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Long-term changes in short-interval intracortical facilitation modulate motor cortex plasticity and L-dopa-induced dyskinesia in Parkinson's disease

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ABSTRACT

Background: Abnormal glutamatergic neurotransmission in the primary motor cortex (M1) contributes to Parkinson's disease (PD) pathophysiology and is related to L-dopa-induced dyskinesia (LID). We previously showed that short-term treatment with safinamide, a monoamine oxidase type-B inhibitor with anti-glutamatergic properties, improves abnormally enhanced short-interval intracortical facilitation (SICF) in PD patients.
Objective: To examine whether a long-term SICF modulation has beneficial effects on clinical measures, including LID severity, and whether these changes parallel improvement in cortical plasticity mechanisms in PD.
Methods: We tested SICF in patients with and without LID before (S0) and after short- (14 days - S1) and long-term (12 months - S2) treatment with safinamide 100 mg/day. Possible changes in M1 plasticity were assessed using intermittent theta-burst stimulation (iTBS). Finally, we correlated safinamide-related neurophysiological changes with modifications in clinical scores.
Results: SICF was enhanced at S0, and prominently in patients with LID. Safinamide normalized SICF at S1, and this effect persisted at S2. Impaired iTBS-induced plasticity was present at S0 and safinamide restored this alteration at S2. There was a significant correlation between the degree of SICF and the amount of iTBS-induced plasticity at S0 and S2. In patients with LID, the degree of SICF at S0 and S2 correlated with long-term changes in LID severity.
Conclusions: Altered SICF contributes to M1 plasticity impairment in PD. Both SICF and M1 plasticity improve after long-term treatment with safinamide. The abnormality in SICF-related glutamatergic circuits plays a role in LID pathophysiology, and its long-term modulation may prevent LID worsening over time.

1. Introduction

Animal models of Parkinson's disease (PD) have shown overactive glutamatergic projections from the subthalamic nucleus to the output basal ganglia nuclei and have found that abnormally increased glutamatergic neurotransmission plays an important role in nigrostriatal degeneration [1–4]. A strong relationship between increased glutamatergic activity and the development of L-dopa-induced dyskinesia (LID) is also present in PD [1,5,6]. The role of enhanced glutamatergic transmission in LID has been confirmed by clinical-pharmacological studies, which have shown that anti-glutamatergic drugs may improve dyskinesia in patients [7,8].

Glutamatergic neurotransmission in the human primary motor cortex (M1) can be non-invasively assessed using transcranial magnetic stimulation (TMS) techniques [9,10]. In PD patients, there is evidence of abnormally enhanced short-interval intracortical facilitation (SICF), a measure that depends on the timing of inputs to corticospinal neurons and acts on a chain of excitatory interneurons, whose activity is mainly mediated by glutamate [11–14]. In a previous study, we demonstrated that patients with

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LID have higher SICF than those without dyskinesia, a finding that supports the hypothesis that increased glutamatergic transmission in M1 contributes to LID pathophysiology in PD [1,5,15]. Moreover, we used a pharmaco-TMS approach to test the short-term effect of safinamide in PD patients. Safinamide is a monoamine oxidase type-B (MAO-B) inhibitor with anti-glutamatergic properties at high doses [16–19]. We found that safinamide 50 and 100 mg/day comparably reduced overall M1 hyperexcitability in PD, while there was a dose-dependent effect on SICF, whereby SICF was restored only after safinamide 100 mg/day [11]. However, it is unknown whether safinamide-related SICF normalization persists or gradually diminishes with long-term treatment and whether this neurophysiological effect has any clinical correlate. In this regard, clinical studies have shown improvements in motor and non-motor symptoms after several months of safinamide treatment and no LID worsening despite the relative increase in dopamine levels and disease progression [20–23]. Experimental studies in animal models of PD showed that overactive glutamatergic neurotransmission is a key mechanism responsible for abnormal corticostriatal synaptic plasticity [1,24]. Accordingly, safinamide-related long-term modulation of glutamatergic neurotransmission might imply changes in long-term synaptic plasticity mechanisms [20,23].

Examining the possible effects of long-term treatment with safinamide on clinical and neurophysiological measures would provide a deeper understanding of the pathophysiological link between altered SICF-related glutamatergic transmission and PD. Moreover, the assessment of possible effects of long-term treatment with safinamide on M1 plasticity would clarify whether drug-induced modulation of motor and non-motor PD complications, including LID, is related to long-term changes in impaired plasticity mechanisms.

We here assessed SICF and other facilitatory intracortical circuits possibly related to glutamatergic neurotransmission using standardized TMS techniques in PD patients [9,10] and evaluated the effects of short- (14 days) and long-term (12 months) treatment with safinamide 100 mg/day on these measures. We then verified whether safinamide-related changes in intracortical glutamatergic circuits are associated with modifications in motor, depressive, or cognitive rating scales, or with dyskinesia severity in patients with LID. Furthermore, we tested the effects of short- and long-term treatment with safinamide on long-term potentiation (LTP)-like plasticity of M1, as assessed by intermittent theta-burst stimulation (iTBS) [25]. Finally, to exclude concomitant modifications in GABA-A-ergic inhibition, we assessed short-interval intracortical inhibition (SICI), a GABA-A-ergic M1 measure [26,27]. All neurophysiological measures were compared to those recorded in a group of healthy subjects (HS).

2. Material and methods

2.1. Participants

Twenty-five PD patients (Table 1) and 18 age- and gender-matched HS (7 F, mean age±standard deviation (SD): 66.17 ± 4.62 years) were enrolled. Patients were recruited from the Department of Human Neurosciences, Sapienza University of Rome. PD diagnosis was based on clinical criteria [28] and all patients manifested motor fluctuations, including wearing-off. Thirteen patients also manifested LID (PD with LID), while the remaining 12 patients did not (PD without LID). Clinical motor assessment was based on the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS-III) [29]. LID intensity was scored according to the impairment section of the Unified Dyskinesia Rating Scale (UDysRS-III) [30]. Depressive symptoms were quantified by the Beck Depression Inventory (BDI-II) [31], whereas cognitive functions by using the Mini-Mental State Examination (MMSE) [32] and the Frontal Assessment Battery (FAB) [33]. No participant was taking drugs known to influence M1 excitability or plasticity or had contraindications to TMS [10,34]. Experimental procedures conformed to the Declaration of Helsinki and were approved by the local institutional review board (CE 5634). All participants gave their written informed consent to the study.

2.2. TMS

Single- and paired-pulse TMS was performed using a MAGSTIM 200 connected to a standard figure-of-eight-shaped coil (Magstim Company Limited). The 'hotspot' of the right first dorsal interosseous (FDI) muscle, resting (RMT) and active motor thresholds (AMT), and the intensity required to evoke MEPs of ≈ 1 mV (MT_{1mV}) were identified following international guidelines [35]. The input/output (I/O) curve was obtained by recording 12 MEPs at seven TMS intensities, from 100% to 160% RMT, in steps of 10% increments. SICF was tested by delivering the first stimulus at MT_{1mV} and a second stimulus at 90% RMT with interstimulus intervals (ISI) of 1.5, 2, 2.5, 3, 3.5, 4, and 4.5 ms [11,36]. Intracortical facilitation (ICF) and SICI were assessed using a conditioning stimulus at 80% AMT, a test stimulus at MT_{1mV}, and ISI of 10 and 15 ms for ICF and 1.5 and 3 ms for SICI [27,37,38]. We specifically assessed SICI at these ISI to exclude a possible influence of GABA-A-ergic changes in safinamide-induced SICF peaks modulation [26,27]. Twelve MEPs were recorded for each ICF, SICI, and SICF ISI, and randomized with 12 single-pulse MEPs at MT_{1mV}. Intermittent TBS was delivered through a MAGSTIM Super Rapid^2 using standardized procedures (20 trains, 600 total pulses, stimulation intensity at 80% AMT) [25,39,40]. Twenty single-pulse MEPs at MT_{1mV} were recorded before (T0) and 5 (T1), 15 (T2), and 30 min (T3) after iTBS. EMG signals were amplified (Digitimer D360, Digitimer) and digitized at 5 kHz (CED 1401; Cambridge Electronic Design). Peak-to-peak MEP amplitude was measured and averaged offline (Signal software). ICF, SICI, and SICF were expressed as the ratio between the amplitude of conditioned and unconditioned MEPs. iTBS-induced effects were quantified by normalizing MEP amplitude at T1, T2, and T3 to pre-iTBS (T0) values. All trials were visually inspected during recordings and those displaying EMG activity >0.1 mV in the 200-ms time window before TMS were rejected online [11,39,41,42]. Additional trials were then recorded to replace the rejected ones. This procedure ensured that background EMG activity was similar between PD patients with and without LID and HS, as also demonstrated by our ad-hoc analysis (see Supplementary Material).

2.3. Experimental design

All patients underwent three sessions: 1) before taking safinamide (S0); 2) after 2 weeks of chronic intake of safinamide 100 mg/day (S1); and 3) after 12 months of chronic intake of safinamide 100 mg/day (S2). Safinamide was taken every day early in the morning, and the remaining antiparkinsonian therapy was not modified between S0 and S2. The three experimental sessions were performed at the same time of day. Since we aimed to evaluate the possible relationship between long-term SICF variations and LID severity, all patients were studied in the ON state. The experiment began with clinical assessment, which was always conducted 1 h after the intake of the patient's usual L-dopa dose. UPDRS-III, UDysRS-III, and BDI-II were performed in all sessions, while MMSE and FAB were not assessed at S1 to avoid possible learning bias. We then examined the I/O curve, ICF and SICF protocols in random order. Finally, in a subgroup of 15 PD patients (7 with LID, 8

Table 1
Clinical-demographic characteristics of PD patients.

	Gender	Age	DD	LEDDs	BDI-II	FAB	MMSE	UPDRS-III	UDysRS-III
1	M	76	6	1055	4	10	24	27	0
2	M	66	4	800	6	18	30	16	1
3	M	74	12	800	10	14	26	41	11
4	M	49	15	1531	6	17	25	26	4
5	F	82	15	800	35	11	23	35	12
6	F	63	8	400	9	18	30	26	0
7	M	65	9	500	20	17	30	27	1
8	M	81	6	400	22	16	28	24	0
9	M	67	6	915	12	13	27	19	0
10	F	65	10	865	15	17	30	14	7
11	M	66	5	650	7	11	25	22	0
12	M	78	4	600	15	12	30	19	0
13	M	71	12	500	8	18	30	23	6
14	M	83	10	700	7	13	29	24	14
15	F	61	5	800	22	15	28	24	14
16	M	68	6	400	1	18	30	24	0
17	M	82	23	900	19	15	27	76	21
18	M	74	4	800	3	17	30	16	0
19	M	55	10	450	2	18	30	12	5
20	M	66	6	900	6	7	24	50	16
21	M	66	5	600	5	18	27	17	0
22	F	67	11	650	11	16	29	30	0
23	M	81	20	700	3	13	23	33	0
24	F	65	5	600	3	18	30	26	8
25	F	69	7	700	16	15	28	28	0
Mean	–	69.6	9.0	720.6	10.7	15.0	27.7	27.2	4.8
SD	–	8.6	5.0	246.4	8.2	3.1	2.5	13.2	6.4

DD: disease duration (years); LEDDs: L-dopa Equivalent Daily Doses; BDI-II: Beck Depression Inventory; FAB: Frontal Assessment Battery; MMSE: Mini-mental state examination; UPDRS-III: Unified Parkinson's Disease Rating Scale, part III; UDysRS-III: Unified Dyskinesia Rating Scale, impairment section; SD: standard deviation.

without LID), we also tested iTBS-induced plasticity (Fig. 1). SICI was assessed at S0, S1, and S2 in 18 patients.

2.4. Statistical analysis

We used Mann-Whitney U and Fisher exact tests to compare age and gender between patients and HS, respectively. Differences in motor thresholds and single-pulse MEP amplitude between groups were assessed by unpaired t-tests.

Separate repeated-measures analyses of variance (rmANOVA) were used to compare the I/O curve, ICF, SICI, SICF, and iTBS-induced plasticity between patients and HS. The between-subject factor 'group' (2 levels: PD, HS) was used in all rmANOVAs. The within-subject factor 'intensity' (7 levels: 100–160%) was adopted for the I/O curve, the factor 'ISI' (ICF, 2 levels: 10, 15 ms; SICI, 2 levels: 1.5, 3 ms; SICF, 7 levels: 1.5, 2, 2.5, 3, 3.5, 4, and 4.5 ms) was applied for ICF, SICI and SICF, and the factor 'timepoint' (3 levels: T1, T2, T3) was used for iTBS-induced plasticity. To assess iTBS effects in patients at S0, we applied a rmANOVA with the factor 'timepoint' (4 levels: T0, T1, T2, T3). To compare the I/O curve, SICF, and iTBS-induced plasticity between patients with and without LID, we used separate rmANOVAs with the between-subject factor 'group'

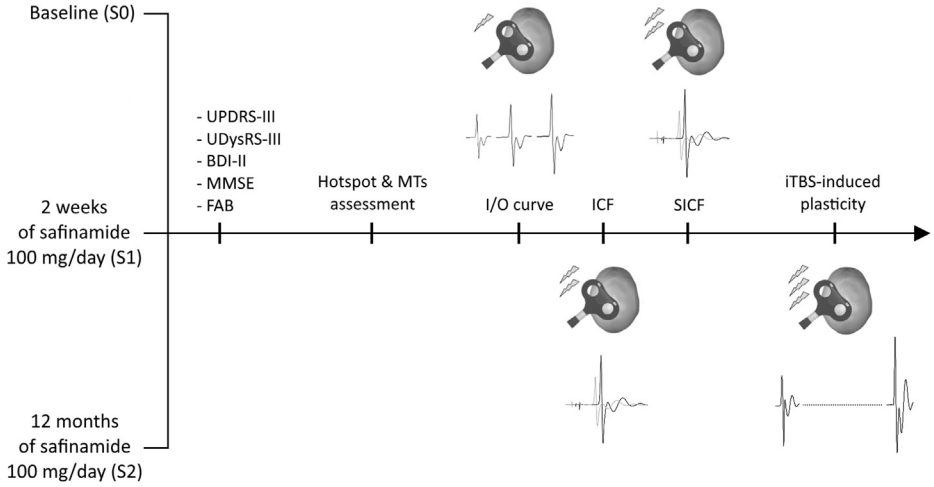

Fig. 1. Experimental design.
In all sessions (S0, S1 and S2), patients underwent a clinical assessment. Then, we conducted the neurophysiological evaluation, which included hotspot and motor thresholds (MTs) identification, evaluation of input-output (I/O) curve, intracortical facilitation (ICF) and short-interval intracortical facilitation (SICF), and, finally, the application of intermittent theta-burst stimulation (iTBS) protocol. UPDRS-III: Movement Disorders Society Sponsored Revision of the Unified Parkinson's Disease Rating Scale, part III; UDysRS-III: Unified Dyskinesia Rating Scale, part III; BDI-II: Beck Depression Inventory; MMSE: Mini-Mental State Examination; FAB: Frontal Assessment Battery.

Table 2
Motor thresholds and single-pulse MEP size.

		S0	S1	S2	Unpaired *t*-test HS vs. PD (S0)	rmANOVA PD (S0, S1, S2)
AMT (%)	*HS*	37.6 ± 7.9	–	–	$p = 0.79$	$F_{2,48} = 2.81$, $p = 0.08$
	PD	36.8 ± 10.2	37.3 ± 10.2	38.8 ± 9.7		
RMT (%)	*HS*	48.4 ± 13.1	–	–	$p = 0.43$	$F_{2,48} = 2.24$, $p = 0.12$
	PD	45.5 ± 10.9	47.2 ± 11.3	47.9 ± 10.2		
SP amplitude (mV - ICF protocol)	*HS*	0.90 ± 0.26	–	–	$p = 0.96$	$F_{2,48} = 0.21$, $p = 0.81$
	PD	0.90 ± 0.39	0.95 ± 0.38	0.91 ± 0.29		
SP amplitude (mV - SICF protocol)	*HS*	0.86 ± 0.35	–	–	$p = 0.30$	$F_{2,48} = 1.28$, $p = 0.28$
	PD	0.96 ± 0.30	1.10 ± 0.40	0.98 ± 0.38		
SP amplitude (mV - pre-iTBS)	*HS*	0.89 ± 0.25	–	–	$p = 0.40$	$F_{2,48} = 0.22$, $p = 0.71$
	PD	0.97 ± 0.24	0.98 ± 0.36	0.92 ± 0.26		

HS: healthy subjects; PD: patients with Parkinson's disease; AMT: active motor threshold; RMT: resting motor threshold; SP: motor evoked potential elicited by single TMS pulses; ICF: intracortical facilitation; SICF: short-interval intracortical facilitation; iTBS: intermittent theta-burst stimulation. Data reflect mean values ± 1 standard deviation.

(2 levels: PD with LID, PD without LID) and the within-subject factor 'intensity' (7 levels: 100–160%), 'ISI' (2 levels: 1.5, 3 ms) or 'timepoint' (3 levels: T1, T2, T3). Friedman test with the factor 'session' (3 levels: S0, S1, S2) was adopted to evaluate safinamide effects on UPDRS-III, UDysRS-III, and BDI-II. Wilcoxon test was used to compare MMSE and FAB, and for post-hoc analyses. Separate rmANOVAs with the within-subject factor 'session' were applied to compare motor thresholds and single-pulse MEP amplitude between patients at S0, S1, and S2. RmANOVAs were also used to test changes in the I/O curve (factors 'session' and 'intensity'), ICF, SICI, and SICF (factors 'session' and 'ISI'), and iTBS-induced plasticity (factors 'session' and 'timepoint'). In the various rmANOVAs, post-hoc analyses were performed using t-tests, with Tukey Honest Significant Difference test applied to correct for multiple comparisons.

Neurophysiological and clinical-neurophysiological correlations were evaluated by Pearson's correlation and Spearman's rank-correlation test, respectively. For correlation analyses, SICF was considered as the average between ISI 1.5 and 3 ms, iTBS-induced plasticity reflected average T1-T3 values, and the slope of the I/O curve was measured. To quantify safinamide-induced short- and long-term changes in clinical and neurophysiological measures, we calculated the difference between S1 or S2 values and values at S0 (e.g., UDysRS-III S2–S0).

The significance level was set at $p < 0.05$. Statistical analyses were performed using Statistica (TIBCO software, US). Sample size was computed with the desired power of 0.80 and an alpha error of 0.05. The effect size was estimated assuming a 20% change in SICF (1.5 ms) and post-iTBS MEP amplitude from session S0 to S2 using values (mean and variance) of our published data in PD [11,39]. The minimum required sample was 20 for SICF and 14 for iTBS-induced plasticity.

3. Results

3.1. Baseline neurophysiological measures

Age ($p = 0.19$), gender distribution ($p = 0.52$), motor thresholds, and single-pulse MEP amplitude were comparable between patients and HS (Table 2).

The I/O curve was steeper in patients than HS, as suggested by the significant 'group'x'intensity' interaction ($F_{6,246} = 5.79$, $p < 0.001$), and the greater MEP size at 140% ($p = 0.05$), 150% ($p < 0.01$), and 160% RMT ($p < 0.01$) in patients as compared to HS in post-hoc analyses. SICF also differed between groups, as indicated by the significant factor 'group' ($F_{1,41} = 11.58$, $p = 0.001$) and the 'group'x'ISI' interaction ($F_{6,246} = 3.47$, $p < 0.01$). Post-hoc analysis showed enhanced SICF in patients as compared with HS at ISI 1.5 ms ($p < 0.001$) and 3 ms ($p = 0.03$) (Fig. 2). SICI was less effective (i.e., higher values) in patients than HS at both ISIs tested, as shown by the significant factor 'group' ($F_{1,34} = 12.90$, $p = 0.001$) and the lack of a 'group'x'ISI' interaction ($F_{1,34} = 0.01$, $p = 0.97$) in the rmANOVA (Supplementary Material, Fig. S1). Conversely, ICF did not differ between groups ('group': $F_{1,41} = 0.49$, $p = 0.49$; 'group'-x'ISI': $F_{1,41} = 0.67$, $p = 0.42$). MEP facilitation post-iTBS was lower in patients than in HS regardless of the timepoint considered, as revealed by the significant factor 'group' ($F_{1,31} = 12.48$, $p = 0.001$) and the lack of a 'group'x'timepoint' interaction ($F_{2,62} = 0.44$, $p = 0.65$). The rmANOVA conducted on PD data demonstrated comparable MEP size before and after iTBS ('timepoint': $F_{3,42} = 1.35$, $p = 0.27$), suggesting defective iTBS-induced plasticity (Fig. 2).

When comparing the I/O curve, SICF, and iTBS-induced plasticity abnormalities between patients with and without LID, the analysis demonstrated a similar I/O curve ('group': $F_{1,23} = 0.15$, $p = 0.70$; 'group'x'intensity': $F_{6,138} = 0.50$, $p = 0.80$) and MEP facilitation post-iTBS ('group': $F_{1,13} = 0.40$, $p = 0.54$; 'group'x'timepoint': $F_{2,26} = 0.04$, $p = 0.96$) between subgroups. Conversely, SICF at 1.5 and 3 ms was higher in patients with LID than in patients without LID, as confirmed by the significant factor 'group' ($F_{1,23} = 7.60$, $p = 0.01$) and the lack of a 'group'x'ISI' interaction ($F_{1,23} = 2.10$, $p = 0.16$) (Fig. 2).

3.2. Short- and long-term effects of safinamide

Concerning the short- and long-term effects of safinamide on clinical measures, UPDRS-III scores differed in the three sessions, as demonstrated by the Friedman test ($p = 0.03$). Post-hoc analysis demonstrated lower values at S1 than at S0 ($p < 0.01$) and S2 ($p = 0.01$), and similar values between S0 and S2 ($p = 0.14$). UDysRS-III scores variably changed across patients, and a slight increase in LID severity was present from S0 to S2, as revealed by the Friedman test ($p = 0.04$) and post-hoc analysis (S0 vs. S2: $p = 0.01$; S1 vs. S2: $p = 0.04$; S0 vs. S1: $p = 0.29$). BDI-II was modulated over time ($p = 0.03$), with lower values at both S1 ($p = 0.02$) and S2 ($p = 0.04$) than at S0 (S1 vs. S2: $p = 0.92$). Finally, MMSE ($p = 0.10$) and FAB scores ($p = 0.90$) were similar between S0 and S2 (Fig. 3A).

Concerning the short- and long-term effect of safinamide on neurophysiological measures, motor thresholds and single-pulse MEP amplitude were comparable between sessions (Table 2). The I/O curve did not change between S0, S1, and S2, as demonstrated by the non-significant factor 'session' ($F_{2,48} = 2.61$, $p = 0.09$) and the lack of a 'session'x'intensity' interaction ($F_{12,288} = 1.78$, $p = 0.14$). ICF ('session': $F_{2,48} = 0.21$, $p = 0.76$; 'session'x'ISI': $F_{2,48} = 0.01$, $p = 0.99$) and SICI ('session': $F_{2,34} = 0.01$, $p = 0.99$; 'session'x'ISI': $F_{2,34} = 1.67$, $p = 0.20$) were also similar between sessions in

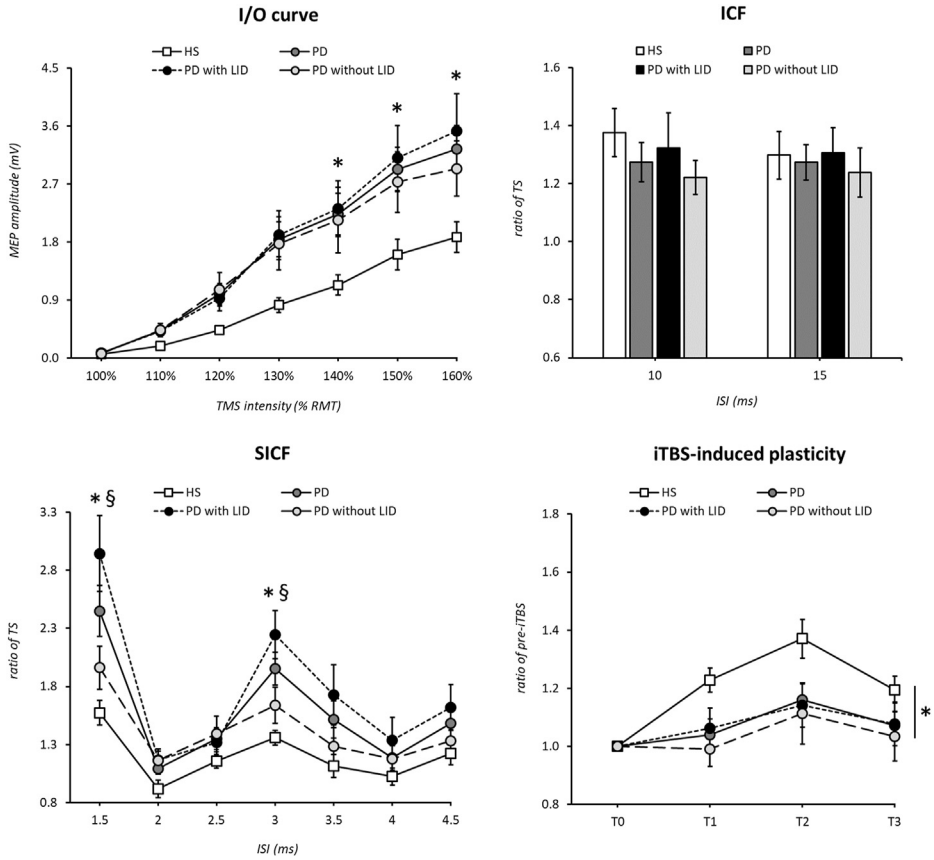

Fig. 2. Baseline neurophysiological measures in PD patients with and without LID.
Parkinson's disease (PD) patients showed increased input-output (I/O) curve steepness, enhanced short-interval intracortical facilitation (SICF) at interstimulus intervals (ISI) of 1.5 and 3 ms and impaired intermittent theta-burst stimulation (iTBS)-induced plasticity compared to healthy subjects (HS). The intracortical facilitation (ICF) was comparable between groups. Importantly, SICF alteration was greater in PD patients with L-dopa-induced dyskinesia (LID) than in those without. The asterisk denotes significant differences ($p < 0.05$) between PD and HS. The double S indicates significant differences between PD patients with and without LID.

patients. Conversely, SICF was modulated over time, as suggested by the significant factor 'session' ($F_{2,48} = 8.53$, $p < 0.001$) and the 'session'x'ISI' interaction ($F_{12,288} = 2.44$, $p < 0.01$). SICF 1.5 ms decreased at both S1 ($p < 0.001$) and S2 with respect to S0 ($p < 0.001$), while no difference was observed between S1 and S2 ($p = 0.99$). SICF 3 ms was lower at S2 than at S0 ($p < 0.001$), a decreasing trend was present between S1 and S0 ($p = 0.09$), and values were similar between S1 and S2 ($p = 0.90$) (Fig. 3B). When comparing SICF between HS and patients, similar values were found at S1 ('group': $F_{1,41} = 1.66$, $p = 0.20$; 'group'x'ISI': $F_{6,246} = 0.63$, $p = 0.70$) and S2 ('group': $F_{1,41} = 2.91$, $p = 0.11$; 'group'x'ISI': $F_{6,246} = 0.73$, $p = 0.63$) between groups. Finally, iTBS-induced plasticity changed over time regardless of the timepoint considered, as indicated by the significant factor 'session' ($F_{2,28} = 4.58$, $p = 0.02$) and the lack of a 'session'x'timepoint' interaction ($F_{4,56} = 0.14$, $p = 0.97$). Post-hoc analysis demonstrated a significant iTBS-induced plasticity increase at S2 with respect to S0 ($p = 0.01$). No differences were found between S1 and S0 ($p = 0.22$) or between S1 and S2 values ($p = 0.39$) (Fig. 3B). As compared to HS, there was a strong trend toward reduced iTBS-induced plasticity at S1 in patients ('group': $F_{1,31} = 3.60$, $p = 0.06$; 'group'x'timepoint': $F_{2,62} = 0.09$, $p = 0.91$). Conversely, iTBS-induced plasticity was similar between HS and patients at S2 ('group': $F_{1,31} = 0.45$, $p = 0.51$; 'group'x'timepoint': $F_{2,62} = 0.54$, $p = 0.58$).

3.3. Neurophysiological and clinical-neurophysiological correlations

At baseline (S0), there was a negative correlation between abnormal SICF and impaired iTBS-induced plasticity of M1 ($r = -0.65$, $p < 0.01$), i.e., the higher the SICF, the lower the M1 plasticity. Also, the long-term effects of safinamide (S2–S0) on altered SICF and iTBS-induced plasticity were negatively correlated ($r = -0.63$, $p = 0.01$), i.e., the greater the SICF reduction after 12 months of therapy, the higher the M1 plasticity.

Clinical-neurophysiological correlations showed that in patients with LID there was a negative relationship between SICF at baseline (S0) and the long-term effect of safinamide on UDysRS-III scores (S2–S0) ($r = -0.84$, $p < 0.001$), i.e., the more altered the SICF at baseline (higher values), the greater the reduction in LID severity after 12 months of treatment. Furthermore, long-term changes in SICF and UDysRS-III scores were positively correlated ($r = 0.85$, $p < 0.001$), i.e., patients who showed a greater SICF reduction demonstrated more positive effects on LID (less worsening or even improvement) (Fig. 4).

There was no relationship between short-term changes in neurophysiological measures (S1–S0), and no other clinical-neurophysiological correlations were present at either short- or long-term evaluation (p always >0.05). In addition, there was no correlation between the I/O curve slope and the degree of iTBS-induced plasticity impairment at S0 ($r = -0.43$, $p = 0.10$).

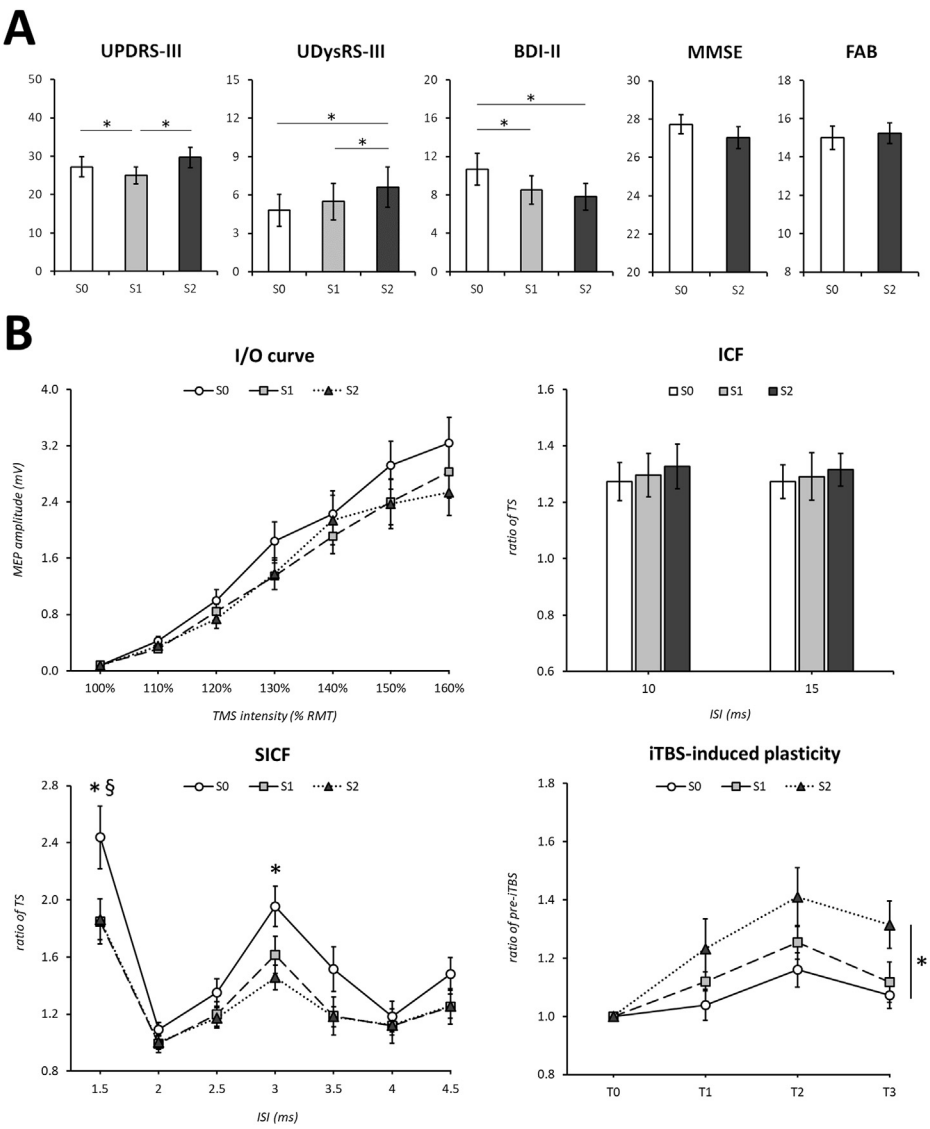

Fig. 3. Changes in clinical and neurophysiological measures at short- and long-term evaluation.
Panel A. Unified Parkinson's Disease Rating Scale, part III (UPDRS-III) scores were lower at S1 than at S0 and S2, Unified Dyskinesia Rating Scale, part III (UDysRS-III) scores slightly increased at S2 and Beck Depression Inventory (BDI-II) scores decreased at both S1 and S2. Mini-Mental State Examination (MMSE) and Frontal Assessment Battery (FAB scores) did not change between sessions. The asterisk indicates significant differences ($p < 0.05$) at post-hoc analysis. The bars reflect the standard error of the mean. *Panel B.* Short-interval intracortical facilitation (SICF) peak at interstimulus interval (ISI) of 1.5 ms decreased at both short- (S1) and long-term (S2) evaluation compared to baseline (S0), while SICF peak at 3 ms significantly decreased only at S2. Moreover, intermittent theta-burst stimulation (iTBS)-induced plasticity increased at S2 compared to S0. The input-output (I/O) curve steepness and intracortical facilitation (ICF) did not change between the three experimental sessions. The asterisk denotes significant differences ($p < 0.05$) between S0 and S2. The double S indicates significant differences between S0 and S1. MEP: motor-evoked potential; TMS: transcranial magnetic stimulation; RMT: resting motor threshold; TS: test stimulus (i.e., MEP evoked by single-pulse TMS).

4. Discussion

In this study, we found increased I/O curve steepness, abnormally enhanced SICF, and impaired iTBS-induced plasticity at baseline in the whole group of PD patients compared to HS. SICF was more altered in patients with LID than in those without, whereas the I/O curve and iTBS-induced plasticity were comparable between the two patient subgroups. Following safinamide administration, UPDRS-III decreased at S1 and BDI-II decreased at S1 and S2. UDysRS-III scores slightly increased at S2. Safinamide normalized SICF at S1 and this effect persisted at S2. Moreover, the drug restored iTBS-induced plasticity at the long-term evaluation. Abnormal SICF correlated with the amount of iTBS-induced plasticity at S0. Similarly, there was also a correlation between long-term changes in these neurophysiological measures (S2). Finally, in patients with LID, long-term modifications in the UDysRS-III score were related to the degree of SICF alterations at S0 and the amount of SICF modulation at S2. Overall, these findings provide novel insights into the pathophysiological link between abnormal glutamatergic transmission in SICF circuits, altered M1 plasticity, and LID severity in PD.

Despite a mild worsening of motor symptoms over time, the UPDRS-III score did not significantly differ between S0 and S2 in our patients. This factor, which reveals relatively long-term clinical stability, allowed us to maintain the pre-existing antiparkinsonian therapy unmodified from S0 to S2, thus excluding neurophysiological changes secondary to drugs other than safinamide. Moreover, the overall cortical excitability state, as assessed by AMT and

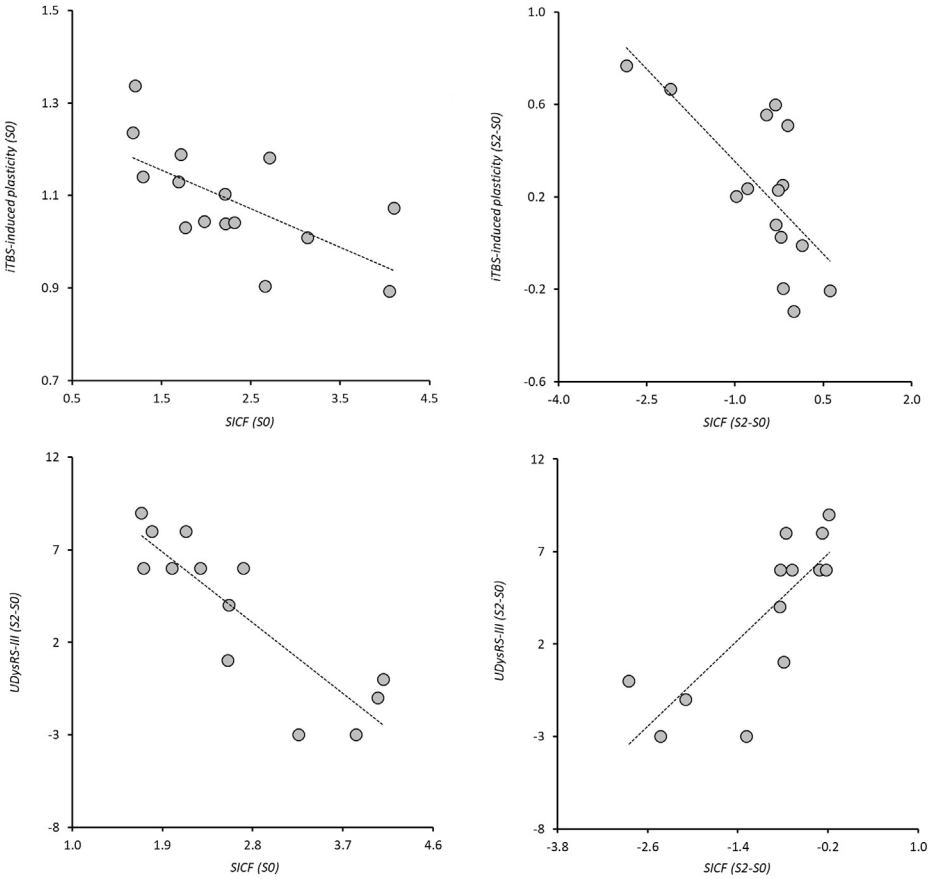

Fig. 4. Clinical-neurophysiological correlations.
Abnormally enhanced short-interval intracortical facilitation (SICF) and impaired intermittent theta-burst stimulation (iTBS)-induced plasticity negatively correlated at baseline (S0), i.e., the higher the SICF, the lower the iTBS-induced plasticity (upper left panel). In addition, SICF and iTBS-induced plasticity changes at long-term evaluation (S2–S0) correlated, i.e., the greater the SICF reduction, the higher the iTBS-induced plasticity (upper right panel). Abnormally enhanced SICF was also related to LID severity changes at long-term evaluation, as assessed by the Unified Dyskinesia Rating Scale, impairment section (UDysRS-III). The more altered the SICF at S0, the greater the reduction in LID severity at S2 (lower left panel). Furthermore, the greater the SICF reduction at S2, the more positive the effects on LID (less worsening or even improvement) (lower right panel).

RMT, was similar between S0, S1, and S2. Consistent with previous studies [27,39,41,42], we found reduced SICI in patients as compared with HS, reflecting less effective GABA-A-ergic neurotransmission in M1 in PD. Importantly, we found no effect of safinamide on SICI tested at the same ISI as SICF peaks, thus excluding that modifications in GABA-A-ergic inhibition contributed to drug-induced SICF changes [11,17].

4.1. Long-term modulation of SICF and M1 plasticity in PD

In the whole group of patients, safinamide normalized SICF not only at S1 but also after 12 months of treatment. SICF acts on a chain of excitatory interneurons whose activity is thought to be mediated by glutamate [11,13,14]. In PD, altered SICF possibly reflects a pathological increase in neuronal synchronization and hyperexcitability of excitatory glutamatergic interneurons in M1 [11,14,43]. Since safinamide inhibits glutamate release through the blockage of voltage-gated sodium and calcium channels in a frequency-dependent manner [19], short-term SICF normalization in PD may reflect the reduction in abnormally synchronized activity of excitatory glutamatergic interneurons [11]. The persistence of this effect over long-term evaluation suggests that the safinamide-related decrease in glutamatergic interneuronal synchronization and excitability does not diminish over time. Rather, while safinamide reduced SICF 1.5 ms both at S1 and S2, the normalization of SICF 3 ms was evident only at S2, which indicates that safinamide effects may strengthen over months.

In line with animal studies [16–19], we recently demonstrated that safinamide effects on SICF are dose-dependent, with prominent SICF modulation occurring at the high dose, which has marked anti-glutamatergic properties [11]. However, besides anti-glutamatergic properties, safinamide exerts dopaminergic effects as an MAO-B inhibitor. To date, it is unclear whether SICF is influenced by dopaminergic medications [11,12,14]. Moreover, pure dopaminergic effects may not necessarily be identical to those of MAO-B inhibition. Therefore, it is difficult to determine whether SICF normalization exclusively reflects safinamide anti-glutamatergic effects or whether it depends on the long-term interaction between glutamate release inhibition and MAO-B inhibition. Moreover, in this study we found no long-term changes in I/O curve steepness or ICF. The I/O curve is a measure of corticospinal excitability, which relates to the overall glutamate concentration within M1 [44], while ICF reflects intracortical NMDA glutamatergic neurotransmission [10]. Our results showing long-term SICF modulation without effects on the I/O curve or ICF suggest that safinamide does not exert a general effect on glutamate neurotransmission but instead selectively modulates the intracortical glutamatergic circuits underlying SICF [11].

Another novel result concerns the changes we found in iTBS-induced plasticity of M1 over time. In line with previous reports,

the iTBS-induced LTP-like plasticity was impaired in patients compared to HS at baseline [25,39,45–48]. Interestingly, defective LTP-like plasticity of M1 was restored after 12 months of chronic treatment with safinamide, i.e., iTBS facilitated MEP to the same extent in patients and HS. Also, there was no difference in iTBS-induced plasticity between S0 and S1, suggesting that safinamide-related effects on impaired M1 plasticity in PD require a long time to occur. Pharmacological studies in animals found that increased extracellular glutamate exerts negative effects on synaptic plasticity [49]. Abnormally enhanced glutamate levels also contribute to altered corticostriatal plasticity in animal models of PD [1,24]. A recent study showed that chronic administration of safinamide plus L-dopa in dopamine-denervated rats induced the recovery of corticostriatal LTP [50]. Consistent with these data, our findings of restored iTBS-induced LTP-like plasticity after chronic intake of safinamide 100 mg/day suggest that the anti-glutamatergic properties of the drug may be responsible for the improvement of M1 LTP-like plasticity in PD. Given that calcium dynamics contributes to plasticity processes [51] and that safinamide-related anti-glutamatergic mechanisms include the modulation of calcium channels [19], the iTBS-induced plasticity improvement may also reflect modifications in calcium channels activity. We also found a negative relationship between increased SICF and iTBS-induced plasticity at baseline (S0), i.e., the greater the SICF abnormality, the lower the LTP-like plasticity of M1. Moreover, there was a negative correlation between long-term changes in SICF and iTBS-induced plasticity, i.e., the greater the SICF reduction, the higher the M1 plasticity at S2. In contrast, long-term changes in iTBS-induced plasticity were not accompanied by changes in ICF or overall corticospinal excitability, as assessed by the I/O curve. These data suggest a dissociation between M1 hyperexcitability and impaired plasticity in PD. Moreover, our data point to a relationship between altered neurotransmission in specific glutamatergic circuits within M1, i.e., SICF, and impaired LTP-like plasticity in PD [3,4].

It may be conjectured that the long-term interaction between L-dopa and safinamide, rather than the effects of the drug *per se,* underlies the normalization of M1 plasticity in PD at S2. Although we cannot fully exclude this hypothesis, we previously found comparable SICF in patients under safinamide therapy between OFF and ON dopaminergic states, which suggests that L-dopa does not influence safinamide effects on M1 [11]. Also, assessing patients after a long-term L-dopa washout is necessary to clarify this hypothesis. However, this experimental condition may be difficult to test for ethical reasons and since safinamide is approved as an add-on therapy to L-dopa in PD.

4.2. Abnormal SICF and LID pathophysiology

We provide evidence on the pathophysiological link between abnormally enhanced glutamatergic transmission in SICF circuits and LID severity. We found comparable I/O curve steepness and iTBS-induced plasticity in patients with and without LID, suggesting common neurophysiological abnormalities in the two patient subgroups [52]. Conversely, SICF alterations were greater in patients with LID than in those without, consistent with our previous report [11]. Hence, although excessive glutamate release in SICF circuits plays a role in PD pathophysiology, this abnormality is specifically involved in LID [15,53].

Our longitudinal study allowed us to examine the effect of long-term SICF modulation on LID outcome. A further novel finding was the negative relationship between the degree of SICF alterations at baseline and the effect of long-term treatment with safinamide on UDysRS-III scores in patients with LID, i.e., the more altered the SICF at S0, the more positive the safinamide-related effect on LID (less worsening or even LID improvement at S2). LID pathophysiology is complex and involves abnormalities in multiple neurotransmitter systems, including dopaminergic, serotoninergic, adrenergic, and glutamatergic, and in the interaction among these systems [5,6,8]. The correlation between SICF alterations at baseline and LID changes at S2 suggests that patients with greater abnormalities in SICF-related glutamatergic circuits are those in whom safinamide produced more beneficial effects on LID. We also observed a correlation between long-term changes in SICF and UDysRS-III scores, i.e., patients with a greater SICF reduction demonstrated more positive effects on LID. Safinamide is not a treatment for LID and experimental studies have confirmed that it has no direct anti-dyskinetic effects [23,54]. However, data from LID animal models showed that safinamide prevented the L-dopa-induced increase in glutamate release in the striatum associated with dyskinesia [16]. The authors suggested that this mechanism may explain why safinamide long-term use as L-dopa add-on therapy improved motor function without worsening LID [16,54]. In line with these animal data, the relationship we found between changes in SICF and LID severity at the long-term evaluation indicates that patients with the greatest improvement in SICF-related glutamatergic circuits did not show LID worsening over time. The lack of correlation between SICF and LID severity changes at the short-term evaluation suggests that safinamide-related LID modulation requires time to occur, possibly due to concomitant long-term M1 plasticity reorganization. Overall, these findings demonstrate that altered SICF is an important pathophysiological substrate of LID in PD [11], and that restoration of SICF has beneficial long-term effects on LID.

This study has some limitations. Due to the relative clinical stability of our patients, the dopaminergic therapy unchanged from S0 to S2, apart from safinamide. Thus, our long-term results cannot be generalized to patients undergoing significant adjustments in their dopaminergic medication over time. Also, ethical reasons precluded the possibility of re-assessing the patients after a washout of safinamide, a condition that could have helped to further discriminate the effects of the long-term dopaminergic treatment from those strictly related to safinamide intake. SICF peaks were measured at a fixed ISI, though individual variation may exist in the optimal timing of SICF [12,26]. Moreover, safinamide could have changed SICF timing and this factor could have partly influenced our long-term results.

5. Conclusions

In this study, we demonstrated that SICF-related glutamatergic transmission within M1 is abnormally enhanced in PD and that this abnormality plays a role in LID pathophysiology. The alteration in SICF-related circuits in PD can be normalized with safinamide 100 mg/day, and this effect persists after long-term treatment. Moreover, we provided the first evidence of a relationship between SICF-related glutamatergic dysfunction and impaired LTP-like plasticity in PD. We suggest that a possible physiological target of long-term safinamide effects is the modulation of synaptic plasticity mechanisms in M1. Future studies in larger patient cohorts are needed to validate SICF as a marker of glutamatergic transmission in PD patients with LID and to assess the possible clinical correlates of M1 plasticity improvement over time.

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CRediT authorship contribution statement

Andrea Guerra: Conceptualization, Methodology, Investigation, Formal analysis, Writing – original draft. **Francesco Asci:** Methodology, Investigation, Formal analysis. **Alessandro Zampogna:** Methodology, Investigation. **Valentina D'Onofrio:** Methodology, Investigation. **Antonio Suppa:** Conceptualization, Writing – review & editing, Supervision. **Giovanni Fabbrini:** Writing – review & editing, Supervision. **Alfredo Berardelli:** Conceptualization, Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2021.11.016.

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