Neuroplasticity in post-stroke gait recovery and noninvasive brain stimulation

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Abstract

Gait disorders drastically affect the quality of life of stroke survivors, making post-stroke rehabilitation an important research focus. Noninvasive brain stimulation has potential in facilitating neuroplasticity and improving post-stroke gait impairment. However, a large inter-individual variability in the response to noninvasive brain stimulation interventions has been increasingly recognized. We first review the neurophysiology of human gait and post-stroke neuroplasticity for gait recovery, and then discuss how noninvasive brain stimulation techniques could be utilized to enhance gait recovery. While post-stroke neuroplasticity for gait recovery is characterized by use-dependent plasticity, it evolves over time, is idiosyncratic, and may develop maladaptive elements. Furthermore, noninvasive brain stimulation has limited reach capability and is facilitative-only in nature. Therefore, we recommend that noninvasive brain stimulation be used adjunctively with rehabilitation training and other concurrent neuroplasticity facilitation techniques. Additionally, when noninvasive brain stimulation is applied for the rehabilitation of gait impairment in stroke survivors, stimulation montages should be customized according to the specific types of neuroplasticity found in each individual. This could be done using multiple mapping techniques.

Key Words: nerve regeneration; stroke; cerebrovascular disorders; transcranial magnetic stimulation; neuroplasticity; transcranial direct current stimulation; electrical stimulation therapy; gait; walking; gait disorders; rehabilitation; neural regeneration

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Introduction

The American Heart Association estimates that approximately 795,000 individuals in the United States have a stroke each year (Go et al., 2014). A lack of mobility is the main obstacle for stroke survivors seeking to regain daily living independence and social integration. Thus, restoring impaired gait is one of the major goals of post-stroke rehabilitation.

Recently, traditional rehabilitation techniques have been augmented by the use of a new methodology, noninvasive brain stimulation (NIBS), which facilitates neuroplasticity. To better understand the use of NIBS, this paper reviews literature regarding the neurophysiology of human gait, post-stroke neuroplasticity in the motor control system underlying gait, and finally, approaches for using NIBS to enhance gait recovery.

Neurophysiology of Human Gait

Involvement of the cerebral cortices

In functional neuroimaging studies of human walking, the premotor cortex (PMC) and the supplementary motor cortex (SMC) are activated prior to step onset (Huppert et al., 2013). However, lesions in these two areas often lead to problems with gait initiation and the negotiation of narrow passages (Jahn et al., 2004), indicating their importance in the initiation and planning of walking. Furthermore, corticospinal inputs significantly facilitate muscular responses in the lower limbs, especially during the swing phase of the step cycle (Pijnappels et al., 1998). These observations suggest that cortical outputs play a critical role in the modulation of lower limb locomotion.

The cerebral cortices are also involved in making adjust-
ments during walking. For instance, when vision and proprioceptive inputs degrade during walking (e.g., switching from a lighted fixed floor to a dark sway-referenced floor), bilateral temporal-parietal areas are activated (Karim et al., 2013). If, in this condition, experimental participants lose their balance, more cortices, such as the anterior parietal, anterior cingulate, and parietal cortices, are activated (Sipp et al., 2013). These results suggest that the cerebral cortices closely monitor posture and balance during walking. Furthermore, there is evidence that the SMC and PMC are implicated in anticipatory postural adjustments made while walking, which work to maintain equilibrium by counteracting the destabilizing effect induced by expected perturbations (Takahusaki et al., 2001; Chang et al., 2010). When dealing with unfamiliar circumstances or overcoming obstacles, multiple cerebral cortices, such as the PMC, SMC, and temporoparietal-posterior parietal cortices, may work closely to integrate different senses and inputs so that adjustments can be made promptly and properly (Takahusaki, 2013).

Nonetheless, the aforementioned observations do not necessarily indicate that supraspinal outputs directly control the locomotion of walking. For example, transcranial magnetic stimulation (TMS) pulses, delivered at various phases of the step cycle, have no effect on the timing or duration of phasic tibialis anterior EMG bursts, suggesting that the cerebral cortices do not have a direct influence on muscle activities (Capaday et al., 1999). Instead, it is more likely that supraspinal neurons regulate the synergy of walking, rather than participate directly in controlling the locomotion of the lower limbs (Krouchev and Drew, 2013).

Involvement of the subcortical regions and spinal cord

For subcortical control of human gait, the locomotor region, located in the mid-brain, and the reticular formation, located in the ventromedial medulla, generate and maintain the rhythm of walking (Takahusaki, 2013). After receiving proprioceptive feedback that is integrated and distributed by the cerebral, vestibular somatosensory cortex, and basal ganglion, these two aforementioned brain stem regions signal to motor neurons in the spinal cord to initiate the switch between the swing phase and the stance phase (Martinez et al., 2012). The reticular formation in the brain stem also distributes facilitative or inhibitory information from the cortex, basal ganglion, and cerebellum through descending pathways, which automatically modulates posture and muscle tone during walking (Takahusaki et al., 2004; Takahusaki, 2013). Therefore, in the hierarchical control system underlying human walking, subcortical regions work more as secondary command centers than as relay stations, and are especially responsible for the control of automated locomotion during walking.

Animal studies have demonstrated that the spinal cord also has a subprime control center that regulates walking, which appears to be a network of nerve cells called central pattern generators (CPGs). With modulation from the supraspinal descending pathways, the CPGs organize the activities of motor neurons so that the agonists and antagonists are excited alternately and are reciprocally balanced (Boothe et al., 2013). In this way, the CPGs drive the rhythmic movements of the limbs. Based on the observation that human infants exhibit stepping behavior even before birth, that is, prior to descending corticospinal fiber myelination (Ivanenko et al., 2013), it seems likely that human beings have CPGs in the spinal cord as well. This extrapolation is also supported by reports of patients who can walk despite complete lateral corticospinal tract injuries (Ahn et al., 2006). Simultaneously, these reports also suggest that spinal cord CPGs can work, to some extent, independently from supraspinal control.

Post-stroke Neuroplasticity in the Motor Control System Underlying Human Gait

The adult brain retains the capability to reorganize itself under conditions of peripheral stimulation, learning, and injury (including stroke), through a process known as neuroplasticity. To date, post-stroke neuroplastic reorganization has been verified at levels ranging from synapses and neurons to brain networks. This has been confirmed in both animal models and humans (Clarkson et al., 2013; Karabanov et al., 2013), and is increasingly recognized as a critical driving force of post-stroke motor recovery. Some characteristics and mechanisms of post-stroke neuroplasticity in the motor control system underlying human gait are as follows:

Comprehensive neuroplastic reorganization

Using fMRI, researchers have found that post-stroke motor recovery of a paretic lower limb is associated with hyperactivation in multiple brain regions, including those in the contralateral hemisphere. Such regions may include the bilateral M1 cortex, secondary somatosensory cortices, SMC, PMC, cingulate gyrus, cerebellum, and thalamus (Luft et al., 2005; Enzinger et al., 2008). These results are consistent with those obtained using fNIRS (Miyai et al., 2003) or TMS during walking (Yang et al., 2010), and with the results of fMRI connectivity analyses that do not require movement to activate the cortices during examination (Jang et al., 2013). Furthermore, a strong correlation has been documented between the hyperactivation of these brain areas and walking improvement (Enzinger et al., 2009; Yang et al., 2010). Thus, these comprehensive instances of post-stroke hyperactivation are not likely to be merely a reflection of unmasked interhemispheric or intrahemispheric inhibition.

Increased activity has also been observed in subcortical structures during the recovery of walking after a stroke. For example, researchers examined a group of chronic stroke patients who could walk independently using diffusion tensor imaging. They found increased fractional anisotropy values corresponding to the ipsilesional pedunculopontine nuclei, which is part of the mid-brain locomotor region (Takahusaki et al., 2004), that were positively correlated with the degree of walking recovery (Yeo et al., 2011). Such increased activation has also been reported in the cerebellum and midbrain (Luft et al., 2008). Furthermore, analyses of muscular EMG activities in the lower limbs of post-stroke patients during hip or knee movement unveiled reflex-mediated cou-
plunging between the rectus femoris and hip adductors (Finley et al., 2008), indicating that neuromuscular reorganization is processed in the spinal cord after stroke. Several important studies have identified comprehensive post-stroke neuroplasticity for gait recovery, as summarized in Table 1.

### Temporally dynamic neuroplastic reorganization

A longitudinal fMRI investigation of 10 stroke patients revealed that paretic lower limb movement-triggered activation of the M1 cortex was initially prominent in the contralesional hemisphere after stroke. However, the original prominent activation pattern in the ipsilesional hemisphere was gradually restored over time. Additionally, the timing of this transition was correlated with the recovery of walking in these patients (Kim et al., 2006). Another investigation further demonstrated that appropriate gait training promotes this activation shift in somatotopic representations (Miyai et al., 2003). These observations provide insight into the temporal dynamics of post-stroke neuroplastic reorganization in the motor control system underlying walking.

The temporal dynamics of neuroplastic reorganization appear to be driven mainly by a dynamic imbalance in neuronal excitability that lies between the affected brain areas and those regions with which they have functional connections. After a stroke, the interhemispheric inhibition between the affected lesion and contralesional hemisphere is destroyed, and so sequential hyperactivation of the latter region may, in turn, suppress the excitability of the perilesional neurons (Manganotti et al., 2008; Clarkson et al., 2010). However, the excitability of perilesional neurons generally recovers, and may even exceed normal levels approximately 8 weeks after a stroke, according to observations from a mouse stroke model (Brown et al., 2009). Furthermore, the inhibitory strength from the contralateral hemisphere decreases over time (Kim et al., 2014; Takechi et al., 2014). These dynamic differences in excitability facilitate the unmasking of silent synapses, the formation of new synapses, and help adjust the threshold of selectivity in neuronal processing, thus allowing neurons

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Table 1: Studies identified with post-stroke comprehensive neuroplasticity for gait recovery

<table>
<thead>
<tr>
<th>Authors &amp; year</th>
<th>Patients (n)</th>
<th>Techniques used</th>
<th>Eliciting activity</th>
<th>Findings</th>
<th>Site of neuroplasticity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luft et al., 2005</td>
<td>31 Chronic ischemic stroke (9 cortical, 12 subcortical, 10 brainstem lesions)</td>
<td>BOLD-weighted fMRI</td>
<td>Knee movement</td>
<td>Ipsilateral thalamus, S2, and cingulate gyrus were activated in patients with cortical stroke. Contralateral leg M1, SMA, PMC, and thalamus, as well as ipsilateral S2 were activated in patients with brainstem stroke. Bilateral leg M1, SMA, supramarginal gyrus corresponding to S2, anterior cingulate gyrus, and contralateral thalamus were activated in patients with subcortical stroke.</td>
<td>Brain</td>
</tr>
<tr>
<td>Enzinger et al., 2008</td>
<td>18 Chronic subcortical ischemic stroke patients</td>
<td>fMRI</td>
<td>Active and passive ankle dorsiflexion</td>
<td>Ipsilateral SMC, SMA.</td>
<td>Brain</td>
</tr>
<tr>
<td>Miyai et al., 2003</td>
<td>8 Patients (ischemic or hemorrhagic stroke)</td>
<td>fNIRS</td>
<td>Recorded during walking on treadmill</td>
<td>Bilateral SMC, PMC, SMA, and prefrontal regions.</td>
<td>Brain</td>
</tr>
<tr>
<td>Yang et al., 2010</td>
<td>18 Chronic stroke patients</td>
<td>TMS mapping</td>
<td>Elicite abductor hallucis muscle with TMS</td>
<td>After rehabilitation training, map size of abductor hallucis muscle in the ipsilesional hemisphere increased, and the motor threshold decreased.</td>
<td>Brain</td>
</tr>
<tr>
<td>Jang et al., 2013</td>
<td>54 Subcortical and chronic stroke patients and 20 healthy controls</td>
<td>DTI</td>
<td>None</td>
<td>Patients who were able to walk showed significantly increased fiber volume in the corticoreticular pathway.</td>
<td>Brainstem</td>
</tr>
<tr>
<td>Yeo et al., 2011</td>
<td>55 Chronic stroke patients and 22 healthy controls</td>
<td>DTI</td>
<td>None</td>
<td>In patients who were able to walk independently, the FA value of the PPN in the affected hemisphere was increased.</td>
<td>Brainstem</td>
</tr>
<tr>
<td>Luft et al., 2008</td>
<td>71 Chronic stroke patients</td>
<td>BOLD-weighted fMRI</td>
<td>Knee movement</td>
<td>Rehabilitation intervention enhanced the recruitment of cerebellum-midbrain circuits.</td>
<td>Brainstem and cerebellum</td>
</tr>
<tr>
<td>Finley et al., 2008</td>
<td>10 Stroke patients and 8 healthy controls</td>
<td>EMG</td>
<td>None</td>
<td>The presence of a reciprocal, reflex-mediated coupling between rectus femoris and adductor lateralis following stroke suggests changes in the excitability of spinal networks.</td>
<td>Spinal cord</td>
</tr>
</tbody>
</table>

BOLD: Blood oxygenation level dependence; S2: secondary somatosensory area; M1: primary motor cortex; PMC: premotor cortex; SMC: secondary sensorimotor cortex; SMA: supplementary motor area; fNIRS: functional near-infrared spectroscopy; TMS: transcranial magnetic stimulation; DTI: diffusion tensor imaging; FA: fractional anisotrophy; PPN: pedunculopontine nucleus; EMG: electromyography.
that have been recruited for walking recovery to build new anatomic connections (Winship and Murphy, 2008).

The critical role of excitability differences in driving the evolution of cortical reorganization was demonstrated by a pharmacological prevention experiment, in which researchers found that abolishing hyperexcitability via diazepam within the first 3 weeks after a brain injury delayed functional recovery, while applying the same treatment more than 3 weeks after the brain injury did not have the same effect (Schallert et al., 1986). Moreover, the observation that treatment-associated cortical reorganization preferentially occurs where intracortical inhibitory properties are low further supports the role of varied excitability as a driving force in neuroplastic reorganization after stroke (Liepert et al., 2006).

Heterogeneity among individual reorganization

The size and location of the lesion and the extent of secondary motor cortex involvement is thought to add to the diversification of post-stroke neuroplastic reorganization. However, as suggested by Weiller and colleagues in their study of patients with capsular limited stroke, there are likely many additional factors governing neuroplastic reorganization that have yet to be discovered. They found that, despite relative homogeneity in lesion size, location, and clinical symptoms, patterns of cortical activation, as a measure of neuroplastic reorganization, were idiosyncratic (Weiller et al., 1993). This observation is not surprising considering how the brain remedies the loss of the cerebrospinal tract (CST) via stroke. After the projections from the M1 cortex to the spinal cord are destroyed by a stroke, survivors tend to recruit the impaired descending fibers arising from the SMC and PMC to “take over” the role of the lost CST in recovering walking ability. This may be possible because both the SMC and PMC have projections to the bilateral M1 cortices and the spinal cord, and the outputs of their projections to the spinal cord have a facilitating effect on muscle activity (Boudrias et al., 2006; Dancause, 2006). This “take over” could be achieved by 1) enhancing the intrasulcus (Starkey et al., 2012), intrahemispheric (Carmichael et al., 2001), or interhemispheric connectivity (Wang et al., 2012a) between the two aforementioned areas in the bilateral hemispheres, as well as enhancing their connectivities with the affected M1 cortex, 2) by building up a bypass via the corticoreticular pathway (Jang et al., 2013), or by 3) recruiting additional relay connections at the spinal cord level (Courtine et al., 2008). The extent of the “take over” and the contribution of these different processes likely varies markedly from person to person. In a longitudinal fMRI functional connectivity network analysis of 10 patients with stroke, who were analyzed across five consecutive time points in a single year, the authors discovered that the motor execution network in the patients gradually shifted towards a random mode during the recovery process (Wang et al., 2010). Therefore, post-stroke reorganization of walking control might be individualized by the varying degrees of participation of the entire residual motor system during the recovery process.

Noninvasive Brain Stimulation

TMS and transcranial direct current stimulation (tDCS) are the two most common types of noninvasive brain stimulation. Neither of these are new to the medical practice, as

Not every incidence of post-stroke hyperactivation aids functional recovery

Because there are large differences in lesion characteristics among existing studies, it is difficult to compare different types of post-stroke hyperactivation among the literature. Additionally, the differing clinical states of the patients among studies influences whether contralesional reorganization can be classified as “beneficial” or “non-beneficial.” For example, contralesional reorganization-related compensatory movements from the trunk and proximal limb may be beneficial for severely impaired patients, but may not be beneficial for complete recovery in mild or moderately impaired patients. Madhavan et al. (2010) studied this effect in a carefully selected cohort of stroke survivors and demonstrated that, regardless of lesion location or size, individuals with strong ipsilesional motor projections to the paretic lower limb showed inversely greater degradation of tracking accuracy in the non-paretic limb. Additionally, a higher rate of mirror movements has been documented in patients with greater degrees of ipsilesional cortical or cerebellum recruitment after stroke (Luft et al., 2005). These findings indicate that not all post-stroke cortical activation contributes to functional recovery, and suggest that some activation might even be maladaptive, for example, leading to mirror movements, spasm, dystonia, or interjoint coupling movements (Luft et al., 2005; Finley et al., 2008; Levin et al., 2009; Huynh et al., 2013).

Intra- and interhemispheric competitive interaction has been reported to be the main mechanism of maladaptive plasticity (Takeuchi and Izumi, 2012). First, neurophysiological studies have revealed a long-lasting interhemispheric imbalance after stroke, with the unaffected hemisphere inhibiting the affected hemisphere, while widespread disinhibition exists in the affected hemisphere (Carmichael et al., 2001; Sun et al., 2012). Furthermore, motor function of the paretic limb is improved by inhibiting the contralesional hemisphere or nearby ipsilesional motor areas (Floel et al., 2008; Takeuchi and Izumi, 2012), while excessive training of the non-paretic limb can impair or delay functional recovery of the paretic limb (Kerr et al., 2013). Second, researchers have demonstrated that task-specific rehabilitative training, even when conducted for a short period of 5 consecutive days, can induce remapping of cortical activation from the contralesional hemisphere to the ipsilesional hemisphere (Boyd et al., 2010). Additionally, 6 weeks of unilateral high-intensity dorsiflexor resistance training has been found to produce bilateral neuromuscular plasticity in stroke survivors (Dragert and Zehr, 2013). This evidence suggests that the two hemispheres compete in terms of rewiring to the affected limbs, which might hinder, rather than facilitate, further recovery.

Not surprisingly, during the complex process of post-stroke repair, some of the numerous outgrowths of new connections may be maladaptive (Wang et al., 2010).
TMS has been used clinically since 1985, and the use of tDCS can be traced back to the 1800s. In both NIBS techniques, an electric current is applied to cortical neurons (directly in tDCS or indirectly in TMS), which modulates the excitability of cortical circuits and augments neural plasticity (Romero Lauro et al., 2014). The focal modulating effect of NIBS can be either excitatory or inhibitory, depending on the stimulation protocols used. For example, with “conventional” repetitive TMS (rTMS) protocols (TMS pulses are delivered at a constant rate), the low-frequency stimulation (1 Hz or less) is inhibitory and the high-frequency stimulation (5 Hz or more) is excitatory. In theta burst stimulation (TBS, TMS pulses are delivered in short rTMS bursts at frequency rates in the theta range, and with pauses between each stimulation burst), continuous TBS (pause periods = 2 seconds, cTBS) is inhibitory and intermittent TBS (pause periods = 10 seconds, iTBS) is excitatory. Likewise, both paired associative stimulation (PAS) with an interval duration of 10 milliseconds (PAS10) and cathodal tDCS (c-tDCS) are inhibitory, while PAS25 and anodal tDCS (A-tDCS) are excitatory. In addition to the instant focal excitability modulating effect upon stimulation, tDCS and TMS also have remote effects (via projecting fibers to distant structures) and after-effects on the brain network that facilitate neural plasticity (Lang et al., 2004; Chib et al., 2013; Notturno et al., 2014).

The use of NIBS has been infrequent until recently, when the efficacy of these techniques in facilitating neural plasticity was determined. To date, NIBS has shown promising efficacy in improving the motor function of paretic upper limbs (Takeuchi et al., 2009) and in treating aphasia (Kheder et al., 2014). Additionally, several primary studies have reported that NIBS techniques are efficacious in the rehabilitation of post-stroke gait impairments (Wang et al., 2012b; Kakuda et al., 2013). However, a large inter-individual variability in response to NIBS interventions has been increasingly documented (Lefaucheur et al., 2014; Lopez-Alonso et al., 2014). Thus, we believe it necessary to reevaluate our understanding of gait impairment recovery after stroke.

Based on the above review of the neurophysiology of human gait and post-stroke reorganization in the motor control system underlying human gait, we herein propose several guidelines for the optimization of future NIBS applications:

**NIBS should be used in combination with meaningful rehabilitation training**

Neuroplastic reorganization is, above all, a use-dependent plasticity. It is therefore not surprising that functional recovery achieved by NIBS is usually greater when applied in combination with active task performance (Zimerman et al., 2012).

Central to this point is a discussion regarding what constitutes meaningful rehabilitation training: First, rehabilitation training should be meaningful with respect to skill learning. For instance, non-skill and passive training, that is, repeated voluntary and assisted dorsi- and plantarflexion movements, did not increase cortical excitability, while motor skill training had a positive effect (Perez et al., 2004). Second, the combined training should be task-specific. In animals with complete spinal cord transections, those that were trained to stand did not walk well on a treadmill, while those that were trained to walk did not stand well (Wolpaw and Tennissen, 2001). Thus, by extrapolation, we surmise that specific task training facilitates individual performance of that task. Third, to reduce the risk of maladaptive reorganization, pathological movement should be avoided in jointly applied rehabilitation training. We therefore recommend the use of body weight support or robotics support in gait training, as these two therapeutic devices allow both automatic and manual correction of pathological movement patterns during gait training, and thus facilitate near normal patient gait. These recommendations are supported by recent successful experiences with the combined application of NIBS and rehabilitation training strategies (Wang et al., 2012b; Danzl et al., 2013).

**NIBS should be used in combination with other concurrent neuroplasticity facilitation techniques**

Each neuroplasticity facilitation measure has limitations and might only target limited parts of cortical circuits. For instance, when healthy adults learn motor adaptations, anodal tDCS stimulation can increase anterograde interference, but not savings (Leow et al., 2014). In a study that compared three different experimental models of the organization of the human motor cortex, TMS only increased the amplitudes of motor evoked potentials (MEP), and had no effect on short-interval intracortical inhibition (Rosenkranz and Rothwell, 2006).

Therefore, to activate neuroplastic reorganization at multiple levels, it is advisable to administer NIBS in combination with other concurrent neuroplasticity facilitation techniques. For this purpose, body weight support treadmill training, functional electrical stimulation of the lower limbs, and augmented bio-feedback treatments can facilitate activation of the locomotor circuits of the spinal cord (Stein et al., 2013), thus strengthening the remote effects of NIBS treatment. Balance training can enhance cerebellar-brainstem interactions, and therefore can be jointly used to facilitate the rebuilding of connectivity at the brain stem level (Reisman et al., 2007). Additionally, as constraint-induced movement therapy can reduce interhemispheric inhibition and prevent learned non-use of the paretic limbs, it appears to enhance the therapeutic effects of NIBS (Williams et al., 2010). Furthermore, pharmacological treatments may also work with NIBS to yield greater rehabilitation.

**Timing of NIBS treatment**

The natural recovery of the residual brain proceeds at a defined pace after an injury. For instance, perilesional tissues exhibit a depression in metabolism and a decrease in neurite density within several days after a stroke (Ito et al., 2006; Jablonka et al., 2010) and new prosperous connectivity is not observed until 2 weeks after stroke onset (Nudo, 2006). Thus, NIBS therapy is likely to be most effective when it is performed in consideration of the natural pace of endogenous
neuroplastic reorganization.

In animal studies, the difference in hyperexcitability that drives neuroplastic reorganization subsequently dissipates over several weeks following a stroke (Schallert et al., 1986), indicating that there is a critical time window for rehabilitative interventions. Accordingly, rehabilitative efficacy declined over time in an ischemic stroke animal model within a 30-day observation period (Takeuchi et al., 2004), signifying the importance of early NIBS treatment. Nonetheless, limited observations in animal models also suggest that tDCS treatment may be less effective if initiated too soon after an injury. These models favor initiation of tDCS therapy 1 week after a stroke rather than 1 day after a stroke (Kim et al., 2010; Jiang et al., 2012). Consistent with this, in a recent clinical trial, researchers applied anodal tDCS stimulation to the affected motor cortex of 25 patients 2 days after a stroke (20 minutes once a day for 5 consecutive days), and did not find any significant functional improvements between the treatment group and controls (Nudo et al., 2006). Therefore, the optimal timing for the initiation of NIBS treatment in the acute phase after a stroke is still unclear. Thus, although results regarding the application of NIBS to subacute and chronic stroke patients are mostly favorable, no studies have precisely identified the optimal timing for postacute phase NIBS treatment.

Based on the above, it is clear that attention should be paid to the temporal relationships between NIBS interventions, the application of other neuroplasticity facilitation rehabilitative techniques, and the timing of NIBS delivery during a gait cycle. For instance, improvements in behavioral performance were observed only when tDCS was delivered prior to, but not during a task (Pirulli et al., 2014). Additionally, when the PAS protocol of TMS is applied in different phases of gait cycle, it can increase the muscular response if it is delivered in the late swing phase, or suppress it if it is delivered in the mid swing phase (Prior and Stinear, 2006). Thus, the timing of NIBS delivery during a gait cycle should be considered with respect to the design of NIBS protocol.

Customized considerations for NIBS treatment

Because post-stroke neuroplastic reorganization evolves over time, is idiosyncratic, and may develop maladaptive characteristics, NIBS application requires a customized stimulation paradigm designed for each individual patient.

First, decisions regarding which hemisphere to stimulate are not trivial. Although ipsilesional facilitation stimulation has been found to be beneficial, recent research is more in support of inhibitory stimulation of the contralesional hemisphere. A study comparing the motor recovery of 36 patients who were randomly divided into 3 groups to receive ipsilesional facilitating stimulation, contralesional inhibitory stimulation, or sham stimulation, showed that contralesional inhibitory stimulation was more effective than ipsilesional facilitating stimulation (Khedr et al., 2009). Also, greater degrees of functional recovery and activated connectivities have been reported for protocols involving contralesional inhibitory stimulation compared with those without (Takeuchi et al., 2009; Sehm et al., 2013). However, as the role of the contralesional hemisphere in stroke recovery varies for each individual patient and at different stages of recovery (Schallert et al., 1986; Ago et al., 2003; Lotze et al., 2006), only careful cortical mapping can delineate which patients will most benefit from ipsilesional, contralesional or bihemispheric stimulation.

Second, the location and extent of stimulation for each hemisphere needs to be identified. Although experimental investigations have indicated that distributed stimulation works better than focalized stimulation (Boychuk et al., 2011), non-selective extensive stimulation may not be acceptable for clinical application. Cortical stimulation might reduce or even reverse the motor outputs from the representations for a nearby body part. For example, stimulation of the face or hand representations can cancel and even reverse the increase of motor output from the arm representation (Ziemann et al., 2002). Additionally, stimulating different portions of non-motor cortices might result in completely different effects on the excitability of bilateral M1 regions. For example, stimulation of the anterior portion of the inferior-parietal lobule resulted in inhibition of the ipsilateral M1 in both hemispheres, while stimulation of the central and posterior portion of this region facilitated the excitability of ipsilateral M1 in the left but not the right hemisphere (Karabanov et al., 2013). However, different TMS protocols may target different preferential cortical circuits, e.g., low frequency rTMS selectively excites late I-wave producing circuits, while cTBS preferentially inhibits early I-wave producing circuits (Di Lazzaro et al., 2005, 2008). Even reproducible “excitability” or “inhibitory” effects can be achieved based on tissue physiology. Thus, the functional outcome of a specific NIBS protocol is still highly related to the pre-stimulation state of the tissue (Daskalakis et al., 2006; Giacobbe et al., 2013; Pirulli et al., 2014). Accordingly, clinical applications of NIBS have stringent requirements regarding the determination of stimulation targets and methods. While at present, stimulation sites are most commonly determined by fMRI and/or TMS mapping, these two methods have limitations. Because of gantry size and image degradation, fMRI studies are only able to incorporate very limited limb movements during activation mapping, such as using finger movement to mimic the movement of the whole upper limb, and using ankle flexion to mimic walking. TMS also has limitations with respect to mapping changes in the somatosensory cortices, as it basically relies on testing muscle activities. Ideally, multiple mapping techniques should be integrated for identification of the sites and extent of NIBS interventions. Subsequently, we recommend the use of computer modeling to test the accuracy of the stimulation montage, or alternatively, the use of magnetoencephalography to monitor neuro-magnetic brain activity during tDCS stimulation (Datta et al., 2011).

Third, the optimal stimulation paradigm for each patient should be determined. Recent studies have indicated that rTMS can improve the gait performance of stroke survivors after either being applied alone or in combination with task-oriented training (Wang et al., 2012b; Kakuda et al., 2013). PAS applied to chronic stroke patients has also
Conclusions

Given the high inter-individual variability in responses to NIBS, we recommend a customized stimulation montage for each individual, and a real-time monitoring system that allows for adjustments during stimulation. In this regard, the following issues need to be addressed in future research:

1. Identify genetic or imaging biomarkers that can be used to predict responses to NIBS interventions.
2. Define target sites more precisely. This includes a need for improved surrogate models for approximating gait during imaging, or alternatively, incorporating brain computer interface techniques into future target site-mapping procedures. This may improve interpretations of the role of detected hyper-activations in the recovery of post-stroke gait impairment.
3. Develop a system that monitors the effect of stimulation and provides real-time feedback during the stimulation, thus allowing for any needed adjustments.

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