Contacts: C+, 1–	UHDRS score (27 to 12)	1 year	(K *et al.*, 2018)

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Indication	Sex/Age (At Surgery)	Ischemic Location	Injury	Stimulation Target	Stimulation Parameter	Reported Outcome	Follow-Up	Reference
Ataxia	F/53	R cerebellar hemisphere	NR	L DN	20 Hz, 60 μs, 1.9 mA	TRS score (38 to 25) SARA score (25 to 17)	4 years	(Diniz *et al.*, 2021)
Hemiparesis	33.3%M/ 57.4 ± 6.5	Unilateral MCA	2.2 ± 0.7	DN contra-lateral to the stroke affected cerebral hemisphere	30 Hz	FM-UE seven-point median improve-ment (P = 0.0005)	20-24 months	(Baker *et al.*, 2023)
Hemiparesis	18-80	For ischemic stroke: unilateral supratentorial ischemic	6 months to 1 years	Mesen-cephalic locomotor region	NR	FMA	1 year	ClinicalTrials.gov ID NCT05968248
Hemiparesis	18-80	For ischemic stroke: unilateral supratentorial ischemic	6 months to 1 years	Mesen-cephalic locomotor region	NR	FMA	1.5 year	ClinicalTrials.gov ID NCT06121947

Table 3. Clinical trials of DBS treatment for ischemic stroke.

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List of Abbreviations

PLIC: posterior limb of the internal capsule
VAS: visual analogue scale
PVG: periventricuiar grey matter
PAG: periaqueductal grey matter
VPL: ventroposterolaterathalamic nucleus
VS: ventral striatum
VC: ventral capsule
VO: ventralis oralis thalamic area
VCPCI: nucleus ventrocaudalis parvocellularis internis
STN: subthalamic nucleus
BFMDRS: Burke-Fahn-Marsden Dystonia Rating Scale
M1-rTMS: motor cortex repetitive transcranial magnetic stimulation
MCS: motor cortex stimulation
Vc-DBS: deep brain stimulation of the sensory thalamus
CL: central lateral thalamus
MD: medial dorsal thalamus
CL/MD: the junction of the Cl and MD, lateral to the habenula
MCA: middle cerebral artery
ACC: anterior cingulate
OFC: orbitofrontal cortex
VIM: ventralis intermedius nuclei
Voa: ventralis oralis anterior nuclei
ZI: zona incerta
TRS: Fahn-Tolosa-Marin Tremor Rating Scale
PSA: posterior subthalamic area
DN: dentate nucleus
UPDRS: Unified Parkinson's Disease Rating Scale
HADS: Hospital Anxiety and Depression Scale
BFMDRS: Burke-Fahn-Marsden Dystonia Rating Scale
SF-36: Short-Form 36
UDRS: Unified Dystonia Rating Scale
QOLS: Quality of Life Scale
UHDRS: Unified Huntington's disease rating scale
SARA: Scale for the assessment and rating of ataxia

DECLARATIONS

Ethics approval and consent to participate

The authors report no involving human participants or animals in this research.

Consent for publication

Not applicable

Availability of data and materials

Not applicable

Competing interests

The authors report no competing interests in this research.

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Search strategy and selection criteria

We searched WOS (Web of Science) using the search terms TS= (((deep) AND (stimulation)) AND ((brain) OR (Cerebellar))) AND (stroke). For specific sections, additional search terms included "neurogenesis", "neurorestoration", "DBS", "LCN", "post-stroke depression", "motor dysfunction", "cerebellum", "rehabilitation", or "clinical trials". We also searched the references within the selected papers for relevant articles. We reviewed papers in English and Chinese. We did not apply date restrictions to the search. The last search was done on November 21, 2023. Results from 2013 and older papers were included only if deemed necessary to understand the subject under discussion. The final reference list was generated based on relevance to the topics covered in this Review.

REFERENCES

A, M., B, H., M, B., J, S., D, B., K, D., J, O.-F., Pr, E., & Sh, A. (2021). *Deep brain stimulation for post-thalamic stroke complex movement disorders. Neurological Sciences : Official Journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology, 42*(1). https://doi.org/10.1007/s10072-020-04572-6

Abdulbaki, A., Jijakli, A., & Krauss, J. K. (2023). Deep brain stimulation for hemidystonia: A meta-analysis with individual patient data. *Parkinsonism & Related Disorders, 108*, 105317. https://doi.org/10.1016/j.parkreldis.2023.105317

Akyuz, G., & Kuru, P. (2016). Systematic Review of Central Post Stroke Pain: What Is Happening in the Central Nervous System? *American Journal of Physical Medicine & Rehabilitation, 95*(8), 618. https://doi.org/10.1097/PHM.0000000000000542

Alawieh, A., Zhao, J., & Feng, W. (2018). Factors affecting post-stroke motor recovery: Implications on neurotherapy after brain injury. *Behavioural Brain Research, 340*, 94-101. https://doi.org/10.1016/j.bbr.2016.08.029

Albers, G. W., Marks, M. P., Kemp, S., Christensen, S., Tsai, J. P., Ortega-Gutierrez, S., McTaggart, R. A., Torbey, M. T., Kim-Tenser, M., Leslie-Mazwi, T., Sarraj, A., Kasner, S. E., Ansari, S. A., Yeatts, S. D., Hamilton, S., Mlynash, M., Heit, J. J., Zaharchuk, G., Kim, S., … Lansberg, M. G. (2018). Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging. *New England Journal of Medicine, 378*(8), 708-718. https://doi.org/10.1056/NEJMoa1713973

Ananda, R., Roslan, M. H. B., Wong, L. L., Botross, N. P., Ngim, C. F., & Mariapun, J. (2023). Efficacy and Safety of Vagus Nerve Stimulation in Stroke Rehabilitation: A Systematic Review and Meta-Analysis. *Cerebrovascular Diseases (Basel, Switzerland), 52*(3), 239-250. https://doi.org/10.1159/000526470

Arber, S., & Costa, R. M. (2022). Networking brainstem and basal ganglia circuits for movement. *Nature Reviews Neuroscience, 23*(6), Article 6. https://doi.org/10.1038/s41583-022-00581-w

Astrup, J., Siesjö, B. K., & Symon, L. (1981). Thresholds in cerebral ischemia – The ischemic penumbra. *Stroke, 12*(6), 723-725. https://doi.org/10.1161/01.STR.12.6.723

Baek, H., Sariev, A., Lee, S., Dong, S.-Y., Royer, S., & Kim, H. (2020). Deep Cerebellar Low-Intensity Focused Ultrasound Stimulation Restores Interhemispheric Balance after Ischemic Stroke in Mice. *IEEE Transactions on Neural Systems and Rehabilitation Engineering: A Publication of the IEEE Engineering in Medicine and Biology Society, 28*(9), 2073-2079. https://doi.org/10.1109/TNSRE.2020.3002207

Bagatti, D., D'Ammando, A., Franzini, A., & Messina, G. (2019). Deep Brain Stimulation of the Caudal Zona Incerta and Motor Thalamus for Postischemic Dystonic Tremor of the Left Upper Limb: Case Report and Review of the Literature. *World Neurosurgery, 125*, 191-197. https://doi.org/10.1016/j.wneu.2019.01.183

Baker, K. B., Plow, E. B., Nagel, S., Rosenfeldt, A. B., Gopalakrishnan, R., Clark, C., Wyant, A., Schroedel, M., Ozinga, J., Davidson, S., Hogue, O., Floden, D., Chen, J., Ford, P. J., Sankary, L., Huang, X., Cunningham, D. A., DiFilippo, F. P., Hu, B., … Machado, A. G. (2023). Cerebellar deep brain stimulation for chronic post-stroke motor rehabilitation: A phase I trial. *Nature Medicine, 29*(9), 2366-2374. https://doi.org/10.1038/s41591-023-02507-0

Baron, J.-C. (2018). Protecting the ischaemic penumbra as an adjunct to thrombectomy for acute stroke. *Nature Reviews. Neurology, 14*(6), 325-337. https://doi.org/10.1038/s41582-018-0002-2

Benjamin, E. J., Muntner, P., Alonso, A., Bittencourt, M. S., Callaway, C. W., Carson, A. P., Chamberlain, A. M., Chang, A. R., Cheng, S., Das, S. R., Delling, F. N., Djousse, L., Elkind, M. S. V., Ferguson, J. F., Fornage, M., Jordan, L. C., Khan, S. S., Kissela, B. M., Knutson, K. L., … American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. (2019). Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. *Circulation, 139*(10), e56-e528. https://doi.org/10.1161/CIR.0000000000000659

Betancur, D. F. A., Tarragó, M. da G. L., Torres, I. L. da S., Fregni, F., & Caumo, W. (2021). Central Post-Stroke Pain: An Integrative Review of Somatotopic Damage, Clinical Symptoms, and Neurophysiological Measures. *Frontiers in Neurology, 12*, 678198. https://doi.org/10.3389/fneur.2021.678198

Boese, A. C., Le, Q.-S. E., Pham, D., Hamblin, M. H., & Lee, J.-P. (2018). Neural stem cell therapy for subacute and chronic ischemic stroke. *Stem Cell Research & Therapy, 9*, 154. https://doi.org/10.1186/s13287-018-0913-2

Bohr, A., Schuhmann, M. K., Papp, L., Volkmann, J., & Fluri, F. (2020). Deep Brain Stimulation for Stroke: Continuous Stimulation of the Pedunculopontine Tegmental Nucleus has no Impact on Skilled Walking in Rats After Photothrombotic Stroke. Current Neurovascular Research, 17(5), 636-643. https://doi.org/10.2174/1567202617666201201141046

(Bud) Craig, A. D. (1998). A new version of the thalamic disinhibition hypothesis of central pain. Pain Forum, 7(1), 1-14. https://doi.org/10.1016/S1082-3174(98)70004-2

Campbell, B. C. V., De Silva, D. A., Macleod, M. R., Coutts, S. B., Schwamm, L. H., Davis, S. M., & Donnan, G. A. (2019). Ischaemic stroke. Nature Reviews Disease Primers, 5(1), Article 1. https://doi.org/10.1038/s41572-019-0118-8

Chan, H. H., Cooperrider, J., Chen, Z., Gale, J. T., Baker, K. B., Wathen, C. A., Modic, C. R., Park, H.-J., & Machado, A. G. (2018). Lateral Cerebellar Nucleus Stimulation has Selective Effects on Glutamatergic and GABAergic Perilesional Neurogenesis After Cortical Ischemia in the Rodent Model. Neurosurgery, 83(5), 1057-1067. https://doi.org/10.1093/neuros/nyx473

Cooperrider, J., Furmaga, H., Plow, E., Park, H.-J., Chen, Z., Kidd, G., Baker, K. B., Gale, J. T., & Machado, A. G. (2014). Chronic Deep Cerebellar Stimulation Promotes Long-Term Potentiation, Microstructural Plasticity, and Reorganization of Perilesional Cortical Representation in a Rodent Model. The Journal of Neuroscience, 34(27), 9040-9050. https://doi.org/10.1523/JNEUROSCI.0953-14.2014

Cooperrider, J., Momin, A., Baker, K. B., & Machado, A. G. (2020). Cerebellar Neuromodulation for Stroke. Current Physical Medicine and Rehabilitation Reports, 8(2), Article 2. https://doi.org/10.1007/s40141-019-00253-4

Diniz, J. M., Cury, R. G., Iglesio, R. F., Lepski, G. A., França, C. C., Barbosa, E. R., de Andrade, D. C., Teixeira, M. J., & Duarte, K. P. (2021). Dentate nucleus deep brain stimulation: Technical note of a novel methodology assisted by tractography. *Surgical Neurology International*, *12*, 400. https://doi.org/10.25259/SNI_338_2021

Dum, R. P., & Strick, P. L. (2003). An Unfolded Map of the Cerebellar Dentate Nucleus and its Projections to the Cerebral Cortex. Journal of Neurophysiology, 89(1), 634-639. https://doi.org/10.1152/jn.00626.2002

Duncan, P. W., Goldstein, L. B., Matchar, D., Divine, G. W., & Feussner, J. (1992). Measurement of motor recovery after stroke. Outcome assessment and sample size requirements. Stroke, 23(8), 1084-1089. https://doi.org/10.1161/01.str.23.8.1084

Egger, P., Evangelista, G. G., Koch, P. J., Park, C.-H., Levin-Gleba, L., Girard, G., Beanato, E., Lee, J., Choirat, C., Guggisberg, A. G., Kim, Y.-H., & Hummel, F. C. (2021). Disconnectomics of the Rich Club Impacts Motor Recovery After Stroke. Stroke, 52(6), 2115-2124. https://doi.org/10.1161/STROKEAHA.120.031541

Ej, S., C, H., Am, L., Yy, P., & E, M. (2015). Deep brain stimulation for treatment of dystonia secondary to stroke or trauma. Journal of Neurology, Neurosurgery, and Psychiatry, 86(9). https://doi.org/10.1136/jnnp-2014-308943

Elias, G. J. B., Namasivayam, A. A., & Lozano, A. M. (2018). Deep brain stimulation for stroke: Current uses and future directions. Brain Stimulation, 11(1), 3-28. https://doi.org/10.1016/j.brs.2017.10.005

Feng, W., Wang, J., Chhatbar, P. Y., Doughty, C., Landsittel, D., Lioutas, V.-A., Kautz, S., & Schlaug, G. (2015). Corticospinal Tract Lesion Load—A Potential Imaging Biomarker for Stroke Motor Outcomes. Annals of Neurology, 78(6), 860-870. https://doi.org/10.1002/ana.24510

Fluri, F., Malzahn, U., Homola, G. A., Schuhmann, M. K., Kleinschnitz, C., & Volkmann, J. (2017). Stimulation of the mesencephalic locomotor region for gait recovery after stroke. Annals of Neurology, 82(5), 828-840. https://doi.org/10.1002/ana.25086

Fluri, F., Mützel, T., Schuhmann, M. K., Krstić, M., Endres, H., & Volkmann, J. (2017). Development of a head-mounted wireless microstimulator for deep brain stimulation in rats. Journal of Neuroscience Methods, 291, 249-256. https://doi.org/10.1016/j.jneumeth.2017.08.024

Franzini, A., Cordella, R., Rizzi, M., Marras, C. E., Messina, G., Zorzi, G., & Caldiroli, D. (2014). Deep brain stimulation in critical care conditions. Journal of Neural Transmission, 121(4), 391-398. https://doi.org/10.1007/s00702-013-1122-x

Ganapa, S. V., Ramani, M. D., Ebunlomo, O. O., Rahman, R. K., Herschman, Y., & Mammis, A. (2019). Treatment of Persistent Hemiballism with Deep Brain Stimulation of the Globus

Pallidus Internus: Case Report and Literature Review. World Neurosurgery, 132, 368-370. https://doi.org/10.1016/j.wneu.2019.08.247

Gonzalez, V., Le Bars, E., Cif, L., van Dokkum, L. E. H., Laffont, I., Bonafé, A., Menjot de Champfleur, N., Zanca, M., & Coubes, P. (2015). The reorganization of motor network in hemidystonia from the perspective of deep brain stimulation. Brain Imaging and Behavior, 9(2), 223-235. https://doi.org/10.1007/s11682-014-9300-5

Grabska, N., Rudzińska, M., Dec-Ćwiek, M., Tutaj, M., Pietraszko, W., Michalski, M., & Szczudlik, A. (2014). Deep brain stimulation in the treatment of Holmes tremor—A long-term case observation. Neurologia I Neurochirurgia Polska, 48(4), 292-295. https://doi.org/10.1016/j.pjnns.2014.06.002

Griauzde, J., Ravindra, V. M., Chaudhary, N., Gemmete, J. J., & Pandey, A. S. (2019). Neuroprotection for ischemic stroke in the endovascular era: A brief report on the future of intra-arterial therapy. Journal of Clinical Neuroscience, 69, 289-291. https://doi.org/10.1016/j.jocn.2019.08.001

Guo, J., Wang, J., Sun, W., & Liu, X. (2022). The advances of post-stroke depression: 2021 update. Journal of Neurology, 269(3), 1236-1249. https://doi.org/10.1007/s00415-021-10597-4

Hamani, C., Schwalb, J. M., Rezai, A. R., Dostrovsky, J. O., Davis, K. D., & Lozano, A. M. (2006). Deep brain stimulation for chronic neuropathic pain: Long-term outcome and the incidence of insertional effect. Pain, 125(1), 188-196. https://doi.org/10.1016/j.pain.2006.05.019

HEAD, H., & HOLMES, G. (1911). SENSORY DISTURBANCES FROM CEREBRAL LESIONS1. Brain, 34(2-3), 102-254. https://doi.org/10.1093/brain/34.2-3.102

Hoshi, E., Tremblay, L., Féger, J., Carras, P. L., & Strick, P. L. (2005). The cerebellum communicates with the basal ganglia. *Nature Neuroscience*, *8*(11), 1491-1493. https://doi.org/10.1038/nn1544

Hunsche, S., Sauner, D., Runge, M. J. R., Lenartz, D., El Majdoub, F., Treuer, H., Sturm, V., & Maarouf, M. (2013). Tractography-Guided Stimulation of Somatosensory Fibers for Thalamic Pain Relief. Stereotactic and Functional Neurosurgery, 91(5), 328-334. https://doi.org/10.1159/000350024

Jiang, S., Geng, R., Wang, R., Li, X., & Bao, X. (2023). The potential of hydrogels as a niche for promoting neurogenesis and regulating neuroinflammation in ischemic stroke. Materials & Design, 229, 111916. https://doi.org/10.1016/j.matdes.2023.111916

Juruena, M. F., Bocharova, M., Agustini, B., & Young, A. H. (2018). Atypical depression and non-atypical depression: Is HPA axis function a biomarker? A systematic review. Journal of Affective Disorders, 233, 45-67. https://doi.org/10.1016/j.jad.2017.09.052

K, A., Y, H., Y, O., M, Y., T, M., Y, Y., T, Y., S, H., & Y, I. (2018). Effects of bilateral pallidal deep brain stimulation on chorea after pulmonary thromboendarterectomy with deep hypothermia and circulatory arrest: A case report. Acta Neurochirurgica, 160(2). https://doi.org/10.1007/s00701-017-3433-4

Kilbane, C., Ramirez-Zamora, A., Ryapolova-Webb, E., Qasim, S., Glass, G. A., Starr, P. A., & Ostrem, J. L. (2015). Pallidal stimulation for Holmes tremor: Clinical outcomes and single-unit recordings in 4 cases. Journal of Neurosurgery, 122(6), 1306-1314. https://doi.org/10.3171/2015.2.JNS141098

King, M., Kelly, L. P., Wallack, E. M., Hasan, S. M. M., Kirkland, M. C., Curtis, M. E., Chatterjee, T., McCarthy, J., & Ploughman, M. (2019). Serum levels of insulin-like growth factor-1 and brain-derived neurotrophic factor as potential recovery biomarkers in stroke. Neurological Research, 41(4), 354-363. https://doi.org/10.1080/01616412.2018.1564451

Klit, H., Finnerup, N. B., & Jensen, T. S. (2009). Central post-stroke pain: Clinical characteristics, pathophysiology, and management. The Lancet. Neurology, 8(9), 857-868. https://doi.org/10.1016/S1474-4422(09)70176-0

Kobayashi, K., Katayama, Y., Oshima, H., Watanabe, M., Sumi, K., Obuchi, T., Fukaya, C., & Yamamoto, T. (2014). Multitarget, dual-electrode deep brain stimulation of the thalamus and subthalamic area for treatment of Holmes' tremor. Journal of Neurosurgery, 120(5), 1025-1032. https://doi.org/10.3171/2014.1.JNS12392

Krämer, S. D., Schuhmann, M. K., Schadt, F., Israel, I., Samnick, S., Volkmann, J., & Fluri, F. (2022). Changes of cerebral network activity after invasive stimulation of the mesencephalic locomotor region in a rat stroke model. Experimental Neurology, 347, 113884. https://doi.org/10.1016/j.expneurol.2021.113884

Krämer, S. D., Schuhmann, M. K., Volkmann, J., & Fluri, F. (2022). Deep Brain Stimulation in the Subthalamic Nucleus Can Improve Skilled

Forelimb Movements and Retune Dynamics of Striatal Networks in a Rat Stroke Model. International Journal of Molecular Sciences, 23(24). Scopus. https://doi.org/10.3390/ijms232415862

Krause, T., Brunecker, P., Pittl, S., Taskin, B., Laubisch, D., Winter, B., Lentza, M. E., Malzahn, U., Villringer, K., Villringer, A., & Jungehulsing, G. J. (2012). Thalamic sensory strokes with and without pain: Differences in lesion patterns in the ventral posterior thalamus. Journal of Neurology, Neurosurgery & Psychiatry, 83(8), 776-784. https://doi.org/10.1136/jnnp-2011-301936

Lawrence, E. S., Coshall, C., Dundas, R., Stewart, J., Rudd, A. G., Howard, R., & Wolfe, C. D. (2001). Estimates of the prevalence of acute stroke impairments and disability in a multiethnic population. Stroke, 32(6), 1279-1284. https://doi.org/10.1161/01.str.32.6.1279

Liu, J., Li, J., Yang, Y., Wang, X., Zhang, Z., & Zhang, L. (2014). Neuronal apoptosis in cerebral ischemia/reperfusion area following electrical stimulation of fastigial nucleus. Neural Regeneration Research, 9(7), 727-734. https://doi.org/10.4103/1673-5374.131577

Machado, A., & Baker, K. B. (2012). Upside down crossed cerebellar diaschisis: Proposing chronic stimulation of the dentatothalamocortical pathway for post-stroke motor recovery. Frontiers in Integrative Neuroscience, 6, 20. https://doi.org/10.3389/fnint.2012.00020

Machado, A. G., Baker, K. B., Schuster, D., Butler, R. S., & Rezai, A. (2009). Chronic electrical stimulation of the contralesional lateral cerebellar nucleus enhances recovery of motor function after cerebral ischemia in rats. Brain Research, 1280, 107-116. https://doi.org/10.1016/j.brainres.2009.05.007

Machado, A. G., Cooperrider, J., Furmaga, H. T., Baker, K. B., Park, H.-J., Chen, Z., & Gale, J. T. (2013). Chronic 30-Hz deep cerebellar stimulation coupled with training enhances post-ischemia motor recovery and peri-infarct synaptophysin expression in rodents. Neurosurgery, 73(2), 344-353; discussion 353. https://doi.org/10.1227/01.neu.0000430766.80102.ac

Mergenthaler, P., Dirnagl, U., & Kunz, A. (2022). Ischemic Stroke: Basic Pathophysiology and Clinical Implication. In D. W. Pfaff, N. D. Volkow, & J. L. Rubenstein (Eds.), Neuroscience in the 21st Century: From Basic to Clinical (pp. 3807-3827). Springer International Publishing. https://doi.org/10.1007/978-3-030-88832-9_97

Morimoto, T., Yasuhara, T., Kameda, M., Baba, T., Kuramoto, S., Kondo, A., Takahashi, K., Tajiri, N., Wang, F., Meng, J., Ji, Y. W., Kadota, T., Maruo, T., Kinugasa, K., Miyoshi, Y., Shingo, T., Borlongan, C. V., & Date, I. (2011). Striatal stimulation nurtures endogenous neurogenesis and angiogenesis in chronic-phase ischemic stroke rats. Cell Transplantation, 20(7), 1049-1064. https://doi.org/10.3727/096368910X544915

Morishita, T., Foote, K. D., Archer, D. B., Coombes, S. A., Vaillancourt, D. E., Hassan, A., Haq, I. U., Wolf, J., & Okun, M. S. (2015). Smile without euphoria induced by deep brain stimulation: A case report. Neurocase, 21(6), 674-678. https://doi.org/10.1080/13554794.2014.973883

Murphy, S. JX., & Werring, D. J. (2020). Stroke: Causes and clinical features. Medicine (Abingdon, England : UK Ed.), 48(9), 561-566. https://doi.org/10.1016/j.mpmed.2020.06.002

Murphy, T. H., & Corbett, D. (2009). Plasticity during stroke recovery: From synapse to behaviour. Nature Reviews. Neuroscience, 10(12), 861-872. https://doi.org/10.1038/nrn2735

Nakawah, M. O., & Lai, E. C. (2016). Post-stroke dyskinesias. Neuropsychiatric Disease and Treatment, 12, 2885-2893. https://doi.org/10.2147/NDT.S118347

Ng, Y. S., Stein, J., Ning, M., & Black-Schaffer, R. M. (2007). Comparison of clinical characteristics and functional outcomes of ischemic stroke in different vascular territories. Stroke, 38(8), 2309-2314. https://doi.org/10.1161/STROKEAHA.106.475483

Nicholson, C. L., Coubes, P., & Poulen, G. (2020). Dentate nucleus as target for deep brain stimulation in dystono-dyskinetic syndromes. Neuro-Chirurgie, 66(4), 258-265. https://doi.org/10.1016/j.neuchi.2020.04.132

Nowacki, A., Zhang, D., Barlatey, S., Ai-Schläppi, J., Rosner, J., Arnold, M., & Pollo, C. (2022). Deep Brain Stimulation of the Central Lateral and Ventral Posterior Thalamus for Central Poststroke Pain Syndrome: Preliminary Experience. *Neuromodulation: Technology at the Neural Interface*. https://doi.org/10.1016/j.neurom.2022.09.005

Nsengiyumva, N., Barakat, A., Macerollo, A., Pullicino, R., Bleakley, A., Bonello, M., Ellis, R. J. B., & Alusi, S. H. (2021). Thalamic versus midbrain tremor; two distinct types of Holmes' Tremor: A review of 17 cases. Journal of Neurology, 268(11), 4152-4162. https://doi.org/10.1007/s00415-021-10491-z

Obeso, J. A., Rodríguez-Oroz, M. C., Benitez-Temino, B., Blesa, F. J., Guridi, J., Marin, C., & Rodriguez, M. (2008). Functional organization of the basal ganglia: Therapeutic implications for Parkinson's disease. *Movement Disorders: Official Journal of the Movement Disorder Society, 23 Suppl 3*, S548-559. https://doi.org/10.1002/mds.22062

Onder, H., Kocer, B., Turan, A., & Comoglu, S. (2023). Illustration of the Long-Term Efficacy of Deep Brain Stimulation of the Thalamic Ventral Intermediate Nucleus in a Patient with Holmes Tremor Secondary to Stroke. *Movement Disorders Clinical Practice, 10*(7), Article 7. https://doi.org/10.1002/mdc3.13741

O'Shea, S. A., Elkind, M., Pullman, S. L., & Ford, B. (2020). Holmes Tremor due to Artery of Percheron Infarct: Clinical Case and Treatment Using Deep Brain Stimulation of the Vim and ZI Targets. *Tremor and Other Hyperkinetic Movements, 10*. https://doi.org/10.7916/tohm.v0.732

Paciaroni, M., & Bogousslavsky, J. (1998). Pure Sensory Syndromes in Thalamic Stroke. *European Neurology, 39*(4), 211-217. https://doi.org/10.1159/000007936

Pang, X.-M., Liu, J.-L., Li, J.-P., Huang, L.-G., Zhang, L., Xiang, H.-Y., Feng, L.-B., Chen, C.-Y., Li, S.-H., & Su, S.-Y. (2015). Fastigial nucleus stimulation regulates neuroprotection via induction of a novel microRNA, rno-miR-676-1, in middle cerebral artery occlusion rats. *Journal of Neurochemistry, 133*(6), 926-934. https://doi.org/10.1111/jnc.13094

Papuć, E., Obszańska, K., Trojanowski, T., Szczepańska-Szerej, H., Rejdak, K., & Stelmasiak, Z. (2013). Reduction of thalamic tremor with deep brain stimulation performed for post stroke chronic central pain. *Annals of Agricultural and Environmental Medicine: AAEM, Spec no. 1*, 45-47.

Park, H.-J., Furmaga, H., Cooperrider, J., Gale, J. T., Baker, K. B., & Machado, A. G. (2015). Modulation of cortical motor evoked potential after stroke during electrical stimulation of the lateral cerebellar nucleus. *Brain Stimulation, 8*(6), 1043-1048. https://doi.org/10.1016/j.brs.2015.06.020

Phipps, M. S., & Cronin, C. A. (2020). Management of acute ischemic stroke. *BMJ (Clinical Research Ed.), 368*, l6983. https://doi.org/10.1136/bmj.l6983

Pj, S., A, P., & Cr, H. (2015). A prospective, randomized, blinded assessment of multitarget thalamic and pallidal deep brain stimulation in a case of hemidystonia. *Clinical Neurology and Neurosurgery, 138*. https://doi.org/10.1016/j.clineuro.2015.07.012

Plecash, A. R., Chebini, A., Ip, A., Lai, J. J., Mattar, A. A., Randhawa, J., & Field, T. S. (2019). Updates in the Treatment of Post-Stroke Pain. *Current Neurology and Neuroscience Reports, 19*(11), 86. https://doi.org/10.1007/s11910-019-1003-2

Powers William J., Rabinstein Alejandro A., Ackerson Teri, Adeoye Opeolu M., Bambakidis Nicholas C., Becker Kyra, Biller José, Brown Michael, Demaerschalk Bart M., Hoh Brian, Jauch Edward C., Kidwell Chelsea S., Leslie-Mazwi Thabele M., Ovbiagele Bruce, Scott Phillip A., Sheth Kevin N., Southerland Andrew M., Summers Deborah V., Tirschwell David L., & null null. (2019). Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke, 50*(12), e344-e418. https://doi.org/10.1161/STR.0000000000000211

Rezaei Haddad, A., Ughratdar, I., & Ashkan, K. (2015). A single thalamic target for deep brain stimulation to treat hemi-body pain syndrome. *Acta Neurochirurgica, 157*(9), 1519-1523. https://doi.org/10.1007/s00701-015-2504-7

Sathyanesan, A., Zhou, J., Scafidi, J., Heck, D. H., Sillitoe, R. V., & Gallo, V. (2019). Emerging connections between cerebellar development, behaviour and complex brain disorders. *Nature Reviews. Neuroscience, 20*(5), 298-313. https://doi.org/10.1038/s41583-019-0152-2

Savoiardo, M. (1986). The vascular territories of the carotid and vertebrobasilar systems. Diagrams based on CT studies of infarcts. *Italian Journal of Neurological Sciences, 7*(4), 405-409. https://doi.org/10.1007/BF02283018

Schuhmann, M. K., Papp, L., Stoll, G., Blum, R., Volkmann, J., & Fluri, F. (2021). Mesencephalic Electrical Stimulation Reduces Neuroinflammation after Photothrombotic Stroke in Rats by Targeting the Cholinergic Anti-Inflammatory Pathway. *International Journal of Molecular Sciences, 22*(3), 1254. https://doi.org/10.3390/ijms22031254

Schuhmann, M. K., Stoll, G., Bohr, A., Volkmann, J., & Fluri, F. (2019). Electrical Stimulation of the Mesencephalic Locomotor Region Attenuates Neuronal Loss and Cytokine Expression in the Perifocal Region of Photothrombotic Stroke in Rats. *International Journal of Molecular Sciences, 20*(9), 2341. https://doi.org/10.3390/ijms20092341

Shik, M. L., Severin, F. V., & Orlovskiĭ, G. N. (1966). [Control of walking and running by means of electric stimulation of the midbrain]. *Biofizika, 11*(4), 659-666.

Siegel, J. S., Ramsey, L. E., Snyder, A. Z., Metcalf, N. V., Chacko, R. V., Weinberger, K., Baldassarre, A., Hacker, C. D., Shulman, G. L., & Corbetta, M. (2016). Disruptions of network connectivity predict impairment in multiple behavioral domains after stroke. *Proceedings of the National Academy of Sciences of the United States of America, 113*(30), E4367-E4376. https://doi.org/10.1073/pnas.1521083113

Tacyildiz, A. E., Bilgin, B., Gungor, A., Ucer, M., Karadag, A., & Tanriover, N. (2021). Dentate Nucleus: Connectivity-Based Anatomic Parcellation Based on Superior Cerebellar Peduncle Projections. *World Neurosurgery, 152*, e408-e428. https://doi.org/10.1016/j.wneu.2021.05.102

Tambirajoo, K., Furlanetti, L., Samuel, M., & Ashkan, K. (2020). Subthalamic Nucleus Deep Brain Stimulation in Post-Infarct Dystonia. *Stereotactic and Functional Neurosurgery, 98*(6), 386-398. https://doi.org/10.1159/000509317

Ten Brinke, T. R., Arnts, H., Schuurman, R., & van den Munckhof, P. (2020). Directional sensory thalamus deep brain stimulation in poststroke refractory pain. *BMJ Case Reports, 13*(8), e233254. https://doi.org/10.1136/bcr-2019-233254

Troche, M. S., Brandimore, A. E., Foote, K. D., & Okun, M. S. (2013). Swallowing and deep brain stimulation in Parkinson's disease: A systematic review. *Parkinsonism & Related Disorders, 19*(9), 783-788. https://doi.org/10.1016/j.parkreldis.2013.05.001

Tsao, C. W., Aday, A. W., Almarzooq, Z. I., Alonso, A., Beaton, A. Z., Bittencourt, M. S., Boehme, A. K., Buxton, A. E., Carson, A. P., Commodore-Mensah, Y., Elkind, M. S. V., Evenson, K. R., Eze-Nliam, C., Ferguson, J. F., Generoso, G., Ho, J. E., Kalani, R., Khan, S. S., Kissela, B. M., … Martin, S. S. (2022). Heart Disease and Stroke Statistics-2022 Update: A Report From the American Heart Association. *Circulation, 145*(8), e153-e639. https://doi.org/10.1161/CIR.0000000000001052

Wang, J., Dong, W., Zhang, W., Zheng, J., & Wang, X. (2014). Electrical Stimulation of Cerebellar Fastigial Nucleus: Mechanism of Neuroprotection and Prospects for Clinical Application against Cerebral Ischemia. *CNS Neuroscience & Therapeutics, 20*(8), 710-716. https://doi.org/10.1111/cns.12288

Wathen, C. A., Frizon, L. A., Maiti, T. K., Baker, K. B., & Machado, A. G. (2018). Deep brain stimulation of the cerebellum for poststroke motor rehabilitation: From laboratory to clinical trial. *Neurosurgical Focus, 45*(2), E13. https://doi.org/10.3171/2018.5.FOCUS18164

Witt, J., Starr, P. A., & Ostrem, J. L. (2013). Use of Pallidal Deep Brain Stimulation in Post-infarct Hemidystonia. *Stereotactic and Functional Neurosurgery, 91*(4), 243-247. https://doi.org/10.1159/000345262

Wu, Z., Sun, F., Li, Z., Liu, M., Tian, X., Guo, D., Wei, P., Shan, Y., Liu, T., Guo, M., Zhu, Z., Zheng, W., Wang, Y., Zhao, G., & Wang, W. (2020). Electrical stimulation of the lateral cerebellar nucleus promotes neurogenesis in rats after motor cortical ischemia. *Scientific Reports, 10*(1), 16563. https://doi.org/10.1038/s41598-020-73332-5

Zhang, S., Zhang, X., Zhong, H., Li, X., Wu, Y., Ju, J., Liu, B., Zhang, Z., Yan, H., Wang, Y., Song, K., & Hou, S.-T. (2022). Hypothermia evoked by stimulation of medial preoptic nucleus protects the brain in a mouse model of ischaemia. *Nature Communications, 13*(1), 6890. https://doi.org/10.1038/s41467-022-34735-2

Zhang, X., & Bi, X. (2020). Post-Stroke Cognitive Impairment: A Review Focusing on Molecular Biomarkers. *Journal of Molecular Neuroscience, 70*(8), 1244-1254. https://doi.org/10.1007/s12031-020-01533-8