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Review Article

Non-Invasive Brain Stimulation Techniques May Improve Language Recovery in Stroke Patients Modulating Neural Plasticity

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Abstract

The ability of the brain to reorganize connections functionally and structurally in response to experience is termed "plasticity". Non-invasive transcranial electrical or magnetic stimulation have been demonstrated to modulate neurons' activity in human brain. In the last two decades new neurophysiological tools such as repetitive transcranial magnetic stimulation and transcranial direct current stimulation have been used in experimental and clinical settings for studying physiology of the brain and modulating cortical activity. Depending on stimulation parameters, cortico-subcortical networks' activity might be enhanced, inhibited or modulated. On this basis, these techniques have been rapidly becoming valuable tools to investigate physiology of the human brain and have been applying to treat drug-resistant neurological and psychiatric diseases. Moreover these techniques have been used to boost efficacy of neurorehabilitation protocols improving outcome and reducing recovery time in stroke patients. On the basis of these results, non-invasive brain stimulation has been applied as add-on treatment in stroke patients with aphasia to enhance language performances and improve language capabilities. We describe these techniques and literature, review mechanisms of action that may explain the therapeutic effects and discuss the rationale for their using in clinical setting.

INTRODUCTION

The most intriguing skill of the brain is the ability to reorganize its connections functionally and structurally in response to changes in environmental experience and this capability is termed "plasticity" [1]. A key role in this process is played by synapses that are not static structures, but rather dynamic connections between neurons that are constantly changing in response to neural activity and other influences [2]. Memory storage is thought to depend on activity-dependent modifications in synaptic efficacy, such as LTD (long-term depression) and LTP (long-term potentiation). By these changes, synaptic transmission can be strengthened or weakened. Because the mechanisms underlying LTP and LTD are able to modify the strength of synapses for a long period of time, LTP and LTD are the most widely held candidate mechanism for learning and memory [3,4]. Mounting evidence suggests that synaptic plasticity plays a central role in adaptive changes and neural recovery after brain lesions [5,6]. Recently new neurophysiological tools such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) have been used in experimental and clinical settings for studying physiology of the brain and modulating cortical activity. These techniques use non-invasive transcranial electrical or magnetic stimulation to modulate neurons activity in human brain. Depending on stimulation parameters cortical stimulation might enhance or inhibit the activity of cortico-subcortical networks with variable effects [7-9]. On this basis, in the past two decades these techniques have rapidly become valuable tools to investigate physiology of the human brain [8], have been applied as adjunctive treatment for neurological and psychiatric diseases [10,11] and have been used in neurorehabilitation field

as adjunctive therapy in stroke patients [12] to boost efficacy of rehabilitation protocols improving outcome and reducing recovery time.

Non invasive brain stimulation techniques

Transcranial magnetic stimulation (TMS) is a useful tool to investigate in vivo human brain [9,13,14]. TMS has been also used as diagnostic and prognostic tool in different neurological diseases as dementia [15,16], stroke [17], movement disorders [18] and epilepsy [19]. When TMS is applied in a repetitive manner it can induce changes in cortical excitability that outlasts the period of stimulation [8,14,20] and it is called rTMS.

rTMS is a stimulation protocol of the TMS and it has been used to investigate human cortical excitability and short-term synaptic plasticity [7]. The frequency-dependence of the outcome of repetitive TMS closely resembles the frequency-response function observed with tetanic stimulation of the Schaffer collateral projection to area CA1 of the rat hippocampus [21].

Transcranial direct current stimulation (tDCS) uses weak constant direct currents delivered by an active anode or cathode placed on the scalp over a targeted cortical area with a reference electrode over the contralateral forehead. Polarizing currents are able to cross the skull for inducing sustained changes in membrane potential and excitability of cortical cells and fibers that outlast the stimulation period [22]. For these features, rTMS and tDCS have been introduced in experimental and clinical settings for studying the physiology of the human brain and modulating cortical activity [8,14,20]. An interesting theory is that the effects of rTMS and tDCS on the brain are LTD- or LTP-like phenomena and duration of the effects seems to trigger changes in synaptic plasticity [7]. These non-invasive techniques of transcranial stimulation have advanced our knowledge of the physiology of human motor cortex and also have been used for modulating activity of the human brain.

Cortical stimulation may enhance, inhibit or otherwise interfere with the activity of different cortico-subcortical networks, depending on stimulus frequency and intensity, current polarity [23], and configuration of the induced electric field [24]; these functional and clinical effects occur during or beyond the time of stimulation [25,26].

tDCS and rTMS are the most used and promising tools to investigate in vivo human cortex by stimulating and modulating cortical activity and these effects may have clinical and therapeutic relevance [10,27-29].

General principles of TMS and rTMS

TMS is a non-invasive technique based on Faraday's principle of electromagnetic induction, consisting in the passage of a brief, high-intensity current pulse in a coil of wire, which in turn produces a magnetic field that can reach up to about 2 Tesla and lasts for about 100 ms. When the magnetic field enters the brain, it generates an electric field and this induced current is able to excite neural circuits. The motor cortex can be activated by TMS producing excitatory and inhibitory phenomena in muscles controlled by the activated cortical areas [30]. The first TMS devices for clinical use were built in the mid-eighties [31].

TMS allows in vivo cortical activity and connectivity evaluation and underlying mechanisms are not completely understood; moreover the complexity of the interactions between induced currents and neural circuits in vivo, circadian rhythm, hormonal cycles and genetic polymorphisms might determine the variability of effects showed among subjects [32,33]. Specific stimulation protocols, called paired stimulation, have been used to study intracortical circuits. In paired stimulation two magnetic stimuli or a magnetic and an electrical stimulus, are given paired at short or long interval between stimuli [30] and these protocols are named in accordance to stimulus or intervals used as: short latency intracortical inhibition, long latency intracortical inhibition, afferent inhibition, intracortical facilitation and have been demonstrated to activate specific neurotransmitter systems such as glutamatergic, cholinergic and GABAergic circuits [15,34,35]. When a coil is used to deliver a repetitive stimulation it is able to induce changes in cortical activity that outlast period of stimulation and depending on frequency and stimulation pattern [24] it may enhance (usually high-frequency stimulation) or reduce (low-frequency stimulation) cortical excitability. In the original low frequency study, supra-threshold stimulation at 0.9 Hz for 15 minutes reduced MEP amplitudes for 15 minutes after the period of stimulation [36]. The pattern of modulation and duration of effects depend on many factors, but in general it has been noted that low frequency stimulation (0.2 – 2 Hz) results in a reduction in excitability whereas high frequency (5 – 25 Hz) results in an increase [7]. Moreover a different repetitive magnetic stimulation protocol called theta burst stimulation (TBS) has been used to induce cortical lasting effects. Patterns of TBS consist of a total of 600 pulses at an intensity of 80% active motor threshold. The basic element of all of these patterns is a burst of 3 stimuli at 50 Hz (i. e. , 20 ms between each stimulus), which is repeated at intervals of 200 ms (i. e. , 5 Hz). These patterns are known as continuous TBS (cTBS) and intermittent TBS (iTBS). cTBS has been demonstrated to reduce cortical excitability whereas iTBS enhances it [37]. Different patterned protocols are also been described such as low intensity paired pulse rTMS [38] or high intensity paired-pulse rTMS [39]. rTMS can also be coupled with peripheral median nerve stimulation in order to obtain an "hebbian-like" form of plasticity in the so-called paired associative stimulation (PAS) protocols [40]. It is also possible to revert the effects of PAS, changing the time interval between peripheral and cortical stimuli: when peripheral stimulus is delivered 25 ms before the TMS this form of repetitive stimulation increases cortical excitability, but if the time interval is 10 ms a reduction in cortical excitability has been observed [41].

General principles of tDCS

Differently from TMS that uses magnetic fields, in tDCS weak electric currents (below the perceptual threshold, 1 to 2 mA) are used. tDCS consists in a weak constant direct current delivered by an active anode or cathode placed on the scalp over a targeted cortical area with a reference electrode over the contralateral forehead. Usually a battery-driven portable stimulator is used. tDCS modulates cortical excitability by weak electric fields in the form of direct current brain polarization [42]. During tDCS, low amplitude direct currents are applied via scalp electrodes

and partially penetrate the skull to enter the brain. Polarizing currents, able to cross the skull, can induce sustained changes in membrane potential and excitability of cortical cells and fibers that outlast the stimulation [22]. First studies about stimulation using weak currents date back in 1960-1970. In those studies researchers evaluated effects of currents in human and animal stimulation. Animal studies demonstrated effects on the spontaneous activity and evoked response of neurons [43,44].

tDCS has recently been introduced also as a tool to modulate non-invasively the activity of intact human brain and several studies described potential therapeutic effects in some neurological diseases [29,45,46]. Neurobiological mechanisms underlying tDCS effects are not completely defined yet, but some studies explored this topic in animal models [47] and *in vivo* in humans [23] demonstrating that polarity might induce different changes in cortical excitability: anodal tDCS may increase excitability while cathodal tDCS may have opposite effects [23]. rTMS and tDCS are quite different techniques not only because use different fields (magnetic and electric) but also for their effects. tDCS is a neuromodulator tool because of a low-intensity induced electric field whereas rTMS is both a neurostimulator and neuromodulator tool depending on intensity of stimulation (below motor threshold or above) and frequency of induced magnetic field [25]. Moreover, tDCS and rTMS have another important difference about the accuracy of the stimulation. tDCS produces a wide electric field whereas rTMS, using focal coil, may produce a more focal stimulation [9].

NIBS techniques may support neuroplasticity

Substantial evidence suggests that synaptic plasticity plays a central role in adaptive changes associated with learning, memory and recovery after injuries of CNS as stroke [6]. Although a direct link between rTMS, tDCS and synaptic plasticity has not been demonstrated yet, several evidences suggest that rTMS and tDCS effects may reflect a form of plasticity inducing changes in synaptic strength depending on genetic background: studies regarding genetic polymorphisms showed that interindividual differences in NMDA receptor and BDNF might influence the responsiveness of cortical excitability and plasticity to NIBS techniques [20,33,48,49]. Moreover, merging neurophysiologic studies with drugs studies new insights have been found in understanding mechanisms underlying TMS effects. Memantine can block the after-effect of intermittent Theta Bust Stimulation (iTBS) suggesting that the effects of iTBS rely on NMDA-receptor potentiation [37]. The after effects of tDCS on motor evoked potentials (MEPs) are abolished for both anodal and cathodal polarities using NMDA receptor antagonists, such as dextromethorphan [23]. On the other hand, specific drugs may disrupt or block neuromodulatory effects [23,50]. Altogether these studies demonstrate that NIBS acts on neuroplasticity and shares at least some common pathways with LTD and LTP processes. Given the central role of neuroplasticity in learning and in functional recovery after CNS damages and considering LTP- and LTD-like effects of NIBS [7,51] there is a basis for therapeutic use of NIBS as add on treatment for rehabilitation protocols enhancing physiological plasticity, boosting functional recovery and improving outcome [17].

NIBS in aphasia

Stroke is the main cause of severe long-term disability in western industrialized country [52] and impairment, mainly when left hemisphere is involved, may affect language capabilities. Despite of recent developments in acute stroke therapy mostly due to intravenous and intra-arterial thrombolysis [53,54], the most part of stroke patients have been facing the burden of stroke consequences. Aphasia is a common consequence of stroke that typically results from injury to an extended network of cortical and subcortical structures perfused by the middle cerebral artery in the left hemisphere and determines several impairments in the ability to speak, understand, repeat, write and read differ from patient to patient [55].

NIBS has been used during language tasks to evaluate language areas location and using several protocols the effects on language performances such as naming performance, verbal reaction time and attentive tasks. Repetitive TMS has been used for studying language function in normal subjects mainly through disruption paradigms [56-58], interestingly picture-naming latencies can be facilitated in normal subjects with both suprathreshold single pulse TMS [59] and rTMS over Wernicke's area [60]. Several studies assessed effects of tDCS in normal subjects, stimulating DLPFC e Broca's area in frontal lobe and evaluating different language parameters such as verbal fluency naming performance and verbal reaction times [61,62]. A brief review on protocols and effects of NIBS on language tasks in healthy subjects is reported in table 1.

On the basis of these effects described in healthy subjects, NIBS has been applied in aphasic patients to promote recovery and enhance residual language capabilities.

Recent studies about neurophysiological and clinical effects of rTMS and tDCS on language tasks in aphasic patients are summarized in tables 2 and 3.

A number of factors have been shown to influence aphasia recovery, including lesion site and size, and the existence of prior strokes [63]. Acute stroke patients with aphasia show some degree of spontaneous recovery, most notably during the first 2–3 months following stroke onset [64], however, the majority of patients with post-stroke aphasia have chronic deficit for which current rehabilitative treatments are only marginally effective [65].

Several explanations on the physiological basis of the language recovery after stroke have been proposed. Current evidence suggests that changes in neural activity after stroke may be most relevant for aphasia recovery and in particular 3 patterns might concur for recovery: (a) recruitment of lesioned or perilesional regions for language-related tasks, (b) acquisition, unmasking or refinement of language processing ability in the non-dominant hemisphere, and (c) dysfunctional activation of the non-dominant hemisphere that may interfere with language recovery [66]. As proposed for motor control after unilateral brain lesion, affected hemisphere may influence unaffected hemisphere determining a worse performance by a rivalry mechanism [19]. Studies with fMRI have showed over-activation of the right hemisphere homologue in patient with a left hemisphere stroke [67-69]. This kind of over-activation would represent a consequence of

Table 1: NIBS on language tasks in normal subjects.

Authors	Protocol	Experiment	N. of subjects	Clinical effects
Hoffman et al. 2010	Offline rTMS: 1 session, 10 minutes, 600 pulses, 1 HZ, 120% RMT, left VLPFC	Synonyms and numbers judgment tasks	13	rTMS to left VLPFC slowed comprehension of abstract words but only when these were presented without contextual cues
Pobric et al. 2010	Offline TMS: 1 session, 10 minutes, 600 pulses, 1 HZ, 120% RMT, left ATL, left IPL, OL	Semantic tasks: living versus nonliving items, low- versus high-manipulable objects	9	Stimulation over ATL generates a category general effect (slowing the naming of both living and nonliving items and of both sets of man-made items), left IPL stimulation generates a category-specific effect (slowing responses only for nonliving items and for high-manipulable items), TMS over OL has no significant effects on naming times
Holland et al. 2010	Offline rTMS: 1 session, 10 minutes, 600 pulses, 1 HZ, 120% RMT, left ATL	Generation past tense of English verbs	12	rTMS over left ATL leads to a relative slowing of elicitation times for irregular verbs, but speeds up elicitation times for regular and novel verbs
Pobric et al. 2009	Offline rTMS: 1session, 10 minutes, 600 pulses, 1Hz, 120% RMT, left ATL, right ATL, OL	Semantic task (word semantic association vs picture semantic association)	10	rTMS significantly slows performance for both the picture association task and the word association task, over either the right or the left ATL
Pobric et al. 2009	Offline rTMS:2 session, 10 minutes,600 pulses, 1 Hz, 120%RMT,right and left TP	Synonym and number judgment tasks	12	Stimulation of either right or left TP increases RT on a semantic task; stimulation of left TP significantly impaired performance for medium and low imageability items, right TP stimulation also impaired performance for low imageability items
Pobric et al.2007	Offline rTMS:1 session, 10 minutes, 600 pulses, 1 HZ, 120%RMT, left ATL	Basic and specific naming tasks, synonym and number judgment tasks	12	rTMS over left ATL significantly increases naming latencies for a specific naming-level naming task but not for number naming and it slows synonym judgment times but not number quantity decision
Cattaneo et al. 2011	tDCS: anodal/sham: 1 session, 20 minutes, 1 mA, left Broca's area	Phonemic and semantic tasks	10	tDCS over Broca's area improves semantic and phonemic fluency
de Vries et al. 2009	tDCS: anodal/sham, 1 session, 20 minutes,1 mA, left Broca's area	2 phases: an acquisition phase and a classification phase; an additional control over a different area	48	tDCS over Broca's area does not enhance working memory but enhances implicit learning of an artificial grammar, especially it improves ability to recognize syntactic violations

Abbreviations: **RMT**: rest motor threshold, **VLPFC**: ventrolateral prefrontal cortex; **ATL**: anterior temporal lobe; **IPL**: inferior parietal lobule; **OL**: occipital lobe; **TP**: temporal pole; **RT**: response time.

Table 2: rTMS studies in aphasic patients.

Authors	Protocol	Stroke type	N. of patients	Clinical effects
Waldowski et al. 2012	rTMS/sham: 15 sessions,5 days/week, 30 minutes, 1 Hz, 90% RMT, right IFG	Ischemic stroke	26 subacute patients	Both groups improve, but no differences are noted between the rTMS and sham stimulation groups
Szaflarski et al. 2011	iTBS: 10 sessions (5days/week), 600 pulses, 80% AMT, left Broca's area	Ischemic stroke	8 chronic patients	iTBS improves semantic fluency for 6 out of 8 aphasics
Naeser et al. 2011	rTMS: 10 sessions: 5days/week, 20 minutes,1 HZ, 90% RMT, 4sites:right PTr, right POp, M1, right posterior STG	Ischemic and hemorrhagic stroke	8 chronic patients	Suppression of right PTr improves picture naming and decreases RT; Suppression of right POp leads to a significant increase in RT
Barwood et al. 2010	rTMS: real/sham; 10 sessions, 1200 pulses,1 HZ, 90% RMT, 20 minutes, right PTr	Ischemic stroke	12 chronic patients	rTMS modulates N400 event-related brain potentials 2 months post stimulation, but not 1 week post stimulation
Hamilton et al. 2010	rTMS: 10 sessions: 5days/week; 600 pulses,10 minutes, 1 Hz, 90% MT, ROI determined by stimulation of multiple targets, right PTr selected	Ischemic stroke	1 chronic patient	rTMS improves object and action naming; benefits persist at 2,6 and 10 months
Kakuda et al. 2010	rTMS:10 session over 6 consecutive days; 1200 pulses, 20 minutes, 1 HZ, 90%MT; ROI determined by fMRI activation during naming tasks: left frontal and right frontal lobe	Ischemic and hemorrhagic stroke	6 chronic patients	Presumed improvement in WAB, SLTA, and SLTA-ST (no statistical analyses)
Martin et al. 2009	rTMS: 10 sessions: 5 days/week, 20 minutes, 1 Hz, 90% MT; ROI determined by stimulation of multiple targets, r PTr selected	Ischemic stroke	2 chronic patients	1Good responder: improvement on BNT,BDAE, cookie Theft, new perilesional left frontal activation fMRI 16 months post-TMS; 1 poor responder: no significant language improvement or fMRI changes
Naeser et al. 2005	rTMS:10 sessions: 5days/week, 20 minutes, 1Hz, 90% MT, right PTr	Hemorrhagic stroke	1 chronic patient	Improvements in BNT, animal and tool implement subtests of BDAE; improvement persists 2 and 8 months post-rTMS
Naeser et al. 2005	rTMS:10 sessions: 5 days/week; 1200 pulses, 20 minutes, 1Hz, 90% MT, right PTr	Ischemic Stroke	4 chronic patients	Improved accuracy and speeded reaction time for S&V items after 10 TMS sessions; improvement on BNT and Animal and Tool/implement subtests of BDAE 2 and 8 months after stimulation

Abbreviations: **RMT**: rest motor threshold; **AMT**: active motor threshold; **IFG**: inferior frontal gyrus; **PTr**: pars triangularis, **POp**: pars opercularis; **M1**: motor cortex mouth area; **STG**: superior temporal gyrus; **ROI**: region of interest; **RT**: response time; **WAB**: western aphasia battery; **SLTA:** standard language test of aphasia**; SLTA-ST**: supplementary test of SLTA; **BNT:** Boston naming test**; BDAE**: Boston diagnostic aphasia exam; **S&V**: Snodgrass and Vanderwart

Table 3: tDCS studies in aphasic patients.

Authors	tDCS protocol	Stroke Type	N. of patients	Clinical effects
Jung et al. 2011	Cathodal tDCS: 10 sessions, 20 minutes, 1mA intensity, right IFG	Ischemic and hemorrhagic stroke	37 subacute and chronic patients	tDCS improves the aphasia quotient; better results in fluent aphasic patients whose treatment begins within after 30 days after stroke
Vines et al. 2011	tDCS: anodal/sham, 2 series of 3 days/week, 20 minutes, 1,2 mA, right IFG; stimulation overlapped with a 20-min session of MIT	Ischemic stroke	6 chronic patients	anodal-tDCS improves fluency of speech
Marangolo et al. 2011	tDCS: anodal/sham; 10 sessions:5 days/week; 20 minutes, 1mA; left IFG	Ischemic and hemorrhagic stroke	3 chronic patients	tDCS increases accuracy both in sham and anodal condition, but the effect persists only after anodal condition
Dae Sang You et al. 2011	tDCS: anodal/cathodal/sham: 10 sessions : 5days/week;30 minutes,2 mA; anodal:left STG, cathodal: right STG	Ischemic stroke	33 subacute patients	Cathodal tDCS improves auditory verbal comprehension more than anodal and sham
Fridriksson et al. 2011	tDCS: anodal/sham;10 sessions:5days/week, 20 minutes, 1 mA , left posterior cortex	Not specified	8 chronic patients	Anodal tDCS reduces reaction time, the effect persists for 3 weeks after treatment
Baker et al. 2010	tDCS: anodal/sham; 10 sessions: 5 days/ week,20 minutes,1mA, left frontal cortex	Not specified	10 chronic patients	Anodal tDCS increases accuracy
Monti et al. 2008	tDCS:anodal/cathodal/sham: single session, 10 minutes, 2 mA, left frontotemporal cortex	Ischemic and hemorrhagic stroke	8 chronic patients	Cathodal tDCS improves accuracy of the picture naming tasks

Abbreviations: IFG: inferior frontal gyrus; **MIT**: melodic intonation therapy; **STG**: superior temporal gyrus

transcallosal disinhibition of the healthy hemisphere which would lead to its aberrant reorganization with "maladaptive" plasticity, which prevents recovery from aphasia [70]. Basically the right hemisphere undergoes changing resulting from the damage occurring in the controlateral one. Experimental data suggest that brain reorganization during language recovery proceeds in three phases: a strongly reduced activation of remaining left language areas in the acute phase is followed by an up-regulation with recruitment of homologue language zones, which correlates with language improvement. Thereafter, a normalization of activation is observed, possibly reflecting consolidation in the language system [71].

The reactivation of undamaged network areas of the left hemisphere usually leads to better long-term outcomes than the activation of homotopic contralateral regions [72]. Restoration of language-related networks in the damaged left hemisphere is crucial for language improvement among non-fluent aphasic patients who undergo speech therapy [73]. This is in line with functional imaging studies which have demonstrated that better functional outcome in aphasia recovery is associated with greater activation of the left hemisphere networks [74]. These and other studies suggest that reactivating or enhancing activity of networks of the affected left lobe are more important than recruitment of the right lobe [71,73,74]. The first study investigating tDCS on damaged frontotemporal areas in chronic non-fluent aphasic patients demonstrated an improving of the accuracy in picture-naming task of cathodal stimulation, while anodal and sham tDCS failed to improving naming abilities [75]. Overall these studies confirm that the functions of the left impaired lobe improve language abilities, while others argue that the hyperactivation of the right lobe would represent inefficient mechanism of language production and a form of maladaptive strategy.

CONCLUSION

Transcranial stimulation performed in accordance to international standard did not show relevant safety issues [76], however, mechanisms underlying the effects of rTMS and tDCS on language and recovery are different and not completely understood. A recent review summarized studies evaluating the effects of tDCS but several studies are "proof of principles" studies and small groups of patients were studied. No side effects were reported and a potential beneficial effect in improving language tasks were noted [77]. The differences among NIBS techniques, in terms of stimulation sites and neuronal activation, make results not completely comparable. Moreover neuronal structures activated by rTMS and tDCS are different and results about the development of LTP and LTD processes are not interchangeable [7,8,47]. This might be due to different cortical areas stimulated or different currents and protocols used. For instance, tDCS polarization is considered as a technique of neuromodulation, producing changes in membrane potential of axons, while rTMS is a technique of neurostimulation, eliciting propagated trains of action potentials [25]. Overall these studies encourage about the usefulness of NIBS on language recovery after brain injury, although relatively transient effects have been noted. Conceivably in next future, better understanding neural basis of NIBS, more specific and durable protocols might be developed that may be used as add-on therapy for rehabilitation and may improve recovery enhancing language capabilities.

PERSPECTIVES

Some mechanisms underlying neuromodulatory effects induced by these neurophysiological tools are not fully understood and it is a mandatory step to reveal their full potential as new therapeutical tools. Moreover it is conceivable that complementary effects may be discovered improving current protocols. In next few years hopefully mechanisms underlying the effects of rTMS and tDCS will be better defined spreading their use in clinical setting. However further studies are needed to elucidate the most effective strategies, the most useful protocol and which patients could benefit from a single tool or both. Whether these neurophysiological approaches might improve aphasia or language performances effectively should be proved by well-designed clinical trials. Based on currently available data, we speculate that therapies targeting synaptic processes have clinical potential and neurophysiological approaches deserve further explorations. Interindividual differences in TMS susceptibility, which seem to depend on a number of technical

as well as biological factors have been reported [20,33,48,49]. Genetic state might be a key point in future studies because it might influence individual response to neuromodulatory techniques. Probably genes involved in neuroplasticity processes might influence individual responses and their discovering might be helpful to forecast individual responsiveness to specific protocols. Furthermore, brain reorganization after stroke is a dynamic process, which considerably differs across patients, depending on lesion location, time since stroke, severity of functional impairment, comorbidity, age and even genetics. All these factors make unlikely that one stimulation protocol might be suitable for all patients. It is possible that surrogate markers obtained by neuroimaging may help to identify patients responsive to specific stimulation paradigms [78,79]. Better understanding molecular and neuronal mechanisms underlying LTP- and LTD-like phenomena produced by rTMS and tDCS hopefully in next future will make available new and more effective stimulation protocols capable of long-lasting and clinically relevant effects.

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