Neurorehabil Neural Repair OnlineFirst, published on June 16, 2009 as doi:10.1177/1545968309336661

Neurorehabilitation and Neural Repair
Volume XX Number X
Month XXXX xx-xx
© 2009 The Author(s)
10.1177/1545968309336661
http://nnr.sagepub.com

Interhemispheric Competition After Stroke: Brain Stimulation to Enhance Recovery of Function of the Affected Hand

Dennis A. Nowak, MD, PhD, Christian Grefkes, MD, Mitra Ameli, MD, and Gereon R. Fink, MD, PhD

Background and purpose. Within the concept of interhemispheric competition, technical modulation of the excitability of motor areas in the contralesional and ipsilesional hemisphere has been applied in an attempt to enhance recovery of hand function following stroke. This review critically summarizes the data supporting the use of novel electrophysiological concepts in the rehabilitation of hand function after stroke. *Summary of review*. Repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) are powerful tools to inhibit or facilitate cortical excitability. Modulation of cortical excitability may instantaneously induce plastic changes within the cortical network of sensorimotor areas, thereby improving motor function of the affected hand after stroke. No significant adverse effects have been noted when applying brain stimulation in stroke patients. To date, however, the clinical effects are small to moderate and short lived. Future work should elucidate whether repetitive administration of rTMS or tDCS over several days and the combination of these techniques with behavioral training (ie, physiotherapy) could result in an enhanced effectiveness. *Conclusion*. Brain stimulation is a safe and promising tool to induce plastic changes in the cortical sensorimotor network to improve motor behavior after stroke. However, several methodological issues remain to be answered to further improve the effectiveness of these new approaches.

Keywords: *Stroke rehabilitation; Repetitive transcranial magnetic stimulation; Transcranial direct current stimulation; Interhemispheric competition*

Stroke is the leading cause for disability in Europe and the United States.[1] Recovery of motor deficits following stroke is incomplete in the majority of affected subjects despite intensive rehabilitation.[2-4] Six months following stroke up to 60% of stroke survivors still suffer from impaired manual dexterity, which affects their activities of daily living, and only a minority of those patients return to their professional life.[1,3,4] Given these epidemiological facts there is a socioeconomic need to develop and implement innovative, neurobiologically founded strategies in stroke rehabilitation.

Modern neurophysiological, noninvasive, brain-stimulation techniques, such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS), can be used to modulate cortical excitability for several minutes outlasting the stimulation period.[5] Depending on the stimulation parameters, cortical excitability can be reduced (inhibition) or enhanced (facilitation). Purposeful modulation of cortical excitability may induce plastic changes within the network of sensorimotor areas of the cortex and at the same time improve dexterity of the affected hand. Indeed, several research groups have demonstrated independently the potential efficacy of rTMS[6-15] and tDCS[16-20] in the rehabilitation of impaired hand function after stroke. The application of brain stimulation after stroke is mainly used based on the concept of interhemispheric competition.[21-24]

Based on a PubMed database search through December 2008, this review critically summarizes the pertinent literature on the application of both rTMS and tDCS to treat impaired hand function following stroke.

Recovery, Neuroplasticity, and the Effects of Brain Stimulation Following Stroke

Spontaneous recovery from stroke is attributed to plastic changes within the brain. Neuroplasticity occurs by means of regeneration, such as axonal and dendritic sprouting, and/or reorganization within cortical motor areas, such as modulation of synaptic plasticity or remapping of functional representations from lesioned areas onto ipsilesional unaffected areas surrounding the lesion or homologous areas within the unaffected (contralesional) hemisphere. Recent functional magnetic resonance imaging (fMRI) studies have shown increased neural activation within motor areas of both hemispheres when the affected hand or arm is moved early after stroke.[25-28]

From the Department of Neurology, University Hospital, University of Cologne, Cologne, Germany (DAN, CG, MA, GRF); Human Sensorimotor Control Laboratory, School of Kinesiology, University of Minnesota, Minneapolis, MN (DAN); Hospital for Neurosurgery and Neurology, Kipfenberg (DAN); Neuromodulation and Neurorehabilitation Group, Max Planck Institute for Neurological Research, Cologne (CG), Germany. Address correspondence to Dennis A. Nowak, MD, PhD, Klinik Kipfenberg, Neurochirurgische und Neurologische Fachklinik, Kindinger Strasse 13, D-85110 Kipfenberg, Germany. E-mail: dennis.nowak@neurologie-kipfenberg.de

The extent and pattern of neural reorganization depend on both the site and extension of the lesion. Reactivation of lateralized neural activity within motor areas of the affected hemisphere commonly correlates with good recovery of function of the affected hand.[25-27] The significance of neural activations within the unaffected (contralesional) hemisphere during motor performance of the affected hand or arm after stroke is still under debate. Possible explanations range from an epiphenomenon of physiological recovery or an adaptive plasticity of neural activation to a phenomenon of maladaptive changes in neural activation, which may hamper the process of recovery.

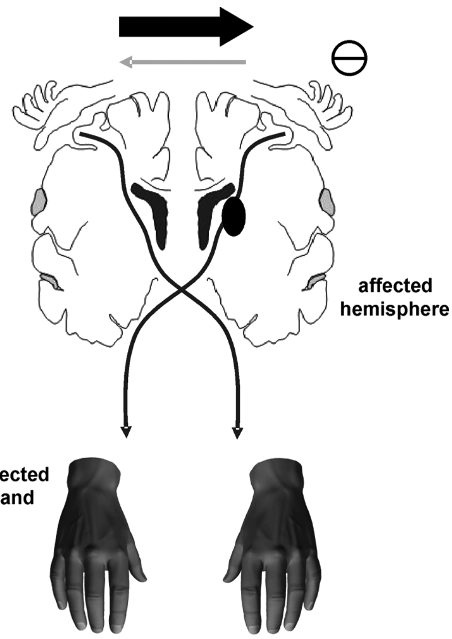
Interest in brain stimulation to promote recovery of function after stroke has been fuelled by the observation of long-term effects on the excitability of cerebral cortex that occur after repeated stimulation. These aftereffects appear to be analogous to long-term potentiation or long-term depression seen in the hippocampus after repeated activation of neural synaptic activity.[29] The role of neuroplasticity in recovery of motor function after stroke is well documented in both animal and human models.[30,31] Neuroplasticity refers to the ability of the brain to adjust its functional capacities to novel contexts. In case of stroke this may include modulation of neural activation within the remaining network of motor areas to maximize neural resources for recovery of function.[30] The application of brain-stimulation techniques in assisting recovery of function after stroke should prompt a critical evaluation of the distribution of neural activation in the affected brain and direct the induction of plastic changes in neural activation toward patterns that are known to be translated into motor recovery.

Evidence for the effectiveness of brain stimulation to promote recovery of function of the affected hand after stroke comes from studies in animals and humans. Squirrel monkeys with chronic small lesions of the primary motor cortex (M1) recover sensorimotor hand function better when a continuous subthreshold electrical stimulation of the lesioned M1 is given in conjunction with a rehabilitative training for several weeks.[32] Cortical mapping revealed large-scale emergence of new hand representations in peri-infarct motor cortex, primarily in cortical tissue underlying the electrode. In a similar approach, rTMS was used in stroke patients to increase excitability of M1 of the affected hemisphere and thereby enhance the effectiveness of rehabilitative training of the affected hand.[6,20,33] In healthy humans, temporary interference with neural processing in the hand area of the left M1 during right-hand finger movements induced by low-frequency (1 Hz) rTMS caused increased synaptic activity in the stimulated M1 and widespread changes in neural activity throughout areas engaged by the task.[34] In particular, movement-related activity in the premotor cortex of the nonstimulated hemisphere increased after inhibitory, for example, 1 Hz, rTMS, a finding closely resembling the pattern to be found after unilateral stroke.[12,27,28,35] So there is a strong rationale for applying brain-stimulation techniques in stroke survivors to promote or speed the processes of neuroplasticity underlying restoration of hand motor function.

The question is how brain stimulation facilitates restoration of sensorimotor function of the affected hand after stroke. In an interaction approach, rTMS or tDCS may provide unspecific input to the cortical motor system that should facilitate synaptic plasticity and shift neural activation into patterns necessary to obtain recovery of function during rehabilitative training. The idea is that changes in synaptic strength are the first and most essential step toward recovery of motor function. How exactly rTMS or tDCS develops such an effect on synaptic plasticity is unclear. Synaptic plasticity depends on the timing of input and output discharges of cortical neurons.[31,32] Stroke may cause a reduction or even loss of excitability of cortical neurons within the affected motor area and therefore affect the temporal coupling between synaptic input and output on a neuronal level. Reduced firing rates of cortical neurons within M1 on receipt of synaptic input reduce the effectiveness of synaptic binding. Enhancement of cortical excitability of the stroke-affected motor areas, induced either by direct facilitation of these areas or by reduction of transcallosal inhibition from the contralateral unaffected homologous motor areas, may improve the input–output coupling of neuronal firing rates and therefore enable synaptic plasticity, such as long-term potentiation or long-term depression, to be restored. Enhancement of cortical excitability of the stroke-affected motor areas might therefore promote synaptic plasticity and recovery of function.[32]

The details underlying the changes in cortical excitability within the bilateral cortical motor network and their impact on recovery of function of the affected arm and hand after stroke are far from being understood. Within this context, the brain-stimulation techniques under discussion here, namely rTMS and tDCS, have a major advantage: they are noninvasive and safe. Only recently, invasive brain-stimulation techniques found their way into clinical motor rehabilitation of stroke victims. Two randomized feasibility studies of cortical electrical stimulation of the affected M1 to improve upper limb motor recovery in human stroke victims have been conducted.[36,37] Patients receiving cortical electrical stimulation via an epidural electrode with either an external pulse generator (n = 8)[36] or with a fully implanted pulse generator (n = 24)[37] in combination with a motor rehabilitation training targeting the affected arm and hand improved significantly on the Upper Extremity Fugl-Meyer score, whereas control subjects receiving rehabilitation alone showed only minimal change. Neither of these feasibility studies was powered to test for efficacy. A recently initiated prospective, randomized, single-blinded, multicenter comparison study (Everest trial) of the safety and efficacy of epidural cortical stimulation delivered in conjunction with intensive task-oriented functional motor retraining of the affected arm and hand after ischemic stroke (investigational group: 91 patients received epidural electrical stimulation of affected M1 in combination with rehabilitation; control group: 55 patients received rehabilitation alone) did not meet its primary efficiency end-point at 4-week follow-up (http://ir.northstarneuro.com/releasedetail.cfm?ReleaseID=345646).[38] Improvement of hand function as measured by the Upper Extremity Fugl-Meyer test and the Arm Motor Ability Test was about 30% in both the investigational and control groups. These data have disappointed; however, they should be treated with great caution. The study protocol allowed enrolment of patients with 1 or more strokes, either subcortical or cortical, and the most recent stroke should be more than 4 months old. Subgroup analyses are urgently needed, but still lacking, as the efficiency of cortical stimulation may well differ between patients with 1 or more stroke locations, may differ between patients with cortical and subcortical stroke, and may also vary with time from stroke.[25-28,39] In addition, it is still unclear if the mechanisms on cortical processing and reorganization induced by epidural electrical stimulation are comparable with those elicited by tDCS or rTMS. More research is needed until definitive conclusions can be drawn on this issue.

Figure 1
Interhemispheric Competition After Stroke



Following a subcortical stroke in the left hemisphere resulting in a sensorimotor deficit of the right hand, the primary motor cortex of the unaffected (contralesional) hemisphere is disinhibited and exerts enhanced transcallosal inhibition of the primary motor cortex of the affected (ipsilesional) hemisphere. Enhanced transcallosal inhibition of the primary motor cortex of the affected hemisphere hampers motor recovery of the affected hand.

The Concept of Interhemispheric Competition

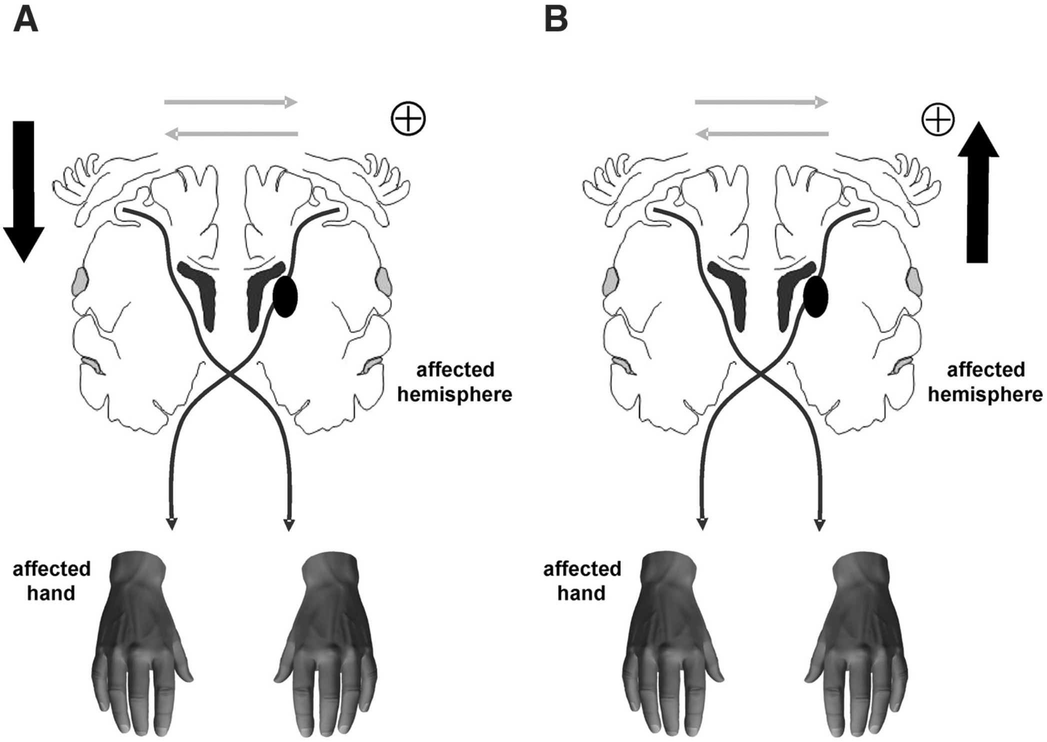
The adjuvant use of rTMS and tDCS may help improve the efficacy of rehabilitative strategies employed after stroke. The idea is that modulation of cortical excitability may induce synaptic plasticity and/or interfere with putative maladaptive processes developing after stroke. The electrophysiological correlate of an obvious maladaptive neural activation pattern after stroke is an imbalance of interhemispheric inhibition. Abnormal interhemispheric inhibition is the hypothetical model underlying experimental therapies of modulating cortical excitability within motor areas of the affected and unaffected hemispheres by means of rTMS or tDCS.[5,40] Reducing the influence of brain regions disturbing the physiological network architecture and normalization of cortical processing in the affected hemisphere might yield a better motor performance at the stroke-affected hand. In the healthy brain, neural activity in the motor areas of both hemispheres is functionally coupled and equally balanced in terms of mutual inhibitory control.[22] Movements of one hand are associated with enhanced neural activity in predominantly contralateral motor areas and increased inhibition from the activated contralateral motor areas toward homologous areas of the ipsilateral hemisphere.[23,24] Thus, the lateralization of neural activity during unimanual movements is likely to be related—at least in part—to interhemispheric inhibition between motor areas exerted via transcallosal connections.[23] This results in an inhibition of motor areas ipsilateral to the moving hand, ultimately reducing muscular activity in the nonactive hand.[24]

Stroke may affect the balance of transcallosal inhibitory circuits between the motor areas in both hemispheres. Such stroke-induced changes are regarded as one possible reason for the frequent finding that neural activity is often enhanced in motor areas of the unaffected hemisphere following ischemia.[5,21] Furthermore, movements of the affected hand have been reported to be associated with a pathological inhibition of M1 of the affected hemisphere originating from homologous cortical areas of the unaffected hemisphere.[5,21] Such increased inhibition of motor areas in the lesioned hemisphere may additionally influence the motor function of the affected hand, going beyond the deficit resulting from damage to corticospinal fibers. The amount of transcallosal inhibition exerted from the unaffected hemisphere on the affected hemisphere is positively correlated with the severity of the functional impairment of the affected hand.[21] Within the concept of interhemispheric competition, decoupled inhibitory interactions between the motor areas may hamper motor recovery, thereby deteriorating motor function of the affected hand after stroke (Figure 1).[5]

Following the concept of interhemispheric competition,[21-23] externally induced inhibition of M1 of the unaffected (contralesional) hemisphere or facilitation of excitability of M1 of the affected (ipsilesional) hemisphere have been suggested to normalize the balance of transcallosal inhibition between both hemispheres resulting in improved motor function of the affected hand (Figure 2).[5,21]

In healthy subjects, inhibition of the primary motor cortex induced by 1-Hz rTMS (intensity, 90% of the resting motor threshold; duration, 10 minutes; total number of pulses, 600) significantly accelerates movement speed in a sequential finger movement task with the ipsilateral hand.[41] The behavioral effect of 1-Hz rTMS on motor performance of the ipsilateral hand is very likely to result from enhanced cortical excitability of M1 contralateral to the stimulated hemisphere. One-hertz rTMS

Figure 2
Therapeutic Modulation of Cortical Excitability After Stroke



Inhibition of cortical excitability of the primary motor cortex of the unaffected (contralesional) hemisphere (A) or facilitation of cortical excitability of the primary motor cortex of the affected (ipsilesional) hemisphere (B) enables rebalancing of the shift of activity toward the affected (ipsilesional) hemisphere after stroke. Brain stimulation affects the motor performance of the affected hand.

(intensity, 100% of the resting motor threshold; duration, 10 minutes; total number of pulses, 600) also accelerates simple index and hand tapping movements as well as grasping movements performed with the ipsilateral hand.[42] Compared with sham stimulation (sham coil), inhibition of the right M1 (intensity, 90% of the resting motor threshold; 2 successive blocks of 10 trains at 1 Hz of 1-minute duration each with an intertrain interval of 10 seconds; total number of pulses, 1200) caused a significant increase of regional cerebral blood flow as measured with positron emission tomography during right hand movements in left M1.[43] This observation suggests that inhibition of the right M1 induced by 1-Hz rTMS results in a release of the left M1 from transcallosal inhibition derived from the right M1. Facilitation of cortical excitability of M1 (10 Hz; intensity, 80% of the resting motor threshold; 20 trains of 2 seconds duration) has been shown to improve learning of a sequential finger movement task with the *contralateral* hand compared with a sham stimulation (with the stimulation coil oriented in a 90° inverted position relative to the scalp surface) in healthy subjects.[44] These data acquired from healthy subjects lend strong support to the interhemispheric competition model and provide the neurobiological framework for the application of noninvasive brain-stimulation techniques, such as rTMS and tDCS, in the rehabilitation of impaired hand function after stroke. In the following, we summarize current data on inhibition of the motor areas of the unaffected hemisphere and facilitation of motor areas of the affected hemisphere aiming at enhancing recovery of function of the stroke-affected hand.

Inhibition of Motor Areas of the Unaffected Hemisphere

The studies that investigated the effect of inhibitory rTMS or tDCS over the primary motor cortex (or premotor cortex[8]) of the unaffected (contralesional) hemisphere on recovery of function of the affected hand after stroke are summarized in Table 1. Inhibition of M1 of the unaffected hemisphere after stroke is safe, and no serious adverse effects have been reported. Despite the overall small number (N = 136, including those receiving sham stimulation only) of patients investigated, the consistent finding across several independent groups (with the exception of a lacking effect of continuous theta burst stimulation[11]) suggests that inhibition of cortical excitability of M1 of the unaffected (contralesional) hemisphere may help improve recovery of function of the affected hand after stroke.

(text continues on page 8)

Table 1
Summary of Previous Studies Investigating the Effectiveness Of Inhibitory rTMS or tDCS Over the Primary Motor Cortex of the Unaffected Hemisphere on Motor Behavior of the Affected Hand After Stroke

Technique	Area of Stimulation	Number of Patients (Mean Age)	Lesion Location	Disease Duration at the Time of Stimulation	Study Design	Application of rTMS/ tDCS	Stimulation Parameters	Outcome Measure (Percentage Improvement of Motor Performance of the Affected Hand)	Reference
rTMS	Hand area of the primary motor cortex of the unaffected hemisphere	20 adults (60 ± 10 years)	20 subcortical	6-60 months	Double-blinded, crossover, sham-controlled	10 patients received real rTMS, 10 patients received sham stimulation (positioning the coil perpendicularly to the scalp over M1)	Frequency, 1 Hz; intensity, 90% of the resting motor threshold; duration, 25 minutes	Peak pinch acceleration (20% immediately after rTMS over M1); peak pinch force (no improvement immediately after rTMS over M1)	Takeuchi et al[7]
	Hand area of the primary motor cortex and dorsal premotor cortex of the unaffected hemisphere	10 adults (53 ± 12 years)	10 subcortical	≤12 months	Single-blinded, crossover, sham-controlled	Real rTMS and sham stimulation (sham coil) over M1 and real rTMS over the premotor cortex of the unaffected hemisphere	Frequency, 1 Hz; intensity, 100% of the resting motor threshold; duration, 10 minutes	Simple and choice reaction times (16% and 11% immediately after rTMS over M1, respectively), Purdue Pegboard Test (33% immediately after rTMS over M1), index finger tapping (<5% immediately after rTMS over M1); no significant improvement following rTMS over the premotor cortex	Mansur et al[8]
	Hand area of the primary motor cortex of the unaffected hemisphere	15 adults (56 ± 12 years)	2 cortical and 13 subcortical	1-11 years	Single-blinded, longitudinal, randomized, sham-controlled, phase II (1:2, sham–real rTMS)	10 patients received real rTMS; 5 patients received sham stimulation (sham coil)	Frequency, 1 Hz; intensity, 100% of the resting motor threshold; duration, 20 minutes; repeated daily over 5 days	Jebsen–Taylor Hand Function test (15% and 5% improvement immediately and 14 days after 5 days of rTMS over M1), simple (50% improvement immediately and 14 days after 5 days of rTMS over M1) and choice reaction times (30% improvement immediately and 14 days after 5 days of rTMS over M1), and Purdue Pegboard test (60% improvement immediately and 14 days after 5 days of rTMS over M1)	Fregni et al[10]
	Hand area of the primary motor cortex of the unaffected hemisphere	74-year-old woman	Subcortical	23-107 months	Double-blind, crossover, single-case study	Real rTMS and sham stimulation (sham coil) over M1	Frequency, 1 Hz; intensity, 100% of the resting motor threshold; duration, 20 minutes	No movements possible prior to rTMS over M1; 4 months after a first rTMS over M1 improvements of thumb and finger movements (5° to 15°); a second rTMS session over M1 4 months after the first caused additional improvements of thumb and finger movements (10° to 20°); modified Ashworth scale for spasticity (no change after first and second rTMS session over M1)	Boggio et al[45]

(continued)

Table 1 (continued)

Technique	Area of Stimulation	Number of Patients (Mean Age)	Lesion Location	Disease Duration at the Time of Stimulation	Study Design	Application of rTMS/tDCS	Stimulation Parameters	Outcome Measure (Percentage Improvement of Motor Performance of the Affected Hand)	Reference
	Hand area of the primary motor cortex of the unaffected hemisphere	6 (61 ± 14 years)	3 cortical and 3 subcortical	12-108 months	Single-blinded, crossover, sham-controlled	Real rTMS and sham stimulation (sham coil) over M1	Frequency, 3 pulses at 50 Hz given at a frequency of 5Hz, 80% of the active motor threshold; duration, 20 seconds; total number of pulses, 300	Speed (no significant effect) and peak grip force (no significant effect) as assessed by a whole hand gripping task	Talelli et al[11]
	Hand area of the primary motor cortex of the unaffected hemisphere	15 adults (46 ± 8 years)	15 subcortical	1-4 months	Double-blinded, crossover, sham-controlled	Real rTMS over M1 and sham stimulation (over vertex) in each patient	Frequency, 1 Hz; intensity, 100% of the resting motor threshold; duration, 10 minutes	Kinematics (velocity and frequency) of index finger tapping (25% immediately after rTMS over M1) and kinematics (velocity and timing) of grasping movements (30% immediately after rTMS over M1)	Nowak et al[12]
	Hand area of the primary motor cortex of the unaffected hemisphere	20 adults (62 ± 8 years)	20 subcortical	7-121 months	Double-blinded, crossover, sham-controlled	10 patients received real rTMS, 10 patients received sham stimulation (positioning the coil perpendicularly to the scalp over M1)	Frequency, 1 Hz; intensity, 90% of the resting motor threshold; duration, 25 minutes; followed by a metronome-paced pinching task between index finger and thumb as motor training for 15 minutes	Pinch acceleration (30% and 20%, immediately following and 1 week after motor training following rTMS over M1, respectively); peak pinch force (30% and 20%, immediately following and 1 week after motor training following rTMS over M1, respectively)	Takeuchi et al[13]
	Hand area of the primary motor cortex of the unaffected hemisphere	12 adults (45 ± 9 years)	12 subcortical	1-15 months	Double-blinded, crossover, sham-controlled	Real rTMS over M1 and sham stimulation (over vertex) in each patient	Frequency, 1 Hz; intensity, 100% of the resting motor threshold; duration, 10 minutes	Efficiency (30% immediately after rTMS over M1) and timing (40% immediately after rTMS over M1) of grip force kinetics when grasping and lifting an object	Dafotakis et al[14]
	Hand area of the primary motor cortex of the unaffected hemisphere	12 adults (63 ± 11 years)	12 subcortical	<14 days	Double-blinded, crossover, sham-controlled	Real rTMS and sham stimulation (sham coil) over M1	Frequency, 1 Hz; intensity, 90% of the resting motor threshold; duration, 20 minutes	Peak grip force (no improvement immediately after rTMS over M1); Nine Hole Peg Test (10% immediately after rTMS over M1)	Liepert et al[15]

(continued)

Table 1 (continued)

Technique	Area of Stimulation	Number of Patients (Mean Age)	Lesion Location	Disease Duration at the Time of Stimulation	Study Design	Application of rTMS/ tDCS	Stimulation Parameters	Outcome Measure (Percentage Improvement of Motor Performance of the Affected Hand)	Reference
	Hand area of the primary motor cortex of the unaffected hemisphere	10 children (14 ± 4 years)	10 subcortical	3-13 years	Single-blinded, longitudinal, randomized, sham-controlled (1:1, sham–real rTMS)	5 children received sham stimulation (positioning the coil perpendicularly to the scalp over M1); 5 children received real rTMS	Frequency, 1 Hz; intensity, 100% of the resting motor threshold of the unaffected M1; duration, 20 minutes; repeated daily for 8 days	Melbourne assessment of upper extremity function (9% after 8 days of daily rTMS over M1, improvement persists for at least 1 week poststimulation); grip strength as assessed by a hand dynamometer (20% after 8 days of daily rTMS over M1, improvement persists for at least 1 week poststimulation)	Kirton et al[46]
tDCS	Hand area of the primary motor cortex of the unaffected hemisphere	6 adults (54 ± 17 years)	3 cortical and 3 subcortical	12-72 months	Single-blinded, crossover, randomized, sham-controlled	Sham tDCS, anodal tDCS of the affected hemisphere and cathodal stimulation of the unaffected hemisphere	Cathodal electrode placed over the hand area of the primary motor cortex of the unaffected hemisphere; intensity, 1 mA; duration, 20 minutes	Jebsen–Taylor Hand Function Test (12% improvement immediately after tDCS over M1)	Fregni et al[18]
	Hand area of the primary motor cortex of the unaffected hemisphere	9 adults (57 ± 13 years)	9 subcortical	13-85 months	Double-blinded, (i) crossover and (ii) longitudinal, randomized, sham-controlled	Sham tDCS, anodal tDCS of the affected hemisphere and cathodal stimulation of the unaffected hemisphere	Cathodal electrode placed over the hand area of the primary motor cortex of the unaffected hemisphere; intensity, 1 mA; duration, 20 minutes; administered (i) once and (ii) daily over 5 consecutive days	Jebsen–Taylor Hand Function Test (10% improvement immediately after tDCS over M1; 17% cumulative improvement immediately after 5 days of daily tDCS over M1 lasting for 14 days after stimulation)	Boggio et al[20]

Abbreviations: rTMS = repetitive transcranial magnetic stimulation; tDCS = transcranial direct current stimulation.

The effectiveness of inhibitory rTMS over M1 of the unaffected (contralesional) hemisphere has been investigated in 121 stroke patients so far.[7,8,10-15,45,46] The study design most commonly applied was a crossover, sham stimulation controlled design.[7,8,11-15,45] The effect size of a single session of inhibitory (eg, 1 Hz) rTMS over M1 of the unaffected hemisphere on motor function of the affected hand after stroke is usually in the range of 10% to 60% improvement, depending on the outcome measures applied (see Table 1). The only study testing the effectiveness of a recently developed high-frequency, but inhibitory, rTMS (continuous theta burst stimulation) protocol on potential improvement of motor function of the affected hand after stroke did not detect significant effects.[11] Although the majority of studies focused on chronic stroke patients (>6 months after stroke),[7,10,11,13,14,45,46] inhibitory, for example, 1 Hz, rTMS over M1 of the unaffected hemisphere appears to be equally effective in acute stroke patients (<6 months after stroke).[8,12,14,15] Interestingly, a recent study also demonstrated safety and effectiveness of 1-Hz rTMS over M1 of the unaffected hemisphere in children with impaired sensorimotor function of the hand due to stroke.[46] Inhibitory rTMS over M1 of the unaffected hemisphere has been mainly applied to patients with subcortical stroke (N = 116, including those receiving sham stimulation only), and more studies are needed to answer the question if it is equally effective in cortical stroke subjects. In case inhibitory (1 Hz) rTMS over M1 of the unaffected (contralesional) hemisphere was applied repetitively over several (5-8) days, the beneficial effects on motor function of the affected hand appeared to last for at least 1 to 2 weeks after the stimulation period.[10,46] No cumulative effect on effect size has been found. Similarly, the combination of 1-Hz rTMS over M1 of the unaffected hemisphere with a motor training session caused the improvement of behavior to last at least 1 week.[13]

Improvement of hand motor performance following inhibitory rTMS over M1 of the unaffected (contralesional) hemisphere is associated with a reduction of transcallosal inhibition from the unaffected toward the affected hemisphere after stroke.[7] Hence, inhibition of contralesional M1 should be effective in those patients in whom the unaffected hemisphere is overactive causing enhanced transcallosal inhibition toward ipsilesional motor areas. Indeed, rTMS-induced inhibition of M1 of the unaffected (contralesional) hemisphere results in a normalization of neural overactivity within the cortical motor network in both hemispheres as assessed by fMRI (Figure 3).[12,35] In addition, fMRI is a sensitive tool to identify surrogate markers indicating a likely positive effect of inhibitory rTMS on motor function of the affected hand after stroke.[12] For example, increased neural activity within the dorsal premotor cortex or the parietal operculum of the unaffected (contralesional) hemisphere before rTMS intervention was significantly correlated with the behavioral improvement of the affected hand observed after inhibitory rTMS treatment in stroke patients.[12]

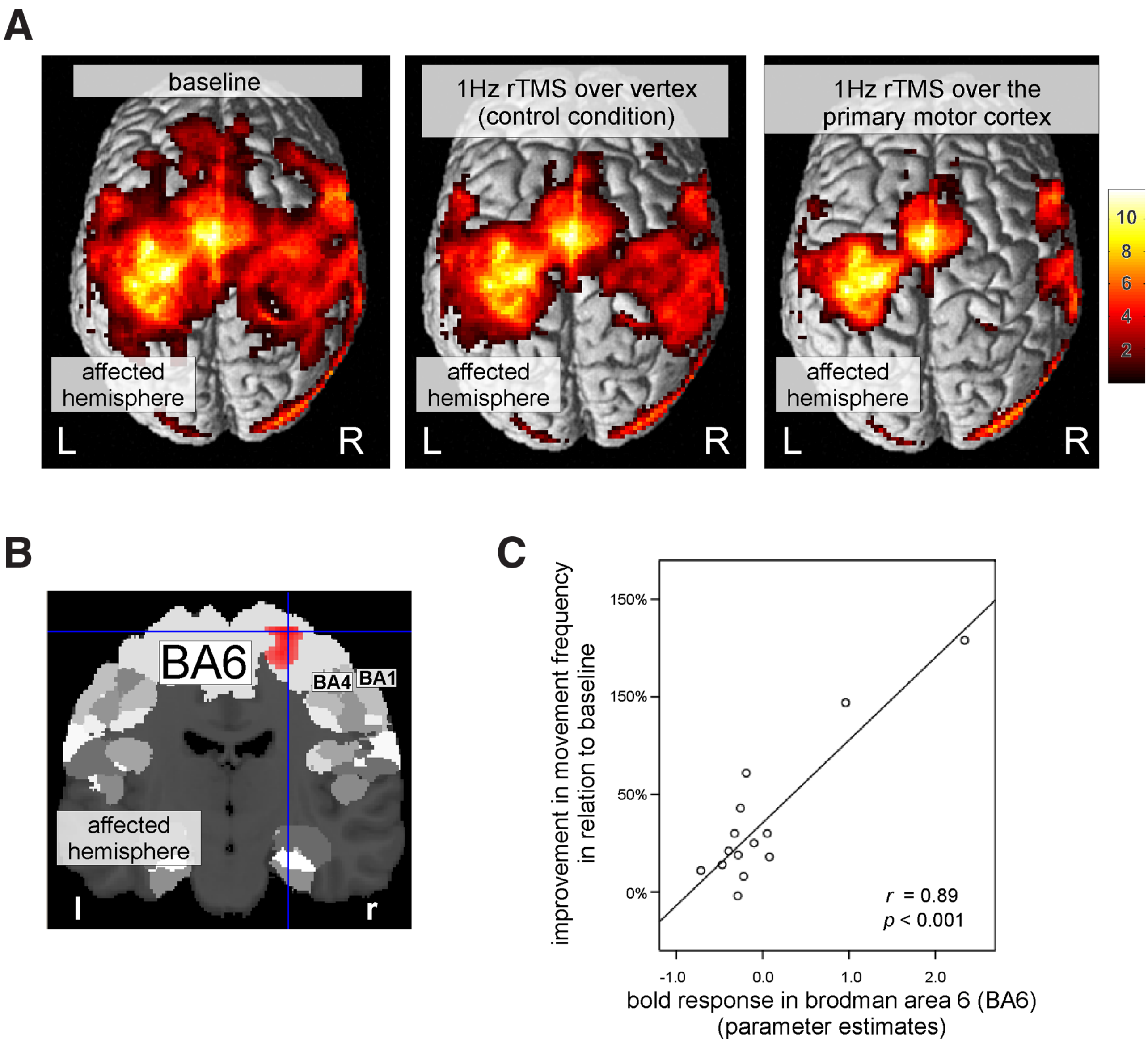
Inhibition of M1 of the unaffected hemisphere can also be induced by cathodal (inhibitory) tDCS. Two studies tested in a crossover, sham-controlled, randomized design if a single session of cathodal tDCS applied over contralesional M1 improves motor function of the stroke-affected hand in chronic (>12 months after stroke) stroke (N = 15).[18,20] Twelve of the 15 patients investigated had a subcortical stroke (see Table 1). No acute stroke patients have been tested. Cathodal tDCS over M1 of the unaffected hemisphere is safe and no adverse effects have been reported. The effect size of cathodal tDCS over M1 of the unaffected hemisphere on motor function of the affected hand is about 10% improvement as assessed with the Jebsen–Taylor Hand Function Test. Repeated application of cathodal tDCS over M1 of the unaffected hemisphere over 5 consecutive days causes no cumulative increase in effect size, but the beneficial effect on the function of the affected hand lasted at least 14 days after the stimulation period.[20] Given the small sample size of the study population, more data are needed to draw definitive conclusions regarding the usefulness of cathodal tDCS to enhance recovery of function of the affected hand after stroke.

In summary, inhibitory (1 Hz) rTMS and (cathodal) tDCS applied over M1 of the unaffected hemisphere are safe and effective procedures to improve motor function of the affected hand after stroke. Effects size ranges from 10% to 60% for both methods (see Tables 1 and 2). This is in the range or below the effect sizes to be achieved by behavioral training, such as constraint-induced movement therapy (CIMT).[49] Mainly patients with mild to moderate sensorimotor impairment of the affected hand have been investigated. Studies testing the effectiveness of either 1-Hz rTMS or cathodal tDCS applied over M1 of the unaffected hemisphere on severely impaired hand function in stroke survivors are yet to be designed. Repeated application over several days[10,20,46] and/or the combination with a motor training[13] appear to produce a lasting effect on hand motor function (1-2 weeks) without an increase in overall effect size. Open questions refer to the effectiveness of cathodal tDCS in acute stroke patients and the carryover of improvements in basic hand motor function to daily life motor activities.

Facilitation of Motor Areas of the Affected Hemisphere

Several fMRI studies have shown that neural overactivity in motor areas of the unaffected hemisphere correlates with a less favorite recovery of the motor deficit of the affected hand in the subacute phase after stroke.[25-28] In the chronic phase after stroke, however, neural overactivity of motor areas within the unaffected (contralesional) hemisphere was demonstrated to have beneficial effects regarding motor function of the affected hand.[26,28] This most likely reflects that the unaffected hemisphere compensates functional impairments of the affected hemisphere. In these cases facilitation of the motor areas of the affected hemisphere appears to be a more useful approach to enhance motor function of the affected hand after stroke. Studies investigating the effectiveness of facilitatory rTMS or tDCS over the primary motor cortex of the affected (ipsilesional) hemisphere after stroke are summarized in

Figure 3
Changes in Neural Activation After Stroke



A, Illustration of neural activity within the motor areas of both hemispheres during grasping movements performed with the affected hand in a group of subcortical stroke patients (N = 15) prior to (baseline) and after inhibitory 1-Hz rTMS applied over vertex (control condition) or the hand area of the primary motor cortex of the unaffected (contralesional) hemisphere. One-hertz rTMS over the primary motor cortex of the unaffected (contralesional) hemisphere, but not over the vertex, causes a *normalization* of neural activity with reduced activity in motor areas of the unaffected (contralesional) hemisphere ($P < .05$, cluster-level corrected). B, C, The intensity of neural activity in Brodman area 6 (BA6, dorsal premotor cortex) of the unaffected (contralesional) hemisphere at baseline correlates with motor improvement of the affected hand after inhibitory (1 Hz) rTMS over the hand area of the primary motor cortex of the unaffected (contralesional) hemisphere.[12]

Table 2. Facilitation of M1 of the affected hemisphere is safe and no serious adverse events have been documented. The majority of patients investigated suffered from mild to moderate impairment of sensorimotor function of the affected hand. Despite the overall limited number of patients investigated (N = 135, including those receiving sham stimulation only), facilitation of cortical excitability of M1 of the affected hemisphere is effective to improve motor function of the affected hand after stroke.

To date, the effectiveness of facilitatory (3 Hz, 10 Hz, 20 Hz, and intermittent theta burst stimulation) rTMS over M1 of the affected (ipsilesional) hemisphere on recovery of function of the affected hand has been studied in 104 stroke patients (including those receiving sham stimulation only).[6,9,11,47,48] Both acute (<6 months after stroke) and chronic (>6 months after stroke) stroke patients have been investigated. Equal numbers of patients with cortical and subcortical strokes have been tested. Three longitudinal, randomized, sham-controlled

(text continues on page 13)

Table 2
Summary of Previous Studies Investigating the Effectiveness Of Facilitatory rTMS or tDCS Over the Primary Motor Cortex of the Affected Hemisphere on Motor Behavior of the Affected Hand After Stroke

Technique	Area of Stimulation	Number of Patients (Mean Age)	Lesion Location	Disease Duration at the Time of Stimulation	Study Design	Application of rTMS/tDCS	Stimulation Parameters	Outcome Measure (Percentage Improvement of Motor Performance of the Affected Hand)	Reference
rTMS	Hand area of the primary motor cortex of the affected hemisphere	52 adults (54 ± 10 years in the real rTMS group, 52 ± 8 years in the sham rTMS group)	26 cortical and 26 subcortical	5-10 days	Single-blinded, longitudinal, randomized, sham-controlled (1:1, sham–real rTMS)	26 patients received real rTMS, 26 patients received sham stimulation (positioning the coil perpendicularly to the scalp over M1)	Frequency, 3 Hz; intensity, 120% of the resting motor threshold, 10 trains of 10 seconds duration, 50 seconds break in between, stimulation over 10 consecutive days	Scandinavian Stroke Scale (45% and 75% improvement immediately after and 10 days after 10 days of daily rTMS over M1, respectively), National Institute of Health Stroke Scale (50% and 75% improvement immediately after and 10 days after 10 days of daily rTMS over M1, respectively), and Barthel Index (75% and 110% improvement immediately after and 10 days after 10 days of daily rTMS over M1, respectively)	Khedr et al[6]
	Hand area of the primary motor cortex of the affected hemisphere	15 adults (54 ± 5 years)	5 cortical and 10 subcortical	4-41 months	Single-blinded, crossover, sham-controlled	Real rTMS and sham stimulation (positioning the coil perpendicularly to the scalp over M1) over M1 of the affected hemisphere	Frequency, 10 Hz; 80% of the resting motor threshold, 8 trains of 2 seconds duration; each train was followed by a sequential finger movement task for 40 seconds and a 28-second break	Movement accuracy (75% and 125% improvement after first and second sessions of rTMS over M1) and movement time (25% and 20% improvement after first and second sessions of rTMS over M1)	Kim et al[9]
	Hand area of the primary motor cortex of the affected hemisphere	6 adults (61 ± 14 years)	3 cortical and 3 subcortical	12-108 months	Single-blinded, crossover, sham-controlled	Real rTMS and sham stimulation (positioning the coil perpendicularly to the scalp over M1 and reducing stimulation intensity at 50% of the maximum output) over M1	Frequency, 3 pulses at 50 Hz given at a frequency of 5 Hz, 80% of the active motor threshold, 20 trains of 2-second duration; intertrain interval, 8 seconds; total number of pulses, 600	Speed (90% improvement immediately after rTMS over M1 lasting for up to 40 minutes) and peak grip force (no significant effect) assessed by a whole hand gripping task	Talelli et al[11]

(continued)

Table 2 (continued)

Technique	Area of Stimulation	Number of Patients (Mean Age)	Lesion Location	Disease Duration at the Time of Stimulation	Study Design	Application of rTMS/tDCS	Stimulation Parameters	Outcome Measure (Percentage Improvement of Motor Performance of the Affected Hand)	Reference
	Hand area of the primary motor cortex of the affected hemisphere	19 adults (67 ± 7 years)	11 cortical and 8 subcortical	On average 4 ± 3 years from stroke	Double-blinded, longitudinal, randomized, sham-controlled (1:1, sham–real rTMS)	9 patients received real rTMS, 10 patients received sham stimulation (sham coil)	Frequency, 20 Hz, 90% of the resting motor threshold, 50 trains of 2-second duration with an intertrain interval of 28 seconds; total number of pulses, 1200; stimulation over 10 consecutive days followed by immediate constraint-induced movement training, patients wore a restraining mitt for 90% of waking hours	Wolf Motor Function Test and Motor Activity Log (significant improvement in both sham rTMS and real rTMS groups due to constraint-induced movement therapy, but no additive effect of rTMS over M1)	Malcolm et al[48]
	Hand area of the primary motor cortex of the affected hemisphere	12 adults (67 ± 12 years)	No detailed information	>12 weeks	Nonblinded, longitudinal, real rTMS only	Real rTMS over M1 of the affected hemisphere; no sham control	Frequency, 40 trains of 40 pulses at 20 Hz, separated by an intertrain interval of 28 seconds, given at 90% of the resting motor threshold; total number of pulses, 1600	Fugl-Meyer score (no significant effect), grip strength (20% and 20% improvement immediately and 1 week after rTMS, respectively), Nine Hole Peg Test (80% and 120% improvement immediately and 1 week after rTMS, respectively)	Yozbatiran et al[47]
tDCS	Hand area of the primary motor cortex of the affected hemisphere	6 adults (54 ± 17 years)	2 cortical and 4 subcortical	12-72 months	Single-blinded, crossover, randomized, sham-controlled	Sham tDCS, anodal tDCS of the affected hemisphere and cathodal stimulation of the unaffected hemisphere	Anodal electrode placed over the hand area of the primary motor cortex of the affected hemisphere; intensity, 1 mA; duration, 20 minutes	Jebsen–Taylor Hand Function Test (7% improvement immediately after tDCS over M1)	Fregni et al[18]

(continued)

Table 2 (continued)

Technique	Area of Stimulation	Number of Patients (Mean Age)	Lesion Location	Disease Duration at the Time of Stimulation	Study Design	Application of rTMS/tDCS	Stimulation Parameters	Outcome Measure (Percentage Improvement of Motor Performance of the Affected Hand)	Reference
	Hand area of the primary motor cortex of the affected hemisphere	84-year-old man	Subcortical	107 months	Double-blinded, crossover, sham-controlled	Sham tDCS and anodal tDCS of the affected hemisphere	Anodal electrode placed over the hand area of the primary motor cortex of the affected hemisphere; intensity, 1 mA; duration, 20 minutes	Jebsen–Taylor Hand Function Test (9% improvement immediately after tDCS over M1), peak pinch force (17% improvement immediately after tDCS over M1) and simple reaction times (22% improvement immediately after tDCS over M1)	Hummel and Cohen[16]
	Hand area of the primary motor cortex of the affected hemisphere	6 adults (62 ± 8 years)	1 cortical, 5 subcortical	23-107 months	Double-blinded, crossover, sham-controlled	Sham tDCS and anodal tDCS of the affected hemisphere	Anodal electrode placed over the hand area of the primary motor cortex of the affected hemisphere; intensity, 1 mA; duration, 20 minutes	Jebsen–Taylor Hand Function Test (10% improvement immediately after tDCS over M1)	Hummel et al[17]
	Hand area of the primary motor cortex of the affected hemisphere	11 adults (57 ± 16 years)	No detailed information	18-107 months	Double-blinded, crossover, sham-controlled	Sham tDCS and anodal tDCS of the affected hemisphere	Anodal electrode placed over the hand area of the primary motor cortex of the affected hemisphere; intensity, 1 mA; duration, 20 minutes	Simple reaction time(13% improvement immediately after tDCS over M1) and peak pinch force (20% improvement immediately after tDCS over M1)	Hummel et al[19]
	Hand area of the primary motor cortex of the unaffected hemisphere	9 adults (57 ± 13 years)	Subcortical	13-85 months	Double-blinded, crossover, randomized, sham-controlled	Sham tDCS, anodal tDCS of the affected hemisphere and cathodal stimulation of the unaffected hemisphere	Anodal electrode placed over the hand area of the primary motor cortex of the affected hemisphere; intensity, 1 mA; duration, 20 minutes	Jebsen–Taylor Hand Function Test (7% improvement immediately after tDCS over M1)	Boggio et al[20]
	Hand area of the primary motor cortex of the affected hemisphere	10 (63 ± X years)	8 cortical, 2 subcortical	4-8 weeks	Nonblinded, crossover, real tDCS only	Anodal tDCS of the affected hemisphere, no sham or control stimulation	Anodal electrode placed over the hand area of the primary motor cortex of the affected hemisphere; intensity, 1.5 mA; duration, 7 minutes followed by robot-assisted arm training for 20 minutes every working day over 6 weeks	Jebsen–Taylor Hand Function Test (150% improvement immediately after 6 weeks of tDCS over M1), Medical Research Council score (150% improvement immediately after 6 weeks of tDCS over M1)	Hesse et al[31]

Abbreviations: rTMS = repetitive transcranial magnetic stimulation; tDCS = transcranial direct current stimulation.

trials[6,47,48] and 2 crossover, sham-controlled[9,11] trials have been performed. The effect size of a single session of facilitatory rTMS over M1 of the affected hemisphere ranges from 20% to 125% improvement of motor function of the affected hand, depending on the assessment measure used.[9,11,47] The facilitatory rTMS protocols appear not to differ regarding their effect size with the essential constraint that no unique outcome measure has been tested for each protocol (Table 2). One study reported that repeated application of facilitatory rTMS (3 Hz for 10 consecutive days) over M1 of the affected (ipsilesional) hemisphere in acute stroke patients (5-10 days from stroke) caused the beneficial effect on motor improvement of the affected hand to outlast the stimulation period of at least 10 days.[6] In addition, the amount of motor improvement increased over the 10 days following the stimulation period by 20% to 35%.[6] In contrast, repeated application of 20-Hz rTMS over M1 of the affected hemisphere in combination with consecutive CIMT over 10 consecutive days did not cause an additive effect of rTMS on top of the improvement of hand motor function induced by CIMT in chronic stroke patients (4 ± 3 years from stroke).[47] Essentially, more data are needed to judge the effectiveness of repeated sessions of facilitatory rTMS over M1 of the affected hemisphere over several days or weeks on recovery of function of the affected hand after stroke. Preliminary data on the combination of approaches with behavioral training are disappointing.[47]

Anodal tDCS is an alternative approach to increase cortical excitability of M1 of the affected (ipsilesional) hemisphere after stroke and has been applied in 43 stroke patients.[16-20,31] Thirty-three chronic (12-107 months after stroke)[16-20] and 10 acute (4-8 weeks from stroke)[31] patients were tested. No serious adverse events have been reported. Anodal tDCS over M1 of the affected hemisphere has only been applied in a crossover, sham-controlled design.[16-20,31] All chronic patients improved regarding motor function of the affected hand after a single session.[16-20] The effect size of a single session of anodal tDCS over M1 of the affected hemisphere in chronic stroke ranged from 7% to 150%, depending on the outcome measure applied.[16-20] The application of daily anodal tDCS over M1 of the ipsilesional hemisphere followed by a robot-assisted arm training over 6 weeks in a nonblinded, crossover, real stimulation only design improved motor function of the affected hand by 150% as measured with the Jebsen–Taylor Hand Function Test and the Medical Research Council score in 10 acute stroke patients.[31] More data are needed to evaluate if anodal tDCS over M1 of the affected hemisphere in combination with motor training generates (*a*) larger effect sizes than anodal tDCS alone, (*b*) lasting effects over several days or weeks, and (*c*) carryover effects on daily life motor activities performed with the affected hand.

In summary, facilitation of M1 of the affected hemisphere, either by facilitatory (3 Hz, 10 Hz, 20 Hz) rTMS or anodal tDCS, is a safe and efficient strategy to enhance recovery of function of the affected hand both in acute and chronic stroke subjects. Effect sizes as to improvement of motor function of the stroke-affected hand varies between 10% and 150% for both methods (see Tables 1 and 2), which is in the range of effect sizes to be induced by behavioral training.[49] To date, mainly patients with mild to moderate sensorimotor disturbance of the affected hand have been investigated. Future research should address the question if facilitation of M1 of the affected hemisphere is equally effective in patients with moderate and severe impairment of hand function. There are no definitive hints that one rTMS protocol is superior to another regarding the effectiveness of improving the function of the stroke-affected hand. Despite methodological problems, preliminary data from 2 studies suggest that 20-Hz rTMS in combination with motor training is less effective than anodal tDCS in combination with motor training.[31,47]

Limitations and Open Questions

Despite converging evidence for the effectiveness of rTMS and tDCS in the motor rehabilitation of impaired hand function after stroke obtained from proof-of-principle studies, several problems persist that need to be addressed prior to a more widespread application of these techniques within phase II or III study designs.[6] For example, studies must be designed as well as feasible, which includes blinding of patients and assessors. In particular, the following questions should be addressed in future research: (*a*) Which stimulation parameters are most effective? For rTMS it appears essential to clarify which frequency, intensity, and number of pulses result in the best behavioral response in the absence of relevant adverse effects. Based on the pertinent literature it appears that 1-Hz rTMS applied over M1 of the unaffected hemisphere is most effective to enhance motor function of the stroke-affected hand at least in acute or chronic stroke patients with subcortical stroke (see Table 1). However, effect size of motor improvement of the affected hand appears to be larger when a facilitatory rTMS protocol (3 Hz, 10 Hz, 20 Hz) is applied over M1 of the affected hemisphere with the constraint that different outcome measures have been applied (see Table 2). Likewise, for tDCS studies, we need to investigate which amplitude and duration of stimulation produces an optimal behavioral effect. (*b*) Which technique of brain stimulation is most effective in a given clinical situation? For example, from a practical point of view, the application of tDCS is much easier than the application of rTMS. However, it is unknown whether both techniques differ regarding their effectiveness in dependence of clinical determinants, such as age, site, and distribution of stroke or severity of motor impairment. At present, both inhibitory[7,8,10-15,18,20,45,46] and facilitatory[6,9,11,16-20,31,47,48] brain-stimulation techniques have been applied in patients suffering from mild to moderate impairment of hand function after stroke. It is unknown if these techniques can improve more severe motor deficits of the affected hand or spasticity after stroke. (*c*) Which cortical motor area and which hemisphere (ipsilesional or contralesional) should be stimulated? The great majority of studies focused on the primary motor cortex of either the affected or unaffected hemisphere to modulate cortical excitability and behavior after stroke (see Tables 1 and 2). Inhibition of the premotor cortex of the unaffected hemisphere did not cause relevant improvement of motor function of the affected hand in subcortical stroke.[8] Probably, the individual pathological pattern within the cortical motor network of both hemispheres induced by stroke determines the optimal area for stimulation. For this reason, it seems essential to apply standardized neuroimaging paradigms to activate the cortical motor network, to detect individual network pathologies, and to guide brain stimulation for optimally modulating pathological brain activity toward a physiological pattern. (*d*) Is inhibition of motor areas of the unaffected hemisphere or facilitation of motor areas of the affected hemisphere more effective to improve hand motor function? This question cannot be answered yet, based on the current data available. However, it is of particular importance as the compensatory effect of the unaffected hemisphere on motor function of the affected upper limb depends on the location and distribution of stroke.[25-28] A recent study revealed differential effects of facilitatory (10 Hz) rTMS over the primary motor cortex of the affected hemisphere on motor improvement of the affected hand in cortical and subcortical stroke patients.[39] (*e*) Is brain stimulation more effective in the acute or chronic phase after stroke? The majority of previous studies investigated the effects of brain stimulation on motor behavior of the affected hand in chronic stroke (see Tables 1 and 2). However, early modulation of cortical excitability might rebalance interhemispheric communication, thereby preventing the development of maladaptive neural plasticity, which subsequently affects the dexterity of the affected hand.[12]

To date we do not know which changes in neural activation and connectivity within the motor network are induced by focal rTMS over a particular motor area. A recent study demonstrated that focal rTMS induces widespread changes of neural activation within the motor network of both hemispheres as measured by fMRI.[50] Consequently, the positive effects of facilitation or inhibition of the primary motor cortex of the ipsilesional or contralesional hemisphere, respectively, probably result not only from local changes in cortical excitability but also from changes in cortical excitability within areas interconnected with the stimulated area. In this context, the concept of interhemispheric competition is definitely a strong simplification of the actual pathology within the motor network induced by stroke. However, at present the model appears to be legitimate in the absence of alternatives to systematically test current hypotheses.

In addition, it is unclear what effects an ischemic lesion may exert on the integrity of the cortical motor network. In this context, also the factor time from stroke onset seems to be of major importance next to the site of the lesion. A key to the understanding of stroke-induced changes in cortical plasticity is the question what mechanisms underlie a shift of interhemispheric balance in cortical excitability toward the unaffected hemisphere. A subcortical stroke does usually not affect commissural fibers connecting the homologous motor areas of both hemispheres. Thus, the shift of interhemispheric balance toward the unaffected (contralesional) hemisphere might result from indirect adaptive changes induced by, for example, thalamic or cerebellar pathways. To answer these questions, behavioral, electrophysiological, and imaging data from larger patient cohorts with homogenous lesion location are needed. Also, models of effective connectivity, that is, models that estimate the influences one area exerts over the activity of another area, may help identify changes in the network architecture induced by stroke. Assessing changes in connectivity also enables monitoring recovery based on cortical reorganization and modulation thereof using rTMS or tDCS.[35] Diffusion tensor imaging is a novel imaging technology[51] that helps illustrate the fiber tracts within the motor system. The information that fiber tracts are directly affected by the ischemic lesion and/or which fiber tracts have undergone secondary degeneration may further our understanding on how maladaptive processes emerge. A more detailed analysis of the individual lesion anatomy is very desirable given the fact that current studies at best discriminate between cortical and subcortical strokes only. From a functional–anatomic point of view, this approach is insufficient as neither the differentiated fiber anatomy nor the functional anatomy of cortical structures is taken into account.

Conclusions

In recent years, novel noninvasive stimulation techniques, such as rTMS and tDCS, were introduced into the treatment of impaired sensorimotor function of the hand after stroke.[40,52,53] The therapeutic usefulness of these techniques stems from the lasting effects on cortical excitability, which outlast the stimulation period for several minutes to hours.[40,53,54] These effects on cortical excitability may share similar mechanisms as the long-term changes in neuronal excitability (long-term potentiation and long-term depression) observed after repetitive activation of synaptic connectivity on a cellular level within brain tissue.[52]

Despite the limited number of studies (N = 22) with an overall small number of patients investigated so far (N = 277), there is converging evidence that rTMS and tDCS are effective to enhance recovery of function of the affected hand after stroke. Within the concept of interhemispheric competition[21-23] both (*a*) inhibition of cortical excitability of the primary motor cortex of the unaffected (contralesional) hemisphere and (*b*) facilitation of cortical excitability of the primary motor cortex of the affected (ipsilesional) hemisphere can be applied. Until today, no relevant adverse effects of either approach in the treatment of stroke patients, such as induction of an epileptic seizure, have been reported. Thus, rTMS and tDCS appear to be safe techniques if current safety guidelines regarding intensity, frequency, and time of stimulation are adhered to.[55,56]

The amount of behavioral improvement induced by a single session of rTMS or tDCS lies within 10% to 150%, depending on the outcome measure applied (see Tables 1 and 2). Future studies should investigate if brain-stimulation techniques are equally effective in patients with more severe impairment of hand function and/or spasticity after stroke. In addition, there is preliminary evidence that a repeated application of rTMS or tDCS over several days or weeks and/or the combination with consecutive training sessions can enhance the effectiveness, both effect size and duration, of brain stimulation.[6,10,20,31,46]

Acknowledgments

This work was supported by grants of the Deutsche Forschungsgemeinschaft (DFG, NO 737/5-1), the Köln Fortune Programme (173/2006) to Dennis A. Nowak, and the Bundesministerium für Bildung und Forschung (BMBF; 01GO0509) to Gereon R. Fink.

References

1. Kolominsky-Rabas PL, Weber M, Gefeller O, Neundörfer B, Heuschmann PU. Epidemiology of ischemic stroke subtypes according to the TOAST criteria: incidence, recurrence, and long-term survival in ischemic stroke subtypes: a population-based study. *Stroke*. 2001;32:2735-2740.
2. Lai SM, Studenski S, Duncan PW, Perera S. Persisting consequences of stroke measured by the Stroke Impact Scale. *Stroke*. 2002;33:1840-1844.
3. Kwakkel G, Kollen BJ, Wagenaar RC. Long-term effects of intensity of upper and lower limb training following stroke: a randomised trial. *J Neurol Neurosurg Psychiatry*. 2002;72:473-479.
4. Nakayama H, Jorgensen HS, Raaschou HO, Olsen TS. Recovery of upper extremity function in stroke subjects: the Copenhagen Stroke Study. *Arch Phys Med Rehabil*. 1994;75:394-398.
5. Hummel FC, Cohen LG. Non-invasive brain stimulation: a new strategy to improve neurorehabilitation after stroke? *Lancet Neurol*. 2006;5:708-712.
6. Khedr EM, Ahmed MA, Fathy N, Rothwell JC. Therapeutic trial of repetitive transcranial magnetic stimulation after acute ischemic stroke. *Neurology*. 2005;65:466-468.
7. Takeuchi N, Chuma T, Matsuo Y, Watanabe I, Ikoma K. Repetitive transcranial magnetic stimulation of contralesional primary motor cortex improves hand function after stroke. *Stroke*. 2005;36:2681-2686.
8. Mansur CG, Fregni F, Boggio PS, et al. A sham stimulation-controlled trial of rTMS of the unaffected hemisphere in stroke patients. *Neurology*. 2005;64:1802-1804.
9. Kim YH, You SH, Ko MH, et al. Repetitive transcranial magnetic stimulation-induced corticomotor excitability and associated motor skill acquisition in chronic stroke. *Stroke*. 2006;37:1471-1476.
10. Fregni F, Boggio PS, Valle AC, et al. A sham-controlled trial of a 5-day course of repetitive transcranial magnetic stimulation of the unaffected hemisphere in stroke patients. *Stroke*. 2006;37:2115-2122.
11. Talelli P, Greenwood RJ, Rothwell JC. Exploring theta burst stimulation as an intervention to improve motor recovery in chronic stroke. *Clin Neurophysiol*. 2007;118:333-342.
12. Nowak DA, Grefkes C, Dafotakis M, Küst J, Karbe H, Fink GR. Effects of low frequency rTMS over contralesional motor cortex on movement kinematics and movement-related neural activation in subcortical stroke. *Arch Neurol*. 2008;65:741-747.
13. Takeuchi N, Tada T, Toshima M, Takayo C, Matsuo Y, Ikoma K. Inhibition of the unaffected motor cortex by 1 Hz repetitive transcranial magnetic stimulation enhances motor performance and training effect of the paretic hand in patients with chronic stroke. *J Rehabil Med*. 2008;40:298-303.
14. Dafotakis M, Grefkes C, Karbe H, Fink GR, Nowak DA. Effects of rTMS on grip force control after subcortical stroke. *Exp Neurol*. 2008;211:407-412.
15. Liepert J, Zittel S, Weiller C. Improvement of dexterity by single session low-frequency repetitive transcranial magnetic stimulation over contralesional motor cortex in acute stroke: a double-blind placebo-controlled crossover trial. *Restor Neurol Neuosci*. 2007;25:461-465.
16. Hummel F, Cohen LG. Improvement of motor function with noninvasive cortical stimulation in a patient with chronic stroke. *Neurorehabil Neural Repair*. 2005;19:14-19.
17. Hummel F, Celnik P, Giraux P, et al. Effects of non-invasive cortical stimulation on skilled motor function in chronic stroke. *Brain*. 2005;128:490-499.
18. Fregni F, Boggio PS, Mansur CG, et al. Transcranial direct current stimulation of the unaffected hemisphere in stroke patients. *Neuroreport*. 2005;16:1551-1555.
19. Hummel FC, Voller B, Celnik P, et al. Effects of brain polarization on reaction times and pinch force in chronic stroke. *BMC Neurosci*. 2006;7:73.
20. Boggio PS, Nunes A, Rigonatti SP, Nitsche MA, Pascual-Leone A, Fregni F. Repeated sessions of noninvasive brain DC stimulation is associated with motor function improvement in stroke patients. *Restor Neurol Neurosci*. 2007;25:123-129.
21. Murase N, Duque J, Mazzocchio R, Cohen LG. Influence of interhemispheric interactions on motor function in chronic stroke. *Ann Neurol*. 2004;55:400-409.
22. Kinsbourne M. Mechanisms of hemispheric interaction in man. In: Kinsbourne M, Smith WL, eds. *Hemispheric Disconnection and Cerebral Function*. Springfield, IL: Thomas; 1974:260-285.
23. Bütefisch CM, Wessling M, Netz J, Seitz RJ, Hömberg V. Relationship between interhemispheric inhibition and motor cortex excitability in subacute stroke patients. *Neurorehabil Neural Repair*. 2008;22:4-21.
24. Grefkes C, Eickhoff SB, Nowak DA, Dafotakis M, Fink GR. Dynamic intra- and interhemispheric interactions during unilateral and bilateral hand movements assessed with fMRI and DCM. *Neuroimage*. 2008;41:1382-1394.
25. Nair DG, Hutchinson S, Fregni F, Alexander M, Pascual-Leone A, Schlaug G. Imaging correlates of motor recovery from cerebral infarction and their physiological significance in well-recovered patients. *Neuroimage*. 2007;34:253-263.
26. Gerloff C, Bushara K, Sailer A, et al. Multimodal imaging of brain reorganization in motor areas of the contralesional hemisphere of well recovered patients after capsular stroke. *Brain*. 2006;129:791-808.
27. Ward NS, Brown MM, Thompson AJ, Frackowiak RSJ. Neural correlates of outcome after stroke: a cross-sectional fMRI study. *Brain*. 2003;126:1430-1448.
28. Lotze M, Markert J, Sauseng P, Hoppe J, Plewnia C, Gerloff C. The role of multiple contralesional motor areas for complex hand movements after internal capsular lesion. *J Neurosci*. 2006;26:6096-6102.
29. Zhang W, Linden DJ. The other side of the engram: experience-driven changes in neuronal intrinsic excitability. *Nat Rev Neurosci*. 2003;4:885-900.
30. Maldonado MA, Allred RP, Felthauser EL, Jones TA. Motor skills training, but not voluntary exercise, improves skilled reaching after unilateral ischemic lesions of the sensorimotor cortex in rats. *Neurorehabil Neural Repair*. 2008;22:250-261.
31. Nudo RJ, Wise BM, SiFuentes F, Milliken GW. Neural substrates for the effects of rehabilitative training on motor recovery after ischemic infarct. *Science*. 1996;272:1791-1794.
32. Plautz EJ, Barbay S, Frost SB, et al. Post-infarct cortical plasticity and behavioral recovery using concurrent cortical stimulation and rehabilitative training: a feasibility study in primates. *Neurol Res*. 2003;25:801-810.
33. Hesse S, Werner C, Schonhardt EM, Bardeleben A, Jenrich W, Kirker SG. Combined transcranial direct current stimulation and robot-assisted arm training in subacute stroke patients: a pilot study. *Restor Neurol Neurosci*. 2007;25:9-15.
34. Lee L, Siebner HR, Rowe JB, et al. Acute remapping within the motor system induced by low-frequency repetitive transcranial magnetic stimulation. *J Neurosci*. 2003;23:5308-5318.
35. Grefkes C, Nowak DA, Eickhoff SB, et al. Cortical connectivity after subcortical stroke assessed with functional magnetic resonance imaging. *Ann Neurol*. 2008;63:236-246.
36. Brown JA, Lutsep HL, Weinand M, Cramer SC. Motor cortex stimulation for the enhancement of recovery from stroke: a prospective, multicenter safety study. *Neurosurgery*. 2006;58:464-473.
37. Levy R, Ruland S, Weinand M, Lowry D, Dafer R, Bakay R. Cortical stimulation for the rehabilitation of patients with hemiparetic stroke: a multicenter feasibility study of safety and efficacy. *J Neurosurg*. 2008;108:707-714.
38. Harvey RL, Winstein CJ; Everest Trial Group. Design for the Everest randomized trial of cortical stimulation and rehabilitation for arm function following stroke. *Neurorehabil Neural Repair*. 2009;23:32-44.
39. Ameli M, Grefkes C, Wang L, et al. Differential effects of high-frequency rTMS on movement kinematics and neural activation in subcortical and cortical MCA stroke [abstract]. *Neurology*. 2008;70:A206.

40. Schlaug G, Renga V, Nair D. Transcranial direct current stimulation in stroke recovery. *Arch Neurol*. 2008;65:1571-1576.
41. Kobayashi M, Hutchinson S, Théoret H, Schlaug G, Pascual-Leone A. Repetitive TMS of the motor cortex improves ipsilateral sequential simple finger movements. *Neurology*. 2004;62:91-98.
42. Dafotakis M, Grefkes C, Wang L, Fink GR, Nowak DA. The effects of 1 Hz rTMS over the hand area of M1 improves movement kinematics of the ipsilateral hand. *J Neural Transm*. 2008;115:1269-1274.
43. Kim YH, Park JW, Ko MH, Jang SH, Lee PK. Facilitative effect of high frequency subthreshold repetitive transcranial magnetic stimulation on complex sequential motor learning in humans. *Neurosci Lett*. 2004;367:181-185.
44. Conchou F, Loubinoux I, Castel-Lacanal E, et al. Neural substrates of low-frequency repetitive transcranial magnetic stimulation during movement in healthy subjects and acute stroke patients. A PET study [published online ahead of print December 15, 2008]. *Hum Brain Mapp*. doi: 10.1002/hbm.20690.
45. Boggio PS, Alonso-Alonso M, Mansur CG, et al. Hand function improvement with low-frequency repetitive transcranial magnetic stimulation of the unaffected hemisphere in a severe case of stroke. *Am J Phys Med Rehabil*. 2006;85:927-930.
46. Kirton A, Chen R, Friefeld S, Gunraj C, Pontigon AM, Deveber G. Contralesional repetitive transcranial magnetic stimulation for chronic hemiparesis in subcortical paediatric stroke: a randomised trial. *Lancet Neurol*. 2008;7:507-513.
47. Yozbatiran N, Alonso-Alonso M, See J, et al. Safety and behavioral effects of high-frequency repetitive transcranial magnetic stimulation in stroke. *Stroke*. 2009;40:309-312.
48. Malcolm MP, Triggs WJ, Light KE, et al. Repetitive transcranial magnetic stimulation as an adjunct to constraint-induced therapy: an exploratory randomized controlled trial. *Am J Phys Med Rehabil*. 2007;86:707-715.
49. Wolf SL, Winstein CJ, Miller JP, et al. Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: the EXCITE randomized clinical trial. *JAMA*. 2006;296:2095-2104.
50. Bestmann S, Baudewig J, Siebner HR, Rothwell JC, Frahm J. Functional MRI of the immediate impact of transcranial magnetic stimulation on cortical and subcortical motor circuits. *Eur J Neurosci*. 2004;19: 1950-1962.
51. Anwander A, Tittgemeyer M, von Cramon DY, Friederici AD, Knösche TR. Connectivity-based parcellation of Broca's area. *Cereb Cortex*. 2007;17:816-825.
52. Fregni F, Pascual-Leone A. Technology insight: noninvasive brain stimulation in neurology-perspectives on the therapeutic potential of rTMS and tDCS. *Nat Clin Pract Neurol*. 2007;3:383-393.
53. Talelli P, Rothwell J. Does brain stimulation after stroke have a future? *Curr Opin Neurol*. 2006;19:543-550.
54. Siebner H, Rothwell JC. Transcranial magnetic stimulation: new insights into representational cortical plasticity. *Exp Brain Res*. 2003;148:1-16.
55. Poreisz C, Boros K, Antal A, Paulus W. Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients. *Brain Res Bull*. 2007;72:208-114.
56. Wassermann EM. Risk and safety of repetitive transcranial magnetic stimulation: report and suggested guidelines from the International Workshop on the Safety of Repetitive Transcranial Magnetic Stimulation, June 5-7, 1996. *Electroencephalogr Clin Neurophysiol*. 1998;108:1-16.

For reprints and permission queries, please visit SAGE's Web site at http://www.sagepub.com/journalsPermissions.nav