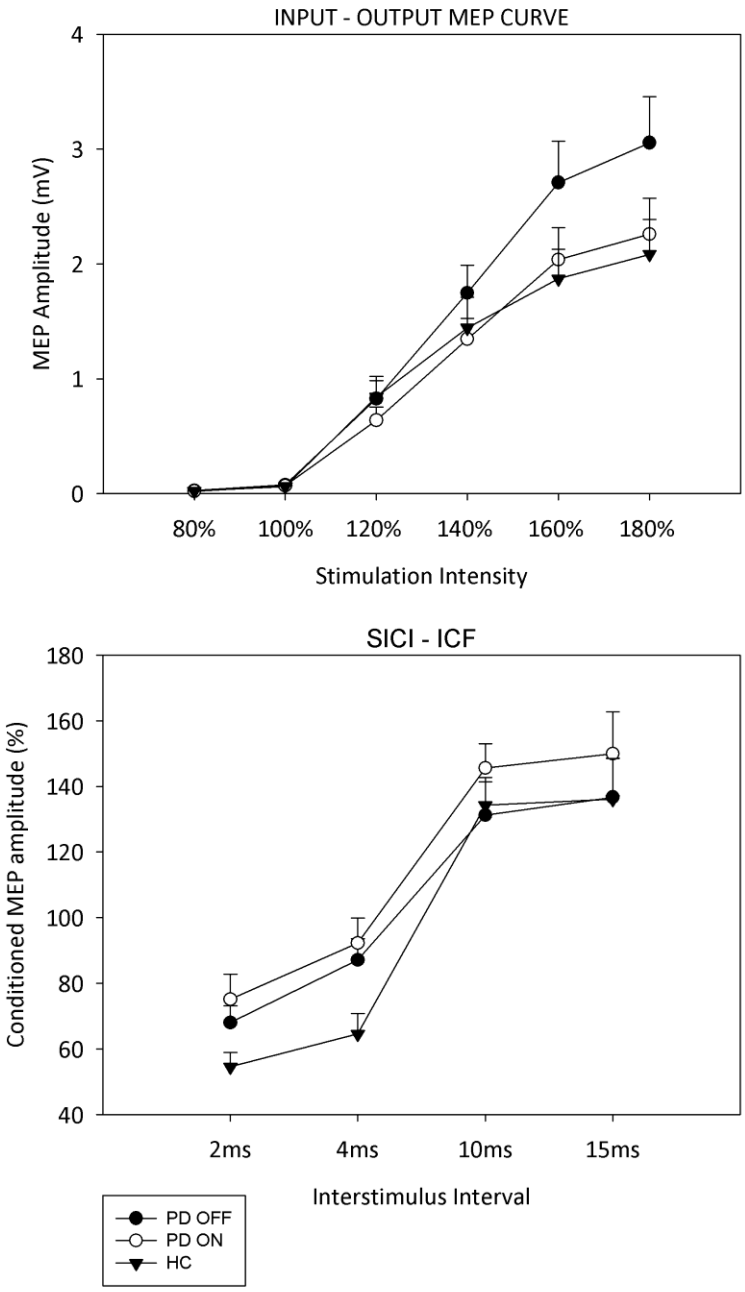

Figure 1: Upper panel: Input-output (I/O) curve of motor-evoked potentials (MEP) at baseline in patients with Parkinson disease (PD) 'OFF' medication and 'ON' medication and in healthy controls (HC). The Y axis shows the MEP amplitudes (mV); the X axis shows the six stimulation intensities (80%, 100%, 120%, 140%, 160% and 180% of resting motor threshold – RMT). Lower panel: short-interval intracortical inhibition – SICI and intracortical facilitation – ICF at baseline in patients with PD 'OFF' medication and 'ON' medication and in HC. The Y axis shows the ratio between unconditioned and conditioned MEP amplitudes; the X axis shows the four interstimulus intervals (2ms and 4ms for SICI and 10ms and 15ms for ICF).

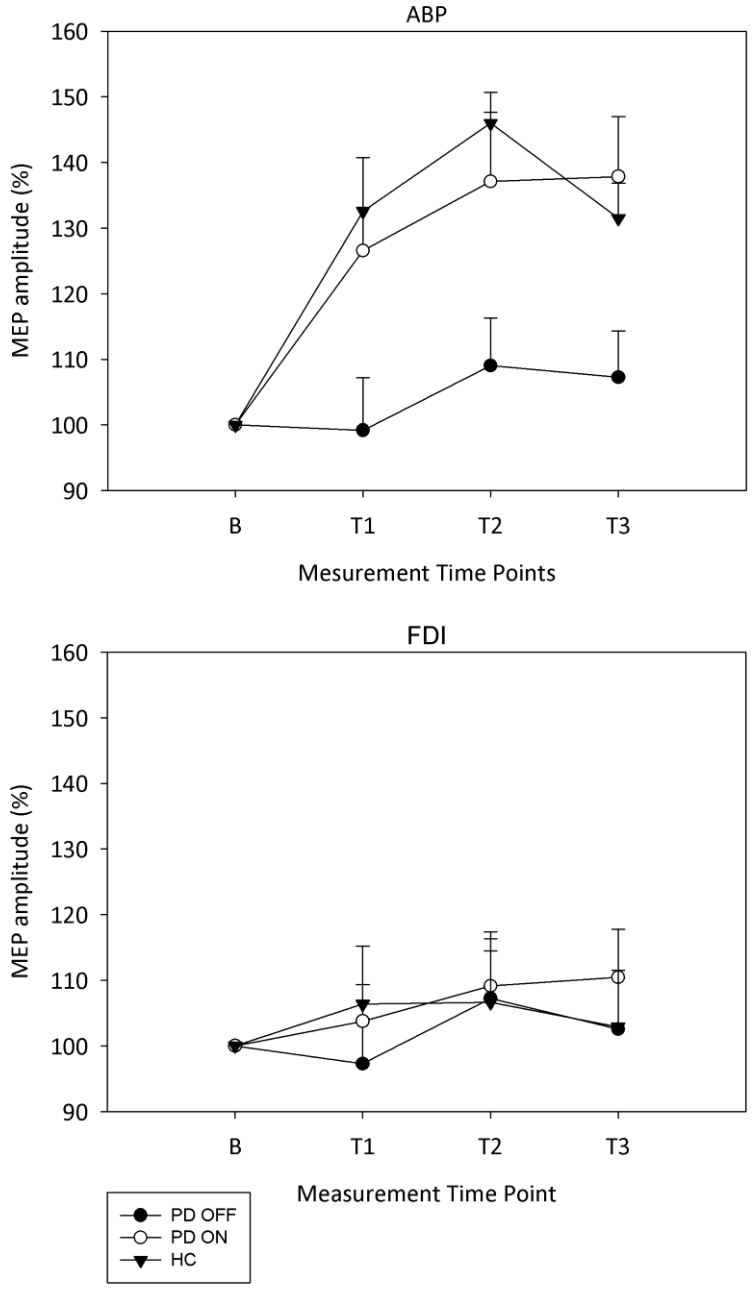

Figure 2: Course of motor-evoked potentials (MEP) after the paired associative stimulation (PAS) protocol in the abductor pollicis brevis – APB (upper panel) and in the first dorsal interosseous – FDI muscles (lower panel) in patients with Parkinson disease (PD) 'OFF' medication and 'ON' medication and in healthy controls (HC). The Y axis shows MEP amplitudes normalized to baseline. 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.

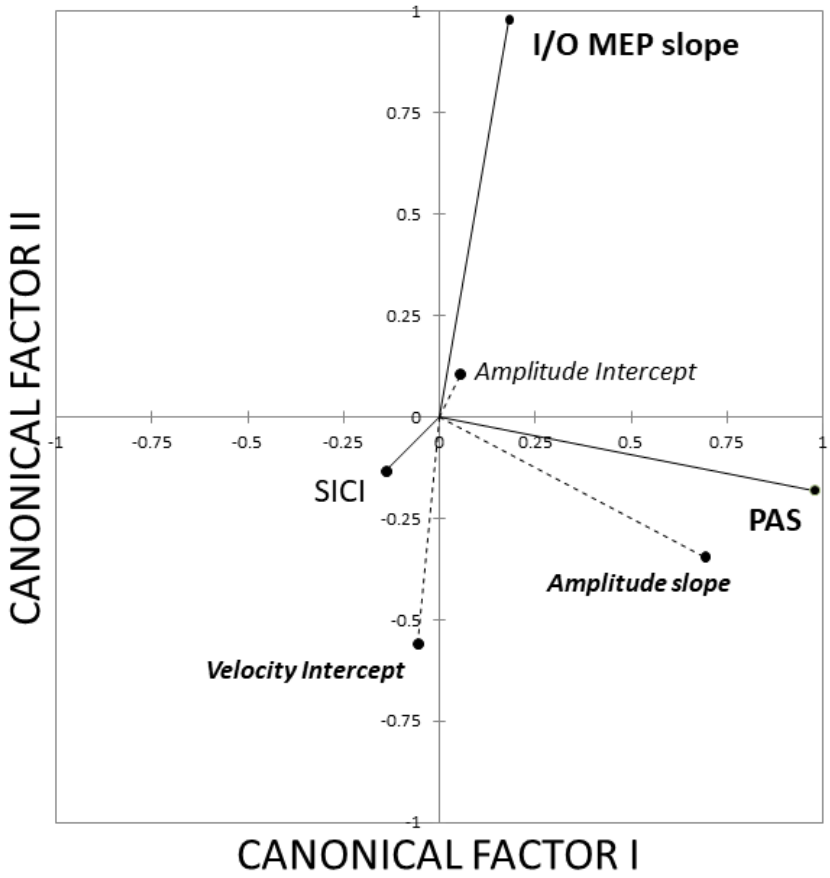

Figure 3: Schematic plot showing how the original input variables are loaded onto canonical factors I and II. The x and y- axis indicate the loadings for FI and FII respectively. For example, PAS has a strong loading on FI but very little on FII. Kinematic variables (dashed line) are shown in italic. The parameters with the highest loadings are embolded.

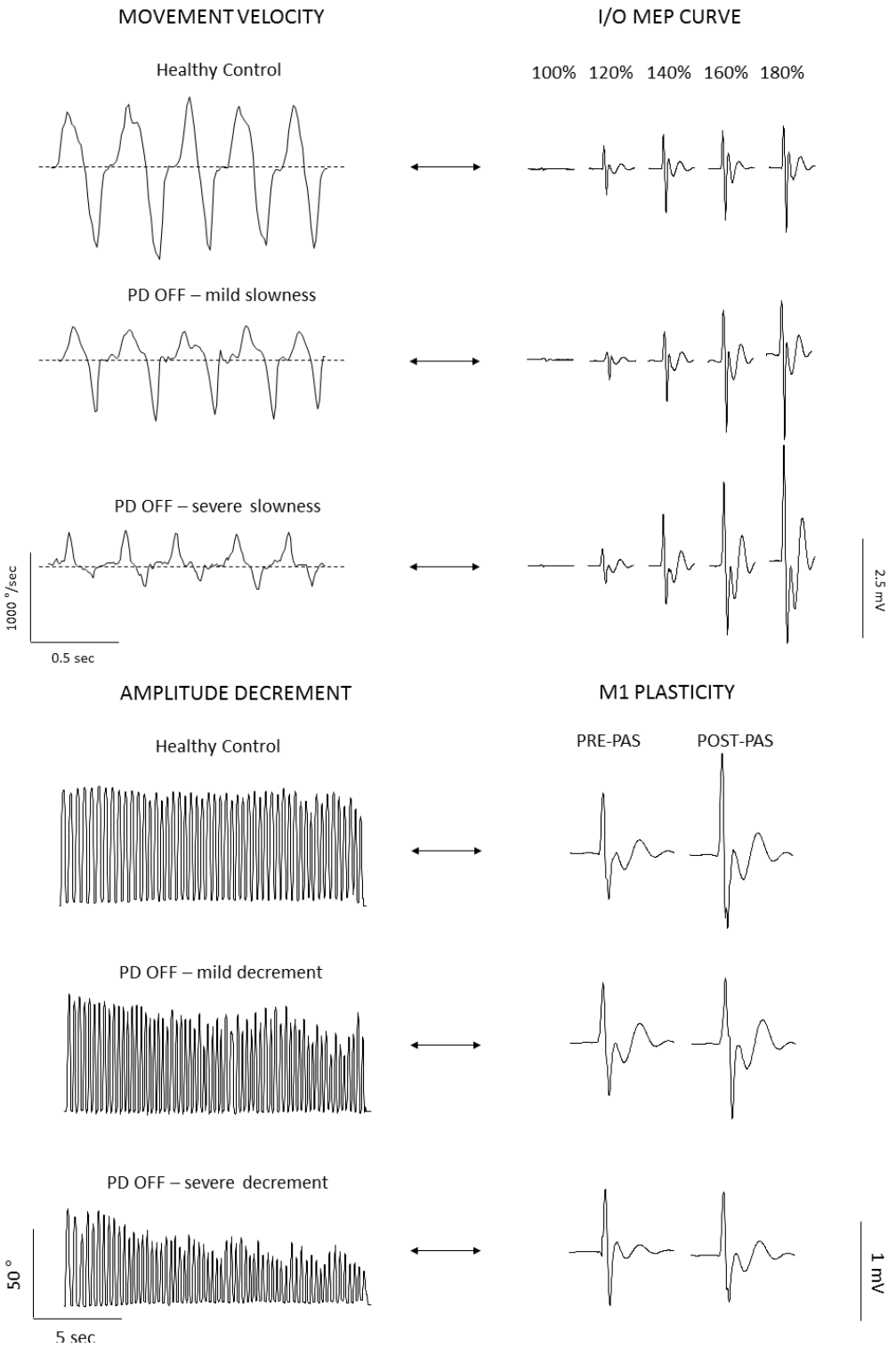

Figure 4: Schematic representation of the two major findings of the study. The upper panel illustrates the inverse relationship between movement velocity and the input-output (I/O) MEP curve. Note that the representative patient with Parkinson's disease (PD) with severe movement slowness has a steeper I/O curve. The lower panel illustrates the direct relationship between amplitude decrement, i.e. the sequence effect and the MEP amplitude change after PAS. Note that the representative PD patient with more severe sequence effect has no MEP amplitude increase after PAS.

	Age	Gender	Disease duration (years)	H&Y	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

Table 1: Demographic and clinical data of patients with Parkinson's disease. Hoehn and Yahr (H&Y), Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS), Beck Depression Inventory (BDI), Montreal cognitive assessment (MoCA), Frontal Assessment Battery (FAB), Fatigue Severity Scale (FSS). Levodopa equivalent daily dose (LEDD).

	PD OFF	PD ON	HC	*P values	**P values
N° mov.	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

Table 2: Kinematic variables in patients with Parkinson's disease (PD) and in healthy controls (HC). Results are shown as mean values ± 1 standard error of the mean (SEM). * P values by unpaired, two tailed t-tests (PD OFF vs. HC). **P values by paired, two tailed t-tests (PD OFF vs. PD ON). Significant P values are bold type printed. Corrected alpha level 0.021 by false discovery rate.

	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

Table 3: Motor thresholds (active motor threshold – AMT and resting motor threshold - RMT) in patients with Parkinson's disease (PD) and in healthy controls (HC). Results are shown as mean values ± 1 standard error of the mean (SEM). * P values by unpaired, two tailed t-tests (PD OFF vs. HC). **P values by paired, two tailed t-tests (PD OFF vs. PD ON). Significant P values are bold type printed. Corrected alpha level 0.021 by false discovery rate.

	Canonical Factors		
	F I	F II	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

Table 4: Canonical correlation analysis between kinematic variables and TMS parameters. 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 and the input variables. Significant P values are bold type printed.

Variables	Amplitude Intercept	Velocity Intercept	Amplitude Slope

Slope I/O MEP	0.08	**-0.35**	-0.14
SICI	-0.13	-0.04	0.04
PAS	0.03	0.03	**0.49**

Table 5: Canonical correlation analysis - correlation matrix. The most relevant correlation coefficients between kinematic variables and TMS parameters are bold type printed.

SUPPLEMENTARY RESULTS: ANALYSYS ON THE POSSIBLE EFFECTS OF HANDEDNESS

Finger tapping kinematics

The one-way ANOVA comparing PD patients 'OFF medication' tested on the right and left sides and HC yielded a significant between-group difference for movement amplitude (F2, 37=6.01, P=0.005) and velocity ($F_{2,37}$=9.52, P<0.001), with lower values being observed in both PD patients sub-groups than in HC. The analysis also confirmed a between-group difference for movement amplitude slope (sequence effect), ($F_{2,37}$=3.02, P=0.04) with higher values (indicating more decrement) being observed in both PD patients sub-groups than in HC. No significant effect of the factor 'GROUP' emerged in the analyses of other variables (movement number: $F_{2,37}$=2.59, P=0.08; CV values of the inter-tap intervals: $F_{2,37}$=1.21, P=0.30 and velocity slope: $F_{2,37}$=0.52, P=0.59).

Corticospinal excitability: motor thresholds and I/O curve

The one-way ANOVA did not reveal any differences in RMT or AMT between both PD patients subgroups and HC (all Ps>0.05). M1 excitability, as assessed by means of the I/O MEP curve, was greater in both PD patients sub-groups than in HC, as demonstrated by a significant interaction 'GROUP' x 'STIMULUS INTENSITY' ($F_{10, 185}$=2.20, P=0.019). As expected, the ANOVA yielded a significant effect of the main factor 'STIMULUS INTENSITY' (F5, 185=83.007, P<0.001), with an increasing MEP amplitude being observed with increasing stimulation intensity. Lastly, the factor 'GROUP' was not found to be significant ($F_{2, 37}$=1.05, P=0.35).

Intracortical excitability: SICI and ICF

When analyzing SICI, the ANOVA revealed a significant effect of the main factors 'GROUP' ($F_{2,37}$=3.84, P=0.03), with less inhibition being observed in both PD patients sub-groups than in HC. The main factor 'ISI' was also significant ($F_{1,37}$=10.96, P=0.002), indicating more profound

inhibition at 2 ms than at 4 ms while there was no significant interaction 'GROUP' x 'ISI' ($F_{2, 37}$=0.82, P=0.45).

Excitability of the intracortical facilitatory interneurons, as assessed by means of ICF, did not differ between both PD patients sub-groups and HC, as is demonstrated by a lack of significant effect of GROUP ($F_{2,37}$=0.64, P=0.53), ISI ($F_{1,37}$=0.93, P=0.34) and interaction 'GROUP' x 'ISI' (F2,37)=0.81, P=0.45).

M1 plasticity: PAS-related effects

The analysis indicated that the MEPs increased after PAS in HC but not in both PD patients subgroups. This finding is supported by a repeated-measures ANOVA showing a significant effect for the interaction 'GROUP' x 'MUSCLE' ($F_{2,37}$=3.61, P=0.03) with higher facilitation being observed in the APB (target muscle) than in the FDI in HC but not in both PD patients subgroups. ANOVA also yielded a trend toward a significant effect of the main factor 'GROUP' ($F_{2,37}$=3.04, P=0.05), with lower values being observed in both PD patients sub-groups than in HC. There was a significant effect also for the main factors 'MUSCLE' ($F_{1,37}$=4.86, P=0.03) and 'TIME POINT' ($F_{2,74}$=3.40, P=0.03). Conversely, no significant effects were observed for the interactions 'GROUP' x 'TIME POINT' ($F_{4,74}$=2.11, P=0.08); 'MUSCLE' x 'TIME POINT' ($F_{2,74}$=0.06, P=0.93) and 'GROUP' x 'MUSCLE' x 'TIME POINT' ($F_{4, 74}$=1.44, P=0.22).