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Neurophysiological correlates of bradykinesia in Parkinson's disease

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Many neurophysiological abnormalities have been described in the primary motor cortex of patients with Parkinson's disease. However, it is unclear whether there is any relationship between them and bradykinesia, one of the cardinal motor features of the condition. In the present study we aimed to investigate whether objective measures of bradykinesia in Parkinson's disease have any relationship with neurophysiological measures in primary motor cortex as assessed by means of transcranial magnetic stimulation techniques. Twenty-two patients with Parkinson's disease and 18 healthy subjects were enrolled. Objective measurements of repetitive finger tapping (amplitude, speed and decrement) were obtained using a motion analysis system. The excitability of primary motor cortex was assessed by recording the input/output curve of the motor-evoked potentials and using a conditioning-test paradigm for the assessment of short-interval intracortical inhibition and facilitation. Plasticity-like mechanisms in primary motor cortex were indexed according to the amplitude changes in motor-evoked potentials after the paired associative stimulation protocol. Patients were assessed in two sessions, i.e. OFF and ON medication. A canonical correlation analysis was used to test for relationships between the kinematic and neurophysiological variables. Patients with Parkinson's disease tapped more slowly and with smaller amplitude than normal, and displayed decrement as tapping progressed. They also had steeper input/output curves, reduced short-interval intracortical inhibition and a reduced response to the paired associative stimulation protocol. Within the patient group, bradykinesia features correlated with the slope of the input/output curve and the after-effects of the paired associative stimulation protocol. Although dopaminergic therapy improved movement kinematics as well as neurophysiological measures, there was no relationship between them. In conclusion, neurophysiological changes in primary motor cortex relate to bradykinesia in patients with Parkinson's disease, although other mechanisms sensitive to dopamine levels must also play a role.

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Abbreviations: CCA = canonical correlation analysis; ICF = intracortical facilitation; M1 = primary motor cortex; MDS-UPDRS = Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; MEP = motor-evoked potentials; PAS = paired associative stimulation; SICI = short-interval intracortical inhibition; TMS = transcranial magnetic stimulation

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Introduction

Bradykinesia, or slowness of movement, is one of the cardinal motor features of Parkinson's disease (Berardelli *et al.*, 2013; Postuma *et al.*, 2015). Objective kinematic measures show that this is also accompanied by other changes, including low amplitude (hypokinesia) and a progressive reduction in amplitude and velocity during movement repetition (decrement) (Agostino *et al.*, 1992, 2003; Berardelli *et al.*, 2001; Espay *et al.*, 2009, 2011; Kang *et al.*, 2010; Heldman *et al.*, 2014; Bologna *et al.*, 2016*a*; Hasan *et al.*, 2017). Bradykinesia is believed to result primarily from a failure of basal ganglia output to the primary motor cortex (M1) (Berardelli *et al.*, 2001). However, there is also evidence from animal studies that there are additional intrinsic deficits in M1 that may contribute towards production of symptoms (Pasquereau and Turner, 2011; Pasquereau *et al.*, 2016; Xu *et al.*, 2017). The question we address here is whether these may also play some role in determining bradykinesia in human patients.

Neurophysiological studies in humans using transcranial magnetic stimulation (TMS) have revealed changes in resting measures of excitability and plasticity in M1. There is enhanced corticospinal excitability and reduced M1 inhibition (Cantello *et al.*, 2002; Currà *et al.*, 2002; Lefaucheur *et al.*, 2005; Berardelli *et al.*, 2008; Bologna *et al.*, 2016*b*), together with reduced long-term potentiation-like plasticity in M1 (Morgante *et al.*, 2006; Ueki *et al.*, 2006; Schwingenschuh *et al.*, 2010; Suppa *et al.*, 2011; Kojovic *et al.*, 2012, 2015; Kawashima *et al.*, 2013; Kishore *et al.*, 2017). Some studies have reported a weak relationship between changes in plasticity and clinical motor scores, i.e. lower plasticity associated with more severe motor symptoms (Ueki *et al.*, 2006; Kojovic *et al.*, 2012, 2015; Kishore *et al.*, 2017).

The aim of the present study was to investigate possible relationships between movement kinematics and neurophysiological changes in the M1 of patients with Parkinson's disease. Movement was assessed objectively during repetitive finger tapping and the excitability and plasticity of M1 was measured in the resting state using various TMS techniques. To evaluate the effects of dopaminergic treatment on the neurophysiological measures, we assessed patients in two separate sessions, i.e. both OFF and ON their usual therapy. Data obtained from patients with Parkinson's disease were compared with those obtained from a group of healthy subjects.

Materials and methods

Participants

Twenty-two patients with Parkinson's disease, [four females, mean age ± 1 standard deviation (SD): 67.2 ± 10.3; Table 1] and 18 healthy controls (six females, mean age ± 1 SD: 63.0 ± 11.8) were enrolled in the study. The diagnosis of Parkinson's disease was based on clinical criteria (Berardelli *et al.*, 2013; Postuma *et al.*, 2015). The clinical assessment included the Hoehn and Yahr, the motor section (part III) of the Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) (Goetz *et al.*, 2008; Antonini *et al.*, 2013); side of predominance of motor symptoms was considered evaluating the current most affected side. The clinical assessment also included the Beck Depression Inventory (BDI; Beck *et al.*, 1961), the Montreal Cognitive Assessment (MoCA; Nasreddine *et al.*, 2005) the Frontal Assessment Battery (FAB; Dubois *et al.*, 2000) and the Fatigue Severity Scale (FSS; Friedman *et al.*, 2010). The clinical assessment was performed by a clinician blinded to the experimental procedures. The experimental procedures, which adhered to the Declaration of Helsinki regulations and to international safety guidelines (Rossi *et al.*, 2009; Rossini *et al.*, 2015), were approved by the local institutional review board. All the participants gave their written informed consent to the study.

Kinematic assessment

The participants were comfortably seated in a chair and were asked to perform repetitive finger tapping. Three 15-s trials were recorded from the more affected side in patients and from the dominant side in healthy controls. Participants were allowed to rest for 45–60 s between acquisition trials to avoid fatigue. Before the kinematic recordings, one practice trial was allowed for the participants to become familiar with the motor task.

Kinematic recordings were performed using an optoelectronic system (SMART motion system, BTS Engineering). Three infrared cameras followed the 3D displacement of reflective markers taped to the participant's upper limb (sampling rate of 120 Hz). We used reflective markers with a 5-mm diameter and of negligible weight. Two markers were placed on the tips of the index finger and thumb. A further three markers were placed on the hand to define a reference plane that was used to mathematically exclude possible contamination due to unwanted hand movements from repetitive finger movement recordings (Bologna *et al.*, 2016*a*).

Movement analysis was performed using dedicated software (SMART Analyzer, BTS Engineering). To quantify repetitive finger movement kinematics, we used linear regression techniques to determine the intercept, which reflects the movement amplitude (degree) and velocity (degree/s), and the slope, which reflects the amplitude and velocity decrement during the movement repetition. Movement rhythm was also measured by the coefficient of variation of the inter-tap intervals (with higher values representing a lower regularity of repetitive movements) (Iansek *et al.*, 2006; Bologna *et al.*, 2016*a*).

Transcranial magnetic stimulation techniques and electromyographic recordings

Single- and paired-pulse TMS was delivered using two Magstim magnetic stimulators (Magstim Company) connected to an 8-shaped coil, with the intersection of the coil held tangentially to the scalp and the coil handle positioned at a ~45° angle from the midline pointing backward. We defined the hot spot of the

Table 1 Demographic and clinical data of patients with Parkinson's disease

Patient ID	Age	Gender	Disease duration	Hoehn and Yahr	MDS-UPDRS III OFF	MDS-UPDRS III ON	BDI	MoCA	FAB	FSS	LEDD
1	70	M	1.5	2	26	21	19	29	14	48	300
2	63	M	4	1	19	16	6	24	10	34	420
3	78	M	3	2	41	34	5	27	17	37	300
4	66	M	1	2	28	22	4	24	16	30	300
5	77	M	6	2	29	35	3	26	18	29	452
6	42	M	1	1	13	10	6	27	17	26	105
7	59	M	3	2	33	24	7	28	16	22	450
8	77	M	10	2	49	40	15	26	16	27	700
9	79	F	7	2	47	33	15	17	9	67	500
10	79	F	2	2	32	32	8	24	12	33	300
11	55	F	10	2	32	25	12	28	12	52	557
12	75	M	1.5	2	31	29	0	30	16	9	400
13	64	M	6	1	33	23	7	26	18	25	505
14	82	M	4	3	52	47	16	28	16	44	300
15	56	M	1.5	1	20	9	3	27	18	20	160
16	72	M	3	3	25	17	5	26	16	33	400
17	61	F	4	1	18	13	4	26	18	16	352
18	72	M	1.3	2	27	17	6	26	17	23	300
19	67	M	3	2	38	37	0	30	18	9	257
20	52	M	3	1	22	19	0	29	18	9	257
21	72	M	3	1	19	16	2	30	18	13	205
22	62	M	1.5	2	38	27	2	30	18	32	105

Age and disease duration are expressed in years. BDI = Beck Depression Inventory; FAB = Frontal Assessment Battery; FSS = Fatigue Severity Scale; LEDD = levodopa equivalent daily dose; MoCA = Montreal cognitive assessment.

abductor pollicis brevis muscle, i.e. the optimal scalp position for eliciting motor-evoked potentials (MEP) of maximal amplitudes in the muscle.

We first determined the resting motor threshold and the active motor threshold to the nearest 1% of the maximal stimulator output (Rossi *et al.*, 2009; Rossini *et al.*, 2015). We then measured the MEP input-output curve to probe M1 excitability. We used 60 single pulses at six stimulation intensities, ranging in 20% increments from 80% to 180% of the resting motor threshold, delivered in groups of 10. The intensity order was randomized to avoid hysteresis effects (Möller *et al.*, 2009).

We also assessed short-interval intracortical inhibition (SICI) and facilitation (ICF) using paired-pulse TMS with a subthreshold conditioning stimulus (90% active motor threshold) and a supra-threshold test stimulus (1 mV MEP) with an interstimulus interval between conditioning and test stimuli of 2 and 4 ms for SICI and 10 and 15 ms for ICF (Peurala *et al.*, 2008; Rossini *et al.*, 2015). We chose the intensity of 90% active motor threshold for the conditioning stimuli and 4-ms interstimulus intervals because in previous studies (Peurala *et al.*, 2008) it was demonstrated that in these experimental conditions there is no overlap between SICI and short-interval ICF. Moreover, it has been reported in Parkinson's disease patients OFF medication that no short-interval ICF occurs at 2 and 4 ms interstimulus intervals (Ni *et al.*, 2013). Ten trials were acquired for each interstimulus interval. SICI and ICF were expressed as the percentage ratio between the unconditioned and conditioned MEP.

To study cortical plasticity, paired associative stimulation (PAS) was delivered over M1 contralateral to the more affected side of the body in patients (Kojovic *et al.*, 2012, 2015). PAS consisted of 200 electrical stimuli, delivered to the median nerve at the wrist by means of a Digitimer DS7, paired with TMS stimuli (adjusted to 1 mV MEP intensity), delivered over the contralateral abductor pollicis brevis hot spot (rate 0.25 Hz, electrical stimulation intensity two or three times the perceptual threshold) (Wolters *et al.*, 2003; Kojovic et *al.*, 2012, 2015). Each TMS stimulus was preceded by an electrical conditioning stimulus at an interstimulus interval of 21.5 ms. We chose this specific interstimulus interval because, unlike PAS 25 ms, PAS 21.5 ms is not affected by cerebellar activity (Hamada *et al.*, 2012). During PAS, participants were instructed to look at their hand and to report every 20th peripheral electrical stimuli they perceived to ensure constant attention levels and comparable conditions between sessions (Stefan *et al.*, 2004; Kojovic *et al.*, 2012, 2015).

EMG activity was recorded from the abductor pollicis brevis and first dorsal interosseous muscles of the more affected side in patients and of the dominant side in healthy controls, using surface electrodes taped in a belly-tendon montage. EMG signals were amplified and filtered (20 Hz–1 kHz) using Digitimer D360. EMG signals were recorded and stored on a laboratory PC (sampling rate of 5 kHz) through an analogue-digital converter AD1401 plus (Cambridge Electronic Design) for subsequent off-line analyses performed using a dedicated software (Signal® version 4.00, Cambridge Electronic Design). The MEP peak-to-peak amplitude was measured within a time window of 20–40 ms after the TMS artefact. Traces with background EMG activity exceeding 100 μV in the 200 ms time window preceding the TMS artefact were rejected online.

Experimental design

Patients underwent two sessions (OFF and ON medication). All the patients were studied after overnight withdrawal (at least 12 h) of their medication, in the 'practically defined OFF condition' (Defer *et al.*, 1999) or while they were on their usual therapeutic regimen (ON medication), expressed in terms of levodopa equivalent daily dose (LEDD) (Tomlinson *et al.*, 2010). Each session was randomly performed and counter-balanced across patients at least 1 week apart. Kinematic recordings and TMS measures of corticospinal and intracortical excitability were collected in each session at baseline. To assess M1 plasticity, we then performed the PAS protocol and followed up the M1 excitability changes at three time points: T1 (5 min after PAS), T2 (15 min after PAS) and T3 (30 min after PAS) using single-pulse TMS. Fifteen MEPs were recorded at 1 mV intensity at each measurement time point (including baseline); for the subsequent analysis, data at T1, T2 and T3 were normalized to baseline. The examiners who collected the neurophysiological measures were blinded to the patients' medication status.

Statistical analysis

Age and gender differences between patients with Parkinson's disease and healthy controls were evaluated using the Mann-Whitney U-test and Fisher's exact test, respectively. The MDS-UPDRS (part III) scores in the OFF and ON sessions in patients were compared using the Wilcoxon test.

Group comparisons on kinematic variables and on motor thresholds between patients with Parkinson's disease (OFF medication) and healthy controls were performed by means of two tailed unpaired *t*-tests. Group comparisons on M1 excitability were evaluated using a repeated-measures ANOVA with the between-group factor 'Group' (patients with Parkinson's disease OFF medication and healthy controls) and the within-group factor 'Stimulus intensity' (80%, 100%, 120%, 140% 160% and 180% resting motor threshold). When evaluating SICI and ICF, we used the within-group factor 'interstimulus interval' (2, 4 ms and 10, 15 ms, respectively) in addition to group; SICI and ICF were analysed in two separate ANOVAs as they represent different cortical circuits. When evaluating the effects of PAS, we used the factors 'Group', 'Muscle' (abductor pollicis brevis and first dorsal interosseous) and 'Time point' (T1, T2 and T3). We excluded the possible influence of handedness on movement kinematics and TMS data in patients with an additional analysis comparing the two patient subgroups (patients with Parkinson's disease tested on the left/dominant hemisphere and patients with Parkinson's disease tested on the right/non-dominant hemisphere) and healthy controls (Supplementary material).

To evaluate the effects of medication in patients, we added the within-group factor 'Session' (two levels: OFF and ON medication) to the various ANOVAs. Two tailed *t*-tests were used for *post hoc* analyses in ANOVAs. Greenhouse-Geisser corrections were applied whenever we found a violation of sphericity in Mauchly's tests. Different neurophysiological variables were evaluated in separate ANOVAs.

For subsequent analysis we computed the steepness of the input-output MEP curve (i.e. the slope of the regression line across the scatter plot of the MEP amplitude—*y*-axis versus the stimulation intensity—*x*-axis) and the average percentage changes after PAS of the MEP amplitude values across the three measurement time points (T1, T2 and T3).

A multiple logistic model was also used to determine the variables best predicting disease status and medication status. For this purpose, we considered the least absolute shrinkage and selection operator (LASSO) algorithm with l1-norm penalty. This procedure can be considered as a variable selection tool since it can estimate some variable coefficients to be zero (Tibshirani, 1996).

A canonical correlation analysis (CCA) was used to assess the relationship between (i) neurophysiological measures and kinematic parameters; and (ii) neurophysiological measures and clinical-demographic data. Rather than assuming that there is a simple relationship between, for example, a neurophysiological variable and a particular kinematic parameter as assumed with a linear correlation, a CCA examines whether combinations of neurophysiological measures are better predictors of kinematic variables. The procedure can reveal relationships that would otherwise be missed by simple linear correlation analysis (Hotelling, 1936). We only included variables in the CCA that had been demonstrated to be significantly different in the univariate analysis (also predictive of the disease or medication status, as demonstrated by the LASSO procedure).

Unless otherwise stated, the results are indicated as mean values ± 1 standard error of the mean (SEM). The level of significance was initially set at $P < 0.05$, with the false discovery rate subsequently being applied to multiple comparisons (Curran-Everett, 2000). Data were analysed using STATISTICA® (StatSoft, Inc) and implemented with R.

Results

All the study participants completed the experimental procedure. None of the participants reported adverse effects during the experiments. No difference was found in age ($P = 0.37$) or gender distribution ($P = 0.23$) between patients with Parkinson's disease and healthy controls. As expected, the MDS-UPDRS part III score in patients with Parkinson's disease was significantly higher in the OFF medication session than in the ON medication session (30.4 ± 10.9 versus 24.8 ± 10.1; $P < 0.001$).

Patients with Parkinson's disease OFF medication versus healthy controls

Finger tapping kinematics

The analysis yielded a significant between-group difference for movement amplitude and velocity (with lower values for both parameters being observed in patients with Parkinson's disease than in healthy controls; both *P*'s < 0.01, Table 2). The analysis also revealed a between-group difference for movement amplitude slope (sequence effect) ($P = 0.02$), with higher decrement being observed in patients with Parkinson's disease than in healthy controls. No significant difference emerged between patients with Parkinson's disease and healthy controls in

Table 2 Kinematic variables in patients with Parkinson's disease and in healthy controls

	PD OFF	PD ON	HC	*P*-values*	*P*-values**
Movements, *n*	46.91 ± 3.03	44.75 ± 3.24	39.42 ± 2.74	0.07	0.03
CV	0.14 ± 0.01	0.16 ± 0.01	0.11 ± 0.01	0.08	0.03
Amplitude intercept	41.78 ± 2.84	53.13 ± 2.20	53.25 ± 2.48	**<0.001**	**<0.001**
Velocity intercept	871.86 ± 54.51	1005.37 ± 62.01	1165.66 ± 60.33	**<0.001**	**<0.001**
Amplitude slope	−0.30 ± 0.05	−0.36 ± 0.05	−0.12 ± 0.01	**0.02**	0.14
Velocity slope	−8.24 ± 1.16	−8.28 ± 1.87	−9.12 ± 1.12	0.29	0.46

Results are shown as mean values ± 1 SEM. *P-values by unpaired, two tailed *t*-tests (PD OFF versus HC). **P-values by paired, two tailed *t*-tests (PD OFF versus PD ON). Significant *P*-values are in bold. Corrected alpha level 0.021 by false discovery rate. CV = coefficient of variation; HC = healthy controls; PD = Parkinson's disease.

the movement number, coefficient of variation values of the inter-tap intervals and velocity slope (Table 2).

Corticospinal excitability: motor thresholds and input-output curve

The analysis did not reveal any differences in resting or active motor thresholds between patients with Parkinson's disease and healthy controls (Table 3).

As expected, the ANOVA yielded a significant effect of the main factor Stimulus intensity [$F(5,190) = 77.26$, $P < 0.001$], with an increasing MEP amplitude being observed with increasing stimulation intensity. M1 excitability, as assessed by means of the input-output MEP curve, was greater in patients with Parkinson's disease OFF medication than in healthy controls (Fig. 1), as demonstrated by a significant interaction Group × Stimulus intensity [$F(5,190) = 3.19$, $P = 0.009$]. Lastly, the factor Group was not found to be significant [$F(1,38) = 2.06$, $P = 0.15$].

Intracortical excitability: short-interval intracortical inhibition and facilitation

When analysing SICI, the ANOVA revealed a significant effect of the main factor Group [$F(1,38) = 7.89$, $P = 0.007$], with less inhibition being observed in Parkinson's disease than in healthy controls. The main factor Interstimulus interval was also significant [$F(1,38) = 8.87$, $P = 0.005$], indicating more profound inhibition at 2 ms than at 4 ms while there was no significant Group × Interstimulus interval interaction [$F(1,38) = 0.86$, $P = 0.35$] (Fig. 1). Excitability of the intracortical facilitatory interneurons, as assessed by means of ICF, did not differ between patients with Parkinson's disease and healthy controls (Fig. 1), as is demonstrated by a lack of significant effect of Group [$F(1,38 = 0.006$, $P = 0.93$], Interstimulus interval [$F(1,38) = 0.45$, $P = 0.50$] and Group × Interstimulus interval interaction [$F(1,38) = 0.11$, $P = 0.73$].

M1 plasticity: paired associative stimulation-related effects

The analysis of normalized values indicated that the MEPs increased after PAS in healthy controls but not in patients (Fig. 2). This finding is supported by a repeated-measures ANOVA, which yielded a significant effect of the main factor Group [$F(1,38) = 6.12$, $P = 0.01$], with lower values being observed in patients with Parkinson's disease than in healthy controls. The analysis also showed a significant effect for the main factor Muscle [$F(1,38) = 6.33$, $P < 0.01$] and for the interaction Group × Muscle [$F(1,38) = 5.82$, $P = 0.02$] with higher facilitation being observed in the abductor pollicis brevis (target muscle) than in the first dorsal interosseous in healthy controls but not in Parkinson's disease. No significant effects were observed for the main factor Time point [$F(2,76) = 2.43$, $P = 0.09$] or for the interactions Group × Time point [$F(2,76) = 0.66$, $P = 0.51$]; Muscle × Time point [$F(2,76) = 0.54$, $P = 0.58$] and Group × Muscle × Time point [$F(2,76) = 0.76$, $P = 0.47$].

Patients with Parkinson's disease OFF versus ON medication

Finger tapping kinematics

The analysis revealed higher movement amplitude and velocity values in the ON medication condition than in the OFF medication condition (both *P*'s < 0.001). By contrast, no significant effect of medication was observed for the movement number, coefficient of variation values of the inter-tap intervals and for the amplitude and velocity slopes (all *P*'s > 0.05) (Table 2).

Corticospinal excitability: motor thresholds and input-output curve

The analysis did not reveal any differences in resting motor threshold ($P = 0.69$) or active motor threshold ($P = 0.08$) between patients with Parkinson's disease OFF medication and those ON medication (Table 3).

The input-output MEP curve was less steep in patients ON medication than in those OFF medication (Fig. 1). Repeated measures ANOVA showed a significant effect for the main factor Session [$F(1,21) = 10.90$, $P = 0.003$] and for the interaction Session × Stimulus intensity [$F(5,105) = 4.66$, $P < 0.001$], indicating higher MEP amplitude values in patients OFF therapy than in patients ON therapy. Lastly, as expected, a significant effect was detected for the main factor Stimulus intensity [$F(5,105) = 55.68$, $P < 0.001$].

Intracortical excitability: short-interval intracortical inhibition and facilitation

There were no clear effects of dopaminergic medication on SICI (Fig. 1). Repeated measures ANOVA revealed no statistical significance for the main factor Session [$F(1,21) = 1.18$,

Table 3 Motor thresholds in patients with Parkinson's disease and in healthy controls

	PD patients OFF	PD patients ON	HC	*P*-values*	*P*-values**
AMT	33.1 ± 6.7	34.5 ± 6.7	33.7 ± 7.5	0.79	0.09
RMT	43.9 ± 8.4	44.2 ± 7.6	46.1 ± 8.0	0.39	0.69

Results are shown as mean values ± 1 SEM. **P*-values by unpaired, two tailed *t*-tests (PD OFF versus HC). ***P*-values by paired, two tailed *t*-tests (PD OFF versus PD ON). AMT = active motor threshold; HC = healthy controls; PD = Parkinson's disease; RMT = resting motor threshold.

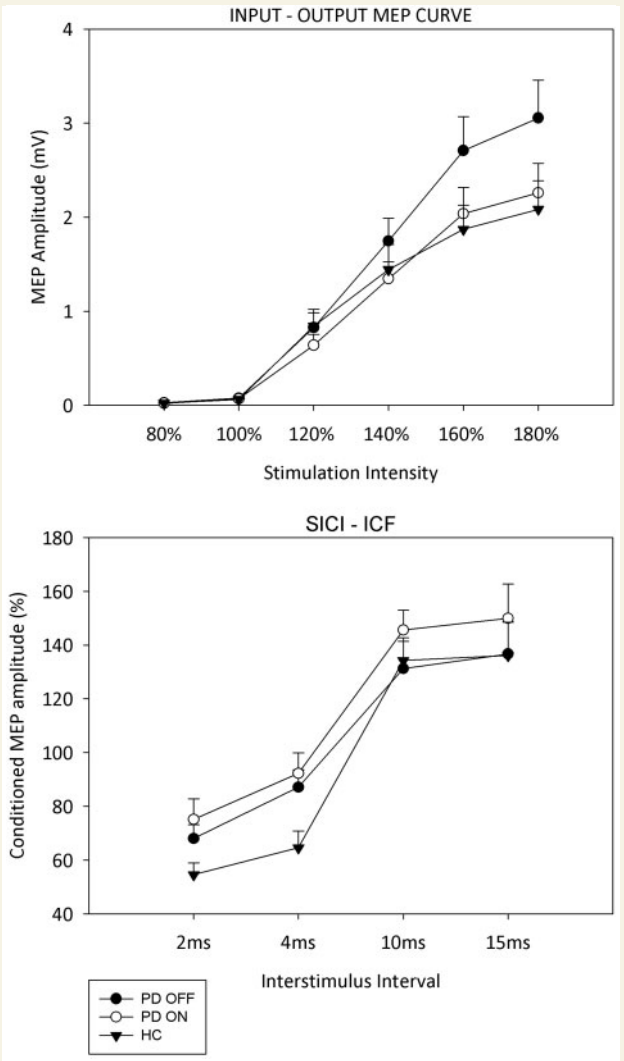

Figure 1 Excitability of primary motor cortex. *Top*: Input-output curve of MEPs at baseline in patients with Parkinson's disease (PD) OFF and ON medication and in healthy controls (HC). The *y*-axis shows the MEP amplitudes (mV); the *x*-axis shows the six stimulation intensities [80%, 100%, 120%, 140%, 160% and 180% of resting motor threshold (RMT)]. *Bottom*: SICI and ICF at baseline in patients with Parkinson's disease OFF medication and ON medication and in healthy controls. The *y*-axis shows the ratio between conditioned and unconditioned MEP amplitudes; the *x*-axis shows the four interstimulus intervals (2 ms and 4 ms for SICI, and 10 ms and 15 ms for ICF).

$P = 0.28$] or for the interaction Session × Interstimulus interval [$F(1,21) = 0.04$, $P = 0.84$]. Further, the analysis revealed a significant effect for Interstimulus interval [$F(1,21) = 7.47$, $P = 0.01$], thus confirming the reduced MEP amplitude values at 2 ms in comparison to those observed at 4 ms interstimulus interval. Similarly, there were no effects of dopaminergic medication on ICF (Fig. 1) as revealed by the lack of statistical significance for the main factor Session [$F(1,21) = 1.08$, $P = 0.30$] and for the interaction Session × Interstimulus interval [$F(1,21) = 0.009$, $P = 0.92$]. Lastly, there was no significant effect for Interstimulus interval [$F(1,21) = 0.75$, $P = 0.39$].

M1 plasticity: paired associative stimulation-related effects

Dopaminergic medication increased M1 plasticity in patients with Parkinson's disease (Fig. 2). This was demonstrated by a significant effect of the main factor Session [$F(1,21) = 4.86$, $P = 0.03$], with the *post hoc* analysis yielding higher values in patients with Parkinson's disease ON medication than in those OFF medication ($P < 0.01$). There was also a significant effect of the main factor Muscle [$F(1,21) = 7.10$, $P = 0.01$], with higher responses being observed in the abductor pollicis brevis (target muscle) than in first dorsal interosseous muscle, as well as for the interaction Session × Muscle [$F(1,21) = 4.50$, $P = 0.04$], as demonstrated by the increase in MEP amplitude after PAS in the ON medication session observed in the abductor pollicis brevis though not in the first dorsal interosseous muscle. These findings are in line with previous reports indicating that the effects of dopaminergic medication on PAS are muscle-specific (Morgante *et al.*, 2006; Ueki *et al.*, 2006). Lastly, no significant effect was detected for the main factor Time point [$F(2,42) = 2.48$, $P = 0.09$] or for the interactions Session × Time point [$F(2,42) = 0.18$, $P = 0.82$], Muscle × Time point [$F(2,42) = 0.03$, $P = 0.96$] and Session × Muscle × Time point [$F(2,42) = 0.23$, $P = 0.79$].

Multiple logistic model

When considering neurophysiological data at baseline, the LASSO procedure confirmed that all the variables that differed between patients with Parkinson's disease (OFF medication) and healthy controls were predictors of the disease status (amplitude intercept: −0.01; amplitude

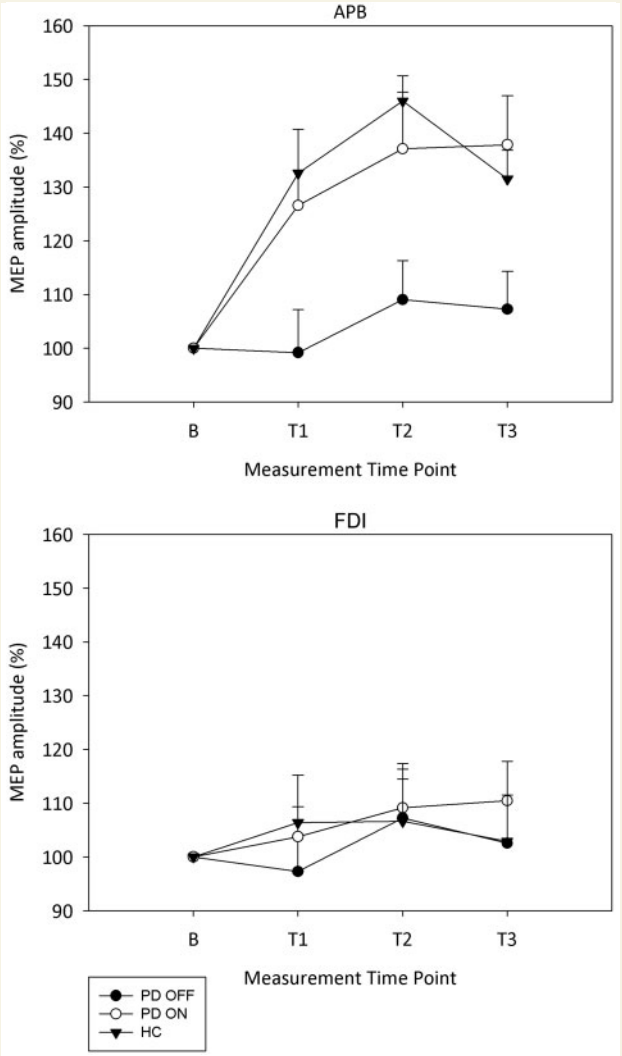

Figure 2 Plasticity of primary motor cortex. Course of MEPs after the PAS protocol in the abductor pollicis brevis (APB, *top*) and in the first dorsal interosseous (FDI, *bottom*) in patients with Parkinson's disease (PD) OFF and ON medication and in healthy controls (HC). The *y*-axis shows MEP amplitudes normalized to baseline (B). The *x*-axis shows measurements at the four time points: before PAS (B) and 5 min (T1), 15 min (T2) and 30 min (T3) after PAS.

decrement: −1.55; velocity intercept: −0.001; input-output MEP curve slope: 0.31; SICI: 1.16; PAS: −0.009).

When considering neurophysiological data of patients with Parkinson's disease OFF and ON medication, the LASSO procedure indicated that three of the variables that differed between patients with Parkinson's disease OFF and ON medication were predictors of the medication status (amplitude intercept: 0.05; input-output MEP curve slope: −0.34; PAS: 0.013).

Canonical correlation analysis

CCA computes linear combinations of the original kinematic and neurophysiological variables that correlate with each other. The first canonical factor consists of one combination of the original variables, the second and third factors (which are uncorrelated with the first) consist of other combinations of original variables. Note that CCA develops as many canonical factors as there are variables in the smaller of the two variable sets. Wilks' lambda test demonstrated significant effects for two canonical factors (FI = 0.68; $P = 0.01$ and FII = 0.66; $P = 0.03$ but not for FIII = 0.12; $P = 0.60$); these results show that there is an overall relationship between movement kinematics and TMS variables in Parkinson's disease. Table 4 shows the canonical coefficients and the canonical factor loadings for the three canonical factors (FI–FIII). Canonical coefficients correspond to the values in the linear combination that generates the canonical factors from the input variables. The canonical factor loadings indicate the relationship between the canonical factor and the input variables. Amplitude decrement and PAS response had the largest contribution to FI (Table 4 and Fig. 3). Velocity intercept and the input-output MEP had the largest contribution to FII (Table 4 and Fig. 3). As further orientation to the relationships between pairs of variables, Supplementary Table 1 displays the bivariate correlation matrix and indicates: (i) the slower the movement velocity, the higher the slope of the input-output MEP curve (Fig. 4); and (ii) the greater the decrement in amplitude during movement repetition the lower the PAS response (Fig. 4).

No relationship emerged in the ON medication state between changes in the kinematic variables of repetitive finger tapping and changes in the excitability and plasticity TMS measures of M1 after dopaminergic medication. This result was confirmed by the CCA: Wilks' lambda test showed no significant effects of canonical factors (all P's > 0.05).

Lastly, no significant correlations were detected between clinical scores and neurophysiological parameters (all P's > 0.05).

Discussion

The novel aspect of this study is the correlation analysis we performed between movement kinematics and neurophysiological abnormalities in the M1 of patients with Parkinson's disease. We found that bradykinesia features correlated with M1 excitability and plasticity abnormalities in patients. Dopaminergic therapy improved movement amplitude and speed, though not the sequence effect. Dopaminergic therapy also improved M1 excitability and plasticity, but no correlation was detected with kinematic changes.

Parkinson's disease versus healthy subjects

Our results confirmed many previous reports in patients with Parkinson's disease. Finger tapping movements had a lower amplitude and velocity in patients than in healthy

Table 4 Canonical correlation analysis between kinematic variables and TMS parameters

	Canonical factors		
	FI	FII	FIII
Kinematic variables			
Amplitude intercept	1.28 (0.05)	1.08 (0.10)	0.82 (0.99)
Velocity intercept	−0.05 (−0.05)	−1.45 (**−0.55**)	0.18 (−0.82)
Amplitude slope	1.29 (**0.69**)	−0.24 (−0.34)	−0.05 (−0.63)
TMS parameters			
Slope I/O MEP	0.20 (0.18)	1.00 (**0.97**)	−0.16 (−0.09)
SICI	0.11 (−0.14)	0.07 (−0.13)	−1.04 (−0.98)
PAS	1.00 (**0.97**)	−0.17 (−0.18)	−0.12 (0.09)
Canonical correlation	**0.68, *P* = 0.01**	**0.66, *P* = 0.03**	0.12, *P* = 0.60

Shown are the canonical coefficients and the canonical factor loadings (within brackets). Canonical coefficients correspond to the values in the linear combine that generates the canonical factors from the input variables. The canonical factor loadings indicate the relationship between the canonical factors (FI, FII, FIII) and the input variables (kinematic or TMS parameters); note that loadings higher than ±0.50 (bold) are considered practically significant. Significant *P*-values for FI and FII are in bold. I/O = input-output.

controls. Movement amplitude also decreased progressively during finger tapping in patients, confirming that the sequence effect is another motor feature of Parkinson's disease (Agostino *et al.*, 2003; Espay *et al.*, 2009, 2011; Bologna *et al.*, 2016*a*). We also observed that corticospinal excitability was increased in the resting state and that M1 plasticity was reduced in Parkinson's disease (Cantello *et al.*, 2002; Currà *et al.*, 2002; Lefaucheur *et al.*, 2005; Berardelli *et al.*, 2008; Bologna *et al.*, 2016*b*). Similar to some (Ridding *et al.*, 1995; Kojovic *et al.*, 2012, 2015; Ni *et al.*, 2013) but not all (MacKinnon *et al.*, 2005) previous reports, we also observed less effective SICI in patients with Parkinson's disease than in healthy subjects but no changes in ICF.

Correlation between kinematic and neurophysiological abnormalities

To our knowledge, no prior study has assessed the relation between kinematic and neurophysiological abnormalities using CCA in Parkinson's disease. With this approach, we were able to detect a global correlation between these two sets of variables, and to identify the most influential kinematic and neurophysiological variables based on their loadings in the analysis. Our analysis demonstrates that neurophysiological abnormalities of M1 are strong predictors of altered movement kinematics in Parkinson's disease. This finding is in line with current models emphasizing the pathophysiological role of M1 in generating movement abnormalities in Parkinson's disease.

Correlates of bradykinesia

M1 is a principal source of corticospinal input to control of skilled movement. Consistent with this, many previous authors have suggested that dysfunction of M1 contributes to symptoms of bradykinesia (movement slowness) in Parkinson's disease (Berardelli *et al.*, 2001). Pasquereau *et al.* (2016) confirmed in hemiparkinsonian MPTP monkeys that the resting discharge of corticospinal neurons in M1 was lower than normal and that the correlations between changes in discharge rate and movement parameters such as direction, force and acceleration were all reduced during active movement. They concluded that a general 'hypoactivation' of M1 during movement could contribute to bradykinesia in Parkinson's disease.

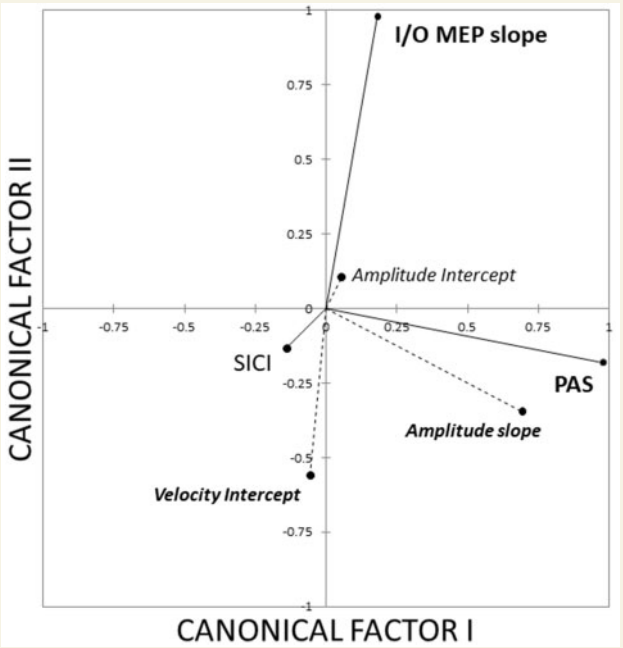

Figure 3 Schematic plot showing how the original input variables are loaded onto canonical factors I and II. The *x*- and *y*-axes indicate the loadings for canonical factors (F) I and II, respectively. For example, PAS has a strong loading on FI but very little on FII. The input-output (I/O) MEP slope and velocity intercept have a strong loading on FII and these two variables are anti-correlated. Kinematic variables (dashed line) are shown in italics. The parameters with the loadings higher than ±0.50 are in bold.

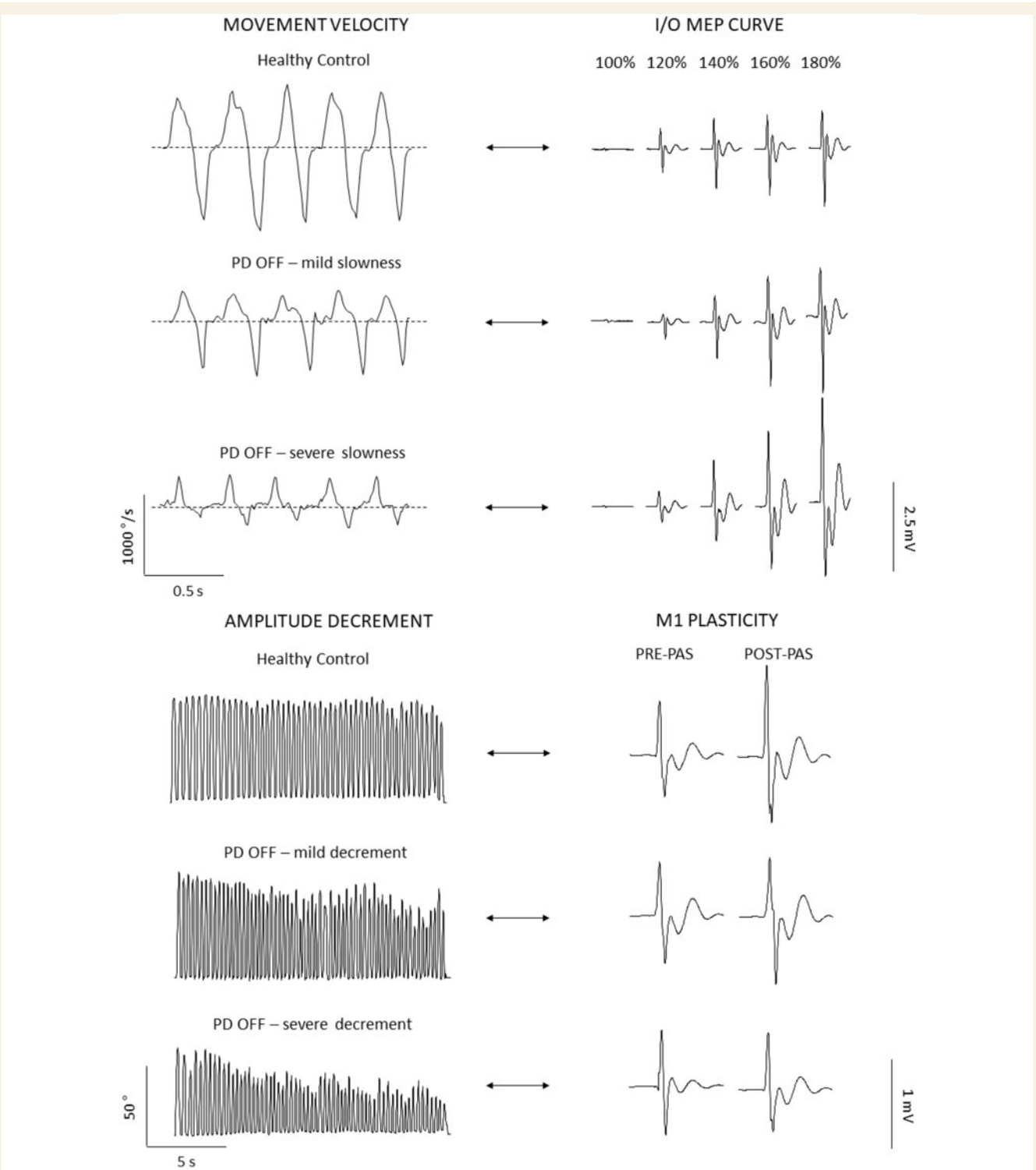

Figure 4 Schematic representation of the two major findings of the study. *Top*: The relationship between movement velocity intercept (corresponding to the values at the beginning of the motor sequence) and the input-output (I/O) MEP curve; note that the representative patient with Parkinson's disease (PD) with severe movement slowness has a steeper input-output curve. *Bottom*: The relationship between amplitude decrement, i.e. the sequence effect and the MEP amplitude change after PAS. Note that the representative Parkinson's disease patient with more severe sequence effect has no MEP amplitude increase after PAS.

At first sight, these data in monkeys appear to be opposite to the increased input-output slope of resting corticospinal output that we observe. However, this is not necessarily the case. TMS directly stimulates axons that have synaptic inputs to corticospinal neurons. Given that axonal excitability is unlikely to be different in Parkinson's disease than normal, increased corticospinal recruitment indicates that these synapses are more effective than in the

control state. One possibility is that this may be an adaptation (Blesa *et al.*, 2017) that attempts to boost the power of reduced input from other areas. Indeed the present data, showing that the steeper the input-output slope the slower the movement, would be compatible with a gradual recruitment of this mechanism as symptoms progress. It would also be consistent with the absence of any changes in excitability in early Parkinson's disease (Kojovic *et al.*, 2012, 2015), where abnormalities of voluntary movement velocity are less prominent (Bologna *et al.*, 2016*a*) and with enhanced excitability in more advanced patients with Parkinson's disease (Valls-Solé *et al.*, 1994), where voluntary movement velocity is more severely affected (Bologna *et al.*, 2016*a*).

An alternative hypothesis is that, rather than being compensatory, increased M1 excitability interferes with processing of inputs from upstream areas. High excitability can, in fact, disrupt encoding of motor parameters and this could contribute to slowness of movement (Kumar *et al.*, 2010). If this were the case, we would speculate that as the disease progresses, corticospinal excitability increases, further worsening the integrity of command encoding, thus leading to bradykinesia.

Correlates of the sequence effect

A second feature of bradykinesia is the sequence effect, a gradual reduction in amplitude and velocity of a repetitive movement. This was not related to the input-output slope, but correlated with the PAS effect: the greater the decrement in amplitude during movement repetition the smaller the long-term potentiation-like effect of PAS. At the present time there is little information on the pathophysiological basis of decrement. Based on the present result we speculate that repetitive movement is assisted by short-term facilitation of movement-related synapses in M1. Reduced or absent facilitation in Parkinson's disease, if uncompensated by other mechanisms, might then result in a decline of corticospinal output as movement progresses, resulting in a gradual reduction of movement amplitude. The PAS effect is usually short-lived (15–30 min), and probably depends on short term synaptic effects on synaptic transmission rather than the longer-lasting processes responsible for long term potentiation. If these short term effects employ the same mechanisms as responsible for short term facilitation it would explain why reduced PAS is accompanied by greater decrement in volitional movements. This explanation would also be consistent with previous findings that short-term synaptic facilitation produced by 5 Hz repetitive TMS is also reduced in Parkinson's disease (Gilio *et al.*, 2002). The hypothesis that reduced M1 plasticity is a possible pathophysiological mechanism of the sequence effect in Parkinson's disease, is supported by the observation that this abnormality is present in early Parkinson's disease (Kang *et al.*, 2011; Lee *et al.*, 2014; Bologna *et al.*, 2016*a*). Moreover, early synaptic impairment may represent the key event in patients with Parkinson's disease, as shown in TMS studies (Kishore *et al.*, 2012; Kojovic *et al.*, 2012, 2015) and in both pathogenic and genetic animal models of parkinsonism (Schirinzi *al.*, 2016). In contrast to our findings, which point to a relationship between the sequence effect and M1 plasticity, Kang *et al.* (2010) observed that high-frequency repetitive TMS of M1 did not modify the sequence effect in Parkinson's disease and concluded that M1 is unlikely to be involved in generating this movement abnormality in Parkinson's disease. The authors, however, assessed the sequence effect during the pegboard test, which does not require such a fine M1 activation as that required by repetitive finger tapping (Agostino *et al.*, 2003). Second, Kang *et al.* (2010) based their study on repetitive TMS, which, unlike the PAS protocol used in this study, does not involve mechanisms of sensorimotor integration (Wolters *et al.*, 2003; Classen *et al.*, 2004; Carson and Kennedy, 2013).

Although we detected a correlation between the sequence effect and M1 plasticity measures, we acknowledge that alternative mechanisms may also contribute to this abnormality in Parkinson's disease. For example, it has been suggested that altered activity in premotor areas, basal ganglia or cerebellum may be responsible for the sequence effect in Parkinson's disease (Kang *et al.*, 2010; Little *et al.*, 2012; Tan *et al.*, 2013*a*, *b*, 2015; Lee *et al.*, 2014; Steiner *et al.*, 2017).

Acute effect of dopaminergic therapy

We found that dopaminergic medication improved movement amplitude and velocity but not the sequence effect (Espay *et al.*, 2009, 2011; Bologna *et al.*, 2016*a*). We also found that dopaminergic replacement normalized M1 excitability, as assessed by the slope of the input-output MEP curve, and normalized plasticity measures (Bologna *et al.*, 2016*b*; Suppa *et al.*, 2017). However, there was no correlation between changes in neurophysiology and changes in movement suggesting that abnormalities in performance of movement are not due solely to deficits in M1 but probably involve distributed systems at cortical and subcortical levels. Dopamine could exert acute effects at these sites and improve movement independently of changes in M1 excitability and plasticity. For example, neuroimaging studies have shown that dopaminergic replacement induces changes not only in basal ganglia regional activity but also in premotor-M1 and corticostriatal connectivity in patients (Michely *et al.*, 2015). Moreover, our results possibly indicate that kinematics and TMS have different sensitivity to change to dopaminergic medication (Espay *et al.*, 2011; Suppa *et al.*, 2017). For example, TMS studies indicate non-linear effect of levodopa dosage on PAS-induced plasticity in humans (Monte-Silva *et al.*, 2010; Thirugnanasambandam *et al.*, 2011). It is also possible that some pathophysiological abnormalities in Parkinson's disease (including for example those related to altered GABAergic transmission) are not strictly dependent on dopaminergic loss.

Limitations of the study

Unlike electrophysiological recordings in animals or DBS recordings in patients with Parkinson's disease, TMS provides only indirect measures of cortical activity, which may be affected by several sources of variability. Also, it should be borne in mind that this study was performed on a relatively small sample of patients with mild/moderate Parkinson's disease. Since M1 excitability increases and M1 plasticity decreases as the disease worsens (Lefaucheur, 2005; Bologna *et al.*, 2016*b*), we cannot fully exclude that the relationships we found (either between movement slowness and the slope of the input-output MEP curve as well as between amplitude decrement and PAS response) could perhaps be the result of a common correlation with disease progression. However, this seems unlikely since we found no relationship between neurophysiological data and clinical and demographic features. Further studies on patients in different stages of Parkinson's disease as well as longitudinal studies are needed to investigate intraindividual correlations. This approach would also allow one to better understand whether the electrophysiological changes of M1 reflect compensatory/adaptive changes following the disease onset.

Conclusions

This study provides novel information on the role of M1 in patients with Parkinson's disease and a deeper understanding of the pathophysiological mechanisms that may underlie the various features of bradykinesia. The results support the hypothesis that the various movement abnormalities reflect different pathophysiological mechanisms. Namely, excitability and plasticity changes in M1 may play distinct roles. While M1 excitability changes underlie movement slowness, plasticity changes underlie the sequence effect. Further studies are needed to elucidate how neurophysiological abnormalities of M1 contribute to motor abnormalities in Parkinson's disease. Clarifying this issue is an important step toward the development of novel therapeutic approaches, based on non-invasive brain simulation techniques, targeting the specific neurophysiological abnormalities underlying the various bradykinesia features in Parkinson's disease.

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Supplementary material

Supplementary material is available at *Brain* online.

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