RESEARCH ARTICLE

Corticospinal Suppression Underlying Intact Movement Preparation Fades in Parkinson's Disease

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ABSTRACT: Background: In Parkinson's disease (PD), neurophysiological abnormalities within the primary motor cortex (M1) have been shown to contribute to bradykinesia, but exact modalities are still uncertain. We propose that such motor slowness could involve alterations in mechanisms underlying movement preparation, especially the suppression of corticospinal excitability—called "preparatory suppression"—which is considered to propel movement execution by increasing motor neural gain in healthy individuals.

Methods: On two consecutive days, 29 PD patients (*on* and *off* medication) and 29 matched healthy controls (HCs) underwent transcranial magnetic stimulation over M1, eliciting motor-evoked potentials (MEPs) in targeted hand muscles, while they were either at rest or preparing a left- or right-hand response in an instructed-delay choice reaction time task. Preparatory suppression was assessed by expressing MEP amplitudes during movement preparation relative to rest.

Results: Contrary to HCs, PD patients showed a lack of preparatory suppression when the side of the responding hand was analyzed, especially when the latter was the most affected one. This deficit, which did not depend on dopamine medication, increased with disease duration and also tended to correlate with motor impairment, as measured by the Movement Disorder Society Unified Parkinson's Disease Rating Scale, Part III (both total and bradykinesia scores).

Conclusions: Our novel findings indicate that preparatory suppression fades in PD, in parallel with worsening motor symptoms, including bradykinesia. Such results suggest that an alteration in this marker of intact movement preparation could indeed cause motor slowness and support its use in future studies on the relation between M1 alterations and motor impairment in PD. © 2022 International Parkinson and Movement Disorder Society.

Key Words: Parkinson's disease; motor cortex; bradykinesia; motor control; transcranial magnetic stimulation

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Parkinson's disease (PD) is characterized by pathognomonic nigrostriatal neurodegeneration, leading to dopamine depletion in the striatum and dysfunctional cortico-basal ganglia loops.[1,2] This entails a decreased thalamocortical output onto the primary motor cortex (M1)[3,4] and a disruption of the preparatory and executive phases of voluntary movements, clinically translating into deficits like bradykinesia.[5-8] Interestingly, advancements in research have revealed that alterations in M1 activity and deriving corticospinal motor projections directly contribute to PD pathophysiology.[9-13] How exactly these intrinsic motor neural abnormalities are related to movement deficits like bradykinesia is, however, still a matter of debate.[7,14,15] Here, we propose that such motor slowness could be related to pathological changes in

dynamics of corticospinal excitability supporting voluntary movement preparation.

Studies using single-pulse transcranial magnetic stimulation (TMS) over M1 in healthy participants have repeatedly observed a transient decrease in the amplitude of motor-evoked potentials (MEPs) during movement preparation, suggesting a paradoxical suppression of excitability within the corticospinal tract preceding the execution of an action.[16-18] Even if this "preparatory suppression" is highly reproducible, its function has not been fully elucidated yet.[19-21] Initially, it was linked only to behavioral inhibition,[22-25] but more recently, a new hypothesis has emerged, based on which preparatory suppression could also facilitate movement release and speed[17,26] in a "gain modulation" manner.[27-30] Following that idea, greater motor inhibition could enhance sensitivity to excitatory inputs,[31] increasing the signal-to-noise ratio of neurons controlling forthcoming movements and favoring rapid response execution.[32] Accordingly, in healthy humans, the strength of preparatory suppression correlates with the speed of motor responses: the stronger the motor suppression, the faster the response execution.[17,26] Dopamine appears as a likely source for this mechanism given its role in activating cortical interneurons and in increasing the signal-to-noise ratio in cortical regions;[33] it has also been shown to enhance the gain of cells, both in the striatum[34,35] and in the motor output pathway.[36]

Previous TMS studies in PD already uncovered abnormal changes within the motor system, including attenuated levels of M1 inhibition accompanied by an increase in corticospinal output.[12,15,37-39] Interestingly, some past findings suggest that dopaminergic medication can normalize alterations in M1[38,40,41] and corticospinal[15,42] excitability, in parallel to alleviating bradykinetic symptoms;[15,43] still, the effects of dopamine on motor excitability are not fully elucidated,[7,39,44] as other studies failed to demonstrate such findings.[14,15,45,46] Moreover, work on motor excitability in PD has focused mainly on measures at rest or during simple reaction time (RT) tasks, without considering measures characterizing intact movement preparation in particular.

In the present study, we tested the hypothesis that PD patients display a lack of corticospinal suppression during movement preparation and that this deficit may contribute to their bradykinesia. Furthermore, we postulated that dopamine intake in patients reduces bradykinesia at least in part by restoring preparatory suppression. Finally, given that dopaminergic neurodegeneration increases with disease duration,[47,48] we expected deficits in preparatory suppression to worsen as a function of the years since diagnosis. To address these predictions, in PD patients and healthy controls (HCs), we applied TMS over M1 during an instructed-delay choice RT task in two sessions on separate days; patients were tested either *off* or *on* dopamine replacement therapy (DRT). Neurophysiological measures were cross-analyzed with task behavior and clinical data.

Patients and Methods

We recruited 29 patients with idiopathic PD (13 women, aged 64.7 ± 10.5 years) and 29 HCs, matched for age (62.9 ± 9.5 years), gender, and education. All controls and 25 patients were right handed.[49] Exclusion criteria comprised the presence of severe cognitive decline (based on Montreal Cognitive Assessment)[50,51] and a history of major psychiatric, neurological (except PD), or substance use disorder (except nicotine). Participants provided written informed consent, following a protocol approved by the Biomedical Ethics Committee of the Saint-Luc University Hospital (Brussels, Belgium), in accordance with the Declaration of Helsinki.

Demographic and clinical features of patients are summarized in Table 1. All were diagnosed based on Movement Disorder Society (MDS) clinical diagnostic criteria[52] and recruited at Saint-Luc University Hospital (Brussels, Belgium). We did not include tremor-dominant nor dyskinetic patients. All were treated by DRT and were physically independent (Hoehn & Yahr stage ≤3),[53] and none had impulse control disorders or dopamine dysregulation syndrome,[54] to preclude a lack of preparatory suppression due to deficits in behavioral inhibition.[22,24]

Every participant underwent two testing sessions at the same hour on two consecutive mornings. PD patients performed one session 1 hour after their first dose of DRT ("*on*-DOPA") and the other after a withdrawal of at least 12 and 24 hours for levodopa and dopamine agonists (and any other PD medication), respectively ("*off*-DOPA"), in a randomised order. Patients underwent the MDS-Unified Parkinson's Disease Rating Scale, Part III (MDS-UPDRS-III), at the beginning of each session,[55] to obtain a global motor impairment score as well as a subscore reflecting more specifically the degree of bradykinesia (see Supplementary Material for details on this subscore). Matched controls performed two identical sessions; we randomly turned one into a fictive *off*-DOPA while turning the other into a fictive *on*-DOPA session. All participants filled in the French version of the Beck Depression Inventory (second edition [BDI-II])[56] and the UPPS Impulsive Behavior Scale (measuring trait impulsivity),[57] both validated for use in PD.[58-60]

For the assessment of preparatory suppression, participants sat in a quiet dimly lit room, facing a computer screen positioned 60 cm in front of them, to

TABLE 1 *Details of demographic and clinical data in PD patients*

Patient	Gender	Age (years)	Handedness	Disease duration (Y)	Hoehn & Yahr	MDS-UPDRS-III, Total, OFF-DOPA	MDS-UPDRS-III, Total, ON-DOPA	LEDD (mg)	Most affected side based on PD dominance	MoCA	BDI-II	UPPS
1	M	74	R	1	2	24	19	400	L	25	13	107
2	F	78	R	1	2	39	34	200	L	27	14	102
3	F	68	R	2	2	21	16	450	R	27	3	81
4	M	64	L	2	2	23	23	126	R	28	3	81
5	M	59	R	3	2	12	6	790	R	28	6	57
6	M	43	R	3	2	25	15	610	R	27	3	111
7	M	75	R	3	2	15	16	600	R	25	13	100
8	F	48	R	3	2	17	16	330	L	26	8	114
9	M	79	R	4	2	18	12	652	L	27	9	63
10	M	69	R	4	2	44	46	400	L	26	12	72
11	M	50	R	4	2	28	24	1895	R	29	14	81
12	F	68	R	5	2	9	3	760	R	28	5	85
13	M	41	R	5	2	29	17	810	L	29	*NA*	89
14	M	70	R	5	2	28	19	985	L	28	5	65
15	F	59	R	5	2	28	17	760	L	30	21	103
16	F	55	R	5	2	29	15	775	R	26	15	85
17	F	66	R	6	3	38	29	864	R	29	13	80
18	M	68	L	8	3	36	27	953	L	27	24	104
19	M	58	L	8	2	32	26	805	R	29	21	103
20	F	77	R	8	3	51	37	650	L	29	23	95
21	F	64	R	9	2	38	17	771	R	27	19	85
22	F	61	L	9	2	25	16	540	R	26	7	70
23	F	55	R	10	2	37	25	610	R	28	11	115
24	M	73	R	11	3	35	26	875	L	29	8	95
25	M	69	R	11	2	40	33	460	R	27	9	86
26	M	74	R	12	2	44	27	890	L	26	*NA*	*NA*
27	M	72	R	13	2	42	34	938	L	29	12	59
28	F	59	R	15	2	33	27	745	L	30	13	80
29	F	79	R	16	3	37	28	680	L	26	15	91
Mean/%	45% F	64.7	86% R	6.6	2.2	30.2	22.4	700.8	48% R	27.5	11.8	87.8
SD	/	10.5	/	4.2	0.4	10.3	9.4	318.9	/	1.4	6.6	22.9

Note that patients are ranged according to their disease duration, that is, the years since their diagnosis. Data from outlier patient P22 are shown in gray.

Abbreviations: MDS-UPDRS-III, Movement Disorder Society Unified Parkinson's Disease Rating Scale, Part III; *off*-DOPA, session performed after overnight withdrawal of dopamine replacement therapy (minimum 12 hours withdrawal for levodopa and minimum 24 hours withdrawal for dopamine agonists (and other PD medication); *on*-DOPA, session performed 1 hour after the intake of dopamine replacement therapy; LEDD, levodopa equivalent daily dose; PD, Parkinson's disease; MoCA, Montreal Cognitive Assessment; BDI-II, Beck Depression Inventory, Second Edition; UPPS, UPPS Impulsive Behavior Scale; SD, standard deviation; NA, not available.

perform a virtual 3D "Rolling Ball" game previously used in several studies (Fig. 1A).[22,24,26,61-64] Each hand was placed palm down on a specifically engineered response device allowing to detect horizontal movements of index fingers (Fig. 1B).[24,25,63] Briefly, participants had to choose between abducting the left or right index finger according to the display of a ball (preparatory cue), whose position on the screen indicated the side of the required response. Subjects then had to prepare their response to release it as quickly as possible after the onset of a bridge (imperative signal), allowing the ball to roll over the bridge into a goal. The arrival time (AT) corresponded to the time elapsed from the imperative to the moment the responding finger reached an inner metal contact on the response device. Importantly, we classified finger responses of patients according to PD dominance, that is, depending on whether they were made with the most affected (MA) or least affected (LA) hand. These hand conditions were matched with the nondominant (ND) and dominant (D) hands of HCs, respectively, given that a majority of patients (17 of 29) displayed higher motor impairment on their ND side (see Table 1).

Participants performed this task in two sessions, following the same sequence of blocks (Fig. 1C). The first training block always served to familiarize subjects with the task (training 1, no TMS), whereas the second one (training 2, with TMS) served to estimate the individual median AT. The latter was used (1) to adapt the maximum time allowed to respond after the imperative signal (AT + 2 standard deviation [SD]) and (2) to individualize feedback scores on correct trials.[64] Then, the main phase of the experiment involved four blocks of 36 trials each; TMS was applied in 30 of 36 trials. Each main block consisted of an equal proportion of left- and right-hand trials. TMS pulses were delivered bilaterally[64-66] at one of two possible timings during the task (Fig. 1D) (see Fig. 1E and Supplementary Material for details on TMS protocol). First, to establish a baseline measure of corticospinal excitability, some trials involved TMS during the intertrial interval ($TMS_{BASELINE\text{-}IN}$, 10 trials per block), eliciting MEPs within the task context but when participants were at rest. Second, in other trials, TMS was delivered between the preparatory cue and the imperative signal (TMS_{PREP}, 20 trials per block), while patients were preparing a response with either their MA ($RESP_{MA}$, 10 trials per block) or LA ($RESP_{LA}$, 10 trials per block) hand, comparable to $RESP_{ND}$ or $RESP_{D}$, respectively, in HCs. The remaining 6 of 36 trials did not involve any TMS and were included to prevent participants from anticipating a TMS_{PREP} whenever there had been no $TMS_{BASELINE\text{-}IN}$. Finally, we also obtained MEPs outside the task context, with participants at complete rest, in front of a blank screen ($TMS_{BASELINE\text{-}OUT}$; 3 blocks per session; 15 TMS trials per block) (Fig. 1C).

Electromyography (EMG) was used to measure the peak-to-peak amplitude of the First Dorsal Interosseus (FDI) (task agonist) MEPs in the MA (MEP_{MA}) and LA (MEP_{LA}) hands of patients and corresponding conditions in HCs (MEP_{ND} and MEP_{D}, respectively), which were then sorted according to the experimental condition in which they had been elicited ($TMS_{BASELINE\text{-}OUT}$, $TMS_{BASELINE\text{-}IN}$, TMS_{PREP} with $RESP_{MA/ND}$ or $RESP_{LA/D}$). Trials with any background EMG activity exceeding 3 SD above the mean of the root mean square in the 200-ms window preceding the TMS pulse were excluded from the analysis.[24-26] EMG also allowed us to extract the RT in the task; the movement time (MT) was then obtained by deducting the RT from the AT in the corresponding trial. More details on EMG recording and extraction as well as data-cleaning procedures are presented in the Supplementary Material, including comments on managing intermittent tremor in some PD patients.

Statistical analyses were carried out using JASP (version 0.16.3; JASP Team, 2022). Patients and controls were compared for age and depression (BDI-II) using Mann-Whitney *U* tests and for trait impulsivity using a multivariate analysis of variance (MANOVA) on the four UPPS subscale scores. In patients, we compared motor symptoms (total MDS-UPDRS-III and bradykinesia subscore) between the *off*- and *on*-DOPA sessions using a Wilcoxon test. For the assessment of preparatory suppression, we expressed MEPs acquired at TMS_{PREP} in percentage of MEPs elicited at $TMS_{BASELINE\text{-}IN}$ in the corresponding hand. Group comparisons were then conducted using a four-way mixed repeated-measures ANOVA (RM-ANOVA), with GROUP (PD patients, HCs) as the between-subject factor and with DRT (*on*-DOPA, *off*-DOPA), $RESP_{SIDE}$ ($RESP_{MA/ND}$, $RESP_{LA/D}$), and MEP_{SIDE} ($MEP_{MA/ND}$, $MEP_{LA/D}$) as within-subject factors (Mauchly tests were used to exclude data sphericity). Post hoc comparisons were run using Tukey's honestly significant difference. Besides, to assess the presence of preparatory suppression in each subcondition, we used paired *t* tests comparing the raw MEP values (mV) at TMS_{PREP} to those at $TMS_{BASELINE\text{-}IN}$. Further analyses on raw baseline MEPs are reported in the Supplementary Material. To assess participants' task behavior, we focused on trials in which TMS pulses were applied during the intertrial interval ($TMS_{BASELINE\text{-}IN}$) or trials in which there was no TMS pulse, to avoid its possible disturbance effect;[67,68] all such trials were pooled together. For the analyses of RT and MT, we conducted two separate three-way mixed RM-ANOVAs, with GROUP (PD patients, HCs) as between-subject factor and with DRT (*on*-DOPA, *off*-DOPA) and $RESP_{SIDE}$ ($RESP_{MA/ND}$, $RESP_{LA/D}$) as within-subject factors. Finally, we used Spearman's rank correlations to check for a possible relation between the levels of preparatory suppression in PD patients and

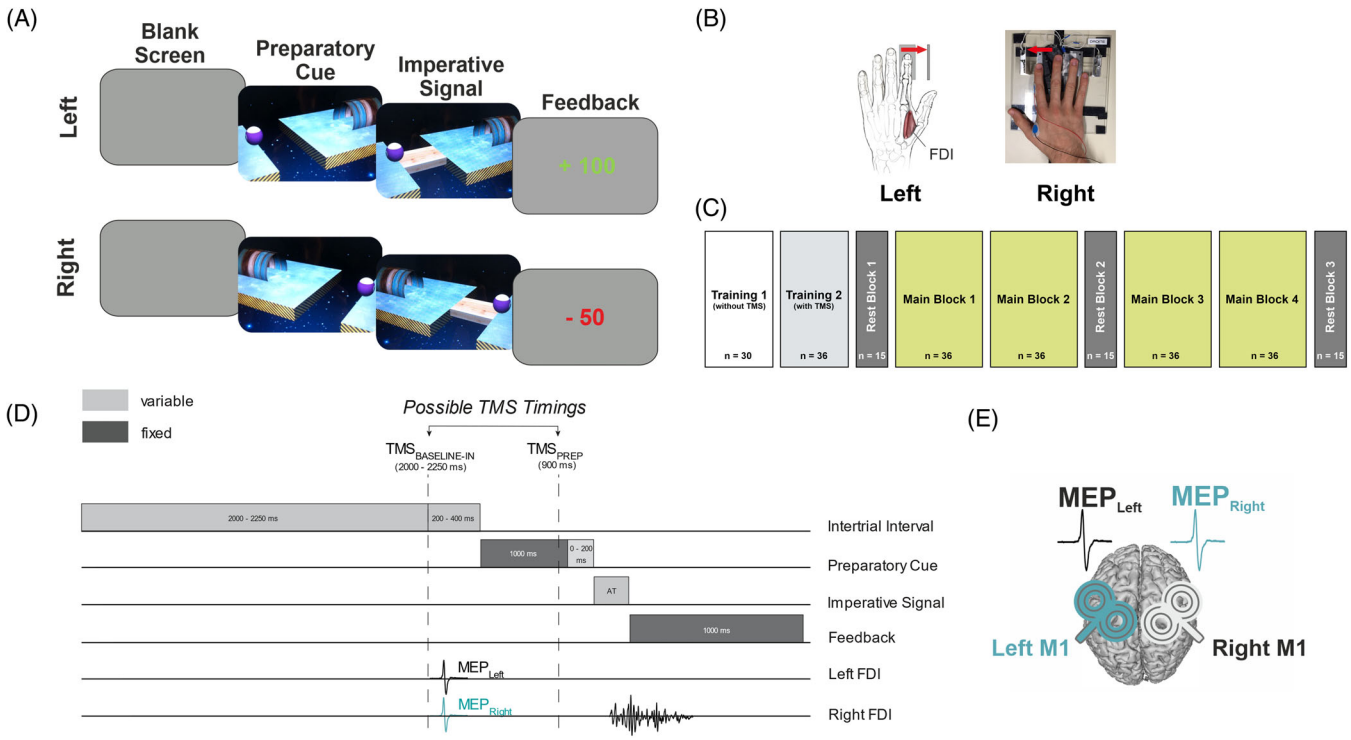

FIG. 1. Experimental procedure. A. Rolling Ball task. Participants performed an instructed-delay choice reaction time task which required them to choose between a left or right index finger abduction according to the position of a ball (preparatory cue) opposite to a goal and separated from it by a gap. The side of the ball indicated the side of the required forthcoming movement response. Importantly, subjects were asked to withhold their response until the onset of a bridge (imperative signal) closing the gap between the ball and the goal. Once the bridge appeared, they had to release their response as quickly as possible, with the correct finger, in order to make the ball roll over the bridge into the goal on the other side of the gap. The imperative screen disappeared once a response was detected (or after a maximum time given to respond, individualised for each participant based on training performance) and a feedback was presented. Note that responses provided before the imperative signal caused the ball to fall into the gap. Following a correct response, participants received a positive score inversely proportional to the arrival time (AT) (the faster, the higher the score), ranging from 1 to 100 and depicted in green at the centre of the screen. Negative scores occurred when subjects responded too early (before the imperative signal), too late (more than the individualized maximum time) or with the incorrect finger. B. Response device and EMG recording. A response device was positioned under each hand (left = graphic representation; right = photographic representation). Each device was composed of a pair of metal edges fixed on a plastic support which detected responses by registering abduction movements from the outer to the inner metal edge of the left and right index fingers. Subjects always had to go back to the outer reference position before providing the next response. EMG activity was recorded from surface electrodes placed on the first dorsal interosseous (FDI) in both hands. C. Experimental design. After two training blocks, participants performed four main blocks of n=36 trials each, during which motor-evoked potentials (MEPs) were elicited either at $TMS_{BASELINE-IN}$ or TMS_{PREP}, in a random order. MEPs were also elicited in three rest blocks, outside the context of the task ($TMS_{BASELINE-OUT}$). D. Time course of a trial. Each trial began with the presentation of the preparatory cue displayed on the screen for a variable duration (1000–1200 ms), followed by the imperative signal which remained visible until a finger response was provided (within the maximum AT given to respond). Then, the feedback score based on the trial's performance appeared for 1000 ms, followed by a blank screen lasting for a variable interval of 2200–2650 ms (intertrial interval). TMS pulses could occur either during the intertrial interval (2000–2250 ms after the onset of the blank screen; $TMS_{BASELINE-IN}$) or during the delay period (900 ms after the onset of the preparatory cue; TMS_{PREP}). E. TMS protocol. Two small figure-of-eight coils were placed tangentially over both primary motor cortices, with the handle pointing backward and laterally at a 45° angle away from the midline, approximately perpendicular to the central sulcus. This way, a posterior-anterior current was induced in the underlying neural cells,[16,20] thus eliciting MEPs in the left and right FDI with a 1 ms inter-pulse interval.

disease duration (ie, years since diagnosis), as well as motor impairment, as measured by both total and bradykinesia MDS-UPDRS-III scores. Further correlations are provided in the Supplementary Material, including with MT in the task as well as with age. Data are shown as mean ± SD; for multiple comparisons, we used FDR corrections. Statistical significance was set at $P < 0.05$.

Results

A summary of demographic and clinical characteristics for PD patients and HCs is provided in Table 2. As expected, the two groups did not differ in age but were also comparable when considering scores of the trait impulsivity UPPS questionnaire; in contrast, patients displayed higher depression scores than HCs at the BDI-II, as expected. Patients also scored significantly higher on the MDS-UPDRS-III (total and bradykinesia scores) *off*-DOPA than *on*-DOPA (both $P < 0.001$), confirming the alleviation of motor symptoms through stimulation of their dopaminergic system with DRT.

The analysis of preparatory suppression disclosed one patient with aberrant values (P22 in Table 1), who was identified as an extreme outlier, based on the IQR rule (+3 IQRs) (see inset in Fig. 2A); this patient and

the corresponding control were subsequently removed from all MEP and behavioral analyses. The four-way RM-ANOVA run on the remaining PD patients and HCs revealed a significant effect of GROUP ($F(1, 54) = 4.7$, $P = 0.03$) due to overall higher percentage MEP values in patients (91.3 ± 29.2%) than in controls (81.7 ± 24.3%), indicating less preparatory suppression in the PD group in general. Besides, analyses revealed a significant GROUP × $RESP_{SIDE}$ × MEP_{SIDE} interaction ($F(1, 54) = 21.44$, $P < 0.001$). As shown in Figure 2A, healthy participants exhibited similar levels of MEP suppression during action preparation no matter the hand considered for MEPs or the hand required for the upcoming response (all $P > 0.57$). Accordingly, FDR-corrected paired t tests between raw MEPs measured at TMS_{PREP} versus $TMS_{BASELINE\text{-}IN}$ were all significant (all $t(27) < -3.85$, all $P < 0.001$), confirming the systematic presence of preparatory suppression in HCs, as repetitively shown in past studies.[21,69] In contrast, post hoc analyses revealed that, in patients, preparatory suppression varied according to the condition: corticospinal suppression was systematically weaker when MEP_{MA} and MEP_{LA} were on the responding side (ie, $RESP_{MA}$ and $RESP_{LA}$, respectively) compared to when these MEP_{MA} and MEP_{LA} were on the non-responding side (ie, in $RESP_{LA}$ and $RESP_{MA}$, respectively) (Fig. 2A). FDR-corrected t tests between raw MEPs at TMS_{PREP} versus $TMS_{BASELINE\text{-}IN}$ further supported a distinctive lack of preparatory suppression on the responding side (both $t(27) > -0.92$, both $P > 0.42$), with percentage MEPs even leaning visually toward a facilitation, especially in the MA hand. On the non-responding side, preparatory suppression was significant for both MEP_{MA} (in $RESP_{LA}$ trials; $t(27) = -2.91$, $P < 0.01$) and MEP_{LA} (in $RESP_{MA}$ trials; $t(27) = -5.94$, $P < 0.001$), suggesting preservation of preparatory suppression on that side in PD patients. Interestingly, when directly comparing levels of suppression between groups, a significant difference emerged between MEP_{MA}–$RESP_{MA}$ trials in PD patients and the analogous responding condition in HCs (ie, MEP_{ND}–$RESP_{ND}$, see Fig. 2A) (note that this specific condition in PD was also found altered when compared to D hand responses in controls, ie, MEP_{D}–$RESP_{D}$ trials; $P = 0.02$). Importantly, the equivalent group comparison was not significant for the MEP_{LA}–$RESP_{LA}$ trials ($P = 0.49$), suggesting an alteration in preparatory suppression on the responding side consistent with PD dominance (ie, most prominent deficit on the MA side). Surprisingly, we did not detect any effect of medication on preparatory suppression in patients, as revealed by the absence of a GROUP × DRT interaction ($F(1, 54) = 0.02$, $P = 0.89$) or any other interaction involving the factor DRT (all $P > 0.49$; see Fig. S2 for individual data points in both sessions).

Next, as shown in Figure 2B, the three-way RM-ANOVA performed on RT in the task did not reveal an effect of the main factor GROUP ($F(1, 54) = 0.42$, $P = 0.52$) nor significant interactions for GROUP × $RESP_{SIDE}$ ($F(1, 54) = 0.20$, $P = 0.66$) or GROUP × DRT ($F(1, 54) = 2.7$, $P = 0.11$), showing the absence of an effect of PD dominance or medication on patients' RT in our task. In contrast, the RM-ANOVA performed on MT yielded a main effect of the factor GROUP ($F(1, 54) = 6.75$, $P = 0.01$), revealing longer MT in patients. However, this result was not specific to the MA side, as revealed by the absence of a GROUP × $RESP_{SIDE}$ interaction ($F(1, 54) = 0.82$, $P = 0.37$), nor was it influenced by medication (GROUP × DRT: $F(1, 54) = 0.98$, $P = 0.33$).

We then ran Spearman's rank correlations in PD patients (Fig. 3), focusing on preparatory suppression in the MA hand (MEP_{MA}) preceding responses on the MA side ($RESP_{MA}$), given that this is the condition in which patients displayed the strongest deficit. We also pooled data from the *on*- and *off*-DOPA sessions for these correlations, as the RM-ANOVA did not reveal any effect of medication (but see correlations on non-pooled data in Fig. S3). Interestingly, preparatory suppression data were found to significantly correlate with disease duration (rho = 0.44, $P = 0.02$; Fig. 3A): the

TABLE 2 *Demographic and clinical data in PD patients and HC subjects*

	PD patients (n=29)		HC subjects (n= 29)		PD patients vs. HC subjects
	Mean (± SD)	Range (min–max)	Mean (± SD)	Range (min–max)	P-values*
Age (years)	64.7 (± 10.5)	41–79	62.9 (± 9.5)	41–79	$P = 0.37$
UPPS (trait impulsivity)	87.8 (± 22.9)	57–115	87.6 (± 15.6)	59–130	$P = 0.06$
BDI-II (depression)	11.8 (± 6.6)	3–24	3.8 (± 4.8)	0–21	**$P < 0.001$**

Means (± SD) include outlier patient P22 (see Table 1), who showed aberrant values for preparatory suppression, but who did not display abnormal outlier values in demographic, clinical or behavioural task data.

Abbreviations: PD, Parkinson's disease; HCs, healthy controls; SD, standard deviation; UPPS, UPPS Impulsive Behavior Scale; BDI-II, Beck Depression Inventory, Second Edition; MANOVA, multivariate analysis of variance.

*P-values for comparisons between PD patients and HCs (obtained from Mann-Whitney U-tests, except for the UPPS, which was analysed using a MANOVA).

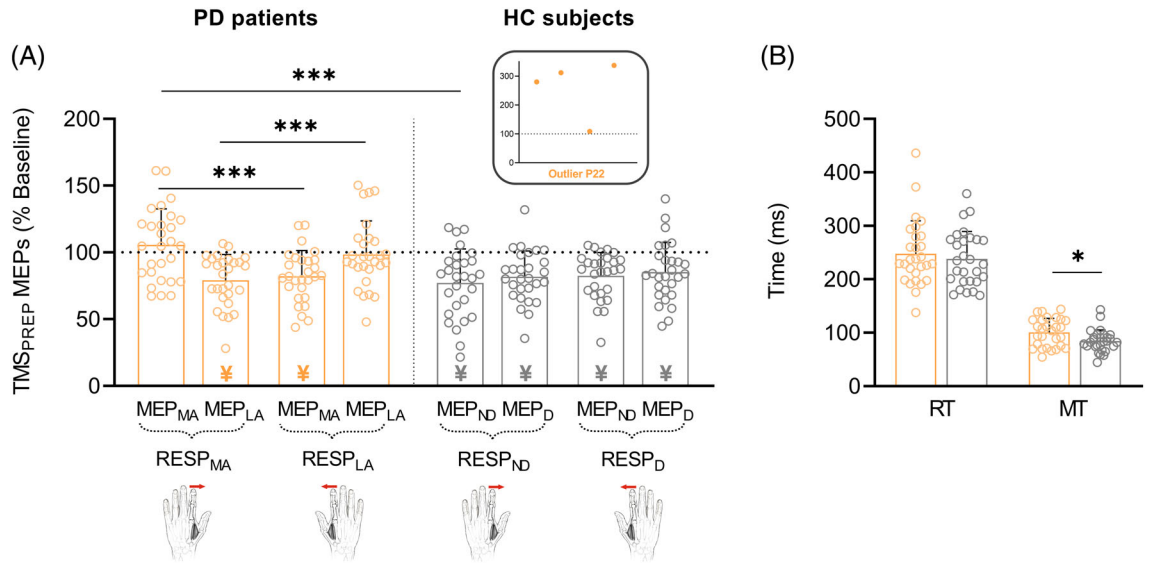

FIG. 2. Preparatory suppression and behaviour during the Rolling Ball task in Parkinson's disease (PD, n=28) patients (in orange) and healthy control (HC, n=28) subjects (in grey), after exclusion of outlier patient P22 (see Table 1) and the corresponding control subject. Note that for every participant, results of both sessions are pooled together, as the analysis did not reveal any significant difference between the *on*- and *off*-DOPA state in PD patients (but see Supplementary Fig.2 for non-pooled data in PD patients). Each individual dot represents data for a single subject, while the bar plot represents the mean value (+ SD) for the condition. A. Neural measures of preparatory suppression were obtained by expressing the amplitude of motor-evoked potentials (MEPs) recorded at TMS_{PREP} as a percentage of those elicited at $TMS_{BASELINE-IN}$, shown for the most-affected (MEP_{MA}) and least-affected (MEP_{LA}) hand sides in PD patients, corresponding to the non-dominant (MEP_{ND}) and dominant (MEP_{D}) sides in HC subjects. The hand figures represent the responding side ($RESP_{SIDE}$); for the purpose of illustration, in patients the left and right hands are used to represent MA and LA hand responses ($RESP_{MA}$ and $RESP_{LA}$), respectively. For each group, the bars thus represent MEPs according to the hand in which they were elicited and as a function of whether that hand was responding (two peripheral bars) or not responding (two central bars) in the trial. The inset shows the values of outlier patient P22 (with both axes of the inset representing the same variables and conditions as those of the barplot). This figure illustrates the presence of preparatory suppression in all conditions in control subjects, but reveals the lack of this mechanism in the responding hand of PD patients (i.e. peripheral bars), especially on the MA side, which was found to significantly differ from the corresponding condition in HC subjects ($P < 0.001$; all other $P > 0.35$). B. Reaction (RT) and movement time (MT) data (in ms) show that RT did not differ between both groups (mean RT: 247.9 ± 68.0 ms and 238.1 ± 57.3 ms in patients and controls, respectively), while MT were significantly longer in patients compared to control subjects (mean MT: 100.8 ± 35.6 ms and 84.4 ± 25.3 ms, respectively), regardless of PD dominance. Paired t-tests: ¥ = MEPs probed at TMS_{PREP} significantly different from those probed at $TMS_{BASELINE-IN}$; mixed RM-ANOVA: $^{*}P < 0.05$ and $^{***}P < 0.001$.

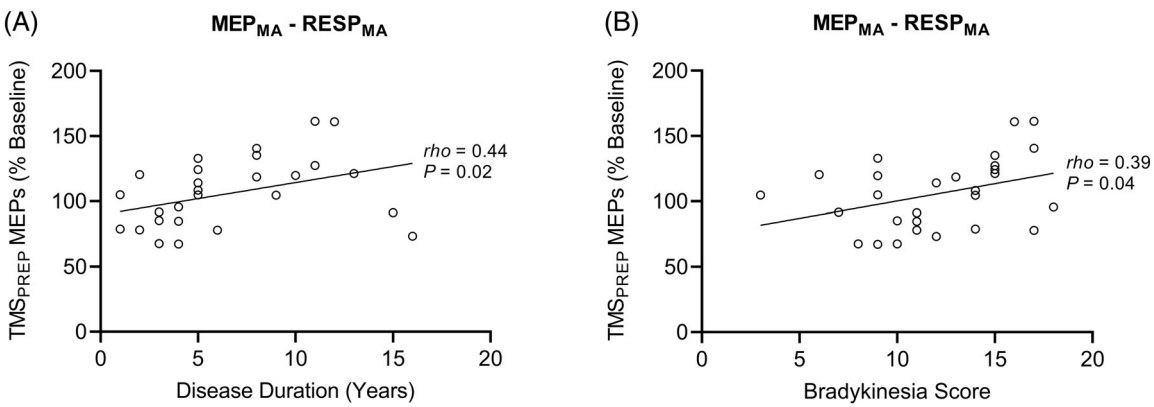

FIG. 3. Spearman's rank correlations in PD patients. Correlations are shown for preparatory suppression (i.e. percentage MEPs at TMS_{PREP}) on the most-affected (MEP_{MA}) side when the latter was responding in the task ($RESP_{MA}$) in relation to A. Disease duration (in years) and B. Bradykinesia subscores in the MA hand (based on the MDS-UPDRS-III), *off*-DOPA. Note that outlier patient P22 was excluded from these correlations. In the absence of an effect of DRT, data from both sessions are pooled together. Note the relationship between preparatory suppression and both disease duration (*rho* = 0.44, both uncorrected and FDR-corrected $P < 0.05$) and bradykinesia subscores (*rho* = 0.39, uncorrected $P = 0.04$, FDR-corrected $P = 0.07$).

longer the disease duration, the stronger the deficit in preparatory suppression, an effect that survived FDR correction (corrected $P = 0.04$). We also observed a significant correlation with the MDS-UPDRS-III scores *off*-DOPA, both total (rho = 0.38, $P = 0.048$) and bradykinesia (rho = 0.39, $P = 0.04$; Fig. 3B), though

here, significance became marginal after FDR corrections (both corrected $P = 0.07$). Except for the tight link between disease duration and clinical scores, none of the other correlations were significant, including those with MT data (see Supplementary Material).

Discussion

PD patients exhibited a lack of corticospinal suppression during movement preparation—contrary to what is typically reported in healthy subjects—no matter their medication status. Interestingly, this deficit was observed only when probed on the responding side but not when preparatory suppression was assessed in the resting, non-responding hand; this was especially true for trials involving the MA side. Critically, such alteration was related to disease duration and also to severity of motor impairment in the same hand (even so marginally).

Our results in HCs are consistent with numerous studies reporting a strong suppression of corticospinal excitability during movement preparation,[16,21,69,70] regardless of whether a trial requires moving the ND or D hand and whether MEPs are obtained on the side of the responding or non-responding hand.[20,25,64] Interestingly, preparatory suppression was substantial in our control group, even though participants were on average markedly older than those typically included in other papers,[24,26] and there exists evidence of an age-related decline in this mechanism.[71] Yet our findings here indicate that, even so, preparatory suppression is still notable in healthy aging.[72] We did not identify a relationship between levels of preparatory suppression and MT in control subjects, probably because the MEP size depends on several overlying processes, precluding a direct link with specific behavioral features of the task used to probe it[21] (but see also Hannah and colleagues and Vassiliadis and colleagues[17,26]).

In PD patients, corticospinal suppression was preserved when probed on the non-responding side, therefore resembling HC levels in that condition. The shortage concerned only the responding hand, where MEPs systematically failed to show suppression during movement preparation and even appeared to become facilitated—though nonsignificantly—on the MA side; importantly, it is also in the latter condition, specifically, that preparatory suppression significantly differed from control subjects. Notably, such a deficit in PD patients occurred in parallel with slower movements during the task (though here both hands displayed comparably longer MT), but similar to HC findings, we could not yet formally establish a significant correlation between MT and corticospinal suppression. However, and even more relevant, levels of preparatory suppression on patients' MA side were related to global MDS-UPDRS-III and bradykinesia scores (*off* medication) in the same hand (albeit marginally after FDR corrections): the stronger the lack of preparatory suppression, the higher the motor impairment based on clinical scores. The fact that patients displayed altered corticospinal suppression only when probed on the responding side, while showing normal levels in the non-responding hand, supports the idea that several influences contribute to generate such an effect in corticospinal excitability during movement preparation.[21,27,69] One influence has been related to inhibitory inputs from the dorsal premotor cortex,[70,73,74] and the deficit observed in our PD patients—related to bradykinesia—suggests that this source may control motor neural gain.[27] Indeed, following the gain modulation hypothesis,[21,28] suppression of motor cortical background activity could increase neuronal sensitivity to excitatory drives, thus accelerating movement execution in effectors selected for upcoming actions.[17,26] Accordingly, several studies in PD have demonstrated early alterations in the frontostriatal motor loop[75] —in parallel with early dopamine deficiency in the putamen[76,77] —including premotor cortex hyperactivity with facilitatory influences on M1, which has been interpreted as an early compensatory mechanism to ease movement initiation.[11,44,78,79] Such premotor hyperactivity could potentially lead to an altered capacity to direct inhibitory influences onto responding effectors during action preparation, especially on the MA side. Besides, past studies have also related preparatory suppression to an impulse control process,[22] considered to rely on influences originating in the lateral prefrontal cortex and generating a global downregulation encompassing also the non-responding side.[63,69,73] Based on our results on the latter side, this mechanism might still be effective in PD patients, in line with observations that prefrontal activity appears preserved until advanced disease stages.[75,80-82]

Importantly, the deficit on the MA responding side was related to disease duration, pointing toward a progressive loss of this mechanism over the course of PD.[83] Consequently, operational nigrostriatal dopaminergic projections may be considered critical for the generation of preparatory suppression on the responding side,[47] which would be consistent with the previously suggested role of dopamine in gain modulation.[33,34] Yet this view appears less compatible with the observation that corticospinal suppression was comparable in the *off*- and *on*-DOPA states. Note that MDS-UPDRS-III scores significantly improved *on*-DOPA, rendering it unlikely that the absence of an effect on preparatory suppression was due to an insufficient stimulation of the dopaminergic system *on* medication. Based on such results, one is led to consider alternative—but not exclusive—explanations, such as the possibility that, rather than being a pathological mechanism, the

increasing lack of preparatory suppression with disease duration actually reflects a compensatory mechanism,[84] possibly linked to cortical disinhibition observed in PD.[14,37,85] Furthermore, our findings may be due to the increasing involvement of other, non-dopaminergic neurotransmitter systems,[86] in particular the cholinergic one.[87]

In conclusion, our study provides novel insights into motor system alterations in PD, by uncovering a clear deficit in corticospinal suppression typically shaping neural activity during movement preparation in healthy populations. Our results point toward a gradual loss of this marker of intact motor control with disease duration, in parallel with worsening motor symptoms, including bradykinesia, supporting the importance of moving to more task-related functional markers—such as preparatory suppression—in future studies on the relation between M1 alterations and motor impairment in PD. Naturally, our study presents certain limitations and has posed new questions to be addressed. First, although we considered disease duration in our analyses, it is not a perfect variable as there is heterogeneity inherent to a diagnosis being established by different movement disorder specialists. Furthermore, the question remains of what changes in intracortical motor circuits underlie the lack of preparatory suppression in PD; this could be tested in the future, using paired-pulse or directional TMS.[20,69] Finally, bradykinesia in PD has been related to altered motivation due to dopamine depletion,[88] leading to depression[89] (in line with our BDI-II findings); therefore, it would be of interest to investigate how preparatory suppression relates to this cognitive feature of PD in future studies. ■

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Data Availability Statement

The data supporting the findings of the present study are available upon reasonable request to the authors.

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Supporting Data

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