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Use of Non-Invasive Brain Stimulation in Stroke

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1. Introduction

Stroke is the leading cause of permanent disability in the Western world (Kolominsky-Rabas *et al.*, 2001). Clinically, stroke is defined as a neurological deficit of cerebrovascular cause that persists beyond 24 hours. The clinical outcome of a stroke depends on which part of the brain is injured and how severely it is affected. The most common symptom of a stroke is sudden weakness or numbness of the face, arm or leg, most often on one side of the body. Other symptoms include: confusion, difficulty in speech production or comprehension; visual deficits; difficulty walking, dizziness, loss of balance or coordination; severe headache with no known cause; fainting or unconsciousness. The clinical presentation is closely associated with the affected artery, which is occluded by a clot or plaque (ischemic stroke), or ruptured (hemorrhagic stroke), and the extent of tissue infarct (Amarenco *et al.*, 2009).

In recent decades, the introduction of thrombolysis and the establishment of stroke units in hospitals have led to a significant reduction of mortality rate after stroke (Howard *et al.*, 2001). However, declining mortality rate has resulted in increased proportion of patients to be left with moderate to severe disability, affecting their daily activities. It is now well-established that early rehabilitation provides more effective recovery of function than would occur in the natural course of recovery (Maulden *et al.*, 2005). However, in most cases this recovery is still incomplete. Up to 60% of patients still have impaired manual dexterity six months after the onset of stroke (Kolominsky-Rabas *et al.*, 2001; Kwakkel *et al.*, 2002).

Advances in neuroscience in the last two decades unequivocally established the brain's capacity to reorganize itself (Nudo, 2007). This has led to the development of various techniques that could potentially improve the rehabilitation of stroke patients. Most widely researched and experimented non-invasive techniques are transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS).

2. Non-invasive brain stimulation methods

2.1 Transcranial Magnetic Stimulation (TMS)

In the 1980's Merton and Morton (1980) were able to stimulate the human brain non-invasively by means of transcranial electrical stimulation (TES). However, contraction of scalp muscles and activation of nociceptive fibres evoked intense unpleasant pain sensation.

Introduction of TMS by Barker, Jalinous and Freeston in 1985 instantly attracted more attention over electrical stimulation, as in this method the current in the coil could activate cortical structures without causing pain. In the following two decades there have been significant advances in this method both technologically and scientifically.

2.1.1 Basics of TMS

TMS is based on the concept of electromagnetic induction. It involves the generation of a brief but strong magnetic field capable of activating cortical elements in the brain of conscious subjects without causing pain (Wasserman *et al.*, 2008). This magnetic field is derived from a changing primary electric current circulating in a coil which then passes through the skull to induce a secondary electric current capable of altering the neurons' transmembrane potential. Rapid depolarization of the membrane leads to action potential generations (Figure 1).

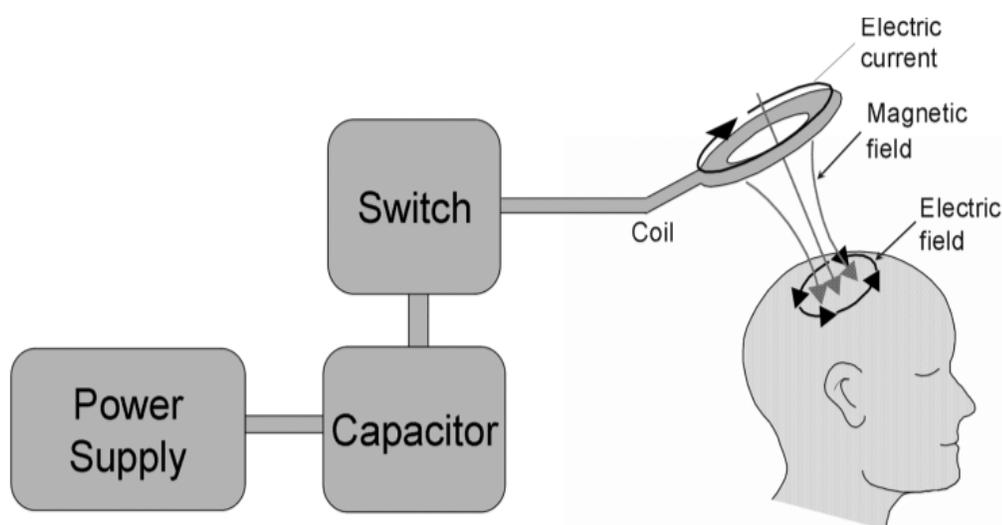


Fig. 1. TMS setup. A brief pulsed electric current passes through the coil, which results in a rapidly changing magnetic field that is perpendicular to the coil's surface. This magnetic field passes through the skull and scalp, and generates an electric field flowing in the opposite direction to the flow of current in the coil. This current leads to the activation of excitable structures in the brain tissue (from Fyre *et al.*, 2008).

The extent of activation within the cortex during magnetic stimulation is influenced by a number of variables, including the coil shape and its position over the head (Tings *et al.*, 2005); number, intensity and frequency of pulses; output waveforms (monophasic vs. biphasic); induced current direction; and the anatomy of the region stimulated. For example, a circular shaped coil generates a relatively large and diffuse magnetic field over the brain, whereas a figure-of-eight (butterfly) coil produces a more focalized field (Wassermann *et al.*, 2008). More recently introduced coils, such as the double-cone coil and H-coil, were designed to stimulate deeper structures within the brain (Hayward *et al.*, 2007; Zangen *et al.*, 2005). However, in general the depth of stimulation is restricted to 2-3 cm below the scalp and the stimulated area within the cortex to around 1-3 cm². Increasing the stimulation intensity to activate deeper brain regions would result in wider and stronger stimulation of more superficial areas.

2.1.2 TMS techniques

A number of different stimulation techniques and paradigms have been introduced over the past two decades. Initially *single-pulse* TMS was used to primarily evaluate the excitability changes of the motor cortex and its output. It is still widely used to determine the best location (hot-spot) of recorded muscles within the motor homunculus and the active/passive motor thresholds, and to assess the effect of interventions on various intracortical influences (Wassermann *et al.*, 2008). *Paired-pulse* TMS utilizes two individual magnetic pulses, separated by a variable inter-stimulus interval (ISI). This method is used to evaluate the intracortical influences of magnetic stimulation, such as short- and long-interval intra-cortical inhibition (SICI and LICI) and intra-cortical facilitation (ICF) (for review see Reis *et al.*, 2008). The ICF of a test motor evoked potential (MEP) elicited from the target muscle can be observed at ISIs of 6-25 ms, using a subthreshold conditioning stimulus (CS) to influence the response to a subsequent suprathreshold test stimulus (TS) (Kujirai *et al.*, 1993). This effect tends to become stronger with increasing CS intensity and weaker with increasing TS intensity. A SICI on the other hand, can be observed when a subthreshold CS suppresses the MEP evoked in response to the suprathreshold TS if the interval between the stimuli is 5 ms or less (Kujirai *et al.*, 1993). In LICI a suprathreshold CS strong enough to produce an MEP in the target muscle could suppress an MEP to a later stimulus of the same intensity if the ISI was 50-200 ms.

Paired associative stimulation (PAS) technique involves applying pairs of peripheral and central stimuli repeatedly (Stefan *et al.* 2000). When around 100 peripheral electrical stimuli and central TMS pulses are paired at an ISI of 25 ms over 30 min, the cortical excitability increases. At an ISI of 10 ms a reduced cortical excitability is observed.

Technical advances in magnetic stimulator and coil designs led to more recent TMS techniques based on delivery of a series of pulses by means of multiple capacitors. This method, referred to as “repetitive transcranial magnetic stimulation” (rTMS), enabled researchers and clinicians to explore the potential benefits of TMS in clinical conditions (Pascual-Leone *et al.* 1994; Wassermann *et al.*, 2008; Hoogendam *et al.*, 2010).

2.1.3 Clinical and diagnostic applications of TMS

Since its introduction, TMS has been used to measure and evaluate the motor evoked potential (MEP) responses from target muscles and commonly applied as a non-invasive tool to clinically evaluate aspects of sensorimotor cortex and pyramidal tract function (Chen *et al.*, 2008). *Motor threshold* (MT) measurements are useful in determining the level of excitability within the motor cortex. MT is defined as the lowest stimulation required for a single pulse to produce a criterion amplitude MEP on a pre-specified fraction of consecutive trials (Wassermann *et al.*, 1998). MT measurements are also useful in establishing and following-up the hemispheric differences in clinical conditions, such as stroke. MEP *amplitude* and *onset latency* measurements are also useful parameters in the assessment and comparison of motor cortex excitability and its output. For example, in pathologies involving upper motor neurons, such as multiple sclerosis, MEP amplitudes are often reduced or absent, and central motor conduction times are prolonged (Cruz-Martínez *et al.* 2000). Somatosensory information processing at the cortical level is also influenced by TMS and can be evaluated by psychophysical measurements, such as vibration detection thresholds (Morley *et al.* 2007).

Cerebral hemispheres exert various influences on each other through interhemispheric connections. Therefore, TMS could be useful for investigating inter-hemispheric dynamics which can be investigated using paired-pulse TMS. In this paradigm, a *conditioning stimulus* is applied to one hemisphere, followed by a *test stimulus* applied to the other. Although a number of studies have reported some complex and inconsistent interhemispheric facilitatory influences dependent on background motor activity, coil position and conditioning stimulus intensity (Hanajima *et al.* 2001, Chowdhury & Matsunami, 2002), more consistent effects are observed in interhemispheric inhibition. The response to the test stimulus can be inhibited by the conditioning stimulus at inter-stimulus interval range of 6-50 ms (Ferber *et al.*, 1992; Daskalakis *et al.* 2002). These transcallosal effects appear to be important in influencing the cortical excitability. For example, interhemispheric inhibition abnormalities have been found in patients with amyotrophic lateral sclerosis (Karandreas *et al.*, 2007).

Another method, called "*triple stimulation technique (TST)*", delivers a single magnetic pulse in association with two timed peripheral electrical pulses and is used to evaluate the integrity of neuronal pathways by means of collision (Magistris *et al.* 1999). It is reported that in amyotrophic lateral sclerosis patients TST provides a quantitative tool for assessing the upper motor neuron conduction failure and when used together with silent period measurements provides a sensitive diagnostic tool (Attarian *et al.*, 2007).

In short, TMS has been shown to be an important non-invasive diagnostic tool for evaluation of certain aspects of motor cortex function and its output. In clinical settings TMS could therefore be a useful tool to determine subclinical presentations in which clear clinical signs are not yet present or indecisive.

The most talked about adverse effect of magnetic brain stimulation is the induction of seizures. A number of cases of accidental seizures induced by rTMS have been reported over the years (total of 16 cases from 1998 to 2008). However, given the large number of subjects and patients who have undergone rTMS in over 3,000 published studies, it is suggested that the risk of rTMS to induce seizures is very low (Rossi *et al.*, 2009). Comprehensive screening of participants with regards to medication and predisposition to seizures will certainly further eliminate the possibility of this adverse effect.

2.1.4 Therapeutic applications of TMS

Since the introduction of repetitive stimulation capable stimulators, rTMS has been increasingly investigated and applied as a therapeutic tool. Using 'simple' rTMS, in which a series of regularly repeated magnetic pulses are delivered in trains and then separated by constant inter-train intervals, it is possible to induce changes to the excitability of motor cortex that outlast the stimulation period from several minutes up to 30 minutes (Touge *et al.*, 2001; Peinemann *et al.*, 2004). In this method, stimulation frequency plays a crucial role in producing selective changes in motor cortex excitability. Overall, low frequency (< 5Hz) rTMS results in suppression of corticospinal excitability, while high frequency (≥ 5 Hz) stimulation leads to facilitatory after-effects (for review see Siebner & Rothwell, 2003).

Another form of repetitive stimulation involves patterned stimuli. *Theta-burst stimulation (TBS)* is a burst of three to five pulses at high frequency (30-100 Hz) delivered at a repeated frequency (usually 5 Hz). This method has been shown to be safe and effective in producing

changes in the excitability of motor systems (Huang & Rothwell, 2004). The typical form of TBS contains three pulse 50Hz bursts given every 200 ms (i.e. at 5 Hz) at the stimulus intensity of 80% of active motor threshold. When a 2-sec train of TBS is given every 10 sec (*intermittent TBS* - iTBS), the cortical excitability is enhanced due to a long-term potentiation (LTP) like effect. Conversely, when bursts are given every 200 ms continuously without interruption (*continuous TBS* - cTBS), the cortical excitability is suppressed due to a long-term depression (LTD) like effect (Huang *et al.*, 2005).

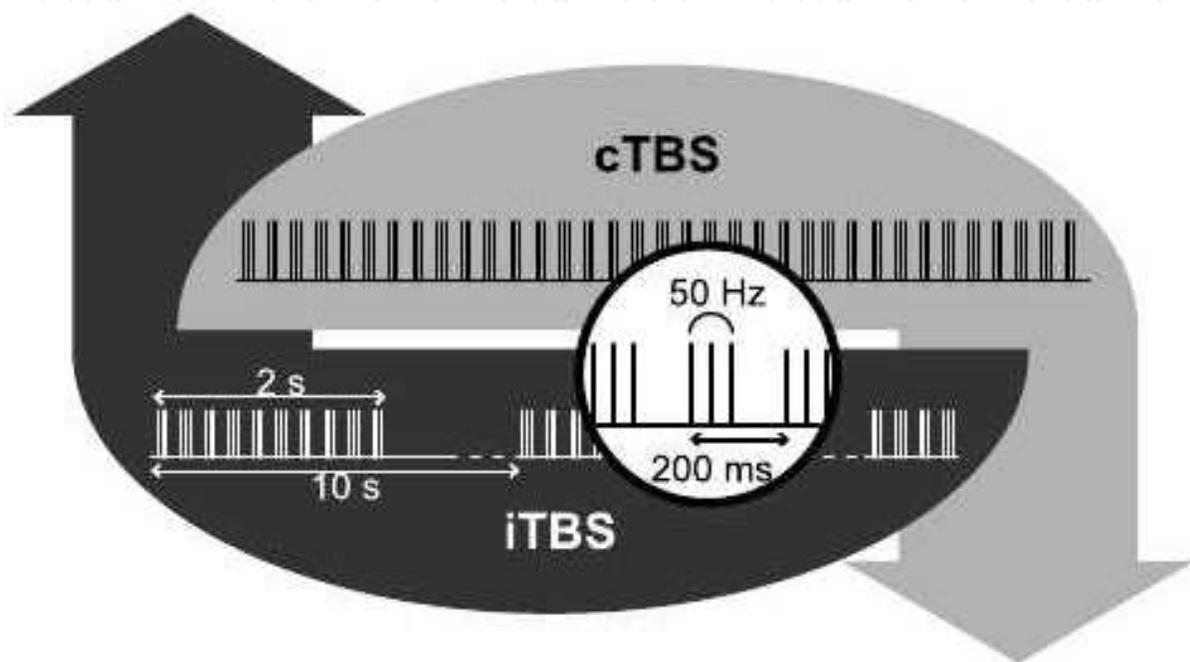


Fig. 2. Theta burst stimulation patterns. A usual TBS contains 3-pulse 50Hz bursts given every 200 ms. When a 2-sec train of TBS is given every 10 sec (iTBS), the cortical excitability is enhanced, while the excitability is suppressed when bursts are given every 200 ms continuously (cTBS) (from Huang, 2010).

More recently, *quadripulse stimulation* (QPS) has been introduced as a patterned rTMS protocol in which repeated trains of four mono-phasic pulses are separated by inter-stimulus intervals of 1.5-1250 ms to produce facilitation (at short intervals) or inhibition (at longer intervals). This protocol appears to induce long-term changes in cortical excitability, probably through a modulatory action on intracortical excitatory circuits (Hamada *et al.*, 2008).

Over the years, many studies have investigated the therapeutic use of rTMS in psychiatric disorders, particularly in depression. For this clinical condition many stimulation paradigms and durations have been trialled. At the end of 2008, the United States Food and Drug Administration (FDA) approved the NeuroStar TMS Therapy System™ for “the treatment of Major Depressive Disorder in adult patients who have failed to achieve satisfactory improvement from one prior antidepressant medication at or above the minimal effective dose and duration in the current episode”. However, there is still no consensus on the treatment protocols and durations, and the efficacy, tolerability, cost and inconvenience of TMS over electroconvulsive therapy and medication are still debatable (Rasmussen, 2011).

Other clinical conditions in which rTMS has been investigated as a therapeutic tool include amyotrophic lateral sclerosis (ALS), dystonia, migraine and stroke. Studies on ALS patients revealed some promising preliminary data. However, recent studies have demonstrated a lack of significant long-term beneficial effects of rTMS on neurological deterioration in ALS (Dileone *et al.*, 2011).

Both inhibitory (low frequency) and excitatory (high frequency) rTMS over the primary motor cortex (M1) appear to reduce chronic pain. A number of studies have assessed the efficacy of rTMS in patients with drug-resistant chronic pain of various causes and a meta-analysis showed that rTMS was associated with a significant reduction in pain (Lima and Fregni, 2008). Analgesic effects were also shown after stimulation of other cortical areas, such as the prefrontal cortex. However, as the induced effects are relatively short duration, the therapeutic use of rTMS in chronic pain is limited, unless repeated sessions over several weeks are considered (for review see Lefaucheur *et al.*, 2008).

2.2 Transcranial Direct Current Stimulation (tDCS)

Transcranial direct current stimulation (tDCS) is a non-invasive, low-cost and easy-to-use technique that has the potential to modify cortical excitability and behavior in a range of clinical and experimental conditions. Historically, strong electrical currents have been delivered to patients for the relief of headache and epilepsy using torpedo electric fish (Kellaway, 1946). Since the rediscovery of tDCS about 10 years ago, interest in this method has grown significantly.

2.2.1 Basics of tDCS

The constant direct current delivered to the brain in tDCS is caused simply by positioning the two poles of an electric battery-based stimulator to the brain (Nitsche & Paulus, 2000). In order to stimulate the motor cortical region, the stimulating (active) electrode is placed over the motor cortex (M1) and the reference electrode over the contralateral supraorbital ridge or the neck region. More accurate stimulation of a representation within M1, such as the hand area, could be achieved after TMS assessment of the hand area's "hot spot". Two surface conductive rubber electrodes (sized 25 cm² - 35 cm²) attached to the device are usually placed inside sponges soaked in NaCl solution. The sponge-electrodes are then placed and kept on their desired region by a non-conducting rubber band, which is strapped firmly around the subject's head (Figure 3). Current intensities used during sessions vary between 1 mA - 2 mA and are commonly applied for 10 to 20 minutes.

Physical modeling of currently available stimulators suggests that only around 50% of the applied current is actually delivered to the brain tissue. The remaining current is shunted across the scalp following the path of least resistance towards the other electrode (Miranda *et al.*, 2006). However, the portion of the current which does eventually reach the brain can be sufficient in altering neuronal activity (Wagner *et al.*, 2007). The current delivered by tDCS cannot directly generate action potentials in cortical neurons, as the electric field in the brain tissue is not capable of inducing a rapid depolarization (Nitsche *et al.*, 2008). Therefore, tDCS might be considered a neuromodulatory intervention. The electric field modifies the excitability of exposed cells by a tonic depolarization or repolarization of their resting membrane potential by only few millivolts. Evidence that the effects of anodal stimulation

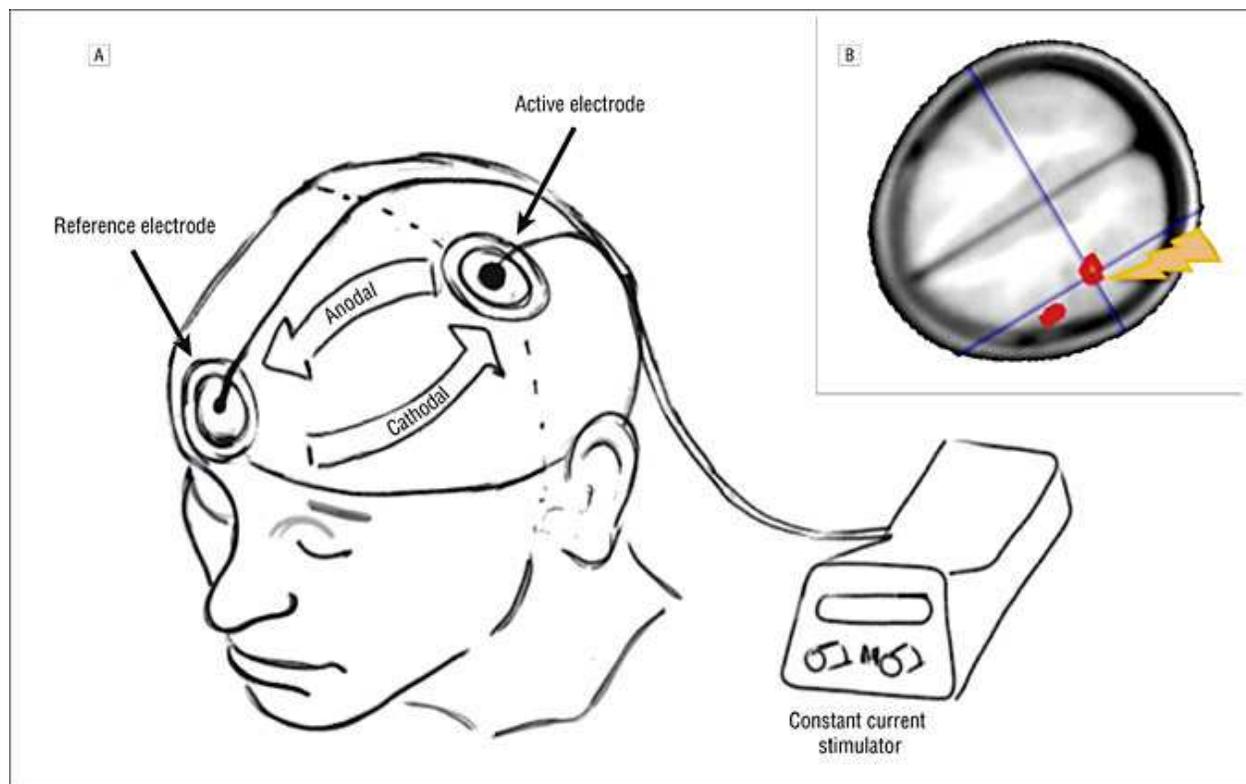


Fig. 3. tDCS setup and montage. (A) The setup using a battery-operated direct current stimulator connected with two electrodes. One electrode (active) is positioned over C3 (corresponding to the precentral gyrus), and the reference electrode is positioned over the contralateral supraorbital region. If current flows from C3 to the supraorbital region, then the tissue underlying C3 is subjected to anodal (increase in excitability) stimulation. If current is reversed, then the tissue underlying C3 is subjected to cathodal (decrease in excitability) stimulation. (B) Regional cerebral blood increases in the motor region underlying the electrode positioned over C3 after anodal stimulation. Regional cerebral blood was determined using a non-invasive arterial spin-labeling technique (from Schlaug *et al.*, 2008).

appear to be solely dependent on changes in membrane potential comes from studies using pharmacological agents. For example, while calcium channel blocker flunarizine reduces and the sodium channel blocker carbamazepine abolishes the effects of anodal stimulation, NMDA receptor antagonist dextromethorphan does not alter current-generated excitability changes (Nitsche *et al.*, 2003a). In terms of the effects of tDCS on cortical interneurons, anodal tDCS does not modify the TMS measures of either glutaminergic interneurons (intracortical facilitation – ICF) or GABAergic interneurons (short-interval cortical inhibition – SICI); suggesting that GABAergic or glutaminergic interneuronal pools are not significantly modulated (Nitsche *et al.*, 2005). During cathodal stimulation, blockade of calcium or sodium channels does not alter the effects of tDCS, suggesting a hyperpolarisation of neurons generated by tDCS itself (Nitsche *et al.*, 2003a). However, ICF and the input/output curve for TMS motor threshold were modulated during cathodal stimulation (Nitsche *et al.*, 2005), suggesting that the membrane potential of glutaminergic interneurons, rather than pyramidal neurons, is modulated by tDCS (for review see Stagg & Nitsche, 2011). Overall, the evidence so far suggests that the modulation observed with tDCS are shaped by a combination of non-synaptic mechanisms, which alter the resting

membrane potential of neurons, and synaptic mechanisms, which alter the signaling strength of neurons.

2.2.2 Variables in the application of tDCS

The current density in the tissue is the quotient of current strength and electrode size. Hence, stimulation efficacy can be augmented by either increasing the current strength or reducing the electrode size (Nitsche & Paulus, 2000). Furthermore, the duration of stimulation sessions also affects the strength of the tDCS induced response; longer session durations result in prolonged after-effects (Nitsche & Paulus, 2001; Nitsche *et al.*, 2003b).

The direction of current flow is another parameter that influences the electrical stimulation effects. The population of neurons exposed to the electrical field and the shifts in their membrane potential depend mainly on the positions of the electrodes and their polarity. In tDCS, both positive electrode (anode) and negative electrode (cathode) are used for stimulation. In this circuit the current flows from the cathode to the anode. The positioning of these electrodes on the scalp is important in determining the overall effects elicited in the underlying cortex. For example, during anodal tDCS of the primary motor cortex, the anode is generally placed over the primary motor cortex (M1) and the cathode over the contralateral supraorbital region. In this montage most studies report an increase in the cortico-motor excitability (Nitsche & Paulus, 2001; Jeffery *et al.*, 2007). Conversely, reversing the current flow (cathodal stimulation) generally diminishes the cortical excitability (Ardolino *et al.*, 2005).

In the literature, so far over 100 studies with tDCS in healthy and patient populations have been published; with no serious side effects. At the start of stimulation, most subjects report a slight itching sensation, which then normally fades. It is possible to reduce or avoid this sensation by ramping the current up and down at the beginning and end of session. Poreisz *et al.*, (2007) in a group of 567 subjects, reported most commonly a mild tingling sensation (~70%), moderate fatigue (~35%) and slight itching under the electrode (~30%), and in ≤10% of cases, headache, nausea and insomnia. Other studies, for example evidence of neuronal damage as assessed by serum neuron-specific enolase, MRI measures of edema using contrast-enhanced and diffusion-weighted MRI measures, EEG waveform analyses and neuropsychological measures, reported no evidence of neural damage or brain pathology (for review see Stagg & Nitsche, 2011).

The large size of stimulating electrodes could result in the stimulation of a larger cortical region than intended. Furthermore, as the reference electrode is not physiologically inert because of current flow between electrodes, there might be modulatory effects in remote brain areas. Therefore, other brain regions and structures between electrodes should be taken into consideration during the application of tDCS. Moreover, modulations of cortical excitability can be focused by reducing the size of the stimulating electrode and by increasing the size of the reference electrode (Nitsche *et al.*, 2007). An extracephalic (e.g. neck region) reference could be used to avoid the undesirable effects of two electrodes with opposite polarities over the brain (Nitsche & Paulus, 2000).

As subjects only occasionally experience any sensation related to the stimulation, controlled placebo sessions could be conducted without the need for additional equipment or attachments. During sham stimulation the stimulator can be initially ramped up (around 10

sec), and after a 30 sec period of stimulation it can be slowly turned down (within 10 sec). With this method placebo and real stimulation sessions are indistinguishable (Gandiga *et al.*, 2006). It should be noted that with motor cortex stimulation, strong cognitive effort by the subject unrelated to the stimulated area, as well as strong activation of the stimulated motor cortex by voluntary prolonged muscle contraction abolishes the effects of tDCS (Antal *et al.*, 2007)

2.2.3 Time course and after-effects of tDCS

With short duration (seconds) tDCS, changes in cortical excitability are observed during the stimulation period, but these effects do not outlast the stimulation itself (Nitsche & Paulus, 2000). However, when applied for several minutes long lasting excitability shifts are produced. For example, around 10 minutes of tDCS can produce stable effects for up to an hour (Nitsche & Paulus, 2001).

The changes in cortical output measures that outlast a tDCS session are dependent on membrane depolarization. The after-effects induced by anodal stimulation could be abolished by calcium or sodium channel blockers or prolonged by NMDA receptor agonists (Nitsche *et al.*, 2003a, 2004). Results from other studies using TMS mediated measures and neuropharmacological applications suggest that the after-effects of anodal tDCS are dependent on modulation of both GABAergic and glutaminergic synapses, and these effects are modulated by acetylcholine, serotonin and catecholamines (for review see Stagg & Nitsche, 2011).

In order to achieve relatively stable changes in cortical function, repeated sessions of tDCS is necessary. For example, recently it was reported that tDCS enhances motor skill acquisition over multiple days through an effect on consolidation (Reis *et al.*, 2009). However, the optimal number and duration of sessions, as well as intersession intervals will depend on the objective of the study or therapeutic application, and requires more research.

2.2.4 Therapeutic applications of tDCS

tDCS has been shown to have beneficial effects in a wide range of clinical pathologies; such as refractory epilepsy (Fregni *et al.*, 2006), stroke (Fregni *et al.*, 2005; Hummel *et al.*, 2005) and various pain conditions (for review see O'Connell *et al.*, 2011), as well as psychiatric conditions, like depression and addiction (Arul-Anandam & Loo 2009; Utz *et al.*, 2010). However, the measurable effects induced in a single session are usually short lived. With repeated session tDCS, growing number of clinical trials is reporting long-term benefits, in particular for depression. For example, in a recent double-blind clinical trial with 40 patients with major depression, significantly large reductions in depression scores were reported after dorsolateral prefrontal cortex (DLPFC) anodal tDCS applied for 10 sessions during a 2-week period (Boggio *et al.*, 2008). These results suggest promising potential for tDCS as an antidepressant treatment.

3. Use of non-invasive brain stimulation in stroke

Following stroke, the neuroplastic changes within the brain lead to reorganization that is attributable to spontaneous recovery of function. Possible mechanisms of such reorganization include; axonal and/or dendritic regeneration or sprouting, reorganization

within the lesioned cortical region by means of synaptic modulation, and remapping of functional representations from the lesioned region onto neighboring unaffected areas surrounding the lesion or homologous areas within the unaffected hemisphere.

During local ischemia various cytotoxic and metabolic reactions result in the loss of structural and functional integrity of neural tissue (Schallert *et al.*, 2000). However, early repair mechanisms, such as expression of developmental proteins and other substrates of molecular plasticity, as well as structural changes, such as regeneration and sprouting, modulation of synaptic plasticity, changes in cortical excitability due to neurotransmitter alterations take place locally and in remote areas of the brain (Witte & Stoll 1997). There is increasing evidence that suggests functional reorganization in both hemispheres. Functional magnetic resonance imaging (fMRI) studies reveal bilateral activation in recovered stroke patients (Gerloff *et al.*, 2006; Nair *et al.*, 2007).

A network of cortical and subcortical areas constitutes the motor system. The final motor output is determined by complex interactions between multiple excitatory and inhibitory circuits within and between these areas. After stroke, the balance in this system could be vitally disturbed as a result of damage to neurons or their fibers within the white matter which connects these areas. For example, in recovered stroke cases, magnetic stimulation over the dorsal premotor cortex, the superior parietal lobe, as well as the primary motor cortex results in significant interference with recovered finger movement performance (Lotze *et al.*, 2006). Furthermore, experimental results using TMS in stroke patients suggest that the motor output from the lesioned hemisphere could be further reduced by pathologically enhanced inhibitory influences from the intact hemisphere (Murase *et al.*, 2004; Duque *et al.*, 2005; Hummel & Cohen, 2006). Although the exact mechanism of this interhemispheric interaction is still unclear, the possibility that suppressing the inhibitory influences exerted by the intact hemisphere could improve recovery has gained interest in recent years.

As stated earlier, depending on the stimulation parameters, cortical excitability can be reduced (inhibition) or enhanced (facilitation). Therefore, non-invasive brain stimulation could accelerate, facilitate or potentiate the functional recovery process and provide better rehabilitation outcomes. TMS and tDCS are the most extensively researched methods in stroke recovery and rehabilitation (for review see Nowak *et al.*, 2010). These techniques not only cause a local change in cortical excitability, but can also evoke changes within remote parts of the cortical motor system, hence improve recovery after stroke (Nowak *et al.*, 2008; Ameli *et al.*, 2009; Grefkes *et al.*, 2010).

3.1 Application of TMS in stroke

In the last decade a number of studies using rTMS in stroke patients have been conducted. These include, single session interventions, in which patients are assessed before and after rTMS and longer term treatment strategies in which patients are given daily sessions of rTMS for up to two weeks. In multiple session interventions rTMS is usually combined with conventional physical therapy to assess and compare the benefits of rTMS in rehabilitation (for review see Khedr & Abo-El Fetoh, 2010; Nowak *et al.*, 2010). Majority of these studies have been conducted in chronic stroke patients whose baseline performance is likely to be stable, compared to acute and subacute stroke cases.

So far, there have been over twenty clinical studies conducted using low or high frequency simple rTMS, or theta-burst stimulation (TBS) of the lesioned or intact hemisphere in acute or chronic patients (for review see Khedr & Abo-El Fetoh, 2010). For example, Koganemaru *et al.*, (2010) used 5 Hz rTMS of the upper-limb area of the primary motor cortex, combined with extensor motor training, and suggested that combining motor training with rTMS can facilitate use-dependent plasticity and achieve functional recovery of motor impairments that cannot be accomplished by either intervention alone. Overall, rTMS gives a 10–30% improvement over sham in a range of performance measures, from simple reaction times to timed behavioral tests. In addition, the effects of multiple session intervention tend to be similar in size but longer lasting than those seen in single session trials.

Even more complex intervention protocols, by stimulating multiple target areas have been trialed. For example, in a group of thirty chronic stroke patients, comparison of unilateral and bilateral rTMS (1 Hz over intact hemisphere and 10 Hz over affected hemisphere) revealed improved motor training effect on the paretic hand after bilateral rTMS (Takeuchi *et al.*, 2008).

Although still relatively few, there are studies conducted to investigate the possible benefits of rTMS in other disabilities associated with stroke; such as, dysphagia, aphasia and hemispatial neglect. The underlying concept of rTMS treatment is based on “upregulating” the lesioned hemisphere or “downregulating” the intact hemisphere (for review see Platz & Rothwell, 2010). Altered connectivity within the cortex as a result of stroke influences the modulatory effects of afferent inputs (Tarlaci *et al.*, 2010). Therefore, combining TMS intervention with afferent inputs, such as vibrotactile stimuli could also be effective.

Overall, the application of rTMS as a therapeutic tool is still in its infancy. According to available evidence, cortical magnetic stimulation could be an effective method for improving functional recovery of acute and chronic stroke. Table 1 summarizes the studies undertaken using rTMS. Although the majority of results report improvements in various behavioral functions, the overall methodology remains to be optimized, in particular regarding the number and duration of rTMS sessions, the site, frequency and intensity of stimulation and the exact timing of rTMS application after stroke

3.2 Application of tDCS in stroke

Human studies using electrical brain stimulation can be divided into invasive and non-invasive. The invasive method principally involves implantation of epidural electrodes through a small craniotomy around a “hot spot” within the perilesional area determined by fMRI. Cortical stimulation is then applied together with physical therapy. Initial cortical stimulation feasibility studies in combination with a motor rehabilitation training targeting the affected arm and hand reported significant improvements compared to control patients receiving only rehabilitation (Brown *et al.*, 2006; Levy *et al.*, 2008). However, in a subsequent larger, multi-center study (Everest Clinical Trial) involving 174 chronic stroke patients (implant and control groups) who underwent six weeks of upper limb rehabilitation, the outcome measures did not meet its primary efficiency end-point at 4-week follow-up, with improvement of 30% in both implant and control groups (Harvey & Winstein, 2009). It is clear that more basic and clinical research into the efficacy of invasive cortical electrical stimulation is needed.

Study	Stimulation Side	Lesion location	Time of stroke	Stimulus	Behavioral results on affected hand
Khedr et al., 2005	IL	26 cortical, 26 subcortical	acute	3 Hz, 10 daily stimulation sessions	Improved hand function (Scandinavian Stroke Scale, National Institute of Health Stroke Scale, Barthel index)
Mansur et al., 2005	CL	10 subcortical	subacute, chronic	1 Hz	Shortened simple and choice reaction times, improvement of hand function (Purdue Pegboard Test)
Takeuchi et al., 2005	CL	20 subcortical	chronic	1 Hz	Improved peak pinch acceleration
Boggio et al., 2006	CL	one subcortical	chronic	1 Hz	Improved hand function (clinical testing), no change in spasticity (modified Ashworth scale for spasticity)
Fregni et al., 2006	CL	2 cortical, 13 subcortical	chronic	1Hz , 5 daily stimulation sessions	Shortening of simple and choice reaction times, improvement of hand function (Jebsen-Taylor Hand Function Test, Purdue Pegboard Test)
Kim et al., 2006	IL	5 cortical, 10 subcortical	chronic	10 Hz	Improved movement accuracy and movement time (sequential finger movement task)

Study	Stimulation Side	Lesion location	Time of stroke	Stimulus	Behavioral results on affected hand
Malcom et al., 2007	IL	11 cortical, 8 subcortical	chronic	20 Hz, followed by constraint induced movement therapy, 10 daily stimulation sessions	Improved hand function (Wolf Motor Function Test, Motor Activity Log) after constraint induced movement therapy, no additive effect of rTMS
Talelli et al., 2007	CL	3 cortical, 3 subcortical	chronic	continuous theta burst stimulation	No change in acceleration and amount of peak grip force
Talelli et al., 2007	IL	3 cortical, 3 subcortical	chronic	intermittent theta burst stimulation	Improved movement speed, no effect on peak grip force
Nowak et al., 2008	CL	15 subcortical	subacute	1 Hz	Improved grasping movements (kinematic motion analysis)
Takeuchi et al., 2008	CL	20 subcortical	chronic	1 Hz, stimulation session with metronome-paced pinching between index finger and thumb	Improved of pinch acceleration and peak pinch force
Dafotakis et al., 2008	CL	12 subcortical	subacute, chronic	1 Hz	Improved timing and efficiency of grasping (kinetic motion analysis)
Liepert et al., 2007	CL	12 subcortical	acute	1 Hz	No change in peak grip force, improved hand function (Nine Hole Peg Test)

Study	Stimulation Side	Lesion location	Time of stroke	Stimulus	Behavioral results on affected hand
Kirton et al., 2008	CL	10 children with subcortical stroke	chronic	1 Hz, 8 daily stimulation sessions	Improved hand function (Melbourne assessment of upper extremity function)
Carey et al., 2009	CL	1 subcortical, 1 cortical	chronic	1 Hz primed by 6Hz	Improved hand function (clinical testing)
Carey et al., 2009	CL	10 cortical	chronic	1 Hz primed by 6Hz	No change in hand function (clinical testing); transiently deteriorated verbal learning (Hopkins Verbal Learning Test-Revised)
Khedr et al., 2009	IL	48 subcortical and cortical	acute	3 Hz or 10 Hz, 5 daily stimulation sessions	Improved hand function 1,2,3 and 12 months after rTMS
Yozbatiran et al., 2009	IL	No detailed information	subacute, chronic	20 Hz	Improved grip strength, improved hand function (Nine hole peg test)
Koganemaru et al., 2010	IL	9 subcortical	chronic	5 Hz	Better improvement of extensor movement when rTMS is combined with extensor motor training
Grefkes et al., 2010	CL	11 subcortical	subacute	1 Hz	Improved hand function supported by fMRI

Table 1. A summary of studies and their outcomes conducted with rTMS in stroke patients IL: ipsilesional, CL: contralesional. Time of stroke after symptom onset; acute: < 1month, subacute 1-6 months, chronic > 6 months (modified from Nowak *et al.*, 2010).

Introduction of tDCS as a research tool a decade ago also attracted attention for its clinical application in stroke. tDCS would have advantages over direct cortical stimulation by stimulating a wider region of brain involving not only the primary motor cortex but also premotor, supplementary motor and somatosensory areas, all of which have been

Study	Stimulation side	Lesion location	Time of stroke	Stimulus	Behavioral results on affected hand
Fregni et al., 2005	IL	2 cortical, 4 subcortical	chronic	anodal	Improved hand function (Jebsen-Taylor Hand Function Test)
Fregni et al., 2005	CL	3 cortical, 3 subcortical	chronic	cathodal	Improved hand function (Jebsen-Taylor Hand Function Test)
Hummel and Cohen., 2005	IL	1 subcortical	chronic	anodal	Improved hand function (Jebsen-Taylor Hand Function Test, peak pinch force), shortened simple reaction times
Hummel et al., 2005	IL	1 cortical, 5 subcortical	chronic	anodal	Improved hand function (Jebsen-Taylor Hand Function Test)
Hummel et al., 2006	IL	No detailed information	chronic	anodal	Shortened simple reaction time, increased peak pinch force
Boggio et al., 2007	IL	1 subcortical	chronic	anodal	Improved hand function (Jebsen-Taylor Hand Function Test)
Boggio et al., 2007	CL	9 subcortical	chronic	cathodal, 5 daily stimulation sessions	Improved hand function (Jebsen-Taylor Hand Function Test)
Hesse et al., 2007	IL	8 cortical, 2 subcortical	acute, subacute	anodal, followed by robotassisted arm training, 6 daily stimulation sessions	Improved hand function (Jebsen-Taylor Hand Function Test, Medical Research Council score)
Celnik et al., 2009	IL	9 cortical and subcortical	chronic	anodal, followed by peripheral nerve stimulation to the affected hand and a key pressing task	Improved key pressing task performance
Lindenberg et al., 2010	IL	20 cortical and subcortical	chronic	bihemispheric (anodal on IL, cathodal on CL)	Improved key pressing task performance

Table 2. A summary of studies and their outcomes conducted with tDCS in stroke patients IL: ipsilesional, CL: contralesional. Time of stroke after symptom onset; acute: < 1month, subacute 1-6 months, chronic > 6 months (modified from Nowak *et al.*, 2010).

implicated in the recovery process (Nair *et al.*, 2007). Furthermore, as a non-invasive technique, tDCS is less risky, portable and flexible in its montage parameters. Studies investigating the effects of anodal tDCS of the lesioned hemisphere on rehabilitation measures suggest limited benefits of this intervention. For example, Hummel *et al.* (2005, 2006) reported beneficial effects of anodal tDCS on reaction times and a set of hand functions that mimic activities of daily living in the paretic hand of patients with chronic stroke. However, in a study involving robot-assisted arm training during anodal tDCS of ten stroke patients, the arm function of only three patients improved significantly (Hesse *et al.*, 2007). Based on the concept of modulation of corticomotor excitability by peripheral sensory inputs (Kaelin-Lang *et al.*, 2002), Celnik *et al.*, (2009) investigated the effects of tDCS and peripheral nerve stimulation (PNS) on motor training in chronic stroke patients and reported a significant facilitatory effect of combining tDCS with PNS compared with each intervention alone.

In recent years, most clinical studies have been designed with the concept of interhemispheric competition. Hence, abnormal interhemispheric inhibition is the hypothetical model for these experimental therapies. It is possible to modulate cortical excitability within motor areas of the lesioned and intact hemispheres by means of tDCS, as well as rTMS. These modulatory influences may induce synaptic plasticity and/or interfere with maladaptive processes that could develop after stroke. Although still limited, studies so far with cathodal stimulation of the intact hemisphere and/or anodal stimulation of the lesioned hemisphere suggest improvements in hand function (Fregni *et al.*, 2005; Boggio *et al.*, 2007; Lindenberg *et al.*, 2010).

In summary, research on the efficacy of tDCS as a therapeutic intervention is well underway. Table 2 summarizes the cases, stimulation protocols and outcomes of tDCS studies in stroke patients. It is clear that more clinical data are required to establish efficient protocols, including the optimal stimulation locations, dose, duration and frequency of treatment.

4. Controversies

In a recent review, the key opinion leaders in the area of brain stimulation identified and addressed the controversial aspects of “therapeutic” cortical stimulation in stroke (Hummel *et al.*, 2008). These controversies include the following:

1. *Mechanism of effect:* Increased cortical excitability with brain stimulation suggests plastic changes in glutamergic and GABAergic intracortical networks, resembling the mechanism of LTP-like changes at the cellular level. However, these assumptions are indirect and have not been proven directly. With regards to inhibitory stimulation of the intact hemisphere to suppress transcallosal inhibition, clinical reports are encouraging, but still there are relatively few studies and the exact neuronal mechanism of this interhemispheric interaction is not clear.
2. *Site of stimulation:* There is evidence of beneficial clinical outcomes from stimulation of the lesioned, as well as the intact hemisphere. Although theoretically susceptibility to seizures with lesioned hemisphere stimulation is possible, so far no such incident has been reported. Other possible adverse effects include the excitotoxicity and metabolic changes in the vicinity of the lesion due to induced hyperexcitability and the current

shunting effects of the scar tissue within brain. In this regard, targeting the intact rather than the lesioned hemisphere as the site of stimulation could have advantages. However, if post-stroke reorganizational changes leading to functional recovery are, at least in part, due to inputs originating from the intact hemisphere, reducing the activity of this region with excitability-decreasing stimulation could have unintended consequences and lead to impaired performance of the paretic hand (Lotze *et al.*, 2006). Interaction between multiple cortical areas, such as premotor and supplementary areas, and the posterior parietal cortex during motor performance makes these regions a possible target for up-regulation or down-regulation during stroke recovery. However, our understanding of the role and interaction of these areas is still limited, and more basic research is necessary.

3. *Type of stimulation and its parameters:* Although epidural electrical stimulation has advantages over non-invasive methods due to its proximity to the cortical tissue, still more patient data is needed to establish its benefits. In terms of practical use, tDCS is advantageous over TMS because it is safer, easier to apply, portable and well-tolerated by patients. It is also a cheaper option as a device. However, technological advances and expanding markets will certainly lead to cheaper and more portable magnetic stimulators in the near future.

Currently, most stimulation parameters for stroke patients are based on the effectiveness of polarity, electrode/coil size, stimulus amplitude, frequency, duration, and session repetition and interval reported in previous studies, in particular in healthy subjects. As more data become available on the efficacy of clinical studies using different parameters, eventually consensus on this controversy will be reached.

4. *Combining stimulation techniques:* Studies so far indicate that stimulation alone might not produce significant improvement in motor function. If combined with other interventional techniques, such as peripheral nerve stimulation (Celnik *et al.*, 2009), better outcomes could be achieved. However, studies that combined brain stimulation with constrained-induced movement therapy (Malcolm *et al.*, 2007) or robot-aided training (Hesse *et al.*, 2007) failed to show clear additive effects. Clearly, more clinical studies are needed in order to determine which combinations could produce better clinical outcomes of motor function.
5. *Commencement of stimulation:* As mentioned earlier, most clinical studies are conducted on chronic stroke patients (>6 months). Although in the chronic stage the deficits are stable and it is easier to assess motor function, within the brain the scar tissue has already formed and natural reorganizational changes have occurred. On the other hand, interference during the acute stage when there is NMDA-induced calcium influx, which might be involved in neuronal toxicity, could result in unintended changes in the brain. Several studies report dynamic changes in neural activation patterns within both lesioned and intact hemispheres during the functional recovery process (for review see Hummel *et al.*, 2008). Therefore, as we better understand the exact mechanisms of post-stroke reorganization, it will be easier to determine the optimal commencement times for intervention by non-invasive brain stimulation. There are a number of variable factors that can influence the magnitude and direction of plastic changes induced during and after non-invasive brain stimulation. These include; age, sex, genetic profile, regular daily activity level, attention, use of neuropharmacological drugs and time of

day (for review see Ridding & Ziemann, 2010). Future therapeutic application of brain stimulation will most likely be part of personalized medicine which takes into account all these variable factors.

6. *Effect size*: Reports so far on the effectiveness of brain stimulation on various motor tasks indicate an improvement of only 10-30% over placebo (for review see Khedr & Abo-El Fetoh, 2010). The transient nature of these improvements is also a shortcoming and raises the question that if these outcomes are obvious improvements to daily activities of patients. As the controversies outlined above are resolved in time, the effect size of clinical measures will also improve and produce accepted meaningful functional improvements after stroke.

5. Conclusion

In the last two decades, non-invasive brain stimulation techniques have been increasingly employed as a therapeutic tool in the rehabilitation of stroke patients. However, these methods are still experimental and there are many questions and unknowns to be addressed before agreed intervention prescriptions are determined for optimal and desired outcomes. In conclusion, non-invasive brain stimulation techniques are novel and promising but still in their infancy as universally accepted clinical tools.

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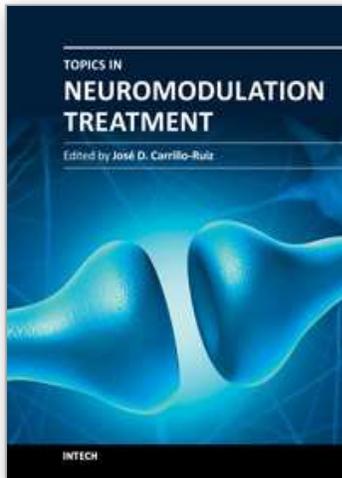
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"Topics in Neuromodulation Treatment" is a book that invites to the reader to make an update in this important and well-defined area involved in the Neuroscience world. The book pays attention in some aspects of the electrical therapy and also in the drug delivery management of several neurological illnesses including the classic ones like epilepsy, Parkinson's disease, pain, and other indications more recently incorporated to this important tool like bladder incontinency, heart ischemia and stroke. The manuscript is dedicated not only to the expert, but also to the scientist that begins in this amazing field. The authors are physicians of different specialties and they guarantee the clinical expertise to provide to the reader the best guide to treat the patient.

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