REVIEW/MISE AU POINT

Methods of therapeutic cortical stimulation
Méthodes de stimulation corticale thérapeutique

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Summary In the nineties, epidural cortical stimulation (ECS) of precentral region has been performed to treat drug-resistant neuropathic pain and repetitive transcranial magnetic stimulation (rTMS) of prefrontal region has shown antidepressant effects in episodes of major depression. These were among the first attempts to treat neurological or psychiatric disorders with cortical stimulation. Actually, a variety of invasive and noninvasive techniques of cortical stimulation could serve therapeutic purpose, including ECS, rTMS, but also transcranial electrical stimulation using pulsed currents (TCES) or direct currents (tDCS). This review presents the methods of therapeutic cortical stimulation that are currently applicable and some of their principles. In particular, it must be emphasized that the site(s) of action can be distant from the site of stimulation because axons with remote projections are more prone to be activated than local cell bodies. Hence, cortical stimulation may activate, inhibit or otherwise interfere with the activity of various cortico-subcortical networks, depending on stimulus frequency and intensity, current polarity, and the configuration of the induced electric field. Functional and clinical effects occur during or beyond the time of stimulation. The existence of after-effects relates to processes of synaptic plasticity induced by the stimulation. Cortical stimulation may also have neuroprotective effects against disease-related excitotoxic phenomena. Considering the multiple techniques and the various potential clinical indications, it is a challenge to determine the place of cortical stimulation in the treatment of neurological and psychiatric diseases, in particular by the side of deep brain stimulation.

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MOTS CLÉS
Champ électrique ; Neuroprotection ; Plasticité synaptique ;

Résumé Au début des années 1990, la stimulation corticale a été proposée dans le traitement de diverses pathologies neurologiques ou psychiatriques résistant aux médicaments, à savoir : la stimulation corticale épidurale précentrale pour les douleurs neuropathiques et la stimulation magnétique transcrânienne répétitive préfrontale pour les épisodes dépressifs. En fait, différentes techniques invasives et non-invasives de stimulation corticale pourraient être utilisées dans un but thérapeutique, parmi lesquelles la stimulation corticale épidurale et les stimulations transcrâniennes magnétiques, électriques et à courant continu. Cette revue présente les
Introduction

Since early nineties, stimulation of selected cortical regions has been proposed to treat various neurological and psychiatric disorders (Table 1). First, Tsukahara et al. [123,124] showed the potential of chronic precentral cortex stimulation with surgically implanted electrodes in the epidural space to relieve drug-resistant neuropathic pain. In parallel, methods of transcranial stimulation have been developed. Using the principle of electromagnetic induction, magnetic stimulators were capable of delivering very safely repetitive magnetic pulses of sufficient power to induce efficacious depolarizing currents into the brain [93]. One of the earliest attempts to use magnetic brain stimulation as a therapeutic procedure was performed in major depression [39,95]. The goal of therapeutic neurostimulation or neuromodulation is to change the excitability or activity of some cortical-subcortical networks involved in the pathophysiological mechanisms of a disease. The respective value of superficial cortical and deep brain targets remains to be determined for each application.

A variety of invasive and noninvasive methods of cortical stimulation may have therapeutic application. These methods include transcranial electric or magnetic stimulation and the use of surgically implanted electrodes for chronic stimulation (Fig. 1). This review presents the methods that are currently available and some of their principles. In contrast to deep brain stimulation, none of the mentioned technique of cortical stimulation has been fully approved for clinical use, except maybe in a few countries.

General principles of transcranial magnetic stimulation (TMS)

TMS consists in the passage of a brief, high-intensity current pulse in a coil of wire, which in turn produces a magnetic field that can reach up to about 2 Tesla and lasts for about 100 ms. When the magnetic field enters the brain, it generates an electric field. The induced current is able to excite neural structures. The first TMS devices for clinical use were built in the mid-eighties [9].

Various parameters are capable of modulating the geometry of the induced electric field and thereby the nature of the neural structures that can be activated by TMS pulses. These parameters include the type and orientation of the TMS coil and the waveform of the magnetic pulse (monophasic, biphasic, sinusoidal...). Figure 2 shows that the production of I-waves or D-waves is a function of horizontal fibers at the surface of a gyrus and that D-waves result from direct activation of the corticospinal tract, while I-waves are high-frequency repetitive discharges revealing indirect, trans-synaptic activation of pyramidal cells evoked by a single cortical stimulus [24,97]. The production of I-waves suggests a tangential stimulation of horizontal fibers at the surface of a gyrus (Fig. 3). These observations may be relevant for stimulation applied outside the motor cortex, at least in the neocortex [1].

Biphasic stimulations are thought to be more powerful than monophasic stimulations, in particular to produce motor evoked potentials (MEP) in response to the stimulation of the motor cortex [51,88]. However, biphasic pulses generate a more complex pattern of neural activation [23]. When applied repetitively (repetitive TMS [rTMS]), monophasic pulses preferentially activate a relatively uniform population of neurons and could therefore be more effective in producing sustained after-effects [3,115]. For example MEP size reduction following 1 Hz-rTMS delivered to the motor cortex [119] and MEP enhancement following 10 Hz-rTMS [4] are more marked and prolonged when monophasic pulses are used. Modulating magnetic pulse waveform surely represents a challenge for future therapeutic applications of rTMS.

The intensity of stimulation also frankly impacts on TMS effects [59,122]. The induced electric field spreads and goes deeper into the brain as intensity increases, likely recruiting additional neural networks. For example, when the motor cortex is stimulated at high intensity using a figure-of-eight coil, D-waves arising from the axonal hillock of pyramidal cells can be elicited in addition to I-waves,
Table 1  Overview of the neurological and psychiatric disorders in which clinical trials using repetitive transcranial magnetic stimulation (rTMS) or transcranial direct current stimulation (tDCS) has been performed.

<table>
<thead>
<tr>
<th>Disorder</th>
<th>rTMS trials</th>
<th>tDCS trials</th>
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| Stroke                          | Motor deficit: low-frequency rTMS over the unaffected M1 or high-frequency rTMS over the affected M1  
Visuospatial neglect: brief high-frequency or prolonged low-frequency rTMS of the unaffected hemisphere  
Aphasia: low-frequency rTMS of the unaffected hemisphere (reviewed in [61]) | Motor deficit: cathodal tDCS over the unaffected M1 or anodal tDCS over the affected M1 [32] |
| Amyotrophic lateral sclerosis   | Low-frequency rTMS [26] or continuous TBS [29] over the motor cortex         |                                                                              |
| Spinocerebellar degeneration    | Repeated single pulses delivered over the cerebellum with a circular coil [47,111] |                                                                              |
| Parkinson’s disease             | Low- and high-frequency rTMS over the motor cortex (reviewed in [63])        | Anodal tDCS over the motor cortex [35]                                       |
| Dystonia                        | Low-frequency rTMS over the premotor or primary motor cortex (reviewed in [125]) |                                                                              |
| Chorea                          | Low-frequency rTMS [18] or continuous TBS [28] over the motor cortex         | Cathodal tDCS targeting the epileptogenic focus [38]                         |
| Refractory epilepsy             | Low-frequency rTMS over the vertex [120] or the epileptogenic focus [37] or high-frequency rTMS over the cerebellum [17] | Anodal tDCS over the motor cortex [33]                                       |
| Neuropathic pain                | High-frequency rTMS over the motor cortex (reviewed in [62])                |                                                                              |
| Migraine                        | High-frequency rTMS over the left prefrontal cortex [16]                    |                                                                              |
| Tinnitus                        | Brief high-frequency or prolonged low-frequency rTMS over the auditory cortex (reviewed in [72]) | Anodal tDCS over the auditory cortex [36]                                     |
| Refractory depression           | High-frequency rTMS over the left prefrontal cortex or low-frequency rTMS over the right prefrontal cortex (reviewed in [103]) | Anodal tDCS over the left prefrontal cortex [34]                             |
| Schizophrenia                   | Negative symptoms: high-frequency rTMS over the left prefrontal cortex       |                                                                              |
|                                 | Auditory hallucinations: low-frequency stimulation over the left auditory cortex (reviewed in [109]) |                                                                              |
| Obsessive-compulsive disorder or Tourette’s syndrome | High-frequency rTMS over the right prefrontal cortex or low-frequency rTMS over the SMA [76,78] |                                                                              |
| Posttraumatic stress disorder   | High-frequency rTMS over the right prefrontal cortex [107]                  |                                                                              |

M1: primary motor cortex; SMA: supplementary motor cortex; TBS: theta burst stimulation.

even if the coil has postero-anterior orientation [22]. However, stimulation frequency is more often put forward to explain the direction of cortical excitability changes that are induced by rTMS [30].

rTMS

There are two classical rTMS procedures (Fig. 4): low-frequency rTMS (1 Hz or less) consists of continuous trains of single pulses, while high-frequency rTMS (5 Hz and higher) consists of bursts of stimuli that usually last for 5–10 seconds and are separated by pauses of 20–50 seconds. In most therapeutic trials, the total duration of an rTMS session is about 20 minutes. Physiological or clinical effects outlasts the period of stimulation for minutes or hours, likely due to long-term depression (LTD) of synaptic transmission for low-frequency rTMS and long-term potentiation (LTP) for high-frequency rTMS [19,96,98]. When applied to the motor cortex, low-frequency rTMS is able to reduce MEP size [19], while the reverse is produced by high-frequency rTMS [94] (Table 2). However, we cannot assume from these MEP size changes that low- or high-frequency rTMS effects are due to LTD or LTP process in all cases.
The repetition of the sessions can reinforce and prolong rTMS after-effects that are often weak, variable, and short-lasting following a single session. Besides these classical rTMS procedures, other TMS protocols have been proposed more recently. These protocols may also have the potential to modulate cortical activities at therapeutic level.

**Paired-pulse rTMS**

When paired pulses consisting of a subthreshold pulse followed by a suprathreshold pulse, are repetitively delivered to the motor cortex, sustained MEP changes can be observed during the stimulation or a short time after [113,114]. The most efficacious settings include an interval of 10 ms between the two pulses of a pair (inter-stimulus interval [ISI]) and a frequency of stimulation of 1 Hz or an ISI of 2 ms with a frequency of 5 Hz [113]. However, such types of paired-pulse rTMS did not show superior efficacy to conventional suprathreshold single-pulse rTMS in producing lasting MEP size changes in controls [113] or in increasing motor ability in parkinsonian patients [114].

Paired-pulse rTMS may also consist of pulses delivered at the same intensity. Pairs of subthreshold stimuli (that

<table>
<thead>
<tr>
<th>Type of stimulation</th>
<th>Effect on motor cortex excitability</th>
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<tbody>
<tr>
<td>Low-frequency rTMS (equal or less than 1 Hz)</td>
<td>Decreased [19]</td>
</tr>
<tr>
<td>High-frequency rTMS (equal or higher than 5 Hz)</td>
<td>Increased [94]</td>
</tr>
<tr>
<td>Low intensity paired-pulse rTMS (ISI 3 ms; rate 0.6 Hz)</td>
<td>Decreased [53]</td>
</tr>
<tr>
<td>High intensity paired-pulse rTMS (ISI 1.5 ms; rate 0.2 Hz)</td>
<td>Increased [121]</td>
</tr>
<tr>
<td>Continuous TBS</td>
<td>Decreased [45]</td>
</tr>
<tr>
<td>Intermittent TBS</td>
<td>Increased [45]</td>
</tr>
<tr>
<td>Low-frequency PAS (equal or less than 0.1 Hz)</td>
<td>Increased [116]</td>
</tr>
<tr>
<td>High-frequency PAS (5 Hz)</td>
<td>Increased [102]</td>
</tr>
<tr>
<td>Pulsed TCES</td>
<td>Unknown</td>
</tr>
<tr>
<td>Cathodal tDCS</td>
<td>Decreased [89]</td>
</tr>
<tr>
<td>Anodal tDCS</td>
<td>Increased [89]</td>
</tr>
<tr>
<td>Cathodal ECS</td>
<td>Unknown</td>
</tr>
<tr>
<td>Anodal ECS</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

ECS: epidural cortical stimulation; ISI: inter-stimulus interval; PAS: interventional paired associative stimulation; rTMS: repetitive transcranial magnetic stimulation; TBS: theta burst stimulation; TCES: transcutaneous cranial electric stimulation; tDCS: transcranial direct current stimulation.
Methods of cortical stimulation

**Figure 2** Basic principles of transcranial magnetic stimulation. A. Direction of the high-intensity discharge current that flows through the figure-of-eight coil winding. B. A brief magnetic field is generated and the magnetic lines of force are perpendicular to the direction of the current circulating in the coil. This brief magnetic pulse in turn induces a current into the brain. The direction of this induced current is perpendicular to the magnetic lines of force (electromagnetic induction). C. Pattern, voltage, and duration of the current produced by monophasic or biphasic pulse at a distance of 1.5 cm from a figure-of-eight coil (inspired from [61]). D. A 3D-representation of the electrical field generated by a figure-of-eight coil on a plane situated at a distance of 1—1.5 cm from the coil. The induced current peaks under the centre of the coil, where the two windings meet.

do not produce any MEP or excitability changes when given alone) with an ISI of 3 ms, administered at a low frequency (0.6 Hz) for a prolonged time (25 minutes), were shown to frankly decrease motor cortex excitability and to increase inhibitory controls beyond the period of stimulation [53]. Pairs of suprathreshold pulses with an ISI of 1.5 ms, applied at 0.2 Hz for 30 minutes, can lead to the opposite result (MEP facilitation) [121]. The marked changes in cortical excitability induced by paired-pulse rTMS could originate from the convergence of inputs elicited by the paired pulses on common interneurons. In fact, MEP facilitation may result from the repetition of paired pulses at suprathreshold intensity and I-wave periodicity.

More recently, Hamada et al. [42] have shown that increasing the number of pulses per train at the same periodicity was able to produce greater changes in motor cortex excitability. They applied repetitive trains of four suprathreshold monophasic magnetic pulses (quadro-pulse rTMS) with an ISI of 1.5 ms, every 5 seconds (0.2 Hz frequency) over the cortical representation of hand muscles. The amplitude of hand MEP was significantly more enhanced by quadro-pulse rTMS than by paired-pulse rTMS applied with the same number of trains at the same intensity, both during the stimulation and up to 75 minutes beyond the stimulation time. In subsequent experiments, Hamada et al. [43] assessed the influence of ISI (ranging from 1.5 to 1250 ms) on MEP size changes induced by quadro-pulse rTMS. They found MEP facilitation at short ISI and MEP inhibition at long ISI: opposite changes in cortical plasticity may result from different summations of the inputs in temporal domain.

**Theta burst stimulation (TBS)**

TBS consists 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). The continuous application of TBS for 40 seconds over the motor cortex results in MEP inhibition, whereas the intermittent application of TBS (2 seconds every 10 seconds, for a total stimulation time of 200 seconds) results in MEP facilitation [45]. Excitatory effects build up within one second, whereas inhibitory effects occur with a delay of several seconds. The process at the origin of MEP inhibition is different between continuous TBS and paired-pulse rTMS: TBS affects the earliest I-waves while paired pulses affect the latest I-waves [27]. The duration of the after-effects depends on the number of pulses applied, e.g., 20 minutes for 20 seconds of stimulation and one hour for 40 seconds of stimulation. TBS paradigms were shown to produce greater and less variable effects on motor cortex excitability than conventional 1 Hz/10 Hz-rTMS protocols [45]. Animal experiments suggested that TBS effects were related to long-term synaptic changes [60].

It must be underlined that the so-called “theta burst protocol” reflects various patterns of stimulation. For instance, it has been reported that TBS applied over the frontal eye field had inhibitory effects on saccade triggering [92], associated with a strong and long-lasting decrease of activity in the stimulated cortical area [46] and an increased EEG synchronization of the stimulated hemisphere [110]. In these experiments, each TBS burst consisted of three pulses at 30 Hz repeated at intervals of 100 ms, while in the original
Figure 3  Motor cortex stimulation: orientation of the recruited cortical fibers and type of elicited descending volleys recorded at spinal level (D: direct, I: indirect) following monophasic TMS (transcranial magnetic stimulation) or ECS (epidural cortical stimulation). TMS delivered by a coil with postero-anterior orientation and cathodal ECS activate cortical fibers tangential to the surface of the scalp and elicit I-waves. In contrast, TMS delivered by a coil with latero-medial orientation and anodal ECS activate cortical fibers perpendicular to the surface of the scalp and elicit D-waves.

Figure 4  The different patterns of repetitive transcranial magnetic stimulation (rTMS). About one minute of stimulation is illustrated. Usual duration and total number of delivered pulses are indicated. The detail of the stimulation is presented when the delivered pulses are not single pulses. Regarding paired-pulse rTMS (pp-rTMS), an inter-stimuli interval of 3 ms is indicated. Paired associative stimulation (PAS) is the association between a single electrical stimulus delivered at peripheral level (for instance at the wrist) and a single TMS pulse delivered over the motor cortex, separated by a fixed interval (for instance 20 ms). Theta burst stimulation (TBS) includes bursts of three pulses delivered at 50 Hz. A TBS train has a frequency of 5 Hz and lasts two seconds. TBS trains can be applied intermittently every 10 second for 200 seconds (iTBS) or continuously for 40 seconds (cTBS).
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method published by Huang et al. [45], each burst consisted of three pulses at 50 Hz repeated every 200 ms.

**Paired associative stimulation (PAS)**

PAS is the association between a single electrical stimulus delivered at peripheral level and a single TMS pulse delivered over the motor cortex [116]. The TMS pulse can be replaced by anodal direct current stimulation [126]. The two stimuli are separated by a fixed interval to generate approximately synchronous events within the primary motor cortex. PAS can be produced by pairing the stimulation of a sensory or mixed nerve [116] or of the motor point of a muscle [81,105] to cortical stimulation. When this paired stimulation is applied at 0.02—0.1 Hz for 30 minutes, this leads to increase MEP amplitude up to 60 minutes at least after the intervention [116]. The repetition of this “dual stimulation” for three days induces a strong expansion of the cortical representation of the stimulated muscle that persists for at least two days beyond the last stimulation session [81]. When applied at 5 Hz, PAS also induces long-lasting somatotopic increase in corticospinal excitability [102].

PAS effects can be blocked by N-methyl-D-aspartate (NMDA) receptor antagonist, arguing for LTP-like phenomenon [117]. Motor cortex reorganization can be improved by PAS after brain injury, as shown in post-stroke chronic hemiplegics [127]. In this latter study, electrical stimulation of the common peroneal nerve at the leg was associated with single-pulse TMS delivered to the primary motor cortex corresponding to the lower limbs. Following four weeks of PAS, significant clinical improvement was observed on several measurements.

**Transcranial electrical stimulation (TES) with pulsed currents**

The first devices built to stimulate the motor cortical areas of the human brain through the scalp used brief, high-voltage electric shocks (TES). High voltage was required to cross the high electric resistance of the skull and to produce efficacious currents into the motor cortex [82]. Due to the strong scalp pain that is generated, the clinical use of TES has been restricted to the monitoring of motor pathways under general anesthesia, especially in the case of spinal cord or aortic surgery [21,73]. Pyramidal tract activation by TES is assessed by recording the descending volley at the level of the spine or the resulting MEP in the limbs.

Another form of TES, called “transcutaneous cranial electrical stimulation” (TCES) was based on pulsed currents delivered at low intensities but very high frequencies [69]. In particular, Aimé Limoge developed the “Limoge’s current”, consisting of trains of stimuli applied at 77—100 Hz. Each train was composed of positive sharp pulses, delivered at 125—167 kHz and separated by large negative pulses of smaller intensity but with the same area than the positive pulses [6] (Fig. 5). This results in a non-polarized stimulus train of 3—4 ms in duration and 30—35 V (200—350 mA) in peak-to-peak amplitude. Specific generators have been developed to deliver the Limoge’s current into the brain, using a cathode placed between the eyebrows and two anodes in each retro-mastoid region. The Limoge’s current was satisfactorily used for several years, mostly in France and Russia, to produce anesthesia (electroanesthesia) and pain control [69]. Experimental results have suggested that TCES could act on endogenous opioids [77], while TCES effects on cortical excitability remain unknown.

**Transcranial direct current stimulation (tDCS)**

Like TCES, tDCS has been developed a long time ago [91,99]. Since its recent reintroduction in neurophysiological research [89,100], tDCS has been applied in a variety of neurological and psychiatric disorders (Table 1). In this technique, weak constant direct currents are delivered by an active anode or cathode placed on the scalp over a targeted cortical area with a reference electrode over the contralateral forehead or the chin. Battery-driven portable stimulators can be used. Polarizing currents are produced, that are able to cross the skull for inducing sustained changes in membrane potential and excitability of cortical cells and fibers that outlast the stimulation.

Cortical neurons have an exquisite sensitivity to weak DC fields and this includes a variety of nonsynaptic changes, relative to local fluctuations in transmembrane ionic concentrations or conductance [50]. Such nonsynaptic events may contribute to tDCS after-effects [5]. However, the main mechanism of action of tDCS is thought to result from plastic changes in synaptic connectivity, especially mediated by NMDA receptors [68,90]. Neuronal networks respond to DC fields even more sensitively than single neurons [31] and tDCS may interfere with oscillatory brain activities [79].

The general opinion is that the modulation of neuronal excitability by DC stimulation is a relatively simple function: cortical excitability is reduced by cathodal stimulation and increased by anodal stimulation, due to processes of neuronal hyperpolarization and depolarization [15]. However, various factors can explain that, in fact, tDCS effects are more difficult to predict.

Firstly, the resulting effect of DC stimulation highly depends on the orientation and distance of the axonal or dendritic-somatic axis with respect to the electrical field [40,101]. Recent experiments showed that the spatial and temporal effects of DC fields could be more complex than expected from initial reports [14]. Therefore, little variation in the technique, e.g. in reference electrode placement or in stimulation intensity, can strongly influence the clinical changes provided by tDCS [89,99].

Secondly, although weak DC fields can coherently depolarize or hyperpolarize a neuronal network with respect to electrode polarity, the resulting effect of the stimulation depends on whether the affected network is inhibitory or excitatory and also on the baseline activity of this network and its afferent synaptic inputs. All these factors could explain the variable results of tDCS trials in diseases.

**Implanted cortical stimulation**

Techniques of intraoperative electrical stimulation (IES) have been developed for mapping cortical functions during brain tumor or epilepsy surgery. For this purpose, the exposed cortex is directly stimulated by prolonged...
Figure 5 The different patterns of transcranial and epidural electrical stimulation. In transcutaneous cranial electric stimulation (TCES), trains are composed of positive pulse of high intensity and short duration (A1) followed by negative pulse of low intensity and long duration (A2). The two pulses have the same area (A1 = A2). Trains of 4 ms-duration are separated by pauses of 8 ms-duration. Regarding epidural cortical stimulation (ECS) and transcranial direct current stimulation (tDCS), pulse duration and intensity are indicated. ECS is applied at a frequency ranging from 20 to 130 Hz. tDCS is applied as a single pulse of long duration (7–20 minutes).

(2–5 seconds) trains of pulses of 0.2–1 ms duration delivered bipolarily at 50–60 Hz [11] or by short trains of 5–7 pulses of 0.1–0.7 ms duration delivered monopolarly (anodally) at 400–500 Hz [118]. For therapeutic application, cortical stimulation settings are different (Fig. 5). Cortical electrodes are implanted chronically with an epidural or subdural placement through a Burr hole or a small craniotomy. Compared to subdural stimulation, epidural implantation increases activation threshold and reduces the risk of induced seizure [12]. Compared to Burr hole, craniotomy improves the accuracy of electrode placement and reduces the risk of hematoma [87].

The frequency, intensity, and polarity of the stimulation govern the efficacy of epidural cortical stimulation (ECS). In particular, the intensity of stimulation, as well as the thickness of the cerebrospinal fluid layer between the dura mater and the underlying cortex, influence the distribution of the electric field induced into the brain [74]. Regarding stimulation polarity, an epidural electrode selected as a cathode excites preferentially the fibers that run horizontally under it (tangential component), whereas an anode excites the fibers that are perpendicular to it (radial component), at least when the motor cortex is stimulated [41,75,106] (Fig. 3). In fact, there is hyperpolarization under the anode, but excitation (depolarization) occurs at distant regions, called virtual cathodes, if the stimulus has a relatively high strength [10]. In the cerebral cortex, fibers are not straight and uniformly oriented, but curved and bend in various directions. Stimulation may have the lowest activation threshold at fiber ending, but the bend acts as a focal point for excitation. Therefore, the nature of the circuits recruited by cortical stimulation is difficult to determine and depends on the placement of the respective anode(s) and cathode(s) over the cortical folds (gyri and sulci). Additional factors of variation include pulse width, duty cycle, montage (monopolar or bipolar), and the distance between the electrodes [104]. The wide spacing between contacts of the ECS leads that are generally used do not increase cortical activation volume as previously suggested [55], but results in activating more distinct neural pathways according to bifocal “monopolar” stimulation (both anode and cathode are active) [74].

Induced currents into the brain

Several studies reported similar values of current density induced into the brain by the various methods of cortical stimulation. In a simple, spherical head model, 2 mA-tDCS with an anode of 25 cm² was shown to produce a mean current density of 0.1 A/m² [84]. Using an MRI-guided finite element head model, Wagner et al. [132] found that the current density injected in the cortex by 1 mA-tDCS with an electrode of 25–35 cm² can reach values up to 20 A/m². For monopolar cathodal ECS set at 1 V, current density estimates ranged from 5 to 14 A/m² [74]. Finally, TMS yields current densities of 1.5 to 120 A/m² [8,49,108]. High values are only present in the cerebrospinal fluid layer, which has 6–7-fold higher conductivity than grey matter. Therefore, rTMS-induced current densities reaching the cortical layers possibly range from 1.5 to 4.5 A/m² [130]. However, these are estimates from models and not in vivo data. Direct measurement of current density induced in the cortex by a TMS pulse was performed only once, providing maximal values of 0.12 A/m² at a very low intensity of stimulation [129]. Variations in the conductivity of the tissues or the distance between the target and the stimulating coil or electrode may greatly influence the results. In addition, the maxima and location of current density can be altered in pathological versus normal conditions [131,132].
Comparisons between the methods of stimulation

It is difficult to compare the different methods of cortical stimulation for most of their characteristics. For instance, tDCS polarization is considered as a technique of neuromodulation, producing changes in membrane potential of axons, while ECS and rTMS are techniques of neurostimulation, eliciting propagated trains of action potentials. However, ECS and rTMS differ according to the duration and frequency of pulse delivery. Chronic ECS consists of continuous trains of stimuli delivered all day long at a frequency ranging from 2–3 Hz to 130–250 Hz. In contrast, rTMS procedure consists of daily sessions lasting for less than 1 hour and repeated for only several weeks, with a frequency of stimulation ranging from 0.2–1 Hz to 10–50 Hz. In one published case, the descending volleys elicited by ECS and rTMS applied over the primary motor cortex were found to be almost similar [25]. However, this is not our experience (unpublished data). This may explain a part of the difference observed between rTMS and ECS procedures in targeting the precentral cortical region to obtain optimal analgesic effects in patients with chronic neuropathic pain [66].

Safety and contraindications

Adverse effects of cortical stimulation are rare. Regarding rTMS, safety guidelines have been published 10 years ago [133] and will be reappraised very soon. A mild and transient headache can be induced by TMS, but the main side effect is seizure induction. The risk depends on the intensity and the frequency of stimulation and can be limited by following the published safety guidelines and by withdrawing drugs that reduce seizure threshold. However, it must be underlined that no chronic epileptic disorder can be generated by rTMS sessions. The possibility of hearing loss should be also taken into consideration, because the loud clicking sound evoked from the TMS coil may theoretically exceed limits for noise exposure and potential hearing damage. The use of hearing protection devices (earplugs) is recommended for rTMS sessions, especially in the case of temporal target. The other adverse effects are more hypothetical, including heating of the brain and effects on pulse rate, blood pressure or hormone levels. The contraindications for TMS are similar to those of MRI, mainly involving intracranial ferromagnetic material. Cardiac pacemaker is usually considered a contraindication, although it is unlikely to be damaged by TMS.

Regarding tDCS, current intensity and duration also should not exceed published safety limits [91]. One particular adverse event in the practice of tDCS is the occurrence of scalp burns from stimulating electrodes. Finally, the main risk for surgically implanted ECS remains infection at the level of the implanted device but not epilepsy.

Principles of therapeutic cortical stimulation

The principles and mechanisms of action of the various methods of cortical stimulation have been reviewed elsewhere [64] and will be briefly discussed herein.

One key feature of therapeutic brain stimulation is that fibers are more prone to be activated than cell bodies. The selective activation of neuronal cell bodies should require asymmetrical charge-balanced biphasic stimuli [80] and such a pattern of stimulation is not provided by standard neurostimulation techniques. Axonal excitation can give rise to both orthodromic and antidromic volleys. This implies that the site(s) of action may be distant from the site of stimulation. Orthodromic volleys induce postsynaptic excitation or inhibition in cortical or subcortical targets, whereas antidromic volleys reach the neural structures from which efferents arise. Both antidromic and orthodromic volleys can modulate activities in the same distant structures through reciprocal interconnections. Even if the site of stimulation is not the site of action, it must be precisely determined to allow between-study comparability. This goal is achieved by using navigation systems dedicated for rTMS or ECS practice. Image-guided navigation can be fruitfully associated with electrophysiological techniques, e.g., MEP recording for motor cortex mapping, to optimize the localization of cortical stimulation site [44].

Fiber activation is able to generate various types of effects, during or beyond the stimulation time. For instance, neural changes occurring during the stimulation can result from stimulus-locked activation, inhibition, or modification of oscillatory activities in cortico-subcortical networks. In contrast, plastic synaptic changes are considered to govern after-effects. Plasticity depends on temporal and spatial summations of the inputs at presynaptic level and also on the baseline level of activity at postsynaptic level. Synaptic depression is more likely when postsynaptic activity is high, while synaptic potentiation is more likely when postsynaptic activity is low, according to the so-called “Bienstock-Cooper-Munro (BCM) model” [13]. This principle influences the effects of cortical stimulation. For example, rTMS is able to increase intracortical inhibition more particularly in normal subjects with less cortical inhibition at baseline [20] or in patients with disease-related defective inhibition [65]. Therefore, a “priming stimulation” can be proposed to modulate the initial state of cortical excitability in order to influence the effects of a subsequent cortical stimulation. Priming strategies include tDCS [58,112], subthreshold rTMS [48], TBS [2], repeated PAS sessions [85], or paired pulses. The priming effects of medications and various types of interventions, such as physical therapy, can also be taken into consideration [64].

Neuroprotection

Another potential effect of cortical stimulation deals with neuroprotection. Cortical stimulation is able to increase the expression and the release of neuroprotective substances within the brain but also to promote neuroprotection by reducing neural cell degeneration due to excitotoxic processes. Excitotoxicity includes cellular and synaptic phenomena. “Cellular” excitotoxicity relates to membrane depolarization and intra-axonal Na+ overloads associated with energetic resource failure. This results in increased Ca2+ influx and neural cell death or apoptosis [70]. Increased Ca2+ influx may also result from an excessive synaptic activation of the NMDA-type glutamate receptors
decrease motor cortex excitability (Table 2). Various methods of cortical stimulation were the goal of recent experiments performed in patients with amyotrophic lateral sclerosis (ALS). In ALS, NMDA-mediated excitotoxicity is known to be one of the leading mechanisms of motoneuronal degeneration [128]. Therefore, it was particularly encouraging that ALS patients could benefit on clinical grounds from low-frequency rTMS [26] or continuous TBS [29], both conditions of stimulation that are able to decrease motor cortex excitability (Table 2). Various methods of “inhibitory” cortical stimulation might be proposed for neuroprotection purpose. Whether these procedures should be equally effective, and in which pathological condition, remains to be determined.

Conclusion

Cortical stimulation includes a variety of noninvasive (transcranial) and invasive (epidural) techniques. Overall, cortical stimulation can be used to reactivate hypoactive structures, to inhibit overactive structures, to enhance the natural process of cortical reorganization or to modulate synchronization and oscillatory activities in cortico-subcortical networks. The resulting changes can last beyond the time of stimulation, mostly due to processes of synaptic plasticity, but other potential effects could only last during the time of stimulation. In these conditions, rTMS should be restricted to transient application, even if daily repeated sessions are able to prolong the after-effects of a single session, as demonstrated for instance in the treatment of chronic neuropathic pain [54]. Indication of tDCS for more chronic use is conceivable, along with the development of portable battery-driven stimulators. Certainly, rTMS and tDCS are techniques of great future but we are still at the beginning of their potential use in therapy. In particular, there is so much variability in their action that it is difficult to predict when there will be a clear recipe for rTMS and tDCS application to treat neurological diseases.

Finally, only chronic ECS procedure is surely able to make permanent the results that are transiently obtained by transcranial approach. ECS can be applied continuously, delivered with another type of stimulation in associative patterns or even triggered by some specific neuronal activity detected by implanted sensors. These are the fields of development of brain-computer interface procedures [57] and of “responsive” neurostimulation, currently in progress to treat refractory epilepsy [56]. The place of cortical stimulation by the side of deep brain stimulation remains to be determined. Considering the variety of applicable methods, the main challenge is to find the optimal strategy of brain stimulation for each disease condition or more precisely for each type of clinical symptom.

References


Methods of cortical stimulation


