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Usefulness of movement time in the assessment of Parkinson's disease

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Abstract Reaction time (RT) and movement time (MT) are reported to be delayed in Parkinson's disease (PD), but their clinical utility and relationship with clinical findings is still uncertain. We investigated RT and MT in 22 PD patients at baseline conditions and following acute oral trials of levodopa and biperiden, an anticholinergic drug. At baseline conditions, RT and MT of PD patients were abnormally delayed compared with those of 16 normal control subjects. Both RT and MT were longer in more severely affected patients compared with the mild PD patients; in the mild PD patients with asymmetrical signs both responses were longer on the more affected side. Bradykinesia was the clinical symptom that best correlated with the objective measurements, with a stronger correlation for MT than for RT. The oral administration of levodopa significantly improved both the responses, whereas biperiden was ineffective. The magnitude of RT and MT improvement after levodopa differed; MT improvement was related to PD severity, whereas RT improvement was not. These results suggest that MT, rather than RT, is an objective, simple, and reliable tool to evaluate bradykinesia and its levodopa-induced modifications in PD.

Key words Parkinson's disease
Reaction time · Movement time
Levodopa · Biperiden

Introduction

In 1925 Wilson [63] first described quantitative abnormalities in initiation and execution of movement in patients suffering from Parkinson's disease (PD), measuring reaction time (RT) and movement time (MT) by means of a dynamometer. Many authors confirmed Wilson's earlier findings, demonstrating that MT [1, 3, 4, 8, 10, 12, 15, 19, 30, 33, 50, 52, 53, 55, 59–61] and RT [5, 9, 11, 21, 42, 43, 64, 66] were abnormally delayed in PD subjects when compared with normal subjects. However, relatively few studies have investigated the relationship between these objective measurements and the severity of PD, often reporting conflicting results. Indeed, while some authors demonstrated that RT was slower in patients with more advanced PD [66] or on the more affected side in mild PD patients [44, 67], other studies did not show a correlation between prolonged RT or MT and severity of PD [8, 61]. Moreover, in spite of the general assumption that delayed RT and MT are related to bradykinesia [24] studies that investigated the relationship between RT or MT and PD clinical findings failed to show such a correlation [11, 30, 61]. Thus, it is questionable whether these incongruities were due to poor data reproducibility between studies, or if the experimental settings, with diverse criteria in patient selection, caused the conflicting results.

The aim of the present study was to investigate further the relationship between RT, MT and the clinical symptoms of PD, both at baseline conditions and following levodopa or biperiden administration.

Subjects and methods

Subjects

Twenty-two patients with idiopathic PD (7 men and 15 women, aged 41 to 74 years; mean and standard deviations of 62 and 8.8 years) and 16 age-matched control subjects (6 men and 10 women, aged 45–74 years, mean 59.3 SD 8.4 years) were studied. All subjects gave their informed consent for participation in the study. The PD patients had a history of disease lasting from 6 months to 13.5 years, with a mean disease duration of 42 months. Ten patients were taking levodopa (mean dosage of 610 SD 223 mg/day, range 375 to 1000 mg) at the time of entry into the study; treatment duration ranged from 8 months to 13 years (mean 38.8 months). Twelve patients had never been treated with antiparkinsonian drugs. According to the Hoehn-Yahr scale [22], PD patients were subdivided in two groups: mild PD (MPD) and severe PD (SPD). The MPD group consisted of 15 patients in stage I or II, and the SPD group consisted of 7 patients in stage IV or V.

Clinical evaluation

Clinical evaluation was determined by Webster scale [62] and by Unified Parkinson's Disease Rating Scale (UPDRS) [14]. Global motor status was estimated by the Motor Examination section (UPDRS-ME) of the UPDRS. To enable a balanced evaluation of the three major symptoms of PD (bradykinesia, rigidity, and tremor), four subscores related to two or more items of UPDRS-ME were chosen and added to give the total score (rated 0–16) for each symptom (items 23 through 26 for bradykinesia, items 22 and 28 for rigidity, and items 20 and 21 for tremor). Furthermore, each side was evaluated in order to ascertain the more affected side (MAS) and the less affected side (LAS) by PD symptoms, independent of axial involvement. The Mini Mental State Examination [17] provided a general cognitive screen.

Objective evaluation

RT and MT were evaluated by means of computed tachistoscope measurement of a visual directional-choice task. The apparatus consisted of a 31×42 cm rectangular surface with six stimulus lights, each coupled to one button electrode 1 cm in diameter on a circle arc 6.5 cm apart and 15 cm equidistant from a central start button electrode. The subject held the index finger of his hand over the central start button and, after the randomized appearance of one of the six stimulus lights, had to switch off the light as quickly as possible by moving his finger from the central start button to the button electrode next to the illuminated light. RT was considered the interval elapsed between the onset of the stimulus and the release of the central start button. MT was the time between the release of the central start button and the pressing of the button electrode next to the illuminated light. All the subjects were allowed to practice until proficient, and then the mean values of 30 consecutive trials for both RT and MT were run in each session. Both left- and right-side responses were recorded in each subject.

Experimental design

Clinical and objective evaluations were assessed separately by two observers blinded to each other.

Baseline conditions

All the patients were evaluated without medication. The patients medicated with levodopa were tested at the time of entry in the study, but afterwards the drug was gradually withdrawn and then completely stopped; clinical and instrumental assessments were recorded daily and conditions were considered baseline when both clinical and objective measurements were the same on two consecutive days.

Response to levodopa

All patients were investigated after ingestion of a single oral dose of 250 mg of levodopa associated with 25 mg of carbidopa. The drug was administered to the patients at baseline conditions at 8:30 a.m. after an overnight fast. A low protein snack was served 120 to 150 min later. A clinical evaluation was done and RT and MT for both sides were assessed immediately before and 1, 1.5, 2, 4, and 24 h after drug administration. In 13 patients, blood samples were drawn at the time of the clinical and objective evaluations and later assayed for levodopa using high-performance liquid chromatography with electrochemical detection [36]. We evaluated in all the patients the maximal improvement of RT and MT, if any, after drug administration. The amplitude of this improvement gave the gain as compared with baseline values and was calculated for both RT and MT as the percentage between the actual maximal improvement (the difference between baseline and peak values) and the theoretical maximal improvement (the difference between patient baseline values and the lower range of normal controls, consisting of the mean values minus three standard deviations). The gain was calculated by the formula $(B–P)\times100/(B–N)$, where B was the baseline value, P was the peak value, and N was the lower range of normal.

Response to biperiden

Eleven patients were studied following oral administration of 4 mg of biperiden, an anticholinergic drug. Clinical, RT, and MT assessments were performed at baseline conditions and 1, 2, and 4 h after drug administration.

Statistical analysis

RT and MT statistical comparisons were carried out by Student's t-test for unpaired and paired data and by analysis of variance for repeated measurements with Tukey's test for post-hoc multiple comparisons. For clinical scores, non-parametric tests were used: the Mann-Whitney U test, the Wilcoxon sign rank test, and the Friedman test for repeated measurements with the Neuman-Keuls test for post-hoc multiple comparisons. Pearson product-moment correlation coefficients were used to evaluate further the clinical and objective data.

Results

Baseline conditions

Table 1 shows the baseline clinical characteristics of 22 PD patients, divided into two groups according to the Hoehn-Yahr stage as described above. The two groups were comparable for age and cognitive status, whereas disease duration was longer and clinical scores were higher in the SPD group than in the MPD group. Bradykinesia and rigidity were the predominant symptoms; tremor was unremarkable and no difference was observed between groups for this symptom.

RT and MT were assessed on both sides in all patients and in 16 normal controls. A preliminary study of normal subjects tested the influence of handedness on both the responses, but no significant differences were found be-

Table 1 Clinical characteristics of 22 Parkinson's disease patients at baseline conditions[a]

	Mild Parkinson's disease group (n = 15)	Severe Parkinson's disease group (n = 7)
Age (years)	62.2, 9.6	61.6, 7.5
Disease duration (months)*	22.1, 18.7	84.4, 51.6
Mini-mental score	24.5, 2.9	24.9, 3.7
UPDRS score**	31.1, 9.3	71.4, 8.0
UPDRS-ME score**	17.0, 6.3	37.1, 5.6
UPDRS bradykinesia score[b].*	5.7, 2.5	11.8, 3.5
UPDRS rigidity score[b].**	4.9, 1.8	9.9, 2.2
UPDRS tremor score[b]	1.9, 1.5	1.6, 1.3

[a] Values reported are means, standard deviations for the number of patients indicated

[b] Clinical scores for bradykinesia, rigidity, and tremor were rated on scale 0 to 16 considering specific items of the Motor Examination section of the Unified Parkinson's Disease Rating Scale (see Methods)

* $P<0.01$ for difference between groups (Mann-Whitney U test)
** $P<0.001$ for difference between groups (Mann-Whitney U test)

tween the right and left side for RT or for MT (RT: $t=1.305$, $P>0.1$; MT: $t=1.623$, $P>0.1$; values reported on Table 2). Another preliminary test investigated data reproducibility in 11 controls and in all PD patients: no significant differences were found among the recordings performed 1, 2, 4, and 24 h after initial baseline assessment, either for the normal subjects (right RT: $F=1.927$, $P>0.1$; left RT: $F=1.751$, $P>0.1$; right MT: $F=1.930$, $P>0.1$; left MT: $F=1.168$, $P>0.1$) or for the PD patients (right RT: $F=0.678$, $P>0.5$; left RT: $F=0.708$, $P>0.5$; right MT: $F=1.269$, $P>0.1$; left MT: $F=0.605$, $P>0.5$; data not shown).

RT and MT were significantly delayed on both sides in PD patients as compared with normal subjects (Table 2). Both responses were more abnormal in the severely affected patients than in the mild PD patients, and in the MPD group, RT and MT were significantly longer on the MAS than on the LAS. Clinically, the laterality scores of bradykinesia showed a higher involvement from both sides of SPD patients as compared with the LAS and the MAS of the MPD group, with the MAS significantly more bradykinetic than the LAS in patients with milder disease. For rigidity, the MPD group showed significant side differences, with the MAS score larger than the LAS score; however, comparing the groups of patients, unlike bradykinesia, the rigidity LAS score of the SPD group was not significantly higher than the MAS score of the MPD group. For tremor, significant statistical differences were evident only for the LAS scores versus the MAS scores of both groups.

The correlation study (Table 3) showed that RT and MT recorded from the MAS were significantly related to the severity of PD (Hoehn-Yahr stages as well as global clinical scores), with stronger correlations for MT. On the same level, bradykinesia had a higher correlation with MT than to RT, and rigidity had weak correlations with both the responses; tremor showed no correlation. Disease duration as well as treatment duration were significantly

Table 2 Reaction time, movement time, and clinical laterality scores in 16 normal subjects and 22 Parkinson's disease patients[a]. *MPD-LAS* Mild Parkinson's disease – less affected side, *MPD-MAS* mild Parkinson's disease – more affected side, *SPD-LAS* severe Parkinson's disease – less affected side, *SPD-MAS* severe Parkinson's disease – more affected side

Groups	Side	Reaction time (ms)[b]	Movement time (ms)[b]	Bradykinesia laterality score[c]	Rigidity laterality score[c]	Tremor laterality score[c]
Controls (n = 16)	Right	304, 24	203, 36			
	Left	298, 26	213, 42			
	Average	301, 23*1	208, 37*1			
Mild Parkinson's disease (n = 15)	Less affected (MPD-LAS)	349, 69*2	313, 74*2	1.8, 0.9*2	1.7, 1.2*2	0.3, 0.5*3
	More affected (MPD-MAS)	375, 60*4	369, 78*4	3.5, 1.9*4	3.1, 1.6*5	1.1, 1.0
Severe Parkinson's disease (n = 7)	Less affected (SPD-LAS)	475, 40	540, 135	5.3, 1.7	4.0, 1.4	0.3, 0.5*3
	More affected (SPD-MAS)	473, 56	613, 165	6.0, 1.7	4.9, 1.5	1.0, 0.8

*1 $P<0.05$ for difference between control group and both sides of both groups of parkinsonians
*2 $P<0.05$ for difference between MPD-LAS vs MPD-mas, SPD-LAS and SPD-MAS
*3 $P<0.05$ for difference between MPD-LAS or SPD-LAS vs MPD-mas and SPD-MAS
*4 $P<0.05$ for difference between MPD-MAS vs SPD-Las and SPD-MAS
*5 $P<0.05$ for difference between MPD-MAS vs SPD-MAS

[a] Values reported are means, standard deviations for the number of subjects indicated

[b] Reaction time and movement time were compared testing side differences in the same group by paired t-test and testing for each side the differences between the groups by unpaired t-test

[c] Bradykinesia, rigidity and tremor laterality scores were rated on a scale of 0 to 8. The clinical scores were compared testing side differences in the same group by Wilcoxon sign rank test and testing for each side the differences between the groups by Mann-Whitney U test

Table 3 Correlations between clinical characteristics and objective measurements (reaction time and movement time) in 22 Parkinson's disease patients[a]. *NS* Not significant

	Reaction time[b]		Movement time[b]	
	r	*P*	*r*	*P*
Age	−0.009	NS	0.096	NS
Hoehn-Yahr stage	0.603	<0.01	0.720	<0.001
Disease duration	0.246	NS	0.653	<0.001
Levodopa dosage[c]	0.124	NS	0.503	NS
Treatment duration[c]	0.334	NS	0.753	<0.05
Mini-mental score	−0.240	NS	−0.071	NS
UPDRS score	0.621	<0.01	0.685	<0.001
UPDRS-ME score	0.662	<0.001	0.768	<0.001
Bradykinesia laterality score[d]	0.538	<0.05	0.617	<0.01
Rigidity laterality score[d]	0.458	<0.05	0.442	<0.05
Tremor laterality score[d]	−0.042	NS	0.114	NS

[a] Correlation coefficients were obtained by Pearson's correlation analysis
[b] Reaction time and movement time values recorded from the most affected side
[c] Correlation analysis for ten patients
[d] Clinical score from the most affected side

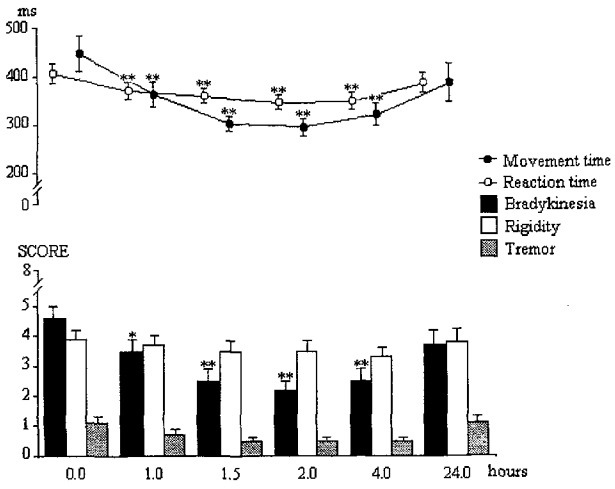

Fig. 1 Reaction time and movement time responses *(top)*, and clinical laterality scores *(bottom)* before (time 0) and after oral administration of 250 mg of levodopa. Reported data points are the means with standard errors of the values recorded from the most affected side of 22 Parkinson's disease patients. $*P<0.05$ for difference with respect to the value at time 0. $**P<0.01$ for difference with respect to the value at time 0

related to MT, but not to RT. Age, cognitive status, and levodopa dosage did not show any correlation with either response.

Response to levodopa

Figure 1 shows the MAS response of 22 PD patients to the oral administration of 250 mg of levodopa. RT, MT, and bradykinesia laterality score significantly improved at the same time, one hour following drug intake, reaching maximal improvement at two hours, lasting up to four hours, and returning to the baseline values within 24 h (RT: $F=14.062$, $P<0.0001$; MT: $F=14.718$, $P<0.0001$; bradykinesia: Chi-square = 63.305, $P<0.0001$). Rigidity and tremor clinical scores showed a slight improvement, but no significant differences were found among the different recordings (rigidity: Chi-square = 8.039, $P>0.1$; tremor: Chi-square = 10.82, $P>0.05$).

Table 4 shows the RT and MT values at the time of maximal improvement following 250 mg of levodopa ingestion and the amplitude of this improvement, that is the gain with respect to the baseline values. RT and MT of patients with more severe PD were still significantly slower from both sides than patients with milder disease and, in this latter group, MT but not RT was more significantly delayed on the MAS than on the LAS. The RT gain was similar and not significantly different in both groups of patients regardless of the side recorded, whereas the MT gain was significantly larger in the SPD patients than in the MPD patients. Moreover, in the MPD group, the MT gain was significantly larger on the MAS with respect to the LAS.

In the 13 patients whose plasma levodopa levels were measured, the time course of instrumental and clinical measurements followed the same pattern observed for the entire group; in these patients the mean peak plasma concentration was 4.1, SD 2.2 nmol/ml, and the mean peak time was 92.3 (SD 49.7) min: no significant differences for either of these peripheral pharmacokinetic parameters of levodopa were observed between patients with mild disease (9 subjects) and patients with severe disease (4 subjects).

Response to biperiden

We tested the LAS and the MAS clinical and objective responses of 11 patients to the oral administration of 4 mg of biperiden (Fig. 2). Only the rigidity laterality score showed a significant improvement, detectable on MAS 1, 2 and 4 h after drug intake (Chi-square = 16.2, $P<0.01$). The tremor laterality score showed a slight improvement, but no significant differences were found. Bradykinesia, RT and MT did not show any change.

Discussion

In the present study we clearly established that MT, rather than RT, may detect clinical bradykinesia and its levodopa-induced modifications in PD. These data suggest

Table 4 Maximal improvement of reaction time and movement time following 250 mg of levodopa[a]. *MPD-LAS* Mild Parkinson's disease – less affected side, *MPD-MAS* mild Parkinson's disease – more affected side, *SPD-LAS* severe Parkinson's disease – less affected side, *SPD-MAS* severe Parkinson's disease – more affected side

Groups	Side	Reaction time		Movement time	
		Peak[b] (ms)	Gain[c] (%)	Peak[b] (ms)	Gain[c] (%)
Mild Parkinson's disease ($n = 15$)	Less affected (MPD-LAS)	306, 46*	36.4, 15.8	232, 48**	28.0, 11.2**
	More affected (MPD-MAS)	311, 41*	46.9, 16.0	257, 36*	40.0, 9.1***
Severe Parkinson's disease ($n = 7$)	Less affected (SPD-LAS)	380, 37	37.3, 19.0	299, 50	53.3, 13.5
	More affected (SPD-MAS)	373, 33	38.7, 20.2	318, 66	56.4, 8.6

*$P<0.05$ for difference between MPD-LAS or MPD-MAS vs SPD-Las and SPD-MAS

**$P<0.05$ for difference between MPD-LAS vs MPD-Mas, SPD-LAS and SPD-MAS

***$P<0.05$ for difference between MPD-MAS vs SPD-MAS

[a] Values reported are means, standard deviations for the number of patients indicated

[b] Peak values refer to the maximal improvement achieved following a single oral dose of levodopa. Statistical analysis was performed by paired t-test comparing side differences in the same group, and by unpaired t-test comparing for each side differences between groups

[c] Gain is the improvement percentage of the peak values with respect to the basal values (see Methods). Statistical analysis was perfomed by Wilcoxon sign rank test comparing side differences in the same group, and by Mann-Whitney U test comparing for each side the differences between groups

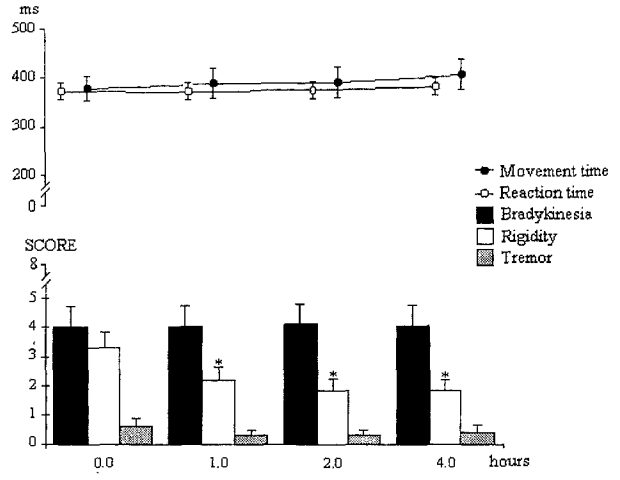

Fig. 2 Reaction time and movement time responses *(top)*, and clinical laterality scores *(bottom)* before (time 0) and after oral administration of 4 mg of biperiden. Reported data points are the means with standard errors of the values recorded from the most affected sides of 11 Parkinson's disease patients. *$P<0.01$ for difference with respect to the value at time 0

that MT is an objective, simple and reliable tool in the assessment of PD patients.

RT and MT of PD patients at baseline conditions were abnormally delayed as compared with normal subjects; patients in Hoehn-Yahr stage IV or V exhibited more prolonged latencies than patients in Hoehn-Yahr I or II, and in this latter group, RT and MT were significantly longer on the most affected side when compared with the side less affected by the PD symptoms.

Our results do not confirm previous studies reporting normal RT in parkinsonians [3, 5, 33, 50], or abnormal RT and MT unrelated to the severity of PD [8, 61]. Methodological differences could explain the discrepancies with our findings, especially the criteria followed for assessment of baseline conditions. Indeed, the studies reporting normal RT values in PD patients, or abnormal RT and MT unrelated to PD disability, were performed only a few hours after levodopa withdrawal [8, 33] or without specifying the time of the study with regard to drug intake [3, 5, 50, 61]. As pointed out by Muenter and Tyce [35], when prolonged therapy with levodopa is discontinued, it can take up to 5 days for the pretherapy level of disability to be reached. Thus, it is conceivable that in other studies a long-lasting effect due to chronic levodopa therapy precluded detection of significant RT differences between normal subjects and PD patients, or between patients in different stages of disability. In our study, the PD patients were tested at absolute baseline conditions: indeed, 12 of 22 were "de novo" patients, never treated with antiparkinsonian drugs before the study, whereas for the remaining 10 patients who were taking levodopa at the time of entry into the study the antiparkinsonian therapy was gradually withdrawn and then completely stopped, and baseline conditions were established when both clinical and objective measurements were the same on two consecutive days.

Our data concur with previous reports showing that MT [1, 3, 4, 8, 10, 12, 15, 19, 30, 33, 50, 52, 53, 55, 59–61] and RT [5, 9, 11, 21, 42, 43, 64, 66] were slower in PD patients than in controls, and that RT was correlated to the Webster score [47] and to Hoehn-Yahr staging [66]. Moreover, our results also agree with previous studies showing that in patients with asymmetry of bilateral neurological signs [67] or in patients with hemiparkinsonism [44] RT was slower on the more affected side.

An important question remains regarding the parkinsonian symptom to which RT and MT are related. Studies

that have systematically investigated the relationships in PD between RT, MT and clinical symptoms have reported conflicting results: Ward et al. [61] found positive correlations for RT and manual dexterity, and for MT and rigidity; Lichter et al. [30] reported that RT was more correlated with tremor and rigidity than with bradykinesia; Dubois et al. [11] showed that RT was not correlated either with akinesia or rigidity; Yanagisawa et al. [66] found that RT was positively correlated with bradykinesia and rigidity. These discrepancies may be explained by the fact that in these studies different clinical rating scales were used and each symptom was graded differently, without considering the side dominance of the disease, and thus precluding homogeneous results. Since RT and MT are influenced by the sidedness of PD, a correlation study should consider the laterality scores of PD symptoms. In the present study, we evaluated the three main symptoms of PD in a balanced way, scoring each symptom with an equal number of UPDRS items and assigning to each side a symptom laterality score. In this way, testing unmedicated patients, clinical bradykinesia was more correlated with RT and MT than rigidity, with a stronger correlation for MT than for RT. Following levodopa administration, the only clinical score showing significant changes, timed to RT and MT changes, was the bradykinetic score; after biperiden intake, bradykinesia as well as RT and MT remained unchanged and the only detectable change was the rigidity laterality score. To our knowledge, no data have previously been reported about the effect of anticholinergic drugs on RT and MT in PD patients, whereas it is well known that rigidity is reduced by anticholinergic drugs and bradykinesia responds poorly [38].

RT and MT responsiveness to the administration of a single oral dose of levodopa suggests that dopaminergic mechanisms may regulate these responses in PD. Previous studies in monkeys support this conclusion, since electrolytic lesions of substantia nigra [57] as well as treatment with methylphenyltetrahydropyridine [31] prolonged RT and MT, whereas levodopa administration reversed these abnormalities [27]. On clinical grounds, it has already been shown in PD that levodopa administration improves RT [23, 43], MT [4, 51, 52], or both [8, 33, 42, 56, 58, 59]. Nonetheless, only a few studies [56, 58] have focused their attention on the different responsiveness of RT and MT to levodopa administration. Our findings clearly show that these responses are differently modified by levodopa: (1) the MT recorded after levodopa ingestion still allowed, in the mild PD group, differentiation of the more involved side from the less affected side, as in the baseline conditions study, whereas RT did not; (2) the magnitude of the responses, measured as the percentage gain of peak values as compared with baseline values, showed an increase in MT gain proportionate to the severity of the disease, whereas the RT gain did not. These features suggest a dopaminergic control acting in a quantitatively distinct fashion to regulate RT and MT in PD patients.

It has been suggested that several factors are involved in the delayed RT of PD patients: attentive [11, 19, 23, 54, 66], cognitive [5, 12, 16, 48, 50], and motor [25, 53].On the other hand, only motor mechanisms are implicated in MT [20]. Since only the motor components of both the responses seems to be sensitive to levodopa administration in PD [2, 4, 43, 54] and the contribution of motor factors to the generation of RT is limited, it is conceivable that dopamine repletion can improve the delayed RT of PD patients only a limited amount regardless of the severity of the disease.

Following levodopa administration, the magnitude of MT improvement related to severity of PD may be explained by pharmacokinetic as well as by pharmacodynamic mechanisms. However, it is presumable that peripheral pharmacokinetic mechanisms related to levodopa did not play a relevant role in determining the magnitude of MT improvement for two reasons: first, our mildly and severely affected patients did not differ in the peripheral pharmacokinetic parameters of levodopa, in agreement with previous reports [8, 13, 18], whereas their MT improvement was significantly different; second, in patients with mild disease and asymmetrical signs, the MT improvement was significantly greater on the more involved side than on the less affected side.

Concerning the pharmacodynamic mechanisms, only indirect conclusions can be drawn from our data. The pattern of MT improvement may be explained by a postsynaptic receptor model, since there is evidence that the amplitude of motor response to dopaminergic drugs in PD is related to dopaminergic postsynaptic receptors stimulation [26]. It is well known that postsynaptic receptor modifications begin early in PD to compensate for the loss of the nigrostriatal dopaminergic neurons [7, 65]. An increase of striatal D2 dopaminergic receptors has been documented in animals with lesions of the nigrostriatal pathway [49], in PET studies in primates [29] and in humans exposed to methylphenyltetrahydropyridine [41], and in post-mortem examinations [28, 40] as well as in vivo receptor-binding studies of untreated PD patients [6, 39, 46]. On the other hand, there is no clear evidence that striatal dopaminergic receptors are up-regulated in the advanced stages of the disease [6]. In these patients, long-term treatment with dopaminergic drugs might preclude conclusive issues, since chronic exposure to levodopa or D2 agonist therapy can down-regulate striatal dopamine receptors [32, 45]. Thus, it is possible that the larger MT improvement after levodopa administration observed in the present study in more severe PD patients with respect to milder PD patients may be related to greater D2 receptor activation, as may occur in more advanced PD. Our data are in agreement with previous studies [34, 35, 37] in which the amplitude of the motor response to levodopa, measured by clinical ratings, was related to the severity of PD.

In conclusion, RT and MT are objective and reliable indicators of PD progression; moreover MT, better than

RT, represents the instrumental counterpart of clinical bradykinesia and may be usefully employed in the assessment of basal ganglia dysfunction underlying PD, as well as in the evaluation of the efficacy of antiparkinsonian drugs.

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