# 14 Therapeutic Applications of Transcranial Magnetic Stimulation/Transcranial Direct Current Stimulation in Neurology

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## 14.1 INTRODUCTION

Studies in both animals and humans have demonstrated that transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS) can modulate brain activity in a noninvasive manner. Both techniques can induce changes in cortical excitability outlasting the duration of the stimulation itself (Chen et al. 1997; Gangitano et al. 2002; Hummel and Cohen 2005; Romero et al. 2002). Depending on stimulation parameters, activity in the targeted brain region can be facilitated or suppressed, with variable behavioral consequences.

Because of their noninvasive nature, there has been significant interest in exploring the diagnostic and therapeutic applications of TMS and tDCS in neurology.

Noninvasive brain stimulation offers a complementary therapeutic modality to pharmacological treatments. While most psychoactive drug therapies work by substitution of endogenous neurotransmitters (e.g., replacement of dopamine in Parkinson's disease), brain stimulation is thought to utilize mechanisms of plasticity to promote changes in neural circuitry. The ultimate goal in neurostimulation is to tune neural network activity and brain plasticity toward adaptive behavior.

In TMS, a brief pulse of current passing through a coil of wire held over the subject's head generates a rapidly changing magnetic field. This alternating field penetrates through skin, scalp, and skull with minimal distortion or attenuation to generate a secondary electric current in the underlying cortex. This current can be of sufficient magnitude to depolarize neural elements.

Applied in trains of repetitive TMS (rTMS), the pulse frequency and pattern can be regulated to either enhance or suppress neural activity. In most subjects, a continuous train of low-frequency ($\leq$1 Hz) pulses results in suppression, while bursting, intermittent trains of high-frequency ($\geq$5 Hz) pulses results in facilitation of excitability in the targeted cortical region. Variations in coil geometry can generate a more restricted field of stimulation. For example, a figure-of-8 coil delivers a spatially more precise impulse than a circular coil (Hallett 2000).

More recently, newer protocols using theta burst stimulation (TBS), which deliver continuous or intermittent asynchronous trains with high- or low-frequency components, have demonstrated more durable and potent effect sizes. In most instances, when applied to healthy subjects, continuous TBS (cTBS) depresses cortical excitability, while intermittent (iTBS) enhances cortical excitability via the induction of long-term depression (LTD)- or long-term potentiation (LTP)-like mechanisms, respectively (Huang et al. 2005). However, prolonged theta burst paradigms have been demonstrated to induce a contrary effect. For example, when applied for twice the duration or number of pulses per session compared to standard protocols, normally facilitatory iTBS has been demonstrated to be inhibitory, while normally inhibitory cTBS becomes excitatory.

By contrast, tDCS is a method of applying a low-intensity (1–2 mA) direct current to the scalp to influence underlying cortical excitability. TDCS may depolarize or hyperpolarize neurons to modulate spontaneous firing rates (SFRs). Thus, tDCS can be thought of as a purely "neuromodulatory" intervention. Generally, both animal and human studies demonstrate increased spontaneous neuronal firing activity under the anode and decreased activity under the cathode (Bindman et al. 1964; Creutzfeldt et al. 1962; Nitsche and Paulus 2000; Purpura and McMurtry 1965). The direction of effect is also influenced by variables such as duration of stimulation, electrode montage, and concurrent cognitive activities (Brunoni et al. 2011b).

tDCS is an older technique than TMS and has some recognized advantages and disadvantages. From a pragmatic perspective, some benefits of tDCS include its low cost, portability, and ease of use. Because it induces less scalp sensation than TMS, tDCS has a more reliable sham condition, which allows for improved double-blinding in controlled clinical trials (Gandiga et al. 2006). Adequate blinding is particularly significant when testing subjective outcomes, such as mood and cognitive improvement, which are highly vulnerable to placebo effect.

The major limitation of tDCS is the delivery of a less focused stimulation than TMS. Direct current is delivered over relatively large electrodes (20–35 $cm^2$), which makes precise stimulation and cortical mapping more difficult. Some studies have reduced electrode size to produce a more restricted current, comparable to TMS-delivered stimulation (Nitsche et al. 2007). On the other hand, the inherently wider surface of stimulation delivered with tDCS may be beneficial when detailed knowledge about the cortical topography is unavailable. Furthermore, tDCS can easily be combined with other interventions such as mental imagery, computerized cognitive interventions, or robot-assisted motor activity. Much of the appeal of tDCS lays in its potential for use in these multimodal synergistic approaches and its practicality.

One reassuring aspect of continued use of TMS and tDCS in future clinical research is their safety and tolerability, now well established when practitioners follow consensus guidelines (Nitsche et al. 2008; Rossi et al. 2009). In TMS, reported adverse events have been infrequent and generally mild. The most common side effects include headache (23%) and neck pain (12%); rare events include nausea, tinnitus, mood fluctuations, and psychosis (Machii et al. 2006).

The induction of a seizure is the most serious possible complication associated with rTMS application. The risk of seizures seems greatest for high-frequency rTMS with short interval periods, during or immediately after stimulation. Up to 2008, there were 16 TMS-induced seizures reported, an exceptionally low figure given the number of subjects who have undergone TMS (Rossi et al. 2009). Most seizures induced from rTMS occurred before safety parameters were introduced and in the setting of subjects taking medications known to lower the seizure threshold (Rossi et al. 2009). Even in patients with epilepsy, the crude per-subject risk of developing a seizure has been reported to be 1.4% (Bae et al. 2007) with all but one case consisting of a typical seizure and no instances of status epilepticus reported. Likewise, there have been no reported seizures from published series of stroke patients, thought to have a lowered event threshold, who have received various forms of stimulation (50 Hz epidural stimulation, anodal tDCS, high-frequency rTMS) (Brown et al. 2006; Hummel et al. 2005; Khedr et al. 2005a; Kim et al. 2006).

To avoid adverse events, current guidelines recommend careful consideration of patient variables that may affect the seizure threshold, such as use of pro-epileptogenic medications (i.e., antidepressants, neuroleptics), timing in the menstrual cycle, age, level of anxiety, and sleep deprivation. Further safety parameters for stimulation intensity, frequency, train duration, and intertrain interval, as well as appropriate monitoring methods have been published (Rossi et al. 2009).

Because tDCS delivers only weak electric currents to modulate cortical excitability, it is widely considered to be even safer and more tolerable than TMS. Indeed, the most commonly reported adverse events have been itching, tingling, headache, burning sensation, nausea, fatigue, and insomnia. Seizures have never been reported (Brunoni et al. 2011a; Poreisz et al. 2007). Instead, the major possible complication is a heat-induced skin lesion (Palm et al. 2008). However, one meta-analysis has identified a selective bias for underreporting, as fewer than half of tDCS studies have systematically queried subjects for experienced side effects (Brunoni et al. 2011a).

## 14.2 MECHANISMS OF ACTION

The preliminary success of neurostimulation in diverse neurological conditions contrasts with the limited understanding of the underlying neurobiological effects. Neurophysiologic and neuroimaging studies in humans and animals reveal that TMS and tDCS induce both local and distant effects and that the effects are state dependent. However, further studies are needed to provide greater mechanistic insights. Specifically, animal and in vitro experiments promise to further clarify the mechanisms of action of tDCS and TMS and enable more specific therapeutic approaches.

There are several lines of evidence that demonstrate the local effect of TMS in altering concentrations of neurotransmitters, cerebral perfusion, and cortical excitability. In a landmark study using cat visual cortex, Allen et al. (2007) applied rTMS to induce a brief increase in spontaneous neural spiking, with augmented neural activity and hemodynamic changes at higher stimulation frequencies, intensity, and duration. When TMS was applied during visual activity, a longer-lasting depression in evoked baseline neural activity was induced, coupled with a more sustained decrease in hemoglobin concentration and tissue oxygenation (Allen et al. 2007). Together, these findings provide a hemodynamic explanation of how TMS can induce local effects outlasting TMS stimulation and underscore the state-dependent nature of the response (Bestmann 2008).

Glutamate appears to play a key neurotransmitter role in mediating cortical excitability. Luborzewski et al. performed a magnetic resonance spectroscopy (MRS) study investigating high-frequency (20 Hz) TMS applied to the dorsolateral prefrontal cortex (DLPFC) in patients with depression. Responders had decreased baseline concentrations of glutamate in the prefrontal cortex, which increased after stimulation in an intensity-dependent manner (Luborzewski et al. 2007). Similarly, a significant relationship between MRS-assessed glutamate levels and TMS measures of cortical excitability has been found, whereas no relationship was found for GABA activity (Stagg et al. 2011).

Newer protocols combining rTMS with neuroimaging have begun to elucidate the widespread interconnected networks affected beyond local stimulation (Bestmann et al. 2003, 2004, 2008). For example, rTMS applied to the sensorimotor cortex induces MRI BOLD signal changes in a network of primary and secondary motor regions including M1/S1, supplementary motor area, dorsal premotor cortex, cingulate, putamen, and thalamus (Bestmann et al. 2004; Denslow et al. 2005), comparable to the regions activated in volitional movement.

The neuromodulatory effects of tDCS have been broadly attributed to LTP- and LTD-like mechanisms of synaptic plasticity (Hattori et al. 1990; Islam et al. 1995; Moriwaki 1991). Liebetanz et al. conducted a series of pharmacologic experiments demonstrating the role of specific membrane elements in tDCS-induced neuroplasticity. Dextromethorphan, an NMDA (*N*-methyl-D-aspartic acid) antagonist, decreased the post-tDCS effects of both anodal and cathodal stimulation. Carbamazepine, which blocks sodium channels, selectively suppressed the effect of anodal stimulation, suggesting that LTP requires the depolarization of action potentials (Liebetanz et al. 2002). In animal models, Kabakov et al. (2012) recently showed that tDCS induces changes in excitability and synaptic plasticity that are dependent on the precise spatial relation of the direction of induced current and the orientation of affected neural pathways.

Investigations combining functional neuroimaging with tDCS have begun to define the local and distant effects of neuromodulation. A recent MR spectroscopy study demonstrated a local reduction of GABA in response to anodal stimulation, while cathodal stimulation resulted in a local decrease in glutamatergic activity (Stagg et al. 2009). An MR arterial spin labeling (MR-ASL) study applying tDCS to the primary motor cortex in healthy subjects demonstrated that anodal stimulation induced a significant increase in resting-state cerebral blood flow (rCBF) both during and after stimulation, in a linear relationship to current intensity. However, cathodal tDCS induced a smaller increase in perfusion during stimulation but a sustained decrease in the poststimulation period (Zheng et al. 2011). Of interest, the magnitude of observed increase in rCBF in anodal tDCS is comparable to the range of changes seen in PET or ASL studies of high-frequency (10 Hz) TMS (Moisa et al. 2010), while the lower increases in rCBF in cathodal stimulations is comparable to the changes seen with low-frequency (<2 Hz) TMS (Fox et al. 1997, 2006; Moisa et al. 2010).

Anodal tDCS applied to primary motor cortex has elicited more widespread perfusion changes in functionally related but distant regions such as the ipsilateral premotor cortex, with a lesser influence on the contralateral motor and premotor regions (Zheng et al. 2011). Distant effects of tDCS have also been demonstrated in PET (Lang et al. 2005) and fMRI studies (Kwon et al. 2008; Stagg et al. 2011) and resembled the patterns discovered in TMS studies (Moisa et al. 2010). Similarly, anodal tDCS applied to the primary motor cortex, with cathodal tDCS applied to the contralateral frontopolar cortex, has been demonstrated to increase functional connectivity patterns within premotor, motor, and sensorimotor areas within the stimulated hemisphere (Polania et al. 2011a,b).

A recent fMRI study applying tDCS to the DLPFC illustrates how stimulation can alter resting-state network connectivity (Keeser et al. 2011). Real tDCS caused significant changes in regional brain connectivity in the default mode network (DMN) and the fronto-parietal networks (FPNs), both local to the stimulation site and in associated brain regions. Similar insights have been obtained in studies in patients with Parkinson's disease (Pereira et al. 2012). Strengthened connectivity within the DMN has been associated with improved working memory (Hampson et al. 2006) and semantic memory (Wirth et al. 2011). Similarly, increased coactivation in the frontal and parietal regions has been implicated in attention and working memory. In particular, increased connectivity within the left FPN has been observed after cognitive training (Lewis et al. 2009; Mazoyer et al. 2009).

## 14.3 NEUROTHERAPEUTIC EXPERIENCE WITH TMS/tDCS TO DATE

This review summarizes recent research on therapeutic applications of TMS and tDCS in neurology, concentrating on developments in the field over the last 6 years. We conducted a literature search for articles published from 2005 to 2011, using the search terms "transcranial magnetic stimulation," "transcranial direct current stimulation," with "stroke rehabilitation," "epilepsy," "pain," "Parkinson's disease," "tinnitus," and "ataxia." We included mostly randomized controlled

trials in our review, although occasionally smaller case series are included when prospective or controlled studies were sparse or unavailable.

### 14.3.1 Focal Epilepsy

Seizure foci are characterized by an increase in focal irritability, caused by a pathological increase in excitatory (glutaminergic) terminals with a decrease in inhibitory (GABA-ergic) activity (Lowenstein 1996). It seems reasonable to assume that inhibitory neuromodulation (slow repetitive TMS or cathodal tDCS) might be able to induce LTD or normalization of a hyperexcitable territory, and that this may translate into a therapeutic advantage. Low-frequency stimulation in hippocampal and neocortical rat slices has already been demonstrated to decrease interictal discharge and seizure frequency, in a manner that outlasts the stimulation (Albensi et al. 2004; Schiller and Bankirer 2007). By reducing cortical irritability, targeted suppression could potentially treat medication-refractory focal seizure activity.

Since 2005, there have been several randomized prospective rTMS studies published, which demonstrate mixed efficacy in decreasing seizure frequency (Table 14.1). Fregni et al. (2006f) and Santiago et al. (2008) both performed low-frequency rTMS directly over the epileptogenic cortex and demonstrated a significant reduction in seizure frequency, with clinical benefit persisting at a 2 month follow-up interval. However, Joo et al. (2007) and Cantello et al. (2007) conducted similar randomized prospective studies of low-frequency rTMS, which did not result in a reduction in seizure frequency.

The heterogeneity among the study designs precludes a definitive explanation of the discrepancy in findings. However, one plausible explanation could be the inclusion of patients with multifocal-, indeterminate-, or even generalized-onset epilepsy in the studies performed by Joo et al. (2007) and Cantello et al. (2007). Neurostimulation may have more pronounced effects in patients with well-circumscribed and superficial seizure foci. Of note, while these latter studies did not produce a clinical benefit, they did show a significant decrease in the frequency of interictal spikes, raising the possibility of a subthreshold clinical effect.

Furthermore, there exist a few case reports and case series describing the use of active rTMS for interrupting epilepsy partialis continua (EPC). These small studies demonstrate mixed efficacy, but good safety. The largest series by Rotenberg included seven cases of refractory EPC lasting longer than 1 day. TMS stopped seizures in two patients, caused a 20–30 min seizure cessation in three cases, and had no effect in two cases. However, there were no cases of seizure exacerbation and the reported side effects were mild (Rotenberg et al. 2009).

There have been two prospective controlled studies investigating the use of tDCS to control partial-onset epilepsy. In a randomized controlled trial, Fregni et al. (2006g) found that one 20 min session of 1 mA cathodal tDCS applied over the site of cortical malformation produced a significant reduction in the frequency of interictal discharges and a trend toward decreased seizure frequency (−44%, 95% CI −95% to 7.1%). Varga et al. (2011) also applied one 20 min session of 1 mA cathodal tDCS to the epileptogenic zone in five patients with focal, refractory continuous spike and slow wave during sleep, but did not see a reduction in the spike index. They hypothesize

**TABLE 14.1**
**Comparison of Neurostimulation Protocols for Epilepsy**

| References | No. of Subjects | Diagnosis | Coil Position | rTMS Frequency | No. of Stimuli | Intensity | Coil | Duration | Session Schedule | Effect |
|---|---|---|---|---|---|---|---|---|---|---|
| Kinoshita et al. (2005) | 7 | Medically refractory extratemporal lobe epilepsy | Region of most prominent epileptic activity seen in EEG | 0.9 Hz | 810 pulses (15 min ON–5 min OFF) | 90% MT | Round coil | 15 min | Two sessions daily for 5 days | Nonsignificant decrease in seizure frequency over 2 weeks follow-up |
| Fregni et al. (2005c) | 8 | Cortical malformations | Cortical malformation | 0.5 Hz | 600 pulses | 65% MT | Figure 8 | 20 min | One session | Significant decrease in seizure frequency in 4 week follow-up, with mean reduction in seizure frequency of 51.2%. Decrease in epileptiform discharges at 2 and 4 weeks. |

*(continued)*

**TABLE 14.1 (continued)**
**Comparison of Neurostimulation Protocols for Epilepsy**

| References | No. of Subjects | Diagnosis | Coil Position | rTMS Frequency | No. of Stimuli | Intensity | Coil | Duration | Session Schedule | Effect |
|---|---|---|---|---|---|---|---|---|---|---|
| Fregni et al. (2006f) | 21 | Cortical malformations | Cortical malformation | 1 Hz | 1200 pulses | 70% motor output (MO) | Figure 8 | 20 min | 5 days | Significant decrease in seizure frequency, effect lasting ≥2 months; significant decrease in interictal discharges immediately after and at 4 weeks |
| Joo et al. (2007) | 35 | 18 focal onset, 17 multifocal or indeterminate onset | Cz (n = 17), temporal (n = 12), L. frontal (n = 3), R parietal (n = 3) | 0.5 Hz | 3000 pulses/train (n = 19), 1500 pulses/train (n = 16) | 100% MT | Figure 8 Or round | 100 min (n = 19), 50 min (n = 16) | 5 days | No significant reduction in seizure frequency; over 8 weeks follow-ups decreased frequency of interictal discharges ($p < 0.05$), with disappearance in 17.1% of patients |

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| Cantello et al. (2007) | 43 | Drug-resistant epilepsy. Mixed focal, multifocal, and diffuse onset | Vertex | 0.3 Hz | 500 pulses/ train | 100% MT (n = 34), 65% MO (n = 9) | Round | 30 min | Two trains daily × 5 days | No significant reduction of seizure frequency; decreased interictal EEG discharges in one-third of patients ($p < 0.05$) |
| Santiago-Rodriguez et al. (2008) | 12 | Focal epilepsy (frontal and frontotemporal) | Seizure focus | 0.5 Hz | 900 pulses | 110% MT | Figure 8 | 30 min | 10 days | Significant reduction in seizure frequency by 71% during intervention period; significant reduction in seizure frequency by 50% during 8 week follow-up period |
| Brodbeck et al. (2010) | 5 | Focal epilepsy | Seizure focus | 6 Hz priming/ 1 Hz stim | 1200 pulses | 90% MT/ 110% MT | Figure 8 | 10/10 min | One session | Variable reduction in spike frequency |

(*continued*)

**TABLE 14.1 (continued)**
**Comparison of Neurostimulation Protocols for Epilepsy**

| References | No. of Subjects | Diagnosis | Electrode Position | tDCS Polarity | Intensity | Duration | Session Schedule | Effect |
|---|---|---|---|---|---|---|---|---|
| Fregni et al. (2006f) | 19 | Cortical malformation | Cortical malformation | Cathodal tDCS | 1 mA | 20 min | One session | Significant reduction in interictal discharge frequency; nonsignificant trend toward reducing seizure frequency |
| Varga et al. (2011) | 5 | Focal-refractory continuous spike and waves during slow-wave sleep | Focus of epileptiform discharges | Cathodal tDCS | 1 mA | 20 min | One session | No significant reduction of spike index |
| San-Juan et al. (2011) | 2 | Rasmussen's encephalitis | Focus of epileptiform discharges | Cathodal tDCS | 1 and 2 mA | 60 min | Four sessions | One patient with significant reduction in seizure frequency; second patient seizure free at 6 and 12 month follow-up |

that their use of a 25 $cm^2$ cathodal electrode may have been too small to prevent propagation of the epileptiform discharges. Finally, San-Juan et al. (2011) reported on two patients with atypical (i.e., adult onset) dominant hemisphere Rasmussen's encephalitis, treated with 60 min of 1 or 2 mA tDCS over four sessions in 2 months (days 0, 7, 30, and 60). At the 6 and 12 month follow-up, one patient was completely seizure free and the other had a significant reduction in seizure frequency.

Given these preliminary results, more studies investigating the use of longer and repeated sessions of cathodal tDCS applied to seizure foci are needed. Thus far, studies demonstrate mixed efficacy in decreasing seizure frequency and terminating focal status epilepticus. Future research might employ stricter inclusion criteria, i.e., patients with definitive focal-onset superficial epileptogenic foci such as seen with cortical malformations. Once these superficial malformations are identified, more precise methodologies targeting the irritable cortex are needed, e.g., real-time EEG monitoring and image guidance (Rotenberg 2010).

As described earlier, studies have varied by stimulation parameters, which may partly explain the variability in efficacy. Systematic investigations of variables such as coil size and position, stimulus frequency and intensity, and number of sessions are needed to determine optimal efficacy and effect size. Some novel patterns of stimulation such as TBS seem to offer a more durable depression and deserve further trials. Special coil designs that allow deeper penetration into the brain, reaching structures such as the insula or cingulate cortex, may potentially modulate deeper epileptogenic foci (Roth et al. 2007).

### 14.3.2 Chronic Pain

Chronic pain has been attributed to maladaptive changes in both the central and the peripheral nervous system. Increased activity in peripheral nerve endings leads to oversensitization followed by central changes. Stimulation of cortical targets may normalize the activity of the corticothalamic network. Imaging research demonstrates that stimulation of the motor cortex via high-frequency rTMS or anodal tDCS alters distant activity in the thalamic and subthalamic nuclei, which may explain how pain perception is altered (Garcia-Larrea et al. 1997, 1999; Peyron et al. 1995).

The majority of rTMS and tDCS studies stimulating the M1 motor cortex demonstrate a significant effect on both subjective and objective pain perception (Table 14.2). Clinical benefit has been seen in patients with chronic neuropathic pain (Fregni et al. 2006a; Leung et al. 2009; Antal et al. 2010; Soler et al. 2010), visceral pain (Fregni et al. 2005a) as well as fibromyalgia (Fregni et al. 2006d; Passard et al. 2007; Antal et al. 2010). Response rates are high, ranging between 40% and 80% among patients with central pain refractory to treatment (Brown and Barbaro 2003; Khedr et al. 2005b; Lefaucheur et al. 2004; Nuti et al. 2005b; Pleger et al. 2004; Tsubokawa et al. 1991). Moreover, positive results are clinically meaningful, with rTMS offering a 20%–45% reduction in pain perception (Andre-Obadia et al. 2006; Khedr et al. 2005b; Lefaucheur et al. 2004; Pleger et al. 2004), with perhaps a larger effect with tDCS, up to 58% reduction (Fregni et al. 2006a). There is some evidence that rTMS has a greater effect on centrally over peripherally mediated neuropathic pain states (Leung et al. 2009).

**TABLE 14.2**
**Comparison of Neurostimulation Studies for Pain**

| References | No. of Subjects | Pain Etiology | Coil Position | Method of Localization | rTMS Frequency | No. of Stimuli | Intensity | Type of Coil | Duration | Session Schedule | Effect |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Fregni et al. (2005a) | 5 | Visceral pain from chronic pancreatitis | R/L secondary somatosensory area | MRI–stereotactic guidance | 1/20 Hz | 1600 pulses | 1/20 Hz | Figure 8 | Variable | One session weekly × 6 weeks | Only 1 Hz rTMS to R side with significant pain reduction, mean decrease 62% |
| Khedr et al. (2005b) | 48 | Chronic unilateral neuropathic pain (trigeminal neuralgia or post-stroke) | M1 hand area contralateral to pain | 10/20 EEG system | 20 Hz | 2000 pulses | 80% MT | Figure 8 | 10 min | 5 days | Significant decrease in trigeminal neuralgia and post-stroke pain, lasted 2 weeks after treatment |
| Borckardt et al. (2006) | 20 | Postsurgical (gastric bypass) pain | L DLPFC | 5 cm anterior to motor cortex | 10 Hz | 4000 pulses (10 s ON–20 s OFF) | 100% MT | Figure 8 | 20 min | One session immediately after surgery | Significant pain reduction in real TMS group, with 40% less morphine usage |

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| Passard et al. (2007) | 30 | Fibromyalgia | L M1 | 10/20 EEG system (C3) | 10 Hz | 2000 pulses (8 s ON–52 s OFF) | 80% MT | Figure 8 | 25 min | 10 sessions | Significant reduction of pain after fifth treatment session, persisted up to 2 weeks |
| Borckardt et al. (2008) | 20 | Postsurgical (gastric bypass) pain | L DLPFC | 5 cm anterior to motor cortex | 10 Hz | 4000 pulses (10 s ON–20 s OFF) | 100% MT | Figure 8 | 20 m | One session immediately after surgery | Significant pain reduction in real TMS group, with 35% less morphine usage |

(*continued*)

**TABLE 14.2 (continued)**
**Comparison of Neurostimulation Studies for Pain**

| References | No. of Subjects | Pain Etiology | Electrode Position | Method of Localization | tDCS Polarity | Intensity | Duration | Session Schedule | Effect |
|---|---|---|---|---|---|---|---|---|---|
| Fregni et al. (2006a) | 17 | Central pain, traumatic spinal cord injury | M1 contralateral to side of pain or dominant hemisphere M1 | 10/20 EEG system (C3 or C4) | Anodal tDCS | 2 mA | 20 min | 5 days | Significant pain reduction in 3 days, maximum pain reduction in 5 days during treatment |
| Fregni et al. (2006d) | 32 | Fibromyalgia | L M1 or DLPFC | 10/20 EEG System (C3 or F3) | Anodal tDCS | 2 mA | 20 min | 5 days | Anodal tDCS of M1 with greater pain reduction than sham or stimulation of DLPFC, still significant within 3 weeks after treatment |

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|---|---|---|---|---|---|---|---|---|---|
| Soler et al. (2010) | 39 | Neuropathic pain from spinal cord injury | M1 contralateral to side of pain | 10/20 EEG System (C3 or C4) | Anodal tDCS ± visual illusion | 2 mA | 20 min | 10 days | Real tDCS with visual illusion reduced pain more significantly than any other subgroup, with significant improvement within 12 weeks after treatment |
| Antal et al. 2010 | 21 | Chronic pain (trigeminal neuralgia, poststroke pain position | M1 | Hand area determined by TMS | Anodal | 1 MA | 20 min | 5 days | Anodal tDCS decreased pain rating greater than sham tDCS, lasting 3-4 weeks after treatment |
| Mori et al. 2010 | 19 | Chronic neuropathic pain in MS | M1 | 10/20 EEG system (C3/C4) | Anodal | 2 mA | 20 min | 5 days | Significant decrease in pain scores in patients w real anodal tDCS, lasting 3 weeks |

For example, in a blinded randomized, sham-controlled trial, Passard et al. (2007) demonstrated that 10 days of high-frequency rTMS (10 Hz, 8 s stimulation trains, 52 s intertrain interval, 2000 pulses per day, 80% MT) applied to the primary motor cortex in patients with fibromyalgia showed a significant decrease in subjective pain perception and improved quality of life. The effects were seen at 5 days into stimulation and lasted up to 2 weeks after treatment. There were no significant changes in mood or anxiety. Other studies with slightly different stimulation parameters have shown a more durable effect, up to 15 days after 3 days of consecutive TMS stimulation. There are some reports of longer-lasting effects with tDCS, up to 3 months after treatment (Fregni et al. 2006d; Gabis et al. 2009; Soler et al. 2010)

Antal et al. (2011) applied cathodal versus sham tDCS over the visual cortex in a group of migraineurs using a crossover design (1 mA for 15 min each session, three sessions a week, 3 weeks per treatment arm). Real cathodal tDCS significantly reduced the intensity and duration of headache pain compared to baseline, suggesting that tDCS could be an effective prophylactic therapy in migraine.

In addition, there exists preliminary evidence of synergistic effects with other modalities of pain therapy. Soler et al. (2010) performed a sham-controlled double-blinded parallel group design of tDCS applied to the premotor cortex in patients with neuropathic pain following spinal cord injury. The combination of tDCS and visual illusion reduced the intensity of neuropathic pain significantly more than either treatment alone, with a benefit at 12 weeks after treatment. Furthermore, given that mechanisms of noninvasive brain stimulation are associated with top-down modulation, association with bottom-up approaches such as transcutaneous electrical nerve stimulation or diffuse noxious inhibitory control may augment analgesic effects as recently demonstrated (Boggio et al. 2009; Fregni 2010).

Recently, the modulatory role of the DLPFC in pain sensation has been explored. Some preliminary research on stimulating the DLPFC shows a modest effect size, apparently less than the stimulation of the primary motor cortex. Borckardt et al. (2009b) demonstrated that high-frequency rTMS applied to the left DLPFC exhibited a modest improvement in daily pain ratings in patients with chronic pain (19% decrease lasting 2 weeks), as well as an increase in thermal and mechanical pain thresholds. In the postoperative setting, rTMS applied to the left prefrontal region increased thermal pain thresholds, whereas sham TMS did not (Borckardt et al. 2009a). In the clinical setting, a single 20 min session of rTMS (10 Hz, 10 s stimulation trains, 20 s intertrain intervals, 4000 pulses total, 100% MT) applied immediately after surgery reduced patient-controlled morphine use by approximately 40%, independent of mood effects (Borckardt et al. 2006, 2008). Given the limitations of current pain management and the clinically meaningful results demonstrated thus far, further investigation is warranted. Notably, there have been no studies of tDCS in the postoperative setting to date (Borckardt et al. 2009a).

The role of neurostimulation in managing medication-refractory pain syndromes seems especially promising, with consistent results replicated across a number of studies. However, there are a number of questions still unresolved. For example, further interaction studies are needed to demonstrate the synergistic effect of different therapeutic modalities, i.e., with concurrent administration of analgesics or biofeedback mechanisms. While there has been a suggestion of superior efficacy of stimulation of

the primary motor cortex compared to the DLPFC, more direct comparison studies are needed. Third, quality of life variables should be included in research outcome measures to determine what numerical threshold of pain reduction is clinically significant. Finally, given the suggestion that tDCS may induce longer-lasting effects, more investigations incorporating this technology, especially in the postoperative setting, are needed.

### 14.3.3 Stroke Rehabilitation: Motor Function

Functionality after stroke appears to reflect how the undamaged brain, including both adjacent and contralateral territories, adapts to injury. Severe functional impairment and structural damage to primary motor pathways after stroke result in widespread activation of bilaterally distributed primary and secondary motor regions during a hand grip exercise (Ward 2006, 2011; Ward et al. 2006). Conversely, patients with a better stroke outcome had a more similar activation pattern on fMRI compared to normal subjects (Ward et al. 2003). Together, these observations suggest that disruption of corticospinal tracts after stroke leads to greater reliance on a more distributed secondary motor network (Ward 2011).

However, the relationship between the healthy and lesioned hemispheres during stroke recovery is unclear. Human and animal models of stroke recovery demonstrate an altered interhemispheric dynamic (Dijkhuizen et al. 2003; Marshall et al. 2000). Some perturbations in this dynamic appear maladaptive and may limit recovery. The predominant model proposes that relative overactivity of the unaffected hemisphere may cause excessive transcallosal inhibition of the unaffected hemisphere (Grefkes et al. 2008; Murase et al. 2004). The concept of interhemispheric rivalry has been supported by empirical demonstrations with normal subjects (Kobayashi et al. 2004; Plewnia et al. 2003; Schambra et al. 2003; Williams et al. 2010), where down-regulation of one hemisphere improved function in the ipsilateral hand. A competitive dynamic has also been inferred from functional neuroimaging studies showing increased contralateral activity following stroke affecting motor function, attention, memory, and language (Belin et al. 1996; Duque et al. 2005; Kinsbourne 1997; Murase et al. 2004; Najib and Pascual-Leone 2011; Sparing et al. 2009). Furthermore, some neuroimaging evidence suggests that optimal stroke rehabilitation is associated with the development of alternative pathways from the affected hemisphere, without contribution from the unaffected hemisphere to the paretic limb (Hallett 2001).

Neurostimulation approaches based on this model of interhemispheric competition may work by suppressing activity in the healthy hemisphere or increasing activity in the lesioned hemisphere. Theoretically, restoration of interhemispheric balance can favor a more adaptive plasticity (Fregni and Pascual-Leone 2006; Hummel and Cohen 2006). Indeed, there have been a number of proof-of-principle demonstrations utilizing high-frequency rTMS (Chang et al. 2010; Khedr et al. 2005a) and anodal tDCS (Hesse et al. 2007; Hummel and Cohen 2005) over adjacent cortex in the lesioned hemisphere, as well as low-frequency rTMS over the contralesional motor cortex (Fregni et al. 2006c; Liepert et al. 2007; Mansur et al. 2005; Nowak et al. 2008), which have all shown significant improvement in motor function (Table 14.3). One of the largest studies involved 52 patients who received either real or sham rTMS

**TABLE 14.3**
**Comparison of Neurostimulation Protocols for Motor Rehabilitation**

| References | No. of Subjects | Time Post-Stroke | Coil Position | Methodology | Frequency | No. of Stimuli | Intensity | Coil | Duration | Session Schedule | Effect |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Khedr et al. (2005a) | 52 | Acute 5–10 days | Ipsilesional M1 | Real vs. sham rTMS stimulation to ipsilesional M1 with standard physical therapy | 3 Hz | 300 pulses (10 s ON–50 s OFF) | 120% MT | Figure 8 | 10 min | 10 days | Real rTMS with higher independence scores and milder disability at 10 days posttreatment than sham group |
| Mansur et al. (2005) | 10 | Chronic <12 months | Contralesional M1 and premotor | Crossover design (healthy M1, premotor, sham) | 1 Hz | 600 pulses | 100% MT | Figure 8 | 10 min | One session per arm, 1 h between arms | Decrease in reaction time and improved Purdue Pegboard test in paretic hand with real rTMS to healthy M1 |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Fregni et al. (2006c) | 15 | Chronic >1 year | Contralesional M1 | Inhibitory rTMS to unaffected M1 | 1 Hz | 1200 pulses | 100% MT | Figure 8 | 20 min | 5 days | Significant improvement in motor function of paretic hand lasting for 2 weeks |
| Liepert et al. (2007) | 12 | Acute (mean 7.3 ± 4.5 days) | Contralesional M1 | Inhibitory rTMS to unaffected M1 in crossover design | 1 Hz | 1200 pulses | 90% MT | Figure 8 | 20 min | One session | Significant improvement in dexterity of paretic hand |
| Malcolm et al. (2007) | 19 | Chronic >1 year (mean 3.8± 3.3 years) | Ipsilesional M1 | Constraint-induced therapy (CIT) ± rTMS | 20 Hz | 2000 pulses (2 s ON–28 s OFF) | 90% MT | Figure 8 | 25 min | 10 days | No additional effect of rTMS to CIT |
| Nowak et al. (2008) | 15 | Subacute 4 weeks–4 months | ContralesionalM1 | Unaffected M1, crossover, sham-controlled design | 1 Hz | 600 pulses | 100% MT | Figure 8 | 10 min | One session | Significant improvement in kinematics and finger and grasp movement of paretic hand |

*(continued)*

**TABLE 14.3 (continued)**
**Comparison of Neurostimulation Protocols for Motor Rehabilitation**

| References | No. of Subjects | Time Post-Stroke | Coil Position | Methodology | Frequency | No. of Stimuli | Intensity | Coil | Duration | Session Schedule | Effect |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Takeuchi et al. (2009) | 30 | Chronic >6 months (mean 26.1 ± 28.0 months) | Contralesional M1 (1 Hz) or ipsilesional M1 (10 Hz), or both | rTMS with motor training | 1 Hz/10 Hz | 1000 pulses/ hemisphere | 90% MT | Figure 8 | Variable | 20 sessions | Bilateral rTMS with motor training improved pinch force more than 1 Hz rTMS for 1 week; no effect of 10 Hz rTMS on motor function |
| Khedr et al. (2009a) | 36 | Acute 7–20 days (mean 17.1 ± 3.6 days) | Ipsilesional M1 (3 Hz) or contralesional M1 (1 Hz) | Real TMS with standard physical therapy | 3 Hz/1 Hz | 900 pulses (10 s ON–2 s OFF) | 130% MT (3 Hz)/ 100% MT (1 Hz) | Figure 8 | 15 min | 5 days | Both real 3 and 1 Hz improved in hand function at 3 months, with 1 Hz over contralesional M1 performing better than 3 Hz group |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Chang et al. (2010) | 28 | Acute <1 months (mean 12.9 days ± 5.2) | Ipsilesional M1 | rTMS with motor training | 10 Hz | 1000 pulses (5 s ON–55 s OFF with motor training) | 90% MT | Figure 8 | 20 min | 10 days | rTMS improved motor function greater than motor training alone, with lasting effects 3 months after stroke |
| Emara et al. (2010) | 60 | Subacute >1 month (2–14 months) | Ipsilesional M1 (5 Hz)/ contralesional M1 (1 Hz) | rTMS and standard physical therapy | 5 Hz/1 Hz | 750 pulses 150 pulses | 80%–90% MT/ 110%–120% MT | Figure 8 | 2.5 min | 10 days | Patients with real 5 or 1 Hz rTMS showed improvement on finger tapping, functional status, and disability score at 2 and 12 weeks |

(*continued*)

**TABLE 14.3 (continued)**
**Comparison of Neurostimulation Protocols for Motor Rehabilitation**

| References | No. of Subjects | Time Post-Stroke | Electrode Position | tDCS Polarity | Intensity | Duration | Session Schedule | Effect |
|---|---|---|---|---|---|---|---|---|
| Hummel et al. (2005) | 6 | Chronic >1 year (3.7 ± 1.1 years) | Ipsilesional hand area | Anodal tDCS | 1 mA | 20 min | One session, crossover design | Hand function in paretic side improved with real tDCS, outlasting stimulation |
| Hesse et al. (2007) | 10 | Subacute 4–8 weeks | Ipsilesional hand area | Anodal tDCS with robot-assisted motor training | 1.5 mA | 20 min | 30 sessions | Arm function of three patients (two with subcortical stroke improved significantly |
| Lindenberg et al. (2010) | 20 | Subacute (mean 40.3 ± 23.4) | Bilateral hemisphere | Anodal tDCS to ipsilesional hemisphere and cathodal tDCS to contralesional hemisphere | 1.5 mA | 30 min | Five sessions | Improved motor function for 1 week post-intervention |

over the M1 of the affected hemisphere in the acute phase (5–10 days) after their stroke, in conjunction with standard rehabilitation therapy. Patients who received real rTMS demonstrated a clinical improvement in motor function, without significant side effects (Khedr et al. 2005a). There have also been several studies in laboratory animals demonstrating that electrical stimulation of the motor cortex around the lesion improved performance in the paretic limb, especially when combined with a training regimen (Adkins et al. 2006, 2008; Adkins-Muir and Jones 2003; Kleim et al. 2003).

On the other hand, there is some evidence that the contralateral premotor cortex facilitates the function of the lesioned motor cortex. Disruption of ipsilesional (Fridman et al. 2004) or contralateral (Johansen-Berg et al. 2002) dorsal premotor cortex using online TMS worsens motor performance in patients with chronic stroke, suggesting the supportive role of these regions after injury. Bestmann et al. (2010) used a paired coil TMS technique to probe the influence of the contralateral dorsal premotor (cPMd) cortex over the ipsilateral M1 (iM1) in a group of 12 patients with subcortical stroke. For patients with poor recovery, the influence of cPMd over iM1 appeared more excitatory at rest (Bestmann et al. 2010). This observation appears to contradict the prior finding of excessive inhibition of cM1 over iM1 (Murase et al. 2004). One proposed explanation is that the inhibitory influence of cM1 over iM1, normally regulated by inputs adjacent to iM1, becomes pathologically inhibitory when these neighboring inputs are damaged by stroke. In a similar fashion, the facilitation that cPMd normally provides iM1 becomes overly excitatory after stroke (Ward 2011).

Furthermore, some critics argue that a model of interhemispheric rivalry is too simplistic for purposes of clinical rehabilitation. Most proof-of-principle studies conducted to date include either healthy subjects or small samples of stroke patients (Hummel et al. 2008). Patient variables such as stroke location (cortical/subcortical, motor/premotor), size (i.e., degree of disrupted corticospinal tract integrity), and age (Hummel et al. 2008) will likely influence the interhemispheric balance and should theoretically be considered in the therapeutic approach.

More recent research has explored simultaneous bihemispheric stimulation, i.e., enhancement of lesioned hemisphere, suppression of healthy hemisphere, compared to either enhancement or suppression of either hemisphere alone (Table 14.3). There is limited evidence for favorable outcomes with bihemispheric stimulation. For example, Takeuchi et al. (2009) showed that in the chronic phase of stroke recovery, bilateral rTMS was superior to inhibitory rTMS to the unaffected hemisphere, with the affect lasting 1 week after the stroke. Stimulating the lesioned hemisphere did not improve motor function at all. Lindenberg et al. (2010) also demonstrated that bihemispheric tDCS was superior to sham stimulation when combined with motor training in the chronic phase of recovery, with the effects persisting up to 1 week after treatment.

Moreover, newer protocols combining neuromodulation with more traditional rehabilitation methods can result in a synergistic effect, although the evidence is certainly mixed (Table 14.3). Both suppression of activity in the healthy hemisphere (using low-frequency rTMS) and potentiation of activity in the lesioned hemisphere (using high-frequency rTMS) have demonstrated positive results, with a suggestion of more consistent success with targeting of the healthy hemisphere. In the subacute phase of stroke recovery, Chang et al. (2010) found that rTMS stimulation of the affected primary motor cortex with simultaneous motor training provided

additional improvement over motor training alone, persisting for 3 months after stroke. Lindenberg et al. (2010) found that bihemispheric tDCS modulation in the chronic phase of recovery with simultaneous physical and occupational therapy showed a significant improvement in hand function, with the effects lasting 5 days. However, Malcolm et al. (2007) did not show any additional benefit of stimulatory rTMS to the lesioned cortex tested with constraint-induced therapy in the chronic phase of stroke recovery.

More investigation on the optimal timing of intervention is needed. Most studies occur in the chronic stage (>12 months) after the infarct has remodeled into scar tissue. However, given the enhanced metabolic activity after a stroke and active process of cortical reorganization, earlier intervention might produce larger and more durable benefits. There have been a few studies conducted during the acute and subacute stages, but no studies comparing efficacy at different intervention times during recovery. Studies applying high-frequency rTMS or anodal tDCS stimulation to the affected hemisphere during the acute and subacute phases of recovery showed a significant benefit in performance, with no reports of seizures or other negative outcomes (Chang et al. 2010; Hesse et al. 2007; Khedr et al. 2005a).

### 14.3.4 Stroke Rehabilitation: Language and Cognition

Some beneficial therapeutic effect of neurostimulation in cognitive rehabilitation has been demonstrated, in the realms of aphasia and hemispatial neglect (Table 14.4). Most investigations have been conducted with TMS, using either an online or an off-line stimulation paradigm. Online stimulation uses TMS to temporarily interfere with cognitive tasks. Because the effects last only from milliseconds to seconds, online TMS is useful for proof-of-principle experiments to establish that any given area of cortex is responsible for a certain behavior, rather than clinical effect (Miniussi et al. 2008). Miniussi et al. (2008) propose that transient response to online TMS may be useful to demonstrate residual and compensatory function and therefore potentially useful for patient selection purposes.

There have been several studies showing longer-lasting effects from off-line rTMS stimulation or repeated stimulation before task performance. For example, Naeser et al.'s (2005) study of off-line TMS used to suppress the right homologue of Broca area in four patients with chronic aphasia demonstrated a significant improvement in picture naming at 2 months poststimulation, with effects lasting up to 8 months. Another study investigated the effect of anodal tDCS targeted to the perilesional brain area with greatest fMRI activation during a picture-naming task. In a double-blinded crossover design including only patients with fluent aphasia, subjects who received real anodal tDCS had higher picture-naming speed compared to those who received sham treatment (Fridriksson et al. 2011).

There has also been some promising work in patients with hemispatial neglect, usually following right parietal injuries. Low-frequency rTMS over the unlesioned parietal cortex has shown improvement in attention to the ipsilateral space, which was seen between 2 and 4 weeks after treatment, with lingering effects to 6 weeks (Shindo et al. 2006). A study utilizing tDCS for stroke patients with left hemifield neglect found that real anodal stimulation to the lesioned posterior parietal cortex

## TABLE 14.4
## Comparison of Neurostimulation Protocols for Cognitive Rehabilitation

| References | No. of Subjects | Diagnosis | Coil Position | Method of Localization | Stimulation | Frequency | No of Stimuli | Intensity | Coil | Duration | Session Schedule | Effect |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cotelli et al. (2006) | 24 | AD | L/R DLPFC | MRI guidance | Online rTMS | 20 Hz | 10 pulses | 90% MT | Figure 8 | 500 ms | One session | Stimulation of L/R DLPFC improved accuracy of action naming |
| Naeser et al. (2005) | 4 | Chronic aphasia (5–11 years) | R Broca's homologue | MRI guidance | Off-line rTMS | 1 Hz | 1200 pulses | 90% MT | Figure 8 | 20 min | 10 days | Improved picture naming at 2 months posttreatment |
| Finocchiaro et al. (2006) | 1 | Primary progressive aphasia | L PFC | 6 cm anterior and 1 cm ventral to M1 | Off-line rTMS | 20 Hz | 400 pulses (2 s ON–30 s OFF) | 90% | Figure 8 | 5 min | 5 days | Improved sentence completion at 45 days posttreatment |
| Shindo et al. (2006) | 2 | Chronic R parietal stroke | Unaffected L posterior parietal cortex | 10/20 EEG system (P5) | Off-line rTMS | 0.9 Hz | 900 pulses | 95% | Figure 8 | ~17 m | 6 days | Improved attention to ipsilateral space lasting up to 2–6 weeks |

(*continued*)

**TABLE 14.4 (continued)**
**Comparison of Neurostimulation Protocols for Cognitive Rehabilitation**

| References | No. of Subjects | Diagnosis | Coil Position | Method of Localization | Stimulation | Frequency | No of Stimuli | Intensity | Coil | Duration | Session Schedule | Effect |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cotelli et al. (2008) | 24 | Alzheimer's disease | L/R DLPFC | Template MRI Guidance | Online rTMS | 20Hz | 10 pulses | 90% MT | Figure 8 | 500ms | One session | Improved action naming in mild AD group; improved action and object naming in mod/severe AD group |

| References | No. of Subjects | Diagnosis | Electrode Position | Method of Localization | tDCS Polarity | Intensity | Duration | Session Schedule | Effect |
|---|---|---|---|---|---|---|---|---|---|
| Sparing et al. (2009) | 10 | Subacute stroke-induced L visuospatial neglect | L/R posterior parietal cortex (PPC) | 10/20 EEG system (P3/P4) | Anodal tDCS (ipsi PPC), Cathodal tDCS (contra PPC) | 1 mA | 10 min | One session, 1 h between treatment arms | Both inhibition of unlesioned PPC and stimulation of lesioned PPC reduced symptoms of visuospatial neglect |
| Baker et al. (2010) | 10 | Chronic stroke-induced aphasia | L frontal perilesional | fMRI guidance during picture-naming task | Anodal tDCS | 1 mA | 20 min | 5 days | Improved accuracy of picture naming, lasting up to 1 week |
| Fridriksson (2011) | 8 | Chronic stroke-induced aphasia | L frontal Perilesional | fMRI guidance to active perilesional region on naming tasks | Anodal tDCS | 1 mA | 20 min | 5 days | Decreased processing time in picture-naming task, lasting up to 3 weeks |

and real cathodal stimulation over the unlesioned posterior parietal cortex both reduced symptoms of visuospatial neglect (Sparing et al. 2009)

These positive results in language and neglect rehabilitation should be considered preliminary because of the low numbers of patients, lack of rigorous controls, and testing of restricted functions. Larger studies with tighter controls on patients with stroke and neurodegenerative conditions, with measures of functional improvement, are still needed for clinical validation (Miniussi et al. 2008).

Thus far, neurostimulation protocols in rehabilitation to improve motor function, language, and spatial neglect have shown some promising results. There is some preliminary evidence that stimulation of both hemispheres and concurrent application of traditional rehabilitation practices may provide additional benefits. Further studies combining neurostimulation with more traditional methods of rehabilitation as well as determination of efficacy at various time points during stroke recovery are needed.

### 14.3.5 Parkinson's Disease

Parkinson's disease results from a degeneration of dopaminergic neurons in the substantia nigra pars compacta, resulting in more widespread network dysfunction in the basal ganglia and motor cortex. Treatment generally consists of dopamine supplementation, although existing medications are limited by motor fluctuations and peak-dose dyskinesias, which may be as debilitating as disease itself. While invasive methods of neurostimulation such as deep brain stimulation are widely used, there is significant clinical interest in noninvasive technologies.

One apparent challenge to noninvasive stimulation is the ability to stimulate deeper structures of the basal ganglia. More recently, the H-coil has been used to modulate the activity of deeper neural circuits to maximum depth of 6 cm (Harel et al. 2011, 2012; Bersani 2012).

An alternative method to reach deeper structures may be to use cortical targets as "windows" to influence more distributed neural networks. The primary and supplementary motor regions may qualify as candidate sites for neurostimulation because of their extensive glutaminergic projections to the basal ganglia. Some functional neuroimaging studies have suggested that early, milder PD is associated with a hypoactivity of the primary motor cortex. On the other hand, more advanced PD is associated with hyperactivity, which may represent medication-induced cortical reorganization in response to deficient subcortical motor pathways and may partly explain why advanced PD patients experience dyskinesias (Haslinger et al. 2001; Sabatini et al. 2000). Stimulating motor and premotor cortices may treat hypokinetic features such as bradykinesia or gait freezing, whereas suppressing these regions may treat hyperkinetic features such as dyskinesias.

A number of excitatory neurostimulation protocols have demonstrated a modest benefit on bradykinesia and gait instability (Hamada et al. 2008, 2009, Lomarev et al. 2006, Fregni et al. 2006b). In a metanalysis, Fregni et al. (2005b) pooled 12 studies of TMS and electroconvulsive therapy (ECT) efficacy on motor symptoms of patients with PD and found a small but significant effect size for TMS. ECT carried a larger effect size; however, this finding was supported by a smaller subset of studies.

In another meta-analysis of controlled clinical trials of TMS in PD, Elahi et al. (2009) concluded that high-frequency rTMS studies produced a significant improvement on motor symptoms as reflected by lower UPDRS scores, whereas low-frequency rTMS studies demonstrated significant variability and did not.

Arguably the most robust and durable clinical effect was seen in the study performed by Lomarev et al. (2006). In this study, four cortical targets (left and right M1, left and right DLPFC) received high-frequency (25 Hz) stimulation during each session, with several sessions over a 4 week period. The real rTMS sessions had a significant effect in reducing bradykinesia as well as improving gait speed, which remained significant even 1 month after the end of treatment. Lomarev et al.'s protocol differs from others in several ways, including the extremely high frequency of stimulation, the stimulation of multiple cortical targets, as well as the number of sessions occurring over a prolonged period of time. Each of these variables deserves further exploration in controlled comparative studies.

Fregni et al. (2006b) conducted a double-blind sham-controlled tDCS study of 17 patients, comparing anodal stimulation of M1, cathodal stimulation of M1, anodal stimulation of the DLPFC, and sham stimulation. Only active anodal stimulation of M1 produced a significant motor improvement as measured by UPDRS scores and increased the amplitude and area of the associated motor-evoked potential.

Dyskinesias are another debilitating consequence of long-term dopamine use with some modest benefit demonstrated by pilot neurostimulation studies (Table 14.5). Filipovic et al. (2009) and Wagle-Shukla et al. (2007) both demonstrated that low-frequency rTMS applied to the motor cortex produced a significant decrease in dyskinesias compared to baseline. Koch et al. (2009) performed two studies applying cTBS (inhibitory) to the cerebellum demonstrating significant decrease in dyskinesia. Of interest, their stimulation of both cerebellar lobes for 10 sessions in patients with advanced PD resulted in significant decrease in dyskinesias lasting at least 4 weeks after treatment (Koch et al. 2009). While there has been some evidence that TBS temporarily increases cortical excitability in PD patients (Zamir et al. 2011), none of the studies stimulating the primary motor cortex seems to have demonstrated any motor improvement (Benninger et al. 2011; Eggers et al. 2010; Rothkegel et al. 2009).

In summary, the available research suggests that high-frequency repetitive stimulation and anodal tDCS of the primary motor cortex seem to improve the bradykinetic features of parkinsonism. An ongoing, multisite study supported by the Michael J. Fox Foundation (MASTER-PD) is seeking to provide more definite insights. There is also some evidence that low-frequency repetitive stimulation over the primary motor cortex and TBS over the cerebellum may reduce levodopa-induced dyskinesias, with follow-up studies warranted.

Several other questions merit further investigation, such as the optimal focus for stimulation. Comparative trials of low-, high-, and theta burst frequency stimulation over the primary motor cortex, supplementary motor cortex, and cerebellum are needed to determine which are the optimal parameters for treating bradykinesia, gait disturbance, and levodopa-induced dyskinesias. While most protocols have stimulated only the side contralateral to the more severely affected limb, more studies comparing bilateral to unilateral stimulation are needed as symptoms typically affect both sides. More functional neuroimaging studies are

**TABLE 14.5**
**Comparison of Neurostimulation Protocols for Parkinson's Disease**

| References | No. of Subjects | Diagnosis | Coil Position | Stimulation | Frequency | No. of Stimuli | Intensity | Coil | Duration | Session Schedule | Effect |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Koch et al. (2005) | 8 | Advanced PD with dyskinesia | Supplementary motor area, 3 cm anterior to Cz of 10/20 EEG system | rTMS | 1 Hz/ 5 Hz | 900 pulses (10 s ON–40 s OFF) | 90% MT 110% MT | Figure 8 | 15 min | One session, crossover design | rTMS at 1 Hz significantly decreased drug-induced dyskinesias |
| Koch et al. (2009) | 10 | Advanced PD with dyskinesia | Lateral cerebellum ipsilateral to greatest dyskinesia B cerebellum | cTBS | 50 Hz | 600 pulses (3 pulses every 200 ms) to each cerebellar lobe | 80% MT | Figure 8 | 40 s | One session 10 days | Transient decrease in dyskinesia Significant decrease in dyskinesia lasting up to 4 weeks after treatment |
| Eggers et al. (2010) | 8 | PD | M1 contralateral to more significant bradykinesia | cTBS | 50 Hz | 600 pulses | 80% MT | Figure 8 | 40 s | Two sessions, crossover study with 1 week between real and sham treatments | No effect on motor performance or cortical excitability |

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|---|---|---|---|---|---|---|---|---|---|---|---|
| Benninger et al. (2011) | 26 | Mild–moderate PD | Bilateral M1 + DLPFC | iTBS | 50Hz | 600 pulses | 80% MT | Round | 200 s | 8 days | Safe and improved mood. No effect on gait, UE bradykinesia |
| Rektorova et al. (2008) | 6 | PD with off-related freezing of gait | L DLPFC or M1 leg | rTMS | 10Hz | 1350 pulses | 90% MT | Figure 8 | Variable | Delivered during ON-state × five sessions | No effect on OFF-state freezing of gait |
| Hamada et al. (2008, 2009) | 98 | PD | Supplementary motor cortex | rTMS | 5Hz | 1000 pulses (10 s ON–50 s OFF) | 110% MT | Figure 8 | 20 min | Once weekly × 8 weeks | Modest improvement in bradykinesia |
| Lomarev et al. (2006) | 18 | PD | L/R M1 L/R DLPFC | rTMS | 25Hz | 300 pulses/ target | 100% MT | Figure 8 | 12 s/ target | Eight sessions over 4 weeks | Significant improvement in gait and UE bradykinesia, with effect persisting 1 month past treatment |

(*continued*)

**TABLE 14.5 (continued)**
**Comparison of Neurostimulation Protocols for Parkinson's Disease**

| References | No. of Subjects | Diagnosis | Coil Position | Stimulation | Frequency | No. of Stimuli | Intensity | Coil | Duration | Session Schedule | Effect |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Filipovic et al. (2010) | 10 | PD | M1 contralateral to more severely affected side | rTMS | 1 Hz | 1800 pulses (10 min ON–1 min OFF) | 90% MT | Figure 8 | 32 min | Crossover study with four sessions (real or sham) per arm, with 2 week period between arms | No significant improvement in motor performance by UPDRS total score or subscore |
| Filipovic et al. (2009) | 10 | PD | M1 contralateral to more severely affected side | rTMS | 1 Hz | 1800 pulses | 90% MT | Figure 8 | 32 min | Crossover study with four sessions (real or sham) per arm, with 2 week period between arms | Real rTMS with small but significant reduction in dyskinesias compared to baseline. Major effect on dystonia subscore |

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Wagle-shukla et al. (2007) | 6 | PD | M1 contralateral to more affected side | rTMS | 1 Hz | 900 pulses | 90% MT | Figure 8 | 15 min | 10 days | Significant decrease in dyskinesias immediately after stimulation (day 15), but no difference in other motor features |
| Minks et al. (2011) | 20 | Early PD | R cerebellum | rTMS | 1 Hz | 600 pulses | 100% MT | Round | 10 min | One session. Crossover design with 3 month interval | Significantly faster response on gross motor test, slower response on fine motor task |
| Arias et al. (2010) | 18 | PD | Vertex | rTMS | 1 Hz | 100 pulses | 90% MT | Round | N/A | 10 sessions | No motor improvement |

*(continued)*

**TABLE 14.5 (continued)**
**Comparison of Neurostimulation Protocols for Parkinson's Disease**

| References | No. of Subjects | Diagnosis | Electrode Position | tDCS Polarity | Intensity | Duration | Session Schedule | Effect |
|---|---|---|---|---|---|---|---|---|
| Fregni et al. (2006b) | 17 | PD | M1 DLPFC | Anodal tDCS, Cathodal tDCS | 1 mA | 20 min | One session, crossover design with 48 h washout period between stimulations | Anodal stimulation of M1 associated with significant motor improvement, also increased MEP amplitude and area; no effect with anodal stimulation of DLPFC or cathodal stimulation of M1 |

needed to confirm the more distant, subcortical effects caused by superficial stimulation. Finally, more studies are needed to understand stimulation effects during ON–OFF states, as related to fluctuations in medication level.

### 14.3.6 Tinnitus

Tinnitus is the subjective perception of sound in the absence of an external stimulus. About 5%–15% of the population in Western societies experience tinnitus, with a higher prevalence among the elderly and after hearing loss (Lockwood et al. 2002). This phantom auditory phenomenon can be very distressing. Tinnitus adversely affects quality of life, with high rates of concurrent depression (50%) and insomnia (40%) (Meyeroff and Cooper 1991; Phoon et al. 1993). Despite these significant comorbidities, no reliably effective treatments exist (Elgoyhen and Langguth 2010).

Part of the challenge in developing effective therapies for tinnitus is the absence of a clear pathophysiological model. However, there are several lines of evidence suggesting the importance of distorted central processing of sound, involving the auditory cortex, higher-order association areas, and limbic structures (De Ridder et al. 2006; Kaltenbach 2000; Muhlnickel et al. 1998; Salvi et al. 2000). Deprivation of primary afferent input caused by hearing loss may lead to hyperactivity in the central auditory system, reflected in an increase in the spontaneous firing rate (SFR) in cortical and subcortical structures (Eggermont and Roberts 2004; Kaltenbach 2006). While tinnitus has been associated with increased activity in the primary auditory and temporoparietal auditory association cortices, the manner of reorganization is controversial. For example, the laterality of abnormal auditory processing is unclear (Plewnia 2011).

Specific challenges in combining functional neuroimaging with tinnitus include subjects' sensitivity to external noise and the potential for study contamination with noise artifact. Therefore, quieter magnetoencephalogram (MEG) and PET protocols have been preferred over fMRI protocols, ideally including normal subjects as controls (Plewnia 2011). MEG studies on human subjects have demonstrated a reorganization of the auditory cerebral cortex, such that the tonotopic map may be shifted to the contralateral hemisphere (Muhlnickel et al. 1998). Other PET research suggests a higher level of spontaneous activity on the left-sided auditory cortex, regardless of the laterality of perceived tinnitus (Arnold et al. 1996; Kleinjung et al. 2005; Langguth et al. 2006). Moreover, the severity of tinnitus has been correlated with altered network connectivity (Schlee et al. 2008, 2009) and reduced volume of distant sensory and limbic structures (Landgrebe et al. 2009; Muhlau et al. 2006; Schneider et al. 2009).

Animal studies have demonstrated abnormal synchronized firing in the deprived frequency regions after noise trauma (Norena and Eggermont 2003) and enhanced burst firing in the inferior colliculus and primary and secondary auditory cortices after chemically induced tinnitus (Chen and Jastreboff 1995; Kenmochi and Eggermont 1997; Norena and Eggermont 2003). However, it is unclear what roles these other structures play in modulating sound processing.

Most neurostimulation studies have targeted the temporoparietal cortex to attempt to normalize maladaptive activity (Moller 2003). High-frequency rTMS has been demonstrated to create a "virtual lesion" to transiently suppress tinnitus.

**TABLE 14.6**
**Comparison of Neurostimulation Protocols for Tinnitus**

| References | No. of Subjects | Tinnitus Laterality | Coil Position | Method of Localization | Stimulation | Frequency (Hz) | No of Stimuli | Intensity | Coil | Duration | Session Schedule | Effect |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Fregni et al. (2006e) | 7 | Bi | L temporoparietal and mesial parietal areas | 10/20 EEG system | rTMS (10 Hz); anodal and cathodal tDCS | 10 Hz | 30 pulses | 120% MT, 1 mA | Figure 8 | 3 s/train × 3 trains; 3 min | One session | Three responders for active rTMS and anodal tDCS stimulation of left temporoparietal target |
| Folmer et al. (2006) | 15 | 8 R 7 L | L and R temporal cortices | 10/20 EEG system | rTMS | 10 Hz (3 s ON–57 s OFF) | 150 pulses | 100% MT | Figure 8 | 5 min | One session | Six responders for active stimulation (five left temporal cortex, one right temporal cortex), two responders for sham |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Plewnia et al. (2007a) | 9 | 8 Bi 1 R | Area of maximum tinnitus | PET neuronavigation system | rTMS | 1 Hz | 300, 900, 1800 pulses with intertrain intervals of 30 min | 120% MT | Figure 8 | Three trains of 5, 15, 30 min | One session | Six responders for active rTMS with reduced tinnitus perception. Higher number of pulses with greater suppression. Shorter tinnitus direction with more effect |
| Plewnia et al. (2007b) | 6 | Bi | Area of maximum tinnitus | PET activation, neuronavigation system | rTMS | 1 Hz | 1800 pulses | 120% MT | Figure 8 | 30 min | 10 days real, 10 days sham crossover | Five responders for active rTMS, lasting for 2 weeks |
| Kleinjung et al. (2007) | 45 | 30 Bi, 8 L, 7 R | L primary auditory cortex | Neuronavigation system | rTMS | 1 Hz | 2000 pulses | 110% MT | Figure 8 | 33 min | 10 days | 18 responders, characterized by shorter-duration tinnitus and less hearing impairment |

*(continued)*

## TABLE 14.6 (continued)
## Comparison of Neurostimulation Protocols for Tinnitus

| References | No. of Subjects | Tinnitus Laterality | Coil Position | Method of Localization | Stimulation | Frequency (Hz) | No of Stimuli | Intensity | Coil | Duration | Session Schedule | Effect |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| De Ridder et al. (2007) | 46 | Uni, white noise | Contralateral to tinnitus side | Neuronavigation system | Tonic and burst stimulation | 5/10/20 Hz | 200 pulses | 90% MT | Figure 8 | Variable | One session | 14 responders (5 with maximal suppression with theta burst, 2 with alpha burst, and 7 with beta burst); Burst rTMS suppressed narrow-band/ white tinnitus better than tonic rTMS |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Mennemeier et al. (2008) | 1 | Bi | R posterior superior lateral temporal gyrus | PET guidance | rTMS | 1 Hz | 1800 pulses | 110% MT | N/A | 30 min | 5 days real, 5 days sham crossover | Tinnitus lowest after active rTMS than at baseline, post-sham rTMS, 3 and 6 month follow-up periods. Follow-up PET showed decreased metabolism in R temporal region compared to baseline |
| Poreisz et al. (2009) | 20 | N/A | L inferior temporal cortex | N/A | cTBS/iTBS/ imTBS | Variable | 600 pulses each arm | 80% MT | Figure 8 | 40–190 s | One session | Only cTBS resulted in short-term improvement of symptoms |
| Khedr et al. (2009b) | 66 | N/A | L temporoparietal cortex | 10/20 EEG system | rTMS | 1/10/25 Hz | 1500 pulses/ day | 100% MT | Figure 8 | Variable | 10 days | Some patients treated with real rTMS with lasting benefit at 1 year, suggesting that 10/25 Hz superior to 1 Hz |

*(continued)*

**TABLE 14.6 (continued)**
**Comparison of Neurostimulation Protocols for Tinnitus**

| References | No. of Subjects | Tinnitus Laterality | Coil Position | Method of Localization | Stimulation | Frequency (Hz) | No of Stimuli | Intensity | Coil | Duration | Session Schedule | Effect |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Khedr et al. (2010) | 62 | Uni | Temporoparietal cortex ipsilateral or contralateral to tinnitus side | 10/20 EEG system | rTMS | 1/25 Hz | 2000 pulses/ day | 100% MT | Figure 8 | Variable | 2 weeks | Contralateral stimulation has greater effect than ipsilateral stimulation; twenty patients without tinnitus after 3 months; patients with shortest clinical history of tinnitus responded better |
| Marcondes et al. (2010) | 20 | Bi | L temporoparietal cortex | 10/20 EEG system | rTMS | 1 Hz | 1020 pulses | 110% MT Figure 8 | Figure 8 | 17 min | 5 days | Improvement in tinnitus up to 6 months after stimulation |

| References | No. of Subjects | Electrode Position | Method of Localization | tDCS Polarity | Intensity | Duration | Session Schedule | Effect |
|---|---|---|---|---|---|---|---|---|
| Frank et al. (2012) | 32 | R/L DLPFC | 10/20 EEG system | Anodal/ Cathodal | 1.5 mA | 30 min | 2 days/ week, 3 weeks | Improvement in tinnitus loudness, unpleasantness, and discomfort, but not in tinnitus or depression scales |
| Garin et al. (2011) | 20 | L temporoparietal area | 10/20 EEG system | Anodal, cathodal tDCS | 1 mA | 20 min | One session | Anodal tDCS reduced tinnitus intensity after stimulation; no effect of cathodal tDCS |

These initial studies have been conceptualized as proof-of-principle studies, to help define the functional neuroanatomy of this epiphenomenon (Plewnia 2011).

The largest study by De Ridder et al. involved 114 patients with unilateral tinnitus and investigated the effect of variable frequency of rTMS stimulation (1, 3, 5, 10, 20 Hz). Stimulation resulted in good effect (80%–100% suppression) in about 25% of patients, but no effect (0%–19% improvement) in 47% of patients (Table 14.6). Duration of tinnitus varied inversely with the effectiveness of treatment and also with the frequency of stimulation most likely to induce benefit (i.e., longer duration more likely helped by lower-frequency stimulation) (De Ridder et al. 2005). Other high-frequency rTMS stimulation protocols have also demonstrated significant interindividual variability of response (Folmer 2006; Fregni et al. 2006e; Khedr et al. 2010). Another comparative study found that high-frequency application of rTMS applied to the left temporoparietal cortex, but not real stimulation to the mesial parietal cortex or sham stimulation, resulted in a significant reduction of tinnitus. Likewise, anodal tDCS applied to the left temporoparietal cortex, but not cathodal tDCS or sham tDCS, induced a significant effect (Fregni et al. 2006e).

While high-frequency stimulation may elicit a temporary effect, low-frequency rTMS (≤1 Hz) could result in a more durable suppression of tinnitus. One of the largest studies included 45 patients with bilateral or unilateral (left or right) tinnitus. This group targeted the left primary auditory cortex and found that about one-third of their patients responded (Kleinjung et al. 2007). In a proof-of-principle study by Plewnia et al, nine patients with chronic tinnitus underwent low-frequency rTMS (1 Hz, 120% MT) applied to hyperactive cortical regions as individually determined by PET. Tinnitus loudness was significantly reduced for a brief period, and inversely correlation with prior duration of tinnitus (Plewnia et al. 2007a). Generally, the duration of improvement following serial applications of low-frequency rTMS has been reported to last several weeks, although there are some studies reporting benefit over 6 months (Kleinjung et al. 2005; Marcondes et al. 2010) and even 1 year (Khedr et al. 2009b).

There has been some preliminary investigation of newer stimulation protocols, e.g., TBS (Table 14.6). One study of 46 patients with narrow-band/white noise unilateral tinnitus compared continuous to intermittent TBS applied contralaterally to the side of perceived tinnitus (De Ridder et al. 2007). About one-third of patients responded, with intermittent stimulation more effective than continuous stimulation, at all frequencies. However, another study investigating a single session of different types of TBS (intermittent, continuous, intermediate) applied over the left inferior temporal cortex found a slight attenuation of tinnitus in about 50% of subjects, with no main effect of stimulation type (Poreisz et al. 2009).

In summary, neurostimulation protocols for tinnitus have demonstrated a high interindividual variability of responses, likely a product of the wide range of patient and study attributes. Studies to date have demonstrated a moderate effect size for a subset of patients (Plewnia 2011). There is some evidence that longer duration of tinnitus predicts a poorer response to neurostimulation (De Ridder et al. 2005; Plewnia et al. 2007a). However, further subgroup analyses are needed to better predict who will respond, by variables such as degree and frequency of hearing loss, tinnitus duration, and age (Langguth et al. 2008).

The major source of study heterogeneity has been the choice of stimulation target, reflecting an unclear understanding of underlying pathophysiology. Some protocols stimulated only left-sided temporoparietal cortex, others over the side of perceived tinnitus, others contralateral to the side of perceived stimulus, and still others over hyperactive regions determined by functional neuroimaging. Future studies may compare stimulation sites and protocols to achieve more clinically meaningful results.

### 14.3.7 Other Clinical Indications

There has been an explosion of investigatory applications for neurostimulation within neurology, in fields as diverse as ataxia, dystonia, migraine, tremor, and traumatic brain injury. Overall, such investigations are very preliminary and have to be considered, at best, proof-of-principle trials. While a review of the emerging research in each of these applications is beyond the scope of this chapter, therapeutic applications via TMS stimulation of the cerebellum deserve some consideration.

The cerebellum maintains numerous direct and indirect connections to nearly the entire nervous system. As an important regulatory center within the motor system, cerebellar lesions may result in movement disorders as diverse as limb, truncal, or gait ataxia; speech dysregulation; or extraocular dysmetria (Daskalakis et al. 2004). However, as its efferent connections to the frontal, parietal, temporal, and occipital cortices are being revealed by functional neuroimaging and electrophysiological studies, the role of cerebellum in cognition (including attention, learning, memory, and emotion) is beginning to be appreciated (Minks et al. 2010).

While most TMS studies on the cerebellum have been performed on healthy subjects, there have been small preliminary studies on patients with neurological disease. Shimizu et al. applied rTMS over the, left, right, and middle cerebellum in four patients with spinocerebellar ataxia daily for 21 days and found significant improvements in walking and a balance in all patients (Shimizu et al. 1999). Brighina et al. have used TMS as a diagnostic tool to probe the relationship between the cerebellum and the motor cortex in patients with dystonia, concluding that there is a reduction in cerebellar modulation of motor cortex excitability in these patients (Brighina et al. 2009).

## 14.4 CONCLUDING REMARKS

The last several years have witnessed an exponential increase in the number of well-designed prospective studies in neurostimulation. While studies are still relatively small and limited in number, there exists some convincing evidence of a therapeutic effect in focal-onset epilepsy, chronic pain, stroke rehabilitation, Parkinson's disease, and tinnitus. Some of the variability in results may be a result of diverse patient case mix and variable stimulation parameters. However, the positive effect already demonstrated is encouraging as many of these conditions have no alternative medical therapies or existing therapies are suboptimal. The importance of these results can also be underscored due to the fact that neurostimulation induces therapeutic effects via neuroplasticity, a fundamentally different mechanism than pharmacological treatments.

Here it must be emphasized that positive proof-of-principle evidence does not equal clinical therapeutic utility. Establishing therapeutic utility requires appropriately

powered, controlled clinical trials. While there are a number of randomized, double-blinded, sham-controlled studies, the majority of these studies rely on small sample sizes. Small positive studies may overestimate effect estimates due to the variability and instability of data. On the other hand, small studies that yield negative results carry a higher risk of a type II error and are less likely to be published. Indeed, appropriately powered studies are needed, as are phase IV translational trials. Further studies using neuronavigational devices to specify cortical targets are needed (Lefaucheur 2010).

A host of unanswered questions merit further investigation, most notably effective and optimal stimulation parameters. Drawing helpful distinctions between those studies with and without clinical benefit is nearly impossible because of the heterogeneity of stimulation protocols. For example, little is known about the duration of stimulation required to induce a long-term clinical effect. Yet length of treatment is perhaps the single treatment variable that would most affect patient compliance. Previous studies demonstrating clinical efficacy have generally administered stimulation over a longer duration. While studies that administer a single session of stimulation play a role in establishing functional neuroanatomy and initial clinical effects, future studies hoping to demonstrate clinically meaningful improvement should administer repeated sessions of stimulation. However, such study designs will also require careful longitudinal assessment of safety, and thus controlled trials are warranted prior to broader clinical adoption. Lastly, combining neurostimulation with functional and structural neuroimaging techniques, e.g., fMRI, MR perfusion, PET, DTI, EEG, and voxel-based morphometry, can help elucidate the local and remote cortical and subcortical network changes caused by superficial focal stimulation.

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