Repetitive transcranial magnetic stimulation (rTMS): insights into the treatment of Parkinson’s disease by cortical stimulation

Stimulation magnétique transcrânienne répétitive (SMTr) : aperçu des perspectives de traitement de la maladie de Parkinson par stimulation corticale

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Abstract Repetitive transcranial magnetic stimulation (rTMS) is a potent tool that can be used to modify activity of targeted cortical areas. Significant clinical effects have been obtained in patients with Parkinson’s disease (PD) by stimulating different cortical regions with rTMS at inhibitory (low) or excitatory (high) frequency. These effects were thought to result from plastic changes in motor cortical networks. Actually cortical dysfunction has been documented in PD by neuroimaging and neurophysiologic studies showing either hypo- or hyper-activation of various brain areas. In addition, cortical excitability studies using transcranial magnetic stimulation disclosed significant alterations in intracortical facilitatory or inhibitory processes according to the resting state or to phases of movement preparation or execution. These observations clearly support the therapeutic potential of cortical neuromodulation in PD. Motor cortex stimulation could impact on any station within the cortico-basal ganglia-thalamo-cortical loops that are involved in motor control, providing alleviation of parkinsonian symptoms. Depending on the target, cortical stimulation might improve motor performance or other symptoms associated with PD, like depression. Clinical application of rTMS to treat PD patients is limited by the short duration of the effects beyond the time of stimulation, even if long-lasting improvements have been observed after repeated rTMS sessions. In any case, the place of cortical stimulation in the therapeutic management of PD patients remains to be determined, as an alternative or a complementary technique to deep brain stimulation. The rTMS technique could be used to better define the targets and the parameters of stimulation subsequently applied in chronic epidural stimulation.

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Introduction

Various evidences of therapeutic potential can be found regarding cortical stimulation in Parkinson’s disease (PD). First in 1979, mapping the motor cortex with electrical stimulation during neurosurgical operations, Woolsey et al. [90] induced a transient improvement of rigidity and tremor in two PD patients. More recently, motor cortex stimulation applied to treat patients with chronic pain lead to concomitant improvement of motor disorders, mainly tremor, related to the underlying neurological lesion at the origin of pain [25,39,57]. But more definitive arguments were afforded by the application of repetitive transcranial magnetic stimulation (rTMS) in PD patients. All these data lead to consider motor cortex stimulation as an alternative therapeutic strategy to deep brain stimulation (DBS) for PD, supported at present by the first clinical results of chronically implanted cortical stimulation [9-11,59-61]. In this article, we will review, firstly, the functional changes in cortical activity that characterize PD, and, secondly, the effects that are produced by rTMS applied over various cortical targets in PD patients.

Cortical dysfunction in PD

Positron emission tomography (PET) [37,67], single-photon emission-computed tomography (SPECT) [69,70], and functional magnetic resonance imaging (fMRI) [34,73] showed that the supplementary motor area (SMA) and the dorsolateral prefrontal cortex (DLPFC) are hypoactive in PD. Because the SMA is involved in automated or complex movements [64], SMA hypoactivation could play a role in akinesia. Neurophysiologic recordings of “Bereitschaftspotential”, contingent negative variation or somatosensory evoked potentials, were also consistent with SMA hypoactivity in PD [5,15,16,21,68,72]. Findings are more controversial for the primary motor cortex (M1). In patients with early, untreated PD, fMRI showed M1 hypoactivation [7], according to the classical basal ganglia-thalamo-cortical circuit model [1]. Conversely, in advanced Parkinsonism, M1 and the lateral premotor cortex (L-PMC) were found to be hyperactive [34,73]. These changes represent either primary or compensatory mechanisms due to treatment or adaptive motor strategies. In particular, M1 hyperactivity was attributed to cortical reorganization resulting from drug-induced reafferentation of the deficient subcortical motor system [71].

Imaging studies are based on regional cerebral blood flow measurement. They did not allow differentiation between afferent and local changes in excitatory or inhibitory synaptic activity that were assessed, conversely, by cortical excitability studies using single or paired TMS pulses [44]. TMS studies revealed an excessive corticospinal output at rest in PD patients, concomitant to or resulting from a reduced intracortical inhibition. This excessive descending corticospinal drive could be associated with rigidity. During movement preparation or execution, intracortical or thalamocortical facilitatory inputs may fail to activate correctly all the cortical areas that are involved in the intended movement, leading to akinesia or bradykinesia. This was strongly suggested by the abnormal pattern of motor evoked potential (MEP) size changes according to movement time in patients with PD [13]. Such impairment of motor cortex activation and deactivation was also demonstrated by recording movement-related activity of...
cortical neurons in monkeys intoxicated by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) [88]. These observations may represent the neurophysiologic counterpart of the aforementioned imaging results that were showing SMA and PFC hypo-activation compensated by M1 and PMC hyper-activation. Moreover, PMC hyper-activation could explain the shift towards anterior regions of the center of gravity of TMS-designed motor cortical maps in PD [38]. Such functional changes in cortical activity support the use of cortical stimulation as a therapeutic strategy for PD. This approach was strengthened by various rTMS studies performed in PD patients, which are summarized in Table 1.

Application of rTMS in PD

On the whole, rTMS experiments aim at activating or inhibiting cortical targets, respective of whether high (5 Hz or more) or low (1 Hz or less) frequencies of stimulation are used. The first rTMS study performed in PD patients reported an improvement of reaction and movement times during high-frequency (5 Hz) stimulation of M1 [62]. Such improvement was later shown to last beyond the time of stimulation, reaching statistical significance on motor scores of the Unified Parkinson’s Disease Rating Scale (UPDRS) after single or repeated rTMS sessions that were delivered at high-frequency (5-25 Hz) [4, 18, 40, 41, 45, 78]. Clinical effects induced by rTMS in PD patients depend on the frequency and the site of stimulation. For instance, rTMS of the SMA worsened motor performance [6] when delivered at high-frequency (10 Hz), but improved apomorphine-induced dyskinesia at low-frequency (1 Hz) [43]. Prefrontal targets were also assessed in PD patients: low-frequency (0.5 Hz) DLPFC stimulation was initially found to increase motor performance concomitantly with depression relief [22]. However this was not confirmed in subsequent studies. DLPFC stimulation probably induces antidepressant and cognitive effects, but no motor effects in PD patients [3, 24, 26, 42].

The PMC target was not yet assessed for clinical application in PD. Low-frequency PMC stimulation is known to enhance intracortical motor inhibitory processes more efficaciously than M1 stimulation at the same frequency [2, 30, 55]. Since these inhibitory processes are defective in rigid PD patients, premotor targets could be of value in PD. However, the premotor-motor interaction is absent in “off-drug” PD patients and only partially restored by levodopa intake [8, 53].

The anatomical level on which rTMS acts to alleviate motor disturbance remains to be determined. This may be located within the motor cortex, as suggested by the correlation between rTMS-induced motor improvement and cortical excitability changes [45]. We showed that low-frequency rTMS reduced rigidity and restored intracortical inhibition, whereas movement preparation and execution benefited from a global increase in cortical excitability induced by high-frequency rTMS. However, the effects of cortical stimulation are probably not restricted to the cortex. One may hypothesize that cortical stimulation could impact on various hypo- or hyperactive remote structures, involved in motor control and functionally connected with the motor cortex in cortico-basal ganglia-thalamo-cortical loops (Fig. 1).

Mechanisms of action on cortico-basal ganglia-thalamo-cortical loops

The motor cortex can influence basal ganglia activities through various glutamatergic corticostriatal and cortico-subthalamic projections. In PD patients as in controls, PET studies showed that high-frequency rTMS applied at 10 Hz over M1 or the DLPFC induced a focal release of endogenous dopamine within the ipsilateral dorsal striatum (putamen, caudate nucleus), probably by activating corticostriatal projections [80, 81, 83]. Electrophysiologically, a single TMS pulse delivered over M1 in humans was found to elicit a short-latency neural cell excitation followed by long-lasting inhibition in single-unit recordings from the dorsolateral sensorimotor area of the subthalamic nucleus (STN) [82]. Actually, both the striatum and the STN receive major...
Table 1 Transcranial stimulation in patients with PD

<table>
<thead>
<tr>
<th>Authors</th>
<th>Number of patients</th>
<th>Stimulus frequency</th>
<th>Total number of pulses</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary motor cortex stimulation, rTMS, figure-of-eight coil</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Khedr et al., 2006 [41]</td>
<td>45 (35 active, 10 sham)</td>
<td>25 Hz</td>
<td>3000 per day x 6 days</td>
<td>UPDRS-III, walking speed, key-tapping speed and self assessment scale improvement</td>
</tr>
<tr>
<td>Khedr et al., 2006 [41]</td>
<td>20 (10 active, 10 sham)</td>
<td>10 Hz</td>
<td>3000 per day x 6 days</td>
<td>UPDRS-III mild improvement</td>
</tr>
<tr>
<td>Lefaucheur et al., 2004 [45]</td>
<td>12</td>
<td>10 Hz</td>
<td>2000</td>
<td>UPDRS-III improvement (reduced rigidity and bradykinesia contralateral to the stimulation)</td>
</tr>
<tr>
<td>Bornke et al., 2004 [4]</td>
<td>12</td>
<td>10 Hz</td>
<td>?</td>
<td>UPDRS-III improvement</td>
</tr>
<tr>
<td>Siebner et al., 2000 [78]</td>
<td>10</td>
<td>5 Hz</td>
<td>750</td>
<td>UPDRS-III improvement (reduced rigidity and bradykinesia contralateral to the stimulation)</td>
</tr>
<tr>
<td>de Groot et al., 2001 [18]</td>
<td>9</td>
<td>5 Hz</td>
<td>2250</td>
<td>UPDRS-III and writing improvement</td>
</tr>
<tr>
<td>Khedr et al., 2003 [40]</td>
<td>36 (19 active, 17 sham)</td>
<td>5 Hz</td>
<td>2000 per day x 10 days</td>
<td>UPDRS-III and walking speed improvement</td>
</tr>
<tr>
<td>Dias et al., 2006 [20]</td>
<td>20 (10 active, 10 sham)</td>
<td>5 Hz</td>
<td>2250</td>
<td>Speech improvement</td>
</tr>
<tr>
<td>Siebner et al., 1999 [76]</td>
<td>12</td>
<td>5 Hz</td>
<td>750</td>
<td>Movement time shortening</td>
</tr>
<tr>
<td>Siebner et al., 2000 [77]</td>
<td>10</td>
<td>5 Hz</td>
<td>2250</td>
<td>Prolonged cortical silent period</td>
</tr>
<tr>
<td>Gilo et al., 2002 [32]</td>
<td>15</td>
<td>5 Hz</td>
<td>40</td>
<td>No MEP amplitude increase during suprathreshold rTMS</td>
</tr>
<tr>
<td>Pascual-Leone et al., 1994 [62]</td>
<td>6</td>
<td>5 Hz</td>
<td>-</td>
<td>Movement and reaction time shortening (during rTMS)</td>
</tr>
<tr>
<td>Ghabra et al., 1999 [31]</td>
<td>11</td>
<td>5 Hz</td>
<td>-</td>
<td>No effect on movement (time during rTMS)</td>
</tr>
<tr>
<td>Sommer et al., 2002 [79]</td>
<td>11</td>
<td>1 Hz</td>
<td>900</td>
<td>Movement time shortening</td>
</tr>
<tr>
<td>Lefaucheur et al., 2004 [45]</td>
<td>12</td>
<td>0.5 Hz</td>
<td>600</td>
<td>UPDRS-III improvement (reduced rigidity bilaterally)</td>
</tr>
<tr>
<td><strong>Premotor cortex stimulation, rTMS, figure-of-eight coil</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Mir et al., 2005 [53]</td>
<td>10</td>
<td>5 Hz</td>
<td>300 x 5</td>
<td>Normalization of MEP amplitude in on-drug patients, but no effect in off-drug patients</td>
</tr>
<tr>
<td>Buhmann et al., 2004 [8]</td>
<td>10</td>
<td>1 Hz</td>
<td>1200</td>
<td>Changes in motor cortex excitability, as assessed by a TMS paired-pulse paradigm, depending on levodopa intake</td>
</tr>
<tr>
<td><strong>Supplementary motor area stimulation, rTMS, figure-of-eight coil</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boylan et al., 2001 [6]</td>
<td>10</td>
<td>10 Hz</td>
<td>2000</td>
<td>Increase in reaction time and deterioration of writing</td>
</tr>
<tr>
<td>Koch et al., 2005 [43]</td>
<td>8</td>
<td>5 Hz</td>
<td>900</td>
<td>No significant effect on dyskinesia and UPDRS-III</td>
</tr>
<tr>
<td>Koch et al., 2004 [42]</td>
<td>10</td>
<td>5 Hz</td>
<td>2500</td>
<td>No significant effect on time perception</td>
</tr>
<tr>
<td>Koch et al., 2005 [43]</td>
<td>8</td>
<td>1 Hz</td>
<td>900</td>
<td>Reduced dyskinesia without effect on UPDRS-III</td>
</tr>
<tr>
<td><strong>Dorsolateral prefrontal cortex stimulation, rTMS, figure-of-eight coil</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Koch et al., 2004 [42]</td>
<td>10</td>
<td>5 Hz</td>
<td>2500</td>
<td>Time perception improvement</td>
</tr>
<tr>
<td>Fernandez del Olmo et al., 2006 [24]</td>
<td>13 (8 active, 5 sham)</td>
<td>10 Hz</td>
<td>450</td>
<td>No significant effect on motor performance</td>
</tr>
</tbody>
</table>

(continued)
excitatory glutamatergic inputs from various cortical areas, mainly PFC, SMA and M1 [56,84,85]. These glutamatergic projections can either increase or reduce dopamine release in the striatum, via the activation of GABAergic striatoni-gral pathways [54], and strongly influenced by the mesocorticolimbic dopaminergic system. Degeneration of this latter system leads to corticofugal glutamatergic hyperactivity in PD. Consequently, this was thought to explain the high level of oscillatory synchronization between the cortex and the basal ganglia that could play a key role in parkinsonism pathophysiology, as shown in 6-hydroxydopamine-lesioned rats, MPTP monkeys and in PD patients [33,48,89].

Interconnectivity between the cortex and the basal ganglia could explain why stimulation at any station of the cortico-basal ganglia loops could provide similar functional changes in neural activities and clinical symptoms. High-frequency stimulation of the ventralis intermedius (VIM) nucleus of the thalamus (cerebellar thalamus), the internal globus pallidus (GPI) or the STN might affect motor cortex activation as reflected by induced changes in TMS para-

Table 1 (continued)

<table>
<thead>
<tr>
<th>Authors</th>
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<th>Total number of pulses</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fregni et al., 2004 [26]</td>
<td>42 (21 active, 21 sham)</td>
<td>15 Hz</td>
<td>3000 per day × 10 days</td>
<td>Improvement of depression score similar to fluoxetine, with better results than fluoxetine on cognitive and motor scores</td>
</tr>
<tr>
<td>Boggio et al., 2005 [3]</td>
<td>25 (13 active, 12 sham)</td>
<td>15 Hz</td>
<td>3000 per day × 10 days</td>
<td>Improvement in neuropsychological testing similar to fluoxetine</td>
</tr>
<tr>
<td>Dias et al., 2006 [20]</td>
<td>20 (10 active, 10 sham)</td>
<td>15 Hz</td>
<td>3000</td>
<td>Improvement of depression score without speech effects</td>
</tr>
</tbody>
</table>

**Bilateral motor and prefrontal stimulation, rTMS, figure-of-eight coil**

| Lomarev et al., 2006 [47]     | 18                  | 25 Hz              | 1200 per day × 8 days | Improvement in walking time and reduced bradykinesia for the right hand |

**Motor cortex stimulation, rTMS, circular coil**

| Tergau et al., 1999 [86]      | 7                   | 20, 10, 5, 1 Hz    | 1500                   | No significant effect on UPDRS-III and reaction time                    |
| Strafella et al., 2005 [83]   | 7                   | 10 Hz              | 150 × 4                | Increase in dopamine neurotransmission in the putamen of both hemispheres (reduced [11C]raclopride binding) |
| Mally and Stone, 1999 [49,50] | 10, 49              | 1 Hz               | 30 × 2 per day × 7-10 days | UPDRS-III, HY and ADL improvement                                      |
| Mally et al., 2004 [51]       | 46                  | 1 Hz               | 30 × 2 per day × 7-10 days, 2 × per year, × 3 years | Reduction in HY deterioration and in levodopa dose increase due to disease advance |
| Shimamoto et al., 2001 [75]   | 9                   | 0.2 Hz             | 30 × 2 per week × 2 months | UPDRS-III, HY and ADL improvement                                      |
| Ikekuchi et al., 2003 [36]    | 12                  | 0.2 Hz             | 30 × 2/2-days × 2 weeks | UPDRS-III and ADL improvement                                           |
| Okabe et al., 2003 [58]       | 85                  | 0.2 Hz             | 50 × 2 per week × 2 months | No significant effect on UPDRS-III                                     |

**Prefrontal cortex stimulation, rTMS, circular coil**

| Dragasevic et al., 2002 [22]  | 10                  | 0.5 Hz             | 200 per day × 10 days | UPDRS-III and depression score improvement                              |

**Motor cortex stimulation, tDCS**

| Fregni et al., 2006 [27]      | 17 (9 anodal, 8 cathodal) | tDCS 1 mA, 1 mA, 20 min | No significant motor effect                                          |
| PREfrontal cortex stimulation, tDCS | 9 (anodal) | tDCS 1 mA, 1 mA, 20 min | No significant motor effect                                          |

ADL: activities of daily living; HY: Hoehn and Yahr; MEP: motor evoked potentials; rTMS: repetitive transcranial magnetic stimulation; tDCS: transcranial direct current stimulation; UPDRS-III: unified PD rating scale–motor score.
meters of cortical excitability [14,17,66]. In particular, electroencephalographic studies and functional imaging revealed that STN stimulation decreased M1 activation at rest [12,35,63], but increased pre-SMA and DLPFC activation [29,46,65,74,87]. STN-DBS could act by generating a stimulus-locked activity that breaks pre-existing abnormal synchronization in cortico-basal ganglia loops [28] and improves movement-related desynchronization of the motor cortex activity [19]. Motor cortex stimulation might also alleviate parkinsonian symptoms by reducing such abnormal oscillatory activities, as well as by “reactivating” some hypoactive structures or by normalizing hyperactive ones at cortical or subcortical level (Fig. 1). This dual mechanism was illustrated in MPTP monkeys with chronically implanted motor cortex stimulation [23]. The combined electrophysiological and neuroimaging assessment performed in these animals showed similar effects to those classically observed under STN stimulation [52].

Therapeutic perspectives of cortical stimulation in PD

The strongest arguments for the use of cortical stimulation in the treatment of advanced PD have been provided by the first positive clinical results of implanted cortical stimulation in short case and open studies of PD patients. Most patients were treated successfully by chronic epidural stimulation of M1 at frequencies ranging between 20 and 50 Hz [9-11,59-61]. It is too early to compare the respective efficacy of DBS and cortical stimulation in PD, because controlled studies of chronically implanted cortical stimulation are lacking. However, some interesting points argue for the development of the cortical target. For instance, it was found that speech could be improved in PD patients with dysphonia using rTMS centered over mouth cortical representation [20]. The first results reported with the implanted procedure seem to confirm such improvement, which was rarely or never achieved using DBS.

Indeed, exciting perspectives are opened for the application of implanted cortical stimulation, as an alternative or a complementary technique to DBS. In the near future, technical procedures should improve to identify the best candidates (according to clinical, radiological or electrophysiological presentation), the best parameters of stimulation (regarding frequency, amplitude, pulse width and waveform), and the optimal cortical target (M1 or other cortical regions). The place of non-invasive rTMS in therapeutic management of PD patients remains questionable. The first use of rTMS in clinical practice could be to serve as a tool to select responders for epidural electrode implantation, as proposed in chronic pain patients. However, repeated rTMS sessions can also lead to cumulative and long-lasting effects on motor performance that may reach a therapeutic level [40,47]. This might be considered as an alternative to functional neurosurgery in case of surgical contraindications. Further work should be designed to compare the respective mechanisms of action and therapeutic value of transcranial and epidural cortical stimulation, but both approaches have interesting potential applications in the clinical management of PD patients.

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