Angelo Lavano, Domenico Bosco, Marisa De Rose, Giusy Guzzi,
Giorgio Volpentesta, Sergio Canavero

10 Movement Disorders: Parkinson and Tremor

Parkinson's disease (PD) is a progressive neurological disorder that affects 1% of the population over the age of 65. In PD, two primary sources of dysfunction are identified: a reduction of DA projections from the midbrain to the basal ganglia and from the midbrain to the primary motor cortex (M1). After about 5 years (the "honeymoon period"), L-Dopa (introduced in 1967) and dopaminergic agonists, the mainstays of therapy, lead to dyskinesias or motor fluctuations that can be even worse than the disease itself.

In 1979, Woolsey et al wrote: "*Subthreshold electrical stimulation through implanted electrodes might be used to control marked tremor and strong rigidity in parkinsonian patients*". Twenty years later, Canavero performed the first such surgery in a PD woman (see history in Canavero 2009). Currently, extradural motor cortex stimulation (M1 ICS) represents an alternative neurosurgical treatment for PD with zero disabling morbidity-mortality. It is a valuable and safer option when DBS cannot be employed or patients are unresponsive or do not fulfill DBS inclusion criteria or simply refuse it.

10.1 Literature Review

About 130 patients have been submitted to Motor Cortex Stimulation (M1 ICS) for advanced PD. The published literature include case reports, single-center experiences and the Italian Multicenter Study ([Table 10.1](#)). Almost all studies are unblinded, with two exceptions. Inclusion criteria have been quite homogeneous in all studies: idiopathic PD (PDSBB criteria), at least 5 year-long disease history, advanced stage (UPDRS in off $\geq 40/180$; Hoehn and Yahr ≥ 3 , motor complication fluctuations and disabling dyskinesia), positive response to L-Dopa, DBS not accepted by the patient or contraindicated, patient ability to give informed consent.

M1 ICS achieves a significant and sustained improvement in motor symptoms, with a remarkable effect on axial symptoms, L-dopa induced dyskinesias and quality of life. It must be stressed how the UPDRS III and Hoehn-Yahr scales appear inadequate in assessing the true clinical benefit of M1 ICS. In the only totally negative study, from Toronto (Moro et al 2011), an unsafe subdural approach was elected, with high-frequency, short pulse width stimulation, which is known to be ineffective or deleterious, as highlighted by Canavero et al (2002,2003).

Full clinical benefits observed with M1 ICS are always delayed. Although rigidity and, less so, tremor improve within several minutes of stimulation, the full effect on bradykinesia, gait and axial symptoms grows with time (days to weeks).

Table 10.1: Studies of M1 ICS for PD

Authors/date	Number of patients	Stimulation site	MCS operative technique	Parameters of stimulation	Configuration	Results
Canavero et al. 2000	3	M1 (hand knob)	Unilateral (contralateral to worst clinical side) extradural	2-3.5 V 20-30 Hz 90-180 μ s Continuous	Bipolar (3+/0-), OFF during sleep	Abolition of rigidity and tremor (bilateral); partial improvement of gait, bradykinesia, dysarthria and hypophonia; 50% decrease of UPDRS motor score; 40-80% decrease of LEDD
Canavero et al. 2002						
Canavero et al. 2003						
Verhagen et al. 2006	9	M1(hand knob)	Unilateral extradural (contralateral to worst clinical side)	20-127 Hz 250 μ s (fixed)	-	24 week-long prospective multicenter study. The UPDRS III score OFF medication was 42.13 +/- 13.78 compared to 38.78 +/- 8.08 at baseline.
Benvenuti et al. 2006	1	M1 (knob)	Unilateral Extradural	-	Bipolar (?)	Improvement of 35% on the UPDRS scale: rigidity, dyskinesia and motor fluctuation were reduced significantly as well as standing, gait and motor performance.
Cioni, 2007	7	M1 (hand knob)	Unilateral (contralateral to worst clinical side) extradural in 3 pts; Bilateral extradural in 4 pts	3-4 V 80 Hz 120 μ s continuous	Bipolar 0/3	Prospective study. Follow-up at 1, 3, 6 and 12 months. Five patients showed an improvement during MCS, while 2 patients resulted unresponsive. At 12 months follow-up UPDRS III in "off-med" decreased by 22%, as well as the dosage of L-dopa. Axial symptoms were ameliorated. Effect of unilateral MCS bilateral. After 1 year of unilateral stimulation, 2 patients underwent bilateral MCS that restored the clinical effect.
Cilia et al. 2007	5	M1 (left hand knob)	Unilateral extradural	3.0-4.0 V 40-60 Hz 180-210 μ s	Multiple unipolar in 4/5; bipolar in 1/5	Follow-up performed at 6 months after surgery on and off medication, with stimulator ON, and 2 weeks later with stimulator OFF by the same neurologist in a blinded fashion. Improvement of motor fluctuations(daily OFF time reduction) and of axial symptoms (freezing gait, stooped posture and postural instability) as well as a reduction of dyskinesia in 3 patients. L-dopa dosage reduced (mean) by 16 % and dopamine agonist dosage by 49%. Subjective clinical benefit was reported after variable interval after surgery.

Table 10.1: Studies of M1 ICS for PD

continued

Authors/date	Number of patients	Stimulation site	MCS operative technique	Parameters of stimulation	Configuration	Results
Arle et al. 2008	4	M1 (hand knob)	Unilateral extradural in 1 pt Bilateral extradural in 3 pts	3.2-3.5 V 100-130 Hz 210-240 μ s	Multiple unipolar in 3/5 electrodes; bipolar in 2/5 electrodes (initially all contacts were checked in a monopolar setting at 130 Hz and 210 mcs, with voltage slowly increased to 4 V. Later patient 1 was stimulated at 3.2 A, 240 mcs, 130 Hz; patient 2 at 3.5 A, 210 mcs, 130 Hz; patient 3 at 3.4 A, 210 mcs, 100 Hz. Patient 4 was not detailed)	Prospective study. Benefits seen within the first 6 months in UPDRS III scores (decreased by 60%), tremor was only modestly managed most benefits seen initially lost by the end of 12 months. 1 infection 3 months post implant. Patient M1 (implanted on the left) developed a superficial infection of the extension wire site and required removal of the device. This patient had improvement of about 50% (>75% of day to less than 10% of day) over baseline in dyskinesias and a 30% improvement in the UPDRS III score but significantly regressed when the device was removed (he was the unilaterally implanted patient). After reimplantation of the device line in both dyskinesia reduction and UPDRS III improvement. Overall at 6 months the mean UPDRS III improvement was 46.8% (+/- 24.7%) (this includes the patient M1 at their 6 month time period after re-implant). At 1 year the mean improvement was -14.2% (+/- 66.8%) with one patient asking to have his stimulator kept in the "OFF" state due to no significant improvement. Two patients had a 20-30% (M2 and M3, both implanted bilaterally) reduction in medication requirements at three months, yet patient M3 has started to need more medication at the 6 and 12 month time points. One patient (M5, implanted on the right), however, had a 37% increased medication requirement. One patient had a return of dyskinesias after 3 months (M5); they had initially improved, but then the amplitude of stimulation was reduced and the benefit was lost. Once the patient's stimulation amplitude was increased again, dyskinesias were again better controlled.
Fasano et al. 2008	1 (F/72)	M1 (hand knob)	Bilateral extradural	3-60-130 Hz (benefit at 130Hz only) 120 μ s	Bipolar	Stimulation at 130 Hz improve axial akinesia and walking but benefits gradually disappeared In baseline med-off condition the patient was unable to rise from a chair and to stand without assistance. Consistent axial akinesia and walking amelioration. HMPAO SPECT: increase of rCBF in SMA during stimulation at 130 Hz. After five months, benefit gradually disappeared.

Table 10.1: Studies of M1 ICS for PD

continued

Authors/date	Number of patients	Stimulation site	MCS operative technique	Parameters of stimulation	Configuration	Results
Pagni et al. 2005 (Initial results of Italian Multi-center Study)	16	M1 (hand knob)	Unilateral extradural (contralateral to worst clinical side)	2.5-6 V 25-40 Hz 150-180 μ s	Bipolar	Patients evaluated only in the On-Med state from 4 months to 2.5 years. The improvement was bilateral: global UPDRS decreased by 42-62%, the UPDRS III score decreased by 32-83%, L-dopa dosage decreased by 11-33% in 3 patients and by 70-73% in 2 patients (Turin experience) Very advanced PD, aged 46-81, 15 of which were not eligible for DBS, evaluated at 3-30 months after implantation. Tremor and rigidity in all limbs and akinesia reduced, bilaterally. Standing, gait, motor performance, speech and swallowing improved. Also dyskinesias, motor fluctuations and other side effects of L-dopa administration were improved. Effect of stimulation persistent and not fading over time. Quality of life markedly improved.
Pagni et al. 2008	41	M1 (hand knob)	Unilateral extradural in 33 pts Bilateral extradural in 8 pts	2.5-6.0 V/3-4 V 25-40 Hz/60-80 Hz 150-180 μ s / 90-120 μ s	Bipolar/monopolar	Pts with good response to previous L-dopa treatment. There were 21 male and 20 female, aged 56-81. The study reported only the results of the unilateral stimulation. Follow-up at 1, 3, 6, 12 months and then at least every 6 months. There was no worsening of the total UPDRS score off medication/on stimulation at long term follow-up in each patient. A significant reduction in the off-medication UPDRS III score was observed after stimulation and persisted at long term; improvement was only very moderate in the on-medication state. Improvement in activities of daily living, posture, gait, rising from a chair, balance, bradykinesia. Marked attenuation of levodopa-induced dyskinesia and dystonia. Antiparkinsonian drugs expressed in terms of LEDD showed a trend to reduction when compared to doses used before surgery. Benefits on limbs tremor and rigidity bilateral, more evident in the limbs opposite to the stimulated side and in those patients presenting with lower UPDRS scores. Long term levodopa syndrome symptoms, dyskinesia and painful dystonia reduced in most patients and up to 90% in some of them.
Gutiérrez et al. 2009	6	M1 (hand knob)	Unilateral (contralateral to worst clinical side) extradural	3.0-4.5 V 10-30 Hz 330-450 μ s	All bipolar (3+/0-, except 1: 2+/1-)	Globally, mild daily life activities improvement with a slightly lower levodopa equivalent dose UPDRS part III scores: no significant modification.

continued
Table 10.1: Studies of M1 ICS for PD

Authors/date	Number of patients	Stimulation site	MCS operative technique	Parameters of stimulation	Configuration	Results
Moro et al. 2011	5	Left M1 in 4 pts Right M1 in 1 pt	Unilateral subdural	3.5+/-0.9 V, 114+/-36 Hz, 78+/-27 μ s	Acutely tested mono and bipolar, chronically not specified	Evaluation 3 months after implantation with double-blinded assessment and after 1 year with an open assessment. No changes in the OFF medication/on stimulation motor scores compared with off stimulation. At 1 year no improvement. 1 cortical venous infarct., 3 self-limiting seizures with aggressive trials of stimulation in the period of parameters adjustment
De Rose et al. 2012	10	M1	Unilateral extradural	3.5-4.7 V 40-80 Hz 180 μ s (continuous)	All bipolar (0-/3+)	Single-center prospective observational study. F-up: 36 months (8 pts), 2 died within 24 mos of unrelated causes. Improvement mainly of axial symptoms: UPDRS III items 27-31 off medication: mean percentage of decrease: 25% at 1 month, 30% at 3 months, 20% at 6 months, 22% at 12 months, 26% at 18 months, 24% at 24 months and 28% at 36 months; L-dopa-induced dyskinesia and dystonia: significant reduction of UPDRS IV score up to 18 months : mean percentage of decrease: 29.6% at 6 months, 40.9% at 12 months, 31.8% at 18 months, 15.9% at 24 months and 11.4% at 36 months, quality of life and global condition. Eight patients reported reduced OFF time in clinical fluctuations (UPDRS IV item 39 score from 3 to 1); evident reduction of L-dopa and dopamine agonist dosage: mean percentage of decrease: 39% at 6 months, 38% at 12 months, 33% at 18 months, 37% at 24 months and 29% at 36 months. The benefit on distal tremor, rigidity and bradykinesia bilateral but not significant. with a slight prevalence in the hemibody opposite to the stimulated side. No complications or adverse effects.

Table 10.1: Studies of M1 ICS for PD

Authors/date	Number of patients	Stimulation site	MCS operative technique	Parameters of stimulation	Configuration	Results
Di Giuda et al. 2012	6 (all under 70 years of age)	Right M1 in 5 pts Left M1 in 1 pt	Unilateral (contralateral to worst affected side) extradural	3,0-4,0 V 80 Hz 120 μ s Continuous	All bipolar (cathode) and 3 (anode)	¹²³ I-FP-CIT SPECT preoperatively, 8 and 13 months after MCS. The effect of unilateral M1 ICS was bilateral and clinically evident after a 2-week stimulation. Pts evaluated 8 and 13 months under OFF-MED and ON-STIM conditions: significant improvement in total UPDRS scores (reduced by 22% at 8 months and by 16% at 13 months) and UPDRS part II (improved by 22% at 13 months). Dosage of antiparkinsonian drugs (LEDD) significantly reduced after 8 months, with a tendency towards preoperative values at 13 month evaluation. No significant differences in ¹²³ I-FP-CIT uptake ratios between baseline and follow-up found, except for a progressive reduction in ¹²³ I-FP-CIT uptake ratios in the striatum contralateral to the implant. No further decrease in ¹²³ I-FP-CIT uptake ratios detected in the striatum ipsilateral to the implant. No correlations between changes in ¹²³ I-FP-CIT uptake ratios with disease duration, changes in medication dosage and motor UPDRS scores.
Bentivoglio et al. 2012	9 (initially 11)	M1	Unilateral (contralateral to clinical side) extradural	3,0-5,0 V 80 Hz 120 μ s	All bipolar (distal contacts as cathode and anode)	Single-center prospective study. Assessment: after 1, 3, 6, and 12 months. In the MED-OFF condition, UPDRS motor score at baseline significantly reduced by 14.1%, 23.3%, 19.9% and 13.2% at 1, 3, 6 and 12 months, respectively. The improvement in motor score mostly related to a reduction of the contralateral and axial scores. Significant reduction of the limbs score by 19.3% at 6 months and by 10.0% at 12 months with beneficial effects on bradykinesia of the upper limbs at 3 and 6 months and of the lower limbs at 6 months. As to midline motor function, significant effect for UPDRS III item "arising from chair". Post-op LEDD reduced by 6.3%, 2.5%, 13.5%, 2.5% at 1, 3, 6 and 12 months, respectively. UPDRS II scores of the item "walking" at 3, 6 and 12 months and "FOG" at 6 and 12 months significantly reduced as compared to baseline. MCS also improved the global condition and quality of life. In the MED-ON condition, no significant effect found in any of the explored outcome measurements.

NB all authors implanted a quadripolar paddle electrode, except Verhagen et al in which only the 0 and 3 contacts were available. All electrodes parallel to central sulcus.

There is also a suggestion that M1 ICS may benefit Multiple System Atrophy-Associated Parkinsonism. Canavero et al (2003) improved for 9 months a single patient with extradural, bilateral M1 ICS (continuous stimulation, 22.5V, 90-180 μ s, 25-40Hz), and Kleiner-Fisman et al (2003) reported subjective improvement in 3 out of 5 patients over 6 months.

In all published papers, the surgical technique involved the implantation of a four-contact strip electrode over the hand-knob of M1, extradurally, with one exception (Moro 2011: subdural). The implant was performed through a single burr-hole or two burr-holes drilled in front of the central sulcus under local or general anesthesia or, much less frequently, through a small craniotomy made on the central sulcus under general anesthesia. The subdural implant was performed under local anesthesia with conscious sedation (Moro 2011). In all cases the electrode was placed parallel to the motor strip over the hand knob or the upper limb area. In several cases, the correct position of the electrode was verified neurophysiologically using somatosensory evoked potentials (SSEPs) and/or motor evoked potentials (MEPs).

Surgery has always been performed contralaterally to the most affected side, with the exception of Cilia et al (2007)'s series, in which the dominant (left) hemisphere was elected. In a few patients, the implant was bilateral, but the stimulation was simultaneously on both sides only in two cases. It is known that in early PD one side is more affected, with higher M1 excitability: asymmetric motor involvement is also associated with excessive involuntary mirroring and defective interhemispheric inhibition, both unfavoring the more affected side (Spagnolo et al 2013).

The stimulation parameters differed in the studies. The frequency ranged from 10 to 130 Hz (most commonly 40-80Hz), the pulse duration from 60 to 450 μ s (most commonly 120-240 μ s) and the intensity from 2.5 to 6 V (always subthreshold for movements and sensory feelings). The stimulation was delivered continuously, in almost all cases with bipolar configuration, through the most distal contacts (0-/3+), or, in few cases, with multiple unipolar configurations.

Extradural M1 ICS has proved to be a very benign procedure, in stark contrast to the subdural approach (Moro et al 2011). Local stimulation-induced pain at the site of implantation has been reported.

10.2 DBS vs M1 ICS

Subthalamic (STN) DBS improves rigidity in 63% of patients and bradykinesia in 52% and, when dopaminergic treatment is added concomitantly, 73% and 69% respectively. Decrease in dyskinesia (70% - 90%), reduction of the required equivalent dose of levodopa (mean 55.9%, up to 63%) and reduction in 'off' periods (10%-90%) are reported. Yet, improvements are limited to the cardinal symptoms of PD, with balance (postural instability) and gait (freezing) or non-motor symptoms poorly controlled and limited benefit in activities of daily living. Neuropsychiatric effects (depression, apathy, anxiety, addictions, eating behavior alterations, dementia) have all been correlated to STN DBS (Castrioto et al 2014).

DBS cannot be offered to all PD patients: age over 70 years of age, a poor response to levodopa (less than 40-50% on the Levo-Dopa challenge test), or a score less than 30-40 in the Off-condition on UPDRS III, brain atrophy, dementia, psychiatric and medical co-morbidities represent contraindications to this procedure. Thus, roughly half of all Parkinsonian patients cannot benefit from DBS. DBS has a non-trivial mortality rate (0,4%, up to 1,8%): causes of death include intracranial hemorrhage, pneumonia, pulmonary embolism and suicide (Arle and Shils 2011) (see [Box 10.1](#)). Given the progressive nature of PD and the purely symptomatic effects of DBS, the long-term clinical evolution of these surgical patients currently seems to be associated with a new PD phenotype, mainly characterized by axial motor problems and cognitive impairment (Rodriguez-Oroz et al 2012). In a series (Rizzone et al 2014), at 11 years, DBS was still improving the motor symptoms by only 35.8%, as compared to the preoperative off-state, with an 84.6% improvement of dyskinesias and a 65.8% improvement of motor fluctuations; on the other hand, the UPDRSII-on score worsened by 88.5%, mainly due to advancing poorly levodopa-responsive symptoms.

Intraoperative:

- Hypertension (59%)/ Hypotension (7,9%), Tachycardia (6,2%)/ Bradycardia (18%)
- Venous infarction (caused by the transection or coagulation of large draining veins at the site of the burr hole): 0,9%
- Deep infarcts: case reports but incidence unknown (probably because they remain asymptomatic or are difficult to recognize on the post-operative scans)
- Seizures: 2.4% (0-14%) (intra- or post-operative, usually instigated by cortical irritation at the lead entry site or ischemic\hemorrhagic damage)
- Subdural hemorrhage: <1%
- Intracerebral bleeding: 0,7% - 3,3% per lead, with a permanent morbidity of 0,6-0,8% (increased risk of hemorrhage due to the use of the microelectrode recording, especially with multiple micro-electrodes passes)
- Venous air embolism (DBS is usually performed in a semi-seated position that requires continuous anesthesiological monitoring, since it can occur just after the burr hole placement and can be instigated by accidentally coughing): rare
- Pulmonary embolism: rare

Postoperative:

- Infections: 4-12,2% incidence per patient or 1,5-9,7% risk per lead. Usually *Staphylococcus Aureus* and superficial. Overall 2,8% infection rate, with 1,4% of superficial skin infection. Need for removal: 4,6%. Combined deep infection and erosion rates: 1,5-15,2%.
 - Lead fracture: 2-9,9% per patient or about 1,8% per lead implanted. DBS lead migration: 1,5%-6,3% of patients or approximately 4,4% of leads implanted. Migration from 6 months to 3 years after the initial surgery.
 - Hardware complications (misplaced lead, loss of effect, lack of efficacy, lead fracture, lead migration and infection): 7,8%. 32,9% of patients or 8% per lead-year.
 - STN DBS: impairments in executive functions, verbal fluency and Stroop naming time, dysarthria, paresthesia, blepharospasm; Gpi DBS: visual disturbance, paresthesia, gait and speech difficulties, confusion and depression
 - Increased suicide rate
 - Post-operative confusion, speech difficulties and mental status/cognitive changes
-

Box 10.1: Complications of DBS

The clinical effect of DBS cannot be compared with that of M1 ICS due to different inclusion criteria. DBS is usually contraindicated in those submitted to M1 ICS, because of age or MRI anatomical abnormalities (e.g. cerebral atrophy and vascular lesions). M1 ICS appears to have some advantages over STN DBS: it is more suitable in elderly patients due to minimal surgery-related side effects and lower complications and adverse event rates; verbal fluency is not impaired, axial symptoms and gait disturbances that are poorly responsive to DBS are allayed. Unilateral M1 ICS induces clinical effects bilaterally and it is more cost-effective because it does not require stereotactic equipment.

10.3 rTMS vs M1 ICS

Non-invasive brain stimulation (e.g. repetitive transcranial magnetic stimulation - rTMS, transcranial direct current stimulation - tDCS) can be effective in improving motor symptoms in patients with PD. The analysis of TMS studies has shown that this result is consistent across controlled and uncontrolled trials, but the effect is modest, with a 20% reduction of motor scores at frequencies of 5-25Hz and greater effects with multiple sessions over a longer duration of time (Khedr 2009). Compared to rTMS, M1 ICS guarantees precise stimulation of the target, provides continuous stimulation without interfering with daily activities and reduces the need of repeated treatments as for rTMS. However, rTMS could help select responders for ICS (Canavero and Bonicalzi 2007).

10.4 Mechanism of Action

Several mechanisms of action can be envisioned (Canavero and Bonicalzi 2007, Canavero 2009, Cerasa and Quattrone 2014) (see [chapter 18](#) and [Box 10.2](#)). What is important to remember, though, is that even STN DBS works by alleviating the PD-associated pathological M1 state (Li et al 2014).

In PD, both increased L-Dopa-responsive cortical facilitation (hyperactivity) and concomitant impaired non-L-Dopa-responsive GABA-A inhibition coexist (Ni et al 2013). M1 ICS can up-regulate this defective GABA tone (Canavero 2009). Interestingly, L-Dopa exerts different and opposite effects on cortical excitability within M1 compared to S1, with subtle changes in sensory and motor behavior (Nelson et al 2012). On the other hand, M1 ICS can modulate both M1 and S1 by way of U-fibers.

Several studies posit that synchronized oscillations at multiple frequencies within spatially segregated regions of the M1-basal ganglia circuit relate to distinct components of clinical impairment in PD: the relationship hitherto reported between β activity and bradykinesia-rigidity might be tightly locked with (phase amplitude coupling) or even secondary to effects at both lower and higher γ

frequencies (cross-frequency interactions), with an exaggerated coupling of β phase in the STN and M1 and broad band γ amplitude in M1 specific to PD (Oswal et al 2013). Cortical stimulation may engage these oscillatory patterns (Canavero 2009, Thut and Miniussi 2009).

In M1 ICS the clinical changes are delayed for several days after switching the stimulator ON or OFF or after modifying the parameters of stimulation, whereas they are durable after stopping long-term stimulation (After-Effects). This points to plastic rearrangements induced by M1 ICS (which makes the parameters search stage more labor-intensive than DBS). Transcallosal pathways – and to a minor extent interhemispheric connections at brainstem, thalamic and basal ganglia levels, including a pathway connecting the subthalamic nuclei (Canavero 2009, Groppa et al 2013)- account for the bilateral effects of unilateral stimulation; particularly strong interhemispheric conduction pathways exist between the hand representations of M1s, which explains why the hand area should be targeted for M1 ICS in PD (Canavero 2009, 2011).

Another reason for targeting the hand area is that stimulation involving electrodes overlying the anatomic hand knob has a lower stimulation threshold when compared with stimulations of electrodes overlying M1 outside the hand knob area (2.1m vs 2.8mA) (Kovac et al 2011).

Importantly, Di Giuda et al. (2012) demonstrated that no further DAT (dopamine) level reduction occurred in the striatum ipsilateral to the implant during chronic M1 ICS, suggesting a “neuroprotective” effect.

modulation of the hyperdirect pathway from M1 to STN (see also Baudrexel et al 2011)
 restoration of deficient inhibition (GABAergic interneurons) in M1, abolition of M1 hyperactivity and
 reduction of hyperglutamatergic tone
 reversal of dysfunctional M1 plasticity
 functional restoration of motor maps in M1 and SMA
 interhemispheric compensation
 desynchronization of β (akinetetic) frequency and increase of γ (prokinetic) synchrony between M1
 and striatum

Box 10.2: Possible Mechanisms of Action

10.5 Conclusions

Extradural M1 ICS can relieve all three major symptoms of PD (akinesia, rigidity, tremor) on both sides simultaneously, with zero disabling morbidity-mortality, unlike DBS, although results vary widely. It has a particular and significant effectiveness on axial symptoms, freezing and dyskinesias, whereas DBS appears to have stronger effects on distal symptoms. However the clinical effects of MCS cannot be compared

with those of DBS, due to the different inclusion criteria (age, older in M1 ICS series, MRI anatomical abnormalities,...).

Canavero (2009) suggests that that left MI ECS might be preferable. A fMR study found that in patients with right-sided – but not left-sided- dominant symptoms the brain tries to compensate by employing alternative ipsilateral pathways (Kalmar et al 2011). Also, in right-handers the depth of the CS is greater in the left hemisphere than in the right and the motor hand knob is larger and metabolically more active in the left hemisphere (Caulo et al 2007).

In early stages, maladaptive/compensatory changes take places in M1 and plasticity deteriorates as the symptoms progress (Kojovic et al 2012). Also, older patients –constituting the great majority of patients submitted to MCS- exhibit less distinctive cortical representations and decreased basal interhemispheric inhibition (Bernard and Seidler 2012). These two factors may, in undetermined ways, interfere with M1 ICS and lead to suboptimal results.

PD patients, who very often do not fulfill the inclusion criteria for DBS, may be eligible for M1 ICS. M1 ICS can be performed without the need of general anesthesia, does not require stereotactic frames or microelectrode recording, and virtually eliminates the possibility of intracranial hemorrhage. As opposed to rTMS and its need for repeated treatments, minimally invasive M1 ICS guarantees precise stimulation of the target, along with the possibility of a continuous stimulation. *Subdural MCS is strongly discouraged*. Parameters search should follow the TANG recommendations (Box 10.3): different parameters differentially modulate intracortical and/or interhemispheric processing in M1 and these must be explored as thoroughly as possible.

What emerges clearly is that M1 ICS results cannot be assessed with the same criteria of DBS, given the discrepancy between the UPDRS III and Hoehn-Yahr scales and subjective reports from the patients. M1 ICS effects, unlike DBS, are almost never immediate. Assessment after a change of parameters must be undertaken after about 2-4 weeks due to long after-effects setting in as a result of neuroplastic changes. Moreover, effects, particularly on akinesia, grow over time. After 1-3 months of stimulation, UPDRS scores can be evaluated, after changing parameters, only at -at least- 1 month intervals; at least initially, effects of M1 ICS on motor scores should not be evaluated off medication (Canavero 2009).

Failures of M1 ICS could be put down to individual variations in the organization of MI, i.e. mosaicism, inverted disposition of MI functional areas, wide somatotopic variability of individual distal arm representations, not only between individuals, but also between hemispheres in the same individual (Canavero 2009). Also, state-dependency in brain stimulation (Kundu et al 2014) is even more important in PD where the cognitive state of the patient impacts the course of the illness. Interestingly, in rTMS studies, the shape of the hand knob in M1 determines the physiologic response to coil orientation: the inverted Ω shape responds preferentially to a 45° coil angle, the ϵ shape to a 90° coil angle (Opitz et al 2013): it remains to be seen how the

hand knob shape bears on M1 ICS. Also, the presence of bridging veins may divert part of the electric charge injected.

According to Canavero (2009), new targets are possible, for instance the premotor cortex or the somatosensory cortex SI could be assessed for clinical effects.

According to the model suggested by Zwartjes et al (2012), activation of either the basket cell or pyramidal tract (PT) type axons is involved in the clinical effect of M1 ICS. To selectively target the basket cell axons, either cathodal or bipolar stimulation with the electrode strip placed perpendicular rather than parallel to the gyrus and the cathode overlying M1 seems indicated; selectivity can be increased by using multiple cathodes either adjacent or with an inactive contact in between. PT type axons (hyperdirect pathway) can be selectively targeted with anodal stimulation using electrodes with large contact sizes. Selective stimulation of the PT type axons is reduced when using subdural stimulation and bipolar stimulation with the strip oriented parallel as well as perpendicular to the gyrus: thus, subdural stimulation is discouraged.

Ultimately, the recent proposal of closed-loop cortical stimulation in PD opens new perspectives in this field: modulation, but not suppression, of pathological rhythms (10Hz μ range) might be beneficial, although the causal relationship between M1 activity and PD tremor still remains to be demonstrated (Beuter et al 2014; [Chapter 17](#)).

-Paddle implanted contralateral to side of initial symptoms; also evaluate implant contralateral to less affected side in nonresponders
 -Bipolar stimulation: electrode setting: 0+/3-
 -BLOCK A (4 days)
 60 μ s
 0.5V 10,20,30,40,50, 80, 130 Hz; 1V 10,20,30,40,50, 80, 130 Hz; 2V 10,20,30,40,50, 80, 130 Hz;
 3V 10,20,30,40,50, 80, 130 Hz
 each setting kept 1 hour
 -BLOCK B (4 days)
 180 μ s
 0.5V 10,20,30,40,50, 80, 130 Hz; 1V 10,20,30,40,50, 80, 130 Hz; 2V 10,20,30,40,50, 80, 130 Hz;
 3V 10,20,30,40,50, 80, 130 Hz
 each setting kept 1 hour
 -BLOCK C (4 days)
 450 μ s
 0.5V 10,20,30,40,50, 80, 130 Hz; 1V 10,20,30,40,50, 80, 130 Hz; 2V 10,20,30,40,50, 80, 130 Hz;
 3V 10,20,30,40,50, 80, 130 Hz
 each setting kept 1 hour
 -12 day block repeated with the reverse setting, 0-/3+ (total: 24 days) and then for other settings
 (1-/2+ and 2+/1-...)
 -For definitive stimulation: either continuous or cyclical stimulation (1h On, 1h OFF or the like), with
 switch-off at night

Box 10.3: M1 ICS for PD: Tang Guidelines (Canavero 2009)

References

- Arle JE, Apetauerova D, Zani J, et al. Motor cortex stimulation for Parkinson disease: 12 months follow up in 4 patients. *J Neurosurg* 2008; 109: 133-139
- Arle JE, Shils J. Motor Cortex stimulation for pain and movement disorders. *Neurotherapeutics* 2008; 5:37-49
- Arle JE, Shils J (eds). *Essential neuromodulation*. San Diego: Academic Press, 2011
- Baudrexel S, Witte T, Seifried C, et al. Resting state fMRI reveals increased subthalamic nucleus-motor cortex connectivity in Parkinson's disease. *Neuroimage* 2011;55:1728-38
- Bentivoglio AR, Fasano A, Piano C, et al. Unilateral extradural motor cortex stimulation is safe and improves Parkinson's disease at 1 year. *Neurosurgery* 2012;71:815-25.
- Benvenuti E, Cecchi F, Colombini A, et al. Extradural motor cortex stimulation as a method to treat advanced Parkinson's disease: new perspectives in geriatric medicine. *Aging Clin Exp Res* 2006; 18:347-348
- Bernard JA, Seidler RD. Evidence for motor cortex dedifferentiation in older adults. *Neurobiol Aging*. 2012;33:1890-9
- Beuter A, Lefaucheur JP, Modolo J. Closed-loop cortical neuromodulation in Parkinson's disease: An alternative to deep brain stimulation? *Clin Neurophysiol* 2014; 125:874-885
- Canavero S, Paolotti R. Extradural motor cortex stimulation for advanced Parkinson's disease. *Mov Disord* 2000; 15:2169-171
- Canavero S, Paolotti R, Bonicalzi V, et al. Extradural motor cortex stimulation for advanced Parkinson's disease: report of two cases. *J Neurosurg* 2002; 97 21208-121 1
- Canavero S, Bonicalzi V, Paolotti R, et al. Therapeutic extradural cortical stimulation for movement disorders: a review. *Neurol Res* 2003; 25: 118-122
- Canavero S, Bonicalzi V. Cortical stimulation for parkinsonism. *Arch Neurol* 2004; 61: 606
- Canavero S, Bonicalzi V. Extradural cortical stimulation for movement disorders. In: D Sakas, B Simpson, E Krames, Eds. *Operative Neuromodulation. II Neural Networks Surgery*. Wien: Springer-Verlag, 2007, 223-232
- Canavero S. Invasive cortical stimulation for Parkinson's disease (PD): why, where and how. In: Canavero S (ed) *Textbook of therapeutic cortical stimulation*. New York: Nova Science, 2009, 217-227
- Canavero S Cerebral-Surface. In J Arle and J Shils Eds. *Essential Neuromodulation*, Elsevier, 2011, 19-42.
- Castrioto A, Lhommée E, Moro E, et al. Mood and behavioural effects of subthalamic stimulation in Parkinson's disease. *Lancet Neurol*. 2014;13:287-305.
- Caulo M, Briganti C, Mattei PA, et al. New morphologic variants of the hand motor cortex as seen with MR imaging in a large study population. *AJNR* 2007; 28: 1480-1485
- Cerasa A, Quattrone A. May Hyperdirect Pathway Be a Plausible Neural Substrate for understanding the rTMS-related Effects on PD Patients With Levodopa-induced Dyskinesias? *Brain Stimul* 2014; 7: 488-9
- Cilia R, Landi A, Vergari F, et al. Extradural motor cortex stimulation in Parkinson's disease. *Mov Disord* 2007; 22:111-114
- Cilia R, Marotta G, Landi A, et al. Cerebral activity modulation by extradural motor cortex stimulation in Parkinson's disease: a perfusion SPECT study. *Eur J Neurol* 2008; 15: 22-28
- Cioni B. Motor cortex stimulation for Parkinson's disease. In: D Sakas, B Simpson, E Krames, eds. *Operative Neuromodulation. II Neural Networks Surgery*. Wien: Springer-Verlag, 2007, 233-238
- De Rose M, Guzzi G, Bosco D, et al. Motor cortex stimulation in Parkinson's disease *Neurology research International* 2012;12:502096

- Di Giuda D, Calcagni ML, Totaro M, et al. Chronic motor cortex stimulation in patients with advanced Parkinson's disease and effects on striatal dopaminergic transmission as assessed by ¹²³I-FP-CIT SPECT: a preliminary report Nuclear Medicine Communications 2012; 33:933-940
- Fasano A, Piano C, De Simone C, et al. High frequency extradural motor cortex stimulation dramatically improves axial symptoms in a patient with Parkinson's disease. *Mov Disord* 2008; 23:1916-9
- Groppa S, Muthuraman M, Otto B, et al. Subcortical substrates of TMS induced modulation of the cortico-cortical connectivity. *Brain Stimul*. 2013;6:138-46.
- Gutierrez JC, Seijo FJ, Alvarez Vega M, et al. Therapeutic extradural cortical stimulation for Parkinson's disease: report of six cases and review of the literature. *Clinical Neurology and Neurosurgery* 111 (2009) 703-707
- Kalmar Z, Kovacs N, Perlaki G, et al. Reorganization of motor system in Parkinson's disease. *Eur Neurol* 2011; 66: 220-226
- Khedr EM. Noninvasive stimulation for treatment of movement disorders. In: Canavero S (ed) *Textbook of therapeutic cortical stimulation*. New York: Nova Science, 2009, 183-200
- Kleiner-Fisman G, Fisman DN, Kahn FI, et al. Motor cortical stimulation for parkinsonism in multiple system atrophy. *Arch Neurol* 2003;60:1554-8.
- Kojovic M, Bologna M, Kassavetis P, et al. Functional reorganization of sensorimotor cortex in early Parkinson disease. *Neurology* 2012;78:1441-8.
- Kovac S, Scott CA, Maglajlija V, et al. Extraoperative electrical cortical stimulation: characteristics of motor responses and correlation with precentral gyrus. *J Clin Neurophysiol* 2011;28:618-24
- Kundu B, Johnson JS, Postle BR. Trait-like Differences in Underlying Oscillatory State Predict Individual Differences in the TMS-evoked Response. *Brain Stimul* 2014 (in press)
- Li Q, Qian ZM, Arbutnot GW, Ke Y, Yung WH. Cortical effects of deep brain stimulation: implications for pathogenesis and treatment of Parkinson disease. *JAMA Neurol*. 2014;71:100-3
- Moro E, Schwab JM, Piboolnurak P, et al. Unilateral subdural motor cortex stimulation improves essential tremor but not Parkinson's disease *Brain* 2011; 134(Pt 7):2096-105
- Munno D, Caporale S, Zullo G, et al. Neuropsychological assessment of patients with advanced Parkinson Disease submitted to extradural motor cortex stimulation. *Cog Behav Neurol* 2007; 20: 1-6
- Nelson AJ, Premji A, Rai N, et al. Dopamine alters tactile perception in Parkinson's disease. *Can J Neurol Sci* 2012; 39: 52-57
- Nguyen JP, Pollin B, Fève A, et al. Improvement of action tremor by chronic cortical stimulation. *Mov Disord* 1998; 13:84-88
- Ni Z, Bahl N, Gunraj CA, et al. Increased motor cortical facilitation and decreased inhibition in Parkinson disease. *Neurology*. 2013;80:1746-53
- Opitz A, Legon W, Rowlands A, et al. Physiological observations validate finite element models for estimating subject-specific electric field distributions induced by transcranial magnetic stimulation of the human motor cortex. *Neuroimage* 2013;81:253-64.
- Oswal A, Brown P, Litvak V. Synchronized neural oscillations and the pathophysiology of Parkinson's disease. *Curr Opin Neurol*. 2013;26:662-70.
- Pagni CA, Zeme S, Zenga F, et al. Extradural motor cortex stimulation in advanced Parkinson's disease: the Turin experience. *Neurosurg* 2005; 57 (ONS Suppl 3): ONS-402 ([includes Canavero's cases](#))
- Pagni CA, Altibrandi MG, Bentivoglio A, et al. Extradural motor cortex stimulation (M1 ICS) for Parkinson's disease. History and first results by the study group of the Italian neurosurgical society. *Acta Neurochir* 2005 93:113-119 ([includes Canavero's cases](#))
- Pagni CA, Albanese A, Bentivoglio A, et al. Results by motor cortex stimulation in treatment of focal dystonia, Parkinson's disease and post-ictal spasticity. The experience of the Italian Study Group of the Italian Neurosurgical Society. *Acta Neurochir Suppl*. 2008; 101:13-21

- Rizzone MG, Fasano A, Daniele A, et al. Long-term outcome of subthalamic nucleus DBS in Parkinson's disease: From the advanced phase towards the late stage of the disease? *Parkinsonism Relat Disord* 2014 (in press)
- Rodriguez-Oroz MC, Moro E, Krack P. Long-term outcomes of surgical therapies for Parkinson's disease. *Mov Disord* 2012;27:1718-28.
- Spagnolo F, Coppi E, Chieffo R, et al. Interhemispheric balance in Parkinson's disease: a transcranial magnetic stimulation study. *Brain Stimul* 2013;6:892-7.
- Thut G, Miniussi C. New insights into rhythmic brain activity from TMS-EEG studies. *TICS* 2009; 13: 182-189
- Verhagen Metman L, Pahwa R, Lyons K, et al. Motor cortex stimulation in Parkinson's disease: a pilot study. *Neurology* 2006 (suppl 2) 66: A47
- Woolsey CN, Erickson TC, Gilson WE. Localization in somatic sensory and motor areas of human cerebral cortex as determined by direct recording of evoked potentials and electrical stimulation. *J Neurosurg.* 1979;51:476-506.
- Zwartjes DG, Heida T, Feirabend HK, et al. Motor cortex stimulation for Parkinson's disease: a modelling study. *J Neural Eng.* 2012;9:056005