ORIGINAL ARTICLE

Effect of Therapy on Motor Cortical Excitability in Parkinson's Disease

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ABSTRACT: ***Objective:*** To assess the impact of the disease stage and therapy on motor cortical excitability in Parkinson's disease (PD). ***Methods:*** Twenty newly diagnosed and medication-free, early stage patients, 20 late stage patients under antiparkinsonian therapy and 20 normal healthy controls were included. Motor threshold (MT), amplitudes of motor evoked potential (MEP), motor evoked potential amplitude/compound muscle action potential amplitude (MEP/CMAP) ratio, central motor conduction time (CMCT) and cortical silent period (CSP) were measured by stimulation of the motor cortex using a 13.5 cm circular coil and recordings from abductor digiti minimi muscle. Following the first study protocol, early stage patients were given therapy and the same protocol was repeated three months later. ***Results:*** Motor threshold was lower; and the MEP/CMAP ratio was higher in early and late stage patients than normals. In early stage patients after proper therapy, the MTs became higher than before therapy, but still remained lower than normals. In late stage patients, the CMCTs were shorter than the early stage patients before therapy and normals, but there was no difference between the early stage patients and normals. In early stage patients after therapy, the CMCT became longer than before therapy and this difference was significant in both late stage patients and normals. Although more prominent in late stage patients, the CSP duration in both PD groups was found shorter than normals. In early stage patients, after therapy, the CSP durations became significantly longer compared with before therapy. ***Conclusion:*** These findings suggest that the motor cortical excitability increases in PD because of the impairment of the corticomotoneuronal inhibitory system.

RÉSUMÉ: Effet du traitement sur l'excitabilité motrice corticale dans la maladie de Parkinson. ***Objectif :*** Nous avons évalué l'impact du stade de la maladie et du traitement sur l'excitabilité motrice corticale dans la maladie de Parkinson (MP). ***Méthodes :*** Vingt patients dont le diagnostic était récent, qui étaient au début de la maladie et qui ne prenaient pas de médicament, ainsi que 20 patients à un stade avancé de la maladie et qui prenaient des médicaments antiparkinsoniens et 20 sujets témoins en bonne santé ont été inclus dans l'étude. Le seuil moteur (SM), les amplitudes des potentiels évoqués moteurs (PÉM), le ratio amplitude des potentiels évoqués moteurs/amplitude des potentiels d'action musculaire composés (PÉM/PAMC), le temps de conduction motrice centrale (TCMC) et la période de silence cortical (PSC) ont été mesurés par stimulation du cortex moteur au moyen d'une bobine circulaire de 13,5 cm et enregistrement au niveau du muscle abducteur du petit doigt. Après avoir effectué une première fois cette évaluation, les patients qui étaient au début de la maladie ont reçu un traitement et le même protocole a été répété trois mois plus tard. ***Résultats :*** Le SM était plus bas et le ratio PÉM/PAMC était plus élevé chez les patients au début et en phase tardive de la maladie que chez les sujets normaux. Chez les patients en phase précoce de la maladie, le SM a augmenté après un traitement adéquat, mais il est demeuré en deça de celui des sujets normaux. En phase avancée de la maladie, les TCMC étaient plus courts que chez les patients en phase précoce avant traitement et que chez les sujets normaux, mais il n'y avait pas de différence entre les patients en phase précoce et les sujets normaux. Le TCMC s'est allongé chez les patients en phase précoce après traitement par rapport à ce qu'il était avant traitement et cette différence était significative tant chez les patients en phase avancée que chez les sujets normaux. Bien que ce soit plus marqué chez les patients en phase avancée, la durée de la PSC chez les deux groupes de patients parkinsoniens était plus courte que chez les sujets normaux. Chez les patients en phase précoce de la maladie, après traitement, la durée de la PSC a augmenté significativement par rapport à ce qu'elle était avant traitement. ***Conclusion :*** Ces observations sont compatibles avec une augmentation de l'excitabilité motrice corticale dans la MP par suite d'une atteinte du système inhibiteur corticomotoneuronal.

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Parkinson's disease (PD) is a neurodegenerative disorder that is characterized by degeneration of dopaminergic neurons in the substantia nigra pars compacta and degeneration of nigrostriatal pathways.[1-4] Since basal ganglia outputs through the thalamo-cortical pathways play an important role in motor cortex function, alterations in their functions as seen in PD lead to changes in motor cortex excitability.[1,2,5,6] Therefore, transcranial magnetic stimulation (TMS) can be used to investigate the alterations in motor cortex function noninvasively.[1,2,6-12] In the literature, there are some studies evaluating motor cortex functions in PD patients. In those studies, the influence of the stage of the disease on motor cortical excitability was not evaluated and they were done while patients were on antiparkinsonian therapy. The main aim of this study was to

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assess the impact of the stage of the disease and the effect of the therapy on motor cortex excitability in PD. We studied the motor threshold (MT), the amplitudes and the latencies of motor evoked potentials (MEP), the central motor conduction time (CMCT) and the cortical silent period (CSP) in three separate groups consisted of PD patients in early- and late stages of the disease as well as normal controls. After the study protocol, antiparkinsonian therapy was started in early stage patients and the same parameters were also evaluated three months later in order to assess if antiparkinsonian therapy has an influence on the motor cortex excitability changes in PD.

Methods

Subjects

Prior to the study, all selected PD patients underwent a comprehensive neurological examination. The Unified Parkinson's Disease Rating Scale (UPDRS) scores and stages were recorded.[13,14] Patients having prominent tremor and dyskinesia were excluded.

The first study group (Group 1) consisted of 20 newly diagnosed PD patients (8 Female (F), 12 Male (M); mean age ±SD: 67.5±5.5; range: 55-74) who were not given any therapy yet. Duration of the disease ranged from five months to six years (mean±SD: 2.2±1.6 years). According to Hoehn and Yahr's (H&Y) classification, seven patients were in stage I, ten patients in stage II and three patients in stage III. The second group (Group 2) consisted of another 20 PD patients gathered from our PD outpatient clinic (9 F, 11 M; mean age±SD: 64.3±11.6; range: 42-80). In this group, the patients were taking antiparkinsonian therapy and duration of the disease ranged from 4 to 13 years (mean±SD: 8.8±2.5). Considering H&Y classification, six patients were in stage III, 11 in stage IV and three in stage V. Total UPDRS scores ranged from 10 to 88 (mean±SD: 39.6±19.9) in Group 1 and from 60 to 123 (mean±SD: 92.2±16.5) in Group 2. Unified Parkinson's Disease Rating Scale motor examination scores ranged from 8 to 48 (mean±SD: 25.8±12.3) in Group 1 and from 41 to 74 (mean±SD: 54.9±10.1) in Group 2. "Activities of daily living" scores ranged between 1-33 (mean±SD: 10.7±7.5) in Group 1 and 16-42 (mean±SD: 30.5±7.2) in Group 2. The control group (Group 3) consisted of 20 healthy volunteers (8 F, 12 M) with a mean age of 63.1±11.1 years (range: 46-76). Following the first study protocol, Group 1 patients were given antiparkinsonian therapy and the same protocol was repeated after a three month period of proper therapy. The anti-parkinsonian medications taken by Group 1 and Group 2 PD patients are shown on Table 1. After therapy, total UPDRS scores ranged from 3 to 47 (mean±SD: 21.0±12.4); UPDRS motor examination scores were between 1-33 (mean±SD: 10.7±7.54); and activities of daily living scores ranged between 0-18 (mean±SD: 6.0±4.92) of Group 1. Due to ethical considerations, the antiparkinsonian therapy of PD patients in Group 2 were continued as before, and proper therapy was started for each patient in Group 1.

The study was reviewed and approved by local ethical committee. A written, informed consent form was collected from all subjects included in the study.

Table 1: The antiparkinsonian medications taken by Group 1 and Group 2 PD patients

	Group 1	Group 2
L-DOPA	1	(-)
DA	2	(-)
L-DOPA + DA	10	2
L-DOPA + COMT inh	1	5
L-DOPA + DA + COMTinh	3	4
L-DOPA + DA + Ach	3	1
L-DOPA + Ach	(-)	2
L-DOPA + COMT inh + Ach	(-)	3
L-DOPA + DA + COMT inh + Ach	(-)	1
L-DOPA + DA + Amantadine	(-)	1
DA + MAO inh	(-)	1

DA: Dopamine agonist; COMT inh : Cathecol-O-methyl transferase inhibitor; Ach: Anticholinergic; MAO inh: Mono amine oxidase inhibitor

Experimental Procedures and Recordings

Subjects were seated in a semi-darkened, silent room. Motor evoked potential (MEP) responses were recorded from right- and left abductor digiti minimi (ADM) muscle. The active electrode was placed on the muscle belly and the reference on the fifth metacarpophalangeal joint. Magnetic stimulation was given with Magstim200 stimulator using a 135 mm circular coil. The left hemisphere was stimulated and responses were recorded from right ADM muscle and vice versa. The direction of the current in the coil was clockwise to stimulate the right hemisphere, and counterclockwise for the left. Motor evoked potential responses were acquired with a Medelec Saphire 4ME device. Initially, the ulnar nerve was stimulated at the wrist on both sides using electrical stimulator and the amplitude of the resulting compound muscle action potential (CMAP) was measured. The MT, MEP and CMCT studies were done while the subjects were at rest. To ensure that the muscle was fully relaxed, EMG level was displayed on an oscilloscope. In order to maintain muscle relaxation; the subjects were given audio-visual feedback. Motor threshold was defined as the stimulus intensity at which a peak-to-peak MEP amplitude of 50 μV was obtained in at least five of ten consecutive trials. For MEP studies, we used 120% of the motor threshold as stimulus intensity. The response with shortest latency and highest amplitude obtained during seven consecutive stimuli on both sides at rest was considered as MEP. In order to avoid possible amplitude differences between sides due to asymmetrical positioning of the electrodes, MEP/CMAP ratio was calculated. The magnetic coil was applied over the spinous process of the seventh cervical vertebra at maximal stimulator output when the subject was in a sitting position with a slight degree of neck flexion. Central motor conduction time was calculated by subtracting the latency of cervical response from the latency of cortical MEP response.

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Cortical silent period was studied by stimulating the left- and right motor cortex along with recordings from the contralateral ADM muscle during slight contraction of approximately 30% maximum voluntary contraction as determined by audio-visual feed-back. Stimulus intensity was 120% of the motor threshold. A series of five stimuli was given and the shortest CSP value was selected for evaluation. We measured duration of the CSP from the end of the MEP to the return of continous EMG activity.

Statistics

Statistical evaluation of the MEP results of the three groups was done with analysis of variance (ANOVA) with post-hoc Bonferroni test. Student's-t test was used for intergroup comparisons. The paired t-test was used to compare the MEP results for Group 1 between before and after antiparkinsonian therapy. Correlations between MEP results and Hoehn-Yahr scale and UPDRS motor scores of PD patients were made Pearson correlation test. P values <0.01 were considered to indicate significance. For correlation analysis, p values <0.01 were considered to indicate a strong- and p values <0.05 a weak correlation.

Results

There was no significant difference between the mean age of study groups (p= 0,35).

The total UPDRS scores (both before- and after therapy) of Group 1 were significantly lower than those of Group 2 (p<0.001; p<0.001, respectively). In Group 1, both the total and subgroup UPDRS scores (motor- and activities of daily living scores) following therapy became significantly lower than those before therapy (p<0.001; p<0.001, respectively).

Comparison of the MEP values before antiparkinsonian therapy in Group 1 (early stage PD patients) with those of Group 2 (late stage PD patients) and Group 3 (normal controls)

ANOVA analyis revealed a significant difference in the MT values, cortical MEP amplitudes, MEP/CMAP ratios, CMCT and CSP durations between the three groups. (F=712.2; p<0.001; F=38.6; p<0.001; F=63.2; p<0.001; F=39.1; p<0.001; F=223.7; p<0.001, respectively). Post-hoc analysis showed that the MT values of both Group 1 (before antiparkinsonian therapy) and Group 2 were significantly lower than normal controls(p<0.001; p<0.001, respectively). The MT values of Group 2 were also significantly lower than Group 1 (p<0.001). The cortical MEP amplitudes and the MEP/CMAP ratio of both PD groups were significantly higher than controls (p<0.001; p<0.001, respectively). In late stage patients, CMCT was shorter than controls (p<0.001) No difference was found between Group 1 and controls (p=0.587). Compared between Group 2 and Group 3, CMCT was significantly shorter in Group 2 (p<0.001). The CSP duration of both PD groups was shorter than normals (p<0.001; p<0.001, respectively). Similarly, the CSP duration in late stage PD patients appeared significantly shorter than in Group 1 PD patients (p<0.001) (Table 2).

Comparison of the MEP values "after antiparkinsonian therapy " in Group 1 with those of Group 2 (advanced stage PD patients) and normal controls

After the therapy; in group 1, ANOVA analysis demonstrated a significant difference of the MT values, cortical MEP amplitudes, MEP/CMAP ratios, CMCT and CSP durations between the three groups (F=762.7; p<0.001; F=34.7; p<0.001; F=59.7; p<0.001; F=76.6; p<0.001; F=248.4; p<0.001, respectively). The MT in the "early stage" patients became higher after the therapy but still remained lower than controls (p<0.001). Comparing the data observed in all groups, Group 2 patients had lowest MT values . The cortical MEP amplitude and the MEP/CMAP ratio in Group 1 after antiparkinsonian therapy and Group 2 was found to be higher than controls (p<0.001;p<0.001 and p<0.001; p<0.001, respectively). After therapy Group 1 patients had significantly longer CMCT than Group 2 patients and controls (p<0.001;p<0.001, respectively). Although after therapy CSP durations of Group 1 have became longer, they still remained shorter compared with the controls (p=0.002). Moreover CSP was significantly longer than those of Group 2 patients (p<0.001) (Table 3).

Comparison of the MEP values of Group 1 (early stage) PD patients before and after antiparkinsonian therapy

The cortical MEP amplitude and the MEP/CMAP ratio before- and after antiparkinsonian therapy in Group 1 did not

Table 2: MEP results of early stage PD patients before antiparkinsonian therapy (Group 1), late stage PD patients (Group 2) and normals (Group 3)

Before Therapy	Group 1	Group 2	Group 3	F	P
MT (%)	24.3±2.2	20.7±2.2	37.5±1.9	712.2	<0.001
MEP amp (μV)	3.6±1.0	3.1±0.7	2.1±0.3	38.6	<0.001
MEP/CMAP	0.41±0.1	0.36±0.0	0.23±0.0	63.2	<0.001
CMCT (msec)	8.7±1.0	7.6±0.3	8.6±0.4	39.1	<0.001
CSP (msec)	109.3±31.4	79.5±20.5	194.5±22.4	223.7	<0.001

MT: Motor threshold; MEP amp : Cortical MEP amplitude; MEP/CMAP : MEP amplitude/ compound muscle action potential amplitude; CMCT: Central motor conduction time; CSP: Cortical silent period

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Table 3: MEP results of early stage PD patients after antiparkinsonian therapy (Group 1), late stage PD patients (Group 2) and normals (Group 3)

After Therapy	Group 1	Group 2	Group 3	F	P
MT (%)	31.6±1.7	20.7±2.2	37.5±1.9	762.7	<0.001
MEP amp (μV)	3.5±1.1	3.1±0.7	2.1±0.3	34.7	<0.001
MEP/CMAP	0.40±0.1	0.36±0.0	0.23±0.0	59.7	<0.001
CMCT (msec)	9.5±1.1	7.6±0.3	8.6±0.4	76.6	<0.001
CSP (msec)	175.1±30.1	79.5±20.5	194.5±22.4	248.4	<0.001

MT: Motor threshold; MEP amp : Cortical MEP amplitude; MEP/CMAP : MEP amplitude/ compound muscle action potential amplitude; CMCT: Central motor conduction time; CSP: Cortical silent period

show any significant difference (p=0.7; p=0.14, respectively). On the other hand, significantly prolonged CSP and CMCT durations as well as higher MT values were observed after antiparkinsonian therapy in Group 1 patients (p<0.001; p<0.001; p<0.001, respectively) (Figure 1, 2, 3).

Correlations

Before the antiparkinsonian therapy of Group 1, the MT, CMCT and CSP showed strong correlation with the UPDRS total and motor scores and H&Y classification. After the therapy, there was a strong correlation with the MT, CMCT, CSP and UPDRS motor scores and H&Y classification; CMCT had a strong and CSP had a weak correlation with UPDRS total scores; and there was no correlation between the MT and UPDRS total scores (Table 4; Figure 4).

Discussion

Using TMS to study MEP and CSP is a noninvasive method to evaluate the motor cortical excitability in PD and other neurological diseases. In the literature, MEP studies have been performed for PD patients; but in the majority of those studies, patients were under antiparkinsonian therapy and therapy had been stopped before TMS studies.[1,6,14-20] In this study, we investigated the motor cortex excitability in newly diagnosed early stage PD patients who had not yet been treated. After three months of proper antiparkinsonian therapy administration, we repeated the same study protocol for evaluating the response to the therapy and for understanding whether the TMS studies reflect electrophysiological changes consistent with clinical improvement. Moreover, previous studies did not evaluate the influences of the stage of PD on motor cortex excitability. In our study, for evaluating the influences of the stage of PD, we

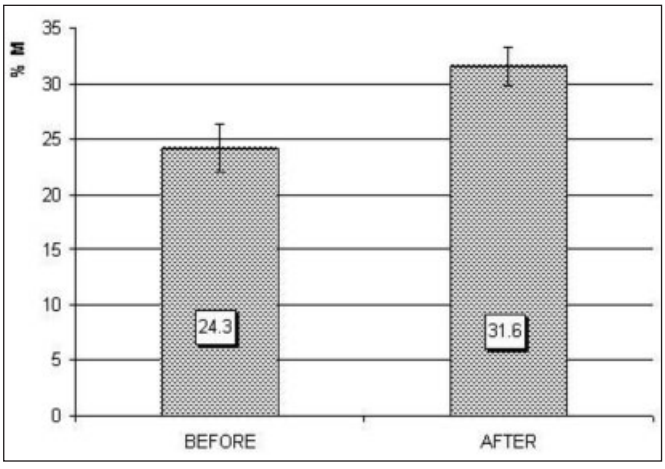

Figure 1: *MT values of Group 1 PD patients before and after antiparkinsonian therapy*

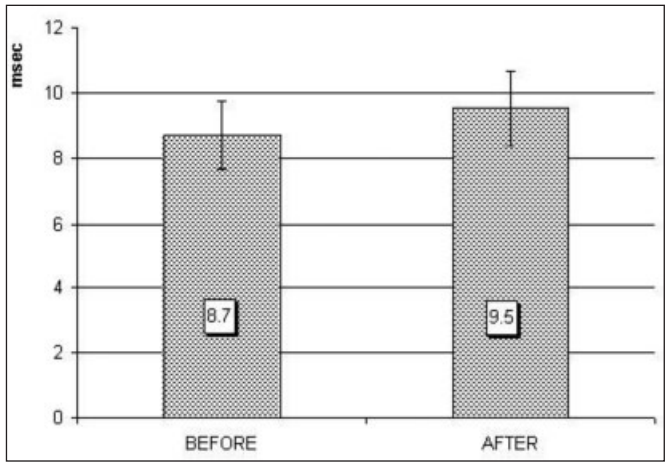

Figure 2: *CMCT values of Group 1 PD patients before and after antiparkinsonian therapy*

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Table 4: Pearson's correlation test values (r) between MEP results and UPDRS scores and Hoehn-Yahr's classification

	UPDRS motor scores	UPDRS total scores	H&Y stage
Before therapy			
MT	-0.69*	-0.73*	-0.65*
CMCT	-0.49*	-0.48*	-0.44*
CSP	-0.58*	-0.63*	-0.51*
After therapy			
MT	-0.93*	-0.13	-0.75*
CMCT	-0.73*	-0.60*	-0.61*
CSP	-0.89*	-0.31†	-0.72*

*p<0.01; †p<0.05

compared both early and late stage PD patients with each other and normal controls.

Motor evoked potentials

The results of the MEP studies of PD patients are controversial and these different results are interpreted in a variety of ways by the authors. Cantello et al found that the MT was lower on the rigid side than that on the contralateral side or than normals. On the other hand, MEP amplitudes of the rigid side were higher than those of controls during rest or slight tonic contraction of the target muscle but CMCT was not different from the normals.[15] Priori et al's study showed that the MT, MEP amplitude and CMCT was not different in PD patients from normals before and after L-Dopa therapy.[1] Similarly, in another three studies, Uozomi et al, Valls-Sole et al and Valzania et al observed that the MT and MEP amplitudes were not different in normals and PD patients.[16-18] Ridding et al also reported that the MT was normal in PD patients but they didn't mention anything about MEP amplitudes.[6] Lou et al studied PD patients in the off state having taken the last dose of antiparkinsonian therapy at least 12 hours before the study and they found that the MT was lower than those of controls before and after L-Dopa therapy, and these results were similar to Cantello's study. In these patients, before L-Dopa, the absolute MEP amplitudes were higher than those of normals during the baseline, exercise and recovery periods; after L-Dopa the MEP amplitudes reduced. The authors reported that corticomotorneuron excitability was increased in PD patients before, during and after fatiguing excercise and L-Dopa normalized this excitability.[19] Paired transcranial magnetic stimulation in Strafella et al's study demonstrated less intracortical inhibition in PD patients as compared to controls. L-Dopa therapy restored this inhibition for 12 months, whereas the restorative effect on intracortical inhibition of pergolide was progressively deteriorated after a period of six months. The MT values, however, did not change in both medication groups over 12 months. The authors explained the deterioration of pergolide's effect over time by development of tolerance or down-regulation of dopamine reseptors.[20] By using paired transcranial magnetic stimulation, Frasson et al compared corticobasal degeneration (CBD) and PD patients with each other and controls. They observed that the MT was higher in CBD patients than in PD patients and control subjects, but there was no difference between PD patients and controls.[21] Chen et al investigated the effects of deep brain stimulation of the internal globus pallidus (GPi) in PD patients. They found that the MT in PD patients did not differ from

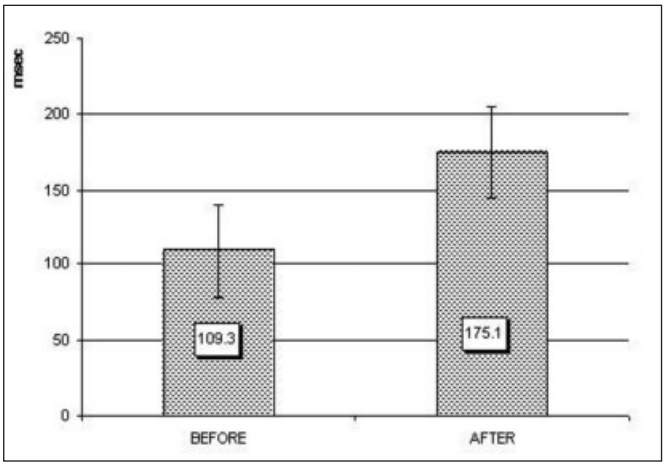

Figure 3: *CSP values of Group 1 PD patients before and after antiparkinsonian therapy*

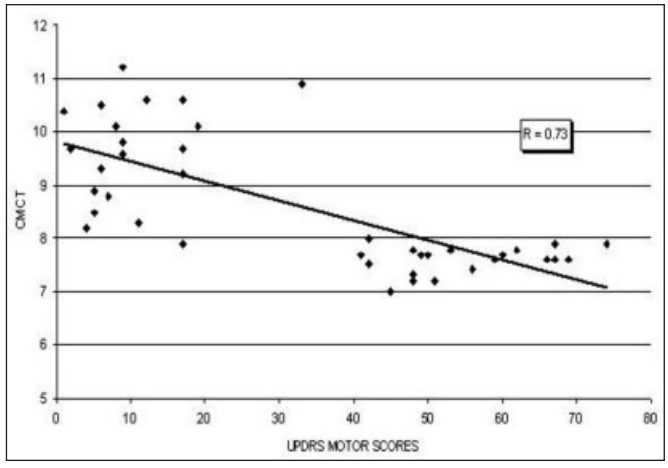

Figure 4: *Correlations between UPDRS motor scores and CMCT*

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controls but the MEP amplitudes were higher in patients with PD than in normal subjects both during on- and off conditions of the GPi stimulator. They suggested that these findings were similar to the Vall's Sole et al's study and could represent an enhancement of cortical or spinal excitability in PD.[22]

We observed that the MT was lower; and the MEP amplitude and the MEP/CMAP ratio was higher in both the early and late PD patients than those of normals. These findings were similar to the Cantello et al's and Lou et al's studies.[15,19] As the subjects in our study were only given audio-visual feedback to maintain a steady muscle relaxation and no quantitative measure of the degree of background EMG activity was performed, we were unable to eliminate subtle background activity in PD patients due to rigidity. Therefore, it can be postulated that our results can partly be explained by this reason. On the other hand, in our early stage patients after proper antiparkinsonian therapy, the MT became higher than before the therapy but it was still lower than that of normals. This finding suggests that the disease itself is more responsible from electrophysiological changes rather than subtle background activity alone. Moreover, in the late stage PD patients, the MT was also lower than the early stage PD patients and these results indicated that the stage of the disease might have an effect on MT.

In previous studies, CMCT was found to be normal in PD patients. This finding was considered by the authors as the CMCT might reveal information about the output of the neural elements of the primary motor cortex and not about the state of the intracortical neural networks.[1,15,23] A recently published study by De Rosa et al showed longer CMCT values in PD patients with parkin mutations, and they suggested that these results might be related to a loss or dysfunction of fast-propagating corticospinal neurons.[24] In another study, Guekht et al demonstrated that the MEP amplitude and MEP duration didn't change but the CMCT decreased in early stage and tremor predominant PD patients. According to Guekht et al, these results might suggest the higher compensational capacity in the cortical and spinal interneurons, but early hyperexcitability of glutamergic central motor pathways in the early period of PD. They found that in akinetic form early stage patients, the MEP amplitude increased asymmetrically and the CMCT was shortened and they suggested that those results had been related to different mechanisms leading to akinesia and bradykinesia.[25] Similarly, in our study we found CMCTs were shorter in late stage patients than early stage patients before therapy and normals. After antiparkinsonian therapy, CMCT became longer in early stage patients and was found to be longer than both normals and late stage patients. Besides short CMCT durations; we also found low MTs, high MEP amplitudes and short CSP durations. All of these findings may be representing hyper-excitability of the cortical motor neurons in PD patients. We suggest that the CMCT might be a valuable tool especially in early stage and medication-free PD patients to demonstrate the response to antiparkinsonian therapy objectively, but it needs to be re-evaluated on further studies.

Cortical silent period

The silent period is defined as temporary decreasing of EMG activity during muscle contraction and it can be obtained by peripheral and cortical stimulation. Transcranial magnetic stimulation evoked CSP evaluates cortical inhibitory systems and it has been used to investigate the motor cortex excitability of PD patients in many studies.[1,9,11,12,15,26] Cantello et al found that the CSP was shorter and the peripheral silent period was longer on the rigid side in PD patients than those of contralateral side and normals.[15] Similarly, Priori et al demonstrated that the CSP was shorter in PD patients than that of normals and after L-Dopa therapy, the CSP became longer than before therapy.[1] After overnight withdrawal antiparkinsonian therapy, Ridding et al showed that the CSP was shorter in PD patients than that of normals and became longer than normals after antiparkinsonian therapy, but these differences were not significant. However, the CSP was significantly prolonged after antiparkinsonian therapy compared with after overnight withdrawal therapy. The authors also found that at short (1-5 ms) interstimulus intervals, corticocortical inhibition decreased in PD patients relative to their controls which improved after L-Dopa intake and they reported that there might be abnormalities of motor cortical inhibitory mechanism in PD patients that were not readily detected using threshold or silent period measurements alone.[6] Berardelli et al demonstrated that the CSP was shorter in PD patients than that of normals but this difference was not significant; using paired stimuli with long (100-250 ms) interstimulus intervals, test response was significantly more inhibited in PD patients compared with normals. The authors also observed that these changes could be partly improved after dopaminergic therapy and they thought that there was a prolonged activity in intracortical inhibitory circuits and because of the response to the antiparkinsonian therapy, pathogenesis of this phenomenon was most probably at basal ganglia levels.[27] Valzania et al also found that the CSP was shorter in PD patients than in normal subjects and they suggested that it could be related to the loss of inhibitory outputs of neurons of the basal ganglia on the motor areas of the cerebral cortex.[18] After stereotactic pallidotomy (PAL) Young et al, demonstrated that the CSP duration was increased in PD patients at stimulus intensities of 200% of MT, compared with before PAL and they proposed that PAL improves the dysfunction of the cortical motor inhibitory circuits in PD patients.[2] With GPi stimulation, Chen et al detected that the CSP durations were significantly decreased in PD patients than those of normals and off condition of the GPi stimulator, but they found that GPi stimulation didn't change corticospinal excitability or intracortical inhibiton and facilitation; and asserted that the decrease of the CSP duration might be related to antidyskinetic and L-Dopa blocking effects of GPi stimulation.[22] Siebner et al indicated that CSP duration increased after 15 trains which lasted 30s with an intertrain interval of 10s trains of subthreshold 5 Hz repetetive TMS (rTMS) over the primary motor hand area in PD patients. In healthy subjects, the CSP didn't change compared to those before and after rTMS. The authors suggested that 5-Hz rTMS had modulatory effects on cortical excitability in PD patients and might be a candidate mechanism that mediates beneficial effect of rTMS on bradykinesia in PD patients.[26]

Our results were similar to the previous studies indicating that the CSP was shorter in PD patients than controls. But these studies didn't consider the stage of the disease and most of them have been performed on patients already under anti-parkinsonian therapy. We evaluated the changes of the motor cortex

excitability in both early- and late stage PD patients as well as in early stage patients taking no antiparkinsonian therapy at the beginning of the study. After a three month period of proper therapy we repeated the same study protocol and our results showed that the prolongation of the CSP duration might be an indicator of the response to the dopaminergic therapy and could be used to follow-up the response of the antiparkinsonian therapy. We found that although more prominent in late stage PD patients, the CSP duration in both PD groups was shorter than normals. In early stage patients, after antiparkinsonian therapy, the CSP duration became significantly longer compared with that before antiparkinsonian therapy. These results may indicate that the disinhibition of corticomotoneuronal pathways are more prominent of the late stage of the disease.

In summary, our results showed that the MT was lower and CMCT and CSP was shorter in PD patients compared with controls, and these changes were more prominent in late stage patients. After starting antiparkinsonian therapy, the MT was increased and the duration of the CMCT and CSP was prolonged in early PD patients. These findings suggest that motor cortex excitability in PD patients increases as a result of the impairment of the corticomotoneuronal inhibitory system, and anti-parkinsonian therapy partly restores the changes of motor cortical excitability.

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