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RESEARCH ARTICLE

New modalities of brain stimulation for stroke rehabilitation

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Abstract Stroke is a leading cause of disability, and the number of stroke survivors continues to rise. Traditional neurorehabilitation strategies aimed at restoring function to weakened limbs provide only modest benefit. New brain stimulation techniques designed to augment traditional neurorehabilitation hold promise for reducing the burden of stroke-related disability. Investigators discovered that repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), and epidural cortical stimulation (ECS) can enhance neural plasticity in the motor cortex post-stroke. Improved outcomes may be obtained with activity-dependent stimulation, in which brain stimulation is contingent on neural or muscular activity during normal behavior. We review the evidence for improved motor function in stroke patients treated with rTMS, tDCS, and ECS and discuss the mediating physiological mechanisms. We compare these techniques to activity-dependent stimulation, discuss the advantages of this newer strategy for stroke rehabilitation, and suggest future applications for activity-dependent brain stimulation.

Keywords Transcranial magnetic stimulation · Transcranial direct current stimulation · Epidural cortical stimulation · Activity-dependent · Stroke rehabilitation · Motor cortex

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Introduction

Stroke is a leading cause of long-term disability in the United States (McNeil and Binette 2001). The number of people living with stroke-related disability continues to rise as advances in acute stroke management decrease stroke-related death. This growing number of survivors increases the urgency for new and more effective therapies. Various contemporary approaches using brain stimulation promise to improve motor recovery after stroke. Noninvasive brain stimulation techniques include repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS). Epidural cortical stimulation (ECS) is another potentially effective but more invasive approach. Incorporating brain stimulation into a strategy for stroke rehabilitation typically involves a session of rTMS, tDCS, or ECS before or during a physical/occupational therapy session. Stimulation of the primary motor cortex (M1) modulates the excitability of neural circuits, purportedly increasing the likelihood of beneficial neuroplastic change with therapy. A potential drawback of rTMS, tDCS, and ECS is that modulatory effects are typically non-specific, affecting large regions of M1. In addition, these therapies are preprogrammed, that is, fixed, whereby the pattern of brain stimulation is not modulated with discrete episodes of volitional activity during therapy sessions.

Activity-dependent brain stimulation is a new, less-studied alternative to stroke rehabilitation that can be designed to create more focused neural plasticity. At the cellular level, connections between two neurons are strengthened when the firing of one neuron repeatedly contributes to the firing of a second, a mechanism termed Hebbian plasticity (Hebb 1949). Animal models demonstrate that activity-dependent brain stimulation in accordance with Hebbian principles can strengthen specific connections between larger populations of neurons in primates (Jackson et al. 2006) and rodents (Rebesco et al. 2010). Clinical investigators are beginning to study activity-dependent brain stimulation in humans (Buetefisch et al. 2011; Bütefisch et al. 2004). In the motor system, activity-dependent stimulation entails making brain stimulation contingent on voluntary neural or muscle activity. Plastic changes presumably occur in connections between motor cortical neurons firing naturally during generation of muscle contraction and those activated artificially by the brain stimulation. With activity-dependent stimulation, it may be possible to target plasticity primarily to the residual cortical representation for paretic muscles, providing a more focused rehabilitation strategy. In this review, we evaluate preprogrammed methods of brain stimulation designed to modulate cortical excitability, including rTMS, tDCS, and ECS. We then compare these methods to activity-dependent stimulation and propose future applications of this new modality for stroke rehabilitation.

Part I: Preprogrammed brain stimulation techniques

Repetitive transcranial magnetic stimulation (rTMS)

Barker et al. (1985) were the first to develop a device to noninvasively depolarize cortical neurons by inducing intracellular currents with a brief focused magnetic pulse delivered over the scalp. When delivered over M1, magnetic stimulation causes contraction of muscles in the contralateral limbs. Non-human primate (NHP) studies suggest that single-pulse TMS to M1 sends a volley down the corticospinal tract to induce this muscle activity (Baker et al. 1995), though the precise physiologic mechanisms at the cortical level remain poorly understood. Modern figure-of-eight TMS coils have a spatial resolution of approximately 1 cm^2 (Thielscher and Wichmann 2009). The induced electric current is maximal at the cortical surface and drops off exponentially with distance (Roth et al. 2007). Situating the stimulating coil over different areas of M1 can activate specific muscles or groups of muscles in a pattern that roughly corresponds to the motor homunculus (Wassermann et al. 1992).

Delivering TMS pulses repetitively at frequencies >0.1 Hz leads to changes in cortical excitability that last well beyond the stimulation session. This post-stimulus *modulation* either excites or inhibits the cortex. High-frequency rTMS ≥ 3 Hz leads to cortical excitation, as evidenced by increased amplitude of the TMS-induced motor-evoked potential (MEP) (Pascual-Leone et al. 1994), whereas low-frequency rTMS, that is, very near 1 Hz, leads to cortical inhibition as evidenced by decreased amplitude of the TMS-induced MEP (Chen et al. 1997). Animal studies offer a possible explanation for opposing modulatory effects at high and low frequencies. Moliadze et al. (2003) stimulated the visual cortex of anesthetized cats with single-pulse TMS while recording the associated neural activity with intracortical microelectrodes. Each TMS pulse caused an initial increase in neuronal activity for up to 500 ms followed by long-lasting suppression. The authors contend that stimulating with rTMS at frequencies >2 Hz for an extended period of time may keep neurons in an excitatory state, with each subsequent pulse reducing or masking the inhibitory phase of the preceding pulse. Conversely, stimulating at frequencies from 0.2 to 1 Hz may lead to cortical inhibition by favoring the manifestation of the long-lasting inhibitory phase.

Though shorter in duration, the modulatory aftereffects of rTMS share many features of long-term potentiation (LTP) and long-term depression (LTD), leading to speculation about a similar cellular mechanism (Thickbroom 2007). The cellular processes that occur following rTMS likely include alterations in gene expression and neurotransmitter levels. Animal studies in rats demonstrate rTMS-induced changes in gene expression (Hausmann et al. 2000; Wang HY et al. 2011; Yoon et al. 2011). Bcl-2 was increased while Bax was decreased following 10 Hz rTMS to lesional M1 in a rat model of stroke (Yoon et al. 2011). Healthy rats chronically stimulated with 20 Hz rTMS for 10 s daily over 2 weeks showed increased c-fos in parietal cortex and hippocampus (Hausmann et al. 2000). A study of 5 Hz rTMS in healthy rats showed improved BDNF-TrkB signaling in the prefrontal cortex (Wang HY et al. 2011). The BDNF gene is critical in neurorehabilitation; humans with polymorphisms in this gene do not demonstrate use-dependent plasticity (Kleim et al. 2006). Investigators suspect that rTMS-induced changes in levels of neurotransmitters like glutamate and GABA also contribute to modulatory aftereffects (Bolognini et al. 2009), but direct experimental evidence remains lacking.

Investigators harnessed the modulatory effects of rTMS with two approaches to stroke rehabilitation: high-frequency rTMS applied to lesional M1 or low-frequency rTMS to contralesional M1 (Fig. 1). Treating stroke patients with high-frequency rTMS to lesional M1 has a plausible rationale. Functional neuroimaging reveals that

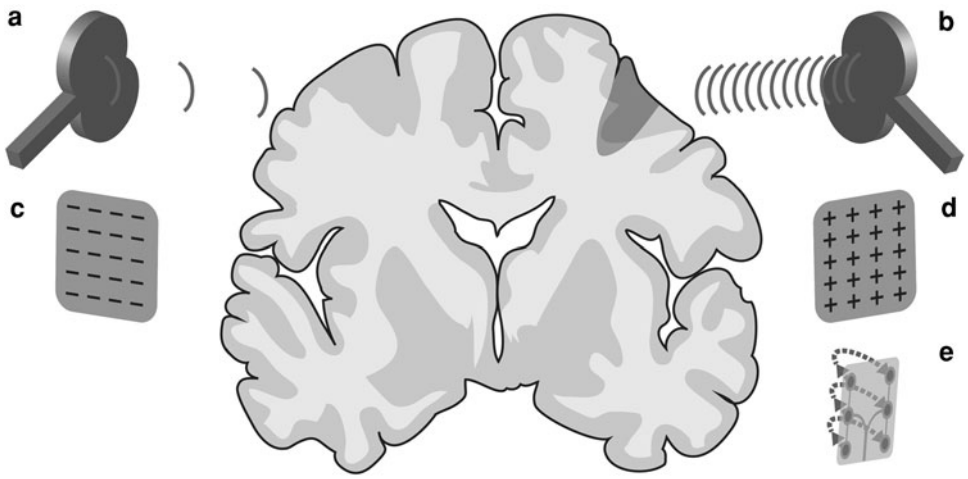


Fig. 1 Preprogrammed methods of brain stimulation for stroke rehabilitation. **a** Low-frequency (1 Hz) rTMS to contralesional M1. **b** High-frequency (≥3 Hz) rTMS to lesional M1. **c** Cathodal tDCS to contralesional M1. **d** Anodal tDCS to lesional M1. **e** Epidural cortical stimulation to lesional M1. *Dark* wedge-shaped region denotes lesion from cortical stroke or region impaired by subcortical stroke. Note that in practice, **a** and **c** are situated directly over contralesional M1 while **b**, **d**, and **e** are situated directly over lesional M1

neurons in the area of lesional M1 surrounding the injury often take over function in patients with good recovery (Zemke et al. 2003), a process called vicariation. In the acute period after stroke, the activity in these perilesional neurons is reduced. Excitatory high-frequency rTMS may render perilesional neurons more responsive to therapy, speeding the process of vicariation. Conversely, application of low-frequency rTMS to contralesional M1 may restore balance between the two cerebral hemispheres. In healthy individuals at rest, the motor cortices inhibit one another through transcallosal inhibition (TCI) (also termed inter-hemispheric inhibition) (Ferbert et al. 1992; Grefkes et al. 2008a). When healthy subjects perform unilateral limb movement, TCI from the ipsilateral hemisphere is released just prior to the activation of the limb (Murase et al. 2004), a mechanism that may promote more accurate unilateral movements. In the case of stroke, however, TCI from contralesional M1 is not released with attempted limb movement, further impairing motor recovery (Grefkes et al. 2008b). Inhibitory modulation in contralesional M1 with low-frequency rTMS may lead to disinhibition, thereby restoring the balance between the two hemispheres and improving the opportunity for neuroplastic change in perilesional M1.

Upper extremity function improved in most stroke patients treated with high-frequency rTMS to lesional M1 and this improvement may depend on the underlying stroke subtype (Ameli et al. 2009; Chang et al. 2010, 2012; Khedr et al. 2005; Kim YH et al. 2006; Koganemaru et al. 2010; Malcolm et al. 2007; Yozbatiran et al. 2009) (Table 1). In three studies, subjects received 10 days of rTMS (or sham rTMS) followed by upper extremity neurorehabilitative therapy (Chang et al. 2010; Khedr et al. 2005; Malcolm et al. 2007). Two of these studies found improvement in motor disability scales post-intervention (Chang et al. 2010; Khedr et al. 2005), while the third (Malcolm et al. 2007) failed to show efficacy with high-frequency rTMS. Unlike the other two, this third study employed constraint-induced movement therapy (CIMT). CIMT is a neurorehabilitation strategy designed to overcome learned nonuse, whereby the unimpaired hand is restricted, forcing the patient to use the impaired limb to perform motor tasks. The results by Malcolm et al. (2007) may suggest a lack of synergy between the effects of high-frequency rTMS to lesional M1 and CIMT, or could be explained by competing homeostatic mechanisms (see discussion below). A fourth study by Koganemaru et al. (2010) alternated motor training enhanced by neuromuscular stimulation with high-frequency TMS, resulting in improved upper limb function even in those with severe impairment. A fifth study by Ameli et al. (2009) separated subjects by stroke subtype and discovered that only those with subcortical stroke showed improvement on a finger tapping task and decreased activity in contralesional M1 by fMRI following high-frequency rTMS. This trend toward greater improvement in subcortical stroke patients was corroborated by a recent meta-analysis (Hsu WY et al. 2012); note that all of the cited studies were small compared to contemporary trials for acute stroke intervention and only the study by Ameli et al. (2009) divided patients by stroke subtype a priori. The extent to which subcortical stroke patients truly respond better to rTMS therapies than those with cortical stroke requires further investigation.

Most studies of low-frequency rTMS to contralesional M1 also demonstrate enhanced upper extremity motor function (see Table 1), presumably by reducing TCI. Two studies showed decreased TCI in chronic stroke patients following low-frequency rTMS, as measured by decreased activity in the motor areas of the intact hemisphere on fMRI (Nowak et al. 2008), and reduced cortical silent period from a MEP in the affected hand induced by the stimulation of contralesional M1 (Takeuchi et al. 2005). A

Table 1 rTMS studies ($N > 1$) to treat motor deficits following stroke

Reference	*N*	Stroke subtype[a]	Freq (Hz)	Study design[b]	Outcome
High-frequency rTMS to lesional motor cortex studies					
Khedr et al. (2005)	52	A MCA	3	DB-RCT: rTMS vs. sham followed by OT × 10 days	Improvement on SSS, NIHSS, BI 10 days post
Kim YH et al. (2006)	15	C mix	10	Cross: rTMS vs. sham followed by motor task	>Increase in lesional MEP amp, improved accuracy on motor task
Malcolm et al. (2007)	19	S,C mix	20	DB-RCT: rTMS vs. sham followed by CIMT × 10 days	No difference on WMFT, MAL, or BBT immediately and 6 mo. post
Yozbatiran et al. (2009)	12	S,C mix	20	Obs: rTMS alone	Improvement in UEFM, pegboard, grip, AROM
Ameli et al. (2009)	29	A,S,C mix	10	Cross: rTMS vs. sham followed by finger tapping	Improvement on finger tapping task, reduced activity in contralesional M1 by fMRI (subcortical grp only)
Khedr et al. (2010)	48	A, MCA	3, 10	DB-RCT: 3 Hz rTMS vs. 10 Hz rTMS vs. sham followed by OT × 5 days	Improvement in limb strength and modified Rankin in both rTMS grps 1 yr post
Chang et al. (2010)	28	A mix	10	DB-Pseudo: rTMS vs. sham followed by OT × 10 days	Trend toward improved grip strength and UEFM
Koganemaru et al. (2010)	9	S, C subcort	9	Cross: rTMS + neMT vs. sham + neMT vs. rTMS alone	Improvement on AROM, mAsh, and grip power in rTMS + neMT grp alone
Chang et al. (2012)	17	S, C mix	10	SB-RCT: rTMS vs. sham with finger tapping task × 10 days	Improved accuracy on finger tapping task, fMRI changes in specific brain regions
Low-frequency rTMS to contralesional motor cortex studies					
Mansur et al. (2005)	10	C mix	1	Cross: rTMS vs. sham	Improvement in sRT, cRT, and pegboard tasks.
Takeuchi et al. (2005)	20	C subcort	1	DB-RCT: rTMS vs. sham	Increased pinch acceleration, decrease in contralesional MEP amp and TCI duration
Fregni et al. (2006)	15	C mix	1	DB-RCT: rTMS vs. sham × 5 days	Improvement in sRT, cRT, pegboard 2 weeks post
Liepert et al. (2007)	12	S subcort	1	DB-Cross: rTMS vs. sham	Improvement on 9 hole peg task
Dafotakis et al. (2008)	12	C subcort MCA	1	Cross: rTMS vs. sham	Improvement in force ratio and time lag lifting instrumented object
Takeuchi et al. (2008)	20	C subcort	1	DB-RCT: rTMS vs. sham followed by pinching task	Improvement in pinch force, acceleration 7 days post
Kirton et al. (2008)	10	C subcort ped	1	DB-RCT: rTMS vs. sham × 8 days	Increased grip force, MAUEF
Nowak et al. (2008)	15	C subcort MCA	1	Cross: rTMS vs. sham	Decreased activity in contralesional M1 by fMRI
Carey et al. (2010)	2	C mix	6, 1	Obs: 6 Hz followed by 1 Hz rTMS × 5 sessions	Decreased TCI by paired pulse TMS, increased cortical activation by fMRI
Kakuda et al. (2010a)	5	C mix	1	Obs: rTMS followed by OT × 10 sessions	Trend toward improved WMFT, UEFM, grip
Kakuda et al. (2010b)	15	C mix	1	Obs: rTMS followed by OT × 22 sessions	Improvement in WMFT, UEFM, mod Ashworth
Kakuda et al. (2011a)	5	C mix	1	Obs: oral levodopa + rTMS followed by OT × 22 sessions	Improvement in WMFT, UEFM
Kakuda et al. (2011b)	39	C mix	1	Obs: rTMS followed by OT × 22 sessions	Improvement in WMFT, UEFM, spasticity 1 mo Post
Kakuda et al. (2011d)	52	C mix	1	Obs/Retro: rTMS followed by OT × 22 sessions	Improvement in WMFT, UEFM. Trend toward > improvement for subjects with mod. disability
Theilig et al. (2011)	24	A, S, C mix	1	DB-RCT: rTMS vs. sham followed by EMG-triggered FNMS × 10 days	No difference between groups on WMFT and spasticity scales

Table 1 continued

Reference	*N*	Stroke subtype[a]	Freq (Hz)	Study design[b]	Outcome
Kakuda et al. (2011e)	14	C mix	1	Obs: botox + rTMS followed by OT × 22 sessions	Improvement in UEFM, FAS
Conforto et al. (2011)	30	S mix	1	DB-RCT: rTMS vs. sham followed by OT × 10 days	Trend toward improved JTT
Wang RY et al. (2011)	24	C mix	1	DB-RCT: rTMS to leg area of M1 vs. sham followed by PT × 10 days	Improvement in LEFM and walking performance
Kakuda et al. (2011c)	11	C mix	6, 1	Obs: 6 Hz followed by 1 Hz rTMS followed by OT × 15 days	Improvement on WMFT and UEFM
Kakuda et al. (2012)	204	C mix	1	Obs: rTMS followed by OT × 22 sessions	Improvement on WMFT and UEFM
Seniów et al. (2012)	40	A, S mix	1	DB-RCT: rTMS vs. sham followed by OT × 15 days	No change in WMFT, UEFM, or NIHSS
High-frequency rTMS to lesional vs. low-frequency rTMS to contralesional motor cortex studies					
Takeuchi et al. (2009)	30	C subcort	5, 1	DB-RCT: 5 Hz lesional M1 vs. 1 Hz contralesional M1 vs. bihemispheric rTMS followed by pinching task	Improved acceleration and pinch force in 1 Hz and bihemispheric groups 1 week post
Khedr et al. (2009)	36	S MCA	3,1	DB-RCT: 3 Hz lesional M1 vs. 1 Hz contralesional M1 vs. sham followed by OT × 5 days	1 Hz > 3 Hz > sham on keyboard tapping, pegboard, NIHSS 3 months post
Emara et al. (2010)	60	C mix	5, 1	DB-RCT: 5 Hz lesional M1 vs. 1 Hz contralesional M1 vs. sham followed by OT × 10 days	Improvement in finger tapping, AI, mRS in 5 Hz and 1 Hz groups 3 months post
Sasaki et al. (2011)	29	S subcort	10, 1	DB-RCT: 10 Hz lesional M1 vs. 1 Hz contralesional M1 vs. sham × 5 days	Improvement in grip strength and finger tapping in 10 Hz group
Theta-burst rTMS studies					
Talelli et al. (2007)	6	C mix	iTBS, cTBS	Cross: iTBS to lesional M1 vs. cTBS to contralesional M1 vs. sham	Improvement in sRT and lesional MEP amplitude for iTBS group
Ackerley et al. (2010)	10	C subcort	iTBS, cTBS	DB-Cross: iTBS to lesional M1 vs. cTBS to contralesional M1 vs. sham followed by grip task	Improvement in grip lift kinetics for cTBS and iTBS, increased lesional MEP amplitude for iTBS
Meehan et al. (2011)	12	C mix	cTBS	SB-Pseudo: cTBS to contralesional M1 vs. cTBS to contralesional S1 vs. sham followed by targeting task × 3 days	Improvement in WMFT and targeting task for M1 and S1 groups
Talelli et al. (2012)	41	C mix	iTBS, cTBS	DB-Pseudo: iTBS to lesional M1 vs. cTBS to contralesional M1 vs. sham followed by PT × 10 days	No difference between groups on JTT, pegboard, and grip strength
Hsu YF et al. (2012)	12	A mix	iTBS	DB-RCT: iTBS to lesional M1 vs. sham followed by OT × 10 days	Improvement on UEFM and NIHSS

AI activity index, *AROM* active range of motion, *BI* barthel index, *BBT* box and block test, *DB* double-blinded, *CIMT* constraint-induced movement therapy, *Cross* crossover, *cRT* choice reaction time, *cTBS* continuous theta-burst rTMS, *FAS* functional ability score, *FNMS* functional neuromuscular stimulation, *Freq* rTMS frequency, *iTBS* intermittent theta-burst rTMS, *JTT* Jebsen–Taylor hand function test, *LEFM* lower extremity Fugl-Meyer score, *MAL* motor activity log rating scale, *mAsh* modified Ashworth scale, *MAUEF* Melbourne assessment of upper extremity function, *MCA* middle cerebral artery, *mix* cortical and subcortical strokes, *mRS* modified Rankin scale, *neMT* neuromuscular stimulation enhanced motor training, *NIHSS* national institutes of health stroke scale, *Obs* observational, *OT* occupational therapy, *ped* pediatric, *Pseudo* pseudorandomized, *RCT* randomized controlled trial, *Retro* retrospective, *RMT* resting motor threshold, *S1* primary somatosensory cortex, *SB* single-blinded, *sRT* simple reaction time, *SSS* Swedish stroke scale, *subcort* subcortical, *TCI* transcallosal inhibition, *UEFM* upper extremity Fugl-Meyer score, *WMFT* wolf motor function test

[a] A (acute) = 1–30 days post-stroke, S (subacute) = 1–6 mo. post-stroke, C (chronic) ≥ 6 mo. post-stroke

[b] In all double-blinded studies, subjects and investigators performing outcome measures blinded to intervention, but investigator performing intervention unblinded

large ($n = 52$) retrospective study by Kakuda et al. (2011d) suggests greater motor improvement with low-frequency contralesional rTMS for chronic stroke patients with moderate rather than mild or severe disability.

Recent studies directly compared high-frequency rTMS of lesional M1 with low-frequency rTMS to contralesional M1 (Emara et al. 2010; Khedr et al. 2009; Takeuchi et al. 2009). Results were mixed: one study demonstrated similar improvement in motor function (Emara et al. 2010) and two others (Khedr et al. 2009; Takeuchi et al. 2009) showed greater motor recovery with low-frequency rTMS to contralesional M1. Takeuchi et al. (2009) compared bihemispheric rTMS (10 Hz rTMS to lesional M1 and 1 Hz rTMS to contralesional M1) to each intervention alone. The groups receiving bihemispheric rTMS or 1 Hz rTMS to contralesional M1 alone outperformed the group

receiving 10 Hz rTMS to lesional M1 alone. These studies might suggest low-frequency stimulation to contralesional M1 is more efficacious than high-frequency rTMS to lesional M1, although more evidence is needed.

A related modality with potential for stroke rehabilitation is theta-burst stimulation (TBS), involving patterned rTMS delivered in short bursts of 3 pulses at 50 Hz, repeated every 200 ms. Intermittent TBS (iTBS), in which TBS is delivered in 2-s trains separated by 10 s, has excitatory modulatory effects on the cortex, whereas continuous TBS (cTBS) causes cortical inhibition (Huang et al. 2005). Two possible advantages of TBS over traditional rTMS include shorter delivery time (Huang et al. 2005) and more potent modulatory aftereffects (DiLazzaro et al. 2011). Two small crossover studies (Ackerley et al. 2010; Talelli et al. 2007) and a larger pseudo-randomized study (Talelli et al. 2012) examined iTBS to lesional M1 or cTBS to contralesional M1 relative to sham stimulation in chronic stroke patients. Motor function improved in both small crossover studies with iTBS to lesional M1; however, the results for cTBS to contralesional M1 were mixed, which might be explained by a study in healthy subjects suggesting that cTBS aftereffects disappear with subsequent motor activity (Huang YZ et al. 2008). The larger study by Talelli et al. (2012), in which physical therapy followed each session of TBS, showed no improvement in motor function for either iTBS or cTBS in comparison with sham. A study comparing cTBS to contralesional M1 vs. cTBS to contralesional primary somatosensory cortex (S1) vs. sham demonstrated a trend toward better motor function in the S1 group compared to the M1 group (Meehan et al. 2011). The authors speculate that contralesional S1 may contribute heavily to inter-hemispheric interactions. Larger, randomized studies are needed to gauge the ultimate utility of TBS for stroke rehabilitation.

Transcranial direct current stimulation (tDCS)

Priori et al. (1998) were the first to pass constant current transcranially between large electrode pads on the scalp of human subjects and document changes in M1 excitability. For tDCS of M1, the investigator places a stimulating pad over M1 and a ground pad over the supraorbital area on the opposite hemisphere. Moving the tDCS stimulating pad over different areas of M1 can target muscles in a pattern that corresponds to the motor homunculus, but in general tDCS is less topographically specific than TMS and ECS.

Nitsche and Paulus (2000) discovered that constant tDCS in humans at intensities below motor threshold for 1–5 min was painless and modulated cortical excitability for several minutes beyond the period of stimulation. In contrast to modulatory effects of rTMS, which are frequency-dependent, modulatory effects of tDCS depend on current direction. With anodal stimulation, the current flows from M1 to the supraorbital area, leading to cortical excitation in M1. Cathodal stimulation of M1 leads to cortical inhibition. Prior studies of cortical excitability both during and after tDCS help to explain why cortical modulation depends on current direction. Anodal tDCS depolarizes somatic membrane potentials, leading to increased neuronal activity (Purpura and McMurtry 1965). Cathodal tDCS decreases spontaneous neuronal activity through hyperpolarization of the somatic membrane potential (Purpura and McMurtry 1965). These polarizing mechanisms do not directly explain subsequent long-lasting changes in cortical excitability, but may induce aftereffects through changes in gene expression (Islam et al. 1995). The long-lasting excitatory effects of anodal tDCS are NMDA receptor-dependent and may relate to increased BDNF secretion (Fritsch et al. 2010), whereas cathodal tDCS decreases cortical excitability by modulating glutamatergic activity (Stagg and Nitsche 2011). Rodent studies applying constant current directly to the cortical surface suggest modulatory aftereffects lasting from several hours (Bindman and Lippold 1964) up to 1 month (Weiss et al. 1998).

The two primary approaches to stroke rehabilitation with tDCS are anodal tDCS to lesional M1 and cathodal tDCS to contralesional M1 (Fig. 1c, d). The aim of these strategies is similar to those for rTMS: excite perilesional neurons with anodal tDCS and reduce TCI with contralesional cathodal tDCS. A recent study of anodal tDCS to lesional M1 in rats by Yoon et al. (2012) found that tDCS in the acute setting following stroke improved motor ability and increased expression of MAP-2 and GAP-43—markers of dendritic and axonal sprouting. Most human studies also suggest anodal tDCS to lesional M1 improves function in the upper (Celnik et al. 2009; Hesse et al. 2007; Hummel et al. 2005; Kim DY et al. 2009) and lower (Madhavan et al. 2011; Tanaka et al. 2011) paretic limb (Table 2). Cathodal tDCS to contralesional M1 also improves motor function in the paretic upper limb of human subjects (Boggio et al. 2007; Bradnam et al. 2011; Fregni et al. 2005; Kim DY et al. 2010; Mahmoudi et al. 2011; Nair et al. 2011), in some cases to a greater extent than anodal tDCS to lesional M1 (Fregni et al. 2005; Kim DY et al. 2010). These positive findings prompted a larger ($n = 96$) randomized trial by Hesse et al. (2011) which combined tDCS (anodal, cathodal, or sham) with robot-assisted therapy. The study failed to show any difference between the 3 groups following intervention. Several factors may have contributed to this negative result. First, most patients had cortically based strokes, which may not be as amenable to stimulation-induced gains as subcortical strokes. Second, the severity of stroke may have contributed to the lack of an observed effect. Enrolled patients were severely disabled with flaccid upper extremity paresis. Additional

Table 2 tDCS studies ($N > 1$) to treat motor deficits following stroke

Reference	*N*	Stroke subtype[a]	Int (mA)	Study design[b]	Outcome
Rat anodal tDCS to lesional motor cortex studies					
Yoon et al. (2012)	30	A MCA	0.2	Post-stroke day 1 tDCS vs. post-stroke day 7 tDCS vs. sham × 5 days	Improved Barnes maze and MBI in both tDCS grps, improved balance beam and GAP-43 expression in 7 day post grp only
Human anodal tDCS to lesional motor cortex studies					
Hummel et al. (2005)	6	C subcort	1	DB-Cross: tDCS vs. sham	Improved JTT 25 min. post
Hesse et al. (2007)	10	S mix	1.5	Obs: tDCS + RAT × 30 days	Improved UEFM in 3/10 subjects
Celnik et al. (2009)	9	C mix	1	DB-Cross: tDCS vs. sham	Trend toward improvement in key pressing task
Kim DY et al. (2009)	10	S mix	1	SB-Cross: tDCS vs. sham	Improvement in BBT, finger acceleration
Madhavan et al. (2011)	9	C mix	0.5	DB-Cross: tDCS vs. sham	Improvement in ankle tracking task, TA MEP amplitude
Tanaka et al. (2011)	8	C subcort	2	DB-Cross: tDCS vs. sham	Improved quadriceps force
Geroin et al. (2011)	30	C mix	1.5	SB-RCT: tDCS + RAT vs. RAT + sham vs. walking exercises alone	Both RAT groups outperformed walking alone group on walking tests
Rossi et al. (2012)	50	A MCA	2	DB-RCT: tDCS vs. sham	No difference between groups on UEFM or NIHSS
Human cathodal tDCS to contralesional motor cortex studies					
Boggio et al. (2007)	5	C subcort	1	Obs: tDCS × 5 days	Trend toward improvement on JTT
Bradnam et al. (2011)	12	S,C mix	1	DB-Cross: tDCS vs. sham	Improved muscle activation for tDCS subjects with mild disability
Nair et al. (2011)	14	C mix	1	DB-RCT: tDCS vs. sham followed by OT × 5 days	Improvement on UEFM and ROM 1 week. post
Human anodal tDCS to lesional vs. cathodal tDCS to contralesional motor cortex studies					
Fregni et al. (2005)	6	C mix	1	DB-Cross: a-tDCS vs. c-tDCS vs. sham	Improvement on JTT in both tDCS groups
Boggio et al. (2007)	4	C subcort	1	DB-Cross: a-tDCS vs. c-tDCS vs. sham × 4 sessions	Improvement on JTT in both tDCS groups
Kim DY et al. (2010)	18	A,S mix	2	DB-RCT: a-tDCS vs. c-tDCS vs. sham followed by OT × 10 days	Improvement in UEFM for c-tDCS group only
Hesse et al. (2011)	96	A,S mix	2	DB-RCT: a-tDCS + RAT vs. c-tDCS + RAT vs. sham + RAT × 30 days	No change in UEFM, BI, BBT, MRC, mod Ashworth
Stagg and Nitsche (2011)	13	C mix	1	SB-Cross: a-tDCS vs. c-tDCS vs. sham. fMRI on subset of subjects	Improvement in response time task in a-tDCS group correlating with increased activity in lesional PMC, SMA, and M1 on fMRI
Human bihemispheric tDCS (Anode placed over lesional motor cortex and cathode placed over contralesional motor cortex) studies					
Lindenberg et al. (2010)	20	C MCA	1.5	DB-RCT: bi-tDCS vs. sham + OT × 5 days	Improvement in UEFM and WMFT 7 days post, improved laterality index by fMRI
Bolognini et al. (2011)	14	C mix	2	DB-RCT: bi-tDCS vs. sham + CIMT × 10 days	Improvement in TCI. Trend toward improvement in UEFM, JTT, handgrip, MAL

Table 2 continued

Reference	*N*	Stroke subtype[a]	Int (mA)	Study design[b]	Outcome
Lindenberg et al. (2012)	10	C mix	1.5	Obs: bi-tDCS + PT/OT × 5 days then repeated × 5 days	Greater improvement on UEFM and WMFT after 1st 5-day period than 2nd
Human bihemispheric tDCS vs. anodal tDCS to lesional vs. cathodal tDCS to contralesional motor cortex studies					
Mahmoudi et al. (2011)	10	S,C mix	1	DB-Cross: bi-tDCS vs. a-tDCS vs. c-tDCS vs. sham	Improvement in JTT for all tDCS groups, trend toward greater improvement for bi-tDCS group
Human cathodal tDCS to lesional motor cortex studies					
Wu et al. (2012)	90	S, C mix	1.2	DB-RCT: tDCS vs. sham × 4 weeks followed by PT	Improvement in mAsh, UEFM, and BI

a-tDCS anodal tDCS, *BBT* box and block test, *bi-tDCS* bihemispheric tDCS, *BI* Barthel index, *c-tDCS* cathodal tDCS, *CIMT* constraint-induced movement therapy, *GAP-43* growth-associated protein 43, *Int* tDCS intensity, *JTT* Jebsen–Taylor hand function test, *M1* primary motor cortex, *MAL* motor activity log rating scale, *mAsh* modified Ashworth scale, *MBI* motor behavioral index, *MCA* middle cerebral artery, *mix* cortical and subcortical, *MRC* medical research council sum score, *OT* occupational therapy, *PMC* premotor cortex, *PMd* dorsal premotor cortex, *RAT* robot-assisted therapy, *SMA* supplementary motor area, *subcort* subcortical, *TA* tibialis anterior, *TCI* transcallosal inhibition, *UEFM* upper extremity Fugl-Meyer score, *WMFT* Wolf motor function test

[a] A (acute) = 1–30 days post-stroke, S (subacute) = 1–6 mo. post-stroke, C (chronic) ≥ 6 mo. post-stroke. Note that in the rat study, lesioning was by temporary MCA occlusion

[b] In all double-blinded studies, subjects and investigators performing outcome measures blinded to intervention, but investigator performing intervention unblinded

investigation of patients with lesions in subcortical locations and less severe disability is warranted. Stroke patients probably require a critical mass of spared neurons in M1 to receive significant benefit from tDCS and other brain stimulation techniques. Recent studies corroborate that tDCS protocols, particularly those involving cathodal tDCS, may need to be tailored to certain patient subpopulations based on stroke severity. Stagg and Nitsche (2011) found that patients receiving anodal tDCS improved on a response time task using the paretic upper limb compared to sham tDCS, but failed to improve with cathodal tDCS. They note that their patient population was more impaired than those in earlier tDCS studies. Bradnam et al. (2011) found that patients with more severe disability at baseline became worse with cathodal tDCS, whereas those with mild disability showed improvement with regard to selective muscle activation. In cases of severe disability, activity of contralesional M1 may be functionally advantageous instead of maladaptive during movement of the paretic limb (Bradnam et al. 2011). Cathodal tDCS to contralesional M1 could impair this compensatory mechanism, particularly in those with chronic stroke.

A new approach to stroke rehabilitation is bihemispheric tDCS, with the anode placed over lesional M1 and the cathode over contralesional M1. This arrangement raises cortical excitability in lesional M1 while decreasing cortical activity in contralesional M1, effectively combining previous anodal and cathodal tDCS techniques (Vines et al. 2008). Studies demonstrate that bihemispheric tDCS improves upper extremity motor function (Lindenberg et al. 2010; Mahmoudi et al. 2011) and decreases TCI (Bolognini et al. 2011) in chronic stroke patients. The gains from daily sessions of simultaneous bihemispheric tDCS and PT/OT appear to be greater in the first week than the second week (Lindenberg et al. 2012). One study directly compared bihemispheric tDCS to either anodal or cathodal tDCS alone and suggested a trend toward improved motor function only in the bihemispheric group (Mahmoudi et al. 2011).

A recent large ($n = 90$) study by Wu et al. (2012) evaluated the effect of cathodal tDCS to *lesional* M1 in stroke patients, demonstrating reductions in post-stroke spasticity and improved motor function. While the results of this study seem to contradict previous efforts to *increase* cortical excitability in lesional M1 using anodal tDCS, the authors attribute the findings to a reduction in cortically mediated post-stroke spasticity (discussed further in the spasticity section below).

Epidural cortical stimulation (ECS)

Penfield and Boldrey (1937) were the first to systematically document the somatotopic organization of the human motor cortex based on the effects of electrical stimulation of the cortical surface. They summarized this topography through the illustration of the homunculus. Many years later, investigators used electrical stimulation over M1 therapeutically to treat post-stroke pain syndromes (Tsubokawa et al. 1993). Anecdotal evidence from a subset of these patients suggested improvement in motor symptoms following cortical stimulation (Tsubokawa et al. 1993).

Studies in healthy rats corroborated these results by showing evidence of LTP (Trepel and Racine 1998) and reorganization in neocortex (Teskey et al. 2002) following cortical stimulation. These preliminary human and animal studies created interest in treating the motor symptoms of stroke with ECS.

Accumulating evidence from animal stroke models indicates that electrical stimulation can promote motor recovery (Table 3). Initial studies in rodents involved induction of cortical strokes in M1 and implantation of subdural stimulating electrodes (Adkins-Muir and Jones 2003; Kleim et al. 2003; Teskey et al. 2003; Zhou et al. 2010). Following stroke, rodents underwent "rehabilitation" which included a reach training task in the presence of cortical stimulation. Relative to non-stimulated animals, those receiving stimulation (either 50 or 100 Hz) showed greater motor improvement (Adkins-Muir and Jones 2003; Kleim et al. 2003; Teskey et al. 2003). These motor gains were accompanied by an increased density of dendritic processes (Adkins-Muir and Jones 2003; Zhou et al. 2010), increased polysynaptic potentiation (Teskey et al. 2003), and expanded forelimb representation (Kleim et al. 2003). In parallel with early studies of cortical stimulation in rodents, Plautz et al. (2003) tested the feasibility of subdural cortical stimulation in squirrel monkeys. In the chronic period following induced stroke, three monkeys received 11–24 days of training on a skilled pellet retrieval task combined with 50 Hz subdural cortical stimulation. These monkeys showed improvement in the pellet retrieval task and expansions of the cortical representation for distal forelimb, with a large proportion of new forelimb sites located under the stimulating electrodes. Subsequent rodent studies employed less invasive epidural stimulating electrodes and achieved similar results (Adkins et al. 2006, 2008; Baba et al. 2009; Moon et al. 2009). Additional evidence of ECS efficacy included a larger proportion of surviving neurons in perilesional cortex (Adkins et al. 2006; Baba et al. 2009), upregulation of neurotrophic factors (Baba et al. 2009), and increased axodendritic synaptic density (Adkins et al. 2008).

ECS studies in humans with chronic stroke looked promising initially, then failed to demonstrate statistical efficacy in larger trials. In a case report (Brown et al. 2003) and subsequent phase I study (Brown et al. 2006), patients with chronic stroke underwent grid implantation and 3 weeks of daily 50 Hz ECS during occupational therapy (OT). Combined ECS and OT were associated with gains in the Upper Extremity Fugl-Meyer Score (UEFM) above non-stimulated controls. This early success led to a phase II study with 24 subjects (Huang M et al. 2008; Levy et al. 2008) who received combined ECS and OT over a longer period of time (6 weeks). Stimulated subjects showed improvement on UEFM and Box and Block Test scores compared to controls 3 months following intervention. The phase III "EVEREST" trial by Northstar Neuroscience examined a larger cohort of patients undergoing 50-Hz stimulation and OT (Harvey and Winstein 2009). The detailed results remain unpublished, but some data were made available at the 2008 International Stroke Conference and later analyzed by Plow et al. (2009) as well as Nouri and Cramer (2011). Overall, subjects receiving ECS showed no statistically significant improvement in UEFM or the Arm Motor Ability Test when compared to controls. This lack of efficacy was surprising considering the successful phase I and II trials, and might be related to the fact that a large proportion of subjects suffered severe motor weakness. Plow et al. (2009) note that intraoperative stimulation of lesional M1 evoked motor responses in only 16 % of treatment group patients in the phase III trial, a much smaller percentage than in the phase I and II studies. The lack of intraoperative MEPs is significant because it suggests there were few, if any, surviving corticospinal projections to spinal motoneurons in this patient cohort. A subanalysis of the small group of patients with intraoperative MEPs showed improvement in motor function in comparison with controls. Nouri and Cramer (2011) determined that study subjects with more severe corticospinal tract damage by fMRI were less likely to achieve improvement in motor function with ECS. Such observations suggest that a critical mass of spared corticospinal tract fibers is necessary to achieve improvement with ECS. A recent observational study by Yamamoto et al. (2011) provides supporting evidence for ECS therapies. Six patients, all with D-waves (the corticospinal equivalent of an intraoperative MEP), showed improved motor function when 25-Hz stimulation was delivered <4 h per day for 6 months.

Physiologic mechanisms leading to improved motor recovery with preprogrammed brain stimulation techniques

rTMS, tDCS, and ECS all modulate cortical excitability, but this cortical modulation tends to be short-lived and fairly non-specific with regard to cortical representation of muscle groups; real gains in motor recovery are likely to occur when these techniques are combined with motor training. The full range of physiologic effects caused by these stimulation techniques in isolation remains poorly understood. We know that rTMS alters gene expression (Hausmann et al. 2000; Wang HY et al. 2011; Yoon et al. 2011), tDCS affects GABA and glutamate activity (Stagg and Nitsche 2011), and ECS upregulates neurotrophic factors (Baba et al. 2009). Yet, studies measuring changes in cortical excitability with short courses of rTMS and tDCS suggest that effects last <24 h (Maeda et al. 2000; Nitsche and Paulus 2000). In addition, rTMS, tDCS, and

Table 3 Subdural and epidural cortical stimulation studies to treat motor deficits following stroke

References	*N*	Stroke subtype[a] or lesion method	Freq (Hz)	Study design[b]	Outcome
Rat subdural cortical stimulation studies					
Adkins-Muir and Jones (2003)	37	Endo-1 inj	50, 250	50 Hz ($n = 17$) vs. control ($n = 7$) + reach training × 10 days	Improvement on Montoya staircase task, increased MAP2 neural processes for 50 Hz group
Kleim et al. (2003)	20	Electro-coag	50	Bi-cath ($n = 7$) vs. mono-cath ($n = 4$) vs. mono-an ($n = 4$) vs. control ($n = 5$) + reach training × 10 days	Improvement on pellet retrieval task for mono-cath group only, increased peri-infarct movement representation for all stim groups
Teskey et al. (2003)	40	Dura, pia removal	25, 50, 100, 250	25 Hz ($n = 8$) vs. 50 Hz ($n = 8$) vs. 100 Hz ($n = 8$) vs. 250 Hz ($n = 8$) vs. control group + reaching task × 10 days	Improvement on pasta matrix task in the 50, 100, and 250 Hz groups
Teskey et al. (2003)	35	Dura, pia removal	10, 25, 50, 100, 250, 500	10 Hz ($n = 5$) vs. 25 Hz ($n = 5$) vs. 50 Hz ($n = 5$) vs. 100 Hz ($n = 5$) vs. 250 Hz ($n = 5$) vs. 500 Hz ($n = 5$) vs. control group + reaching task × 10 days	Increased potentiation of CEPs for 50, 100, 250, and 500 Hz groups. Reduced MT in the 25, 50, 100, 250, and 500 Hz groups
Zhou et al. (2010)	21	MCA occ	10, 25, 50	Mono-cath cycling through 10, 25, and 50 Hz ($n = 12$) vs. control ($n = 9$) × 16 days	Improvement on motor function tasks, increased MAP2 dendritic processes
Rat epidural cortical stimulation studies					
Adkins et al. (2006)	31	Endo-1 inj	100	Mono-cath ($n = 10$) vs. mono-an ($n = 11$) vs. control + reach training × 18 days	Improvement on pellet retrieval task, higher perilesional neuronal density in mono-cath group
Adkins et al. (2008)	48	Endo-1 inj	100	Mono-cath mod impair ($n = 12$) vs. mono-cath severe impair ($n = 12$) vs. control mod impair ($n = 12$) vs. control severe impair ($n = 12$) + reach training × 18 days	Improvement on pellet retrieval task in mono-cath mod impair group, increased axodendritic synaptic density in both stimulation groups
Moon et al. (2009)	82	Photo-thromb	50	Mono-an continuous ($n = 24$) vs. mono-an intermittent ($n = 25$) vs. control ($n = 23$) + reach training × 12 days	Improvement on pellet retrieval task in small lesion rats in intermittent group, large lesion rats in continuous group
Baba et al. (2009)	107	MCA occ	2, 10, 50	Bipolar ECS vs. control × 3 days	Improvement on limb placement task, expanded perilesional movement representations
Non-Human Primate Subdural Cortical Stimulation Studies					
Plautz et al. (2003)	3	Electrocoag	50	Bipolar stimulation + pellet retrieval task × 11–24 days	Improvement in pellet retrieval task and expansion of perilesional movement representations
Human epidural cortical stimulation studies					
Brown et al. (2003)	1	C, subcort	50	Bipolar ECS + OT × 3 weeks.	Improvement in UEFM and SIS
Brown et al. (2006)	8	S, C mix	50	Phase I, RCT: bipolar ECS ($n = 4$) vs. control ($n = 4$) + OT × 3 weeks	Improvement in UEFM 3 mo. post
Huang M et al. (2008); Levy et al. (2008)	24	S, C mix	50, 101	Phase II, RCT: 50 Hz bipolar ECS ($n = 5$) or 101 Hz bipolar ECS ($n = 7$) vs. control ($n = 12$) + OT × 6 weeks	Improvement in UEFM and BBT for pooled 50 Hz + 101 Hz group 6 mo. post

Table 3 continued

References	*N*	Stroke subtype[a] or lesion method	Freq (Hz)	Study design[b]	Outcome
EVEREST trial, 2008, unpublished	146	S, C mix	50	Phase III, SB-RCT: 50 Hz bipolar ECS ($n = 91$) vs. control ($n = 55$) + OT × 6 weeks	No improvement in UEFM or AMAT
Yamamoto et al. (2011)	6	S, C subcort	25	Obs: bipolar ECS avg 89–588 min per day × 6 mo.	Improvement in UEFM with stim <4 h/day

AMAT arm motor ability test, *BBT* box and block test, *CEP* callosal evoked potential, *ECS* epidural cortical stimulation, *electrocoag* electrocoagulation of surface vessels over M1, *endo-1 inj* injection of endothelin-1 into M1, *Freq* stimulation frequency, *M1* primary motor cortex, *MAP2* microtubule-associated protein 2, *MCA* middle cerebral artery, *mix* cortical and subcortical, *mono-an* monopolar anodal, *mono-cath* monopolar cathodal, *MT* motor threshold, *occ* occlusion, *Obs* observational study, *OT* occupational therapy, *photothromb* photothrombosis of M1 with fiberoptic bundle, *RCT* randomized controlled trial, *SB* single-blinded, *SIS* stroke impact scale, *subcort* subcortical, *UEFM* upper extremity Fugl-Meyer score

[a] A (acute) = 1–30 days post-stroke, S (subacute) = 1–6 mo. post-stroke, C (chronic) ≥ 6 mo. post-stroke

[b] No control group subjects in the human studies underwent surgical implantation

ECS affect large regions of M1 instead of targeting the M1 representation for muscles affected by stroke, like the extensors of the hand, which are critical for effective reaching and grasping (Hlustík and Mayer 2006). Though some authors report improved motor recovery with brain stimulation in isolation (see Tables 1, 2, 3), the true long-term gains in functional outcome likely occur when these stimulation modalities are combined with motor training.

Recent studies examining fMRI changes following brain stimulation and motor training are beginning to identify brain regions undergoing physiologic changes with this paired rehabilitation strategy (Ameli et al. 2009; Chang et al. 2012; Stagg et al. 2012). Two studies looked at fMRI changes following 10 Hz rTMS to lesional M1 and a finger tapping task (Ameli et al. 2009; Chang et al. 2012); both demonstrated increased fMRI activity in ipsilesional sensorimotor cortex in subjects responding to intervention. Ameli et al. (2009) also found decreased fMRI activity in the contralesional premotor cortex (PMC) and parietal area while Chang et al. (2012) found increased fMRI activity in the ipsilesional thalamus and contralesional caudate nucleus. Stagg and Nitsche (2011) discovered that anodal tDCS to lesional M1 and motor training in chronic stroke patients increased fMRI activity in ipsilesional M1, PMC, and supplementary motor area (SMA) which correlated with improvement on a response time task.

Brain stimulation before or during motor training probably alters M1 and connections to M1 in ways that enhance functionally appropriate neuroplasticity. In this context, brain stimulation likely primes M1 through the mechanisms discussed above, leading to more robust use-dependent plasticity during motor training. This priming effect could include methods to activate lesional M1 (high-frequency rTMS, anodal tDCS, or ECS) or depress contralesional M1 (low-frequency rTMS or cathodal tDCS) in an effort to reduce maladaptive TCI. Motor training promotes use-dependent plasticity because potentiating effects preferentially target specific functional areas through Hebbian mechanisms (Carey et al. 2002). Thus, brain stimulation and motor training together are likely to be synergistic in promoting functional neuroplastic changes that last well beyond the period of therapy.

The effects of brain stimulation on post-stroke spasticity

Spasticity following injury to the central nervous system was traditionally attributed to a combination of disinhibited spinal reflexes and increased visco-elastic properties of the tissues in the affected limb (Brown 1994). Recent evidence may suggest a third contribution from hyperexcitability of the lesional sensorimotor cortex (Lindberg et al. 2009). Stroke patients initially demonstrate increased cortical activity in the contralesional hemisphere compared to healthy controls when attempting to move the impaired limb, and as these patients recover limb function activity returns to the lesional hemisphere (Carey et al. 2002). While the return of activity to the lesional hemisphere appears advantageous, too much activity could become maladaptive due to increased spasticity. This theory may explain the seemingly contradictory results of studies demonstrating improved motor function with either anodal (Stagg et al. 2012) or cathodal (Wu et al. 2012) tDCS to lesional M1. Yamamoto et al. (2011) provided further evidence for this theory by showing that ECS < 4 h a day improved motor function in stroke patients, whereas ECS > 4 h a day impaired motor function due to increased spasticity. Future research could focus on restoring activity to lesional M1 while preventing the undesired cortical component of spasticity by altering the timing and/or

location of brain stimulation. For example, one might couple excitatory brain stimulation to lesional M1 in the acute period after stroke with inhibitory stimulation to lesional M1 in the subacute to chronic period as spasticity begins to develop. Alternatively, one might use more focal techniques like rTMS to excite hand area of lesional M1 and inhibit areas of suspected involvement in cortical spasticity such as area 3b of the primary sensory cortex (Lindberg et al. 2009).

Homeostatic mechanisms and appropriate timing of brain stimulation and motor training

The optimal time to deliver brain stimulation relative to motor training remains to be determined. Relevant to this discussion is the Bienenstock–Cooper–Munro (BCM) theory of bidirectional synaptic plasticity (Bienenstock et al. 1982), which states that neuronal responses to conditioning stimuli depend on the recent history of neuronal activity. A neuron excited by brain stimulation will eventually undergo inhibition to restore homeostasis and will not respond to motor therapy during that time. The BCM theory applies to heterosynaptic networks where change in recent activity at one synapse affects ensuing plasticity at neighboring synapses. A similar phenomenon can occur in homosynaptic networks where change in recent activity at a synapse affects subsequent plasticity in the same synapse. The term homeostatic metaplasticity describes either heterosynaptic or homosynaptic mechanisms affecting subsequent plasticity (Abraham 2008). The "meta" portion of homeostatic metaplasticity refers to higher-order physiological processes beyond traditional plasticity governing the level of ensuing LTP/LTD. Jung and Ziemann (2009) demonstrated the effects of homeostatic metaplasticity using paired associative stimulation (PAS) combined with motor learning in healthy subjects. PAS involves stimulation of median nerve at the wrist paired with TMS to M1. Depending on the timing of median nerve stimulation relative to TMS, PAS can lead to LTP-like effects (PAS_{LTP}) or LTD-like effects (PAS_{LTD}) in M1. For PAS_{LTP}, the interstimulus interval (ISI) between median nerve stimulation and TMS exceeds the duration of the N20 somatosensory evoked potential by 2 ms; for PAS_{LTD}, the ISI is 5 ms shorter than the duration of the N20 potential. Jung and Ziemann found that motor training immediately following PAS_{LTD} enhanced motor learning. Motor training immediately following PAS_{LTP} also enhanced motor learning, though to a lesser degree than PAS_{LTD}. Motor training 90 min after PAS_{LTD} enhanced motor learning, whereas motor training 90 min after PAS_{LTP} *reduced* motor learning. Thus, rehabilitation protocols invoking excitatory brain stimulation with subsequent motor therapy could be counterproductive if combined over a suboptimal time period due to competition between homeostatic mechanisms and use-dependent plasticity. Further research is needed to determine the best time interval between two successive excitatory therapies.

Homeostatic metaplasticity also affects studies of tDCS and other methods of brain stimulation. Fricke et al. (2011) demonstrated that changing the interval between two successive applications of excitatory tDCS could alter neuromodulatory aftereffects in healthy subjects. When a second application of excitatory tDCS was given 3 min, as opposed to immediately after the first, the expected increase in MEP amplitude with single-pulse TMS was eliminated or even reversed. They emphasized that such a time-dependent reversal of aftereffects is consistent with homeostasis-preserving mechanisms that govern the ease and direction with which neuroplasticity can be induced. This phenomenon appears to apply to any excitability-modulating interventions applied consecutively. Homeostatic mechanisms could explain the lack of efficacy in the trial of rTMS and CIMT by Malcolm et al. (2007). It follows that rehabilitation protocols with simultaneous brain stimulation and motor training may prove most efficacious. While tDCS and ECS are commonly delivered during motor training, rTMS is not due to safety concerns. Strategies that quickly alternate rTMS with motor training, as in the study by Koganemaru et al. (2010), probably best avoid competing homeostatic mechanisms and may explain the success of such studies. Alternative strategies that may avoid competing homeostatic processes, including motor therapy prior to brain stimulation and inhibitory brain stimulation to lesional M1 with delayed motor therapy, remain untested in stroke patients. Clearly, careful consideration of the timing between brain stimulation and motor therapy is critical for future studies.

Part II: Activity-dependent brain stimulation

Cellular studies of spike-timing-dependent plasticity

While the above methods of brain stimulation hold promise for improving motor disability after stroke, they employ delivery of preprogrammed stimuli. Alternative approaches using neural or muscle activity to control brain stimulation may prove more effective in inducing neuroplasticity. Activity-dependent stimulation provides a method of invoking Hebbian mechanisms more closely tailored to functional circumstances. At the cellular level, connections between two neurons are strengthened when the postsynaptic neuron fires within 50 ms after arrival of the presynaptic input (Bi and Poo 1998; Feldman 2000; Markram

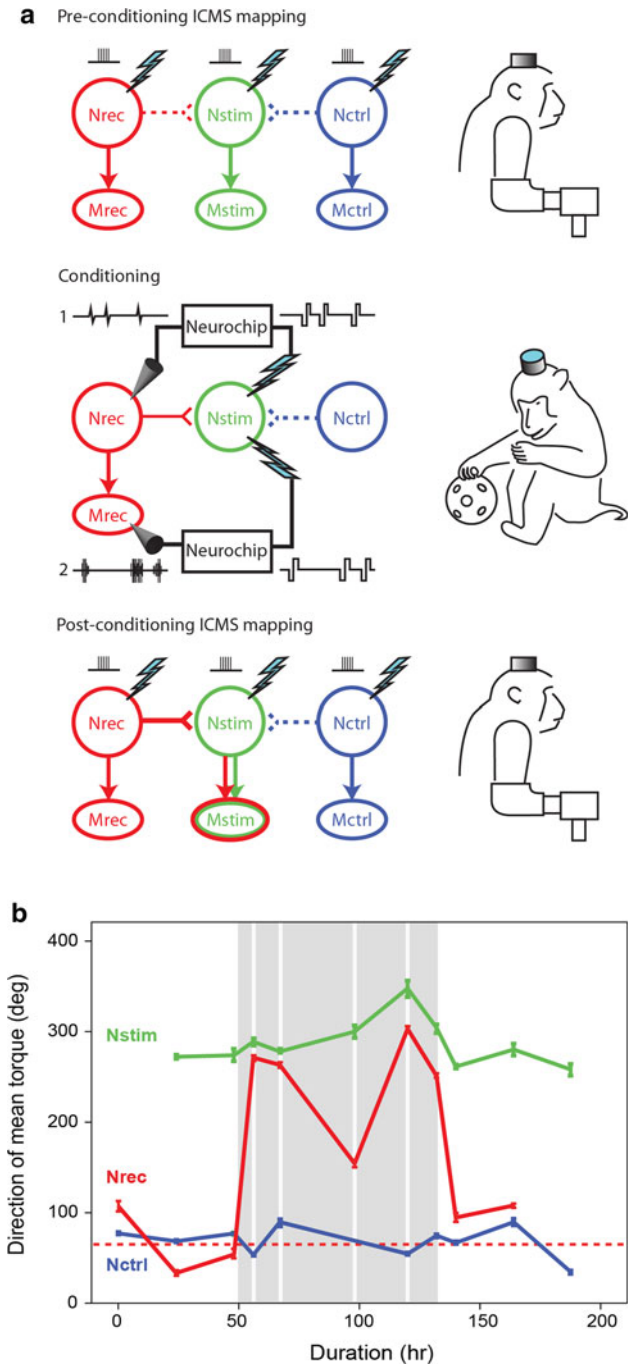
et al. 1997). Markram et al. (1997) showed that the amplitude of excitatory postsynaptic potentials (EPSPs) in motor cortical cells became potentiated or depressed depending on whether the postsynaptic action potential (AP) followed or preceded the presynaptic AP, respectively. Bi and Poo (1998) further described the critical timing between pre- and postsynaptic neural spiking necessary for both LTP and LTD in dissociated rat hippocampal neurons. For LTP, the postsynaptic neuron must fire within 50 ms after the presynaptic neuron, and for depression, no sooner than 50 ms before the presynaptic neuron. The timing window marking the transition from LTD to LTP is narrow, occurring within 5 ms around zero delay.

NMDA receptors mediate spike-timing-dependent plasticity (STDP) and designing stimulation protocols to capitalize on the unique physiology of these receptors may result in the most robust neural plasticity. Whole-cell perforated-patch clamp studies of LTP reveal that NMDA receptors act as coincidence detectors. Not only do they require presynaptic activation in the form of the excitatory neurotransmitter glutamate, but Mg^{2+} must be unblocked from the receptor shortly thereafter by a back-propagating action potential to allow Ca^{2+} influx (Nowak et al. 1984). The dual events required to invoke NMDA receptor-mediated LTP confer spatial specificity to strengthened synapses (Bi and Poo 2001; Caporale and Dan 2008). Preprogrammed techniques like anodal tDCS invoke the NMDA receptor for their aftereffects, but spatial specificity is largely lost when activating an entire cortical region. In contrast, activity-dependent stimulation provides two events—M1 activity specific to a desired limb movement and a single pulse of brain stimulation delivered to sites where conditioning effects should occur. STDP in vivo has been demonstrated in several experimental models (Fetz et al. 2010; Jackson et al. 2006; Meliza and Dan 2006; Rebesco et al. 2010; Zhang et al. 1998). Evidence continues to mount that STDP rules apply to diverse populations of neurons, although the time course and polarity of the rules may differ (Caporale and Dan 2008; Müller-Dahlhaus et al. 2010).

Animal studies of activity-dependent stimulation

Animal studies in NHPs and rodents provide clear evidence that activity-dependent stimulation induces neural connections in M1 (Jackson et al. 2006; Lucas 2009; Lucas and Fetz 2011; Rebesco et al. 2010) (Table 4). NHP studies assessing changes in stimulus-induced motor outputs document the potentiating effects of activity-dependent stimulation. Jackson et al. (2006) used a head-fixed computer chip to convert action potentials of single neurons recorded at a particular M1 site into electrical stimuli delivered to another site with different motor outputs. Following repeated spike-triggered stimulation for 1 or 2 days during free behavior, an effective connection formed between the two sites; electrical stimulation to the recording site now evoked motor responses previously obtained from the site that was stimulated during conditioning (Fig. 2a). These effects lasted for at least 10 days beyond the end of conditioning. Similar effects were not obtained from control sites, indicating that stimulation alone was insufficient to induce plasticity. Moreover, the changes could only be obtained if the interval between action potentials and stimuli was less than 50 ms, consistent with the window for STDP. A similar study in rats (Rebesco et al. 2010) used a computer to convert activity recorded from a single M1 neuron into electrical stimuli delivered to another cortical site while the rats freely behaved for 2–3 days. Neural recordings from a 16-electrode array in M1 after this period of stimulation revealed changes in the "inferred functional connectivity" consistent with strengthened connections between the triggering and target electrodes. This change was not seen for longer delays of 500 ms between the triggering action potential and stimuli, suggesting changes in the inferred functional connectivity were consistent with STDP.

A recent NHP study (Lucas 2009; Lucas and Fetz 2011) showed that triggering M1 stimulation from contralateral forelimb muscle activity could produce plasticity of M1 output effects similar to those obtained by Jackson et al. (2006), indicating that electromyographic (EMG) activity could serve as an effective surrogate for the associated cortical activity (Fig. 2a). In the example illustrated in Fig. 2b, the implanted computer chip discriminated EMG signals from a finger extensor muscle during volitional movements and delivered subthreshold electrical stimuli to the cortical region that activated a forelimb supinator muscle. After nearly 6 h of activity-dependent conditioning, the output effects of the finger extensor area of M1 incorporated supination as well as finger extension (Fig. 2a, b). Output effects evoked from the supinator area of M1 and neighboring control sites remained unchanged, suggesting that activity-dependent plasticity was specific to the motor representation for finger extension. The plasticity effect appeared rapidly, within 25 min of the onset of conditioning, and persisted in the presence of intermittent conditioning for several days. Following discontinuation of recurrent conditioning, the M1 output effects returned to preconditioning levels. Conditioning sessions that used preprogrammed M1 stimulation independent of EMG activity but matched to activity-dependent stimulation in terms of average frequency, intensity, and duration had no effect on cortical reorganization. Overall, this study by Lucas et al. represented a significant advance toward eventual clinical applications by demonstrating the ability



◀ **Fig. 2** Activity-dependent conditioning triggered by cortical or EMG activity in a non-human primate. **a** Summary of experiments demonstrating plasticity obtained with the head-fixed computer ["Neurochip"]. Preconditioning intracranial microstimulation (ICMS) trains activated distinct descending projections from each of 3 cortical sites to corresponding muscles, with monkey at rest. Conditioning during unrestrained behavior by (1) spike-triggered stimulation (Jackson et al. 2006) or (2) EMG-triggered (Lucas 2009; Lucas and Fetz 2011) stimulation induced a strengthening of horizontal connections between Nrec and Nstim. Post-conditioning ICMS now activates Mstim via strengthened horizontal projections to Nstim, as well as Mrec via the direct projection. **b** The direction of mean torque evoked by electrical stimulation of three M1 sites before, during, and after activity-dependent conditioning (*gray regions*) converted into angular degrees. M1 output effects are quantified by measuring forelimb torque responses evoked with trains of intracortical microstimulation (ICMS) before and after conditioning. Nrec (*red*)—cortical site that activates Mrec (EDC) at baseline, Nstim (*green*)—cortical site that activates Mstim (SUP), Nctrl (*blue*)—cortical site that activates Mctrl (APB). During conditioning, Mrec (EDC) muscle activity triggered intracortical stimulation at the Nstim site. Mean baseline responses evoked from Nrec stimulation illustrated with *dotted red line*. *EDC* extensor digitorum communis, *SUP* supinator, *APB* abductor pollicis brevis. *Error bars* SEM. Data represent the initial 50 ms of train-triggered torque responses following ICMS onset converted into angular degrees. Figures adapted from (Jackson et al. 2006) (*a*) and (Lucas 2009; Lucas and Fetz 2011) (*b*)

to drive cortical plasticity with EMG signals instead of invasive cortical recordings.

Activity-dependent TMS in healthy subjects

Studies in healthy human subjects suggest that activity-dependent TMS can induce motor learning (Bütefisch et al. 2004) and change cortical excitability for a specific target muscle (Thabit et al. 2010). Bütefisch et al. (2004) asked subjects to repeatedly flex the thumb at 1 Hz in a direction opposite the naturally occurring MEP evoked by TMS at the abductor pollicis brevis (APB) hot spot. During the main experimental sessions, every 10th episode of thumb flexion triggered a single TMS pulse to contralateral M1 over the APB hot spot. Following repetitive pairing in this manner for 30 min, stimulation with TMS over the APB hot spot primarily caused thumb *flexion* instead of abduction; this effect lasted for at least an hour. Thabit et al. (2010) employed an alternate method of activity-dependent TMS designed to change cortical excitability for a specific muscle. Subjects performed a reaction time task involving thumb abduction in response to a visual cue. After establishing a mean reaction time, subjects repeated thumb abduction at 0.2 Hz for 20 min with paired single-pulse TMS. The TMS pulses occurred at −100, −50, +50, +100, or +150 ms in relation to the anticipated onset of EMG activity based on the mean reaction time. Subjects in the −50 ms group experienced a significant increase and those in the +100 ms group a significant decrease in APB MEP amplitude following conditioning sessions. There were no changes in the MEP amplitude for a control muscle, abductor digiti minimi, suggesting that plasticity was specific to the APB area of M1.

The specificity of changes to particular motor areas of M1 in the study by Thabit et al. (2010) was consistent with Hebbian plasticity, but the temporal window was difficult to interpret in the context of prior STDP studies. The relative timing necessary to cause LTP- and LTD-like effects

Table 4 Activity-dependent brain stimulation studies to promote motor plasticity

Reference	*N*	Stroke subtype[a] (if applicable)	Temporal window[b] (ms)	Freq[c] (Hz)	Int	Study design	Outcome
Rat studies of activity-dependent intracortical microstimulation							
Rebesco et al. (2010)	8	Healthy	+5 ↑	Mean 6	30 μA	Computer used APs from an M1 electrode to trigger ICMS to other M1 locations × 2–3 days	Change in inferred functional connectivity of M1 neurons lasting <24 h. post
Non-human primate studies of activity-dependent intracortical microstimulation							
Jackson et al. (2006)	2	Healthy	+0–50 ↑	0–100, mean 9–19	25–80 μA	Electronic neural implant used APs from an M1 electrode to repeatedly trigger ICMS to another M1 location × 1–4 days	Change in torque evoked with M1 stimulation up to10 days post
Lucas (2009); Lucas and Fetz (2011)	4	Healthy	+1 ↑	0–100, mean 0.5–10.3	18–59 μA	Electronic neural implant used EMG recorded from contralateral forelimb muscle to trigger ICMS to another M1 location × 20 min. −24 h	Change in torque evoked with M1 stimulation lasting <24 h post
Human studies of activity-dependent TMS							
Bütefisch et al. (2004)	6	Healthy	[d]↑	0.1	80 % RMT	Cross: contra AD-TMS vs. asynchronous contra TMS vs. ipsi AD-TMS vs. motor training alone × 30 min	Increase in # of APB hot spot MEPs resulting in thumb flexion in contra AD-TMS group lasting >60 min. post
Thabit et al. (2010)	17	Healthy	−50 ↑, +100 ↓	0.2	120 % RMT	Cross: AD-TMS using RTT comparing temporal window of −100, −50, +50, +100, and +150 ms × 20 min	Increased MEP amplitude and CSP, decreased SRT for −50 ms group. Decreased MEP amplitude for +100 ms group
Buetefisch et al. (2011)	6	C, mix	+30–50 ↑	0.1	80 % RMT	Cross: RAT + lesional AD-TMS vs. RAT + contralesional AD-TMS vs. RAT alone × 30 min	Lateral shift in center of gravity for lesional ECR in both AD-TMS groups

AD-TMS activity-dependent transcranial magnetic stimulation, *AP* action potential, *contra* contralateral, *CSP* cortical silent period, *ICMS* intracortical microstimulation, *Intensity* ICMS current for non-human primate studies and TMS % RMT of a hand muscle for human studies, *ipsi* ipsilateral, *M1* primary motor cortex, *MEP* motor-evoked potential, *mix* cortical and subcortical, *RAT* robot-assisted motor training, *RMT* resting motor threshold, *RTT* reaction time task, *SRT* simple reaction time

[a] C (chronic) ≥ 6 mo. post-stroke

[b] Time from AP (Rebesco et al. and Jackson et al. studies) or EMG onset to brain stimulation. ↑ = potentiating effects, ↓ = depressing effects

[c] Frequency for delivery of each stimulus (non-human primate studies) or each TMS pulse (human studies)

[d] Unpublished but presumed to be +30–50 ms as in the subsequent study on stroke patients

was the *opposite* of what one might expect. In the other activity-dependent stimulation studies (Bütefisch et al. 2004; Jackson et al. 2006; Lucas 2009; Lucas and Fetz 2011), LTP-like effects occurred when brain stimulation *followed* neural or EMG activity. However, Thabit et al. did not test the effect of TMS pulses delivered between 0 and +50 ms after the onset of EMG activity when LTP-like effects might have occurred. Given the pattern of temporal asymmetry discovered by Thabit et al., the most potent LTP-like effects may occur when brain stimulation *precedes* the natural M1 activity necessary to cause movement. This possibility is consistent with the fact that the onset of centrally driven cortical activity precedes the onset of muscle activity by several hundred ms (e.g., Crammond and Kalaska 2000).

Activity-dependent TMS for stroke rehabilitation

Activity-dependent TMS, in which each episode of motor activity from the paretic limb triggers a single TMS pulse to lesional M1, holds promise for stroke rehabilitation (Fig. 3a). A feasibility study of activity-dependent TMS combined with robot-assisted motor training (RAT) in 6 chronic stroke patients by Buetefisch et al. (2011) showed subtle evidence of cortical plasticity. The main intervention entailed 30 min of RAT at 0.2 Hz in which every other episode of wrist extension triggered TMS to lesional extensor carpi ulnaris (ECU) hot spot. Subjects served as their own controls, undergoing additional experiments including RAT alone and RAT plus ECU-triggered TMS to the contralesional ECU hot spot. The most significant finding was a lateral shift in the ECU center of

gravity in both RAT plus activity-dependent TMS groups. No significant changes occurred in MEP amplitude pre- to post-stimulation. The Barthel Index, Motricity Index, and Jebsen–Taylor test were performed at baseline to gauge motor function in the paretic limb, but these were not repeated following stimulation. In short, this study demonstrated the feasibility of activity-dependent TMS in stroke patients but larger studies with functional end points are necessary to prove utility.

Optimal stimulation parameters for activity-dependent TMS

Though activity-dependent TMS holds promise for stroke rehabilitation, the optimal stimulation parameters that maximize cortical plasticity remain to be determined. Key open questions include optimal parameters for timing between EMG onset and TMS delivery, stimulation intensity, stimulation frequency, and type of muscle activity to induce plasticity effects. Of these questions, determining the best timing between EMG onset and TMS delivery is particularly significant. Whole cell (Bi and Poo 1998) and animal studies (Jackson et al. 2006) of spike-timing-dependent plasticity suggest a window for brain stimulation between −50 ms and +50 ms from the onset of neural activity in M1 to induce LTD- and LTP-like effects. It is well documented that this time window may vary across different species, cell types, and modes of stimulation (Bi and Poo 2001; Caporale and Dan 2008). The study by Thabit et al. (2010) suggests this window could extend from −50 ms to +100 ms for movement-triggered stimulation. In NHPs, M1 neurons continue to fire for around 250 ms following the onset of EMG activity with ballistic hand movements, which would be consistent with this broader temporal window (Crammond and Kalaska 2000). A future study of healthy human subjects with TMS delivery staggered at 10–25 ms intervals both before and after EMG onset using a reaction time task could resolve this question.

The optimal stimulation intensity and frequency are also important parameters. Most PAS studies employ a TMS intensity of 120 % (Stefan et al. 2000) to 130 % (Wolters et al. 2003) of resting motor threshold (RMT), and the intensity in the previously described studies of activity-dependent TMS ranged from 80 % (Buetefisch et al. 2011; Bütefisch et al. 2004) to 120 % RMT (Thabit et al. 2010). One would expect more robust plasticity effects with higher stimulation intensity. At frequencies ≤0.2 Hz, for which seizure risk is low (Rossi et al. 2009), a stimulation intensity that parallels PAS studies is likely the best strategy. At higher frequencies, activity-dependent TMS may have more potent plasticity effects; however, frequencies > 1 Hz confer greater risk of cortical spread and seizure. The increased excitability of M1 associated with muscle movement may further increase this seizure risk in the setting of activity-dependent stimulation (Edwardson et al. 2011). With high-frequency stimulation, the intensity should be closer to the active motor threshold (AMT) but probably no greater than 90 % RMT. Intensities < AMT

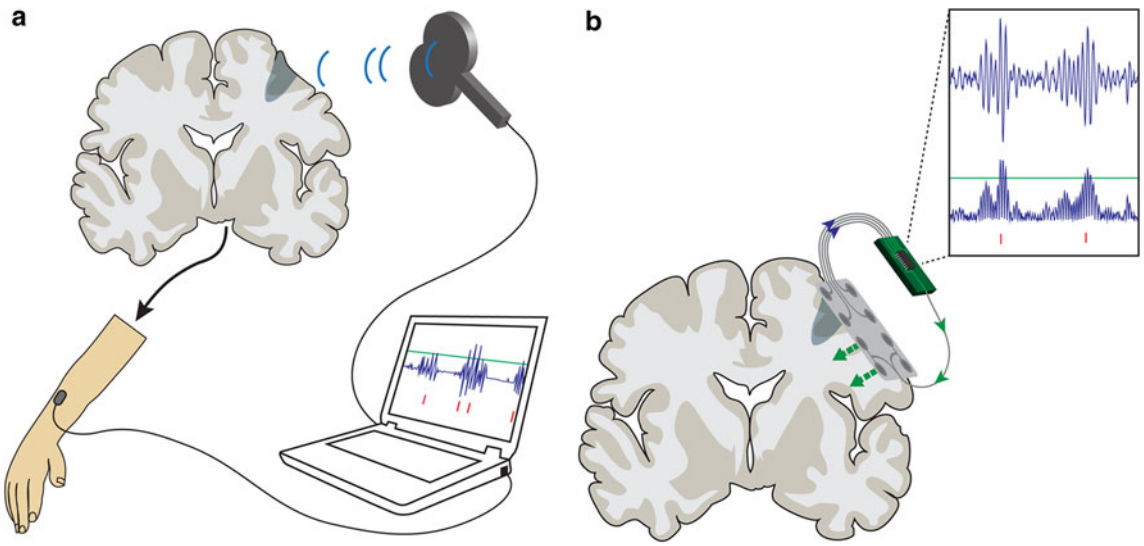


Fig. 3 Activity-dependent methods of brain stimulation. **a** TMS to lesional M1 triggered by EMG activity in the paretic limb. In this schematic, the laptop computer processes EMG activity to create a triggering signal (*red vertical lines*) to the TMS device when the EMG signal rises above a predefined threshold (*horizontal green line*). **b** Epidural cortical stimulation (ECS) to lesional M1 triggered by neural activity in the form of high gamma band (80–120 Hz) filtered electrocorticography (ECoG) signals over hand area of M1. In this schematic, ECS is directed more laterally (*green arrows*) over face area of M1 in an attempt to drive vicariation. An implanted computer chip triggers ECS stimuli (*red vertical lines*) when rectified, high gamma band ECoG rises above a predefined threshold (*horizontal green line*)

are unlikely to be effective and can lead to cortical inhibition (DiLazzaro et al. 1998; Todd et al. 2006). Investigators should include appropriate inter-train intervals with stimulation at high frequencies based on a conservative interpretation of the safety tables established for TMS subjects at rest (Rossi et al. 2009).

Another variable to consider in activity-dependent TMS protocols is the type of muscle activity employed. The previously described studies of activity-dependent stimulation in humans used repetitive ballistic movements, produced largely by a single muscle to create Hebbian plasticity (Buetefisch et al. 2011; Bütefisch et al. 2004; Thabit et al. 2010). Such repetitive movements are quite reproducible between subjects and study sessions; yet, animal studies suggest training on skilled tasks leads to more synaptogenesis and cortical reorganization (Kleim et al. 1998, 2004). It follows that activity-dependent TMS with simultaneous training on a demanding skilled motor task may lead to the greatest gains. When comparing an unskilled task like ballistic movement to a skilled task, one must consider the possibility of a washout effect with low-frequency stimulation. With unskilled tasks, the investigator easily pairs each episode of muscle activity with TMS, whereas with many skilled tasks, the motor units may fire multiple times per second, resulting in fewer appropriately paired stimuli. This could degrade the desired plasticity effects, particularly at low frequencies of stimulation like 0.1–0.2 Hz, as used in the initial activity-dependent TMS studies in humans. Two of the animal studies of activity-dependent stimulation partially allay concern for washout effect. Rebesco et al. (2010) repeated their rodent experiment after rate-limiting the electrical stimuli to 10 Hz and found similar changes in the inferred functional connectivity. In the NHP experiment of EMG-triggered stimulation (Lucas 2009; Lucas and Fetz 2011), reducing the ratio of brain stimuli to EMG triggers to 1:16 caused no decrement in the observed plasticity effects.

Activity-dependent tDCS

Many researchers have explored simultaneous tDCS and motor therapy (see Table 2); yet, no one to our knowledge has administered true activity-dependent tDCS in which very short duration tDCS is repeatedly paired with discrete episodes of volitional activity in an effort to drive LTP. Furubayashi et al. (2008) tested the effects of short duration (100 ms), subthreshold (3 mA) tDCS in healthy subjects at rest by delivering single-pulse TMS at various times after current onset; anodal tDCS to M1 increased MEP amplitude in the first 10 ms and this change was attributed to an increase in the resting membrane potential of cortical neurons. The aftereffects on cortical excitability with tDCS of longer duration (described in part I) were not present for short duration tDCS. Nonetheless, activity-dependent tDCS warrants investigation to determine whether raising the resting membrane potential intermittently to coincide with periods of volitional activity proves a more potent driver of neural plasticity than static direct current administration.

Activity-dependent ECS

Although the failed phase III trial of preprogrammed ECS by Northstar Neuroscience led to the company's demise, careful analysis of the results indicates no reason to abandon ECS as a potential stroke rehabilitation strategy. Benefit did occur in the small subgroup with intraoperative MEPs (Plow et al. 2009), and there is every possibility of greater plasticity effects with prolonged activity-dependent ECS. There are no published studies of activity-dependent ECS in animals or humans. The closest surrogate is the study of activity-dependent intracortical microstimulation in NHPs (Lucas 2009; Lucas and Fetz 2011). One potential advantage of activity-dependent ECS over activity-dependent TMS is the ability to deliver stimuli at high frequency while maintaining low seizure risk. In the study of preprogrammed ECS in NHPs (Plautz et al. 2003), seizure occurred on 5 occasions when the stimulation intensity was inadvertently close to movement threshold. No other stimulation-related seizures were reported in any of the animal or human studies of preprogrammed ECS despite typical stimulation frequencies of 50–100 Hz. Stimulating at intensities $\sim$50 % of movement threshold is considered relatively safe (Bezard et al. 1999). The ability to stimulate at high frequencies would make washout less likely for activity-dependent ECS combined with simultaneous training on skilled motor tasks. As with activity-dependent TMS, the optimal stimulation parameters to induce plasticity with activity-dependent ECS require further study.

Activity-dependent stimulation in the sensory system and implications for activity-dependent stimulation in the motor cortex

A wider body of evidence exists for creating activity-dependent plasticity in sensory systems (Feldman 2000; Stefan et al. 2000; Wolters et al. 2003), and of these experiments, PAS is the most studied methodology in human subjects. PAS was discovered by Stefan et al. (2000) and entails pairing median nerve stimulation (MNS) at the wrist with delayed TMS to contralateral M1 resulting in either LTP- or LTD-like effects (see also further description of PAS in the section on homeostatic mechanisms in Part I above). Wolters et al. (2003) characterized the precise timing required for LTP and LTD; the ISI

between MNS and TMS was 25 ms for LTP and 10 ms for LTD. Altering the timing by just 10 ms eliminated any plasticity effects. In contrast to the narrow 15 ms window between LTP- and LTD-like effects with PAS, the window for activity-dependent plasticity in the motor system may be as wide as 150 ms (Thabit et al. 2010). This greater temporal dispersion can be attributed to the physiological difference between activating M1 neurons with a sensory volley from MNS (as in PAS) or through direct volitional activity; M1 neurons activated through MNS fire for several ms (Lemon 1979), whereas M1 activity sufficient to cause a ballistic hand movement lasts for up to 250 ms (Murphy et al. 1982). The precise timing discovered for maximal plasticity effects with PAS suggests the timing between volitional activity and M1 stimulation can also be manipulated to maximize Hebbian plasticity in activity-dependent stimulation. Further activity-dependent studies altering the timing between volitional activity and M1 stimulation at 10–25 ms intervals could help answer this question. The short duration of M1 activation with MNS might also suggest that motor tasks leading to very brief activation of M1 could improve the precision of the timing window of LTP- and LTD-like effects with activity-dependent stimulation.

Recently, investigators combined peripheral nerve stimulation with volitional activity leading to an alternative form of activity-dependent plasticity. Mrachacz-Kersting et al. (2012) repeatedly paired common peroneal nerve stimulation with imagined foot dorsiflexion and observed LTP-like effects, as evidenced by increased MEPs in the tibialis anterior muscle. Plasticity only occurred when the volley from peripheral nerve stimulation arrived at M1 during the execution phase of the imagined movement. Such studies may shed light on the best timing for activity-dependent stimulation coupling volitional activity with M1 stimulation. We theorize that stimulating M1 directly holds more potential for stroke rehabilitation because peripheral nerve stimulation activates only the subset of M1 neurons receiving afferent projections (Lemon 1979) providing less opportunity for Hebbian plasticity; however, this requires further study. Ultimately, a multimodal approach that includes peripheral nerve stimulation, M1 stimulation, and volitional activity may prove most effective.

Candidates for activity-dependent stimulation

The best candidates for activity-dependent TMS, tDCS, or ECS are similar to those for preprogrammed brain stimulation techniques. The trend toward greater response to brain stimulation in those patients with subcortical stroke will likely also hold true for activity-dependent stimulation because TMS, tDCS, and ECS have their greatest effects on the cortical surface. Those with subcortical strokes would have more neural substrate responsive to the chosen intervention. More severely affected patients may not be candidates for activity-dependent stimulation if they cannot generate activity in the impaired limb or M1. Some patients may be able to generate ECoG activity in lesional M1, yet be unable to generate EMG in the impaired limb, suggesting more severely affected patients may be more appropriate for ECoG-triggered ECS therapies. Severely affected patients may further benefit from some form of peripheral nerve (Mrachacz-Kersting et al. 2012) or neuromuscular (Koganemaru et al. 2010) stimulation.

Advantages of activity-dependent stimulation over preprogrammed brain stimulation and future directions

Activity-dependent stimulation may prove more effective for stroke rehabilitation than the preprogrammed brain stimulation methods described in part I for several reasons. Activity-dependent stimulation may lead to more robust neural plasticity. In most studies of preprogrammed stimulation, plasticity effects lasted <24 h (Kim DY et al. 2009; Takeuchi et al. 2005) unless stimulation was combined with motor training and repeated daily for days to weeks (Bolognini et al. 2011; Conforto et al. 2011; Emara et al. 2010; Huang M et al. 2008; Khedr et al. 2009). In contrast, the NHP study of focal activity-dependent stimulation by Jackson et al. (2006) showed that plasticity effects produced by spike-triggered stimulation lasted at least 10 days after conditioning for 1–2 days. Less invasive techniques like EMG-triggered conditioning were less durable, lasting <24 h unless maintained by periodic conditioning (Bütefisch et al. 2004; Lucas 2009; Lucas and Fetz 2011). This difference may be due to the fact that EMG activity is less tightly timed with respect to related cortical cell activity. Despite plasticity effects of similar duration in the initial studies using EMG-triggered stimulation and studies using preprogrammed stimuli, sustained activity-dependent stimulation may ultimately prove more durable. Recent advances in neurosurgery and microelectronics enable fully implantable devices capable of autonomously recording and stimulating the nervous system (Morrell 2011; Stanslaski et al. 2012). Thus, a system could record neural activity over M1 (Fig. 3b) or surface EMG from the paretic limb and trigger recurrent activity-dependent ECS to lesional M1. This would enhance the efficacy of activity-dependent stimulation in stroke patients by allowing continuous conditioning during normal behavior rather than being restricted to scheduled therapy sessions each day. Indeed, neurorehabilitation studies employing CIMT often encourage continued restraint of the intact limb during normal behavior to maximize therapeutic efficacy (Dahl et al. 2008; Wolf et al. 2006).

Further, using electrocorticography (ECoG) signals to trigger brain stimulation may lead to plasticity more closely resembling that of spike-triggered stimulation if ECoG signals prove more tightly correlated with respect to cortical cell activity than EMG. Optimizing the temporal delivery of activity-dependent stimulation and incorporating skilled motor tasks may further enhance longevity.

Targeted activity-dependent stimulation would provide a higher functional and temporal specificity. The neuromodulatory changes produced by preprogrammed brain stimulation occur in large regions of M1, irrespective of functional usage; thus, the benefits of these techniques are primarily related to the reduction of maladaptive TCI and restoration of balance between the two cerebral hemispheres (Nowak et al. 2010). In contrast, activity-dependent stimulation can target neural plasticity to cortical areas controlling specific muscle groups at appropriate times of activation. This capability could enhance the process of cortical reorganization in lesional M1 that takes place naturally in patients who achieve good functional recovery (Carey et al. 2002; Zemke et al. 2003). For example, one common pattern in patients with good recovery is a ventral shift in the representation for the hand into the face area of M1 (Cramer and Crafton 2006; Zemke et al. 2003). This occurs so frequently that rehabilitation experts see great potential in trying to drive the hand area into the face area of M1 artificially through directed brain stimulation techniques (Cramer 2008). Activity-dependent brain stimulation is the ideal modality for this form of rehabilitation due to the specificity of the conditioning effects. Using ECoG or EMG activity from paretic hand extensor to trigger brain stimulation to face area of lesional M1 (Fig. 3b) should potentiate horizontal connections between cortical hand and face area of lesional M1. This could promote migration of the motor representation and lead to a faster and fuller recovery.

Activity-dependent brain stimulation may also help restore normal patterns of functional connectivity between cortical regions post-stroke. Advances in neuroimaging recently revealed the connectivity between different cortical areas subserving movement (Grefkes et al. 2008a, b). Such studies indicate strong facilitatory connections between M1, SMA, and PMC. To restore these facilitatory connections post-stroke, investigators could use ECoG or EMG activity from paretic hand extensor to trigger brain stimulation to SMA or PMC in the lesional hemisphere. As an alternative approach, investigators could combat maladaptive TCI by timing brain stimulation to contralesional M1 shortly before activity in the paretic hand to create LTD-like effects. For example, stroke patients could be trained to extend the fingers of the paretic hand in response to a visual cue. After establishing a mean reaction time, the visual cue would be timed such that brain stimulation to contralesional M1 occurs between 0 and 50 ms before finger extension in the paretic hand, thus inducing LTD-like effects. This may prove more effective than previously described approaches to combat TCI with low-frequency rTMS or cathodal tDCS to contralesional M1; plasticity would be optimally timed to occur with movement. Thus, there are several reasons why activity-dependent brain stimulation may prove more efficacious than preprogrammed stimuli for stroke rehabilitation. New technologies for implementing targeted and sustained activity-dependent stimulation during daily activity provide many promising avenues for future investigation.

Conclusions

Brain stimulation techniques hold great promise to overcome the motor deficits caused by stroke. Studies in stroke patients using preprogrammed approaches like rTMS and tDCS demonstrate modest improvements in functional outcome. ECS appears effective for appropriately selected patients who have sufficient residual functional circuitry as demonstrated by evoked motor responses. Taken on the whole, rTMS, tDCS, and ECS all have potential to augment existing stroke rehabilitation strategies. Yet, these techniques simply modulate cortical excitability and rely on the associated motor training to cause more localized use-dependent plasticity.

In contrast, activity-dependent stimulation explicitly synchronizes brain stimulation with neural or muscle activity, targeting Hebbian plasticity to required areas. Studies in NHP and human subjects suggest that activity-dependent stimulation leads to plasticity directed to specific motor representations in M1, as evidenced by a change in movement direction or evoked responses of particular muscles. Activity-dependent stimulation may lead to greater recovery from the motor deficits caused by stroke by reinforcing neural connections to the residual motor representation for weakened muscles, promoting cortical reorganization, and restoring normal patterns of functional connectivity. Rehabilitation researchers lament that breakthroughs in our understanding of neural plasticity on a cellular level have not translated into significant clinical improvement for stroke victims (Cheeran et al. 2009). Clinical studies of activity-dependent stimulation, rooted in cellular studies of STDP, may help facilitate this translational process.

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