Acta Neurochir Suppl (2008) 101: 13–21

Printed in Austria

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

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Summary

Extradural motor cortex stimulation has been employed in cases of Parkinson's disease (PD), fixed dystonia (FD) and spastic hemiparesis (SH) following cerebral stroke. Symptoms of PD are improved by EMCS: results were evaluated on the basis of the UPDRS and statistically analysed. In PD EMCS is less efficacious than bilateral subthalamic nucleus (STN) stimulation, but it may be safely employed in patients not eligible for deep brain stimulation (DBS). The most rewarding effect is the improvement, in severely affected patients, of posture and gait. FD, unresponsive to bilateral pallidal stimulation, has been relieved by EDMS. In SH reduction of spasticiy by EMCS allows improvement of the motor function.

Keywords: Extradural motor cortex stimulation; Parkinson's disease; fixed dystonia; spastic hemiparesis; posture and gait disturbances.

Introduction

Woolsey *et al.* in 1979 [43] reported subthreshold stimulation of the sensory-motor cortex blocked tremor and rigidity in Parkinson's disease (PD). Recently it was observed that subthreshold repetitive transcranial magnetic stimulation of the motor cortex (rTMS) might improve, at least temporarily, akinesia, motor performance and others symptoms in PD [7, 20, 22, 32, 36, 37, 39]. Other movement disorders may be improved by rTMS of the motor cortex: writer's cramp [24, 38]; cortical myoclonus-related epileptic activity; tic symptoms in Tourette's syndrome [8]. Lefaucher *et al.* [19] observed that rTMS of the premotor cortex reduced dystonic motor spasm. Hummel *et al.* [14] observed improvement of motor function in the paretic hand in patients with chronic stroke by rTMS. In cases of central pain (CP) due to basal ganglia and brain stem injury extradural motor cortex stimulation (EMCS), proved efficacious in controlling or reducing hemichoreoathetosis, distal resting and action tremor [15–17, 25, 41, 42] and hand dystonia [12, 13] sometime with improvement of the attending hemiparesis. EMCS improves also intentional idiopathic and post-anoxic Myoclonus [12, 13]. EMCS for PD has been employed, for the first time, at the Neurosurgical Clinic of Torino, directed by the senior author (CAP), in 1999. First results have been reported in various papers and lectures [4, 5, 26–30].

Purpose of this paper is to give an overview of the results obtained by EMCS by the Study Group for Movement Disorders of the Italian Neurosurgical Society in: 1. Parkinson's disease, 2. fixed dystonia, 3. hemiparesis in chronic stroke.

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1. Parkinson's disease

Forty-one patients affected by advanced idiopathic PD, who had got a good response to previous L-dopa treatment, were enrolled in this study. There were 21 male and 20 female, aged 56–81 years; mean age 68.76 ± 6.5 yrs. All the patients had a long history of disease (5–22 yrs, mean 13.95 ± 4.97 yrs). They scored III–V on the Hoehn-Yahr scale. The score of the UPDRS off medication was 49–120, mean 91.173 ± 22.189. The patients were either not eligible for or refused (4 cases) deep brain stimulation (DBS). In some patient L-dopa therapy was no more effective, many of them presenting with long term dopa therapy symptoms (dyskinesia, localized dystonia, motor fluctuations etc.). Before implantation patients were submitted to: neurological evaluation (UPDRS off/on), finger tapping, walking time, PDQL (Parkinson disease quality of life scale) psychiatric and neuropsychological evaluation, brain MRI with gadolinium and functional MRI, neurorehabilitative evaluation, EEG, P300, SPECT (99 mTc-ECD; 123I-DATSCAN; 123I-IBZM). Exclusion criteria were: epileptic seizures, psychiatric symptoms (except drug-induced), severe general internal disease, alcohol or drug abuse, severe cognitive deterioration (only one patient with cognitive deterioration was included). Written informed consent was obtained by the patients and/or their relatives or legal representatives.

A quadripolar electrode (Model 3587A; Medtronic, Inc.) with four contacts in line was introduced in the extradural space, over the hand motor area of one hemisphere, usually opposite to the worst clinical side. Eight cases were implanted bilaterally: only the result of the unilateral stimulation will be reported here. The technique for identification of the motor area (including craniometer landmarks, MRI, functional MRI, neuronavigation, evoked sensory potential, motor cortex stimulation) has been described by Cioni [9]. In the first cases the electrode, before definitive implantation of the stimulator, was connected to an external electro-stimulator for a 7–10 days stimulation test; but in the following cases it was connected directly to the implanted stimulator (Kinetra, ITREL II, Medtronic). Stimulation was performed with current values subthreshold for movement, but with different parameters (Table 1) and several setting of the active electrodes by the various members of the study group.

Identification of the best parameters of stimulation is still matter of debate. Benefits were obtained by many combinations of parameters and electrode setting: good results were usually obtained with 2.5–6 Volt, 150–180 μsec, 25–40 Hz, but also with 3–4 Volt, 90–120 μsec, 60–80 Hz. Stimulation was delivered either all over the day and stopped during the night, or during night and day.

Table 1

	Hz	Pulse width (μsec)	Mono- or bipolar	Volt	Side
1	80	120	bipolar	3–6	unilateral and bilateral
2	40–60	180–210	monopolar cath	3–4	unilateral
3	30	120–180	bipolar	2–2.5	unilateral and bilateral
4	60	60–120	bipolar	3–4.3	unilateral
5	25–50	90–180	bipolar	3–6	unilateral
6	25–45	180	bipolar	2–4.5	unilateral

Table 2

	Follow-up					
Months	3	6	12	18	24	36
Case number	41	33	25	11	10	6

Clinical assessment was performed by UPDRS: a) before implantation: baseline evaluation off-medication and on-medication. b) during treatment: at 1, 3, 6, 12 months and then at least every 6 months: on-medication/on-stimulation and off-medication/on-stimulation. (Baseline evaluation off-medication/off-stimulation has not been repeated during the follow-up; a group of cases is now under scrutiny for that). Movie recordings have been taken before and after stimulation. Patients have been followed-up for 3–36 months (Table 2).

Results

General evaluation

Stimulation induced a significant improvement of the Total UPDRS score ($p < 0.050$ Wilcoxon-test), with respect to the baseline value, in the off-medication condition.

In Table 3 the mean value of the UPDRS off-medication before stimulation and during stimulation at 3–36 months is presented.

What is relevant is that there was no worsening of the Total UPDRS score off medication/on stimulation at long term follow-up (24 and 36 months) in each patient.

Motor function. UPDRS section III

Stimulation induced a significant improvement (up to 23.12%, $p < 0.02$) in the motor score with respect to the baseline value in the off-medication condition (Table 4).

Table 3

	UPDRS total off medication						
	Before	3 mos	6 mos	12 mos	18 mos	24 mos	36 mos
Mean	91.73	70.55	76.76	74.63	74.82	81.04	76.49
Standard deviation	22.89	27.14	24.38	21.45	22.07	22.87	23.26
% difference		−23.09	−16.32	−18.64	−18.43	−11.26	−16.70
Wilcoxon text: $p<0.050$		<0.000	<0.020	<0.020	<0.020	<0.020	<0.036

Table 4

	UPDRS section III off medication						
	Before	3 mos	6 mos	12 mos	18 mos	24 mos	36 mos
Mean	49.66	38.18	45.08	43.32	46.89	44.08	40.17
% difference		−23.12	− 9.24	−12.76	−5.58	−9.78	−19.10
Wilcoxon test: p		<0.000	<0.001	<0.020	<0.054	<0.020	<0.032

Table 5

	UPDRS section III on medication						
	Before	3 mos	6 mos	12 mos	18 mos	24 mos	36 mos
Mean	29.64	23.27	24.62	23.48	26.00	27.90	26.50
% difference		−6.37	−5.02	−6.16	−3.64	−1.74	−3.14
Wilcoxon test: p		=0.041	>0.048	=0.054	>0.054	>0.048	>0.062

Table 6

Range of variation of the UPDRS III off med

	12 mos (%)	24 mos (%)	36 mos (%)
Mean	−12.76	−9.78	−19.10
Min.	+15	−3.4	−8.6
Max.	−38.8	−29	−38.7

Table 7

Variation of axial symptoms. UPDRS items 27+28+29

	12 mos (%)	24 mos (%)	36 mos (%)
Mean	−16.26	−13.35	−15.05
Min	+50	0	0
Max	−80	−50	−40

Stimulation reduced also the on-medication scores but this effect reaches statistical significance (Table 5) only at three months follow-up.

Summing up: 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. But it is worth noting (Table 6) that there is a large spectrum of variation between minimal and maximal effect; certain subgroup of patients being well responsive while other not. Reduction of the UPDRS III score reaching a difference of − 38.8% has been observed in some patient and the effect persisted at 36 months follow-up.

Axial symptoms, daily living. UPDRS section III items 27–31

Improvement was observed in activities of daily living, posture, gait, arising from a chair, balance, bradykinesia (and at lesser degree in speech and facial expression) as measured by the UPDRS III, items 27–31 and by the 7 meters walking text. Note (Table 7): for the items 27 + 28 + 29 while the mean reduction is constant up to 36 months ranging −13.35%/−16.26%, at the Wilcoxon Test the variation is significant for the whole series only at 24 months ($p<0.032$).

But in a subgroup of patients, the most severely affected, the maximal reduction is very high, reaching in someone a maximum of −40−80% (Table 7). In those patients, the most severely affected, the improvement of the whole UPDRS III score off medication may be low, but the benefit on those function (UPDRS III 27 + 28 + 29) has a formidable impact not only on the quality of life and patient psychology but also on the assistance needed, so that it is considered by the caregivers to be of relevant significance.

Table 8

UPDRS section IV							
	Before	3 mos	6 mos	12 mos	18 mos	24 mos	36 mos
Mean	8.55	6.27	6.61	5.31		7.4	8.00
% difference		−26.66	−22.69	−37.80		−13.45	−6.45
Wilcoxon test: p		<0.020	<0.020	$=0.000$		<0.032	

Complication of therapy. UPDRS section IV

Stimulation induced significant reduction of the score (Table 8).

Note: there was a marked attenuation of levodopa-induced dyskinesias and dystonia. The effect on therapy complication persisted throughout the 12 months period but it weakened in the following months owing to the fact that in some cases it was necessary to increase the dosage of levodopa. At 36 months the case number is too small for any statistical evaluation.

LEDD variation

Antiparkinsonian drugs (levodopa and dopaminoagonists) expressed in terms of LEDD, showed a trend to reduction when compared to doses used before surgery, but in the whole series reduction was not statistically significant (Table 9).

While in a subgroup of cases reduction was higher than 30%, in other patients no reduction was possible; a third group of patients was needing an increase in therapy up to 35% (see Ref. [2]).

Quality life

At the Parkinson disease quality life scale improvement was significant up to 24 months evaluation; at 36 months the case number is to small to allow statistical evaluation (Table 10).

Table 9

LEDD variation					
	Before	6 mos	12 mos	24 mos	36 mos
Mean	1068	967.6	828.3	905.7	1031
SD±	423.7	399.2	417.9	376.8	387.2

Table 10

Parkinson disease quality life					
Months of stimulation	6	12	18	24	36
Wilcoxon test	<0.022	<0.022	<0.016	<0.016	no ev.

Summing up: Unilateral EMCS alleviates many cardinal symptoms of PD, i.e., akinesia, tremor and rigidity just as bilateral STN DBS does [18, 34]. Three patients out 41 did not get appreciable improvement while some got a marked improvement up to 50% UPDRS score. But the result of stimulation is unpredictable and the benefit on the various symptoms may be very variable; in some case there is a clear improvement of certain symptoms while others present minor or minimal reduction.

The benefit on limbs tremor and rigidity was bilateral, more evident in the limbs opposite to the stimulated side and was more evident in those patients presenting with lower UPDRS scores. But for instance in severely affected cases (Hohen Yahr grades IV–V), who presented satisfactory improvement of axial symptoms, tremor and rigor did not improve markedly. Improvement of motor dexterity too (UPDRS III – items [23, 26]) was bilateral.

Long term dopa syndrome symptoms, dyskinesia and painful dystonia, have been reduced in most of the patients and up to 90% in some of them (see in [2]). One explanation might be that the doses of dopaminergic drugs were reduced (see ahead), but it is possible that this is an effect of the stimulation itself because it was observed before drug reduction. Clinical fluctuations too may be reduced even if not fully abolished.

There is a subgroup of patients severely handicapped owing to difficulty in standing and deambulation which are significantly improved. Some patient (see Ref. [2]) could not walk, not even with assistance and could neither remain seated or rise from a chair; others presented with severe gait disturbance requiring assistance. During EMCS they could sit more comfortably, get up from the chair, stand and walk, even if for short distance without or with minimal assistance. In one case the stimulator broke due to direct injury; in three it switched off for unknown reason: the clinical picture worsened slowly in some week; the UPDRS score rose up to or higher values than before treatment; stimulation having been resumed, after a few days, benefit recurred.

Statistical comparison between benefits by EMCS and by DBS is impossible mainly because nearly all the patients submitted to EMCS were not eligible for DBS owing to age, general conditions, leucoencephalopathy, white matter ischemic foci, agenesia corporis callosi, cerebral atrophy (four eligible for DBS refused intracerebral procedures). By bilateral subthalamic nucleus stimulation an amelioration of motor symptoms at the UPDRS III, with a mean of 42–67%, has been reported at 6–36 months follow-up (see Ref. [34]) patients being evaluated off-medication/off-stimulation at that very moment. Mean values of amelioration after unilateral EMCS are lower and improvement (in spite that in some case it may persist up to 36 months follow-up) seems to decreases in time (see Tables 1–5). That may be due to loss of efficacy of the stimulation but also to worsening of the clinical picture in such a slowly progressive disease as PD: but in this series the evaluation in off-medication/off-stimulation at 24–36 months is lacking. But at least for certain symptoms, such as tremor and rigor, in certain cases the benefits of EMCS seem to parallel those of DBS, and for posture and gait disturbance EMCS seems to be more efficacious.

The most severe adverse events of DBS, intracerebral haemorrhage and infection, are lacking in EMCS (in one case the stimulating apparatus was removed owing to an extracranial infection). But also cognitive deterioration and changes in mood state, worsening of posture, gait and dysphonia (see Refs. [21, 34]), have not been observed. Two patients presented with transitory allucination but in some case improvement of language and speech has been observed by EMCS (see Ref. [2]). Finally 3 out 42 patients (7%) failed to obtain any improvement: in some series of DBS that value reaches 19% (see Ref. [21]).

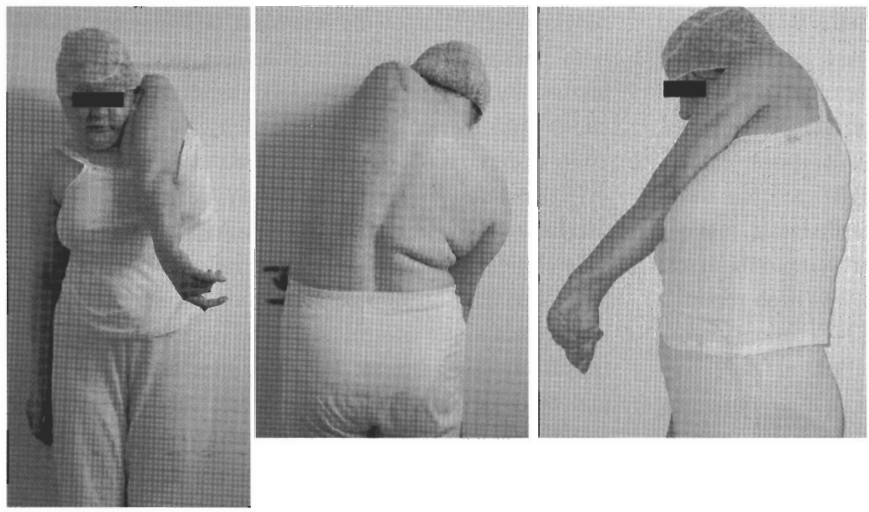
The pathophysiological rationale for EMCS in patients with PD is still not demonstrated. In advanced parkinsonism, the primary motor cortex and the lateral premotor cortex are hyperactive [33]. Cortical excitability studies in PD revealed an increased excitability of the corticospinal projections at rest, either concomitant to, or resulting from a reduced intracortical inhibition. In addition, basal ganglia and cortical neurons have shown a tendency to oscillate and synchronise their activity in the so called antikinetic beta band (13–30 Hz), as demonstrated by recording in humans during functional neurosurgery [3]. EMCS may restore the normal intracortical inhibition acting on small inhibitory interneurons within the motor cortex as postulated for its application in CP; or it may desynchronise the pathological oscillation on the beta band, or it may act through both mechanisms. The clinical changes induced by EMCS are usually delayed (1–4 weeks); therefore the time-consuming processes of synaptic plasticity, long-term potentiation or depression, expression of secondary messengers, or polarisation of brain tissue may be hypothesised as mechanisms of action [9, 33]. Finally, EMCS might provide clinical benefit by acting not only on cortical structures, but also on remote subcortical structures that are involved in motor control (see Refs. [9, 11, 33]). Bi-directional interconnectivity between motor cortical areas and other neural structures, located in the cortex, basal ganglia, or thalamus could explain why EMCS may induce bilateral effects even if delivered unilaterally. An experimental basis for EMCS in Parkinson's disease was given by Drouot *et al.* [11]. In a primate model of Parkinson's disease they observed a marked functional recovery following motor cortex stimulation with improvement of motor symptoms and bradikinesia.

It is actually unknown why EMCS over the motor area of the hand may improve axial symptoms; however, it has to be taken into account that axial symptoms are thought to be related to a dysfunction of cortical areas. Moreover, the topography and the extension of the somatotopic representations within the motor cortex showed modifications in PD patients during the course of the disease: the hand motor map is progressively displaced and enlarged [40].

2. Fixed dystonia

Two cases of idiopathic fixed dystonia, i.e. segmental focal immobile postures which never return to the neutral position, have been treated at the Neurological Institute C. Besta by Broggi and Franzini. Patients were two females; the age of onset of the disease was 32 and 37 years. In one patient dystonia involved neck and upper trunk with latero-collis and scoliosis. In the second one there was elevation and anterorotation of the left shoulder, upper limb hyper-adduction and severe kyphoscoliosis: bilateral Globus Pallidum Internum (GPI) stimulation during 18 months had been a failure [35]. Both presented sympathetic like painful dystrophia. Psychogenic etiology was excluded. Patients were submitted to general anaesthesia: dystonia ceased and recurred before the patient regained consciousness.

The stimulating electrode was implanted on the motor strip over the arm area on the side opposite to the maximal muscular pathological activity. Continuous stimulation was employed. Best parameters were 60 Hz,



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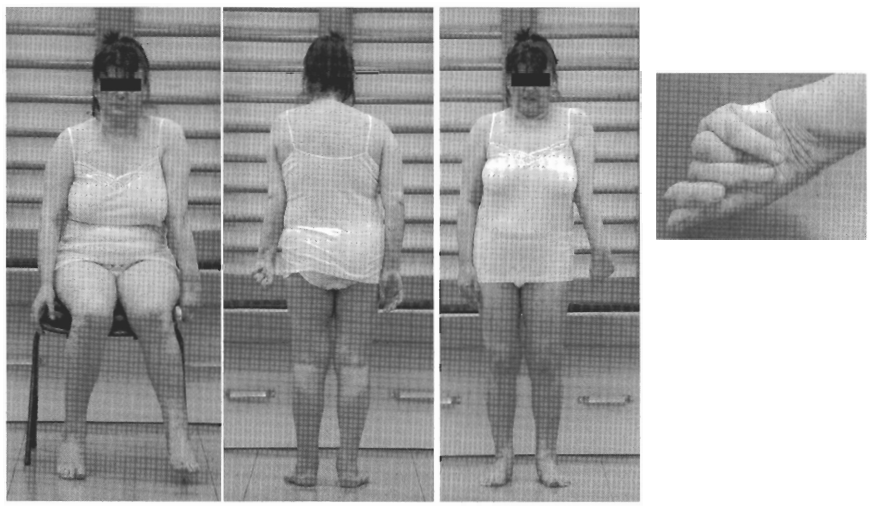

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Fig. 1. Fixed dystonia. (a) After 18 months of Globus Pallidum Internum stimulation (b) After 6 months extradural motor cortex stimulation at 60 Hz, 90 msec, 2.8 V. Note that axial and left limb proximal dystonia is fairly well controlled; no benefit on left hand dystonia

90 μsec, 2.8 Volt. Reduction of the dystonic posture began some weeks after stimulation. There was marked improvement in both the cases: axial dystonic posture and limb proximal dystonia was markedly reduced (while there was no improvement of hand dystonia) (Fig. 1). In both the cases the blind test by off-stimulation was followed in a few days by recurrence of symptoms. Other cases are now treated and under scrutiny. Out of them one is worth noting: in a 8 years old boy affected by neonatal dystonia with fixed posture after some weeks of stimulation there was clear improvement of the speech, trunk dystonia being still unaffected. It seems therefore that as in Parkinson's disease unilateral EMCS allows good control of axial symptoms. Moreover EMCS may be effective in cases in which stimulation of the GPI was ineffective.

3. Post-stroke hemiplegia

The members of the Italian Study Group assessed the effect of EMCS on recovery of the motor function in six cases affected by severe or mild hemiparesis, 1–5 years after stroke (five affected also by CP) (Table 11).

The stimulating paddle was implanted on the hand area of the motor cortex of the stroke-damaged hemisphere. (and in one case also on the unaffected hemisphere). Stimulation parameters were: 50–130 Hz, 2.3–7 V, 190–300 μsec with various electrode setting. Continuous stimulation.

Patients were evaluated neurologically and by the European stroke scale (in one case also Fugl-Meyer scale and Bartex Index was included). Results: marked reduction of the spasticity and improvement of the

Table 11

1	66 yrs ♂	L. Thalamic stroke	Left mild spastic hemiparesis. Hand dystonia. Central pain	70% pain relief; reduction of spasticity; hand and harm movement improved
2	45 yrs ♂	L. Fronto-parietal, thalamic and capsular post-hemorrhagic atrophy, and poroencephalia	Right severe hemiplegia (no motor response to MCS). Aphasia. Hand dystonia. Central pain	50% max. pain relief. No effect on hand dystonia and motor function
3	67 yrs ♀	R. Lenticulo-capsular hemorrhage	Left middle spastic hemiparesis. Central pain	Marked pain reduction. Spasticity reduced. Motor performance mild improvement
4	77 yrs ♂	R. Thalamic stroke	Mild paresis and spasticity left upper limb. Central pain	Mild pain improvement. Marked spastitiey reduction and improvement of hand motor performance
5	57 yrs ♀	R. Postoperative lenticulo capsular ischemia	Mild left spastic hemiparesis and pain	Marked relief from pain and motor improvement
6	42 yrs ♂	L. Internal carotid dissection. Large occipito temporal parietal infarct; total destruction of the internal capsule	Right hand monoplegia, severe right arm paresis. Motor aphasia. Right allodynia	Left EMCS no benefit at the hand and wrist level. Improvement of motor performance at the right arm. Right EMCS did not give any benefit

Nos. 1, 2 Franzini [13]. *Nos. 3–5* Sturiale. *No. 6* Canavero [6].

strength and range of motion of the movements was obtained in the four cases affected by lenticulo-thalamic-capsular lesion. All that allowed better physiotherapy. Note that improvement was long lasting and persisted for days after stimulation ceased.

Two cases deserve emphasis (cases no. 2 and no. 6, Table 11). Both the patients were affected by a severe right hand monoplegia, hand and wrist movements being impossible, and by a severe right-arm paresis due to a large cortico-subcortical infarct or hemorrhage destroying the fronto-parieto-temporo-occipital areas and extensively (no. 2) or completely (no. 6) the internal capsule. In one of them motor cortex stimulation did not give rise to motor response (case no. 2 [13]). In the other one, M1-S1 were not activated on fMRI (case no. 6 [6]). In both the cases there was no benefit. In the last one (Case no. 6) even the stimulation of the contralesional healthy side did not improve the motor status. Improvement of hand dystonia and hemiparesis thus seems possible only if motor area and cortico-spinal pathway is not wholly destroyed. It has been reported that motor cortex stimulation by TMS activates brain plasticity favouring post stroke recovery of motor brain mechanism [23]. May be EMCS of the Motor area M1 of the damaged hemisphere, may give rise to neuroplastic changes with better recruitment of the neural circuits within the motor areas and cortico-spinal pathways of the damaged hemisphere and that may contribute to the recovery of motor function (see [1]). An insight on the mechanisms of action may come from clinical neurophysiology. A rTMS study directly demonstrated that motor cortex stimulation can enhance cortico-spinal excitability in stroke [10]. In a right hemiplegic woman the descending cortico-spinal activity evoked by TMS of the lower limb motor cortex has been recorded from the high dorsal epidural space and simultaneously from the tibialis anterior muscle (TA). A standard TMS pulse at 120% of active motor threshold was used for the right motor cortex and a stimulus intensity corresponding to the max stimulator output for the lesioned hemisphere. They compared the evoked spinal and muscle responses before and after iTBS (intermittent transcranial magnetic theta burst stimulation: 10 bursts of 3 pulses at 50 Hz, 80% of active motor threshold were applied at 5 Hz every 10 sec for a total of 600 pulses). After iTBS, the size and number of cortico-spinal volleys evoked by stimulation of the affected hemisphere was increased, and a small MEP previously absent, was recorded from right TA; whereas there was slight reduction of the amplitudes of cortico-spinal volleys evoked after stimulation of the normal side, and reduction of the amplitudes of left TA MEP. After magnetic iTBS, the increase in cortico-spinal activity evoked by stimulation of the lesioned cortex was associated with a decrease in the excitability of the cortico-spinal output in the opposite hemisphere. This suggest a change in the functional connectivity involving both lesional and non lesional hemispheres.

It seems that to get improvement of the motor status in hemiparetic patients neuroplastic changes must develop in the, at least partially preserved, cortical areas (premotor, motor, parietal) and cortico-spinal pathways of the damaged hemisphere. Up to date motor cortex stimulation has been employed, years after the stroke, in cases of stabilized hemiplegia with moderate or minimal improvement (see also [31]). May be earlier application might facilitate neuroplastic changes and better recruitment of the brain areas involved with better motor function recovery.

Conclusion

Unilateral EMCS seems to be a promising tool improving movement disorders. It is less efficacious than bilateral STN DBS in Parkinson's disease but it may be safely employed in patients not eligible for DBS. The most dramatic effect is the improvement, in severely affected patients, of posture and gait. Also Fixed Dystonia of the trunk, unresponsive to deep bilateral pallidal stimulation may be improved by unilateral EMCS. In cases of severe spastic hemiparesis following cerebral stroke EMCS reducing spasticiy may give an improvement of motor status.

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