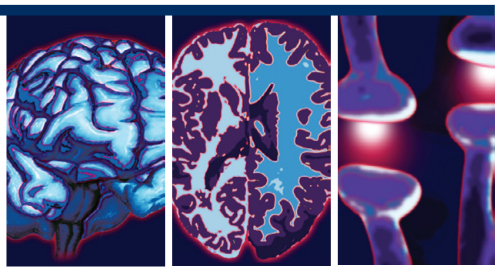
Review



Induction of Neuroplasticity by Brain Stimulation Techniques in Stroke Patients: A Systematic Review

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ABSTRACT

Neuronal plasticity is a core mechanism for learning and memory. Many neurological disorders appear after abnormal neuronal plasticity has emerged. Specifically, in stroke patients it affects widespread brain regions through interhemispheric connections by influencing either motor activity or cognitives abilities.

Stroke is one of the principal causes of morbidity and mortality in adults in the developed world and the leading cause of disability. The potential of noninvasive brain stimulation (NIBS) techniques in stroke rehabilitation has been of particular interest, because of the high incidence of this pathology in all industrialized countries. Survivors can suffer several neurological deficits or impairments, such as hemiparesis, communication disorders, cognitive deficits or disorders in visuo-spatial perception.

Recent research has focused on developing rehabilitation strategies that facilitate neuroplasticity to maximize functional outcome poststroke. This review discusses the evidence for neuroplasticity (structural, synaptic or intrinsic changes that alter neuronal function) of NIBS techniques in stroke patients, such as repetitive transcranial magnetic stimulation (rTMS) or direct current transcranial stimulation (DCTS). Long periods of cortical stimulation can produce lasting effects on brain function, paving the way for therapeutic applications of NIBS in chronic neurological disease.

Keywords

Stroke, Cerebrovascular accident, Neuroplasticity, Rehabilitation

Introduction

Stroke is one of the leading causes of death in the world, and the leading cause of neurological disability in adults [1]. Stroke is the sudden disorder of the cerebral circulatory system, characterized by the loss or modification of cerebral functions, either transiently or definitively [2].

Attempts to limit brain injury after stroke with drugs have met with great success but their use remains limited due to a narrow therapeutic time window and concern over serious side effects. A more promising approach is to promote recovery of function in people affected by stroke using stimulation techniques. Following stroke, there is a heightened critical period of plasticity that appears to be receptive to exogenous interventions (e.g., delivery of growth factors) designed to enhance neuroplasticity processes important for recovery. An emerging concept is that noninvasive brain stimulation (NIBS) techniques can be used to monitor and modulate the excitability of intracortical neuronal circuits

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and appear much more effective than single drugs interventions in improving stroke recovery.

Motor impairment is one of the main disabilities of stroke patients [3]. A common disorder in stroke is ataxia or difficulty in performing motor movements due to involvement of the cerebellum or brainstem [4]. However, most patients who have suffered a stroke have hemiparesis or muscle weakness in the upper extremities. This functional decrease greatly affects the implementation of rehabilitation programs, as well as carrying out activities of daily living [5-7], which is why motor recovery is of great importance.

The neuronal plasticity or cerebral neuroplasticity is the ability of the central nervous system to undergo modifications [8] and may occur in response to external factors such as environmental stimulation, new information, learning, dysfunction or brain damage [9]. Neuroplasticity is defined as the brain's capability to reorganize itself via creating new neural networks and allows the neurons to regulate their actions in response to new circumstances. The induction of neuronal plasticity is key in the process of neurorehabilitation, whose objective is to maximize neuronal recovery and therefore, restore the altered functions after a neurological alteration whether congenital, degenerative and/or acquired [7,10,11]

Currently, NIBS are being used as innovative strategies in the field of motor and cognitive neurorehabilitation of stroke with the aim of inducing changes in neural networks and modulating cerebral excitability [3,5-7,12]. Nevertheless, protocols and optimal stimulation parameters are not yet clearly established. Furthermore, an updated review about brain stimulation techniques and its effectiveness for stroke rehabilitation should be a crucial objective for researchers on neuroplasticity [6,13]. The combination of rTMS with training in motor skills produces improvements in the motor performance produced after a stroke by promoting neuronal plasticity [3,8,14,15]. On the other hand, aphasia is also one of the most frequent deficits in post-stroke patients [16] and the inhibition of homologous areas of language in the right hemisphere, whose activation is related to a maladaptive strategy in language recovery, produces improvements in brain activity in the left hemisphere associated with better performance in language functions [11,12,17,18]. According to new findings obtained by recent studies, the combination of brain stimulation and peripheral nerve stimulation (PNS) produces benefits in the performance of motor training superior to any single intervention performed in patients with stroke [19], but it is necessary more research about changes following stroke.

In this review the available evidence supporting mechanisms of neuroplasticity, with emphasis on implications for stroke recovery are discussed. This is an emerging domain with the potential to offer important insight into the biology of regeneration and recovery after stroke.

Materials and Methods

■ Data research

A literature review was performed on MEDLINE. We included articles from January 2010 until August 2018. Keywords were: stroke, brain stimulation and neuroplasticity.

■ Inclusion criteria

Studies about neuroplasticity-based by brain stimulation techniques in stroke patients was the main inclusion criteria. Only articles with adult patients (aged between 18 and 90 years) were included. Main diagnosis needed to be stroke with motor and/or cognitive deficits. Exclusion criteria were a diagnosis of neurological disorder (neurodegenerative or psychiatric diseases) different to stroke, and underage populations.

■ Selection

The selection of articles was performed as follow. We obtained 713 hits in PubMed. On this total number of articles, 588 were excluded from title or abstract because they did not mention neuroplasticity and/or stroke or NIBS or the population age was under 18 years old. From the 125 studies left for full text reading, 109 were excluded (these articles did not mention a motor or cognitive consequence after stroke, and 15 were reviews). 16 studies are included.

■ Data extraction

The following data were extracted: sample size and patients characteristics – (age, gender), stroke type (time post-ictus), neuropsychological deficits (cognitive and motor consequences), type of NIBS and the neuroplasticity results obtained after the induction of brain stimulation techniques. Regarding the type of brain stimulation technique used, the number of sessions, the time of each session, the total duration of the rehabilitation, and, complementary techniques used to get a better recovey were analyzed.

Data availability

All data analysed during this study are included in this published article.

Results

A systematic analysis of the brain stimulation techniques used in the different investigations was carried out. Afterwards, the contents of the articles are summed up in **Table 1 and Table 2**, showing all the brain stimulation techniques, the stimulation protocols used in the investigations, the measurement techniques of the changes produced at brain level after the interventions, the type of motor/cognitive deficit produced because of stroke in patients, the results obtained, as well as the long-term follow-up of the results.

Four different brain stimulation techniques were used: repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (DCE), transcranial random noise stimulation (ETRA), and vagus nerve stimulation (VNS). These techniques, when used with different parameters and stimulation protocols, can be said that a total of 19 brain stimulation techniques were used in the 16 articles analyzed. The inhibitory EMTR together with the excitatory or anodic DCE are the most used techniques. In addition, we can observe that 12 of the 16 articles analyzed use brain stimulation techniques combined with training tasks like speech and language therapies or mirror therapy with the aim of obtaining possible improvements in the results of cognitive and motor deficits. On the other hand, only 9 articles of the 16 analyzed use neuroimaging techniques such as magnetic resonance imaging (MRI) or neurophysiological techniques such as positron emission tomography (PET) **(Table 2)**. Of these 9 articles, 7 evaluated the changes produced at the cortical level, to check whether the changes produced in the structure and brain function explain the observed clinical improvements [19]. To do this, they compare the images or data obtained before and after the intervention with brain stimulation techniques. The other 2 articles only evaluated brain activity before or after the intervention. The rest of the articles analyzed use the neuroimaging techniques before the intervention to calculate the size, integrity and diffusion of the lesion produced [10] or for the placement of the electrodes in the correct localization [13].

Finally, in **Table 3** we observe the types of motor and/or cognitive deficits produced because of stroke. The deficits analyzed are: dysphagia, hemiparesis or weakness in the upper extremity, ataxias, aphasias, anomias and cognitive deficits without specifying. In addition, we observed improvement in the performance of all the alterations produced after the use of brain stimulation techniques, both in acute, subacute patients and chronic patients (+6 months). The articles that used electrophysiological or neuroimaging measurement techniques associate this improvement with the cortical changes produced. Most of the articles followed up on the results obtained, reaching some type of improvement even up to 6 months after the intervention.

Discussion and Future Research

A high percentage of the articles analyzed show the association of the plastic changes produced in the cerebral cortex and the improvement in the performance of the different motor and/or cognitive deficits evaluated produced because of the brain injuries caused by the stroke.

Brain stimulation techniques target both the ipsilesional or damaged cerebral hemisphere and the contralesional or unaffected cerebral hemisphere, because the effects of brain stimulation techniques are unclear. The first study that used neuroimaging techniques shows that the neural changes produced after the intervention with excitatory EMTR on the ipsilesional CM1 together with motor training, improves the performance of the paretic upper limb, associating this improvement with a hemispheric

Table 1: Articles selected and included in the review.

Number of patients (nº women)	Mean age	Stroke type	Time post-stroke	References
18 (3)	65	I/H	+6 months	[8]
24 (7)	63.2	I/H	+6 months	[17]
4 (-)	61.3	I	+6 months	[1]
17 (7)	58.8	I/H	+3 months	[19]
8 (4)	54.4	I/H	+6 months	[14]
19 (3)	65	I/H	+6 months	[20]
20 (5)	55.8	I	+6 months	[5]
24 (-)	70.5	I	<3 months	[16]
12 (5)	52.3	I	+6 months	[10]
21 (4)	59.3	I	+6 months	[9]
14 (7)	74.9	I	1-7 days	[6]
9 (4)	55.3	I	+6 months	[4]
10 (5)	65.5	I/H	<3 months	[15]
32 (15)	66.7	I	<1 month	[7]
26 (13)	61.2	I	<3 months	[14]
34 (11)	62	I/H	+6 months	[13]
ABB: I: Ischemic; H: Hemorrhagic				

Table 2: Characteristics of the articles and techniques used.

Techniques	Measurement cortical changes	Details Stimulation	References
rTMS/PAS	Pharyngeal EEG. Before and after. Immediate, 30s.	Pharingeal M1 contralesional; 1 day rTMS: 5HZ 10′ 90% RMT PAS: PES+TMS 10′ 20% RMT	[8]
tDCS anodal+training	MRI Before and after Immediate,1s, 1m, 3m	M1 ipsilesional; 9 days 1 mA 20′	[17]
TRNS+training	MRI. Before TRNS.	M1 ipsilesional; 12 days 2 mA 5″	[1]
rTMS+training	MRI before and after rTMS. Immediate and 1s.	M1 ipsilesional; 10 days 10Hz 20′ 80% RMT	[19]
rTMS (iTBS)	MRI 1s before and 1s after.	M1 ipsilesional; 10 days; 50 Hz, 80% RMT	[14]
Dual-tDCS+training	MRI 1s after.	M1 bilateral; 1mA 30′	[20]
tDCS dual+training	MRI before and after.	M1 bilateral; 5 days; 1.5 mA 30′	[5]
rTMS+training	PET+MRI before and after.	RIFG (contralesional) 10 days 20′ 1Hz 90% RMT	[16]
anodal or cathodal tDCS.	-	rTPC (contralesional) 20′ 1mA 3 days	[10]
ENV+training	-	Left VN 0,5″ 3 days 0.8mA 30Hz	[9]
anodal tDCS+training	-	Pharingeal M1 contralesional 2mA 30′ 5 days	[6]
anodal tDCS+PNS+training	-	M1 ipsilesional 4 days 20′ 1mA	[4]
rTMS+training	PET before and after.	RIFG contralesional 10 days 20′ 1 Hz 90% RMT	[15]
rTMS	-	CBH contralesional 5 días 15′ 1Hz 100% RMT	[7]
rTMS+training	-	RIFG contralesional 15 days 30′ 1Hz 90% RMT	[14]
rTMS/tDCS dual+training	-	rTMS: CM1 contralesional 15′ 1 Hz 80% RMT tDCS: CM1 bilateral 1,5 mA 20′	[13]

ABB: tTMS: Repetitive Transcranial Magnetic Stimulation; EEG: Electro encephalogram; PES: Pharyngeal Electrical Stimulation; PAS: Paired Associative Stimulation; tDCS: Transcranial Direct Current Stimulation; RMT: Resting Motor threshold; TRNS: Transcranial Random Noise Stimulation; MRI: Magnetic Resonance Imaging; M1: primary motor cortex; PET: Positron Emission Tomography; iTBS: Intermittent Theta Burst Stimulation; RIFG: right inferior frontal gyrus; rTPC: Right Temporal-Parietal Cortex; VNS: Vagus Nerve Stimulation; VN: Vagus Nerve; PNS: Peripheral Nerve Stimulation; CBH: Cerebellar Hemisphere

Table 3: Types of deficits produced and results of brain stimulation.

Type of deficit	Stimulation results	Follow up results	References
Dysphagia	Increase in cortical excitability of the unaffected hemisphere and improvements in swallowing.	30′	[8]
Upper limb impairment	Motor function improvements were associated with increased activation. Increases in gray matter volume in ipsilesional motor cortex.	3 months	[17]
Upper limb impairment	Clinical improvements in the impairments of the upper limb function.	3 months	[1]
Hemiparesis left/right hand	Improvement of motor performance associated with the modulation of brain activation areas.	1 month	[19]
Aphasia	Increases in white matter in areas close to stimulation and improvements in language.	-	[14]
Upper limb impairment	Improvement in the learning of motor skills associated with a decrease in the cortical activation of the damaged hemisphere.	1 week	[20]
Upper limb impairment	Improvement of motor functions and changes in cortical activation.	1 week	[5]
Aphasia	Improvement in language recovery and recruitment of associated networks.		[16]
Aphasia and anomia	Significant increase in language improvement	2 weeks	[10]
Upper limp weakness	Safety and viability of the VNS with a tendency to neuroplasticity and improvement of the upper extremity.	-	[9]
Dysphagia	Improvement in swallowing.	-	[6]
Upper limb impairment	Beneficial effects of motor impairments.	6 days	[4]
Aphasia	Improvement in speech and language performance prevention of language lateralization in RH.	-	[15]
Ataxia	Improvement in the speed of the march and the balance.	1 month	[7]
Aphasia	Improvement in speech and language in patients with previous injuries.	15 weeks	[14]
Hemiparesis and cognitive deficits	Improvement in motor and cognitive performance.	6 months	[13]
	ABB: VNS: Vagus Nerve Stimulation; RH: Right Hemisphere.		

change of Laterality [14]. This association is also evidenced in subsequent studies that combine the anodic or dual ETCD, reactivating the ipsilesional CM1, with motor training programs, relating the clinical improvements with an increase in the activity of the ipsilesional motor cortex [1,3] and with a tendency to an activation pattern like that of healthy individuals [7]. On the other hand, a single application of excitatory EMTR on dysphagic CM1 does not produce significant increases in the affected hemisphere or improvement in dysphagia [13]. Possibly, this difference in clinical outcomes is due to the number of stimulation sessions or the intensity and intervention protocol used.

D' Agata et al show improvements, although transitory, in the motor and cognitive performance of chronic patients with stroke after the use of rTMS and tCDS, due to the induction of neuroplasticity by stimulating the cortical and subcortical areas motor, pointing out the possible motor and neurocognitive rehabilitation simultaneously. Therefore, brain stimulation techniques somehow reorganize and modulate neural networks, or decrease the inhibition of the right hemisphere on the perilesional areas of the left hemisphere, noting that activation of the right hemisphere is a compensatory maladaptive strategy [11,16,18,20]. However, studies show that clinical improvements can be obtained by increasing cortical excitability in the contralesional hemisphere [15,16]. This suggests that patients will benefit from an increase in cortical activity of the ipsilesional or contralesional hemisphere, depending on the severity of the injury and the possibilities of recruiting the patient's neural networks [3,16].

These results of studies that simultaneously use brain stimulation techniques and training tasks may suggest that the combination of brain stimulation techniques and peripheral sensorimotor stimulation induced by training tasks enhance brain excitability, leading to improvements in cognitive and cognitive deficits./ or associated engines. In this direction, these studies that combine sensorimotor stimulation activities with brain stimulation are consistent with the results obtained in patients with chronic stroke, which combine peripheral nerve stimulation (PNS) of the paretic hand with anodic tDCS in ipsilesional CM1, obtaining beneficial effects in motor performance, even better than those achieved by interventions alone [19].

It is important to highlight the evidence of the maintenance of long-term improvements once the intervention has ended, because thanks to studies that show the maintenance of better performance in motor and/or cognitive deficits over time will serve for the promotion of brain stimulation techniques in the rehabilitation of cerebrovascular accidents. These benefits were found with different paradigms of brain stimulation such as dual tDCS, maintaining the improvement in motor performance up to a week [3,7], and cognitive performance up to two weeks post-intervention [16]. Probably, the combination of peripheral training with brain stimulation helps in the consolidation of motor and/or cognitive abilities by increasing afferent inputs in the cortex while modulating cortical excitability, achieving yields impossible to achieve with these interventions alone [3,15]. These long-term results show that cerebral stimulation modulates brain excitability during a period of time that is longer than the duration of stimulation effects [18,19]. Most studies have been performed in chronic patients, possibly, to control the effect of spontaneous neuroplasticity induced by a CVA in post-stroke recovery [11-13]. This indicates the possibility of using brain stimulation techniques safely and with the possibility of recovery in those patients with motor and/or cognitive deficits for more than 6 months caused by cerebrovascular accidents.

We can conclude that, although the underlying neural plasticity induced by brain stimulation techniques in stroke has not been sufficiently studied and is not yet clear, there is evidence of functional improvement associated with changes in the cortical excitability. The restoration of neuronal activation of injured areas or the activation of perilesional areas within the ipsilesional hemisphere seems to be the best rehabilitation strategy [12] cognitive and/or motor.

On the other hand, the time elapsed after a stroke, the age of the patient, the types of rehabilitative treatments received, the intensity and timing of the application of neurostimulation techniques are crucial factors in the recovery of patients with stroke [13].

In addition, the type of lesion, the size, the topographic location and the volume of the lesion are determining factors in the responses of the patients to the stimulation. The uniform application of stimulation techniques may not benefit all patients in rehabilitation [15].

Therefore, the use of adjustable pulse parameters or EEG monitoring is currently being promoted, with the aim of inducing plasticity with the intensity of stimulation and being able to provide the greatest possible reliability and efficacy [21]. Therefore, more studies are needed to obtain the appropriate parameters and protocols to achieve the earliest possible post-stroke rehabilitation.

Conclusion

Finally, we can say that more studies are required to evaluate the possibility of cognitive recovery because most of the evidence of improvement in the performance of deficits produced as a result of stroke is based on small case studies or pilot studies with deficits engines. In addition, we present articles with a great heterogeneity of patients: stroke located in different cerebral areas, variability of the sizes of the lesions, diversity of motor and/or cognitive deficits, different evaluation examinations of the improvement of the deficits. However, although this could be considered strength for the use of non- invasive brain stimulation (NIBS) in rehabilitation centers with a variety of patients with stroke. Larger studies are needed to address the possible differential effects of the type of treatment depending on the location, size of the lesion, specific deficits produced, timing of the intervention and the stimulation protocol of non-invasive stimulation techniques, and thus compare them and determine the most specific treatment strategy, effective and adequate to the clinical conditions.

Conflict of Interest

The authors declare that they have no Conflict of Interest.

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