Annals of Physical and Rehabilitation Medicine 58 (2015) 220–224

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Update article

Repetitive transcranial magnetic stimulation and transcranial direct current stimulation in motor rehabilitation after stroke: An update

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ARTICLE INFO

Article history:
Received 26 March 2015
Accepted 19 May 2015

Keywords:
rTMS
tDCS
Stroke
Plasticity
Motor control

ABSTRACT

Stroke is a leading cause of adult motor disability. The number of stroke survivors is increasing in industrialized countries, and despite available treatments used in rehabilitation, the recovery of motor functions after stroke is often incomplete. Studies in the 1980s showed that non-invasive brain stimulation (mainly repetitive transcranial magnetic stimulation [rTMS] and transcranial direct current stimulation [tDCS]) could modulate cortical excitability and induce plasticity in healthy humans. These findings have opened the way to the therapeutic use of the 2 techniques for stroke. The mechanisms underlying the cortical effect of rTMS and tDCS differ. This paper summarizes data obtained in healthy subjects and gives a general review of the use of rTMS and tDCS in stroke patients with altered motor functions. From 1988 to 2012, approximately 1400 publications were devoted to the study of non-invasive brain stimulation in humans. However, for stroke patients with limb motor deficit, only 141 publications have been devoted to the effects of rTMS and 132 to those of tDCS. The Cochrane review devoted to the effects of rTMS found 19 randomized controlled trials involving 588 patients, and that devoted to tDCS found 18 randomized controlled trials involving 450 patients. Without doubt, rTMS and tDCS contribute to physiological and pathophysiological studies in motor control. However, despite the increasing number of studies devoted to the possible therapeutic use of non-invasive brain stimulation to improve motor recovery after stroke, further studies will be necessary to specify their use in rehabilitation.

1. Introduction

Since the 1980s, the development of non-invasive techniques (electrodes simply positioned on the scalp over the target brain area) allowing for reversible manipulation of the cortex excitability has paved the way to physiological studies in healthy humans. In a second step, these non-invasive techniques were introduced in pathophysiological studies. To briefly summarize the main data [1,2], these studies reveal that isolated transcranial magnetic stimulation (TMS) applied over the motor cortex induces a motor evoked potential (MEP) in the target muscle recorded by surface electromyography (EMG) (Fig. 1). Low-frequency repetitive TMS (rTMS < 1 Hz) reduces the excitability of the motor cortex, thus decreasing the MEP amplitude, whereas high-frequency rTMS (>5 Hz) increases it (Fig. 1). Anodal transcranial direct current stimulation (tDCS) increases the motor cortex excitability and cathodal tDCS decreases its excitability (Fig. 1). The effects of rTMS and tDCS are not limited to the motor cortex target area but also affect distant interconnected brain and spinal networks [3–9]. Both rTMS and tDCS induce after-effects [3], which is a powerful argument to explore their possible therapeutic effects.

Stroke is a leading cause of long-term adult disability, and the number of patients with chronic motor deficit after stroke is increasing in industrialized countries, despite classical rehabilitation techniques. In the 2004 review by Dobkin, listing the current strategies for stroke rehabilitation, only 60% of patients with hemiparesis achieved functional independence in simple activities of daily living [10]. The author also stressed that the effect of

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http://dx.doi.org/10.1016/j.rehab.2015.05.006
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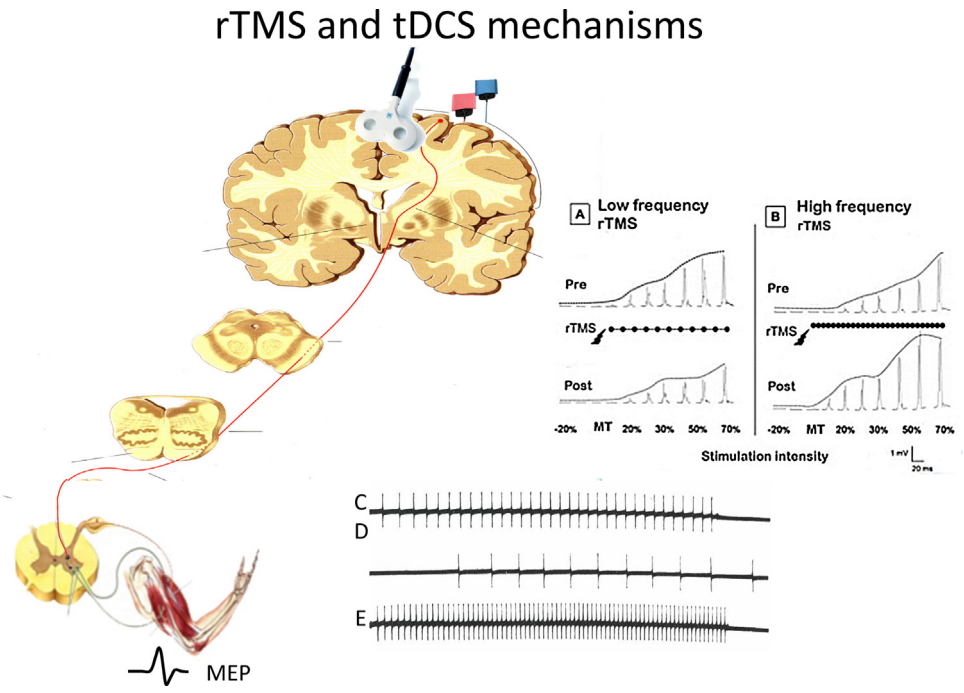

Fig. 1. Action of repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). A–B. rTMS action. A. Low-frequency rTMS effects: the upper line represents motor-evoked potential (MEP) in the target muscle. With increasing intensity of isolated TMS, the amplitude of MEP increases. The lower line represents the MEP size after rTMS. Note that the MEP size decreases after low-frequency rTMS. B. High-frequency rTMS effects: upper line represents MEP in the target muscle. With increasing intensity of isolated TMS, the amplitude of MEP increases. The lower line represents MEP amplitude after rTMS. Note that the MEP size increases after high-frequency rTMS (adapted from Valero-Cabré et al., 2011 [22]). C–E. tDCS action C. Spontaneous discharge of cortical neurons before tDCS intervention. D. Decrease of the spontaneous discharge after inhibitory cathodal tDCS. E. Increase of spontaneous discharge after anodal tDCS.

therapeutics is limited during the acute stage and the management of stroke mainly focuses on secondary prevention and rehabilitation.

The search to improve rehabilitation during the last decades has led to different strategies to manipulate or induce brain plasticity. An increasing number of studies, involving rTMS and tDCS, are devoted to their possible therapeutic effects to improve motor functions after stroke [3,11–15]. These therapeutic trials consisted of excitatory stimuli applied on the motor cortex with a lesion to increase the efficacy of the remaining cells; inhibitory stimuli applied on the non-lesioned cortex to decrease the inhibitory connections from the non-lesioned hemisphere to the lesioned one; and both stimulations combined, with or without traditional rehabilitation and with or without sham stimulation. These studies differ by the characteristics of the stimulation and number of sessions. The outcome measures used to objectively determine the possible effect of these stimulations differed among studies, including in the assessment of the clinical motor function, muscle force or spasticity scales; appreciation of daily living; functional MRI (fMRI); and electrophysiology. They also differed in whether the possible effect was tested during the intervention, immediately after or at longer time after the end of the intervention.

2. Background summary

The mechanisms underlying the effects of rTMS and tDCS applied over the motor cortex are fully described in this special issue [1,2]. Here, we summarize the central nervous system structures that these stimulations likely involve. Excitatory stimulation enhances the excitability of the motor cortex under the electrodes, thus inducing a facilitatory effect on the contralateral corticospinal tract and the spinal motor neurons. This effect is revealed by an increase in MEP amplitude (Fig. 1). The stimulation over the contralateral motor cortex also likely activates the ipsilateral corticospinal tract in stroke patients, but healthy subjects show no evidence of increased ipsilateral MEP amplitudes. The descending projections from upper motoneurones are not limited to the spinal motor neurones but are also propriospinal nuclei and spinal interneurons [4,7–9,16]. In a given hemisphere, fMRI and magneto-encephalography studies have demonstrated that brain stimulation applied over the motor cortex may affect many brain regions at a distance involving other cerebral areas, basal ganglia and cerebellum. Finally, the homologous cortical area exhibits mutual inhibitory connections between the 2 hemispheres [3,17].

In summary, it must be remembered that non-invasive brain stimulation over the motor cortex induces changes in the target motor area but also in many cortico-subcortical and spinal structures. The likely excessive interhemispheric inhibition (IHI) from the non-lesioned hemisphere after stroke has led to exploring the possible therapeutic effects of inhibitory stimulation applied to the non-lesioned hemisphere and also dual stimulation (excitatory on the lesioned hemisphere and inhibitory on the non-lesioned hemisphere) (Fig. 2). In recent years, 4 review articles [11–13,18] have summed up the therapeutic trials of rTMS and tDCS performed for about 10 years. In searching MEDLINE via PubMed in February 2015 to identify the trials of rTMS and tDCS interventions in stroke patients with limb motor deficit, we found about 141 references for rTMS and 132 for tDCS. As reported in the 4 reviews quoted above, about 1400 publications involved non-invasive brain stimulation in humans, 180 of these devoted to stroke patients.

The criteria used by the authors of these 4 reviews to retain studies for meta-analysis differ as follows:

- Ayache et al. [11] retained all studies devoted to the possible therapeutic effects of rTMS and tDCS on motor function in stroke patients. The authors excluded studies of only purely neurophysiological evaluation. Therefore, 66 studies involving

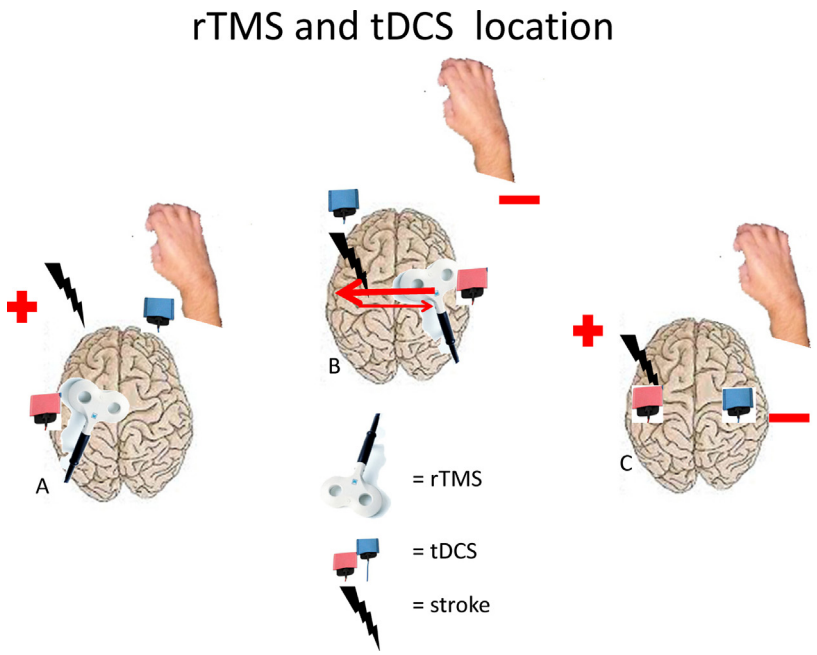

Fig. 2. rTMS and tDCS location. A. tDCS or rTMS is applied over the lesioned hemisphere: an excitatory stimulation is used. B. tDCS or rTMS is applied over the non-lesioned hemisphere: an inhibitory stimulation is used to reduce the interhemispheric inhibition drive from the non-lesioned to the lesioned hemisphere. C. Dual stimulation: excitatory stimulation on the lesioned hemisphere and inhibitory stimulation on the non-lesioned hemisphere.

1785 patients (1343 for rTMS studies and 442 for tDCS studies) were analyzed;

- the review by Hsu et al. [18] related to rTMS effects. The criteria used were number of patients involved in each study >5 and only randomized controlled trials. Thus, the authors retained 18 studies involving 392 patients;
- the Cochrane review [12] focused on the effects of rTMS for improving function after stroke. Randomized controlled trials coupling rTMS therapeutics with sham or control interventions were included. The studies reporting only laboratory parameters were excluded. After screening 2431 titles and abstracts, the authors included 19 papers involving 588 patients;
- the Cochrane review [13] described the effects of tDCS. Only randomized controlled trials and randomized controlled cross-over trials were included. From 6231 records identified via database searching, the authors eliminated duplicate records (2726) and retained only studies meeting Cochrane criteria. Thus, only 18 studies involving 450 patients were retained for further analysis.

3. Main data

Whatever the aim of the non-invasive brain stimulation (excitatory or inhibitory) or type, rTMS or tDCS, the studies mostly dealt with upper-limb motor function. The possible improvement of upper-limb motor function was assessed mainly by clinical tests and clinical scales of generic activities of daily living, improvement of hand functions, muscle force and spasticity. More accurate tests such as neurophysiological and neuroimaging tools were rarely used even though clinical assessment alone has low prognostic accuracy [19]. These studies differed in number of patients (from <10 to >200), the stroke onset, the presence of sham stimulation, the presence of traditional rehabilitation coupled with non-invasive brain stimulation, the type of stroke (cortical or sub-cortical), the time between 2 sessions in case of repetitive sessions, and the time between the test and the end of the intervention.

3.1. rTMS

The Cochrane review [12] included 588 patients aged 50 to 75 years; 30% to 80% were males (according to the different studies). The time between the stroke onset and the start of the intervention varied from 4 hr to 6 years. The aim of the review was to assess efficacy and safety of rTMS for improving motor function in patients with stroke. The side effects were minimal, including small headaches and local discomfort at the site of the stimulation. The possible rTMS efficacy was tested whatever the characteristics of the stroke (area, cortical or subcortical lesions, haemorrhagic or ischemic origin), the characteristics of the stimulation (low frequency applied over the non-lesioned hemisphere or high frequency applied on the lesioned hemisphere), and the time between stroke onset and intervention. The evidence did not support the routine use of rTMS for the treatment of stroke. Subgroup analysis did not reveal any difference between stimulation of the lesioned and non-lesioned cortex.

The review by Hsu et al. published in 2012 [18] targeted upper-limb motor-function studies in 392 stroke patients. Hence, the side effects were extremely limited (4 patients). The meta-analysis suggested that rTMS had a positive effect on motor recovery, especially for patients with subcortical stroke. Low-frequency rTMS over the unaffected hemisphere may be more beneficial than rTMS over the affected hemisphere. However, the authors stressed that further studies in a larger population are required to better elucidate the differential roles of various rTMS protocols in stroke.

The review by Ayache et al. published in 2012 [11] included 1343 patients. The authors divided studies into 4 categories:

- low-frequency rTMS (inhibitory effects applied on the non-lesioned hemisphere) in the acute or post-acute phase (5 days to 3 months after stroke), involving 139 patients;
- the same inhibitory stimulation applied in the chronic phase (4 months to 12 years), involving 682 patients;
- high-frequency rTMS (excitatory stimulation applied on the lesioned cortex) in the acute phase, involving 182 patients;

- the same excitatory stimulation in the chronic phase, involving 327 patients.

Whatever the category, the studies were almost completely devoted to upper-limb motor function. However, the studies were heterogeneous given the characteristics of the stimulation, number of patients, number of sessions when the intervention was repeated, time between stroke onset and intervention, type of stroke (cortical or subcortical), presence of traditional rehabilitation coupled with rTMS intervention, and presence of sham stimulation. In a few cases, the clinical evaluation was coupled with electrophysiological tests. Most of the individual studies reported clinical improvement of upper-limb motor function, more commonly found in patients with subcortical lesions, when the rTMS intervention was coupled with traditional rehabilitation, and when the stimulation was applied over the non-lesioned hemisphere.

3.2. tDCS

The Cochrane review [13] assessed the effects of tDCS on activities of daily living and motor function in stroke patients. It included 455 patients, >18 years old, regardless of the initial level of impairment and duration of stroke. All kinds of tDCS (anodal, cathodal or dual) were tested. Analysis of 6 studies involving 326 patients regarding activities of daily living found an effect of tDCS at follow-up but not at the end of the intervention. Regarding upper-limb function, the authors found an effect of tDCS at the end of the intervention but not at the end of follow-up. The authors concluded low-quality evidence of the effectiveness of tDCS versus control for improving activities of daily living and functions after stroke.

Ayache et al. [11] studied the effects of tDCS in 388 patients, using the same classification as for rTMS: excitatory stimulation (anodal tDCS applied over the lesioned cortex) in the acute or post-acute phase (2 days to 3 months), involving 169 patients; excitatory stimulation in the chronic phase (1–7 years), involving 67 patients; inhibitory stimulation (cathodal tDCS applied on the non-lesioned hemisphere) in the acute or post-acute phase (10 days to 4 months), involving 124 patients; and inhibitory stimulation in the chronic phase (1–7 years), involving 28 patients. The authors also included dual tDCS studies of 54 patients in the chronic phase (5 months to 7 years). The heterogeneity among studies was similar to that for rTMS studies. The smaller number of patients (388 in tDCS studies vs 1343 in rTMS studies) does not allow for more detailed conclusions. All studies performed in the chronic phase suggested an improvement in upper-limb motor function. The effects were more variable in the acute phase.

4. Comments

4.1. rTMS versus tDCS

A recent study by Priori et al. [20] compared rTMS and tDCS in terms of technology and costs, the possibility of obtaining a true sham stimulation, focality of stimulation, the possibility of obtaining stimulation during a motor or cognitive task, and stimulus intensity and safety. The authors cautioned the reader about no strict recommendation on which of the 2 techniques is better for specific use, but they suggested that the high temporal and spatial resolution of rTMS is useful in experiments that probe neurophysiologic effects on specific neuronal networks. In contrast, the simplicity of low-cost tDCS may be better for investigations that do not target a selective population of neurons because it may occur in various clinical studies.

4.2. What is currently acquired?

Physiological studies of both animals and humans have demonstrated that rTMS and tDCS (see corresponding papers in this issue [1,2]) reversibly modulate the excitability of the cortex and may induce after-effects. These findings have opened the way to pathophysiological studies in humans. By coupling non-invasive stimulation with electrophysiological and imaging studies, owing to neural connectivity, rTMS and tDCS modify the excitability of the target brain area and also at a distance (other brain areas, cerebellum, spinal cord networks, contralateral brain area). For both rTMS and tDCS, changes induced at a distance from the motor cortex area targeted by the stimulation have not been fully documented, and their possible role in the effects induced by the stimulation over the motor cortex remain to be explored. To induce after-effects is likely important to favour the therapeutic effects. However, the stimulation parameters needed to regularly evoke after-effects remain to be explored.

4.3. Therapeutic trials

Therapeutic trials of rTMS and tDCS aim to increase the excitability of the lesioned hemisphere to enhance the motor control originating from the lesioned hemisphere and decrease the excitability of the non-lesioned hemisphere to reduce the IHI drive from the non-lesioned to lesioned hemisphere. More recently, dual stimulation (excitatory stimulation on the lesioned hemisphere and inhibitory stimulation on the non-lesioned hemisphere) has been introduced. Guidelines for non-invasive stimulations have been established, and thus side-effects are rarely reported. The possibility of non-invasively modifying the brain cortex excitability and the existence of after-effects have led to a number of therapeutic trials of stroke patients with motor deficits, aphasia or spatial neglect and also patients with psychiatric diseases. However, as stressed by Hao et al. [12] in their Cochrane review, the available evidence does not support the routine use of rTMS for motor function treatment after stroke. The review by Elsner et al. [13], of tDCS, points to low-quality evidence of the effectiveness of tDCS as compared with a control in stroke patients. The rather disappointing conclusions from these reviews differ from those of individual studies, which predominantly indicate an improvement with rTMS or tDCS. The discrepancy between individual studies and meta-analysis findings is likely linked to heterogeneity of patients, clinical tests and features of the intervention, which are not standardized. Indeed, the number of inhibitory rTMS pulses varied from 150 to 1800 among studies [11] and the number of rTMS sessions from 1 to 30 [11]. For tDCS studies, the intensity of the current varied from 1 to 2 mA and the duration of sessions from 7 to 30 min [11]. The context of the therapeutic trials also varied among studies: non-invasive stimulations were applied with or without traditional rehabilitation techniques and with or without sham stimulation. The outcome measures used to detect the possible effects of non-invasive stimulation also differed. In most studies, various clinical tests were performed, including muscle force and spasticity scales, functional tests and activity of daily living assessments. Of note, the means used to detect the possible effects of rTMS and tDCS different greatly in physiological and therapeutic trial studies. Physiological tests may be more appropriate to detect subtle changes than are clinical tests. Therefore, the clinical tools used in most therapeutic studies may not be sufficiently sensitive to detect modifications induced by non-invasive motor cortex stimulations, and physiological studies may be more able to detect them. Different types of stroke are involved; cortical or subcortical, ischemic or haemorrhagic. The time between stroke onset and therapeutic trials also varied. Finally, most studies were devoted to the possible modification of

upper-limb motor functions, mainly hand functions. Almost no study was devoted to lower-limb functions and gait, which are also commonly disordered in stroke patients with motor deficit.

5. Conclusion

The current possibility of non-invasively manipulating the excitability of the cortex without doubt led to therapeutic trials of post-stroke treatment. Demonstrating the therapeutic effects of rTMS and tDCS will require controlled therapeutic trials with sham intervention and standardised features of the stimulations, especially that evoking after-effects. These possible therapeutic effects need to be tested by taking into account the characteristics of the stroke and the time elapsed since the stroke, because the data suggest a critical period in post-lesioned brain plasticity [21].

Disclosure of interest

The authors have not supplied their declaration of conflict of interest.

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