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# Interhemispheric Balance in Parkinson's Disease: A Transcranial Magnetic Stimulation Study

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ABSTRACT

*Background:* Parkinson's disease (PD) is characterized by various changes in motor excitability.
*Objective:* To examine through Transcranial Magnetic Stimulation (TMS) cortical excitability, specifically addressing interhemispheric connections in PD.
*Methods:* Nineteen PD patients with a predominant involvement of the left hemibody (7 females, age 61.7 years,) and 13 controls (6 females, age 61.5 years) entered the study. Patients were subdivided into two groups (early and advanced) according to the time from PD diagnosis. Participants underwent evaluation of Resting Motor Threshold (RMT) and ipsilateral Silent Period (iSP), induced by supra-threshold TMS on the ipsilateral-M1, measured as suppression of voluntary EMG activity. Mirror Movements (MM) were EMG-recorded and scored, in three upper limb muscles, during unilateral voluntary hand movement. Patients were studied at baseline (OFF drug) and after acute levodopa challenge (ON).
*Results:* PD patients showed a general reduction in RMT vs controls ($P < 0.01$ for right and left hemisphere) in both drug conditions. Early PD had a significantly lower RMT over the right vs the left hemisphere ($P = 0.027$); this difference was no longer significant after levodopa. In early PD patients, MM were mainly observed in the right arm during voluntary activation of the left, more affected side both in OFF ($P = 0.033$) and in ON ($P = 0.046$). In PD, RMT of the left, less affected M1 was significantly correlated with the right lateralized motor score ($P = 0.011$; Spearman's coefficient $= -0.585$), as well as with disease duration. In PD patients, a shorter ($P = 0.039$) and smaller ($P = 0.037$) iSP was detected when the stimulus was applied to the worse M1 (right) compared with the contralateral side. This asymmetry was significant only OFF drug. In the PD group iSP-duration from the right, less affected APB was negatively correlated with the MM recorded from the same side during the voluntary movement of the worse side (Spearman's coefficient $= -0.498$; $P = 0.035$).
*Conclusions:* Increased cortical motor excitability in PD, consistent with previous findings, is more evident in the worse hemisphere, particularly in early PD. Asymmetric motor involvement is also associated with excessive involuntary mirroring and defective interhemispheric inhibition, both unfavoring the more affected side. Altogether, these findings suggest that asymmetric motor involvement in PD, particularly in the earlier phases of the disease, affects the interhemispheric balance of cortical excitability, movement lateralization and transcallosal inhibition.


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Movement lateralization and selectivity require the restriction of motor output to the voluntarily activated motor cortex [1,2] in order to inhibit the spreading of activation to the contralateral hemisphere [3]. This process undergoes maturation, as suggested by the characteristic developmental pattern exhibited by Mirror Movements (MM) [4], involuntary movements occurring in homologous contralateral muscles [1]. MM re-emerge in several acquired neurological disorders, such as Parkinson's disease (PD) [5,6]. In untreated patients with early and asymmetric PD, MM are mainly observed in the less affected side during a voluntary motor task performed by the contralateral limb [5].

Transcranial magnetic stimulation (TMS) is a safe, non invasive method to investigate the basis of cross-interactions between hemispheres. Focal TMS of one motor cortex may suppress ongoing voluntary EMG activity also in the ipsilateral hand muscles, leading to a short-lasting disruption of the voluntary motor output, known as ipsilateral Silent Period (iSP) [7–10]. The implication of the corpus callosum in iSP-production has become obvious after noticing the absence of iSP in patients with agenesis of the corpus callosum [11]. iSP is in fact thought to be the result of an inter-hemispheric inhibitory transfer mediated by callosal fibers [10].

To specifically address interhemispheric interactions in PD, as well as to further clarify cortical excitability changes during this condition, we examined a group of PD patients with a left more severe clinical involvement, divided on the basis of their disease stage. We compared the results with a matched control group. Finally, we studied patients ON and OFF levodopa to determine excitability changes induced by treatment.

## Patients and methods

### *Patients*

Nineteen non-demented patients suffering from idiopathic PD according to the UK Parkinson's Disease Society Brain Bank clinical criteria [12] were enrolled in this study.

Inclusion criteria were:

i) age $< 80$ years;
ii) worse motor symptoms and PD onset on their left hemibody (WS), compared with the contralateral side (BS);
iii) ability to provide oral and written informed consent.

Patients were excluded if they had neurological or psychiatric disorders other than PD; personal or familiar history of seizures; recent head trauma; presence of metal implants (including hearing prostheses, pacemaker, neurostimulators). Clinical and demographic characteristics of patients are shown in Table 1. Patients were staged according to the modified Hoehn and Yahr scale [13] to further divide them into two groups, also according to the time since the onset of PD symptoms:

- Early PD (ePD; $n = 10$), with a recent PD diagnosis (H&Y $\leq 2.0$; less than 5 years from onset of symptoms);
- Advanced PD (aPD; n = 9), in a later phase of the disease (H&Y $\geq 2.5$; more than 5 years from onset).

The severity of motor impairment was also scored using the Unified Parkinson's Disease Rating Scale (UPDRS) part III (motor section assessment) [14]; a lateralized score was also obtained (sum of UPDRS III items: 20–26 for each side; range 0–36) [15].

Patients were studied on two separate occasions:

1) OFF medication, after overnight withdrawal of dopaminergic drugs;
2) ON medication, about 1 h after the administration of a levodopa load (dosage of 3 mg/kg).

**Table 1**
Demographic and clinical characteristics of PD patients and controls.

| | Gender (M:F) | Age (y) | Disease duration (y) | H&Y | UPDRS III OFF | UPDRS III ON |
|---|---|---|---|---|---|---|
| ePD | 5:5 | 58.3 ± 9.9 | 2.7 ± 1.3 | 1.8 ± 0.2 | 22.2 ± 7.2 | 12.0 ± 5.5 |
| aPD | 7:2 | 63.6 ± 5.0 | 11.3 ± 4.6 | 2.8 ± 0.4 | 37.9 ± 6.9 | 20.1 ± 5.5 |
| Controls | 7:6 | 61.5 ± 4.5 | | | | |

ePD = early Parkinson's disease; aPD = advanced Parkinson's disease; H&Y = Hoehn and Yahr scale; UPDRS = Unified Parkinson's Disease Rating Scale; OFF = without antiparkinsonian drugs; ON = 1 h after a levodopa load (3 mg/Kg). Data are shown as mean ± SD.

Thirteen volunteers of similar age and sex distribution acted as normal controls (Table 1). All patients and controls were right-handed according to the Edinburgh handedness scale [16]. All participants signed a written informed consent prior to protocol initiation. This study was approved by our institutional ethics committee.

### *Transcranial magnetic stimulation*

Corticomotor excitability using TMS was assessed in controls and in PD patients, before and after levodopa. EMG was recorded through surface electrodes from the left and right abductor pollicis brevis (APB), abductor digiti minimi (ADM) and extensor carpi radialis (ECR) muscles. The EMG signals were then bandpass filtered at 30–1000 Hz. Impedances were kept below 5 kΩ. The amplified analog outputs were digitized at 2 kHz and stored on a PC for off-line analysis. The TMS coil was applied using a figure-of-8 coil connected to a Magstim 200 stimulator (The Magstim Company, Whitland, UK).

Cortical excitability was tested in the fully relaxed APB. The optimal coil position that elicited the largest Motor-Evoked Potentials (MEPs) with the steepest slope was marked on the scalp (Hot Spot). At this site, Resting Motor Threshold (RMT) was determined on each side.

- *Resting Motor Threshold (RMT)* was recorded for each hemisphere as previously described [17]. Threshold intensities were expressed as a percentage of maximum stimulator output.
- *iSP* determination was obtained in each hemisphere with the coil on the hot spot, at the 90% of the maximum stimulator output, asking the patient to perform a maximal voluntary contraction of the APB muscle against an investigator. Fifteen TMS stimuli were delivered during isometric contraction for each APB, in order to obtain a reliable iSP. We stimulated both hemispheres sequentially in patients and controls, in a random order.

iSP parameters were assessed in the final trace obtained from averaging the 15 single rectified EMG traces from each trial. The *iSP-Onset* was defined as the point at which EMG activity became constantly (minimum duration 10 ms) below the mean EMG activity preceding the TMS pulse (baseline EMG). The *iSP-Offset* was defined as the first point after iSP-onset at which the level of EMG activity regained the baseline EMG. The *iSP-Duration* was defined as the difference between iSP-offset and iSP-onset, and was expressed in ms. In order to reduce inter-subject variability related to the degree of pre-stimulus contraction, we calculated iSP-amount (expressed in mV) as follow: [(EMG amplitude−iSP amplitude)/EMG amplitude*100]. Baseline EMG activity was measured between −60 ms and −10 ms pre-stimulus.

iSP-amount and -duration were used to calculate iSP-area (expressed in mV/s) using the following formula: (iSP-amount* iSP-duration).

*Mirror movement recording*

We assessed the presence of MM by asking the subject to perform a voluntary phasic ("brief and brisk") abduction of the thumb in response to a verbal "go" command, for ten trials at inter-trial interval of 4 s. EMG was recorded bilaterally and the occurrence of MM in the opposite muscles was inspected off-line. For each trial, the single rectified EMG traces were averaged. The same procedure was applied bilaterally to ADM and ECR muscles both in OFF and ON conditions. If EMG average showed an involuntary activity in the contralateral homologous muscle MM was considered positive (MM score = 1). Every tested upper limb muscle could obtain a 0 or 1 score according to the EMG absence or presence of MM; for each upper limb the total MM score could then range between 0 and 3.

*Statistical analysis*

Statistical analysis was performed using software SPSS (version 17.0, SPSS Inc., Chicago; IL, USA). After verifying the normal distribution with the Kolmogorov–Smirnov Test, non-parametric tests were used. The significance level was set at $P \leq 0.05$ for all analyses. For between-group comparisons (PD vs controls and ePD vs aPD), a Mann–Whitney test was utilized. For within-group statistics, differences between side (left vs right; WS vs BS) and drug (ON and OFF) were investigated with non-parametric repeated measures ANOVA (Friedman test). If a significant main effect was found, Wilcoxon tests were performed for post-hoc comparisons. Correlations between neurophysiologic and clinical variables were tested using the Spearman rho coefficient.

## Results

*Clinical features*

For both ePD and aPD, levodopa administration induced a consistent improvement in motor performance, with a significant reduction of the left side UPDRS score (ePD: from 10.7 ± 3.3 to 5.4 ± 2.1, $P = 0.008$; aPD: from 13.8 ± 2.8 to 8.1 ± 3.3, $P = 0.007$), of the right side UPDRS (4.3 ± 2.4 in OFF and 2.2 ± 1.9 in ON for ePD, $P = 0.01$; 9.6 ± 3.1 and 4.9 ± 2 in OFF and ON respectively for aPD, $P = 0.007$) and of the total motor score (from 22.2 ± 7.2 to 12 ± 5.5 for ePD and from 37.9 ± 6.9 to 20.1 ± 5.5 for aPD; $P = 0.008$ for both groups).

*Mirror movements*

The between-group analysis, performed in OFF as well as in ON condition, did not show significant differences in MM frequency between PD and controls, also considering early and late subgroups. Within each subgroup, the side-to-side analysis of MM revealed that in ePD MM were more frequent in the right arm during voluntary movement of the left (more affected) side both in OFF ($P = 0.033$) as well as in ON ($P = 0.046$). Controls and aPD showed, instead, a symmetrical frequency of MM. No intra-side differences were identified between OFF and ON in the two PD subgroups.

*Resting motor threshold*

RMT was significantly higher in PD vs healthy subjects (Fig. 1) both the left and right hemispheres showed a lower RMT than controls, in OFF (L-hem: 45.6 ± 11.2 vs 59.6 ± 13.7 in PD and controls respectively, $P = 0.01$; R-hem: 41 ± 6.5 vs 55.8 ± 13.7 in PD and controls respectively, $P = 0.001$) as well as in ON (in PD: L-hem: 42.9 ± 9.3 and R-hem: 40.2 ± 7.3; $P = 0.002$ and $P = 0.005$ respectively vs controls).

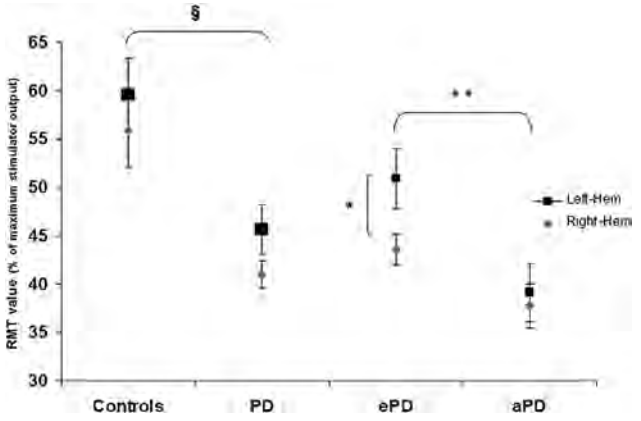


**Figure 1.** RMT in controls and in PD patients, OFF drug. PD display higher excitability than controls (§$P < 0.01$ for both hemispheres). The RMT of the left M1 was significantly higher in early PD (ePD) group vs the opposite M1 (*$P = 0.027$, **$P = 0.025$, Wilcoxon test).

Further analysis was performed examining ePD and aPD subgroups (Fig. 1). No significant difference was observed in the right (i.e., worse) hemisphere while the RMT of the left hemisphere resulted higher for the ePD group in OFF ($P = 0.025$) as well as in ON ($P = 0.014$). In ePD the left RMT was not significantly different compared with the same hemisphere of controls.

No significant interhemispheric difference in RMT was detected for both aPD and controls. On the contrary, in ePD a significant effect of side was detected (chi-square = 9.2; $P = 0.026$); the Right M1 (i.e., worse hemisphere) showed a lower RMT than the contralateral M1 ($P = 0.027$) OFF drug. After L-Dopa this asymmetry in ePD cortical excitability disappeared. The direct comparison between OFF and ON did not reveal a significant effect of drug.

*Interhemispheric inhibition – ipsilateral Silent Period (iSP)*

Compared with controls, PD OFF drug disclosed a significant increase of iSP-duration ($U = -1.96$; $P = 0.05$), as well as iSP-area ($U = -2.4$; $P = 0.016$) for the left hand (iSP-area: $U = 2.9$; $P = 0.08$) (Table 2). However, iSP comparison between PD and controls is burdened by the group difference in RMT [18]. In PD OFF drug, a smaller iSP-area and a shorter iSP-duration to the right (less affected) vs the left side was found (iSP-area: 2250.2 ± 950.1 for the right hand vs 3746.9 ± 2834.8 for the left hand; $P = 0.039$; iSP-duration: 39.4 ± 11 vs 44.5 ± 10.7 for the right- and left-APB respectively; $P = 0.037$, Fig. 2).

No significant difference in iSP parameters was found between ePD and aPD groups. After levodopa, the interhemispheric difference seen in the whole PD group OFF drug was no longer significant (iSP-area: 2809 ± 2542 for the left-APB vs 1897.2 ± 1097.1 for the right-APB, $P = 0.07$; iSP-duration: 45.4 ± 13.7 vs 40.4 ± 10.9, $P = 0.098$). However, considering separately the ePD group, a difference in iSP-duration was still detectable ON drug (35.1 ± 5.3 for the Right-APB vs 40.9 ± 9.5 for Left-APB; $P = 0.036$) between WS and BS. No significant differences emerged in the direct comparison between OFF and ON in iSP parameters.

*Correlations*

In the PD group *iSP-duration* from the right hand (BS) correlated with the MM recorded from the same side (during the voluntary

**Table 2**
iSP-duration and area in controls and PD patients, OFF drug, according to the stimulated hemisphere/recording side.

| | Controls | | | PD | | | *P*-value (R Contr-R PD) | *P*-value (L Contr-L PD |
|---|---|---|---|---|---|---|---|---|
| | Right | Left | *P*-value (R-L) | Right | Left | *P*-value (R-L) | | |
| iSP-duration | 34.4 ± 10.9 | 37.9 ± 6.3 | n.s. | 39.4 ± 10.9 | 44.5 ± 11 | 0.037 | n.s | 0.05 |
| iSP-area | 1582 ± 730.2 | 1798.4 ± 625.2 | n.s. | 2250.2 ± 950.1 | 3746.9 ± 2834.8 | 0.039 | n.s. | 0.016 |

*P*-value (R-L): interhemispheric comparison within each group; *P*-value (R Contr-R PD) and *P*-value (L Contr-L PD): post-hoc group comparison within the same side (right and left respectively). *U* values in the text. Data are shown as mean ± SD.

movement of the WS in OFF; Spearman $\rho = -0.498$, $P = 0.035$; Fig. 3); this was also true when ePD and aPD were separately considered ($\rho = -0.694$, $P = 0.038$ in the former; $\rho = -0.730$, $P = 0.002$ in the latter).

The RMT of the left M1 (less affected hemisphere) of PD patients significantly correlated with the lateralized motor score of the right, less affected side ($P = 0.011$; $\rho = -0.585$, Fig. 4); for the worse PD side this trend did not reach significance. Consistently, a similar correlation between Left RMT and disease duration was found ($\rho = -0.487$, $P = 0.04$), as well as with total motor UPDRS ($\rho = -0.491$, $P = 0.038$).

PD patients disclosed a negative correlation between the H&Y stage in their basal (OFF) condition and the RMT of both motor cortices; the correlation was particularly evident for the right (more affected) hemisphere ($\rho = -0.503$, $P = 0.033$). Interestingly, the *iSP-area* recorded from WS showed a positive correlation with UPDRS in the same hemibody ($\rho = 0.552$, $P = 0.018$).

Finally, in ePD MM recorded from the BS during voluntary movement of the worse side were significantly correlated with the difference in RMT between the two motor cortices ($P = 0.039$; $\rho = -0.692$).

## Discussion

In early PD, a defective movement lateralization exists [5,6,18] and a motor overflow across the midline takes place, accounting for precocious and asymmetrical MM. This represented the first step to address the interhemispheric connections in PD, a particularly underreported issue.

Although the classical model of basal ganglia functioning suggests an hypoactive M1 in PD [19], the dopaminergic deficit of the deep gray structures probably acts leading to an expansion of motor maps and an increased motor cortex excitability [20,21]. In the healthy brain, active and passive reserves provide additional resources when task difficulty increases [22]. During a motor task, PD subjects first recruit the normal network and then, differently from controls, they switch to a different compensatory network, increasing the activity in the bilateral M1 and cerebellum, together with bilateral prefrontal cortex [23].

In the present study, the excitability in PD patients was in general higher than that of controls. In patients with earlier PD, increased excitability involved only the more affected hemisphere, leading to interhemispheric unbalance and thus reverting the physiologic loss of dominance-associated asymmetry occurring with aging [24]. In this subgroup, the dominant and less affected hemisphere did not differ from controls.

In patients with longer disease duration (i.e., more severe functional impairment) RMT lowers instead of increasing as during physiological aging and both hemispheres display abnormal increased excitability, paradoxically rebalancing the exaggerated asymmetry observed in early PD.

In the present study the close relationship between cortical excitability and motor involvement in PD is emphasized by the correlation between motor score and contralateral RMT. This finding was confined to the less affected right PD side. It is possible that for the worse side a ceiling effect toward low RMT values had made any further MEP facilitation unappreciable. However, RMT over the worse M1 correlated with total UPDRS, disease duration as well as H&Y stage, suggesting a link between excitability of the hemisphere with predominant PD manifestations and the natural history of the disease itself.

An important issue concerns the functional significance of an increased cortical motor excitability associated with the severity of the disease. Other authors have hypothesized that overactive motor cortical output at rest could be related to rigidity or tremor [20], however in our study no significant changes in excitability were detected in ON, when both rigidity and tremor are deeply improved

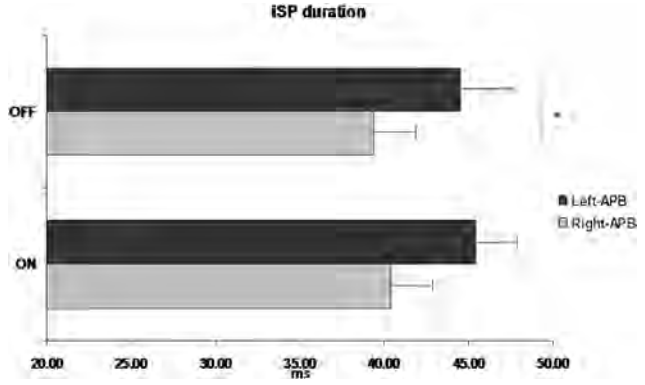


**Figure 2.** iSP-duration in APB of PD patients, OFF drug. The iSP is shorter in the right, less affected hand vs the left (*$P = 0.037$, Wilcoxon test), e.g., less inhibition is obtained when applying TMS to the worse vs the better M1.

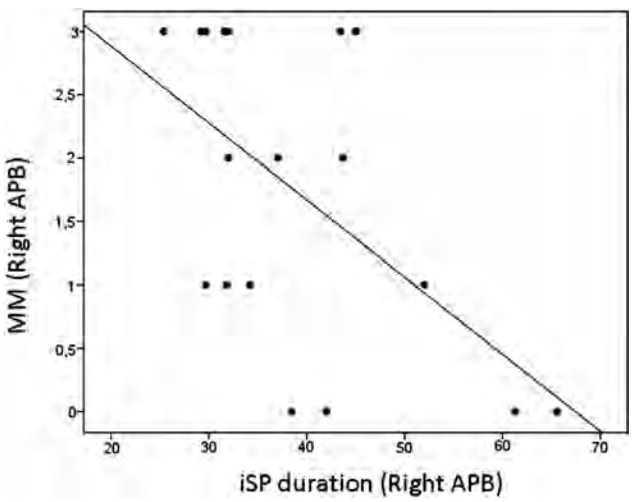


**Figure 3.** Correlation between iSP-duration over the left (more affected) side in PD, OFF drug, and MM score (number of muscles among APB, ADM and ECR) occurring in the right (less affected) arm during voluntary abduction of the left thumb (Spearman $\rho = -0.498$; $P = 0.035$). The linear trend is represented.

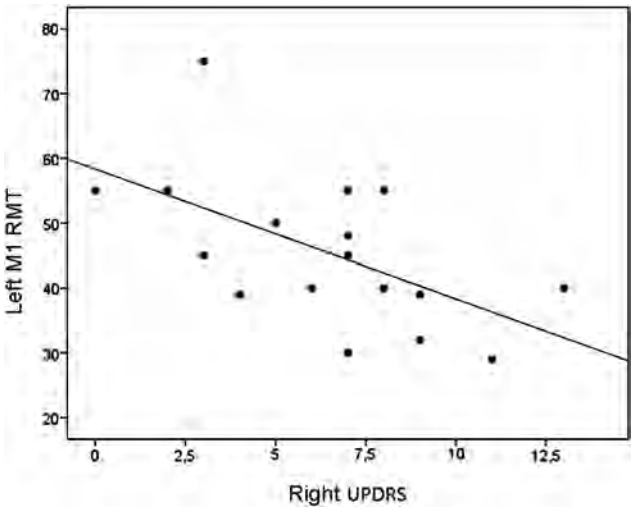


**Figure 4.** Correlation, in PD OFF drug, between Resting Motor Threshold (RMT) in the left (less affected) M1 and lateralized right UPDRS motor score (Spearman $\rho = -0.585$; $P = 0.011$). The linear trend is represented.

by levodopa, vs OFF condition. M1 hyperactivity at rest could then possibly represent a functional compensatory reserve in PD, enabling the motor system to recruit a maximized neuronal pool to counteract dysfunctional striato-frontal motor circuit. A counterpart of this hyperactivity, especially when it is asymmetrical like in early PD, could be the motor overflow across the midline and the consequent impairment in movement selectivity. In advanced PD, the apparent interhemispheric rebalancing of cortical excitability, although associated with extension of hyperexcitability also to the less involved hemisphere, corresponds to a reduction in motor overflow, i.e., of MM. Another possibility is that the RMT lowering in PD is the expression of dysfunctional intracortical inhibitory systems, consistently with the findings of reduced intracortical inhibition reported using double-pulse TMS in PD [25].

iSP represents a negative TMS phenomenon allowing to assess interhemispheric inhibition. The method we used for iSP determination does not allow to assess the influence of RTM changes in determining the increased iSP-area and -duration we found in PD vs controls, predominantly when the less affected (left) hemisphere was stimulated. In fact, iSP parameters are influenced by stimulation intensity and motor threshold [18]. Further studies are needed to better explore this relationship in PD, as few previous studies have addressed this issue [18,26]. Even though at present it is not entirely clear which of the two hemispheres is mainly responsible for iSP, previous studies [27] suggested that iSP modulation takes place in the stimulated M1. The functional significance of iSP seems to be directly linked to mechanisms responsible for lateralization of voluntary movements, supporting the evidence that the M1 contralateral to a voluntary movement contributes to the inhibition of unwanted involuntary activity in the opposite M1 [27]. This is probably one of the mechanisms implicated in motor overflow in PD as well, with iSP recorded from the BS (i.e., stimulus applied to the right, worse M1) shorter and smaller than that recorded from the contralateral hand (i.e., stimulus applied to the left M1, less involved). The weaker iSP recorded from the right hand could then be interpreted as a reduced ability of the worse M1 to adequately inhibit the opposite motor cortex.

Although with methodological differences, the hand showing mirror involuntary activation (MM side) has been previously reported to show less increase in iSP-area in PD compared with the non-MM side and to controls, suggesting that at higher levels of contraction transcallosal inhibition on the MM side is reduced compared with the non-MM side [18]. The latter report is consistent with our findings and could partially explain the pathophysiology of motor overflow in PD: in the same way as the suprathreshold TMS pulse used for iSP determination, the voluntary motor drive from the more affected M1, not controlled by the PD inhibitory intracortical circuits [25], is associated with insufficient inactivation of the contralateral M1, generating motor overflow. In this respect, the higher excitability of the more affected M1 could favor the overflow itself, especially in the earlier phases of the disease when a clear asymmetry in M1 excitability exists. To further support this hypothesis in our study MM are mainly expression of the early, asymmetrical phase of the disease, with a natural tendency to disappear during its progression and the more symmetrical motor involvement.

A discrepancy appears between the effects of levodopa on the examined neurophysiologic parameters and on MM and the clinical improvement after its administration. The lack of MM changes from the "off" to the "on" assessment, consistently with previous reports [5] is probably due to a non specific action of the drug itself on the mentioned cortical processes involved in motor overflow. Namely, after L-dopa administration the asymmetry observed in early PD in RMT disappears. Importantly, the RMT did not significantly change as a function of 'ON'/'OFF' states [28,29], supporting the hypothesis that a true increase in M1 excitability takes place in PD, only modestly, or slowly, influenced by dopamine. On the contrary, the disappearance of RMT asymmetry found in early PD after acute levodopa challenge, was not related to a normalized excitability of the worse, hyperexcitable side, but instead to a mild, non significant increase in excitability over the less affected hemisphere. Our iSP results after levodopa paralleled RMT findings: despite no net effect of the drug was observed on iSP parameters (OFF vs ON), under levodopa no more asymmetry between WS and BS iSP could be appreciated. Thus, levodopa seems to act by rebalancing the asymmetry in cortical excitability and interhemispheric inhibition between the more and the less affected hemispheres.

Asymmetric MMs in early PD, may be viewed as reflecting an initial compensatory mechanism accounting for the delay between dopaminergic cell loss and parkinsonian clinical onset. During a voluntary movement, the motor cortex less involved by PD pathology could be involuntarily activated owing to an impairment in interhemispheric inhibitory circuits and/or an increased excitability in the worse M1, thus producing the mirror activation. However, these proposed mechanisms probably do not completely explain the phenomenon of motor overflow, as other factors are perhaps involved. One possibility is that the dorsal premotor cortex, or the SMA which may both play a role in suppressing MM [30], are hypoactive on the more affected side in PD and, together with reduced transcallosal inhibition, lead to interhemispheric motor overflow. On the other hand, asymmetric MMs in early PD may be the expression of an initial loss of movement selectivity and interhemispheric inhibition, initially predominant over the more affected hemisphere and paradoxically appearing as compensated, as disease progresses, by a similar pathologic process extending to the less affected hemisphere.

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