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RESEARCH ARTICLE

Long-Duration Response to Levodopa, Motor Learning, and Neuroplasticity in Early Parkinson's Disease

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ABSTRACT: Background: Long-duration response (LDR) to levodopa and motor learning could be involved in changes in neuroplasticity of cortical excitability in Parkinson's disease (PD). P300, motor evoked potentials (MEPs), and Bereitschaftspotential (BP) are neurophysiological surrogate markers of neuroplasticity.

Objective: We aimed to define in PD the effects of LDR and motor learning on neurophysiological parameters involved in neuroplasticity.

Methods: Drug-naive PD patients underwent a 15-day treatment with levodopa/carbidopa 250/25 mg daily. Achievement of LDR was assessed on the 15th day of treatment (T15). Patients were grouped based on the achievement of a sustained LDR (LDR+) or no LDR (LDR−) and to the assignment of a learning motor exercise (LME) or no motor exercise (NME). Patients underwent clinical and neurophysiological (P300, MEPs, and BP) assessments at baseline (T0) and on T15.

Results: Forty-one PD patients and 24 age- and sex-matched normal controls (NCs) were enrolled. Neurophysiological parameters differed between untreated PD patients and NCs. Four groups of patients were obtained at the end of treatments: trained patients with a sustained LDR (LDR + LME group), untrained patients with a sustained LDR (LDR + NME group), trained patients without LDR (LDR-LME group), and untrained patients without LDR (LDR-NME group). At baseline, no differences in clinical and neurophysiological parameters were evident among the groups. After the treatments, significant improvements in neurophysiological parameters were observed in the LDR + LME group. No modifications were found in the groups without LDR.

Conclusions: The achievement of a sustained LDR may act synergistically with motor learning to induce adaptive changes in neuroplasticity in basal ganglia and cortical networks. Our findings support LDR as a pharmacological outcome possibly facilitating the action of motor learning on neuroplasticity in early PD. © 2023 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: Parkinson's disease; levodopa; long-duration response; motor learning; treatment

Levodopa (L-dopa) is considered the "gold standard" treatment for Parkinson's disease (PD),[1] and its therapeutic response is expressed by two different components: short-duration response (SDR) and long-duration response (LDR).[2] The SDR is characterized by a clinical improvement lasting a few hours after the administration of a single dose of L-dopa, paralleling drug plasma concentration, whereas the LDR derives from prolonged administration of L-dopa and persists for hours to days after treatment discontinuation independently of the peripheral pharmacokinetics.[3-6] Besides the improvement in parkinsonism, the LDR to L-dopa could be involved in motor learning. Although PITx3-deficient mice, whose dopamine levels in the dorsal striatum are reduced by 90%, do not learn a new motor task, restoration of their dopaminergic activity improves learning, and the LDR to L-dopa was

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fundamental for the acquisition and maintenance of learned skills.[7] Therefore, the LDR could be a manifestation of "rescued" motor learning in dopamine-depleted rodents. Moreover, in humans with PD, the LDR to L-dopa can interact with active motor training, as observed by comparing motor task performance in dominant and nondominant hands and considering the activities of the dominant hand as active training.[8]

Motor learning is classically defined as a set of processes associated with practice or experience that leads to transient or permanent changes in the ability to perform a movement.[9] The striatum is one of the structures most strongly involved in motor learning, and adaptive changes in basal ganglia and cortical networks may develop in PD to compensate for an impaired motor learning.[10,11] Thus, if the LDR to L-dopa is involved in the restoration of motor learning, it should also be related to the mechanisms underlying the adaptive changes, due to the neuroplasticity of the basal ganglia and cortical networks.

Some neurophysiological parameters, such as auditory evoked potential P300, motor evoked potentials (MEPs) and Bereitschaftspotential (BP), are related to cortical excitability and, as such, could be considered surrogate markers of cortical neuroplasticity. The aim of this study was to investigate whether PD patients' achievement of the LDR to L-dopa after a 15-day treatment period could influence neurophysiological markers of neuroplasticity and whether motor learning could benefit from the presence of the LDR.

Patients and Methods

Subjects

Drug-naive patients with a diagnosis of clinically definite PD,[12] a Hoehn and Yahr score[13] ranging from 1 to 2.5, and a Mini-Mental State Examination score >24[14] were eligible from January 2018 to June 2019. A group of healthy age- and sex-matched individuals served as normal controls (NCs) for neurophysiological investigations.

The study was approved by the local ethics committee (Comitato Etico Catania 1, no.: 2024, 2017), and patients were enrolled after signing written informed consent.

Study Design

Drug-naive PD patients underwent a 15-day period of L-dopa treatment aimed at achieving a sustained LDR to the drug. At the end of treatment and based on the achievement of a sustained LDR, the patients were grouped as LDR+ (presence of a sustained LDR) or LDR− (absence of a sustained LDR). Before treatment, the patients were randomly assigned for training involving the learning of a motor exercise (LME) or not learning a motor exercise (NME) during the 15-day treatment period with L-dopa.

Procedure

All enrolled patients underwent an L-dopa challenge before treatment (T0), aimed at detecting the individual SDR to the drug and needed for further calculation of the LDR to chronic treatment.[3] The response was evaluated by movement time (MT) recordings, considered the instrumental counterpart of clinical bradykinesia.[15] MT was assessed by a movement time analyzer, a computer-controlled tachistoscope dedicated to MT recording and described elsewhere.[16] Recordings were conducted from both sides, that is, from the more affected side (MAS) and from the less affected side (LAS), but only MAS recordings were considered in further analysis.

The acute L-dopa test comprised the oral administration of L-dopa/carbidopa 250/25 mg,[3] administered at 8.00 AM, after an overnight fast, and MT recordings were performed immediately before and 1, 2, 4, 6, 8, 10, and 12 hours after drug intake. All patients were treated with domperidone 20 mg thrice a day for 3 days before L-dopa challenge and with domperidone 20 mg 20 min before L-dopa intake on the day of the test.[17]

For calculation of the SDR on the acute L-dopa challenge, the difference between the base and peak values was considered the maximal improvement in the SDR to L-dopa, and the magnitude of the response was calculated using the formula $[(T0_B - T0_P) \times 100/(T0_B - N)]$, where $T0_B$ is the base value, $T0_P$ is the peak value at L-dopa challenge, and N is the lower range of normal.[3] A response with a magnitude of at least 15% indicated a pharmacological responsiveness to the acute challenge with L-dopa.

Then, patients underwent a 15-day regimen scheduling full doses of L-dopa /carbidopa 250/25 mg at fixed interdose intervals of 24 hours, considered to be a regimen allowing the achievement of a sustained LDR in most patients with mild or moderate PD.[3]

On the 15th day (T15) of treatment, we assessed the achievement or not of an LDR to L-dopa therapy. The formula for calculation of the LDR was based on the MT recordings and was given by $[(T0_B - T15_B) \times 100/(T0_B - T0_P)]$, where $T0_B$ is the base value at T0 (ie, the base value in the unmedicated condition), $T15_B$ is the base value on the 15th day of treatment before the patient took the morning dose of L-dopa, and $T0_P$ is the peak value at the L-dopa challenge.[3] An LDR ≥50%, that is, at least 50% of the maximal improvement in the SDR observed after the acute L-dopa challenge, was considered sustained and satisfactory.[3]

Moreover, at T15 the SDR to a single dose of L-dopa during chronic treatment was calculated using the formula $[(T15_B - T15_P) \times 100/(T15_B - N)]$, where $T15_P$ is the peak value at T15.

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Motor Training

The patients were randomly assigned to LME or NME using a dedicated computer software. According to Wu and Hallett,[18] LME comprises the execution of two sequences of finger tapping, defined as "sequence 4" and "sequence 12," based on the number of movements required to complete the sequence. The numbers 1, 2, 3, and 4 refer, respectively, to the index, middle, ring and little fingers, which had to be tapped on the thumb. Therefore, "sequence 4" comprised four movements with fingers "1-3-4-2," whereas "sequence 12" comprised 12 movements with fingers "1-4-3-2-2-4-1-3-4-1-2-3." Sequences 4 and 12 had to be separately performed with both hands. The achievement of automatized motor learning was evaluated by having patients perform a visual letter-counting task simultaneously with these movements. The visual letter-counting task involved the identification of a specific target letter among a random series of letters (A, G, L, O) presented on a screen: patients had to identify the number of times they saw the target letter. Patients performed these tasks until they could execute sequential movements from memory 10 times in a row without errors, as well as accurately perform the dual tasks. The subjects were informed whether their finger movements were correct or incorrect until they achieved completely automatized execution of the motor sequences. The achievement of motor ability was determined on T15.

Patients were trained in five 30-minute sessions per week over 15 days. Each session started at the same time in the morning (10.00 AM) after the first daily intake of L-dopa.

The patients randomly assigned to NME did not conduct any motor exercise during the 15-day period of pharmacological treatment.

Clinical and Neurophysiological Assessments

All patients underwent both clinical and neurophysiological assessments at their unmedicated baseline motor condition ($T0_B$), on the 15th day of treatment before intake of the first daily dose of L-dopa ($T15_B$) and after 2 hours from the intake of L-dopa at the peak of efficacy ($T15_P$). Clinical and neurophysiological assessments were conducted by personnel unaware of the patients' status.

Clinical evaluation was performed using the Unified Parkinson's Disease Rating Scale-Motor Examination (UPDRS-ME).[19] Neurophysiological assessment comprised P300, MEP, and BP evaluations.

P300 was recorded from Fz, Cz, and Pz (10/20 system) following auditory stimuli according to an oddball stimulus paradigm, presented to patients who had to keep a mental count of the rare (20%) target tones (65 dB, 2000 Hz) interspersed against a background of more common (80%) nontarget tones (65 dB, 1000 Hz).[20] P300 was identified as the major positive point in tracing of the rare stimulus, and the latency value was defined as the intersection point of best-fit slope lines.

MEPs were obtained after transcranial magnetic stimulation (TMS) and recorded from the first dorsal interosseous (FDI).[21] A MagPro Compact Magnetic Stimulator (Medtronic, Minneapolis, MN), connected to the stimulating coil (circular type; mean diameter: 9 cm), was used to elicit a single-pulse stimulation to the hemisphere contralateral to the FDI muscle examined. The MEPs obtained with the TMS intensity producing the maximum amplitude were considered, and 10 trials were collected for analysis of mean MEP amplitude. Resting motor threshold (RMT) was determined as the minimum stimulus intensity required to elicit in the relaxed FDI an MEP of at least 50 μV in amplitude in three of five consecutive trials. Active motor threshold (AMT) was defined as the minimum stimulus intensity required to elicit in the FDI an MEP of at least 200 μV in amplitude in three of five consecutive trials during a low-level voluntary index finger abduction. For both RMT and AMT parameters, the latency of the elicited MEPs was calculated. The duration of the cortical silent period (CSP) was obtained by applying TMS at 130% of the RMT, with an FDI at 20% of maximum voluntary contraction. Ten trials were collected, and the mean CSP duration was used for analysis.

BP recordings were derived from electroencephalogram (EEG) and electromyography (EMG) activities

TABLE 1 *Neurophysiological parameters examined in 24 normal control subjects and in 41 patients with Parkinson's disease at the baseline untreated status*

	Normal controls	PD patients
P300 latency (ms)	301.5 ± 37.2	320.9 ± 30.7*
MEP amplitude (μV)	303.4 ± 137.4	191.6 ± 116.8**
MEP RMT latency (ms)	22.0 ± 1.5	22.5 ± 1.9
MEP AMT latency (ms)	19.1 ± 1.6	20.4 ± 2.3*
CSP duration (ms)	79.4 ± 41.7	110.7 ± 49.3*
Early BP amplitude (μV)	3.2 ± 2.2	3.8 ± 2.3
Early BP latency (ms)	1872.9 ± 42.7	1955.3 ± 98.6**
Late BP amplitude (μV)	4.9 ± 3.1	6.5 ± 4.5
Late BP latency (ms)	516.2 ± 35.3	591.9 ± 52.5**

Note: Data are means ± standard deviations. Except for the P300, neurophysiological parameters were recorded from the right side in normal controls and from the most affected side in patients with Parkinson's disease.
Note: Independent-samples *t* test: *$P < 0.05$, **$P < 0.01$.
Abbreviations: PD, Parkinson's disease; MEP, motor evoked potentials amplitude; RMT, resting motor threshold; AMT, active motor threshold; CSP, cortical silent period; BP, Bereitschaftspotential.

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recorded while patients repeated a voluntary muscle contraction at a self-paced rate every 10 seconds.[22] EEG electrodes were positioned in regions C4, Cz, and C3 (10/20 system) referenced to the mastoids. EMG was recorded from the abductor pollicis brevis (ABP) muscle. EEG traces contralateral to the examined MAS or LAS were analyzed offline by visually marking the EMG onset of the ABP. BP amplitude was measured from baseline to the peak negativity from −2000 to −600 ms before EMG onset for the early component of the BP, whereas the amplitude of the BP between −600 and 0 ms before EMG onset represented the size of the late component of the BP. To accurately define the onset of BP latencies, we applied the method by Shibasaki *et al*[23] as follows: the onset of early BP was defined as the point of potential detachment from the baseline, whereas the onset of late BP was defined as the merge point between a line traced on an increasing early BP and a line traced on the steeper BP amplitude.

Statistical Analysis

Data are expressed as means ± standard deviations. Differences in neurophysiological parameters between NCs and PD patients were evaluated by independent-samples *t* test. Differences in demographic, clinical, and neurophysiological parameters among the PD patient groups and within the groups were assessed, respectively, using one-way analysis of variance (ANOVA) and repeated-measures ANOVA after testing for sphericity. Post hoc analysis was performed using Tukey's post hoc test for further comparisons. Pearson's coefficient was used for correlation analyses. The threshold level for statistical significance was established at $P < 0.05$.

Results

Forty-one patients with PD (23 men [56%]; age: 64.7 ± 6.9 years; disease duration: 1.7 ± 1.1 years; Hoehn–Yahr stage: 1.9 ± 0.4) and 24 age- and sex-matched NCs (11 men [46%]; age: 64.5 ± 5.3 years) were enrolled. In PD patients, the neurophysiological parameters detected bilaterally (TMS parameters and BP) showed no differences between the MAS and LAS recordings (Supplementary Table S1) and, thus, only MAS recordings were considered for further analysis. Table 1 presents the neurophysiological parameters

TABLE 2 *Demographic, clinical, and pharmacological characteristics of patients with Parkinson's disease grouped based on the achievement of a sustained long-duration response (LDR+) or no LDR (LDR−) and the assigned training, that is, learning motor exercise (LME) or no motor exercise (NME)*

	LDR + LME group (n = 11, men = 7)	LDR + NME group (n = 10, men = 5)	LDR-LME group (n = 10, men = 5)	LDR-NME group (n = 10, men = 6)
Age (y)	63.9 ± 7.8	63.9 ± 8.2	66.5 ± 5.9	64.4 ± 6.3
Disease duration (y)	2.1 ± 1.4	1.4 ± 0.5	1.6 ± 0.7	1.8 ± 1.5
Hoehn–Yahr score	1.7 ± 0.3	2 ± 0.4	2.1 ± 0.5	1.9 ± 0.2
UPDRS total score	27.8 ± 11.2	33.8 ± 10	35.3 ± 7.9	28.6 ± 7.3
UPDRS-ME score	22.9 ± 10.6	30.2 ± 9.1	28.8 ± 7.9	23.9 ± 6.5
MT at $T0_B$ (ms)°	370.9 ± 102.7	460.9 ± 123.5	390.6 ± 67.8	350.1 ± 78.6
MT at $T0_P$ (ms)°	313.7 ± 81.7	381.5 ± 75	320 ± 53	292.1 ± 64.1
SDR magnitude at T0 (%)°	20.7 ± 3.4	19.9 ± 6.5	22.4 ± 14.2	21.7 ± 14
MT at $T15_B$ (ms)°	303.4 ± 80.2	387 ± 87.5	367.5 ± 57.2	338.5 ± 76.4
MT at $T15_P$ (ms)°	300.9 ± 87.9	364.9 ± 68.1	339 ± 57.2	314.1 ± 47.8
SDR magnitude at T15 (%)°	4.6 ± 5.9	7.8 ± 7.5	9.9 ± 12.9	9.6 ± 11.8
LDR magnitude at T15 (%)°	118.3 ± 54.9[a,b]	103.2 ± 41.5[c,d]	22.2 ± 20.4[a,c]	14.1 ± 15.9[b,d]

Note: Data are means ± standard deviations. LDR + LME, long-duration response present and learning motor exercise; LDR + NME, long-duration response present and no motor exercise; LDR-LME, long-duration response absent and learning motor exercise; LDR, NME, long-duration response absent and no motor exercise; UPDRS-ME,-Unified Parkinson's Disease Rating Scale-Motor Examination section; MT, movement time; SDR, short-duration response; LDR, long-duration response; T0, evaluation day for the levodopa challenge test before treatment and in the unmedicated condition; $T0_B$, base value at T0 condition; $T0_P$, peak value of the levodopa challenge test; T15, evaluation on the 15th day of treatment; $T15_B$, base value on the 15th day of treatment before intake of the morning dose of levodopa; $T15_P$, peak value intake of levodopa on the 15th day of treatment.
Note: °Recorded from the most affected side (except for the P300).
Note: One-way analysis of variance with Tukey's post hoc test comparisons.
Note: *LDR magnitude at T15*: ANOVA F = 21.5, $P < 0.001$. Tukey's post hoc:
[a]LDR + LME versus LDR-LME, $P < 0.001$.
[b]LDR + LME versus LDR-NME, $P < 0.001$.
[c]LDR + NME versus LDR-LME, $P < 0.001$.
[d]LDR + NME versus LDR-NME, $P < 0.001$.

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recorded from the right side in NCs and from the MAS in PD patients at baseline. Latencies of P300, MEPs-AMT, early and late BP components were significantly longer in PD patients than in NCs. The amplitude of MEPs was significantly smaller, and the duration of the CSP was longer in PD patients than in NCs.

Based on the achievement of LDR and the randomization for LME, four groups were obtained: (1) LDR + LME (11 patients), (2) LDR + NME (10 patients), (3) LDR-LME (10 patients), and (4) LDR-NME (10 patients). At T15, all patients belonging to the LME group, regardless of the achievement of a sustained LDR response, learned the motor exercise tasks. The four groups had similar characteristics regarding age, duration of PD, clinical scores at baseline, and SDR magnitude (Table 2). Adverse effects due to L-dopa were not observed. The LDR + LME and LDR + NME groups had significantly larger LDR values than the LDR-LME and LDR-NME groups. Neurophysiological parameters detected under unmedicated conditions ($T0_B$) were almost similar in the groups, except that the amplitudes of MEPs were larger in the LDR + NME and LDR-LME groups with respect to LDR-NME, and the latency of late BP was longer in LDR + LME than in LDR + NME (Supplementary Table S2).

The figures show the effects of the treatments on P300 (Fig. 1), TMS parameters (Fig. 2), and BP (Fig. 3).

Overall, compared with $T0_B$, the achievement of a sustained LDR associated with LME (LDR + LME group) produced a significant improvement in almost all of the neurophysiological parameters (Figs. 1, 2A, C, D, and 3A–C), except for the CSP of MEPs (Fig. 2B) and for the amplitudes of both BP components (Fig. 3B–D). In the LDR + LME group, administration of the last L-dopa dose did not further improve the neurophysiological parameters at $T15_P$ compared with $T15_B$.

In the group that had a sustained LDR but did not perform the motor exercise (LDR + NME), only the latency of late BP significantly improved at $T15_B$ with respect to $T0_B$ (Fig. 3C). In this group of patients, administration of the last L-dopa dose at $T15_P$ produced a significant improvement as compared to $T0_B$ for the latencies of the MEPs at the AMT (Fig. 2D) and of early BP (Fig. 3A).

The other groups not achieving a sustained LDR, both those who did and did not perform the motor exercise (LDR-LME and LDR-NME), did not show changes in any neurophysiological parameter after 15 days of treatment with L-dopa when compared with the baseline values at $T0_B$, neither at $T15_B$ nor at $T15_P$. The only significant change was evident for the latency of late BP in the LDR-NME group at $T15_P$ (Fig. 3C).

Correlation analysis between the magnitude of the LDR to L-dopa and UPDRS-ME scores at T0 did not

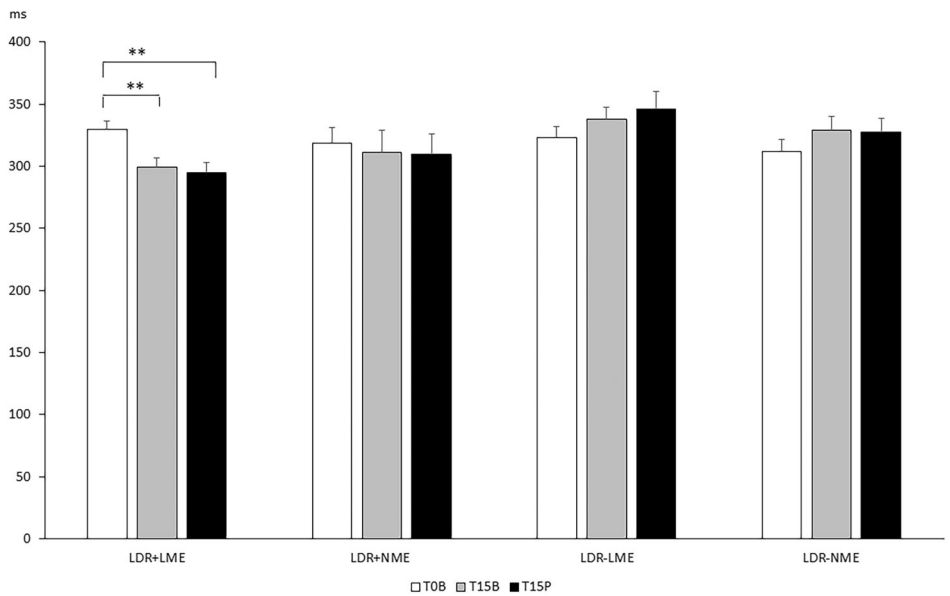

FIG. 1. P300 recorded before and after a 15-day treatment period with levodopa. Patients were grouped based on the achievement of a sustained long-duration response (LDR+) or no (LDR−) and the assigned training, that is, learning motor exercise (LME) or no motor exercise (NME). Data are means ± standard errors. P300 latency in milliseconds. $T0_B$ = base value at T0, that is, the base value in the unmedicated condition (white bars); $T15_B$ = base value on the 15th day of treatment before intake of the morning dose of levodopa (gray bars); $T15_P$ = peak value after 2 hours from intake of levodopa on the 15th day of treatment (black bars). Groups: LDR + LME = long-duration response present and learning motor exercise; LDR + NME = long-duration response present and no motor exercise; LDR-LME = long-duration response absent and learning motor exercise; LDR-NME = long-duration response absent and no motor exercise. Repeated-measures ANOVA (analysis of variance) with post hoc pairwise comparison using Tukey's method. $^{**}P < 0.01$. *P300 LDR + LME $T0_B$ versus $T15_B$*: ANOVA F = 8.49, $P = 0.002$; Tukey's post hoc $P = 0.008$. *P300 LDR + LME $T0_B$ versus $T15_P$*: ANOVA F = 8.49, $P = 0.002$; Tukey's post hoc $P = 0.003$.

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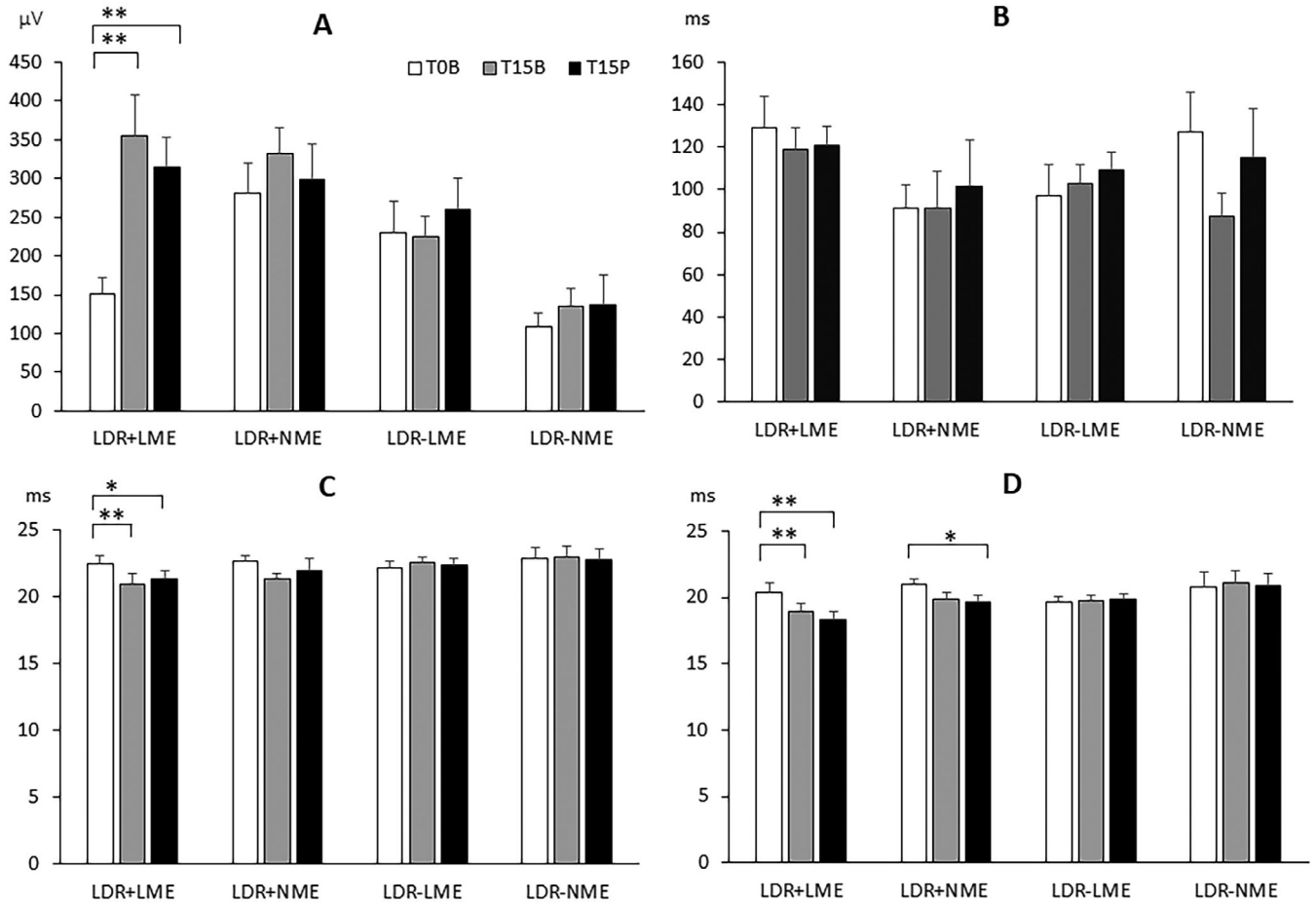

FIG. 2. Motor evoked potentials by transcranial magnetic stimulation before and after a 15-day treatment period with levodopa. Patients were grouped based on the achievement of a sustained long-duration response (LDR+) or no LDR (LDR−) and the assigned training, that is, learning motor exercise (LME) or no motor exercise (NME). Data are means ± standard errors. Motor evoked potential (MEP) parameters were recorded on the more affected side. (**A**) MEP amplitudes (μV). (**B**) Cortical silent period (CSP) duration. (**C**) MEP latencies at the resting motor threshold. (**D**) MEP latencies at the active motor threshold. $T0_B$ = base value at T0, that is, the base value in the unmedicated condition (white bars); $T15_B$ = base value on the 15th day of treatment before intake of the morning dose of levodopa (gray bars); $T15_p$ = peak value after 2 hours from intake of levodopa on the 15th day of treatment (black bars). Groups: LDR + LME = long-duration response present and learning motor exercise; LDR + NME = long-duration response present and no motor exercise; LDR-LME = long-duration response absent and learning motor exercise; LDR-NME = long-duration response absent and no motor exercise. Repeated-measures ANOVA (analysis of variance) with post hoc pairwise comparison using Tukey's method. *$P < 0.05$; **$P < 0.01$. (A) *MEP amplitudes LDR + LME $T0_B$ versus $T15_B$*: ANOVA F = 11.73, $P < 0.001$; Tukey's post hoc $P = 0.001$. *MEP amplitudes LDR + LME $T0_B$ versus $T15_P$*: ANOVA F = 11.73, $P < 0.001$; Tukey's post hoc $P = 0.004$. (C) *MEP latencies at the resting motor threshold LDR + LME $T0_B$ versus $T15_B$*: ANOVA F = 6.73, $P = 0.006$; Tukey's post hoc $P = 0.006$. *MEP latencies at the resting motor threshold LDR + LME $T0_B$ versus $T15_P$*: ANOVA F = 6.73, $P = 0.006$; Tukey's post hoc $P = 0.039$. (D) *MEP latencies at the active motor threshold LDR + LME $T0_B$ versus $T15_B$*: ANOVA F = 11.9, $P < 0.001$; Tukey's post hoc $P = 0.009$. *MEP latencies at the active motor threshold LDR + LME $T0_B$ versus $T15_P$*: ANOVA F = 11.9, $P < 0.001$; Tukey's post hoc $P < 0.001$. *MEP latencies at the active motor threshold LDR + NME $T0_B$ versus $T15_P$*: ANOVA F = 5.93, $P = 0.01$; Tukey's post hoc $P = 0.01$.

show significant correlations. Magnitude of the LDR to L-dopa significantly correlated with some neurophysiological parameters detected at T0, specifically with P300 latency ($r = -0.366$, $P = 0.019$), early BP latency ($r = 0.456$, $P = 0.003$), and late BP latency ($r = 0.368$, $P = 0.018$).

Discussion

The present study shows the synergistic effect between the LDR to L-dopa and motor learning in the recovery of the neurophysiological parameters of cortical excitability in early PD. Our results may shed some light on the different roles of the LDR and motor training in the induction of adaptive changes as an expression of neuroplasticity in basal ganglia and cortical networks.

Neurophysiological Markers of Neuroplasticity

The neurophysiological parameters that we studied could be considered simple surrogate markers of neuroplasticity in different cortical areas. P300, MEPs, and BP could be modified by activities involved in neuroplasticity, such as exercise, and some of these neurophysiological parameters have been reported to be abnormal in PD and recovered by dopaminergic therapy.

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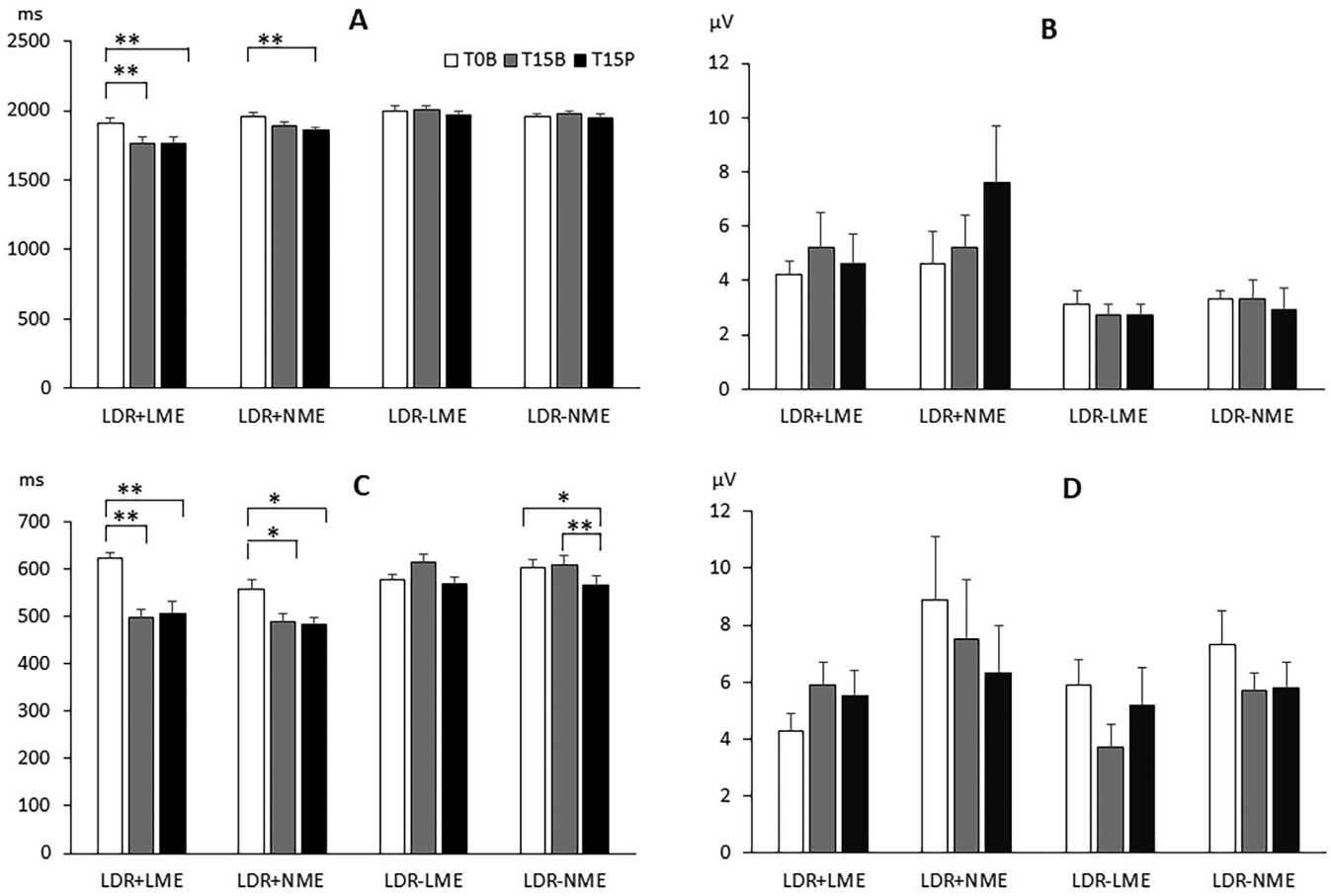

FIG. 3. Bereitschaftspotential parameters before and after a 15-day treatment period with levodopa. Patients were grouped based on the achievement of a sustained long-duration response (LDR+) or no LDR (LDR−) and the assigned training, that is, learning motor exercise (LME) or no motor exercise (NME). Data are means ± standard errors. Bereitschaftspotential (BP) parameters were recorded contralaterally to the more affected side. (**A**) Early BP latencies. (**B**) Early BP amplitudes. (**C**) Late BP latencies. (**D**) Late BP amplitudes. $T0_B$ = base value at T0, that is, the base value in the unmedicated condition (white bars); $T15_B$ = base value on the 15th day of treatment before intake of the morning dose of levodopa (gray bars); $T15_p$ = peak value after 2 hours from intake of levodopa on the 15th day of treatment (black bars). Groups: LDR + LME = long-duration response present and learning motor exercise; LDR + NME = long-duration response present and no motor exercise; LDR-LME = long-duration response absent and learning motor exercise; LDR-NME = long-duration response absent and no motor exercise. Repeated-measures ANOVA (analysis of variance) with post hoc pairwise comparison using Tukey's method. *$P < 0.05$; **$P < 0.01$. (A) *Early BP latencies LDR + LME $T0_B$ versus $T15_B$*: ANOVA F = 15.39, $P < 0.001$; Tukey's post hoc $P < 0.001$. *Early BP latencies LDR + LME $T0_B$ versus $T15_P$*: ANOVA F = 15.39, $P < 0.001$; Tukey's post hoc $P < 0.001$. *Early BP latencies LDR + NME $T0_B$ versus $T15_P$*: ANOVA F = 6.14, $P = 0.009$; Tukey's post hoc $P = 0.008$. (C) *Late BP latencies LDR + LME $T0_B$ versus $T15_B$*: ANOVA F = 28.66, $P < 0.001$; Tukey's post hoc $P < 0.001$. *Late BP latencies LDR + LME $T0_B$ versus $T15_P$*: ANOVA F = 28.66, $P < 0.001$; Tukey's post hoc $P < 0.001$. *Late BP latencies LDR + NME $T0_B$ versus $T15_B$*: ANOVA F = 6.74, $P = 0.006$; Tukey's post hoc $P = 0.018$. *Late BP latencies LDR + NME $T0_B$ versus $T15_P$*: ANOVA F = 6.74, $P = 0.006$; Tukey's post hoc $P = 0.01$. *Late BP latencies LDR-NME $T0_B$ versus $T15_P$*: ANOVA F = 7.67, $P = 0.039$; Tukey's post hoc $P = 0.015$. *Late BP latencies LDR-NME $T15_B$ versus $T15_P$*: ANOVA F = 7.67, $P = 0.039$; Tukey's post hoc $P = 0.005$.

The P300 is related to the activation of frontal, parietal, and hippocampal regions,[24,25] being modified by physical exercise or by the learning of new skills.[26] Previous studies showed drug-naive PD patients recovering prolonged P300 latency after 1 to 2 weeks of dopaminergic treatment.[27,28] These data support a role for dopaminergic transmission in the generation of the P300.[29]

MEP obtained by single-pulse TMS is an index of the overall excitability of the corticomotorneuron connection.[30,31] Previous studies have shown that primary motor cortex (M1) excitability is modulated by motor learning skills in normal subjects[32,33] and in patients with PD.[21]

BP recording reflects voluntary movement preparation, initiation, and execution.[34] The first part of BP, starting 1 to 2 seconds before a movement, is the so-called "early BP." The early BP reflects general preparation for movement and is generated bilaterally by the pre-supplementary motor area, supplementary motor area, and lateral premotor cortex. The early BP is followed by the "late BP," starting 400 to 500 ms before the movement, and is generated by M1. The BP has been shown to be modulated by neurofeedback training, indicating neuroplasticity of cortical areas related to voluntary movement preparation.[35] Abnormalities in the various components of BP could be differently improved by dopaminergic replacement therapy in PD.[36]

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Abnormalities in Neurophysiological Markers in PD

Most of the neurophysiological parameters investigated in the present study were significantly different between patients and NCs, being abnormal in PD. Thus, our findings are consistent with an impaired cortical excitability in untreated PD patients, and most detected abnormalities could be restored by the treatments administered to patients.

Treatment Effects

The effects of treatments were mainly determined by the development of an LDR to L-dopa. Patients who did not achieve the LDR after the 15-day treatment did not exhibit modified neurophysiological values either when trained for a motor exercise or when not trained. Thus, in the absence of a sustained LDR, motor learning alone did not produce any changes in the surrogate markers of cortical excitability. On the contrary, patients who developed a consistent LDR improved some (LDR + NME group) or most (LDR + LME group) of the neurophysiological parameters compared with the untreated baseline values. However, it is worth noting that the optimal recovery was observed in patients who both achieved the LDR and underwent motor training, suggesting a synergistic effect between pharmacological response and the learned motor sequences of finger tapping.

Roles of Motor Training and LDR to L-Dopa

As discussed earlier, motor exercise did not produce modifications in the investigated neurophysiological markers of cortical excitability, at least in the absence of a sustained LDR to L-dopa. Nevertheless, motor training had a noticeable effect on the parameters of neuroplasticity in patients who had a consistent LDR, suggesting that in PD a motor exercise training program could have better results on neuroplasticity in the presence of the LDR to L-dopa. We could speculate that this pharmacological response may facilitate the effects of motor exercise by predisposing the basal ganglia and cortical networks to a different threshold of excitability, allowing motor training to further enhance the beneficial effects on neuroplasticity provided by the LDR alone.

It is worth noting that the effects due to the LDR alone (LDR + NME group) or to the synergy between LDR and motor training (LDR + LME group) were mainly evident for shortening the latencies of the investigated neurophysiological parameters. These findings, taken together with the observed correlations between the magnitude of the LDR to L-dopa and the latencies of both P300 and BP, strongly suggest that these modifications of neuroplasticity due to the treatments could act facilitating the neural transmission at the level of the basal ganglia and cortical networks. We could hypothesize that the synergic interaction between LDR and motor learning could occur at the level of the frontoparietal and primary motor cortex,[24,25,31,34,35] being the analyzed neurophysiological markers mainly generated from these cortical areas. Basal ganglia structures could modulate the increased cortical neuronal excitability.[37]

Relevance of the LDR to L-Dopa

At the given dosages of L-dopa—250 mg every 24 hours for 15 days—some patients developed a sustained LDR, and others did not.[3] This peculiar aspect of the LDR allowed us to study patients with and without LDR. The experimental design of our study involved a 15-day treatment period with L-dopa and, therefore, we cannot ignore the fact that a prolongation of treatment could make possible the achievement of the LDR for most of the patients. Nevertheless, because all the investigated patients, even those who did not develop a sustained LDR to L-dopa, had an SDR to single doses of the drug, we were able to observe the effects on cortical neuroplasticity induced by either an SDR or LDR. The effects of the SDR, measured at the end of treatments, that is, at $T15_P$, were irrelevant for most of the neurophysiological parameters investigated, even in the groups in which the SDR was not influenced by the presence of the LDR.[5] This suggests that improvement in motor disability due to the SDR was not required to induce most of the observed cortical adaptive changes. Thus, the dopaminergic effect on neurophysiological parameters was entirely due to the LDR. This is consistent with previous observations showing maintenance of M1 plasticity in stable parkinsonian patients who presumably had an LDR to L-dopa and loss of plasticity in fluctuating patients, whereas an acute dose of L-dopa producing the SDR had no effect on M1 plasticity.[38]

Besides the improvement in motor performance, the LDR seems to play a relevant role in restoring motor learning and vigor, as demonstrated in experimental parkinsonian models. Indeed, Beeler *et al*[7] showed that in PITx3 knockout mice (mutants exhibiting a loss of dorsal striatal dopamine and impaired in some learning tasks but with normal motor function[39]) motor learning could be recovered by L-dopa administration, with a slow buildup of the learning performance over a few days after treatment initiation and a progressive response decay over several days after L-dopa discontinuation. These results are consistent with the concept that the LDR could be a manifestation of a dopamine-mediated rescued motor learning.[7] Interestingly, the temporal pattern of the learning improvement in PITx3 mice resembled the time course of the motor improvement due to the LDR in patients with PD.[40]

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In parkinsonian patients, motor learning is impaired[41] and worsens with disease progression.[42] It has been suggested that reward pathways may be involved in impaired motor learning,[43] and dopaminergic tonic signaling, such as the activity induced by the LDR, could set the average background rate of reward and thereby provide the motivational set point for action vigor, which influences motor performance.[44] Vigor has been investigated in MitoPark mice having a selective deletion of a mitochondrial transcription factor restricted to midbrain dopaminergic neurons and showing slowly progressive bradykinesia over months.[45] In these mice, repeated L-dopa dosing gradually increases the estimated appropriate movement vigor, as shown by the increase in the number of locomotor bout initiations, similar to an LDR-like effect of L-dopa.[45]

Thus, different impaired activities in parkinsonism could be restored by L-dopa with an LDR-like mechanism in which the slow buildup of the responses could be the expression of some kind of long-duration plasticity.

It has been suggested that the LDR could be better understood in terms of changes in synaptic strength in corticostriatal connections.[46] Our results support the hypothesis that changes in cortical neuroplasticity induced by the LDR represent the common mechanism underlying the improvement in different skills (motor, learning, and vigor) in PD. LDR could predispose the corticostriatal connections to facilitate those activities necessitating tonic dopaminergic signaling, and L-dopa could exert long-lasting effects by inducing adaptive changes at the cortical level.

Conclusions

Our study sheds some light on the mysterious LDR to L-dopa. We recently reported that parkinsonian patients predisposed to the development of this pharmacological response had peculiar structural conditions in the cortical areas involved in motor control.[47] The results of the present study support the evidence that cortical excitability of early PD patients may undergo changes in neuroplasticity due to the development of an LDR to L-dopa acting in synergy with motor exercise. On these grounds, therapeutic strategies based on the LDR[48] should be considered to provide benefit to patients not only in terms of motor improvement without dyskinesia[6] but also considering the beneficial effect of the LDR on the adaptive changes in basal ganglia and cortical networks allowing the normalization of some neurophysiological parameters of cortical excitability. Our findings support the LDR as a pharmacological outcome possibly facilitating the action of motor learning on neuroplasticity in early PD. Further studies are needed to understand the LDR to L-dopa, a pharmacological conundrum influencing a large part of the benefit of dopaminergic drugs.

Author Contributions

M. Zappia: research project: conception, organization, execution; statistical analysis: design, execution, review and critique, manuscript: writing of the first draft, review and critique.

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Data Availability Statement

Data of our study are available to be revised according to the data transparency policy.

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Supporting Data

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