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Chapter 40

Noninvasive brain stimulation in neurorehabilitation

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INTRODUCTION

Stroke is the major cause of long-term disability worldwide (Kolominsky-Rabas et al., 2001) and recovery of motor function is often incomplete (Roger et al., 2011). Six months after the ictal event, two-thirds of stroke survivors are unable to carry out independently activities of daily living with their paretic hand to the extent they could before (Kolominsky-Rabas et al., 2001), and only a few are able to return to their previous job (Lai et al., 2002).

Patients with motor deficits resulting from stroke must confront the need to generate compensatory strategies or to relearn the motor programs utilized to accomplish a particular goal before the lesion (Frey et al., 2011; Pomeroy et al., 2011; Sathian et al., 2011). From a behavioral point of view, there are different ways to accomplish the same goal in neurorehabilitation (e.g., grasp a glass of water). One possibility is to implement a motor strategy different from that utilized before the stroke (i.e., compensation) (Levin et al., 2009). An alternative way is to relearn to perform the task in the same way it was done before the lesion. Clearly, both processes are likely to involve fundamentally different pathophysiological mechanisms, even when the goals and outcomes are the same. Different motor training strategies have been tested in neurorehabilitation of motor function. Examples include constraint-induced movement therapy, bilateral arm training, mirror therapy, randomized training schedules, robotic-based approaches, virtual reality, electromyogram-triggered stimulation, action observation, motor imagery, and brain–computer interfaces between others (Cauraugh and Kim, 2003; Wittenberg et al., 2003; Bolton et al., 2004; Deutsch et al., 2004; Luft et al., 2004; Krakauer, 2006; Sharma et al., 2006; Birbaumer and Cohen, 2007; Ertelt et al., 2007; Page et al., 2007; Buch et al., 2008, 2012; Celnik et al., 2008; Cramer, 2008b; Cheeran et al., 2009a; Lo et al., 2009; Dimyan and Cohen, 2011). Noninvasive somatosensory (Conforto et al., 2007, 2010), transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) (Hallett, 2000; Kaelin-Lang et al., 2002; Nitsche et al., 2008; Wassermann et al., 2008; Sandrini et al., 2011; Tanaka et al., 2011; Brunoni et al., 2012) have been proposed as adjuvant ways to improve the beneficial effects of training protocols on functional recovery.

In this chapter, we discuss the use of noninvasive brain stimulation (NIBS) in the setting of stroke rehabilitation. Interest in NIBS developed after the observation of long-term effects on cortical excitability that occur after repeated stimulation (Huang et al., 2005; Fitzgerald et al., 2006; Nitsche et al., 2008). Depending on the stimulation parameters, motor cortical excitability can be reduced (inhibition) by means of low-frequency repetitive TMS (rTMS), continuous theta-burst stimulation (cTBS), and cathodal tDCS, or enhanced (facilitation) by means of high-frequency rTMS, intermittent theta-burst stimulation (iTBS), and anodal stimulation. There is evidence that links the effects of these NIBS techniques to long-term potentiation (LTP)-like and long-term depression (LTD)-like mechanisms (Cooke and Bliss, 2006; Thickbroom, 2007; Wagner et al., 2007; Ziemann et al., 2008; Fritsch et al., 2010). After stroke, NIBS has been studied as a tool to modulate cortical excitability in the affected and intact hemispheres, predominantly

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with the goal of correcting hypothesized imbalances in interhemispheric interactions (Kinsbourne, 1974; Hummel and Cohen, 2006).

POSTSTROKE REORGANIZATION

The magnitude and type of motor impairments that follow stroke are influenced by multiple factors such as lesion site, size, and time after stroke (Rossini et al., 2003; Ward and Cohen, 2004; Frey et al., 2011; Pomeroy et al., 2011; Sathian et al., 2011).

Recovery of motor function after the first few days poststroke is likely related to the resolution of edema as well as to reperfusion of the ischemic penumbra through collateral circulation (Furlan et al., 1996). At later stages after stroke, other mechanisms such as recruitment of functionally homologous pathways, disinhibition of previously inactive neuronal connections, resolution of diaschisis, and the formation of new neural connections may take over the role of the damaged area, contributing to recovery of function (Rossini et al., 2007; Cramer, 2008a). Both pyramidal tract and alternate motor fibers, including the corticorubrospinal and corticoreticulospinal tracts (Fries et al., 1991; Lang and Schieber, 2003), may contribute to functional recovery (Lindenberg et al., 2010a). In the chronic stage after stroke, damage to corticospinal tract white-matter fibers seems to correlate with motor impairment (Talelli et al., 2006; Schaechter et al., 2009; Zhu et al., 2010). For example, indices of microstructural integrity (e.g., fractional anisotropy, FA) of the posterior limb of the internal capsule correlate with motor function. It has been proposed that FA in this white-matter region may predict the ability of TMS interventions to modulate motor function positively (Stinear et al., 2007). In addition to the corticospinal tract, a recent study (Lindenberg et al., 2012a) showed that FA in interhemispheric white-matter fibers connecting both primary motor cortices (M1) predicted functional gains in an experimental rehabilitation trial (Lindenberg et al., 2010b). Another factor that influences functional recovery is the ability of the lesioned brain to reorganize. Plasticity, defined as "experience-dependent enduring changes in neuronal or network properties either morphological or functional" (Donoghue et al., 1996), is an important contributor to functional recovery after stroke (Nudo et al., 1996).

Local reorganization

In the case of focal cortical lesions, perilesional regions can be recruited to control the function of the damaged motor area through somatotopic reorganization, a phenomenon referred to as vicariation (Merzenich et al., 1984; Donoghue et al., 1990; Sanes et al., 1990). Studies in animals suggest that preservation of the peri-infarct penumbra may provide a substrate for functional recovery after cortical lesions by unmasking redundant motor representations adjacent to the site of injury (Nudo and Milliken, 1996; Nudo et al., 1996). This form of perilesional reorganization has been demonstrated in healthy human subjects undergoing ischemic nerve block (Brasil-Neto et al., 1993) and in chronic stroke patients (Cramer et al., 1997, 2000). In particular, representational plasticity within M1 may contribute to functional gains after a limited ischemic lesion to this area (Jaillard et al., 2005).

Reorganization of ipsilesional secondary motor areas

Regions distant to the lesion do reorganize as well (Ward, 2011). There is evidence that well recovered stroke patients continue to have reduced ipsilesional motor cortical excitability, as evidenced by reduced motor evoked potential (MEP) amplitudes (Byrnes et al., 2001), suggesting that alternative mechanisms such as cortical reorganization and increased activity of ipsilesional secondary motor areas may have contributed to their motor recovery. For example, the premotor cortex (PMC) and the supplementary motor area (SMA) may contribute to motor function (Ward et al., 2006; Swayne et al., 2008). TMS applied over the ipsilesional dorsal PMC disrupted performance of paretic hand motions in stroke patients with mild to moderate motor deficits, in whom corticospinal fibers originated in M1 were lesioned (Fridman et al., 2004). Functional magnetic resonance imaging (fMRI) studies also suggest the involvement of nonprimary motor areas in recovery of motor function after stroke (Nowak et al., 2010). With respect to the activity in the SMA, a study in acute stroke patients showed that decreased blood oxygen level-dependent (BOLD) signal during movements of a paretic hand relative to controls was predictive of slower recovery, whereas higher BOLD activity was associated with faster motor recovery (Loubinoux et al., 2003).

Bihemispheric reorganization

Longitudinal neuroimaging studies have shown initially high bihemispheric BOLD signal activity associated with movements of the paretic hand 2 weeks poststroke. Over time, bihemispheric activation decreases progressively toward levels observed in healthy subjects concomitant to motor recovery (Ward et al., 2003; Tombari et al., 2004; Rehme et al., 2011). In opposition to this pattern, patients with incomplete motor functional recovery in the chronic phase (i.e., more than 6–12 months poststroke) typically maintain increased bihemispheric BOLD signal activity (Chollet et al., 1991; Weiller

et al., 1992; Ward and Cohen, 2004; Gerloff et al., 2006; Grefkes et al., 2008b). Consistent with these findings, it has been reported that lateralized fMRI activation towards ipsilesional regions, similar to that seen in age-matched controls, is associated with more successful functional recovery (Ward et al., 2003; Gerloff et al., 2006; Nair et al., 2007).

Studies using TMS have attempted to discern the functional role of these neuroimaging findings. It is now known that the presence of ipsilateral MEPs to TMS applied over the contralesional M1 is associated with poor clinical outcome (Turton et al., 1996; Netz et al., 1997; Feydy et al., 2002). In addition to M1, TMS applied to the contralesional dorsal PMC in poorly recovered patients disrupted motor performance of the paretic hand (Johansen-Berg et al., 2002). A neuroimaging study carried out during the first 2 weeks after stroke also showed that functional recovery in severely affected patients was associated with gradually increasing activity in contralesional M1 and PMC (Rehme et al., 2011). In line with this, Lotze and colleagues (2006) showed that disruption of activity in contralesional regions (i.e., M1, dorsal PMC, and superior parietal lobe, SPL) active during movements of the paretic hand affected motor performance. While interference with the dorsal PMC and M1 induced timing errors only, SPL stimulation caused both timing and accuracy deficits.

Overall, these results are consistent with the view that patients with more severe motor impairments may engage more actively regions of the contralesional hemisphere to carry out a task with the paretic hand (Johansen-Berg et al., 2002; Ward et al., 2003; Fridman et al., 2004; Buch et al., 2012).

PHYSIOLOGICAL MECHANISMS OF REORGANIZATION

It is possible to study physiological features of cortical organization after stroke using TMS. Paired-pulse TMS delivered through the same magnetic coil over M1, where a suprathreshold test stimulus (TS) is preceded by a subthreshold or suprathreshold conditioning stimulus (CS), can be used to gain insight into the relative contribution of local inhibitory and excitatory inputs to M1 pyramidal tract cells (Reis et al., 2008). Interstimulus intervals of approximately 1–5 ms cause attenuation of MEP amplitudes or short intracortical inhibition (SICI) (Kujirai et al., 1993), whereas longer intervals (~6–10 ms) elicit a facilitatory effect referred to as intracortical facilitation. Decreased SICI has been reported in both affected and unaffected hemispheres of chronic stroke patients (Liepert et al., 2000a, b; Butefisch et al., 2003, 2008). It is not only resting SICI that is abnormal after stroke, but also movement-related SICI. For example, in stroke patients who exhibit relatively good functional recovery, SICI measured immediately preceding performance of a voluntary movement by the paretic hand was abnormal compared with that in age-matched controls (Hummel et al., 2009).

TMS has been also used to study interhemispheric interactions. Early studies in stroke patients examined the excitability of bilateral motor cortices evaluated by differences in MEP amplitudes and in cortical areas (motor maps) producing MEPs in the contralateral hand muscles (Cicinelli et al., 1997; Traversa et al., 1997). These investigations found relative hyperexcitability of the contralesional in comparison with the ipsilesional M1 that normalized with time after stroke. A paired-pulse TMS technique has been used to study interhemispheric inhibition (IHI) between the two M1s, where a suprathreshold CS is applied over the conditioning M1 about 10 ms prior to the TS applied to the opposite conditioned M1 (Ferbert et al., 1992). Abnormalities in resting IHI after stroke may depend on the location of the lesion (Boroojerdi et al., 1996). Other studies started to evaluate movement-related changes in IHI after stroke. In relatively well recovered chronic stroke patients, initially normal levels of IHI from the contralesional to the ipsilesional M1 remain present at the onset of a paretic hand movement, in contrast to the disinhibition that accompanies nonparetic hand movement and motions in age-matched controls (Murase et al., 2004; Duque et al., 2005).

It is also important to consider the interactions between IHI and SICI. Examining whether changes in IHI and SICI after stroke may be related, Butefisch and coworkers (2008) showed that the attenuation of SICI in ipsilesional M1 was not accompanied by a change in resting IHI from contralesional to ipsilesional M1. In contrast, disinhibition of contralesional M1 was accompanied but did not correlate with a decrease in IHI from ipsilesional to contralesional M1s. Altogether these findings were interpreted as indicating that, at rest, local modulation of inhibition within ipsilesional M1 is prominent. However, a more accurate investigation of the resting interactions between SICI and IHI using TMS paired-pulse techniques, as recently implemented in healthy individuals (Daskalakis et al., 2002; Perez and Cohen, 2008), remains to be done after stroke. Additionally, an understanding of IHI–SICI interactions in the process of generation of a voluntary movement by the paretic hand will be important to determine the mechanisms underlying deficits in motor function after stroke. For example, the phenomenon of facilitation of M1 excitability by ipsilateral limb movement has been explored in the healthy brain (Muellbacher et al., 2000; Hortobagyi et al., 2003; Perez and Cohen, 2008), but

remains to be evaluated thoroughly after stroke. It has been proposed that, with isometric force production, nonparetic arm activity in stroke patients does not lead to as much ipsilateral M1 facilitation as seen in healthy controls (Woldag et al., 2004; Renner et al., 2005).

Overall, these findings suggest that motor function of the paretic hand may be influenced by abnormalities in interhemispheric inhibitory interactions. This view has been documented extensively in recent literature using TMS measures in healthy subjects (Tinazzi and Zanette, 1998; Schambra et al., 2003; Kim et al., 2004; Kobayashi et al., 2004, 2009; Dafotakis et al., 2008; Dimyan and Cohen, 2010; Williams et al., 2010) and fMRI (Grefkes et al., 2008a, b; Wang et al., 2010). It was shown that stroke patients experience an increased inhibitory influence from contralesional to ipsilesional M1, which is not present in healthy subjects or when the same patients moved their unaffected hand. Importantly, the strength of this inhibition from contralesional M1 correlated with the motor impairment of the paretic hand (Grefkes et al., 2008b). Similar abnormalities in interhemispheric interactions relating to other cognitive functions have been reported in the fields of language and spatial attention (Kinsbourne, 1980; Chrysikou and Hamilton, 2011; Oliveri, 2011).

NONINVASIVE BRAIN STIMULATION IN NEUROREHABILITATION

Based on the hypothesis of abnormal interhemispheric inhibitory interactions after stroke, two strategies have been proposed to ameliorate paretic hand function: (1) to downregulate excitability of contralesional M1, and (2) to upregulate excitability of ipsilesional M1 (Hummel and Cohen, 2006; Webster et al., 2006) (Fig. 40.1). Depending on the stimulus type and stimulation parameters, NIBS can facilitate cortical excitability in the ipsilesional M1 through direct stimulation of this region or indirectly via inhibition of the contralesional M1. To target simultaneously both components of this imbalance, it is possible to use bihemispheric modulatory approaches (Takeuchi et al., 2009; Lindenberg et al., 2010b).

Studies investigating the effects of NIBS on motor function after stroke are summarized in Table 40.1.

Downregulation of excitability in the contralesional M1

It has been reported that downregulation of cortical excitability in the contralesional M1 with NIBS (i.e., low-frequency rTMS, cTBS, and cathodal tDCS) may contribute to improve recovery of function of the affected hand after stroke. For example, 1-Hz TMS applied over the contralesional M1 after stroke induces a reduction in motor cortical excitability in the unaffected hemisphere (Takeuchi et al., 2005; Fregni et al., 2006), increased cortical excitability in the affected hemisphere (Fregni et al., 2006; Takeuchi et al., 2008), and reduced interhemispheric inhibition (Takeuchi et al., 2005; Avenanti et al., 2012).

Repeated application over several days (Fregni et al., 2006; Boggio et al., 2007; Kirton et al., 2008; Khedr et al., 2009; Emara et al., 2010; Kakuda et al., 2010a, b, 2012; Nair et al., 2011; Sasaki et al., 2011; Avenanti et al., 2012; Conforto et al., 2012), alone or in combination with motor training protocols (Takeuchi et al., 2008, 2009;

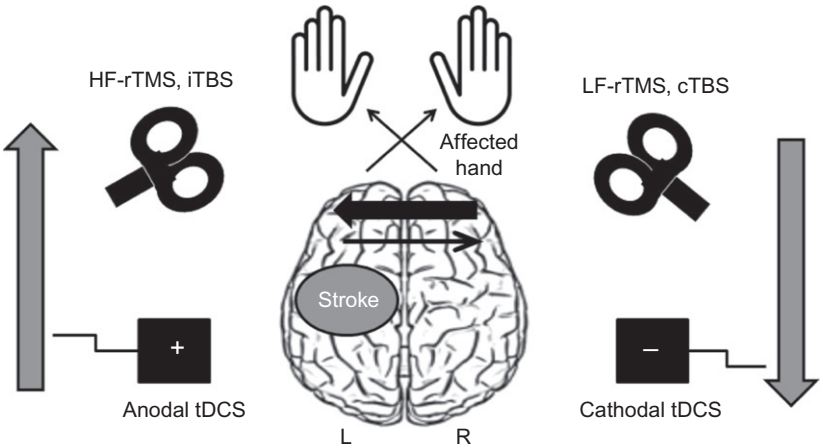

Fig. 40.1. Noninvasive brain stimulation (NIBS) strategies tested to promote recovery of motor function after stroke. Motor deficits following stroke (in this diagram involving the left hemisphere) are associated with disinhibition of the contralesional primary motor cortex and increased interhemispheric inhibition from contralesional to ipsilesional M1. This imbalance of interhemispheric inhibition may be reduced by inhibitory NIBS (low-frequency (LF) repetitive transcranial magnetic stimulation (rTMS), continuous theta-burst stimulation (cTBS) and cathodal transcranial direct current stimulation (tDCS)) applied to the contralesional hemisphere, or facilitatory NIBS (high-frequency (HF) rTMS, intermittent TBS (iTBS), and anodal tDCS) of the ipsilesional M1.

Table 40.1

Summary of previous studies investigating the effectiveness of inhibitory rTMS or tDCS over primary motor cortex of unaffected hemisphere on motor behavior

Technique	Reference	Area of stimulation	No. of patients, mean age, lesion location, and time since stroke	Study design	Control condition	Stimulation parameters	Main results
rTMS, low frequency	Mansur et al., 2005	Hand area of M1 and dorsal PMC, unaffected hemisphere	10 adults, 54 years, 10 subcortical, <12 months	Single-blind, crossover, sham-controlled	Real TMS, sham TMS (sham coil), real TMS over PMC	1 Hz, 100% rMT, 10 min	Decrease in simple and choice RTs and improved performance of Purdue Pegboard Test with affected hand after real rTMS
rTMS, low frequency	Takeuchi et al., 2005	Hand area of M1, unaffected hemisphere	20 adults, 59 years, 20 subcortical, 6–60 months	Double-blind, randomized, sham-controlled	20 patients, 10 real TMS, 10 sham TMS (perpendicular to the scalp)	1 Hz, 90% rMT, 25 min	Real rTMS reduced MEP amplitude in contralesional M1 and abnormal transcallosal inhibition. Moreover rTMS induced improvement in pinch acceleration
rTMS, low frequency	Fregni et al., 2006	Hand area of M1, unaffected hemisphere	15 adults, 56 years, 2 cortical, 13 subcortical, 1–11 years	Single-blind, longitudinal, randomized, sham-controlled, Phase II	15 patients, 10 real TMS, 5 patients sham TMS (sham coil)	1 Hz, 100% MT, 20 min, repeated daily over 5 days	Real TMS resulted in improvement of motor function performance (Jebsen–Taylor Hand Function Test, simple and choice RTs, Purdue Pegboard Test) in affected hand that lasted for 2 weeks. Corticospinal excitability decreased in stimulated unaffected hemisphere and increased in affected hemisphere
rTMS, low frequency	Boggio et al., 2006	Hand area of M1, unaffected hemisphere	1 adult, 74-year-old woman, subcortical, 23–107 months	Double-blind, crossover, single-case study	Real TMS, sham TMS (sham coil) over M1	1 Hz, 100% rMT, 20 min	rTMS improved motor function (thumb and finger movements)
rTMS, low frequency	Liepert et al., 2007	Hand area of M1, unaffected hemisphere	12 adults, 64 years, 12 subcortical, <14 days	Double-blind, crossover, sham-controlled	Real TMS, sham TMS (sham coil)	1 Hz, 90% rMT, 20 min	Real rTMS improved Nine Hole Peg Test results but not grip strength in affected hand
rTMS, low frequency	Dafotakis et al., 2008	Hand area of M1, unaffected hemisphere	12 adults, 45 years, 12 subcortical, 1–15 months	Double-blind, crossover, sham-controlled	Real TMS, sham TMS over vertex	1 Hz, 100% rMT, 10 min	Real rTMS improved efficiency and timing of grasping and lifting with affected hand

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Table 40.1

Continued

Technique	Reference	Area of stimulation	No. of patients, mean age, lesion location, and time since stroke	Study design	Control condition	Stimulation parameters	Main results
rTMS, low frequency	Nowak et al., 2008	Hand area of M1, unaffected hemisphere	15 adults, 46 years, 15 subcortical, 1–4 months	Double-blind, crossover, sham-controlled	Real TMS, sham TMS over vertex	1 Hz, 100 rMT, 10 min	Real rTMS improved kinematics of finger and grasp movements in affected hand and reduced overactivity in contralesional M1 and nonprimary motor areas. Overactivity of contralesional dorsal PMC, contralesional parietal operculum, and ipsilesional mesial frontal cortex at baseline predicted improvement of movement
rTMS, low frequency	Kirton et al., 2008	Hand area of M1, unaffected hemisphere	10 children, 14 years, 10 subcortical, 3–13 years	Single-blind, longitudinal, randomized, sham controlled	10 patients, 5 real TMS, 5 sham TMS (perpendicular to scalp)	1 Hz, 100% rMT, 20 min repeated daily for 8 days	Real rTMS improved grip strength and Melbourne assessment of upper extremity function
rTMS, low frequency	Takeuchi et al., 2008	Hand area of M1, unaffected hemisphere	20 adults, 62 years, 20 subcortical, 7–121 months	Double-blind, randomized, sham-controlled	20 patients, 10 real TMS, 10 sham TMS (perpendicular to scalp)	1 Hz, 90% rMT, 25 min +motor training	Real rTMS induced an increase in excitability in affected hemisphere and improvement in acceleration of affected hand. Improvements in motor function lasted for 1 week
rTMS, priming stimulation	Carey et al., 2008	Hand area of M1, unaffected hemisphere	10 adults, 66 years, 8 cortical, 2 subcortical, 16–192 months	No sham rTMS, sham-controlled	10 patients real TMS	10 min of 6 Hz (600 pulses), 90% rMT. Immediately after, 10 min of 1 Hz (600 pulses), 90% rMT	Safety of treatment. No seizures and impairment in National Institutes of Health Stroke Scale, Wechsler Adult Intelligence Scale (3rd edition), Hopkins Verbal Learning Test–Revised, Beck Depression Inventory (2nd edition)

rTMS, priming stimulation	Carey et al., 2010	Hand area of M1, unaffected hemisphere	2 adults, with middle cerebral artery stroke, 71-year-old male, 52-year-old female, >10 years	Longitudinal, no sham rTMS, sham-controlled	2 patients real TMS	10 min of 6 Hz (600 pulses), 90% rMT. Immediately after, 10 min of 1 Hz (600 pulses), 90% rMT, 5 sessions	fMRI showed that intervention disrupted cortical activation at contralesional M1. Behavioral results (Box and Block Test, Motor Activity Log) were mixed
rTMS, priming stimulation	Kakuda et al., 2011	Hand area of M1, unaffected hemisphere	11 adults, 61 years, 11 subcortical, average 70.2 months	Longitudinal, no sham rTMS, sham-controlled	5 patients real TMS	10 min of 6 Hz (600 pulses), 90% rMT. Immediately after, 20 min of 1 Hz (600 pulses), 90% rMT + OT, 15-day protocol, 22 sessions	rTMS improved Fugl–Meyer score and shortened log performance time of Wolf Motor Function Test
rTMS, low frequency	Kakuda et al., 2010a	Hand area of M1, unaffected hemisphere	5 adults, 66.8 years, 5 subcortical, 14.6 months	Longitudinal, no sham rTMS, sham-controlled	5 patients real TMS	1 Hz (20 min, 90% rMT) + OT, 10 sessions over 6 consecutive days	Improvements in scores of Fugl–Meyer Assessment, Wolf Motor Function Test, and Ten-Second Test. No deterioration of improved upper limb function observed at 4 weeks after treatment
rTMS, low frequency	Kakuda et al., 2010b	Hand area of M1, unaffected hemisphere	15 adults, 55 years, 15 subcortical, 57 ± 55 months	Longitudinal	Real TMS	1 Hz, 1200 pulses, 90% MT, 22 sessions in 2-week period combined with OT	Fugl–Meyer Assessment score increased in all 15 patients. Shortening of performance time on Wolf Motor Function Test noted in 12 patients. Modified Ashworth Scale score for some flexor muscles decreased in 12 patients
rTMS, low frequency	Grefkes et al., 2010	Hand area of M1, unaffected hemisphere	11 adults, 46 years, 11 subcortical, 1–3 months	Single-blind, crossover, sham-controlled	Real TMS, sham TMS over vertex	1 Hz, 100% rMT, 10 min	Real rTMS improved motor performance of paretic hand. Connectivity analysis (Dynamic Causal Modeling) revealed that behavioral improvements were significantly correlated with a reduction of negative influences originating from contralesional M1 during paretic hand movements. Concurrently, endogenous coupling between ipsilesional SMA and M1 was significantly enhanced only after rTMS

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Table 40.1

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Technique	Reference	Area of stimulation	No. of patients, mean age, lesion location, and time since stroke	Study design	Control condition	Stimulation parameters	Main results
rTMS, low frequency	Conforto et al., 2012	Hand area of M1, unaffected hemisphere	30 adults, 55.75 years, 14 corticosub-cortical, 16 subcortical, average 27.65 days	Double-blind, randomized, longitudinal, sham-controlled	30 patients, 15 real TMS, 15 sham TMS (perpendicular to vertex)	1 Hz, 90% rMT, 25 min, 10 sessions	Real rTMS improved performance in Jebsen–Taylor Test (1 month after treatment) and pinch force
rTMS, low frequency	Kakuda et al., 2011	Hand area of M1, unaffected hemisphere	204 adults, 58.4 years, 107 intracerebral hemorrhage, 27 cerebral cortical infarction, 70 lacunar infarction, 5.0 ± 4.5 years	Multi-center, longitudinal, no sham rTMS, sham-controlled	204 patients real TMS	1 Hz, 90% rMT, 20 min, 120-min intensive OT daily, 22 sessions during 15-day hospitali-zation	Fugl–Meyer Assessment score and Wolf Motor Function Test log performance time decreased significantly at discharge. Changes seen persistently up to 4 weeks after discharge in 79 patients
rTMS, low frequency	Avenanti et al., 2012	Hand area of M1, unaffected hemisphere	30 adults, 60.9 years, 29 subcortical, 1 cortical, average 31 months	Double-blind, randomized, parallel, factorial design, longitudinal, sham-controlled, Phase II	30 patients, 8 real TMS + PT, 8 PT + real TMS, 7 sham TMS + PT, 7PT + sham TMS	1 Hz, 90% rMT, 25 min, 45 min physical training daily, 10 sessions	Behavioral improvement (Jebsen–Taylor Hand Function Test, Nine-Hole Peg Test) and reduction of interhemispheric inhibition found after real rTMS, with the group receiving real TMS + PT showing robust and stable improvements, and the other group (PT + real TMS) showing a slight improvement decline over time
tDCS, cathodal	Nair et al., 2011	Hand area of M1, unaffected hemisphere	14 adults, 58.5 years, 9 cortical and 5 subcortical, average 30.5 months	Double-blind, randomized, longitudinal, sham-controlled	14 patients, 7 cathodal tDCS, 7 sham tDCS	60 min of OT and 30 min of tDCS (1 mA) each day for 5 days in a row	Cathodal tDCS + OT results in more improvement in range-of-motion in multiple joints of paretic upper extremity and in upper extremity Fugl–Meyer score than sham tDCS + OT

fMRI, functional magnetic resonance imaging; M1, primary motor cortex; MEP, motor evoked potential; OT, occupational therapy; PMC, premotor cortex; PT, physical training; rMT, resting motor threshold; RT, reaction time; rTMS, repetitive transcranial magnetic stimulation; SMA, supplementary motor area; tDCS, transcranial direct current stimulation.

Emara et al., 2010; Kakuda et al., 2010a, b, 2012; Nair et al., 2011; Avenanti et al., 2012), produces lasting effects on hand motor function. Some of these studies reported improvements maintained for up to 1–2 weeks (Fregni et al., 2006; Boggio et al., 2007; Takeuchi et al., 2008), 1 month (Conforto et al., 2012; Kakuda et al., 2012), and 3 months (Khedr et al., 2009; Emara et al., 2010) after the end of interventions. In one report, however, Talelli and colleagues (2007) did not find beneficial effects of application of cTBS. Direct comparison between these individual trials has been difficult due to substantial differences in stimulation protocols, endpoint measures, and the relationship of stimulation with rehabilitative treatments and environments, as well as patient characteristics.

Although the majority of these studies tested chronic stroke patients (>6 months after stroke), inhibitory 1-Hz rTMS also appears to influence motor function in patients tested less than 6 months after stroke (Liepert et al., 2007; Di Lazzaro et al., 2008; Nowak et al., 2008; Khedr et al., 2009; Grefkes et al., 2010; Conforto et al., 2012). In patients with moderate to severe motor impairment of the affected hand, Conforto and associates (2012) showed improvement of the Jebsen–Taylor test (mean 12.3% 1 month after treatment) and pinch force (mean 0.5 N) in the real NIBS group, but not in the sham group.

In a recent multicenter study (including 5 institutions and 204 patients), each patient received 22 treatment sessions of 20-min low-frequency 1-Hz rTMS and 120-min intensive occupational therapy (OT) daily (Kakuda et al., 2012). The intensive OT, consisting of 60-min one-to-one therapy and 60-min self-exercise, was administered after the application of low-frequency rTMS. Fugl–Meyer Assessment (FMA) and Wolf Motor Function Test (WMFT) were tested serially. The personnel involved in this study received training prior to the study to standardize the therapeutic protocol. All patients completed the protocol without any adverse effects. The FMA score increased and WMFT performance time decreased significantly at discharge, relative to baseline values. These improvements were reported up to 4 weeks following discharge in 79 patients. However, the study did not include a sham control group. It would be useful to compare these effects with those of a control group that received stimulation to another location or sham stimulation. An additional consideration is that the design of the study did not allow dissection of effects induced by each intervention (i.e., rTMS or OT) on motor function of the affected upper limb.

Another interesting technique proposed to modify motor function is the application of "priming" rTMS protocols over the unaffected hemisphere (i.e., priming trains of 6-Hz rTMS immediately before application of the more classic protocol of 1-Hz rTMS) (Carey et al., 2008, 2010; Kakuda et al., 2011). This design of the rTMS application is based on bench work showing that synaptic plasticity can be enhanced by pretreatment with stimulation in the 5–6-Hz range (Christie and Abraham, 1992; Abraham and Bear, 1996). A recent 15-day protocol of 6-Hz primed low-frequency rTMS combined with intensive OT seems safe and a potentially useful strategy to evaluate (Kakuda et al., 2011). Specifically, this protocol increased the FMA score and shortened the performance time of WMFT. However, as in the study described above, a limitation to interpret the results is the absence of a control group (i.e., sham stimulation). The clinical significance of this range of changes in FMA scores is still low.

At the neural level, 1-Hz rTMS-induced inhibition of the contralesional M1 may result in a normalization of interhemispheric functional connectivity patterns as assessed by fMRI (Grefkes et al., 2008a; Nowak et al., 2008). Nowak and colleagues (2008) showed that in subacute stroke patients the application of rTMS over the contralesional M1 improved the kinematics of finger (25%) and grasp (30%) movements in the affected hand and reduced overactivity in the contralesional M1 and nonprimary motor areas. There was no significant correlation between the rTMS-induced reduction in BOLD responses within the contralesional M1 and the degree of behavioral improvement of the affected hand. However, overactivity of the contralesional dorsal PMC, contralesional parietal operculum, and ipsilesional mesial frontal cortex at baseline predicted improvement of movement kinematics of the affected hand after rTMS of the contralesional M1.

A common feature of all correlative approaches to functional connectivity is that they do not provide any direct insight into how correlations are mediated. Therefore, functional integration within a distributed network is usually better described using measures of effective connectivity that refer explicitly to the influence that one neural system exerts over another (Friston, 1994; Grefkes and Fink, 2011; Venkatakrishnan and Sandrini, 2012). Interhemispheric inhibitory interactions after application of 1-Hz rTMS to the contralesional M1 were evaluated using fMRI and a model of effective connectivity (i.e., dynamic causal modeling) (Grefkes et al., 2010). Subacute stroke patients were scanned 1–3 months after stroke while performing whole-hand fist-closure movements. The authors reported that stimulation of contralesional M1 induced a small but significant increase of paretic hand performance compared with both baseline and vertex stimulation in almost every patient. Interestingly, the effective connectivity analysis showed that the behavioral improvements correlated significantly with a reduction of the influence of the stimulated contralesional M1 on the ipsilesional M1 during paretic hand

movements. Concurrently, coupling between ipsilesional SMA and M1 was significantly enhanced.

Hence, a focal stimulation by means of TMS does not alter connectivity only of the region stimulated, but also of areas distant to the stimulation site. The authors implied that a more effective integration of ipsilesional M1 into the motor network architecture might constitute a key factor for improving motor performance of stroke patients by means of rTMS (Grefkes et al., 2010). Such a conclusion is in line with resting state fMRI data (Wang et al., 2010) showing that spontaneous recovery over time is associated with increased connectivity of ipsilesional M1 analyzed using graph theoretical approaches (Sporns, 2010).

Upregulation of excitability in the ipsilesional M1

It has been reported that upregulation of cortical excitability in the ipsilesional M1 with NIBS (i.e., high-frequency rTMS, iTBS, and anodal tDCS) may contribute to improve recovery of function of the affected hand after stroke. Repeated application over several days (Khedr et al., 2005, 2009, 2010; Boggio et al., 2007; Pomeroy et al., 2007; Celnik et al., 2009; Yozbatiran et al., 2009; Chang et al., 2010; Emara et al., 2010; Sasaki et al., 2011) alone or in combination with a motor training protocol (Kim et al., 2006; Chang et al., 2010; Emara et al., 2010) produce lasting effects on hand motor function. Some of these studies reported improvements maintained for 1–2 weeks (Khedr et al., 2005; Boggio et al., 2007), 3 months (Chang et al., 2010; Emara et al., 2010), or even at 1 year (Khedr et al., 2010) after the end of interventions.

Somatosensory stimulation, in the form of peripheral nerve stimulation (PNS) applied to the paretic limb, has also been used to enhance motor cortical excitability (Kaelin-Lang et al., 2002; Celnik et al., 2009). PNS consists of bursts of electrical stimuli delivered to the skin overlying peripheral nerves at regular intervals. The mechanisms underlying the effects of PNS on motor function still remain unclear, but may include modulation of cortical excitability that outlasts the period of stimulation as well (Kaelin-Lang et al., 2002). A recent study demonstrated that combined PNS and tDCS can facilitate a beneficial effect of motor training in chronic cortical and subcortical stroke patients (Celnik et al., 2009). The authors demonstrated that the combination of PNS of the paretic hand with anodal tDCS over the ipsilesional M1 before a sequential finger movement training task induced greater improvement compared with the use of each intervention alone (e.g., 41.3% compared with sham conditions). This effect outlasted the stimulation and training periods by days.

In another study, Koganemaru et al. (2010) examined, in chronic subcortical stroke patients, the single intervention effect of repetitive wrist and finger extension exercises aided by PNS, the single intervention of 5-Hz rTMS over the affected M1, and the combined effect of the two interventions. The findings indicate that the combination of motor training, PNS, and rTMS can facilitate use-dependent plasticity (UDP) and improve motor performance to an extent that cannot be attained by either intervention alone. The authors proposed that these functional improvements in the range of movements, grip power and flexor hypertonia (i.e., Ashworth scale) may be brought about by enhanced UDP in the affected M1 area controlling the agonist muscles involved in the exercises. Moreover, performing this combination of interventions over 6 weeks induced a beneficial effect that remained present 2 weeks later.

Although the majority of studies have focused on chronic stroke patients, high-frequency rTMS has been also tested in more acute stages (Khedr et al., 2005, 2010; Pomeroy et al., 2007; Di Lazzaro et al., 2008; Chang et al., 2010; Sasaki et al., 2011). In patients with moderate to severe motor impairment of the affected hand within the first months after stroke, Khedr and colleagues (2005) showed that high-frequency rTMS compared with sham stimulation resulted in improvements in the Scandinavian Stroke Scale, National Institutes of Health (NIH) Stroke Scale, and Barthel Index (Khedr et al., 2005).

Moreover, Ameli and coworkers (2009) compared ipsilesional high-frequency rTMS in patients with subcortical lesions and in patients with both subcortical and cortical damage. After real rTMS, patients with subcortical lesions had improvement in movement kinematics (i.e., index finger and hand tapping movements) compared with vertex stimulation (control condition), whereas patients with additional cortical lesions showed either no changes or in some cases worsening in movement kinematics. rTMS over ipsilesional M1 reduced neural activity of the contralesional M1 in patients with subcortical stroke, but caused a widespread bilateral recruitment of primary and secondary motor areas in patients with additional cortical stroke. Activity in ipsilesional M1 at baseline correlated with improvement of movement kinematics induced by rTMS. These data suggest that neural activity in ipsilesional M1 may serve as a surrogate marker for the effectiveness of rTMS and may allow for an individual selection of patients most suited for rTMS procedures.

Altogether, these studies in stroke patients suggest that NIBS may represent a possible strategy, in combination with customary neurorehabilitative treatments, to facilitate training effects and improve motor function. However, it remains unclear which hemisphere is the

optimal target for stimulation, or whether a combination of both contralesional and ipsilesional M1 stimulation sites might be more effective. Recent studies have begun to address this question by comparing different forms of NIBS in the affected and unaffected hemispheres in the same experimental design (Fregni et al., 2005; Boggio et al., 2007; Talelli et al., 2007; Di Lazzaro et al., 2008; Khedr et al., 2009; Takeuchi et al., 2009; Ackerley et al., 2010; Emara et al., 2010; Sasaki et al., 2011; Stagg et al., 2012).

Interestingly, a recent study explored functional changes associated with application of anodal tDCS over the ipsilesional M1 or cathodal tDCS over the contralesional M1 in patients with stable, chronic stroke (Stagg et al., 2012). The authors reported that anodal tDCS applied to ipsilesional M1 improved patients' response time (mean 5–10%). Both ipsilesional anodal and contralesional cathodal tDCS were associated with some degree of performance improvement, consistent with previous reports (Fregni et al., 2005; Hummel et al., 2005, 2006). Anodal tDCS to ipsilesional M1 was associated with increased task-related activity in the (stimulated) M1, in the PMC and SMA. The magnitude of improvement immediately following tDCS correlated with the stimulation-induced changes in fMRI signal in the stimulated M1. These results are consistent with TMS neurophysiological evidence showing an increased cortical excitability following stimulation of the affected hemisphere (Hummel and Cohen, 2005; Hummel et al., 2005; Di Lazzaro et al., 2008; Khedr et al., 2010).

See Tables 40.2 and 40.3 for details of these studies.

Bihemispheric regulation

Recent stimulation techniques proposed to target simultaneously the ipsilesional and contralesional regions (Takeuchi et al., 2009; Lindenberg et al., 2010b, 2012b; Bolognini et al., 2011). Lindenberg and colleagues (2010b) combined bihemispheric tDCS and simultaneous physical/occupational therapy. The authors found an improvement of motor function (WMFT scores) in comparison with the sham group, and increased activation of ipsilesional motor regions during paced movements of the affected limb, as assessed by fMRI. These effects outlasted the NBS application by at least 1 week. Furthermore, the same authors (Lindenberg et al., 2012b) reported that the effects of multiple sessions did not lead to a linear stimulus/response function, a finding of relevance for the design of upcoming trials.

Bolognini et al. (2011) investigated the neurophysiological and behavioral effects of bihemispheric tDCS combined with constraint-induced movement therapy (CIMT). These authors reported behavioral gains in the Jebsen–Taylor Hand Function Test (JHFT), handgrip strength, and FMA score after real but not sham tDCS. TMS neurophysiological measurements showed a reduction in transcallosal inhibition from the intact to the affected hemisphere accompanied by increased ipsilesional corticospinal excitability only in the real tDCS/CIMT group. Neurophysiological changes in this study correlated with the magnitude of the behavioral gains: MEP amplitudes correlated with ipsilesional M1 excitability and with FMA scores. Conversely, contralesional-to-ipsilesional M1 transcallosal inhibition showed an inverse correlation with FMA and JHFT scores. Both real and sham TMS groups showed a reduction in corticospinal excitability of the unaffected hemisphere. See Table 40.4 for details of these studies.

CONCLUSION

In summary, there is an increasing body of literature on possible beneficial effects of modulation of cortical excitability in the ipsilesional or contralesional M1s, or a combination of both on motor function. These effects have so far been stronger when NIBS is applied in close relationship with motor training (Takeuchi et al., 2008, 2009; Chang et al., 2010; Koganemaru et al., 2010; Lindenberg et al., 2010b, 2012b; Bolognini et al., 2011; Avenanti et al., 2012). The benefit of coupling NIBS with physical practice may rely on Hebbian principles of synaptic plasticity (Buonomano and Merzenich, 1998). Moreover, data suggest that the effects of facilitation or inhibition of ipsilesional or contralesional M1, respectively, may relate not only to modulation of local changes in cortical excitability, but also to the induction of reorganization in distributed neural networks.

To date, no significant adverse effects have been reported in stroke patients, such as induction of an epileptic seizure. Thus, rTMS and tDCS appear to be safe techniques when used according to current safety guidelines regarding intensity, frequency, and duration of stimulation (Poreisz et al., 2007; Rossi et al., 2009).

Well designed studies (i.e., multicenter, longitudinal, sham-controlled) are needed to determine how effective these techniques are in motor rehabilitation after stroke. It is likely that the outcome of NIBS interventional approaches may be influenced by fluctuations in resting brain activity before or after stimulation, by homeostatic plasticity, as conceptualized by the Binenstock–Cooper–Monroe theory (Bienenstock et al., 1982; Ziemann et al., 2004), and by the specific timing between rehabilitative therapy and cortical stimulation (Avenanti et al., 2012). Additionally, state dependency (i.e., a targeted region's varying response to stimulation based on its previous state of activity) should be studied in the context of combination of rehabilitation with stimulation (Silvanto et al., 2008).

Table 40.2

Summary of previous studies investigating the effectiveness of facilitatory rTMS or tDCS over primary motor cortex of affected hemisphere on motor behavior

Technique	Reference	Area of stimulation	No. of patients, mean age, lesion location, and time since stroke	Study design	Control condition	Stimulation parameters	Main results
rTMS, high frequency	Khedr et al., 2005	Hand area of M1, affected hemisphere	52 adults, 54 years, 26 cortical, 26 subcortical, 6–29 days	Single-blind, randomized, longitudinal, sham-controlled	52 patients, 26 real TMS, 26 sham TMS (perpendicular to scalp)	Ten 10-s trains of 3-Hz stimulation with 50 s between each train, 120% rMT, 10 consecutive daily sessions	Scandinavian Stroke Scale, NIH Stroke Scale, and Barthel Index scale measured before rTMS, at end of the rTMS session, and 10 days later; real rTMS improved patients' scores more than sham
rTMS, high frequency	Kim et al., 2006	Hand area of M1, affected hemisphere	15 adults, 54 years, 5 cortical, 10 subcortical, 4–41 months	Single-blind, crossover, sham-controlled	Real TMS, sham TMS (perpendicular to scalp)	10 Hz, 80% rMT, 8 trains of 2 s duration (160 pulses), each train followed by sequential finger movement task	rTMS resulted in significantly larger increase in MEP amplitude than sham rTMS; plastic change positively associated with enhanced motor performance accuracy in sequential finger motor task
rTMS, high frequency	Malcolm et al., 2007	Hand area of M1, affected hemisphere	19 adults, 67 years, 11 cortical, 8 subcortical, average 4 ± 3 years	Double-blind, longitudinal, randomized, sham-controlled	19 patients, 9 real TMS, 10 sham TMS (sham coil)	20 Hz (1200 pulses), 90% rMT, 10 consecutive, daily for 5 consecutive days followed by constraint-induced therapy	Regardless of group assignment, participants demonstrated significant gains on primary outcome measures: Wolf Motor Function Test and Motor Activity Log–Amount of Use. Participants receiving real rTMS failed to show differential improvement on either primary outcome measure
rTMS, high frequency	Yozbatiran et al., 2009	Hand area of M1, affected hemisphere	12 adults, 67 years, 4.7 ± 4.5 years	No blinding, 2-center study design	Real TMS, no sham control	20 Hz (1600 pulses), 90% rMT	20-Hz rTMS was safe. Modest improvements seen, for example in grip strength, range of motion, and pegboard performance, up to 1 week after rTMS

rTMS, high frequency	Pomeroy et al., 2007	Hand area of M1, affected hemisphere	27 adults, 75 years, average 27 days	Single-blind, randomized, longitudinal	Patients divided in 4 groups: (1) real rTMS + real VMC, (2) real rTMS + placebo VMC, (3) placebo rTMS + real VMC, (4) placebo rTMS + placebo VMC (placebo = sham coil)	1 Hz, 5 trains of 40 pulses, 3 min intertrain interval (total 200 pulses), 120% rMT, treatment: 8 working days	In real rTMS + real VMC group, MEP frequency increased 14% for biceps and 20% for triceps, whereas in placebo rTMS + placebo VMC group, it decreased 12% for biceps and 6% for triceps. For other groups there were changes of intermediate values
rTMS, high frequency	Ameli et al., 2009	Hand area of M1, affected hemisphere	29 adults, 56 years, 16 subcortical, 13 subcortical and cortical, 1–88 weeks	Single-blind, randomized, controlled	Real TMS, vertex TMS	5 Hz, 1000 pulses, 80 rMT	10-Hz rTMS improved movement kinematics in 14 of 16 patients with subcortical stroke, but not in patients with additional cortical stroke. rTMS over ipsilesional M1 reduced neural activity of contralesional M1 in 11 patients with subcortical stroke, but caused a widespread bilateral recruitment of primary and secondary motor areas in 7 patients with cortical stroke. Activity in ipsilesional M1 at baseline correlated with improvement of index finger tapping frequency induced by rTMS
rTMS, high frequency	Chang et al., 2010	Hand area of M1, affected hemisphere	28 adults, 56.6 years, average 13.4 days (subacute)	Single-blind, randomized, longitudinal, sham-controlled	28 patients, 18 real TMS, 10 sham TMS	10 Hz 1000 pulses, 90% rMT, 10 sessions over 2-week period + motor training	Motor function (Motoricity Index improved and Box and Block test) in both groups after treatment; real rTMS additionally improved motor function (Fugl–Meyer Assessment) of affected upper limb. Over 3 months after the stroke, the time and type of intervention for Motoricity Index of affected upper extremity showed significant interaction

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Table 40.2

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Technique	Reference	Area of stimulation	No. of patients, mean age, lesion location, and time since stroke	Study design	Control condition	Stimulation parameters	Main results
rTMS, high frequency	Khedr et al., 2010	Hand area of M1, affected hemisphere	48 adults, 59.53 years, acute ischemic stroke of middle cerebral artery territory, 6.50 ± 3.63 days	Single-blind, randomized, longitudinal, sham-controlled	48 patients, 16 real 3-Hz TMS, 16 real 10-Hz TMS, 16 sham TMS	3 Hz (5 s, 50 trains), with total 750 pulses at 130% rMT, 5 Hz (2 s, 37 trains), with total 750 pulses at 100% rMT, sham TMS perpendicular to scalp, daily for 5 days in a row	Real rTMS produced greater improvement in motor disability scales than sham, which was evident even at 1 year follow-up. These improvements were associated with changes in cortical excitability over treatment interval
rTMS, high frequency	Koganemaru et al., 2010	Hand area of M1, affected hemisphere	9 adults, 51.6 years, 9 subcortical, average 24 months	Crossover (exp. 1, 2), longitudinal (exp. 3)	9 patients (exp. 1), 9 healthy controls (exp. 2), PT + PNS, 5-Hz rTMS, PT + PNS + 5-Hz rTMS	5 Hz rTMS for 8 s (100% MT); exp. 3 12 times of rTMS + PNS + PT on the same 9 patients, with 1 session each day, on 2 separate days per week, for 6 weeks in total	Exp. 1: combined intervention (PT + PNS + TMS), but neither single intervention resulted in improvement of extensor movement and grip power along with reduction of flexor hypertonia in paretic upper limbs. Exp. 2: only combined intervention resulted in selective plastic changes of corticospinal excitability, motor threshold, and silent period for extensors. Exp. 3: combination of interventions over 6 weeks induced a beneficial effect that remained present to some extent 2 weeks later
tDCS, anodal	Hummel and Cohen, 2005	Hand area of M1, affected hemisphere	1 adult, 84-year-old man, subcortical, 107 months	Double-blind, crossover, sham-controlled	Anodal tDCS, sham tDCS	1 mA, 20 min	tDCS led to improvements in pinch force, Jebsen–Taylor Hand Function Test, and simple RTs in paretic hand that outlasted stimulation period for at least 40 min. These changes were accompanied by increased corticomotor excitability and reduced intracortical inhibition to TMS

tDCS, anodal	Hummel et al., 2005	Hand area of M1, affected hemisphere	6 adults, 57 years, 1 cortical, 5 subcortical, 23–107 months	Double-blind, crossover, sham-controlled	Anodal tDCS, sham tDCS	1 mA, 20 min	Jebsen–Taylor Hand Function Test measured in paretic hand improved significantly with anodal but not with sham tDCS. This effect outlasted the stimulation period and was present in every single patient tested. It correlated with an increment in motor cortical excitability within affected hemisphere and reduced short-interval intracortical inhibition
tDCS, anodal	Hummel et al., 2006	Hand area of M1, affected hemisphere	11 adults, 57 years, 18–107 months	Double-blind, crossover, sham-controlled	Anodal tDCS, sham tDCS	1 mA, 20 min	Anodal tDCS shortened RTs and improved pinch force in paretic hand relative to sham, an effect present in patients with higher impairment
tDCS, anodal	Hesse et al., 2007	Hand area of M1, affected hemisphere	10 adults, 63 years, 8 cortical, 2 subcortical, 4–8 weeks	No blinding, longitudinal	Anodal tDCS, no sham or control condition	1.5 mA, 7 min followed by robot-assisted arm training for 20 min every working day over 6 weeks	Arm function of 3 patients (2 with subcortical lesion) improved significantly. In remaining 7 patients, all with cortical lesions, arm function changed little
tDCS anodal	Celnik et al., 2009	Hand area of M1, affected hemisphere	9 adults, 55.3 years, 3 cortical and subcortical, 1 subcortical, 5 cortical, average 55.7 ± 5.57 months	Double-blind, crossover	PNS + tDCS, PNS + tDCS sham, tDCS + PNS sham, PNS sham + tDCS sham	Anodal, 1 mA, 20 min, 2 h of PNS or sham. In last 20 min PNS combined with 20 min of tDCS or sham. Motor training immediately after stimulation	PNS + tDCS resulted in 41.3% improvement in number of correct key presses relative to PNS sham + tDCS sham, 15.4% relative to PNS + tDCS sham, and 22.7% relative to tDCS + PNS sham. These performance differences were maintained 1 and 6 days after end of training

NIH, National Institutes of Health; M1, primary motor cortex; MEP, motor evoked potential; PNS, peripheral nerve stimulation; PT, physical training; rMT, resting motor threshold; RT, reaction time; rTMS, repetitive transcranial magnetic stimulation; tDCS, transcranial direct current stimulation; VMC, voluntary muscle contraction.

Table 40.3

Summary of previous studies investigating the effectiveness of inhibitory and facilitatory rTMS or tDCS over primary motor cortex of unaffected and affected hemisphere on motor behavior

Technique	Reference	Area of stimulation	No. of patients, mean age, lesion location, and time since stroke	Study design	Control condition	Stimulation parameters	Main results
tDCS, anodal, cathodal	Fregni et al., 2005	Hand area of M1, unaffected hemisphere, affected hemisphere	6 adults, 53.67 years, 3 cortical, 3 subcortical, 27.08 months	Single-blind, crossover, randomized, sham-controlled	Sham tDCS, anodal tDCS over affected hemisphere, cathodal tDCS over unaffected hemisphere	1 mA, 20 min	Both anodal and cathodal tDCS improved motor performance in the Jebsen–Taylor Hand Function Test
tDCS, anodal, cathodal	Boggio et al., 2007	Hand area of M1, unaffected hemisphere, affected hemisphere	9 adults, 57 years, 9 subcortical, 13–85 months	Exp. 1: double-blind. Exp. 2: crossover, longitudinal; randomized, sham-controlled	Sham tDCS, anodal tDCS over affected hemisphere, cathodal tDCS over unaffected hemisphere	Intensity 1 mA, 20 min, administered once (exp. 1), only cathodal daily over 5 consecutive days (exp. 2)	Improvement in Jebsen–Taylor Hand Function Test immediately after tDCS. Greater cumulative improvement after 5 days of tDCS (lasting for 14 days)
tDCS, anodal, cathodal	Stagg et al., 2012	Hand area of M1, unaffected hemisphere, affected hemisphere	12 adults, 63.47 years, 7 subcortical, 6 cortical, average 33.8 months	Single-blind, randomized, crossover, sham-controlled	Sham tDCS, anodal tDCS over affected hemisphere, cathodal tDCS over unaffected hemisphere	1 mA, 20 min	Anodal tDCS led to significant improvements in RTs with affected hand, associated with an increase in movement-related cortical activity in stimulated M1 and functionally interconnected regions. Cathodal tDCS led to a functional improvement only when compared with sham stimulation
rTMS, cTBS, iTBS	Talelli et al., 2007	Hand area of M1, unaffected hemisphere, affected hemisphere	6 adults, 57.7 years, 3 cortical, 3 subcortical, 31 months	Single-blind, crossover, sham-controlled	Real TMS, sham TMS (sham coil)	cTBS (300 pulses, 80% aMT), iTBS (600 pulses, 80% aMT)	cTBS suppressed MEPs evoked in healthy hands but did not change motor behavior or electrophysiology of paretic hands. iTBS transiently improved motor behavior and corticospinal output in paretic hands

rTMS, cTBS, iTBS	Di Lazzaro et al., 2008	Hand area of M1, unaffected hemisphere, affected hemisphere	12 adults, 69.4 years, 4 cortical, 8 subcortical, 12 healthy, average 5.1 days. Control subjects, mean age 63.2 years	Single-blind, No sham-controlled, but healthy control group, crossover	cTBS over unaffected hemisphere, iTBS over affected hemisphere	cTBS (600 pulses, 80% aMT), iTBS (800 pulses, 80 % aMT)	In patients, both iTBS and cTBS produced a significant increase in amplitude of MEPs evoked by stimulation of affected hemisphere. Effects in patients comparable to those in controls
rTMS, low frequency, high frequency	Khedr et al., 2009	Hand area of M1, unaffected hemisphere, affected hemisphere	36 adults, 57.9 years, 19 cortical, 17 subcortical, average 17.1 days	Single-blind, randomized, longitudinal, sham-controlled	36 patients, 12 real 1-Hz TMS over unaffected hemisphere, 12 real 3-Hz TMS over affected hemisphere, 12 sham TMS	1-Hz TMS, 100% rMT, 900 pulses, 3-Hz TMS, 130% rMT, 900 pulses, daily over 5 days	At 3-month time point, both real rTMS groups had improved significantly more in different rating scales (NIH Stroke Scale and Barthel Index Scale) than sham group; in addition, 1-Hz group performed better than 3-Hz group in NIH Stroke Scale
rTMS, cTBS, iTBS	Ackerley et al., 2010	Hand area of M1, unaffected hemisphere, affected hemisphere	10 adults, 60 years, 10 subcortical, average 28 months	Double-blind, crossover, sham-controlled	cTBS, over unaffected hemisphere, iTBS over affected hemisphere, sham (sham coil)	cTBS (600 pulses), iTBS (600 pulses), 90% aMT	TBS and training led to task-specific improvements in grip-lift. Specifically, cTBS of contralesional M1 led to an overall decrement in upper-limb function
rTMS, low frequency, high frequency	Emara et al., 2010	Hand area of M1, unaffected hemisphere, affected hemisphere	60 adults, 53.9 years, average 4.1 months	Single-blind, randomized, longitudinal, sham-controlled	60 patients, 20 real 1-Hz TMS over unaffected hemisphere, 20 real 5-Hz TMS over affected hemisphere, 20 sham (perpendicular to scalp)	1 Hz, 110120% rMT, 150 pulses, 5 Hz, 80–90% rMT, 750 pulses, 10 daily sessions + PT	Real rTMS improved finger tapping test, Activity Index score, and modified Rankin Scale in both groups. Effect sustained over 12-week observation period

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Table 40.3

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Technique	Reference	Area of stimulation	No. of patients, mean age, lesion location, and time since stroke	Study design	Control condition	Stimulation parameters	Main results
rTMS, low frequency, high frequency	Sasaki et al., 2011	Hand area of M1, unaffected hemisphere, affected hemisphere	29 adults, 65.7 years, 6–29 days	Single-blind, randomized, longitudinal, sham-controlled	29 patients, 11 real 1-Hz TMS over unaffected hemisphere, 9 real 10-Hz TMS over affected hemisphere, 9 sham (perpendicular to scalp)	1 Hz, 1800 pulses, 10 Hz, 1000 pulses, 5 days, consecutive sessions	Both real rTMS groups had significant increases in both grip strength and tapping frequency. More increase in 10-Hz group vs sham
rTMS, low frequency, high frequency, bihemispheric	Takeuchi et al., 2009	Hand area of M1, unaffected hemisphere, affected hemisphere	30 adults, 59.3 years, 30 subcortical, average 28.8 months	Double-blind, randomized	30 patients, 10 real bihemispheric TMS (alternating 1 Hz vs 10 Hz, 1000 pulses for each hemisphere, 90% rMT), 10 real 1-Hz TMS over unaffected hemisphere and sham 10 Hz over unaffected hemisphere, 10 real 10-Hz TMS over affected hemisphere and sham 1-Hz TMS over unaffected hemisphere	1 Hz vs 10 Hz, 1000 pulses for each hemisphere, 90% rMT, after TMS 15 min motor training	Bilateral and 1-Hz rTMS improved acceleration in paretic hand. Compared with 1 Hz, bihemispheric rTMS decreased inhibitory function of affected motor cortex and enhanced effect of motor training on pinch force. 10-Hz rTMS had no effect on motor function

aMT, active motor threshold; cTBS, continuous theta-burst stimulation; exp., experiment; iTBS, intermittent theta-burst stimulation; M1. primary motor cortex; MEP, motor evoked potential; NIH, National Institutes of Health; PT, physical training; RT, reaction time; rTMS, repetitive transcranial magnetic stimulation; tDCS, transcranial direct current stimulation.

Table 40.4

Summary of previous studies investigating the effectiveness of bilateral tDCS over primary motor cortex of unaffected and affected hemisphere on motor behavior

Technique	Reference	Area of stimulation	No. of patients, mean age, lesion location, and time since stroke	Study design	Control condition	Stimulation parameters	Main results
tDCS, bihemispheric	Lindenberg et al., 2010b	Hand area of M1s	20 adults, 58 years, 55.7 ± 5.57 months	Single-blind, randomized, sham-controlled	20 patients, 10 real bihemispheric (anodal over affected hemisphere and cathodal over unaffected hemisphere), 10 sham bihemispheric	1.5 mA, 30 min with simultaneous physical OT for 60 min, 5 consecutive sessions	Improvement of motor function significantly greater in real rTMS group (20.7% in Fugl–Meyer and 19.1% in Wolf Motor Function Test scores) compared with sham group (3.2% in Fugl–Meyer and 6.0% in Wolf Motor Function Test scores). Effects lasted 1 week. In real TMS group, stronger activation of intact ipsilesional motor regions during paced movements of affected limb found postintervention vs no changes in control group
tDCS, bihemispheric	Lindenberg et al., 2012b	Hand area of M1s	10 adults, 50.3 years, 20.3 ± 20.6 months	Exp. 1: no controls. Exp 2: double-blind, randomized, sham controlled	First treatment: 10 patients bihemispheric tDCS (anodal over affected hemisphere and cathodal over unaffected hemisphere). Second treatment: 4 of 10 patients and 6 new patients	1.5 mA, 30 min with simultaneous physical OT for 60 min, 5-day intervention (1st treatment) + a second 5-day intervention separated from first by 2–29 days (mean 9.9 ± 9.4 days) (2nd treatment)	First 5-day period yielded an increase in Upper-Extremity Fugl–Meyer (UE-FM) scores by 5.9 ± 2.4 points (16.6 ± 10.6%). Second 5-day period resulted in further meaningful, although significantly lower, gains with additional improvement of 2.3 ± 1.4 points in UE-FM compared with end of first 5-day period (5.5 ± 4.2%). Overall mean change after the two periods was 8.2 ± 2.2 points (22.9 ± 11.4%)

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Table 40.4

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Technique	Reference	Area of stimulation	No. of patients, mean age, lesion location, and time since stroke	Study design	Control condition	Stimulation parameters	Main results
tDCS, bihemispheric	Bolognini et al., 2011	Hand area of M1s	14 adults, 46.7 years, average 37 months	Double-blind, randomized	14 patients, 7 real bihemispheric tDCS (anodal over affected hemisphere and cathodal over unaffected hemisphere) and 7 sham bihemispheric	2 mA, 40 min, combined with CIMT	Patients in both groups demonstrated gains on Jebsen–Taylor Hand Function Test, Handgrip Strength, Motor Activity Log Scale, and Fugl–Meyer Motor Score. Gains larger in real tDCS group. Neurophysiological measurements showed a reduction in transcallosal inhibition from intact to affected hemisphere, and increased corticospinal excitability in affected hemisphere only in real tDCS/CIMT group. Such neurophysiological changes correlated with the magnitude of behavioral gains. Both groups showed a reduction in corticospinal excitability of unaffected hemisphere

CIMT, constraint-induced movement therapy; M1, primary motor cortex; OT, occupational therapy; rTMS, repetitive transcranial magnetic stimulation; tDCS, transcranial direct current stimulation.

In the future, it is possible that specific markers will be developed to help identify patients who can benefit the most from NIBS interventions based on individual patterns of cortical activation (Nowak et al., 2008; Ameli et al., 2009), white-matter microstructural integrity (Stinear et al., 2007; Lindenberg et al., 2012a), or presence of certain genetic polymorphisms (Kleim et al., 2006; Cheeran et al., 2009b; Fritsch et al., 2010).

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