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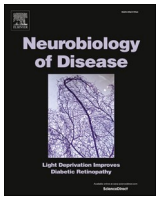

Short-term plasticity of the motor cortex compensates for bradykinesia in Parkinson's disease

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ABSTRACT

Patients with Parkinson's disease (PD) show impaired short-term potentiation (STP) mechanisms in the primary motor cortex (M1). However, the role played by this neurophysiological abnormality in bradykinesia pathophysiology is unknown. In this study, we used a multimodal neuromodulation approach to test whether defective STP contributes to bradykinesia. We evaluated STP by measuring motor-evoked potential facilitation during 5 Hz-repetitive transcranial magnetic stimulation (rTMS) and assessed repetitive finger tapping movements through kinematic techniques. Also, we used transcranial alternating current stimulation (tACS) to drive M1 oscillations and experimentally modulate bradykinesia. STP was assessed during tACS delivered at beta (β) and gamma (γ) frequency, and during sham-tACS. Data were compared to those recorded in a group of healthy subjects. In PD, we found that STP was impaired during sham- and γ-tACS, while it was restored during β-tACS. Importantly, the degree of STP impairment was associated with the severity of movement slowness and amplitude reduction. Moreover, β-tACS-related improvements in STP were linked to changes in movement slowness and intracortical GABA-A-ergic inhibition during stimulation, as assessed by short-interval intracortical inhibition (SICI). Patients with prominent STP amelioration had greater SICI reduction (cortical disinhibition) and less slowness worsening during β-tACS. Dopaminergic medications did not modify β-tACS effects. These data demonstrate that abnormal STP processes are involved in bradykinesia pathophysiology and return to normal levels when β oscillations increase. STP changes are likely mediated by modifications in GABA-A-ergic intracortical circuits and may represent a compensatory mechanism against β-induced bradykinesia in PD.

1. Introduction

Recent evidence suggests that neurophysiological abnormalities in the primary motor cortex (M1) play a relevant role in bradykinesia pathophysiology (Bologna et al., 2018, 2020b; Guerra et al., 2022). Among the various M1 dysfunctions described in PD, including excitability and plasticity mechanisms, it has been previously shown the impairment in short-term potentiation (STP) (Bologna et al., 2020b; Gilio et al., 2002). In healthy humans, STP can be elicited by delivering a short train of suprathreshold repetitive transcranial magnetic stimulation (rTMS) stimuli at 5 Hz. This protocol determines a progressive increase in motor evoked potential (MEP) amplitude from the first to the last stimulus of the train (Berardelli et al., 1998; Pascual-Leone et al., 1994), and its effects are thought to resemble the short-term plasticity mechanisms described in animals (Barroso-Flores et al., 2017; Cooke and Bliss, 2006; Iezzi et al., 2011; Zucker and Regehr, 2002). A previous study showed absent or lower MEP facilitation during the 5 Hz-rTMS train in PD patients compared to healthy subjects, which has been interpreted as reflecting a reduced output from cortical motor areas (Gilio et al., 2002). However, it is unclear whether impaired STP mechanisms are implicated in bradykinesia.

Another unknown issue is whether there is a pathophysiological link between abnormal STP and altered oscillations in the basal ganglia-thalamo-cortical loop observed in PD (Oswal et al., 2013). This is relevant because changes in beta (β) and gamma (γ) oscillatory activity in the motor network play a pivotal role in this condition (Little et al., 2012; Lofredi et al., 2019; Oswal et al., 2013; Wiest et al., 2022). Also, recent evidence suggests that M1 neurophysiological abnormalities are

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related to altered oscillations in PD patients and are likely to reflect compensatory cortical mechanisms against bradykinesia (Blesa et al., 2017; Guerra et al., 2022).

The present study aims to address the role of STP impairment in bradykinesia. For this purpose, a group of PD patients (OFF dopaminergic therapy) underwent the evaluation of STP using the standardized rTMS protocol and objective assessment of bradykinesia through kinematic techniques during repetitive finger tapping movements (Berardelli et al., 1998; Bologna et al., 2018; Gilio et al., 2002; Guerra et al., 2022; Iezzi et al., 2011; Modugno et al., 2001). We also aimed to assess the possible relationship between STP and changes in cortical β and γ oscillations in patients. In line with previous evidence, we used transcranial alternating current stimulation (tACS) to non-invasively drive and enhance cortical oscillations (Johnson et al., 2020; Krause et al., 2019; Witkowski et al., 2016). With a double-blind and randomized design, we recorded STP during tACS delivered at β and γ frequencies as well as during sham-tACS. We thus tested whether STP modifications during tACS were associated with concurrent changes in bradykinesia. Since GABA-A-ergic activity changes are implicated in both STP mechanisms and β-induced bradykinesia (Guerra et al., 2022; Hall et al., 2014; Iezzi et al., 2011; Prokic et al., 2019; Wu et al., 2000), we also recorded short-interval intracortical inhibition (SICI), a GABA-A-ergic TMS measure (Guerra et al., 2022). Finally, to test whether the dopaminergic therapy influences the possible relationship between STP processes, bradykinesia and enhanced cortical β oscillations, all PD patients were also tested ON dopaminergic condition.

2. Materials and methods

2.1. Participants

We enrolled 15 early-to-intermediate stage PD patients from the Department of Human Neurosciences, Sapienza University of Rome, and 15 right-handed healthy subjects (HS) (Table 1). PD diagnosis was based on clinical criteria (Postuma et al., 2015). To minimize the heterogeneity of the clinical sample and to avoid possible confounding related to involuntary EMG activity during the TMS assessment, no patient with a tremor-dominant PD subtype was enrolled in the study. Also, no patient had L-dopa-induced dyskinesia in the ON dopaminergic condition. No participant showed any signs of moderate-to-severe depression or dementia, as demonstrated by Beck Depression Inventory (BDI-II) scores always <20 and Montreal Cognitive Assessment (MoCA) >24, respectively (Beck et al., 1961; Thomann et al., 2020). The experimental procedures conformed to the Declaration of Helsinki, adhered to international safety guidelines (Antal et al., 2017; Rossi et al., 2021), and were approved by the local institutional review board. All participants gave their written informed consent to the study.

Table 1
Clinical-demographic characteristics and motor thresholds of study participants

	PD	HS	*P value*
Gender	13 M; 2 F	10 M; 5 F	0.39
Age (years)	67.1 ± 10.6	65.2 ± 9.2	0.45
BDI-II	9.4 ± 6.5	6.7 ± 5.2	0.26
MoCA	27.2 ± 2.1	27.9 ± 1.6	0.38
Dis duration (years)	6.1 ± 3.4	-	-
LEDD	436 ± 176	-	-
UPDRS-III OFF	33.5 ± 10.9	-	-
UPDRS-III ON	23.3 ± 8.9	-	-
AMT OFF (%)	48.9 ± 9.9	50.7 ± 7.0	0.57
RMT OFF (%)	60.3 ± 12.6	62.5 ± 8.3	0.58
AMT ON (%)	48.5 ± 9.1	-	-
RMT ON (%)	59.5 ± 10.4	-	-

Data reflect the mean ± 1 standard deviation of the mean. P values reflect differences between PD OFF medication condition and HS. AMT: active motor threshold; BDI-II: Beck Depression Inventory; F: female; HS: healthy subjects; LEDD: L-dopa equivalent daily dose; M: male; MoCA: Montreal Cognitive Assessment; PD: patients with Parkinson's disease; RMT: resting motor threshold; UPDRS-III: Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale, part III.

2.2. TMS

Single- and paired-pulse TMS was performed using a Magstim Bistim^2 connected to a figure-of-eight coil (Magstim Company) with the handle pointing posterolaterally, whereas rTMS was delivered through a Magstim Super Rapid^2. The FDI hotspot, resting (RMT) and active motor threshold (AMT) as well as the intensity eliciting MEPs of ~1 mV amplitude (MT_{1mV}) were identified following international guidelines (Rossini et al., 2015). STP was assessed by delivering rTMS trains of 10 stimuli at 5 Hz and 120% RMT intensity, with an intertrain interval of 1 min (total duration of STP assessment: ~10 min) (Berardelli et al., 1998; Gilio et al., 2002; Iezzi et al., 2011; Modugno et al., 2001). SICI was tested using a conditioning stimulus at 80% AMT, a test stimulus at MT_{1mV} and a 2-ms interstimulus interval (ISI). The electromyographic (EMG) activity recorded from the FDI (the more affected side in patients and dominant side in HS) was amplified (Digitimer D360, Digitimer), digitized (CED 1401, Cambridge Electronic Design), and stored on a computer for offline analyses. However, EMG was continuously monitored during recordings and trials with involuntary activity >0.1 mV were discarded on-line. For STP quantification, we measured the peak-to-peak amplitude for all MEPs of the train (from 1st to 10th) and averaged each MEP between all trains for each subject and condition. We then calculated the ratio between the 10th and the 1st MEP in the train (MEP 10th/1st) (Gilio et al., 2002; Iezzi et al., 2011). SICI was expressed as the ratio between the amplitude of conditioned and unconditioned (i.e., single-pulse at MT_{1mV}) MEP.

2.3. tACS

tACS was delivered through a BrainSTIM (E.M.S.) connected to two 5x5 cm electrodes enclosed in saline solution-soaked sponges. The methods used to apply and deliver tACS to M1, including stimulation montage and frequency settings, were identical to our previous studies demonstrating significant effects on neurophysiological and behavioral motor parameters in PD patients (Guerra et al., 2022; Guerra et al., 2020). Briefly, one electrode was centered over the first dorsal interosseus (FDI) hotspot and the other over the site corresponding to Pz. We used a peak-to-peak amplitude of 1 mA, 3-s ramp-up and down periods, and stimulation frequency of 20 Hz and 70 Hz for β- and γ-tACS, respectively. Sham-tACS consisted of ramp-up and down periods and 1-s stimulation only. tACS did not induce visual or skin sensations in any participant, as explicitly asked at the end of the experiment. Therefore, it was impossible to distinguish between the various stimulation conditions for participants. Also, the researcher who set and randomized the stimulation conditions did not actively participate in data recordings and analysis (double-blind study design).

2.4. Kinematic recordings

The finger tapping task consisted in repetitively opening and closing the index finger and thumb as wide and fast as possible for 15 s. Movement recordings were performed using a 3D optoelectronic system (SMART motion system, BTS Engineering) and reflective markers taped to the participant's hand (the more affected side in patients and dominant side in HS), and data analysis was performed using a dedicated software (SMART Analyzer, BTS Engineering). We measured movement amplitude, velocity, rhythm and sequence effect, as detailed in previous studies (Bologna et al., 2020a; Bologna et al., 2018; Guerra et al., 2022; Guerra et al., 2018).

2.5. Experimental design

Participants underwent TMS and kinematic assessment in a single session, which lasted ~2 hours. All recordings were carried out during β-, γ- and sham-tACS, and randomly delivered. Ten trains of 5 Hz rTMS were delivered for each stimulation condition at rest to assess the STP. tACS was activated ~7 s before delivering each train and switched-off immediately at the end of the train. As described in our previous study, SICI (15 trials) was recorded at rest and randomized with 15 single-pulse MEPs at MT_{1mV}. The kinematic evaluation consisted of 9 finger tapping trials (3 trials per stimulation condition) with 3-min resting intervals between trials (Guerra et al., 2022). Importantly, although evidence suggests that β- and γ-tACS effects on M1 do not outlast the stimulation period (Bologna et al., 2019; Guerra et al., 2020; Nowak et al., 2017; Pozdniakov et al., 2021), we decided to wait at least twice the stimulation time after each STP, SICI and kinematic assessment (Figure 1). All PD patients were studied both in the clinical OFF (>12 hours after dopaminergic therapy withdrawal) and ON (on their usual therapeutic regimen) condition, in two separate sessions with at least a 7-day interval.

2.6. Statistical analysis

The Mann-Whitney U and Fisher exact tests were used to analyze differences in age, clinical scores and gender distribution between patients and HS, while two-tailed t-tests were applied to compare AMT and RMT between groups (PD OFF vs. HS: unpaired t-test; PD OFF vs. ON: paired t-test). Separate repeated-measures (rm)ANOVAs were adopted to test for possible changes in neurophysiological variables. The within-group factor 'stimulus number' (10 levels: 1st to 10th) and the between-group factor 'group' (2 levels: PD OFF, HS) were used to verify whether the STP protocol *per se* (i.e., during sham-tACS) modulated MEP size in HS and patients. The within-group factor 'frequency' (3 levels: sham, β, γ) and the between-group factor 'group' were applied to compare the amplitude of the 1st MEP of the train between groups and conditions as well as the effect of tACS on STP (i.e., MEP $10^{th}/1^{st}$), single-pulse MEP amplitude, SICI and kinematic parameters. In case of significant interactions, a rmANOVA with 'stimulus number' or 'frequency' as factor was applied separately for each group (Guerra et al., 2022). To test for possible L-dopa effects on neurophysiological variables, the within-group factor 'condition' (2 levels: PD OFF, PD ON) replaced the factor 'group' in the various rmANOVAs. Post-hoc analyses were performed using t-tests with the Tukey HSD test applied to correct for multiple comparisons. Pearson's correlation and Spearman's rank-correlation tests were used to evaluate any possible relationships between TMS variables and kinematic-TMS correlations, respectively. For these analyses, we quantified tACS effects by computing the ratio between values recorded during real tACS and values recorded during sham-tACS (e.g., STP β-tACS/sham-tACS). The level of significance was set at $p \leq 0.05$. Statistical analyses were carried out using Statistica (TIBCO software, USA). Sample size was computed using the G*Power software (Faul et al., 2007). We set a desired power of 0.80 and alpha error of 0.05, assuming a 20% change in STP between sham (expected MEP $10^{th}/1^{st}$ of $\sim 1.0 \pm 0.4$ based on previously published data in PD (Gilio et al., 2002)) and real tACS conditions. The minimal required sample size to detect a difference in patients (primary study aim) was 14.

3. Results

Age, gender distribution, BDI-II, MoCA and motor thresholds were similar between PD patients OFF and HS (Table 1). Also, AMT ($p=0.84$) and RMT ($p=0.67$) did not differ between PD patients OFF and ON medication.

3.1. Effects of tACS on STP

The STP protocol *per se* (sham-tACS condition) produced different effects on MEP size between HS and patients ('group'x'stimulus number': $F_{9,252}=3.53$, $p<0.001$). In HS, MEP amplitude progressively increased during 5 Hz rTMS ('stimulus number': $F_{9,126}=3.42$, $p<0.001$) and the 10th MEP of the train became larger than the 1st ($p=0.02$), 2nd ($p=0.01$), 3rd ($p=0.01$) and 4th ($p=0.02$). In contrast, MEP size did not change during 5 Hz rTMS in patients ('stimulus number': $F_{9,126}=1.85$, $p=0.07$). Importantly, while the amplitude of the 1st MEP of the train was similar between groups and stimulation conditions ('group': $F_{1,28}=0.44$, $p=0.51$; 'frequency': $F_{2,56}=0.16$, $p=0.85$; 'group'-x'frequency': $F_{2,56}=0.35$, $p=0.71$), the changes of the MEP size produced by the STP protocol were differently modified by tACS in the two groups ('group'x'frequency': $F_{2,56}=7.61$, $p=0.001$). In PD patients ('frequency': $F_{2,28}=13.29$, $p<0.001$), the degree of MEP facilitation was greater during β- than sham- ($p<0.001$) and γ-tACS ($p<0.001$), with no difference being observed between sham- and γ-tACS ($p=0.99$). Conversely, the amount of MEP facilitation produced by the STP protocol was comparable between stimulation conditions in HS

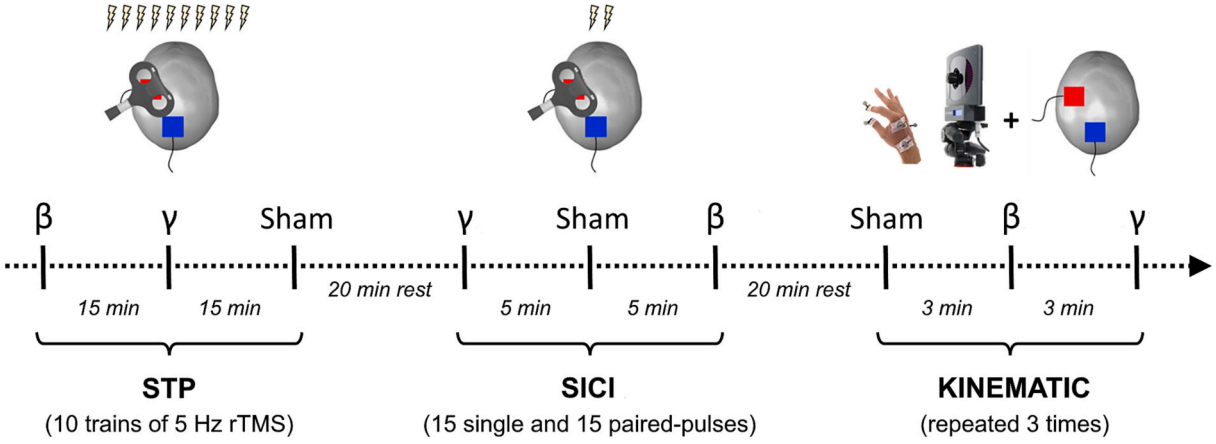

Fig. 1. Experimental design.
The evaluation of short-term potentiation (STP) consisted in 10 trains of 5 Hz repetitive transcranial magnetic stimulation (rTMS) for each stimulation condition (β, γ and sham, tested in a random order). Each rTMS train included 10 stimuli and, thus, lasted 2 s. The interval between trains of the same stimulation condition was 1 min, while we waited 15 min before testing a different stimulation condition. Transcranial alternating current stimulation (tACS) was delivered during rTMS, i.e. it was activated ~7 s before delivering each rTMS train and switched-off immediately at the end of the train (total stimulation time ~9 s). A similar concurrent approach was adopted for short-interval intracortical inhibition (SICI) and kinematic evaluations during tACS, as detailed in Guerra et al., 2022.

('frequency': $F_{2,28}$=1.17, p=0.32) (Figure 2). An unpaired t-test demonstrated that the degree of MEP facilitation during β-tACS in patients was similar to that observed during sham-tACS in HS (MEP $10^{th}/1^{st}$: 1.44 ± 0.36 vs. 1.63 ± 0.55, p=0.26).

3.2. Effects of tACS on SICI

SICI was overall less effective (reduced inhibition) in patients than HS ('group': $F_{1,28}$=20.89, p<0.001). More importantly, SICI changed during tACS with different patterns between groups ('group'-x'frequency': $F_{2,56}$=3.16, p=0.04). In patients, SICI decreased (reduced inhibition) during tACS ($F_{2,28}$=9.02, p<0.001) when delivered both at β (p=0.04) and γ frequency (p<0.001) compared to the sham condition. In HS, SICI decreased ($F_{2,28}$=8.69, p=0.001) during γ-tACS only (γ-tACS vs. sham-tACS: p<0.01; γ-tACS vs. β-tACS: p<0.01; β-tACS vs. sham-tACS p=0.88). The single-pulse MEP amplitude did not change between groups and stimulation conditions (Table 2).

3.3. Effects of tACS on movement

As previously reported (Guerra et al., 2022), tACS modulated movement velocity and amplitude in PD (velocity: $F_{2,28}$=7.18, p<0.01; amplitude: $F_{2,28}$=6.39, p<0.01) but not in HS (velocity: $F_{2,28}$=2.19, p=0.13; amplitude: $F_{2,28}$=0.57, p=0.57). Movement velocity worsened during β-tACS if compared to γ-tACS (p<0.01) and sham-tACS (p=0.02), whereas movement amplitude improved during γ-tACS than β-tACS (p<0.01) and, to a lower extent, sham-tACS (p=0.09). No other movement parameter, including the amplitude decrement during repetitive finger tapping movements, was modulated by tACS. Comprehensive statistical data are reported in Table 2.

3.4. Influence of L-dopa on tACS effects

The amplitude of the 1^{st} MEP of the train was comparable between dopaminergic conditions ('condition': $F_{1,14}$=0.39, p=0.54; 'condition'x'frequency': $F_{2,28}$=0.07, p=0.93). Also, STP (MEP $10^{th}/1^{st}$) was similar between patients OFF and ON condition ('condition': $F_{1,14}$=0.24, p=0.63) and tACS effects were not influenced by dopaminergic medications ('frequency': $F_{2,28}$=10.85, p<0.001; 'condition'x'frequency': $F_{2,28}$=1.64, p=0.21) (Figure 2). Particularly, the post-hoc analysis confirmed that STP was greater during β-tACS than sham- (p=0.001) and γ-tACS (p=0.001).

SICI did not change between OFF and ON conditions ('condition': $F_{1,14}$=0.65, p=0.43), while movement velocity and amplitude improved in patients ON state (velocity: $F_{1,14}$=12.79, p<0.01; amplitude: $F_{1,14}$=9.53, p<0.01). Like STP, tACS-related changes in SICI ('condition'x'frequency': $F_{2,28}$=1.18, p=0.32) and movement kinematics (velocity: $F_{2,28}$=1.99, p=0.15; amplitude: $F_{2,28}$=3.01, p=0.07) were independent of the dopaminergic condition. That is, SICI decreased during β- (p=0.03) and γ-tACS (p<0.001) compared to sham-tACS, movement velocity was slower during β-tACS than γ- (p=0.001) and sham-tACS (p<0.01), and movement amplitude was greater during γ-tACS than β- (p=0.001) and sham-tACS (p=0.03) (see Table 2 for detailed rm-ANOVA statistics).

3.5. Correlation analyses

In PD patients OFF condition, we found a positive correlation between STP (MEP $10^{th}/1^{st}$), movement velocity (r=0.55, p=0.03) and amplitude (r=0.66, p<0.01) during sham-tACS. That is, the lower the MEP facilitation, reflecting greater impairment in STP mechanisms, the lower the movement velocity and amplitude (more severe bradykinesia). Moreover, changes in STP, SICI and movement velocity during β-tACS (i.e., ratio β-tACS/sham-tACS) were correlated. Indeed, the greater the STP amelioration and the SICI reduction, the lower the velocity worsening during stimulation (STP vs. velocity: r=0.79, p<0.001; SICI vs. velocity: r=0.70, p<0.01). Moreover, the greater the STP amelioration during β-tACS, the greater the SICI reduction (r=0.73, p<0.01) (Fig. 3 and 4).

In PD patients ON condition, there was no correlation between STP and movement parameters during sham-tACS (STP vs. velocity: r=0.11, p=0.69; STP vs. amplitude: r=0.26; p=0.35) nor between β-tACS effects on STP, SICI and movement velocity (STP vs. SICI: r=0.19, p=0.50; STP vs. velocity: r=0.07, p=0.80; SICI vs. velocity: r=0.08, p=0.77). Also, no correlation between STP and movement velocity (r=0.17, p=0.53) or amplitude (r=0.08, p=0.77) during sham-tACS was detected in HS.

4. Discussion

This study confirms the lack of MEP facilitation during short trains of 5 Hz-rTMS in PD patients, which suggests impaired STP (Gilio et al., 2002). Interestingly, we found that the degree of STP impairment during sham-tACS was associated to bradykinesia severity, i.e., the weaker the STP, the lower the movement velocity and amplitude. Another novel finding is that rTMS-induced MEP facilitation significantly increased during β-tACS in PD, while γ-tACS had no effect on STP. The amelioration of MEP facilitation was related to SICI changes and movement velocity during β-tACS, being prominent in patients showing greater SICI modulation and less movement velocity worsening. β-tACS-induced effects did not differ between OFF and ON dopaminergic conditions. Overall, these results suggest that abnormal STP mechanisms in PD have a role in bradykinesia pathophysiology, can be restored by driving cortical β oscillations and are linked to GABA-A-ergic activity changes in M1.

The motor thresholds, as well as the amplitude of the 1^{st} MEP of the train were comparable between groups and dopaminergic conditions, which allow us to exclude that different M1 excitability levels may have influenced our results. It is well known that STP effects on M1 excitability last only 600-900ms after the stimulation train (Berardelli et al., 1998; Iezzi et al., 2011), thus the STP protocol had no impact on the following neurophysiological evaluations. Also, the similar size of the 1^{st} MEP of the train between the three stimulation conditions confirms the lack of tACS aftereffects on M1 excitability, which could have biased our recordings. The observation is supported by previous evidence suggesting that tACS delivered on sensorimotor cortices produces online effects only (Fabbrini et al., 2022; Johnson et al., 2020; Lafleur et al., 2021; Pozdniakov et al., 2021). No study participants reported any side effects during tACS and the researchers who carried out the experiments and analyzed the data were unaware of the stimulation conditions. These factors ensured a proper double-blindness throughout the study.

The first novel data of our study is that MEP amplitude progressively increased when 5 Hz-rTMS trains were applied during β-tACS to patients, and the amount of MEP facilitation became comparable to HS. This result implies that the impairment in STP mechanisms can be specifically restored by driving β oscillations of M1 through tACS. Since tACS entrains brain rhythms by modulating the activity of neurons with oscillatory properties at the stimulating frequency (Johnson et al., 2020; Krause et al., 2019), we hypothesize that β-tACS effect on STP is due to the activation of selective neuronal populations, which are resonant to the β rhythm within M1 and are likely to mediate STP mechanisms. We speculate that these neurons are GABA-A-ergic interneurons targeted by SICI (Guerra et al., 2022; Jensen et al., 2005; Lacey et al., 2014; Muthukumaraswamy et al., 2013). Indeed, as demonstrated in our recent study (Guerra et al., 2022), β-tACS modulates SICI in a disease-specific manner (i.e. SICI changed in patients, but not in HS), which suggests that in PD GABA-A-ergic interneurons are susceptible to β oscillations (Guerra et al., 2022; Hall et al., 2014; Prokic et al., 2019). Furthermore, a previous study showed that SICI was transiently suppressed during 5-Hz rTMS trains, raising the hypothesis that GABA-A-ergic transmission plays a role in STP processes (Wu et al., 2000). Importantly, we found a significant relationship between SICI changes and the degree of STP amelioration during β-tACS. That is, the greater

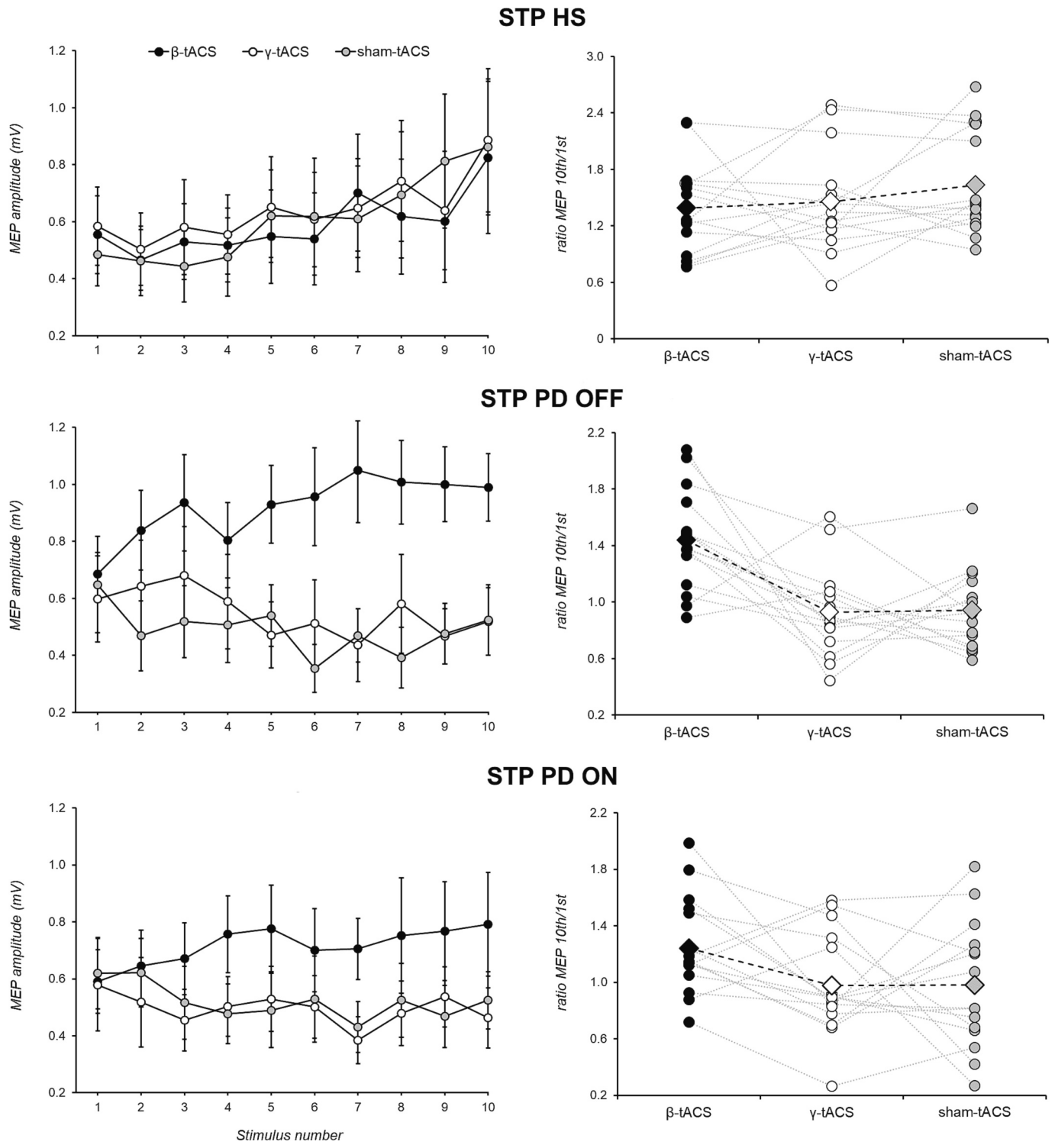

Fig. 2. Changes of short-term potentiation during tACS

The amount of motor evoked potentials (MEP) facilitation during 5 Hz rTMS did not change between β-, γ- and sham-trancranial alternating current stimulation (tACS) conditions in healthy subjects (HS) *(upper left panel)*. In Parkinson's disease (PD) patients, MEP amplitude did not increase during 5 Hz rTMS when tACS was sham and when it was delivered at the γ frequency. In contrast, MEP amplitude progressively increased during 5 Hz rTMS when tACS was delivered at the β frequency. This effect was independent of the dopaminergic condition of patients (*middle and lower left panels*). The markers reflect average values and bars reflect the standard error of the means. The right panels show the amount of short-term potentiation (STP) (ratio MEP amplitude $10^{th}/1^{st}$) during β-, γ- and sham-tACS for each HS and PD patient; the diamonds reflect average values.

Table 2
Statistical results

	rmANOVA	
	HS vs. PD OFF	*PD OFF vs. PD ON*
	df	*df*
	P	*p*
N movements	GROUP: $F_{1,28}$=0.03, p=0.87 FREQUENCY: $F_{2,56}$=1.12, p=0.33 GROUP × FREQ: $F_{2,56}$=0.11, p=0.90	CONDITION: $F_{1,14}$=4.90, **p=0.04** FREQUENCY: $F_{2,28}$=0.64, p=0.53 CONDITION × FREQ: $F_{2,28}$=0.07, p=0.93
Rhythm	GROUP: $F_{1,28}$=9.19, **p<0.01** FREQUENCY: $F_{2,56}$=0.48, p=0.62 GROUP × FREQ: $F_{2,56}$=0.10, p=0.90	CONDITION: $F_{1,14}$=4.51, **p=0.05** FREQUENCY: $F_{2,28}$=0.10, p=0.90 CONDITION × FREQ: $F_{2,28}$=1.04, p=0.37
Amplitude	GROUP: $F_{1,28}$=8.93, **p<0.01** FREQUENCY: $F_{2,56}$=1.94, p=0.15 GROUP × FREQ: $F_{2,56}$=5.67, **p<0.01**	CONDITION: $F_{1,14}$=9.53, **p<0.01** FREQUENCY: $F_{2,28}$=8.05, **p=0.001** CONDITION × FREQ: $F_{2,28}$=3.01, p=0.07
Velocity	GROUP: $F_{1,28}$=13.59, **p<0.001** FREQUENCY: $F_{2,56}$=0.31, p=0.73 GROUP × FREQ: $F_{2,56}$=7.69, **p=0.001**	CONDITION: $F_{1,14}$=12.79, **p<0.01** FREQUENCY: $F_{2,28}$=9.06, **p<0.001** CONDITION × FREQ: $F_{2,28}$=1.99, p=0.15
Amplitude decrement	GROUP: $F_{1,28}$=5.22, **p=0.03** FREQUENCY: $F_{2,56}$=0.24, p=0.79 GROUP × FREQ: $F_{2,56}$=0.74, p=0.48	CONDITION: $F_{1,14}$=0.74, p=0.40 FREQUENCY: $F_{2,28}$=0.58, p=0.57 CONDITION × FREQ: $F_{2,28}$=1.95, p=0.16
Velocity decrement	GROUP: $F_{1,28}$=0.36, p=0.55 FREQUENCY: $F_{2,56}$=0.03, p=0.97 GROUP × FREQ: $F_{2,56}$=1.24, p=0.30	CONDITION: $F_{1,14}$=0.04, p=0.85 FREQUENCY: $F_{2,28}$=0.84, p=0.44 CONDITION × FREQ: $F_{2,28}$=0.23, p=0.79
Single-pulse MEP	GROUP: $F_{1,28}$=1.31, p=0.26 FREQUENCY: $F_{2,56}$=0.82, p=0.44 GROUP × FREQ: $F_{2,56}$=1.33, p=0.27	CONDITION: $F_{1,14}$=0.01, p=0.94 FREQUENCY: $F_{2,28}$=0.43, p=0.65 CONDITION × FREQ: $F_{2,28}$=1.99, p=0.15
SICI	GROUP: $F_{1,28}$=20.89, **p<0.001** FREQUENCY: $F_{2,56}$=14.69, **p<0.001** GROUP × FREQ: $F_{2,56}$=3.16, **p=0.04**	CONDITION: $F_{1,14}$=0.65, p=0.43 FREQUENCY: $F_{2,28}$=14.99, **p<0.001** CONDITION × FREQ: $F_{2,28}$=1.18, p=0.32

HS: healthy subjects; PD OFF: PD patients in the OFF state; PD ON: PD patients in the ON state; MEP: motor-evoked potentials. Significant effects or interactions are in bold. Note that the only parameters showing a GROUP × FREQUENCY interaction were movement velocity, movement amplitude and SICI.

the reduction of SICI effectiveness the greater the STP amelioration. This relationship emphasizes the link between SICI and STP in humans and supports the hypothesis that changes in the activity of GABA-A-ergic circuits may be related to restored STP processes during β-tACS in PD. Particularly, this phenomenon resembles the metaplasticity mechanism of 'gating', whereby the suppression of inhibitory interneurons excitability leads to the enhancement in potentiation-like plasticity of M1 (Siebner, 2010; Ziemann et al., 2001).

Another novel data of the study concerns the correlation between STP and movement abnormalities during finger tapping in PD. We found a positive relationship between MEP facilitation during 5-Hz rTMS and movement velocity and amplitude when tACS was sham, i.e., the greater the MEP facilitation (less altered STP), the greater the movement velocity and amplitude. This data suggests that STP changes in M1 are associated with bradykinesia severity. However, the relative preservation of STP we found in patients with mild bradykinesia may reflect causal or compensatory mechanisms. The neuromodulation approach we adopted through tACS provided useful insights into this issue. As demonstrated in our recent study (Guerra et al., 2022), β-tACS worsened movement slowness in patients. Movement velocity worsening is likely due to the enhancement of β oscillatory activity in the cortico-basal ganglia network, which is a well-known mechanism contributing to bradykinesia pathophysiology in PD (Little et al., 2012; Lofredi et al., 2019; Oswal et al., 2013). We here demonstrate that STP modulation is inversely related to movement velocity changes during β-tACS. That is, the greater the STP amelioration during stimulation, the less the bradykinesia worsening. Interestingly, the subgroup of patients showing the greatest degree of STP amelioration demonstrated no worsening or even bradykinesia improvement during β-tACS (i.e., velocity β-tACS/sham-tACS >1.0). This neurophysiological correlation may thus suggest that STP amelioration has a compensatory functional role against β-induced bradykinesia in PD (Blesa et al., 2017). Moreover, considering the multiple relationships between changes in slowness, SICI and STP during β-tACS, we here propose a unifying view for GABA-A-ergic disinhibition and short-term plasticity in bradykinesia pathophysiology. Functionally similar to the relationship between STP and bradykinesia, we found an inverse correlation between SICI reduction and the negative behavioral effects of β-tACS (i.e., the greater the cortical disinhibition, the lower the β-induced bradykinesia worsening) (Guerra et al., 2022). Since SICI reduction and STP amelioration during β-tACS were also directly related, we hypothesize a common M1 compensatory mechanism against bradykinesia in PD, which consists in STP facilitation mediated by cortical disinhibition of GABA-A-ergic circuits via plasticity 'gating' mechanisms (Siebner, 2010; Ziemann et al., 2001). Of note, in our previous study, cortical disinhibition was also directly related to the positive effects of γ-tACS on bradykinesia (Guerra et al., 2022). In keeping with animal studies (Cardin et al., 2009; Hall et al., 2011; Lacey et al., 2014; Otte et al., 2010; Tremblay et al., 2016), we speculate that GABA-A-ergic disinhibition of M1 during β- and γ-tACS is due to different interneuronal subpopulations resonant to the β and γ rhythm, respectively, which produce convergent (i.e. compensatory) functional effects.

A further study result is that we find no correlation between the sequence effect occurring during finger tapping and STP changes in PD. This data supports the possibility that different bradykinesia features (i.e. movement slowness and sequence effect) may depend on distinct M1 mechanisms (Bologna et al., 2020b). In line with this hypothesis, we previously demonstrated that the sequence effect was associated with the LTP-like plasticity impairment of M1 (Bologna et al., 2018). In this regard, it is important to mention that STP and LTP-like plasticity processes in humans and animals are likely to reflect different phenomena (Iezzi et al., 2011; Ziemann et al., 2008; Zucker and Regehr, 2002). Confirming this data, we recently found that driving cortical β oscillations in PD has no impact on LTP-like plasticity (Guerra et al., 2020), whereas the results of the present study demonstrate significant effects on STP.

Finally, another study finding concerns the comparison of tACS effects between patients in the OFF and ON dopaminergic condition. We found that β-tACS produced similar changes on STP processes regardless of the patients' dopaminergic status. One possibility is that the activity of the M1 circuits targeted by tACS are not significantly influenced by dopaminergic therapies (Guerra et al., 2023; Guerra et al., 2022). In this regard, we highlight that in our patients' cohort both STP mechanisms and SICI *per se* were comparable between the OFF and ON sessions, possibly indicating non-dopaminergic substrates for these measures. However, in keeping with previous studies (Bologna et al., 2018; Guerra et al., 2022), we found that the neurophysiological correlations detected in the OFF dopaminergic condition were not present in the ON state. This may be due to the variable sensitivity of kinematic and TMS measures to L-dopa. Indeed, while a consistent bradykinesia improvement is

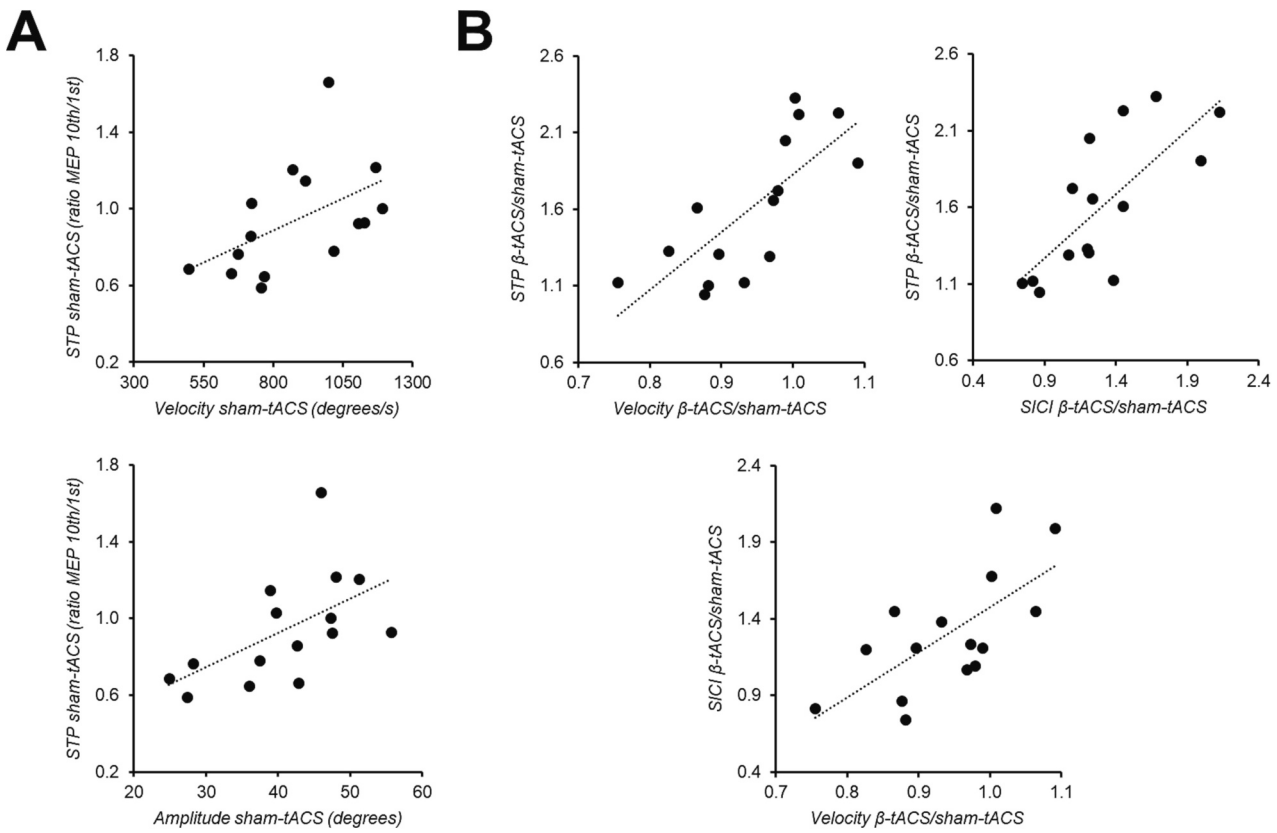

Fig. 3. Neurophysiological correlations
Panel A: Correlation between short-term potentiation (STP) (ratio MEP $10^{th}/1^{st}$, y axis) and movement velocity and amplitude (x axis) during sham-tACS in patients. *Panel B:* Correlation between changes in STP, movement velocity and short-interval intracortical inhibition (SICI) during β-tACS (ratio β-tACS/sham-tACS) in patients.

usually observed after L-dopa intake, L-dopa-related changes in M1 excitability and plasticity in humans are absent or follow non-linear dynamics (Bologna et al., 2018; Espay et al., 2011; Monte-Silva et al., 2010; Thirugnanasambandam et al., 2011). Another possibility is that L-dopa itself has a compensatory effect. Thus, the effects of L-dopa on basal ganglia-cortical circuits possibly blur tACS mechanisms observed in the OFF condition.

Our study has some limitations to mention. In line with tACS mechanism of action (Johnson et al., 2020; Krause et al., 2019), we have interpreted our results as the consequence of resonance phenomena. However, due to the electrical artefact during stimulation it was impossible to provide direct evidence of M1 oscillations entrainment in patients. Also, we tested early-to-intermediate stage PD patients, with relatively low MDS-UPDRS-III scores and no major motor complications (e.g. L-dopa-induced dyskinesia), and no tremor-dominant patient. We cannot exclude that different results may be obtained in patients with different clinical features (e.g. tremor-dominant PD) or in more advanced disease stages, when compensatory mechanisms are supposed to deteriorate (Blesa et al., 2017; Fabbrini and Guerra, 2021; Navntoft and Dreyer, 2016). Finally, due to the relatively limited sample size, which was specifically estimated to detect possible abnormalities of STP in PD, we cannot exclude that the statistical tests were underpowered to detect other effects induced by the stimulation, including the anti-bradykinetic effects of γ-tACS.

5. Conclusions

This study demonstrates a novel M1 mechanism involved in bradykinesia pathophysiology and related to increased β oscillations in PD. Our data suggest that mechanisms underlying STP are impaired in patients but return to normal levels when β oscillations increase. β-induced restoration of STP processes is likely mediated by disinhibition of GABA-A-ergic interneurons and may represent a compensatory mechanism against bradykinesia in PD, which operates regardless of the patients' dopaminergic status (Blesa et al., 2017; Florin et al., 2013; Guerra et al., 2022; Obeso and Schapira, 2009). Based on previous evidence and the new experimental data we have reported here, we suggest that M1 neurophysiological abnormalities in both short- and long-term plasticity mechanisms play an important role in bradykinesia pathophysiology in PD. Whilst changes in LTP-like plasticity are associated to the development of motor symptoms with a possibly causal relationship (Bologna et al., 2020b; Bologna et al., 2018; Guerra et al., 2020; Kishore et al., 2017; Moriyasu et al., 2022), efficient short-term plasticity mechanisms within M1 may have a compensatory role against bradykinesia. Finally, though with a limited direct impact in the clinical setting, the present data enable us to gain a deeper understanding of the pathophysiological mechanisms of bradykinesia, and this will certainly facilitate further studies with therapeutic implications in patients.

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Declaration of Competing Interest

None.

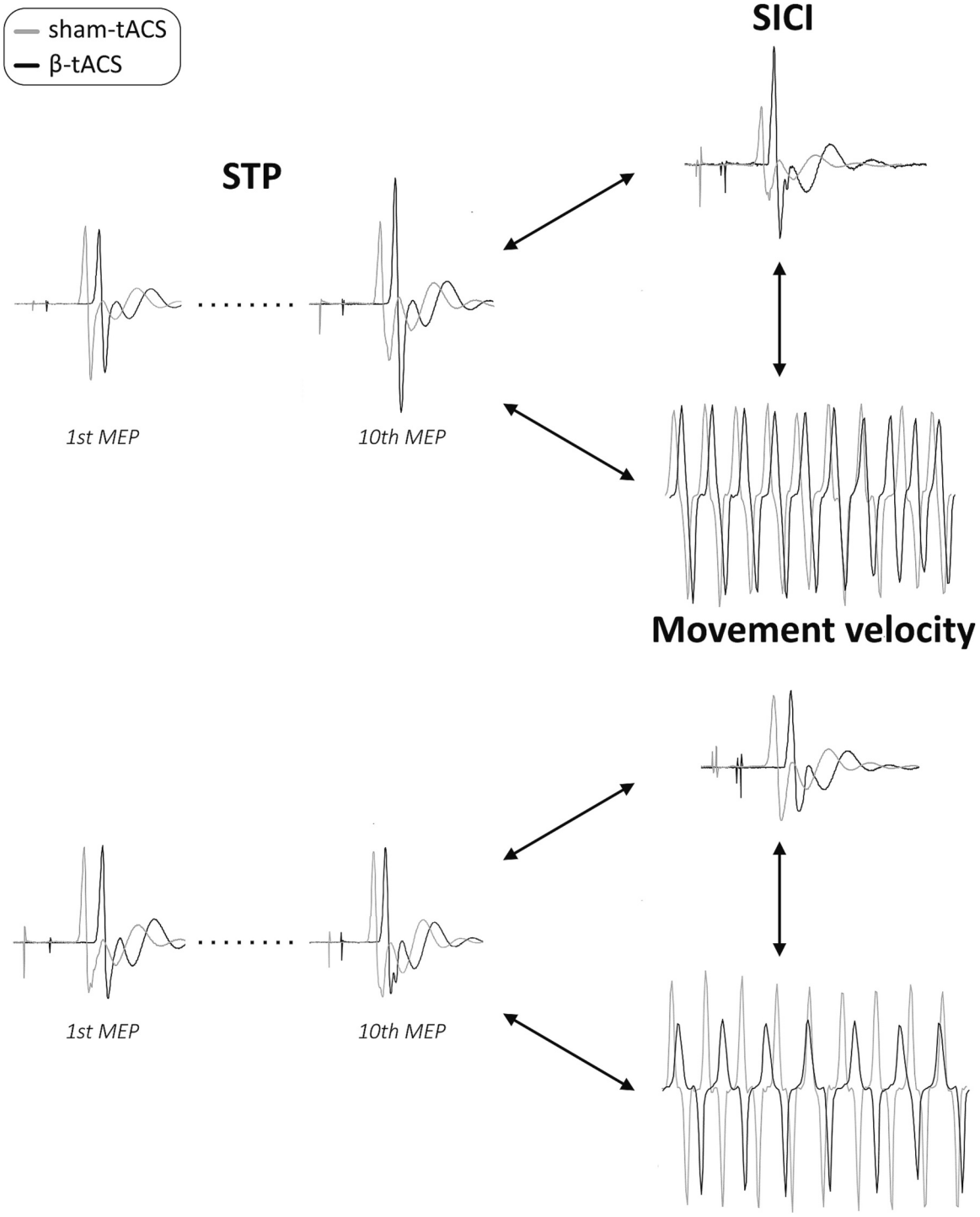

Fig. 4. Schematic representation of the major findings of the study
Relationship between β-tACS-related changes in short-term potentiation (STP), short-interval intracortical inhibition (SICI) and movement velocity in two paradigmatic cases. Patients who had a greater increase in STP during β-tACS demonstrated greater cortical disinhibition and no slowness worsening *(upper panel)*. In contrast, patients who had no change in STP during β-tACS demonstrated less cortical disinhibition and greater slowness worsening *(lower panel)*. Grey traces show neurophysiological measures recorded during sham-tACS, while black traces show the same measures recorded during β-tACS.

Data availability

Data will be made available on request.

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