REVIEW ARTICLE

Neuroplasticity and functional recovery in rehabilitation after stroke

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ABSTRACT

The concept of rehabilitation in stroke is currently based on evidence of neuroplasticity, considered to be responsible for recovery after a stroke. The scarcity of information in the literature, especially concerning methods that specifically evaluate neuroplasticity, does not match its functional importance. In general, the literature discusses the functional evaluations of limbs after a stroke and a few studies focus on cerebral impairment. **Objective:** To review the literature and evaluate current rehabilitation programs for stroke and their potential to promote functional improvement and neuronal plasticity. **Method:** A literature review was conducted searching the PubMed database with articles published from 2000 to 2015. The descriptors used were: "Stroke/rehabilitation" OR "Stroke/therapy" AND "Neuronal Plasticity". **Results:** From the 86 studies found, 36 were classified as Therapy/Narrow, with 17 articles being excluded either for not meeting the inclusion criteria or for not presenting a theme relevant to the study. After the selection by title and abstract, 19 articles were read entirely. Of those, six were excluded for not addressing the objective of the present study. In all, 13 articles were reviewed. The evaluation instruments in those 13 articles varied between functional magnetic resonance, transcranial magnetic stimulation, and single photon emission computed tomography (SPECT). The interventions used were specific for the upper limbs, except for one article about an intervention through hyperbaric oxygen therapy. **Conclusion:** Few studies evaluated the neuronal plasticity in rehabilitation after a stroke, and most articles presented improvements in function as well as in neuroplasticity. However, larger studies should investigate and correlate both aspects in the rehabilitation of stroke patients.

Keywords: Stroke, Neuronal Plasticity, Rehabilitation

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INTRODUCTION

Injuries to the central nervous system (CNS) leave sequelae that can vary in severity, depending on the location injured, on the extent of the injury, and on the general physical condition of the individual. As there is little or no regeneration of the CNS, the search for new treatment strategies is important because, although a partial recovery of behavioral manifestations may occur, the functional improvements observed after injuries stem from synaptic plasticity phenomena and not from structural repair. Despite the high medical relevance of a stroke, there are currently no specific treatments for this type of injury. Thus, the study of the nervous system injury and recovery is important to develop future treatments.

Neural plasticity can be considered as the brain's ability to recover a function through neural proliferation, migration, and synaptic interactions, while functional plasticity is the degree of recovery possible of a function through altered behavior strategies.[1] This phenomenon may be an endogenous repair mechanism by which the brain tries to minimize neural losses.

The concept of rehabilitation in stroke is currently based on evidence of neuroplasticity. Therapeutic methods that induce neuroplastic alterations lead to a better motor and functional recovery than traditional ones.[2] The advancement of our understanding about the neuroplastic changes associated with post-stroke motor impairment and about the innate repair mechanisms is fundamental to this effort.

The scarcity of information in the literature, especially on methods that specifically evaluate neuroplasticity, does not coincide with its functional importance. Generally, the literature discusses the functional evaluations of limbs after a stroke, but few studies focus on cerebral impairment. In view of this context, it is clearly important to choose the right instrument to evaluate function and neuroplasticity in post-stroke patients, as well as to know the types of rehabilitation programs that interfere with neuroplasticity.

OBJECTIVE

The present study sought to review the literature and evaluate the current rehabilitation programs for stroke and their potential to promote improvements in function and neuronal plasticity.

METHOD

A literature review was conducted searching the PubMed databases from articles published from 2000 to 2015. The MeSH descriptors used were: (("Stroke/rehabilitation" [Mesh] OR "Stroke/therapy"[Mesh])) AND "Neuronal Plasticity"[Mesh]. The search filter used was "therapy narrow."

The articles were selected according to the following inclusion criteria: (1) articles published in English; (2) studies that evaluated the effect of a rehabilitation technique having the evaluation of neuroplasticity as the outcome; and (3) clinical trials as type of study. Articles were excluded in the following situations: (1) isolated effects of medication therapy and/ or surgical procedures; (2) ongoing studies; and (3) studies that had no relationship with rehabilitation.

After being selected, the articles were read in their entirety and evaluated through the JADAD[3] scale, which has a score from 1 to 5. The studies were classified as having good quality for JADAD ≥ 3 and low quality for JADAD < 3.

RESULTS

After the PubMed search, of the 86 studies found, 36 were classified as Therapy/Narrow with 17 articles being eliminated for not meeting the inclusion criteria or for not being relevant to the study. After selecting by title and abstract, 19 articles were read in their entirety. Of those, six articles were excluded for not pertaining to the objective of this study. In total, 13 articles were reviewed. The organogram below details the selection process (Figure 1). The summary of the studies is shown in Chart 1.

DISCUSSION

Traditionally, the emphasis in rehabilitating post-stroke patients has been on treating primary neurological deficiencies, that is, treating muscle weakness and loss of coordination through guided exercises. After being discharged from a rehabilitation center, 60 to 80% of the post-stroke patients are able to walk independently. However, the motor recovery of the upper limbs is still a challenge for neurological rehabilitation. In terms of motor ability, the loss of upper limb function is a common and disabling sequelae. Initially, more than 85% of individuals present with motor deficit in the affected upper limb, with functional recovery being reported only by 25 to 35% of the individuals.[17,18]

In order to better understand the impact of a stroke, it is important to incorporate evaluation measures of the disabilities provoked by this disease.

In a healthy cortex, a balance between the cerebral hemisphere interactions, via the corpus callosum, is necessary to produce normal voluntary movements.[19] After a unilateral injury, this balance is shifted, which results in hyperexcitability of the non-affected motor cortex.[20] The intact hemisphere will, then, exert inhibitory action over the injured hemisphere, provoking in this way the phenomenon called interhemispheric inhibition.[21]

The interhemispheric imbalance model provides a structure for the development of two possibilities: 1) upregulating = excitability of the intact parts of the ipsilesional hemisphere in the motor cortex region; and 2) downregulating = excitability of the contralesional motor cortex to modulate its inhibitory influence in ipsilesional regions.[9]

The recent development of techniques that include non-invasive brain stimulation, such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct-current stimulation (tDCS). The use of these instruments is based on neurophysiological studies that demonstrated that an interhemispheric imbalance interferes with cerebral recovery process.

Pilot studies using TMS, tDCS, or rTMS, have shown beneficial effects on motor abilities and motor learning. In addition, the combination of tDCS and peripheral stimulation (e.g., the stimulation of the peripheral nerve or peripheral sensory activities) seemed to increase the effects of each intervention by themselves.

Lindenberg et al.[9] demonstrated the viability and efficacy of using bihemispheric stimulation in patients with chronic stroke. The changes in the motor cortex hemispheric asymmetry index were correlated with changes in the Wolf Motor Function Test (WMFT) scale. This significant correlation between behavior and image reinforced the hypothesis that the modulation activity of the motor cortex with simultaneous sensory-motor and peripheral activities leads to a better functional reorganization of the ipsilesional motor cortex.

Whitall et al.[11] compared the efficacy of the bilateral arm training with rhythmic auditory cueing (BATRAC) *versus* dose-matched therapeutic exercises (DMTEs) on the function of the paretic upper limb in stroke patients. An fMRI was used to examine the effects of cortical reorganization. The authors observed

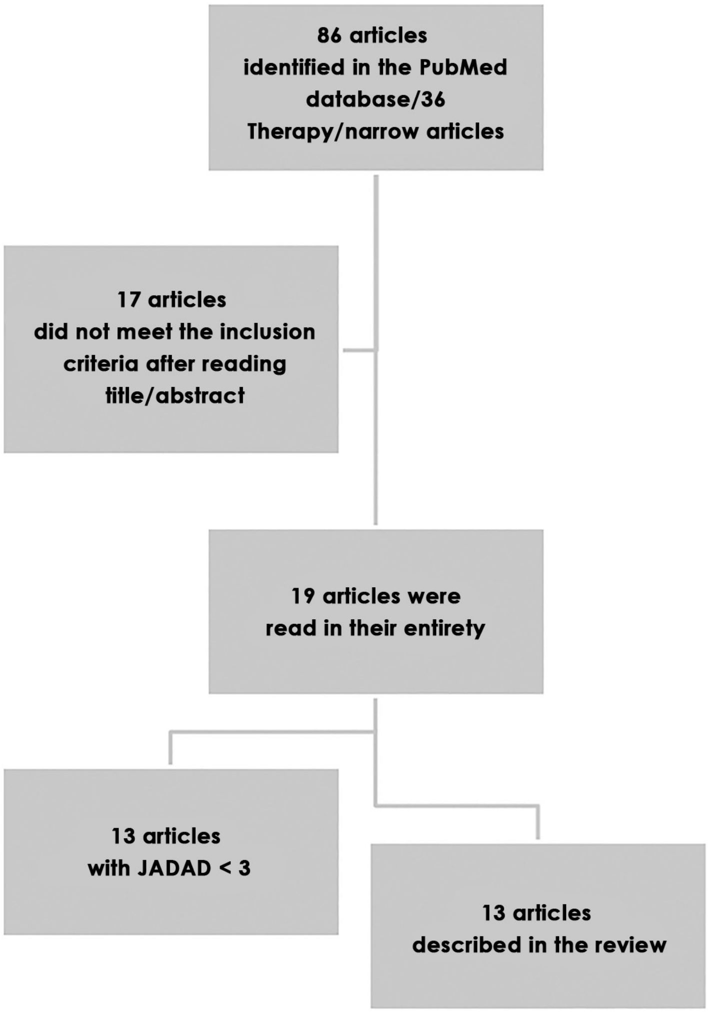

Figure 1. Flowchart of the study

that in six weeks of training, there was improvement in the functional performance of the upper limb of chronic hemiplegic individuals, and that these improvements lasted for at least four months. The improvement after the BATRAC training, at least in part, mediated the cortical remodeling in the pre-central ipsilesional gyrus and in the contralesional superior frontal gyrus (pre-motor cortex), while the DMTEs acted on other neuroplasticity processes. As a conclusion, the authors suggested that both techniques could be used for rehabilitation of the upper limb to maximize the neuroplasticity effects.

According to Stinear et al.,[8] after a stroke, the primary motor cortex function (M1) between the two hemispheres can become unbalanced. Techniques that promote a rebalancing of the excitability of the M1 may prepare the brain to be more sensitive to rehabilitation therapies and lead to better functional results. In that sense, the authors examined the effects of Active Passive Bilateral Therapy (APBT), a conditioning strategy based on putative movements designed to reduce the intracortical inhibition and increase the excitability in the ipsilesional M1 area in one group *versus* a control group with conventional therapy. TMS was used to evaluate the excitability of the M1 immediately after the intervention. The authors observed that the motor function of the affected upper limb improved in both groups. One month after the intervention, the APBT group presented a higher functional improvement when compared to the control group. According to the same authors, the APBT group experienced an increase in the excitability of the ipsilesional M1, an increase

Chart 1. Summary of articles

Author and Year	Country	Evaluation instrument	Therapy
Nelles et al. 2001[4]	Germany	Positron Emission Tomography (PET)	Passive and functional exercises
Bhatt et al. 2007[5]	USA	Functional Magnetic Resonance Imaging (fMRI)	Electrical stimulation, tracking training
Gauthier et al. 2007[6]	USA	Functional Magnetic Resonance Imaging (fMRI)	Induced Contention Therapy *versus* Conventional Therapy
Carey et al. 2007[7]	USA	Functional Magnetic Resonance Imaging (fMRI)	Repetitive movements (tracking) *versus* simple repetitive movements
Stinear et al. 2008[8]	New Zealand	Transcallosal inhibition; Transcranial Magnetic Stimulation (TMS)	Active Passive Bilateral Therapy (APBT)
Lindenberg et al. 2010[9]	Israel	Functional Magnetic Resonance Imaging (fMRI)	Transcranial direct-current stimulation (tDCS)
Wu et al. 2010[10]	China	Functional Magnetic Resonance Imaging (fMRI)	Bilateral arm training (BAT) *versus* Induced Contention Therapy
Whitall et al. 2011[11]	USA	Short-interval Intracortical Inhibition (SICI)	Bilateral arm training with rhythmic auditory cueing (BATRAC) *versus* dose-matched therapeutic exercises (dmtes) on upper limb
Michielsen et al. 2011[12]	Netherlands	Functional Magnetic Resonance Imaging (fMRI)	Mirror Therapy *versus* Conventional Therapy
Avenanti et al. 2012[13]	Italy	Transcranial Magnetic Stimulation (TMS)	Repetitive Transcranial Magnetic Stimulation and Conventional Physiotherapy
Efrati et al. 2013[14]	USA	Single Photon Emission Computed Tomography (SPECT)	Hyperbaric Oxygen Therapy
Orihuela-Espina et al. 2013[15]	Mexico	Functional Magnetic Resonance Imaging (fMRI)	Gesture Therapy (virtual reality with emphasis on basic daily activities)
Tai et al. 2014[16]	China	Transcranial Magnetic Stimulation (TMS)	Thermal Stimulation: noxious heat (46-C° 47-C°) and cold (7-C°8-C°). Control group: innocuous heat (40-C°41-C°) and cold (20-C°21-C°)

of the ipsilesional transcallosal inhibition of the M1, and an increase of the intracortical inhibition of the contralesional M1. None of those alterations were found in the control group. The APBT produced improvements in the motor function of the upper limbs in patients with chronic stroke and produced specific alterations in the inhibitory function of the motor cortex.

Bhatt et al.[5] studied how electrical stimulation combined with motor learning-based tracking training in individuals with stroke can improve cortical reorganization and its relationship with functional recovery. Using fMRI, the following areas of each hemisphere were studied: area (M1), primary sensory area (S1), pre-motor cortex (PMC), and supplementary motor area (SMA). The results showed that only the combination of interventions, that is, the electrical stimulation associated with the motor learning technique presented a significant association between functional recovery and brain reorganization. For this same group, the changes in the laterality index of M1, S1, SMA, and MPC were strongly correlated with the Box and Block Test (BBT) functional evaluation scale. The authors recognized that the fMRI has an important limitation - that is, the inability to differentiate the activation related to the greater motor-sensory processing that refers to motor execution. In contrast, studies showing techniques of stimulation of intracortical microelectrodes in animals have shown directly that, after an infarction in M1, the PMC rapidly assumes the roles of motor execution of the M1, in association with the recovery of dexterity.

Efrati et al.[14] sought to evaluate whether the increase in the oxygen level dissolved by Hyperbaric Oxygen Therapy (HBO) could active the neuroplasticity in stroke patients. The improvement comparison in brain activity after HBO revealed that the treated group showed significant improvement after the treatment. The authors concluded that, in that study, for the first time, convincing results demonstrated that HBO could induce significant neurological improvement in post-stroke patients. Thus, the results have important implications that can be relevant and interesting in neurobiology.

Summarizing, it is observable that rehabilitation causes a great impact on neuroplasticity, however, the plastic mechanisms of the CNS are not well elucidated. Nevertheless, with the advance of intervention techniques and neuromodulation evaluation, it is possible to establish rehabilitation protocols that seek greater potentiation for CNS recovery after an injury and, consequently, an improvement in functionality and quality of life.

CONCLUSION

Few studies have evaluated neuronal plasticity in stroke rehabilitation and have mostly presented functional and neuroplastic improvements. In addition, the correlation between different measurements of functional recovery and neuroplasticity still need more clarification. Future studies should investigate both aspects in the rehabilitation of stroke patients.

For more effectiveness in the process of rehabilitation, pharmaceutical, biological, and electrophysiological treatments that increase neuroplasticity need to be explored to further expand the limits of post-stroke rehabilitation.

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