Brain Stimulation (2008) 1, 326–36

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BRAIN STIMULATION

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ORIGINAL RESEARCH

Efficacy of repetitive transcranial magnetic stimulation/ transcranial direct current stimulation in cognitive neurorehabilitation

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Summary
Cognitive deficits are a common consequence of neurologic disease, in particular, of traumatic brain injury, stroke, and neurodegenerative disorders, and there is evidence that specific cognitive training may be effective in cognitive rehabilitation. Several investigations emphasize the fact that interacting with cortical activity, by means of cortical stimulation, can positively affect the short-term cognitive performance and improve the rehabilitation potential of neurologic patients. In this respect, preliminary evidence suggests that cortical stimulation may play a role in treating aphasia, unilateral neglect, and other cognitive disorders. Several possible mechanisms can account for the effects of transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) on cognitive performance. They all reflect the potential of these methods to improve the subject's ability to relearn or to

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Submitted May 22, 2008; revised July 21, 2008. Accepted for publication July 21, 2008.

doi:10.1016/j.brs.2008.07.002

acquire new strategies for carrying out behavioral tasks. The responsible mechanisms remain unclear but they are most likely related to the activation of impeded pathways or inhibition of maladaptive responses. Modifications of the brain activity may assist relearning by facilitating local activity or by suppressing interfering activity from other brain areas. Notwithstanding the promise of these preliminary findings, to date no systematic application of these methods to neurorehabilitation research has been reported. Considering the potential benefit of these interventions, further studies taking into consideration large patient populations, long treatment periods, or the combination of different rehabilitation strategies are needed. Brain stimulation is indeed an exciting opportunity in the field of cognitive neurorehabilitation, which is clearly in need of further research.

Keywords cognitive deficits; cognitive rehabilitation; memory; attention; language; repetitive transcranial magnetic stimulation; transcranial direct current stimulation

Cognitive dysfunction after a brain insult constitutes one of the major causes of disability worldwide, exerts a major impact on the lives of affected individuals and their families, and represents a major public health and financial burden for society. Therefore, the rehabilitation of disorders of cognitive functions related to language, attention, or memory is a clinically important and promising area. So far, the studies available in this area are few in number, preliminary in nature and the results are often inconclusive.[1,2] With the maturing fields in cognitive neurosciences, the combination of different expertises and methodologies has yielded a new interdisciplinary approach. The central nervous system responds dynamically to degenerative or focal lesion-induced cognitive deficits, thus explaining the clinical observation that, at least in some cases, disturbed or lost functions can be partially or fully restored. Studies of functional neuroimaging have shown that cerebral reorganization may occur after specific rehabilitation interventions.[3-5] Moreover, a number of investigations indicate that interacting with cortical activity by means of cortical stimulation can positively affect the cognitive performance of patients affected by aphasia, unilateral neglect, and other cognitive disorders. In this article, we will present an overview of recent developments in rehabilitation of cognitive function by means of noninvasive brain stimulation.

Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is a technique that uses a magnetic field, inducing an electrical current in the underlying brain tissue,[6] which interacts with ongoing activity in the neural tissue. Trains of repetitive stimuli (rTMS), present the opportunity to interact even more effectively with cortical activity.[7-9]

Interference with cognitive processing when TMS is applied during performance of a task is called online TMS.[10] In contrast, in the case of offline stimulation, TMS is applied for several minutes before the subject is tested on the task. The ability of TMS to temporarily disable neuronal function, thereby interrupting information processing, allows one to investigate the relationship between cortical areas and behavior and to trace the temporal course of the activity of a particular cortical region that contributes to a given task. This allows the mapping of the functional connectivity among brain regions and of the extent of neural reorganization (compensatory plasticity) after an insult.[9,10] The idea is that TMS delivered during the execution of a cognitive task triggers a synchronous activity in a subpopulation of neurons located under the stimulating coil, with the net result of disrupting the task-related pattern of activity that occurred at the time of the stimulation.[12,13]

However, this simplified interpretation cannot explain the observation that sometimes the performance of a cognitive task can also be facilitated by rTMS.[14,15] It must be underlined that behavioral facilitation does not necessarily imply enhanced cortical activity. Behavior after a brain insult is primarily a manifestation of how the undamaged brain adapts to the injury to sustain function. Such adaptive changes can themselves limit recovery (maladaptive changes) and in such instances behavioral facilitation may result from disruption or inhibition of brain activity (paradoxical functional facilitation).[16]

In any case, facilitatory behavioral effects related to TMS are important in two different respects. First, they can provide reassuring proof of principle that the stimulated brain region is part of a circuit critical for performing the task under investigation. However, facilitation effects could be due to unspecific factors such as a general arousal caused by rTMS, and these need to be carefully excluded in the experimental design. The RT enhancements caused by rTMS could, in many cases, be related to auditory intersensory facilitating influences of the auditory click occurring concurrently with discharge of the magnetic stimulator.[17,18] Nevertheless, these effects can be clearly discarded as an explanation of rTMS-induced facilitation in accuracy because it has been shown that the facilitation effects are clearly specific for task, site, type (sham vs real) of stimulation and stage of cognitive decline.[15,19,20]

The second important point, and the most interesting concerning neurorehabilitation, is that this facilitatory function may in fact be used to enhance disrupted function. Although most of these effects are transient, their application in concomitance with a learning process may perpetuate the facilitatory effect beyond even after the end of stimulation.[16,21]

The modification of cortical excitability for an adequate period may affect/promote adaptive organization or affect/disrupt maladaptive functional reorganization, inducing a new balance in the system and enhancing behavioral recovery.

Language

Online studies

Online TMS applied over cortical areas involved in verbal processing (perisylvian cortex of the dominant, usually left hemisphere) has been reported to facilitate picture naming and other language-related tasks in healthy subjects,[22-29] as well as in epileptic patients.[15] Similar facilitatory effects of online rTMS were observed with picture naming after stimulation of prefrontal cortices (PFCs) in healthy volunteers[15] and in patients with Alzheimer's disease (AD).[30] The latter experiment was based on three experimental blocks of naming of pictures of objects and actions (for this and the following experiments, details in Table 1). Anomia is common in the early stages of AD, and in the study by Cotelli et al,[30] patients were instructed to name the picture as quickly as possible while trains of high-frequency rTMS were delivered simultaneously with picture presentation. The main result was that the action-naming performance was improved during TMS applied to both left and right PFC (mean 17%), as compared with sham stimulation, whereas no effect was present for the object-naming performance. A following study by the same group[19] aimed to assess the effect of rTMS in patients with AD with different degrees of cognitive decline. The authors found improved naming accuracy for both classes of stimuli (actions and objects) in the moderate-to-severe group, whereas in the previous experiment, mild AD performance was facilitated only in the case of action naming. These results suggest that effects induced by rTMS influenced performance as long as it did not reach a ceiling at baseline, as in the case of object naming in patients with mild AD. Moreover, the amelioration was short-lived, lasting in the order of minutes. Although the effect size on action naming was quite robust, the underlying mechanisms remain unclear, and the basis for the facilitatory effects of rTMS on lexical retrieval remain essentially unknown. It must be underlined that in healthy subjects a shortening of naming latency for actions was found only after stimulation of left PFC.[15] On the other hand, the improvement of action naming in the AD group was observed after rTMS to both left and right PFC. This result could be attributed to the presence of a compensatory mechanism based on the recruitment of right hemispheric resources to support residual naming performance, suggesting that the brains of the patients with AD retain a significant degree of functional plasticity.[31,32] A crucial role in supporting language performance after left hemispheric damage has been traditionally assigned to the right hemisphere, and recent studies have indicated an increase in right hemispheric activation in progressive aphasia.[33] Although we do not expect that the online experimental procedure used in the current experiments (high-frequency online rTMS) will have a lasting effect on language (ie, beyond the end of the trial, to improve subsequent performance), we believe that the transient response to online rTMS may be a promising method for patient selection. For language function, it has been shown that the type of brain lesion determines the degree to which the activity of the right language areas are compensatory.[34,35] Therefore, it might be possible to use online rTMS over the right/left language areas to separate maladaptive activation from compensatory activation and to identify those patients who will benefit from this treatment.

The changes in behavioral response may be related to changes in cortical excitability, dominated by the area stimulated, or due to secondary effects on an area afferent or efferent to the area stimulated. These factors are in turn dependent on a number of variables, such as the timing of stimulation (ie, before, in the initial or final phase of the task; this is probably the most important factor), stimulus frequency (a relatively unexplored factor), and intensity. Moreover, an important point is that the effects of TMS on cognitive performance are also dependent on task and subject-related factors (eg, young vs old).

Offline studies

The effects induced by online stimulation are generally short lived, probably in the order of a few hundred milliseconds to a few seconds.[26] Therefore, this approach should not be considered a neurorehabilitation intervention, but may represent a suitable methodology for studying candidates in whom offline rTMS might be applied for cognitive rehabilitation or for identifying possible routes for neurorehabilitation. In the latter case rTMS is applied for several minutes (on average 10-15 minutes) before the subject is tested on the task of interest. Obviously this possibility has generated interest as a tool to potentially ameliorate clinical deficits.[36,37] It has been shown that by using offline rTMS, it is possible to transiently modulate neural excitability, with the net effect dependent on the stimulation frequency. Generally, from a physiologic point of view, low-frequency ($\leq$ 1 Hz) results in inhibition, whereas high-frequency ($\geq$ 5 Hz) stimulation results mainly in excitatory changes in the stimulated area.[38,39] However, robust parameters and measures of excitatory and inhibitory consequences of different frequencies remain to be documented in detail.

However, several studies have demonstrated that both types of stimulation (low- and high- frequency) may have similar, positive effects on subjects' performance depending on the site of applications.[40-46] This does not mean that

Table 1 TMS protocols

Study	Pathology domain	No. of patients	Stimulated area	Localization of the site	Type of coil (mm)	Type of stimulation	Hz	Offline/ online	Intensity	Train duration	Treatment duration (d)	Effect duration	Test
Cotelli et al[30]	AD	15	Left and right DLPFC/sham	Template MRI guiding	Double-70	rTMS	20	Online	90%MT	600 ms	—	—	Picture naming
Cotelli et al[19]	AD	24	Left and Right DLPFC/sham	Template MRI guiding	Double-70	rTMS	20	Online	90%MT	600 ms	—	—	Picture naming
Naeser et al[53]	Chronic aphasia (5-11 y ps)	4	Anterior portion of right Broca's homologue	Subject MRI guiding	Double-70	rTMS	1	Offline	90%MT	20 min	10	2 -8 mon	Picture naming
Finocchiaro et al[54]	Primary progressive aphasia	1	Left PFC/sham	6 cm anterior and 1 cm ventral to M1[a]	Double-45	rTMS	20	Offline	90%MT	∼5 min 10 trains of 2 s + 30 s ISI	5	45 d	Sentence-completion
Triggs et al[55]	Major depression	10	Left PFC	5 cm anterior to M1[a]	Double-70	rTMS	20	Offline	80%MT	25 min 50 trains of 2 s + 28 s ISI	10	3 mon	Oral word association task
Oliveri et al[58]	RBD extinction (1-4 mon ps)	14	Left and Right PFC and PC	10/20 EEG system[b]	Double-70	Single pulse	—	Online	110%MT	—	—	—	Bilateral tactile stimulation
Oliveri et al[59]	RBD extinction (1-12 mon ps)	8	Left PFC and PC	10/20 EEG system	Double-70	Single and paired pulse	—	Online	70%MT 130%MT	—	—	—	Bilateral tactile stimulation
Oliveri et al[61]	RBD neglect (1-48 wks ps)	7	PC/sham	10/20 EEG system	Double-70	rTMS	25	Online	115%MT	400 ms	—	—	Bisected line's length judgement
Brighina et al[60]	RBD neglect (3-5 mon ps)	3	Left posterior PC	10/20 EEG system	Double-45	rTMS	1	Offline	90%MT	15 min	14	15 d	Bisected line's length judgement
Shindo et al[62]	RBD neglect (6 mon ps)	2	Left PFC	10/20 EEG system	Double-70	rTMS	0.9	Offline	95%MT	∼17 min	6	2-6 wks	Behavioral Inattention Test
Rektorova et al[71]	CVD	7	Left DLPFC, left M1	5 cm anterior to M1[a]	Double-70	rTMS	10	Offline	100%MT	3 x ∼3 min 15 trains of 1s + 10 s ISI separated by 10 min	1	—	Psychomotor speed, executive function, memory
Sole-Padulles et al[67]	Elderly people with memory complains	40	Bilateral PFC /sham	5 cm anterior to M1[a]	Double cone coil	rTMS	5	Offline	80%MT	5 min 10 trains of 10 s + 20 s ISI	1	—	Associative memory task

AD = Alzheimer disease; DLPFC= dorsolateral prefrontal cortex; MRI = magnetic resonance imaging; rTMS = repetitive transcranial magnetic stimulation; MT = motor threshold; PFC = prefrontal cortex; M1 = primary motor cortex; ISI = interstimulu interval; RBD = right-brain damage with extinction; ps = poststroke; PC = parietal cortex; EEG = electroencephalogram; CVD = cerebrovascular disease and mild executive impairment; d = days; wks = weeks; mon = months; y = years.

[a] Functional identification of M1 for the first dorsal interosseous muscle in the left hemisphere.

[b] In a single patient an MRI was performed after TMS to verify the stimulated site.

both low and high frequencies have the same effects on cortical response, but rather that the effects are strictly correlated to the role of the stimulated cortex and its “activation state” during stimulation.[47] Therefore, we should keep separate the concept of inhibitory/excitatory-induced activity from detrimental/beneficial behavior because both types of activity can induce a beneficial effect. In particular, it has been proposed that in patients with unilateral hemispheric damage, in motor descending pathways, the homotopic contralateral area may be in a state of abnormally high activation and may exert an inhibitory effect on the damaged hemisphere.[48,49] In other words, a focal lesion, such as a stroke, may produce a state of hemispheric imbalance in some patients in the chronic stage. The hypothesis is that rTMS can be used to restore this disequilibrium by enhancing excitability in the ipsilesional motor areas or decreasing it in contralesional motor areas. This postulation is supported by neuroimaging studies in patients affected by stroke-induced aphasia showing a decrease of cortical blood flow in the language areas, as well as an abnormally increased activation of their right hemispheric homologues.[48,50,51] Martin et al[50] hypothesized that this activation was correlated with defective recovery of nonfluent aphasia.[34,35, 52,53] Therefore, the prediction was that the application of offline low-frequency stimulation over the right homologue of Broca area may result in an improved ability to name pictures. Four chronic aphasic patients were included in the study.[52,53] All of them were assigned to a low-frequency TMS treatment on anterior portion of right Broca’s homologue (Table 1). A significant improvement was observed in picture naming at 2 months post-rTMS, with lasting benefit at 8 months in three patients. No sham stimulation as control was used.

The complementary approach was applied on a single patient with a probable diagnosis of primary progressive aphasia.[54] High-frequency offline rTMS was applied to the left hemisphere, with the aim of inducing facilitation directly on the language areas (Table 1). After 5 days of stimulation to the left PFC, the patient’s performance improved for verb production, whereas 5 days of sham stimulation did not showed any beneficial effect. The beneficial effect lasted over the following month.

It is also noteworthy that one study[55] in depressed patients found a significant facilitation on oral word associations task after 2 weeks of high-frequency rTMS, on the left PFC (Table 1). But these data are probably because of a general unspecific effect related to a return to a premorbid baseline cognitive condition with remission of the depression.

In summary, these studies should be considered as preliminary, because of the low number of patients, the absence of critical control conditions and the amelioration of only restricted abilities, suggest the need for adopting a parsimonious view when evaluating the effects of TMS on language performance. Nevertheless, considering the potential benefit induced by TMS, that it is noninvasive and well-tolerated, further studies on large patient populations and with controlled sham or control TMS conditions are needed, to elucidate the possible roles for TMS in the treatment of language disorders caused by stroke or degenerative conditions.

Attention

Online studies

Enhancement of visual attention functions has been found in healthy subjects after stimulation of the parietal cortex.[14,56,57] RTMS can be seen in this area as a interventional tool in sensory extinction[58,59] or unilateral neglect[60-62] patients. Unilateral neglect can be defined as a defective ability to orient, detect, and report novel stimuli presented in the hemispace contralateral to the brain lesion, in which cannot be attributed to sensory-motor impairment functions (ie, hemianopsia or hemiplegia). The disorder usually follows right parietotemporal lesions. There are many interpretations of the physiopathologic mechanisms responsible for the neglect. One of the hypotheses is that unilateral neglect is the consequence of selective impairment of global attention inducing an imbalance in the control of the contralateral, generally left, hemispace.

A first study that used online single-pulse TMS, found improved performance during the execution of a tactile detection task in right brain-damaged patients (Table 1) with extinction.[58] TMS was applied to the left unaffected frontal, prefrontal, or parietal cortices, 40 milliseconds after a bilateral tactile stimulation. Only left frontal stimulation, as compared with other sites, significantly reduced extinction in these patients. In a following study[59] the same researchers, using single- and paired-pulse TMS in a group of right brain-damaged patients with extinction (1-12 months poststroke), found similar results but using different timing between tactile stimulation and TMS. It was found that parietal stimulation reduced the amount of extinction earlier (at 20-30 milliseconds) than frontal stimulation (40 milliseconds). Moreover, paired TMS at 1 millisecond of ISI improved the patients’ performance more than single-pulse TMS, whereas paired TMS at 10 milliseconds of ISI induced a decline of performance. In short, the authors demonstrated that it was possible to test the chronometry of these beneficial effects. These results can be explained as induction of transient inhibition of the unaffected hemisphere reducing the lesion-related interhemispheric attentional imbalance in analyzing the tactile stimuli. Along similar lines Oliveri et al[61] applied high-frequency rTMS over the unaffected parietal cortex of seven neglect patients. The trains started synchronously with the appearance of visual stimuli on the monitor that consisted of black horizontal lines bisected by a marker. After stimulus presentation patients made a forced-choice decision about the respective length of the two segments bisected by the marker with three response possibilities: equal, longer right, or longer left. The result showed that rTMS of the unaffected parietal site reduced contralateral neglect compared with sham or baseline condition. Nevertheless, amelioration was short lived.

Offline studies

The same task described before was also used to evaluate an offline protocol by Brighina et al[60] in three unilateral visual neglect patients (Table 1) using low-frequency rTMS. Patients were tested 15 days before, immediately preceding, at the end and 15 days after stimulation. rTMS induced a significant improvement of visuospatial peformance that persisted 15 days after. Finally, a similar study[62] tested the efficacy of low-frequency rTMS (Table 1) over the unaffected parietal cortex, in two unilateral visual neglect patients. Assessment of attention deficits were performed with the Behavioral Inattention Test and performance improved from 2-4 weeks after the end of rTMS treatment. At 6 weeks, the scores of this test still remained above pre-rTMS levels.

Overall, these results suggest that the hemispheric imbalance caused by unilateral brain damage can be diminished by distractive/inhibitory stimulation of the unaffected hemisphere, thus down-regulating the attentional imbalance characteristic of hemispatial neglect patients.

Even though these positive results are presented as evidence to support the use of this approach to treat attentional deficits, these studies should, nevertheless, be considered as preliminary because they are open label without controls or sham stimulation and with a low number of patients.

Memory

Many studies have used TMS, in healthy young subjects, during the execution of memory tasks.[63,64] Only a few of them have found facilitatory effects by using high-frequency online rTMS on working memory[20,65] or episodic memory formation.[66]

To the best of our knowledge, there is no published evidence of rTMS-induced ameliorations of memory deficits in patients with memory impairments. The memory changes associated with physiologic aging were the focus of an article by Solè-Padulles et al.[67] Using offline rTMS and functional magnetic resonance imaging (fMRI) in a group of elderly participants, they investigated the effects of rTMS on memory performance and brain activity. Between fMRI sessions, sham or real offline rTMS trains were applied randomly in a double-blind design. The use of a double cone allowed the stimulation of bilateral PFC. Trains of rTMS at high-frequency were used (Table 1). Behavioral improvement of recognition accuracy in an associative memory task (ie, association face-name) occurred only for subjects who received active, as opposed to sham, rTMS. The effect was associated with the recruitment of right PFC and bilateral posterior cortical regions, as indicated by the second fMRI session. Several fMRI studies have shown a reduction of the asymmetrical activation of PFC, during episodic memory tasks, in older adults compare with young subjects.[68,69] The results of an fMRI study suggest that high-performing older adults counteract age-related neural decline through plastic reorganization of the complex neural networks involved in encoding and retrieval of information. These include, besides the medial temporal regions, the prefrontal cortex.[68] Converging evidence of such reorganization also comes from an rTMS study of interference with the encoding and recognition of pictures.[70] The general idea is that some older subjects showing a performance comparable with that of young subjects are able to compensate for structural loss. These results can thus be interpreted as an rTMS induction of activation of areas, which were not recruited previously, to solve the task. The compensation mechanisms elicited by TMS may therefore result in a bilateral recruitment of PFC, counteracting structural loss as a form of "functional plasticity."

In conclusion, based on the currently available evidence, the use of TMS to improve memory performance in patients with memory impairments is still an important open field in which much basic work remains to be done.

Others domains

A positive effect on executive functions of offline rTMS has been reported in patients with cerebrovascular disease who have mild executive dysfunction.[71] High-frequency rTMS was applied either over the left PFC or over the left motor cortex (control stimulation site) in one of two sessions. Each patient participated in two stimulation sessions (days 1 and 4). A short battery of neuropsychologic tests was performed before and after each rTMS session. Psychomotor speed, executive function, and memory were evaluated. The only mild but significant stimulation site-specific effect of rTMS was observed in the Stroop interference results after the stimulation of PFC compare with baseline.[71] Evidence of this one session pilot study needs to be replicated in adequate clinical trials.

Transcranial direct current stimulation

At the end of the last century, another stimulation technique received renewed attention from the scientific community,[72,73] although knowledge of its existence and documentation of its clinical applications date back, at least, at the beginning of the 19th century.[74] This method relies on application of direct currents (DC) and is known as transcranial DC stimulation (tDCS).[73,75,76] Electrical currents are applied constantly at low intensities (1-2 mA) over a long period, usually in minutes (5-30 minutes), to achieve changes in cortical excitability by influencing spontaneous neural activity. In this respect, several studies on animal models[77-79] suggest that cathodal stimulation reduces spontaneous neuronal firing rates, whereas anodal stimulation has the opposite effect. Similar effects have also been shown in humans. Nitsche and Paulus[75] have found that cathodal polarization reduces motor cortex excitability, whereas anodal polarization increases it, and these changes, like those induced by rTMS, last beyond the end of stimulation. Excitatory anodal after effects,[80] measured in terms of MEP size, increase the need for longer stimulation than inhibitory cathodal after effects.[81]

In comparison with rTMS, tDCS has some advantages and disadvantages. The main advantages are that this is a simple, nonexpensive procedure, which is painless and allows inducing effects of opposite directions (facilitation or inhibition) on different parts of the brain. It has a reliable sham condition, therefore providing more robust double-blind clinical trials than TMS.[82] In addition, tDCS is a good tool to be used simultaneously with cognitive training as it induces much less scalp sensation than rTMS and therefore is not prey to aspecific effects on attention. The major limitation of tDCS is that it is less focal than TMS. DC is generally delivered over the scalp through relatively large electrodes (20-35 cm^2). Therefore, it is not focal enough to target localized areas and to map cognitive functions accurately. Recently, it has been demonstrated that by reducing electrode size, it can also be as focal as TMS,[83] although results in this trial showed a greater variability on motor cortical excitability compare with a trial that used larger electrodes.

Like rTMS, tDCS has been used to modulate cognitive performance in healthy subjects. The results shows that it is possible to produce interaction between task execution and stimulation, thereby reducing or improving subject performance, depending on the type of stimulation applied (anodal vs cathodal). Nitsche et al[81] showed that anodal polarization over the motor cortex speeds the implicit learning of a motor sequence or a visuomotor coordination task.[84] In a later study,[85] it was found that the same type of stimulation induced facilitation on a probabilistic learning task. Improved long-term memory consolidation for word pairs during sleep[86] or enhanced working memory;[87,88] interference with deception[89] have also been found.

Similar facilitatory effects were demonstrated in healthy subjects during language learning,[90] as well as in other language-related tasks such as verbal fluency[91] or picture naming,[92] and during performance of tactile discriminative tasks.[93] Nevertheless, like rTMS, it is clearly too simplistic to consider that anodal tDCS is beneficial and cathodal tDCS disruptive with regard to behavior in general. Other important factors such as the type of task, the site of application, the excitability status of the underlying cortical tissue, and the timing of stimulation are critical for the results. The effects might also depend on task characteristics as demonstrated by several studies.[84,94-96]

Recently, Monti et al[97] reported the effects of tDCS in chronic aphasia after stroke. Cathodal stimulation, applied to the left frontotemporal cortex of nonfluent aphasic patients (Table 2), resulted in a 34% improvement in the ability to name object pictures correctly[97] with no effects after anodal and sham stimulation. The authors suggested that the facilitatory effects on naming performance of the left-sided tDCS are due to the suppression of inhibitory interneurons in the lesioned hemisphere. The seemingly paradoxical improvement is in line with other findings on detectability of randomly moving dots. Here it was argued that unspecific cathodal inhibition of all cells involved increased the signal-to-noise ratio.[84]

The same group[98] investigated also the effects of tDCS in patients with AD (Table 2). Results showed that after anodal tDCS in temporoparietal areas, accuracy on a word recognition memory task increased, whereas after cathodal tDCS, it decreased and after sham tDCS it remained unchanged. The authors concluded that tDCS over the temporoparietal areas can specifically affect recognition memory performance in patients with AD.

The use of tDCS in cognitive neurorehabilitation is appealing. However, the data to date are insufficient to assess the therapeutic use of tDCS in cognitive rehabilitation.

General discussion

The effects induced by rTMS or tDCS stimulation on cortical function are complex. The observed behavioral modifications reflect changes in cortical activity, which are dependent on a number of variables, such as the frequency of stimulation, its polarity, duration, intensity, and the site of stimulation. Moreover, we should bear in mind that the brain does not react passively to cortical stimulation, but that the response depends on its state of activation. It has been shown that offline rTMS induces modulations of neuronal threshold, or even a rearrangement of synaptic efficiency, and these mechanisms are generally expressed as a form of functional plasticity or metaplasticity.[47,99,100] The effects of rTMS or tDCS may be related to the direct change of activity in the areas immediately underlying the stimulation site, or to the level of connected neural networks. Neuroimaging, (EEG), and sensitivity studies have shown that rTMS induces efficient, sometimes long-lasting modifications of cortical activity both locally[99,101-103] and at distant sites.[102-105] Anodal tDCS induces widespread changes in regional neuronal activity, measured by increased regional cerebral blood flow. This activity is present in many cortical and subcortical regions compared with cathodal tDCS[106] and it is related to an increase in the firing rates of spontaneously active cells. Therefore, there might be differences between the effects induced in

Table 2 tDCS protocols

Study	Pathology domain	No. of patients	Stimulated area	Localization of the site	Type of stimulation	Offline/online	Intensity and duration	Reference	Treatment duration (d)	Effect	Test
Monti et al[97]	Chronic aphasia (2-8 yps)	8	Left frontotemporal-(Broca) Occipital	10/20 EEG system	Anodal/cathodal/sham	Offline	2 mA 10 min	Right shoulder	1	Cathodal improved performance	Picture naming
Ferrucci et al[98]	AD	10	Temporoparietal	10/20 EEG system	Anodal/cathodal/sham	Offline	2 mA 10 min	Right shoulder	1	Anodal improved performance	Word recognition

ps = poststroke; AD = Alzheimer disease; EEG = electroencephalogram; sham = the stimulator was turned off after 10 seconds; d = days; y = years.

the brain by these two stimulation methods. All these aspects should be considered when interpreting the effects induced by cortical stimulation.

In addition, several studies[52,53,62] suggest that, in the case of cognitive disorders associated with unilateral hemispheric damage, different approaches of stimulation are effective. Therefore, they cannot only be used to up-regulate the excitability within the cortex of the lesioned hemisphere, but also to down-regulate the excitability in the contralateral intact hemisphere, resulting in an improvement of the damaged function (also see studies from the motor system[42,46,86,107,108]). The improved cognitive performance after rTMS/tDCS may be attributed to a suppression of interhemispheric inhibition. In this respect, it has been demonstrated that a rightward shift of language may be caused by a reduced transcallosal inhibition[109] of the language dominant left hemisphere. However, it is too soon to be prescriptive and many other combinations of interhemispheric interactions remain to be explored as a function of timing, task, frequency, initial state, and whether one hemisphere is stimulated or both are stimulated at different times. The use of rTMS/tDCS may disrupt an established, but behaviorally maladaptive pattern of brain activity, and thus provide an opportunity for the establishment of a new, more adaptive strategy, therefore pursing the network toward a new pattern of activation restoring interhemispheric equilibrium and resulting in the improvement of cognitive dysfunctions.

We should also consider that the goal of the treatment may not be to restore the functionality of impaired components, but rather to exploit the preserved abilities to compensate for the deficit. Instead of simple cortical stimulation, future applications will include combined rTMS/tDCS-induced modifications of cortical responsiveness with a specific cognitive training, like the approach used to improve motor performance in patients with hemiplegia.[46,110,111] It must be underlined that all these protocols are to be considered as additional treatment options and are not designed to replace conventional treatments.

To summarize, several possible mechanisms can account for the effects of TMS and tDCS on cognitive performance. They all reflect the potential of these methods to improve brain functions. In general, modifications of brain activity may be sufficient to assist the brain to relearn by inhibiting competing regions, facilitating local activity, or suppressing activity to promote changes. Taken together, all these data suggest that we could, theoretically, extend the general framework for using rTMS or tDCS presented here in pathologies that hinder cognitive functions.

Nevertheless, as mentioned previously, changes induced in cortical response are dependent on a number of technical variables. Although some of these parameters meet relative consensus in the scientific community as critical determinants, others are still subject of much debate, especially for tDCS because there are fewer studies present in literature. Moreover, it may be that given parameters that induce a clear result in a normal system lead to an opposite pattern of results in a pathologic system.

Previous results from depression trials[112,113] suggest that at least 4 weeks of treatment are necessary to achieve clinically meaningful benefits. Therefore, the duration of treatment remain a key point in further studies. RTMS or tDCS can be applied in combined protocols. Combining facilitation and inhibition effects for priming effects. So far there are no studies that used combined rTMS/tDCS-induced modifications of cortical responsiveness with traditional rehabilitation strategies. An additional possibility is to combine brain stimulation with drugs that can improve performance as an add-on treatment.[114-116]

Finally, the risk of rTMS use should be assessed carefully, and its dosage should generally be limited according to published safety guidelines[117] especially in stroke patients who are seizure prone. Safety issues should be considered also in using tDCS although there is no evidence that it induces side effects with current stimulation parameters,[82,91,118] but current density at cortical level may induce unforeseen consequences.[74,119]

The general conclusion is that TMS and tDCS promote exogenous plasticity that, combined with endogenous mechanisms, may prove to have a "potentiation effect" on the, generally modest, effects of cognitive rehabilitation. As this brief consensual overview shows, there is both a lot of promise and a lot of uncovered ground in the possibility of TMS and tDCS in rehabilitation. At this point in time, it is not possible to say which cognitive disorders are most likely to yield the optimal combination of brain stimulation and rehabilitation, but there can be no doubt that it is an area with foundations worth building upon.

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