Principles of therapeutic use of transcranial and epidural cortical stimulation

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1. Introduction

Neurostimulation therapy is used increasingly in various neurological disorders as an adjunct to current medical therapy, when drugs cannot achieve a satisfactory level of improvement. Neuro-modulation has specific clinical applications and technical requirements according to the stimulated structure (peripheral nerve, spinal cord, deep brain nucleus, or cortical region). Cortical stimulation is particularly appealing, because it can be performed via invasive (surgical implantation of electrodes and pulse generator) or noninvasive approach (transcranial magnetic or electrical stimulation). Following the groundbreaking work of Cooper on cerebellar stimulation (Cooper and Upton, 1978), implanted cortical stimulation was initially developed to treat chronic refractory neuropathic pain (Tsubokawa et al., 1991). Later, noninvasive transcranial cortical stimulation has been proposed to treat major depression (George et al., 1995; Pascual-Leone et al., 1996b). At present, therapeutic-like effects of noninvasive cortical stimulation have been reported in several neurological and psychiatric disorders (reviewed in Fregni and Pascual-Leone, 2007; Hallett, 2007; Ridding and Rothwell, 2007). This review will focus on the principles and mechanisms of action of various noninvasive and also invasive techniques of cortical stimulation, omitting seizure therapies such as electroconvulsive therapy (Fink, 2001) and magnetic seizure therapy (Lisanby, 2002). The changes induced by cortical stimulation can affect (i) neuronal excitability, as assessed by cortical excitability studies using single and paired magnetic pulses; (ii) regional brain activities, as assessed by functional neuroimaging methods; (iii) behavior or symptoms, as assessed by clinical examination.

2. Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) is based on the scientific principle of electromagnetic induction discovered by Faraday in 1831. The magnetic field pulse delivered by a stimulating coil applied on the scalp is able to pass through the skull bone without being affected and to induce an electrical field into the brain, activating cortical neuron fibers safely and painlessly (Barker et al., 1985). The geometry of the electrical field induced into the brain and then the nature of the activated structures depend on the waveform of the magnetic pulse (monophasic, biphasic, sinusoidal, etc.) and on the type and orientation of the coil.
Repetitive TMS (rTMS) trains can produce sustained changes in cortical excitability and regional brain activities. Low-frequency rTMS (0.2–1 Hz) consists of a single continuous train and is thought to depress synaptic transmission, whereas high-frequency rTMS (5–20 Hz) consists of intermittent bursts and is thought to potentiate synaptic transmission (Chen et al., 1997; Pascual-Leone et al., 1998; Post et al., 1999). The relationships between rTMS-induced changes in motor evoked potential amplitude and motor cortex stimulation pattern have confirmed this concept, but it cannot be generalized. First, high-frequency rTMS has also been given in a continuous mode (i.e., long trains with more than 100 pulses). Second, the direction of excitability changes induced by rTMS may vary according to the nature of the cortical target (the effects may be different between primary motor cortex stimulation and stimulation of other cortical areas) and the prior state of activation of the recruited circuits (see Section 7).

Long-term synaptic changes may explain why rTMS effects can last for minutes or hours beyond the time of stimulation. Nevertheless, following a single rTMS session, after-effects are often weak, short-lasting and variable between individuals. The repetition of the sessions can reinforce and prolong rTMS after-effects, as demonstrated in patients with depression (Gershon et al., 2003), pain (Khedr et al., 2005b), tinnitus (Langguth et al., 2003), or Parkinson’s disease (Khedr et al., 2006; Lomarev et al., 2006).

In addition, several novel paradigms of stimulation have been recently proposed. These methods are able to increase the duration and size of rTMS after-effects and to produce substantial changes on cortical excitability. Descriptions of these techniques can be found elsewhere (Fitzgerald et al., 2006; Hallett, 2007; Ridding and Rothwell, 2007), and therefore will not be detailed herein. They include:

- **Paired-pulse rTMS**, consisting of: (i) a subthreshold pulse followed by a suprathreshold pulse (Sommer et al., 2001); (ii) two subthreshold pulses (Khedr et al., 2004); (iii) two supra-threshold pulses (Thickbroom et al., 2006). The marked changes in cortical excitability induced by paired-pulse rTMS delivered at a low frequency (less than 5 Hz) could originate from the convergence of inputs elicited by the paired pulses on common neurons.

- **Theta burst stimulation** (TBS), consisting of short bursts of three low-intensity pulses with inner high frequency (50 Hz, within the gamma range) that are delivered at 5 Hz (within the theta range) (Huang et al., 2005). Experiments performed on animal brain slice preparations showed that TBS effects were associated with long-term synaptic changes (Larson et al., 1986).

- **Paired associative stimulation** (PAS), consisting of the association between a single electrical stimulus delivered at peripheral level and a single TMS pulse delivered over the motor cortex (Stefan et al., 2000). The repetition of this “dual stimulation” induces a strong and lasting expansion of the cortical representation of the stimulated muscle (McKay et al., 2002).

### 3. Transcranial electrical stimulation

Skull bone has high electrical resistance, and therefore electrical stimuli delivered to the scalp must be specifically designed to penetrate and to produce efficacious currents into the brain. Using high-voltage stimulators, transcranial electrical stimulation has been applied prior to TMS for eliciting motor responses in humans (Merton and Morton, 1980). Other forms of transcranial electrical stimulation have been proposed for potential therapeutic applications. These techniques are based on pulsed or direct currents. Various patterns of pulsed, non-polarizing currents delivered at high frequencies (100 Hz–100 kHz) have been proposed from the beginning of the 20th century to obtain anesthesia (electroanesthesia) (see historical overview in Limoge et al., 1999). Another type of stimulation, developed in the 1950s (see historical overview in Nitsche et al., 2003; Priori, 2003), consists of weak constant direct currents delivered by an active electrode (anode or cathode) placed on the scalp. Such transcranial direct current stimulation (tDCS) has been recently reintroduced in neurophysiological research (Nitsche and Paulus, 2000; Priori et al., 1998) and has been reported efficacious in a variety of neurological and psychiatric disorders (reviewed in Fregni and Pascual-Leone, 2007).

In general, cortical excitability is reduced by cathodal tDCS and increased by anodal tDCS, likely due to neuronal hyperpolarization (Bindman et al., 1964). However, the direction of the polarizing effects strictly depends on the orientation of the dendrites and axons in the induced electrical field. In addition, either inhibitory or excitatory networks can be affected by DC stimulation. Therefore, functional and clinical changes induced by tDCS are influenced by technical parameters, such as the placement of the reference electrode or the intensity of stimulation (Nitsche and Paulus, 2000; Priori, 2003).

### 4. Implanted cortical stimulation

Invasive cortical stimulation was initially performed to map cortical functions in brain tumor or epilepsy surgery. For therapeutic application, cortical stimulation settings are different and electrodes are implanted chronically, with epidural or subdural placement. Compared to subdural stimulation, epidural implantation increases activation threshold and reduces the risk of induced seizure (Bezard et al., 1999). As for transcranial stimulation, the effects produced by epidural cortical stimulation (ECS) highly depend on various technical parameters, such as stimulation frequency and intensity, pulse width, duty cycle, montage (monopolar vs. bipolar), electrode polarity (anode vs. cathode), and the distance between the electrodes and the neural elements (Randk, 1975). For instance, it was shown that the thickness of the cerebrospinal fluid layer between the dura mater and the underlying cortex affected the strength and the distribution of the electrical field induced into the brain (Manola et al., 2005).

Due to stimulation settings and the wide spacing between contacts of electrode leads, ECS usually results in bifocal “monopolar” stimulation (both anode and cathode are active) (Manola et al., 2005). This observation is crucial because stimulation polarity determines the flow of electrons and current direction and orientation, resulting in differential patterns of cortical activation, at least for the motor cortex (Gorman, 1966; Rosenthal et al., 1967). Predictions from a modeling study confirmed the empirical data: when ECS is applied to the motor cortex, a cathode excites preferentially the fibers that run horizontally under it, whereas an anode excites the fibers that are perpendicular to the surface (Manola et al., 2007). The nature of the recruited fibers will therefore depend on the placement of the stimulating anode(s) and cathode(s) over a gyrus or a sulcus.

### 5. Circuit activation

The strength-duration relationship of membrane properties makes fibers of passage more excitable than local cell bodies at the stimulation site (McIntyre and Grill, 2002; Nowak and Bullier, 1998). Axonal excitation can give rise to both antidromic and orthodromic volleys. Antidromic volleys reach the neural struc-
tures from which efferents arise, while orthodromic volleys induce post-synaptic excitation or inhibition in cortical or subcortical targets. The axons recruited by cortical stimulation can be short fibers of intracortical interneurons, as well as afferent or efferent fibers connected with distant cortical or subcortical structures.

A number of physiological studies have reported “local” effects of rTMS and tDCS in the primary motor, somatosensory, or visual cortex. However, the neural activity changes at the origin of the therapeutic effects of cortical stimulation may located at a distance from the site of stimulation. For instance, the analgesic effects produced by motor cortex stimulation in patients with chronic neuropathic pain do not result from “local” activation of the corticospinal motor tract at cortical level. Actually, ECS excites fibers that run in the superficial layers of the motor cortex (Manola et al., 2005, Manola et al., 2007) and project to remote cortical or subcortical structures involved in cognitive-emotional or sensori-discriminative aspects of pain (García-Larrea and Peyron, 2007). Functional neuroimaging also disclosed remote and widespread effects of tDCS and rTMS applied to motor or premotor cortex (Lang et al., 2005; Rounis et al., 2005; Siebner et al., 2003).

At least for the motor cortex, it has been shown that single, brief electrical or magnetic stimuli could elicit various descending volleys at high frequency (above 500 Hz), recordable from the spinal cord (Patton and Amassian, 1954; Kaneko et al., 1996; Nakamura et al., 1996). This corresponds to direct (D) and indirect (I) waves having complex origins (reviewed in Amassian and Stewart, 2003; Di Lazzaro et al., 2004). In fact, a mixture of early excitatory post-synaptic potentials and discharges, followed by prolonged inhibitory post-synaptic potentials can be produced by the stimulation of the motor cortex, depending on the electric field orientation (Rosenthal et al., 1967; Amassian et al., 1987). Periodic discharges similar to that of I waves can be also elicited by the stimulation of other neocortical areas (visual and somatosensory cortices) but probably not by the stimulation of limbic areas (Amassian and Stewart, 2003).

The nature of the recruited circuits depends on various technical parameters: electrode or current polarity for ECS or tDCS; pulse waveform and coil orientation for rTMS. Specificities in the induced electrical field may lead to different targeting strategies between the procedures (ECS, tDCS, and rTMS), as recently highlighted regarding motor cortex stimulation in chronic pain (Lefaucheur et al., 2006b).

6. Temporal relationships

Physiological investigations have shown acute and short-lasting effects of rTMS, such as changes in motor evoked potential amplitude in response to motor cortex stimulation. However, delayed and long-lasting effects have rather been described in therapeutic application of cortical stimulation. For instance, the analgesic effects produced by motor cortex stimulation in patients with chronic pain are prolonged, but delayed by hours or days after the stimulation period (rTMS) (Lefaucheur et al., 2001b) or the time of programming (ECS) (Nguyen et al., 1999). This could relate to time-consuming neurochemical or neuroendocrine processes, expression of secondary messengers, and synaptic plasticity (Padberg et al., 2003). Such delayed effects and prolonged after-effects complicate programming algorithms for ECS.

In other types of neuromodulation, e.g., deep brain stimulation in tremor, clinical changes occur rapidly after switching “on” or “off” the stimulator or after modifying the parameters of stimulation. These rapid changes argue for stimulus-locked processes of activation, inhibition, or modification of disease-related (de)synchronization or oscillations (García et al., 2005).

The careful assessment of the temporal relationship between clinical changes and stimulation time can provide valuable information on the mechanisms of action of a technique of neuromodulation.

7. Priming and plasticity

Synaptic plasticity depends on firing rate, spike timing, and cooperation among inputs arriving at presynaptic level. However, whether a synapse is strengthened or weakened by presynaptic activity depends upon the level of activity in the post-synaptic neuron. The processes leading to depression of synaptic transmission are more effective when post-synaptic activity is high. Conversely, potentiation of synaptic transmission is more likely when post-synaptic activity is low. This is known as the “Bienenstock–Cooper–Munro (BCM) model” (Bienenstock et al., 1982). Generally speaking, previous neuronal activity modulates the capacity for subsequent plastic changes. This has been termed “metaplasticity” (Abraham and Tate, 1997). All these phenomena could help in stabilizing neuronal networks and therefore contribute to “homeostatic plasticity” (Turrigiano and Nelson, 2004).

A recent study showed that rTMS effects on intracortical inhibition depended more on baseline individual values than on stimulation frequency (Daskalakis et al., 2006). Thus, subjects with less inhibition before rTMS tended to have an increased inhibition post-rTMS (and vice versa). A similar observation was made in patients with chronic pain who showed defective intracortical inhibition at baseline and increased inhibition following rTMS delivered at 10 Hz over the motor cortex (Lefaucheur et al., 2006a).

Accordingly, priming cortical stimulation aimed at modulating the initial state of cortical excitability could influence subsequent rTMS-induced changes in cortical excitability. The priming stimulation can have no detectable effects per se on synaptic transmission. There are several reports of efficacious priming protocols in the literature: subthreshold 6 Hz-rTMS was found to reinforce the depression of motor responses induced by suprathreshold 1 Hz-rTMS subsequently applied to the motor cortex (Iyer et al., 2003); tDCS was found to enhance or reverse the effects of 1 Hz- or 5 Hz-rTMS depending on stimulation polarity (Lang et al., 2004; Siebner et al., 2004); a first PAS session was found to affect the changes in motor cortex excitability induced by a subsequent PAS session (Muller et al., 2007). Priming cortical stimulation is likely to be a potent way of improving rTMS efficacy in clinical practice.

Lesions and diseases can also be at the origin of pre-existing homeostatic changes in the activity of a given cortical region. Therefore, the effects of cortical stimulation and priming strategies may differ between patients and healthy subjects. For example, PAS-induced potentiation of synaptic transmission is lacking in Parkinson’s disease (Ueki et al., 2006) but enhanced in patients with focal dystonia (writer’s cramp) (Quartarone et al., 2003) compared to normal controls. Differential effects of dorso-lateral prefrontal cortical stimulation were observed between normal subjects and depressive patients regarding the type of mood changes with respect to the side of stimulation (George et al., 1996; Pascual-Leone et al., 1996a). Actually, abnormal plastic responses and altered excitability changes to cortical stimulation have been found in numerous neuropsychiatric diseases, such as Parkinson’s disease (Gilio et al., 2002; Lefaucheur et al., 2004b), Huntington’s disease (Lorenzano et al., 2006), Alzheimer’s disease (Inghilleri et al., 2006), or schizophrenia (Fitzgerald et al., 2004; Oxlade et al., 2004). Various mechanisms other than pre-existing homeostatic changes may also explain
the differences in the responsiveness to cortical stimulation between healthy subjects and patients. These mechanisms include genetic factors (Edwards et al., 2006; Kleim et al., 2006), hormonal factors (Inghilleri et al., 2004), attentional capacities (Stefan et al., 2004), or inter-individual differences in the anatomy of the brain and possible shift of cortical areas of interest. This latter factor can now be corrected by locating cortical stimulation targets with functional neuroimaging methods.

However, in pathological conditions, medication is likely to be one of the main sources of changes in cortical function because patients with neuropsychiatric disorders are rarely free of drugs affecting brain excitability. For example low doses of dopamine agonists prolong inhibitory tDCS after-effects (Nitsche et al., 2006), while excitatory tDCS after-effects can be extended from 1–2 h to 24 h by concomitant administration of NMDA receptor agonist (Nitsche et al., 2004b) or amphetamine (Nitsche et al., 2004a). In contrast, amphetamine suppresses long-lasting rTMS-induced plastic changes in human motor cortex (Ziemann et al., 2002). The duration of drug administration and drug plasma levels also influence the modulatory effects of cortical stimulation on the excitability of a targeted area. For example low- and high-plasma valproate levels lead to opposite effects of 1 Hz-rTMS on cortico-spinal excitability in patients with juvenile myoclonic epilepsy (Fregnini et al., 2006).

In some applications, medication might be also a prerequisite before considering the therapeutic potential of cortical stimulation. For example there is a strong functional interaction between pre-motor and motor cortices (Bäumer et al., 2003; Rizzo et al., 2004). This interaction supports the efficacy of “suppressive” pre-motor cortex stimulation in dystonia (Siebner et al., 2003; Lefaucheur et al., 2004c; Murase et al., 2005). In Parkinson’s disease, this interaction is defective in untreated patients and needs to be restored by dopaminergic medication (Buhmann et al., 2004; Mir et al., 2005). Cortical stimulation may therefore benefit from the compensatory changes induced by pharmacological treatment.

Other interventions are able to prolong, reinforce or reverse the effects produced by cortical stimulation, such as peripheral sensory stimulation (Conforto et al., 2002), transient sensory deafferentation (Zieman et al., 1998), constraint-induced movements (Liepert, 2006), practice (Pascual-Leone et al., 1995), or learning (Pascual-Leone et al., 1994; Zieman et al., 2004). Conversely, cortical stimulation may be applied to promote the effects of other therapies. For example, left dorsolateral prefrontal rTMS was found to accelerate the onset of action and to augment the response to antidepressant drugs (Rumi et al., 2005). Cortical stimulation could also increase the response to physical therapy in stroke patients, improving practice-dependent plasticity and rehabilitative training (Brown et al., 2006; Kim et al., 2006).

8. General principles

Theoretically, any neurological or psychiatric disorder that includes primary or secondary cortical dysfunction could be a good indication for cortical stimulation. In a simplistic view, the therapeutic effects of cortex stimulation could be conveyed by reactivating hypoactive neuronal structures or inhibiting overactive structures. This concept underlies the application of rTMS in stroke (Lefaucheur, 2006). Stroke lesions in the affected hemisphere result in the loss of interhemispheric inhibition from the affected to the unaffected hemisphere. This leads to the disinhibition of the unaffected hemisphere. In turn the disinhibited unaffected hemisphere could exert a strong inhibitory influence on the affected hemisphere, via transcallosal pathways, reinforcing dysfunction of the stroke-damaged region. Thus, rTMS can be used to restore the balance of activation between the both hemispheres:

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References


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