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RESEARCH REPORT

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Assessing the interaction between L-dopa and γ-transcranial alternating current stimulation effects on primary motor cortex plasticity in Parkinson's disease

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Abstract

L-dopa variably influences transcranial magnetic stimulation (TMS) parameters of motor cortex (M1) excitability and plasticity in Parkinson's disease (PD). In patients OFF dopaminergic medication, impaired M1 plasticity and defective GABA-A-ergic inhibition can be restored by boosting gamma (γ) oscillations via transcranial alternating current stimulation (tACS) during intermittent theta-burst stimulation (iTBS). However, it is unknown whether L-dopa modifies the beneficial effects of iTBS-γ-tACS on M1 in PD. In this study, a PD patients group underwent combined iTBS-γ-tACS and iTBS-sham-tACS, each performed both OFF and ON dopaminergic therapy (four sessions in total). Motor evoked potentials (MEPs) elicited by single TMS pulses and short-interval intracortical inhibition (SICI) were assessed before and after iTBS-tACS. We also evaluated possible SICI changes during γ-tACS delivered alone in OFF and ON conditions. The amplitude of MEP elicited by single TMS pulses and the degree of SICI inhibition significantly increased after iTBS-γ-tACS. The amount of change produced by iTBS-γ-tACS was similar in patients OFF and ON therapy. Finally, γ-tACS (delivered alone) modulated SICI during stimulation and this effect did not depend on the dopaminergic condition of patients. In conclusion, boosting cortical γ oscillatory activity via tACS during iTBS improved M1 plasticity and enhanced GABA-A-ergic transmission in PD patients to the same extent regardless of dopaminergic state. These results suggest a lack of interaction between L-dopa and γ-tACS effects at the M1 level. The possible neural substrate underlying iTBS-γ tACS effects,

Abbreviations: AMT, active motor threshold; EMG, electromyography; FDI, first dorsal interosseus; HS, healthy subjects; ISI, interstimulus interval; iTBS, intermittent theta-burst stimulation; LID, Levodopa-induced dyskinesia; LTP, long-term potentiation; M1, primary motor cortex; MDS-UPDRS, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale; MEP, motor evoked potentials; MoCA, Montreal Cognitive Assessment; PD, Parkinson's disease; RMT, resting motor threshold; SICI, short-interval intracortical inhibition; SP, single-pulse; tACS, transcranial alternating current stimulation; TMS, transcranial magnetic stimulation; γ, gamma.

that is, γ-resonant GABA-A-ergic interneurons activity, may explain our findings.

KEYWORDS
gamma oscillations, L-dopa, motor cortex plasticity, Parkinson's disease, transcranial alternating current stimulation

1 | INTRODUCTION

Although L-dopa is the cardinal pharmacological therapy for treating motor symptoms of Parkinson's disease (PD) (Fox et al., 2018), its effects on neurophysiological abnormalities of motor areas in patients is highly variable (Bologna et al., 2018; Ni et al., 2013; Udupa & Chen, 2013). The amelioration of altered oscillatory activities in basal ganglia-thalamo-cortical network, including high-gamma (γ) oscillations, has been consistently observed after L-dopa administration (Jenkinson et al., 2013; Oswal et al., 2013; Tinkhauser et al., 2017; Wiest et al., 2022). In contrast, it is not yet clear if the most reliable dysfunctions of the primary motor cortex (M1) in PD, that is, defective GABA-Aergic inhibition and impaired long-term potentiation (LTP)-like plasticity, are sensitive to L-dopa intake (Berardelli et al., 2008; Udupa & Chen, 2013). The majority of transcranial magnetic stimulation (TMS) studies in PD have suggested that abnormal short-interval intracortical inhibition (SICI), a well-known GABA-Aergic measure, is largely unresponsive to L-dopa, though earlier reports showed different results (Bologna et al., 2018; Kojovic et al., 2015; MacKinnon et al., 2005; Ni et al., 2013; Ridding et al., 1995; Strafella et al., 2000). L-dopa effects on M1 plasticity in PD are also uncertain. Indeed, defective LTP-like plasticity variably improved after L-dopa intake according to the specific TMS protocol used (paired associative stimulation or theta-burst stimulation) and patient clinical features (Bologna et al., 2018; Kishore, Joseph, et al., 2012; Kishore, Popa, et al., 2012; Morgante et al., 2006; Suppa et al., 2011). Moreover, only a few studies have assessed possible changes in intermittent theta-burst stimulation (iTBS)-induced plasticity between the same patients OFF and ON dopaminergic state and have reported conflicting results (Kishore, Joseph, et al., 2012; Kishore, Popa, et al., 2012; Suppa et al., 2011; Zamir et al., 2012).

In a recent study (Guerra et al., 2020), we applied transcranial alternating current stimulation (tACS), a non-invasive tool that entrains neuronal activity in responsive populations of cells, to boost cortical γ oscillations during iTBS in PD (Johnson et al., 2020; Krause et al., 2019). In PD patients OFF dopaminergic therapy, we found that applying γ-tACS during iTBS (iTBS-γ tACS) restored impaired LTP-like cortical plasticity and ameliorated GABA-A-ergic neurotransmission of M1 (i.e., increased SICI effectiveness). Overall, our results suggested that altered γ oscillations, impaired plasticity and cortical disinhibition in M1 are interconnected phenomena in PD (Guerra et al., 2020).

The objective of this research was to specifically investigate whether L-dopa modulates the beneficial γ-tACS effects on M1 plasticity and GABA-Aergic dysfunction in PD. This approach would help to clarify whether the interaction between γ oscillations, impaired plasticity and cortical disinhibition mechanisms in PD is influenced by dopaminergic pathways. Since tACS effects rely on boosting cortical rhythms and previous evidence has shown that L-dopa enhances γ activity in PD (Ali et al., 2013; Helfrich et al., 2014; Jenkinson et al., 2013; Wiest et al., 2022; Witkowski et al., 2016), we verified if γ-tACS effects can be potentiated by concomitant L-dopa administration. We thus performed a sham-controlled study where PD patients underwent iTBS-γ tACS and iTBS-sham tACS both in OFF and ON dopaminergic states in four separate and randomized sessions. Similar to our previous study, we recorded motor evoked potentials (MEPs) elicited by single TMS pulses and SICI before and after combined iTBS-tACS stimulation (Guerra et al., 2020). In addition, since previous studies suggested that γ-tACS effects are likely mediated by modifications in GABA-Aergic interneuron activity (Guerra et al., 2019; Nowak et al., 2017), we also recorded SICI during γ-tACS delivered alone in a separate experiment conducted in all patients both OFF and ON dopaminergic therapy. Data from all experiments were compared to TMS measurements performed in gender- and age-matched healthy subjects.

2 | MATERIALS AND METHODS

2.1 | Subjects

Thirteen right-handed PD patients (two females, 66.2 ± 9.4 years, disease duration 5.1 ± 2.8 years) and 14 healthy subjects (HS) (five females, 67.5 ± 9.7 years) participated. PD diagnosis matched the latest clinical

international criteria (Postuma et al., 2015). All patients were in the early-to-intermediate disease stage, and none had L-dopa-induced dyskinesia (LID). Also, to minimize the clinical sample heterogeneity and to avoid possible confounding related to involuntary EMG activity during the TMS assessment, we enrolled no patient with the tremor-dominant subtype of PD in the study. No other neuropsychiatric conditions or brain plasticity-affecting drugs were present. Ten out of 13 patients took part in our previous study on the effect of γ-tACS on M1 plasticity in the disease per se (OFF state) (Guerra et al., 2020) (Table S1). Cognitive impairment was assessed using the Montreal Cognitive Assessment scale (MoCA, Nasreddine et al., 2005) and Frontal Assessment Battery (FAB, Dubois et al., 2000). Before every experimental session, the Unified Parkinson's Disease Rating Scale, motor section (MDS-UPDRS-III, Antonini et al., 2013) was completed for PD patients to evaluate motor symptoms. Experimental methods fitted the Declaration of Helsinki. A written informed consent was acquired from all subjects.

2.2 | Transcranial magnetic stimulation

An eight-shaped coil wired to the Magstim BiStim2 or the MagRapid Stimulator (Magstim Company, UK) was used for paired-pulse TMS and iTBS, respectively. The M1 hotspot (first dorsal interosseous muscle, FDI), resting (RMT) and active motor thresholds (AMT) were identified following international guidelines (Rossini et al., 2015). The intensity that reliably elicited a 1-mV amplitude MEP (MT1mV) was also determined. SICI was tested with the conditioning stimulus at 80% AMT, test stimulus at MT1mV and 2-ms interstimulus interval (Bologna et al., 2018; Guerra et al., 2020; Guerra, Colella, et al., 2022). iTBS was delivered using the standard stimulation protocol and a stimulation intensity of 80% AMT (Guerra et al., 2020). Surface electrodes were used to record MEP (dominant FDI for HS and most affected side for patients). Electromyography was amplified with a Digitimer D360 (Digitimer, UK) and digitized with a CED 1401 (Cambridge Electronic Design, UK). MEP amplitude was measured peak-to-peak and averaged for each condition. SICI reflected the ratio between the amplitude of the conditioned MEP (paired-pulse TMS) and the amplitude of MEP evoked by single TMS pulses (Samusyte et al., 2018).

2.3 | Transcranial alternating current stimulation

A BrainStim (EMS, Italy) using two conductive electrodes enclosed in saline-wet sponges (5 × 5-cm size, one applied over the FDI hotspot and the other over Pz) was adopted. γ-tACS was delivered at 1-mA peak-to-peak intensity, with a 3-s ramp-up and down and 70-Hz frequency (Bologna et al., 2019; Guerra et al., 2019, 2020; Guerra, Colella, et al., 2022). In the sham-tACS condition the stimulation lasted only 1 s (excluding ramp-up and down). No participant reported cutaneous or visual sensations in any of the experimental sessions when explicitly asked by one researcher at the end of each experiment. Therefore, subjects were unable to recognize if tACS was real or sham, which ensured a properly blinded study.

2.4 | Experimental design

All PD patients underwent four separate randomized experimental sessions that were conducted at least 7 days apart: (1) iTBS-γ tACS co-stimulation in the OFF dopaminergic state (iTBS-γ tACS OFF); (2) iTBS-sham tACS co-stimulation in the OFF state (iTBS-sham tACS OFF); (3) iTBS-γ tACS in the ON state (iTBS-γ tACS ON); and (4) iTBS-sham tACS in the ON state (iTBS-sham tACS ON). The OFF sessions were conducted 12 h after the last intake of the patient's habitual L-dopa dose, whereas in the ON session patients were assessed 1 h after L-dopa intake, when dopaminergic stimulation is considered to be maximal in the brain (Olanow et al., 1991). HS underwent two sessions: iTBS-sham tACS and iTBS-γ tACS. Sixteen single-pulse (SP) MEP and 16 SICI were recorded before (T0) and 5 (T1), 15 (T2) and 30 min (T3) after iTBS-tACS. Additionally, we recorded 16 SP MEP and 16 SICI during γ- and sham-tACS, both delivered alone, in all participants. This experiment was conducted the same day as the iTBS-γ tACS sessions and about 15 min before the beginning of the combined stimulation. Although previous studies excluded significant aftereffects on cortical excitability following M1-tACS (Bologna et al., 2019; Guerra et al., 2019, 2020; Nowak et al., 2017; Pozdniakov et al., 2021), we preferred to temporally separate the two experiments (tACS alone and iTBS-tACS co-stimulation) (Figure 1).

2.5 | Statistical analysis

We used the Mann–Whitney U and the Fisher's exact test to compare clinical-demographic variables and gender distribution between patients and HS, respectively. To analyse differences in UPDRS-III scores in patients, we applied the Wilcoxon test.

A repeated-measures (rm) analysis of variance (ANOVA) with the factors 'group' (levels: PD OFF, HS)

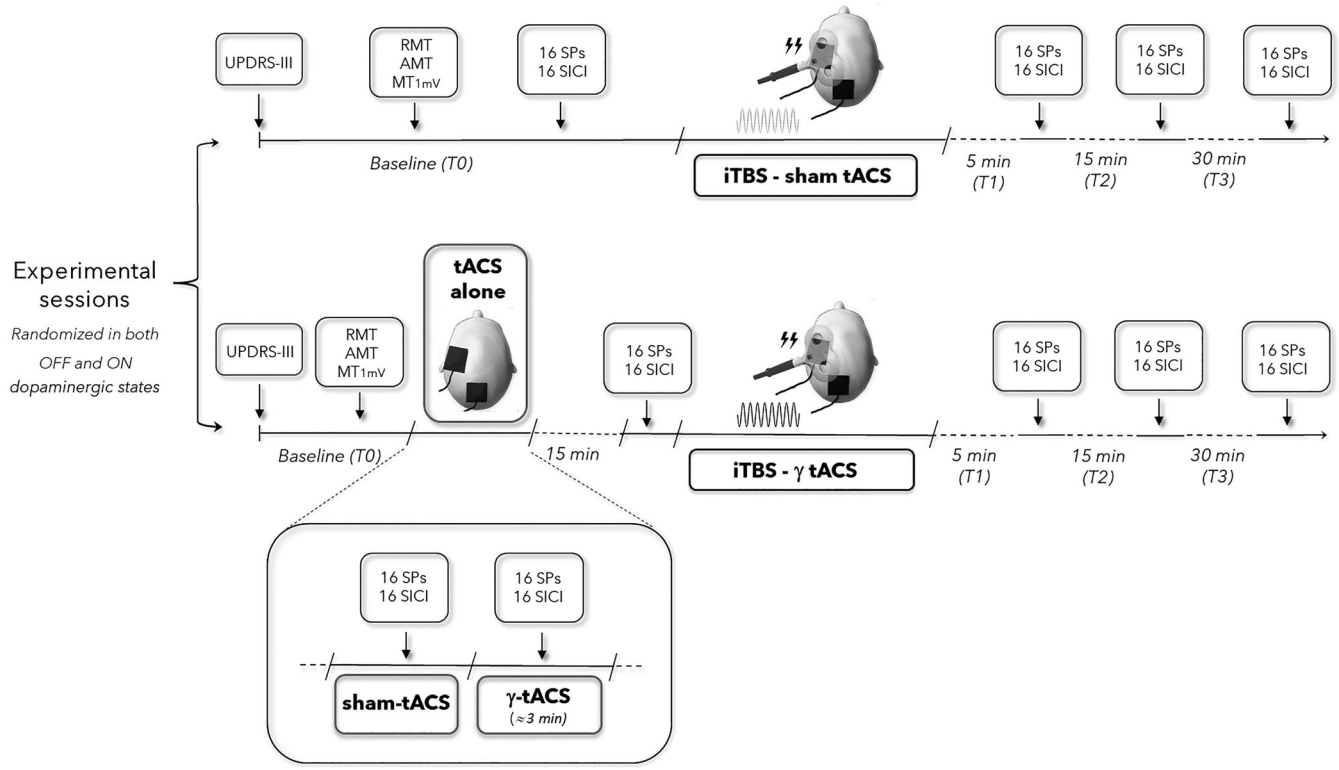

FIGURE 1 Experimental design. All patients underwent intermittent theta-burst stimulation (iTBS)-sham transcranial alternating current stimulation (tACS) and iTBS-γ tACS in both ON and OFF conditions in separate experimental sessions (four sessions in total). In each session, motor thresholds (active motor threshold [AMT], resting motor threshold [RMT]) and MT1mV were determined after the administration of the MDS-UPDRS-III. Then, 16 single-pulse motor evoked potentials (MEPs) and 16 short-interval intracortical inhibition (SICI) were recorded at baseline (T0) and 5 (T1), 15 (T2) and 30 min (T3) after combined stimulation. In a separate experiment performed before iTBS-γ tACS, 16 MEPs and 16 SICI were recorded during sham-tACS and γ-tACS delivered alone.

and 'session' (levels: iTBS-sham tACS, iTBS-γ tACS) was used to compare AMT, RMT, SP MEP and SICI at T0 between PD patients OFF therapy and HS, whereas the factors 'state' (levels: OFF, ON) and 'session' were instead adopted to compare the same parameters between patients OFF and ON therapy. Then, we normalized SP MEP and SICI obtained after iTBS to pre-iTBS (T0) values. To compare responses to the iTBS protocol per se between patients and HS, we performed an rmANOVA on SP MEP recorded in the iTBS-sham tACS session with the factors 'group' and 'timepoint' (levels: T1, T2, T3). We then used three-way rmANOVAs with the factors 'group', 'session' and 'timepoint' to compare iTBS-γ tACS effects on normalized SP MEP and SICI between PD patients and HS. In addition, we performed separate rmANOVAs with 'group' and 'stimulation' (levels: sham-tACS, γ-tACS) as factors to evaluate the γ-tACS (alone) effects on SP MEP and SICI. Finally, to assess possible interactions between L-dopa and γ-tACS effects in patients, we used the aforementioned rmANOVAs but replaced the factor 'group' with the factor 'state'. Possible differences in the iTBS-γ tACS effects between patients OFF and ON therapy (primary aim of the study) were further investigated using Bayesian statistics. Tukey-corrected *t*-tests were used for post hoc analyses (significance at $p < .05$). The Spearman rank correlation was applied to test possible clinico-neurophysiological relationships. As a measure of clinical response to L-dopa, we computed the ratio between UPDRS-III scores ON and OFF therapy (ratio UPDRS-III ON/OFF) (average between sham-tACS and γ-tACS sessions). As a measure of neurophysiological response to L-dopa, we computed the ratio between γ-tACS effects in the ON and OFF state (ratio γ-tACS effect ON/OFF). γ-tACS effects in modulating SP MEP and SICI after iTBS was quantified by normalizing T1–T3 values in the iTBS-γ tACS session to iTBS-sham tACS values (ratio iTBS-γ tACS/iTBS-sham tACS). The effect of γ-tACS alone in modulating SICI was calculated by normalizing SICI recorded during γ-tACS to sham-tACS values (ratio SICI γ-tACS/sham-tACS). The Kolmogorov–Smirnov test was used to check if the data acquired were normally distributed. Unless otherwise specified, values reflect mean ± standard deviation (*SD*). Statistica software (v10, StatSoft) was used for statistical analyses.

TABLE 1 Motor thresholds, single-pulse MEP amplitude and SICI at baseline (T0)

	Raw data		rmANOVA	
	iTBS-sham tACS	**iTBS-γ tACS**	**HS versus PD OFF**	**PD OFF versus PD ON**
AMT (%)				
HS	47.4 ± 10.6	47.7 ± 10.2	G: $F_{(1,25)} = .17$, $p = .68$	St: $F_{(1,12)} = .09$, $p = .76$
PD OFF	48.2 ± 8.1	48.7 ± 7.7	S: $F_{(1,25)} = .49$, $p = .49$	S: $F_{(1,12)} = 1.68$, $p = .22$
PD ON	46.8 ± 11.1	50.4 ± 8.0	S × G: $F_{(1,25)} = .05$, $p = .83$	St × S: $F_{(1,12)} = 1.00$, $p = .34$
RMT (%)				
HS	63.3 ± 14.4	62.6 ± 15.7	G: $F_{(1,25)} = .44$, $p = .51$	St: $F_{(1,12)} = 3.39$, $p = .10$
PD OFF	57.7 ± 12.4	59.2 ± 11.2	S: $F_{(1,25)} = .31$, $p = .58$	S: $F_{(1,12)} = 2.33$, $p = .15$
PD ON	59.5 ± 14.7	63.2 ± 9.3	S × G: $F_{(1,25)} = 2.62$, $p = .12$	St × S: $F_{(1,12)} = .22$, $p = .64$
SP MEP (mV)				
HS	.81 ± .24	.83 ± .24	G: $F_{(1,25)} = .13$, $p = .72$	St: $F_{(1,12)} = .60$, $p = .45$
PD OFF	.89 ± .35	.88 ± .37	S: $F_{(1,25)} = .01$, $p = .95$	S: $F_{(1,12)} = .05$, $p = .82$
PD ON	.79 ± .21	.83 ± .36	S × G: $F_{(1,25)} = .17$, $p = .68$	St × S: $F_{(1,12)} = .21$, $p = .66$
SICI (ratio TS)				
HS	.39 ± .16	.45 ± .19	G: $F_{(1,25)} = 7.58$, $\mathbf{p = .01}$	St: $F_{(1,12)} = 1.05$, $p = .32$
PD OFF	.60 ± .2	.61 ± .22	S: $F_{(1,25)} = 1.83$, $p = .19$	S: $F_{(1,12)} = .44$, $p = .52$
PD ON	.64 ± .2	.66 ± .18	S × G: $F_{(1,25)} = .63$, $p = .43$	St × S: $F_{(1,12)} = .02$, $p = .88$

Note: Raw data are shown as mean ± standard deviation. G: factor 'Group'; F: factor 'Frequency'; G × F: 'Group' × 'Frequency' interaction; S: factor 'Session'; St: factor 'State'; St × S: 'State' × 'Session' interaction. AMT: active motor threshold; HS: healthy subjects; iTBS: intermittent theta burst stimulation; SP MEP: motor evoked potential elicited by single TMS pulses; PD: Parkinson's disease; RMT: resting motor threshold; SICI: short-interval intracortical inhibition; tACS: transcranial alternating current stimulation; TS: test stimulus.

3 | RESULTS

PD patients and HS showed similar age ($U = 83.5$, $p = .73$), gender ($p = .38$), MoCA (26.9 ± 2.4 vs. 28.0 ± 2.1, $U = 68.5$, $p = .39$) and FAB (16.2 ± 1.9 vs. 16.6 ± 1.3, $U = 83.0$, $p = .71$) scores. In PD patients, there were no differences in UPDRS-III between iTBS-sham tACS and iTBS-γ tACS sessions conducted in OFF (25.5 ± 10.5 vs. 25.3 ± 10.9, $Z = .35$, $p = .72$) and ON states (20.4 ± 8.5 vs. 20.3 ± 8.8, $Z = .20$, $p = .83$). As expected, MDS-UPDRS-III scores were lower in ON as compared to OFF state sessions (iTBS-sham tACS: $Z = 3.00$, $p < .01$; iTBS-γ tACS: $Z = 3.06$, $p < .01$).

The distribution of the data acquired before iTBS, after iTBS and during tACS alone in each group and experimental condition was normal (p always >.05, Table S2).

3.1 | TMS measures at baseline

AMT, RMT and SP MEP at T0 were similar between HS and PD patients in all experimental sessions. Conversely, SICI values at T0 were higher (weaker inhibition) in patients than HS (Table 1). In PD patients, AMT, RMT, single-pulse MEP amplitude and SICI at T0 did not differ between OFF and ON states (Table 1). As expected, SP MEP potentiation after iTBS-sham tACS was significantly higher in HS than in patients at all timepoints, as demonstrated by the significant effect of 'group' ($F_{1,25} = 16.10$, $p < .001$) and no 'group' × 'timepoint' interaction ($F_{2,50} = .25$, $p = .78$) (Figure 2).

3.2 | iTBS-γ tACS co-stimulation and L-dopa effects

When testing possible differences in iTBS-tACS effects between HS and PD patients OFF therapy, we found greater MEP potentiation after iTBS-γ tACS than iTBS-sham tACS in both groups at all timepoints, as shown by the significant effect of 'session' ($F_{1,25} = 24.77$, $p < .001$) and no 'session' × 'group' ($F_{1,25} = 2.26$, $p = .14$) or 'session' × 'group' × 'timepoint' interactions ($F_{[2,50]} = .02$, $p = .97$). The factor 'group' was also significant ($F_{1,25} = 8.62$, $p < .01$), suggesting a generally lower degree of MEP facilitation in patients than HS after iTBS irrespective of whether tACS was real or sham. SICI was differentially modulated by iTBS-γ tACS in the two groups at all timepoints tested, as indicated by the

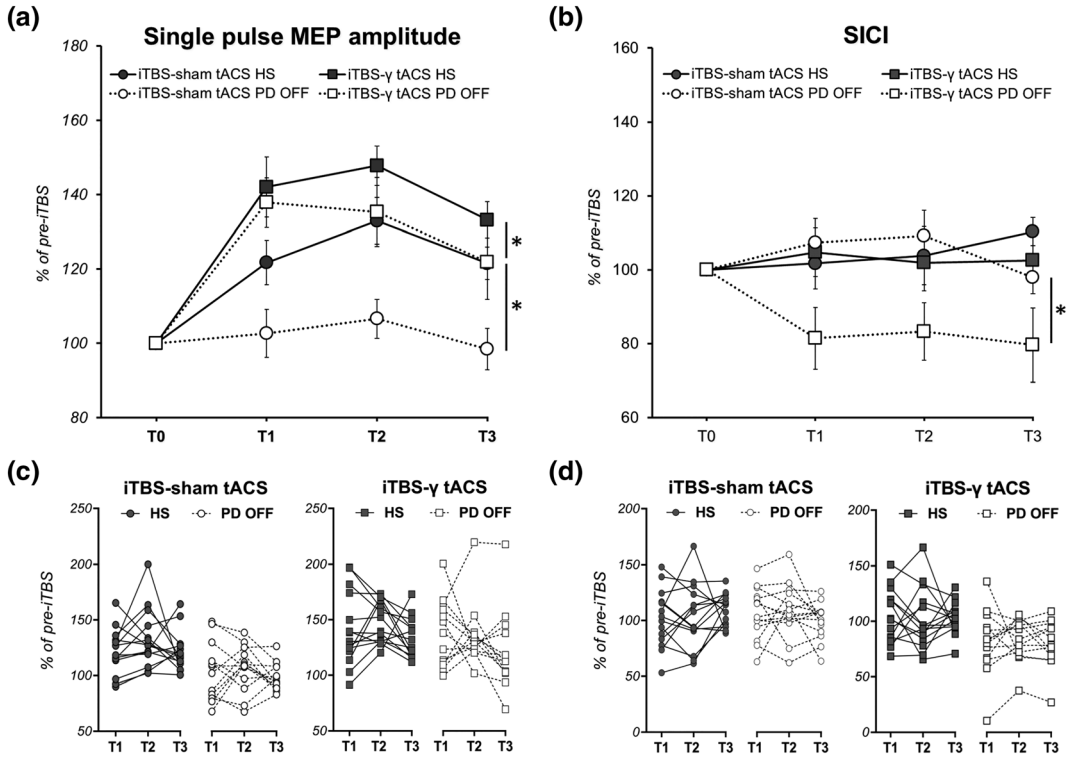

FIGURE 2 Effect of iTBS-γ tACS in healthy subjects and Parkinson's disease patients (OFF therapy). iTBS-γ tACS induced significantly greater facilitation of MEPs evoked by single TMS pulses than iTBS-sham tACS in both HS and PD patients (a) and enhanced SICI effectiveness (i.e., greater inhibition) in PD patients (panel B). The markers reflect average values and bars reflect the standard error of the means. MEP amplitude and SICI at 5 min (T1), 15 min (T2) and 30 min (T3) post-iTBS-tACS are compared with pre-iTBS-tACS values (T0—set as 100%). The asterisks indicate significant differences between sessions. Panels (c) and (d) show the effect of iTBS-sham tACS and iTBS-γ tACS on MEPs evoked by single TMS pulses and SICI for each subject. Abbreviations: HS, healthy subjects; MEP, motor evoked potentials; PD OFF, Parkinson's disease patients OFF dopaminergic therapy; iTBS, intermittent theta-burst stimulation; SICI, short-interval intracortical inhibition, tACS: transcranial alternating current stimulation; TMS, transcranial magnetic stimulation

'session' × 'group' interaction ($F_{1,25} = 7.45$, $p = .01$) and the absence of a 'session' × 'timepoint' × 'group' interaction ($F_{2,50} = 1.05$, $p = .36$). Post hoc analyses disclosed lower (i.e., more effective) SICI after iTBS-γ tACS than iTBS-sham tACS in patients ($p = .001$), whereas SICI did not change between sessions in HS ($p = .98$) (Figure 2).

When testing possible differences in iTBS-tACS effects in PD patients between OFF and ON sessions, the analysis demonstrated greater MEP potentiation after iTBS-γ tACS than iTBS-sham tACS at all timepoints, as indicated by the significant effect of 'session' ($F_{1,12} = 18.15$, $p = .001$) and the absence of a 'session' × 'timepoint' interaction ($F_{2,24} = 1.03$, $p = .37$). The amount of potentiation produced by iTBS-tACS was not modified by L-dopa, as suggested by the non-significant effect of 'state' ($F_{1,12} = .88$, $p = 0.37$) and no 'state' × 'session' ($F_{1,12} = .89$, $p = .36$) or 'state' × 'session' × 'timepoint' ($F_{2,24} = .37$, $p = .69$) interactions. Similarly, the degree of SICI modulation after iTBS-γ tACS was comparable between OFF and ON states, as demonstrated by the absence of effect of 'state' ($F_{1,12} = .07$, $p = .80$) and no 'state' × 'session' ($F_{1,12} = 1.23$, $p = .29$) or 'state' × 'session' × 'timepoint' interactions ($F_{2,24} = .42$, $p = .66$) (Figure 3). The similar MEP potentiation and SICI modulation after iTBS-γ tACS between patients OFF and ON state was also confirmed by Bayesian statistics, which supported the null hypothesis (Supplementary Table S3).

Overall, these data indicate that γ-tACS enhanced iTBS-induced MEP potentiation and increased SICI effectiveness to the same extent in PD patients OFF and ON dopaminergic therapy.

3.3 | Gamma-tACS-related modulation of SICI and L-dopa effects

When analysing the effect of γ-tACS (delivered alone) in HS and PD patients, we observed that SP MEP was similar between sham and γ-tACS in both groups ('group':

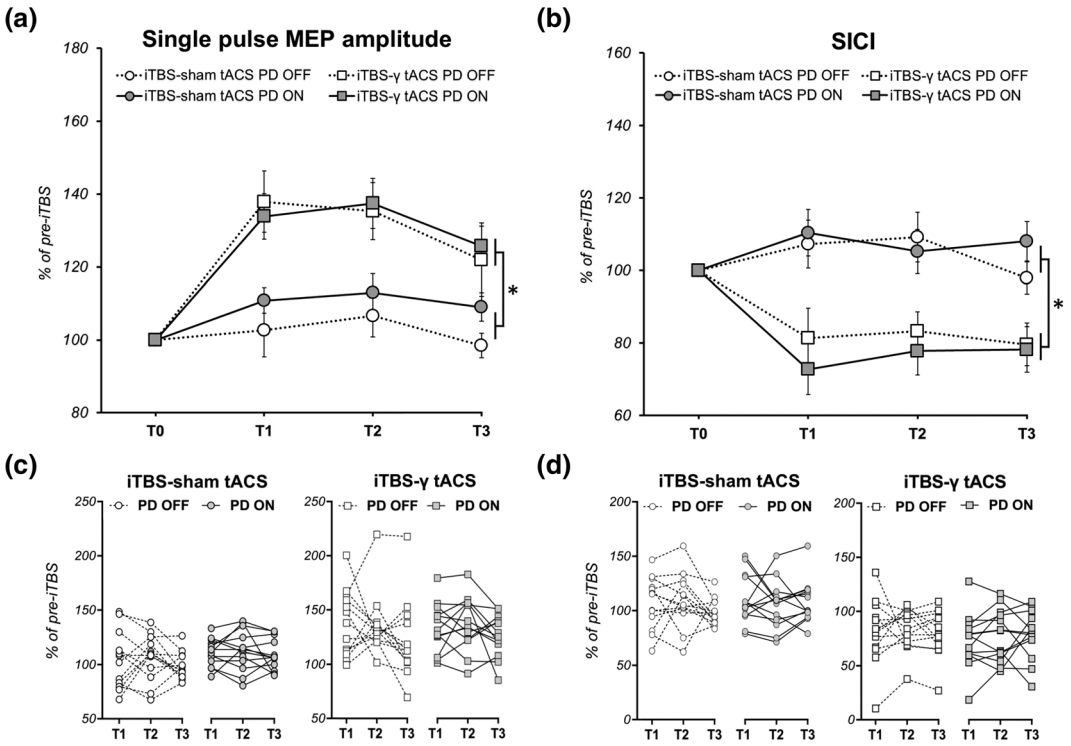

FIGURE 3 Effect of iTBS-γ tACS in Parkinson's disease patients OFF and ON therapy. iTBS-γ tACS induced significantly greater facilitation of MEPs evoked by single TMS pulses than iTBS-sham tACS (a) and enhanced SICI effectiveness (i.e., greater inhibition) (b) in PD patients both OFF and ON dopaminergic therapy. Markers reflect average values and bars reflect the standard error of the means. MEP amplitudes and SICI at 5 min (T1), 15 min (T2) and 30 min (T3) post-iTBS-tACS are compared with pre-iTBS-tACS values (T0—set as 100%). Asterisks indicate significant differences between sessions. Panels (c) and (d) show the effect of iTBS-sham tACS and iTBS-γ tACS on MEPs evoked by single TMS pulses and SICI for each patient. Abbreviations: iTBS, intermittent theta-burst stimulation; MEP, motor evoked potentials; PD OFF, Parkinson's disease patients OFF dopaminergic therapy; PD ON, Parkinson's disease patients ON dopaminergic therapy; SICI, short-interval intracortical inhibition; tACS, transcranial alternating current stimulation; TMS, transcranial magnetic stimulation

$F_{1,25} = .02$, $p = .89$; 'stimulation': $F_{1,25} = .75$, $p = .39$; 'stimulation' × 'group': $F_{1,25} = .41$, $p = .53$). Conversely, SICI was higher (less inhibition) during γ- than sham-tACS in both groups, as suggested by the significant factor 'stimulation' ($F_{1,25} = 16.39$, $p < .001$) and no 'stimulation' × 'group' interaction ($F_{1,25} = .03$, $p = .87$). SICI analysis also showed a significant effect of 'group' ($F_{1,25} = 7.04$, $p = .01$), suggesting reduced inhibition in patients than in HS (Figure 4).

When comparing γ-tACS (delivered alone) effects between patients in ON and OFF states, we found no change in single-pulse MEP amplitude between stimulation conditions or dopaminergic states ('state': $F_{1,12} = 3.59$, $p = .08$; 'stimulation': $F_{1,12} = 1.16$, $p = .30$; 'state' × 'stimulation': $F_{1,12} = .09$, $p = .77$). In addition, γ-tACS induced comparable SICI modulation irrespective of whether patients were ON or OFF therapy, as indicated by the significant factor 'stimulation' ($F_{1,12} = 11.01$, $p < .01$), the lack of effect of the factor 'state' ($F_{1,12} = 1.78$, $p = .21$) and no 'stimulation' × '-state' interaction ($F_{1,12} = .58$, $p = .46$) (Figure 4).

3.4 | Correlation analysis

We found no correlation between the UPDRS-III ON/OFF ratio and the γ-tACS effect ON/OFF ratio as computed based on SP MEP ($r = .26$, $p = .38$), SICI after iTBS ($r = .44$, $p = .13$) and SICI during tACS alone ($r = .42$, $p = .15$). Furthermore, the UPDRS-III ON/OFF ratio and the iTBS-γ tACS/iTBS-sham tACS ratio (SP MEP: $r = -.28$, $p = .35$; SICI: $r = .32$, $p = .28$) or the SICI γ-tACS/sham-tACS ratio ($r = .06$, $p = .84$) were unrelated. These findings indicate the lack of any link between L-dopa-dependent modifications in clinical and neurophysiological variables. In addition, these results suggest that γ-tACS effects were unrelated to patient clinical responsiveness to L-dopa therapy.

4 | DISCUSSION

γ-tACS applied over M1 enhances iTBS-induced MEP potentiation and improves SICI effectiveness in PD. In

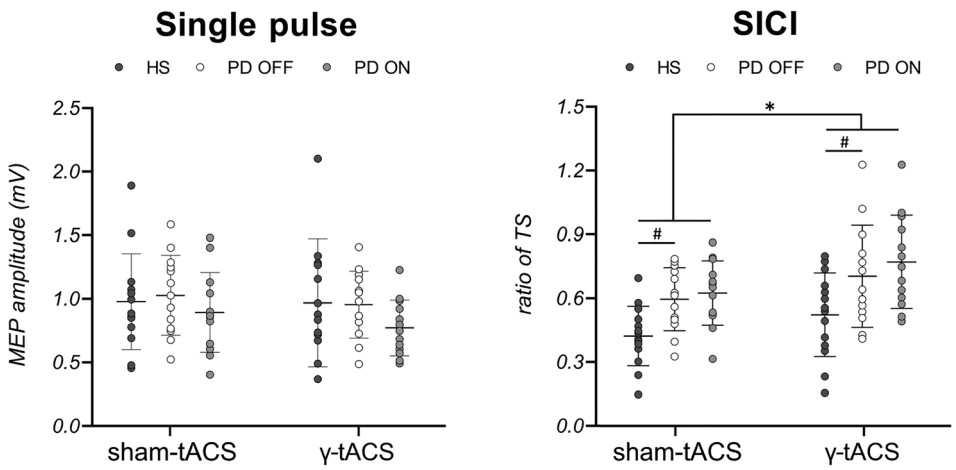

FIGURE 4 Effect of γ-tACS delivered alone in healthy subjects and Parkinson's disease patients (OFF and ON therapy). *Left panel:* MEPs evoked by single TMS pulses were comparable between sham and γ-tACS in all groups. *Right panel*: SICI showed higher values (i.e., weaker inhibition) during γ-tACS than during sham-tACS in all groups. Note that the amount of SICI modulation in PD patients was comparable between OFF and ON dopaminergic conditions. The markers reflect individual data, the horizontal bar indicates mean values, and the bars display 1 standard deviation from the mean. Asterisks reflect significant differences between sessions, whereas the hashes indicate significant differences between groups. Abbreviations: HS, healthy subjects; MEP, motor evoked potential; PD OFF, Parkinson's disease patients OFF dopaminergic therapy; PD ON, Parkinson's disease patients ON dopaminergic therapy; SICI, short-interval intracortical inhibition; tACS, transcranial alternating current stimulation; TS, test stimulus

this research, we specifically aimed to investigate whether L-dopa modulates these beneficial effects. We compared γ-tACS-related effects in the same patients between OFF and ON dopaminergic states and observed that the amount of MEP facilitation and SICI modulation after iTBS-γ tACS was similar between conditions. We also found that γ-tACS delivered alone decreased SICI. Again, the amount of SICI modulation produced by γ-tACS alone did not differ between patients OFF and ON dopaminergic therapy. These data overall demonstrate that γ-tACS beneficial effects produced on LTP-like plasticity of M1 and on GABA-Aergic intracortical activity in PD are independent of the dopaminergic state of patients.

The experimental design allowed us to control many factors that could have biased our results. γ-tACS did not induce cutaneous or visual sensations in any participant, thus ensuring blind experimental procedures. Experimental sessions were conducted at >7 days apart to avoid any possible carryover effect of stimulation. Moreover, since previous studies conducted in both healthy subjects and PD patients demonstrated no aftereffects on M1 excitability following tACS alone (Bologna et al., 2019; Guerra et al., 2019, 2020; Pozdniakov et al., 2021), we exclude that γ-tACS alone delivered 15 min before iTBS-γ tACS influenced the effects of the combined stimulation. Baseline levels of cortical excitability did not differ between PD patients in OFF and ON conditions. UPDRS-III scores were similar between iTBS-sham tACS and iTBS-γ tACS sessions (both when conducted in the OFF and ON state), thus ensuring that γ-tACS effects were not biased by different levels of motor symptom severity. Finally, UPDRS-III was significantly lower in the ON than OFF state in all experimental sessions, allowing us to exclude suboptimal dopaminergic stimulation.

Consistent with previous evidence, our data confirm that mechanisms underlying iTBS-induced LTP-like plasticity and GABA-Aergic intracortical activity are impaired in PD (Ammann et al., 2020; Berardelli et al., 2008; Eggers et al., 2010; Kishore, Joseph, et al., 2012; Stephani et al., 2011; Suppa et al., 2011). Importantly, only a few studies tested possible L-dopa-related changes in iTBS-induced plasticity by directly comparing the same patients OFF and ON therapy. Some studies showed that the impaired M1 plasticity observed in patients OFF state was unmodified by L-dopa (Kishore, Joseph, et al., 2012; Suppa et al., 2011), whereas others found normal responses to iTBS both in the OFF and ON states in stable responders (Kishore, Popa, et al., 2012; Zamir et al., 2012). We found that iTBS-sham tACS did not induce MEP facilitation either in the OFF or ON state in our sample of early-to-intermediate stage patients, supporting the idea that impaired homosynaptic LTP-like plasticity mechanisms in PD cannot be ameliorated by L-dopa (Huang et al., 2011; Kishore, Joseph, et al., 2012; Suppa et al., 2011). The study results also show that both the impaired LTP-like plasticity and GABA-Aergic neurotransmission in PD patients OFF

state can be improved by boosting γ oscillations in M1 through γ-tACS. However, the effect of γ-tACS on the disease per se is not a new finding, since only ∼25% of patients differed from the group tested in our previous research (Guerra et al., 2020).

The main novel finding of our study concerns the comparison of iTBS-γ tACS effects between PD patients OFF and ON dopaminergic therapy. In patients ON therapy, we found that iTBS-γ tACS led to greater MEP potentiation and more effective SICI than iTBS-sham tACS. Importantly, the amount of M1 facilitation and SICI modulation induced by iTBS-γ tACS was similar between OFF and ON states. These data overall indicate that the positive γ-tACS effects on LTP-like plasticity and GABA-Aergic impairments in PD occur irrespective of the dopaminergic condition of patients. The lack of interaction between L-dopa and γ-tACS effects we observed gives rise to some possible explanations. Since the mechanism of action of tACS implies the enhancement of cortical oscillations at the stimulation frequency (Ali et al., 2013; Helfrich et al., 2014; Witkowski et al., 2016), γ-tACS-induced neurophysiological changes likely result from the increase in γ oscillations in M1 (Guerra et al., 2020; Guerra, Colella, et al., 2022). Importantly, there is also evidence that L-dopa enhances γ oscillatory activity, including γ power and synchronization, in both basal ganglia and M1 in PD patients (Jenkinson et al., 2013; Lalo et al., 2008; Litvak et al., 2012; Wiest et al., 2022). Accordingly, it was conceivable that strongly enhancing γ oscillations in M1 through combined stimulation with γ-tACS and L-dopa (i.e., iTBS-γ tACS session, ON state) would have boosted iTBS-γ tACS-induced effects. However, this was not the case and different mechanisms may explain our results. First, since γ-tACS effects on iTBS-induced plasticity was similar between patients OFF therapy and HS, that is, MEP facilitation significantly increased after combined stimulation as compared to after iTBS-sham tACS, the occurrence of ceiling effects could be hypothesized. We nevertheless may exclude this hypothesis because our data indicate a generally lower degree of MEP facilitation in patients than in HS after iTBS regardless of whether real or sham tACS was applied (see also Figure 2a). Therefore, iTBS-γ tACS-induced plasticity of M1 was not fully saturated in the OFF dopaminergic state and could have increased further with L-dopa. Another possibility to explain the comparable response to iTBS-γ tACS in patients OFF and ON condition is that γ-tACS effects do not depend on baseline γ activity in M1; that is, they are comparable despite possible changes in γ oscillations after L-dopa intake (Brown et al., 2001; Jenkinson et al., 2013; Lalo et al., 2008; Litvak et al., 2012). This would also lead to the hypothesis that neural circuits mediating γ-tACS effects differ from those activated by L-dopa. In this regard, experimental studies on animal models have described subpopulations of γ-resonant GABA-Aergic interneurons located in more superficial layers of the cerebral cortex, and previous research has suggested that γ-tACS may target these neurons within M1 (Cardin et al., 2009; Guerra, Colella, et al., 2022; Nowak et al., 2017; Otte et al., 2010; Tremblay et al., 2016). In keeping with these studies, we showed that γ-tACS delivered alone significantly modulated SICI, a GABA-Aergic TMS measure, both in HS and in PD patients. Importantly, consistent with previous evidence (Bologna et al., 2018; Guerra, Colella, et al., 2022; Kojovic et al., 2015; MacKinnon et al., 2005; Ni et al., 2013), SICI per se did not improve after L-dopa administration in our sample of PD patients (SICI during sham-tACS alone OFF vs. ON comparison). Furthermore, the amount of γ-tACS-induced SICI modulation did not differ between patients OFF and ON dopaminergic therapy. These findings overall suggest that the activity of GABA-Aergic interneurons targeted by γ-tACS is not influenced by L-dopa. Since the activation of these specific interneurons has been proposed as the mechanism underlying the potentiation of iTBS-induced plasticity by γ-tACS (Guerra et al., 2020), we speculate that the comparable effects of iTBS-γ tACS between patients in OFF and ON states may depend on the poor sensitivity of γ-resonant GABA-Aergic interneurons to L-dopa. The hypothesis that neural circuits mediating γ-tACS effects differ from those activated by L-dopa is also supported by our correlation analyses. Indeed, we found that γ-tACS effects on iTBS-induced plasticity and GABA-Aergic neurotransmission were unrelated to patient clinical response to L-dopa. Moreover, our results showed no relationship between L-dopa effects on motor symptoms and on neurophysiological measures.

A potential limitation of our study is the absence of a direct assessment of successful entrainment of cortical rhythms induced by γ-tACS in our patients. However, reliable electroencephalographic (EEG) recordings during tACS are difficult to obtain in humans due to electrical stimulation artifacts. Currently available tACS-EEG co-recording techniques are not standardized, and their reliability is a subject of discussion (Kasten & Herrmann, 2019). Moreover, we enrolled patients in early-to-intermediate disease stages, and none had tremor-dominant PD or LID. Since previous studies have shown specific differences in cortical excitability between akinetic-rigid and tremor-dominant PD and differential effects of L-dopa on neurophysiological measures depending on LID presence (Barbin et al., 2013; Guerra, Asci, et al., 2022; Khedr et al., 2021; Kishore, Popa, et al., 2012), our iTBS-γ tACS results cannot be generalized to all PD subtypes and disease stages.

5 | CONCLUSION

In this study, we demonstrated that combining γ-tACS with iTBS improves LTP-like plasticity of M1 and GABA-Aergic transmission in PD patients to a comparable extent between OFF and ON dopaminergic states. The lack of interaction between L-dopa and γ-tACS effects could be due to the neural substrate targeted by the stimulation, that is, GABA-A-ergic intracortical circuit activity, which does not depend on dopaminergic mechanisms. These findings are relevant because they extend the applicability of this novel neuromodulation approach to PD patients who are on their usual dopaminergic therapy. Future studies should clarify whether iTBS-γ tACS positive effects vary between different stages of PD and whether they have clinically detectable correlates, including motor symptom improvement.

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AUTHOR CONTRIBUTIONS

Andrea Guerra: Conceptualization; data curation; formal analysis; investigation; methodology; writing-original draft; writing-review and editing. **Valentina D'Onofrio:** Data curation; investigation; writing-original draft. **Francesco Asci:** Formal analysis; investigation. **Florinda Ferreri:** Validation; writing-review and editing. **Giovanni Fabbrini:** Supervision; writing-review and editing. **Alfredo Berardelli:** Conceptualization; methodology; project administration; resources; supervision; writing-review and editing. **Matteo Bologna:** Conceptualization; methodology; project administration; supervision; writing-review and editing.

CONFLICT OF INTEREST

No competing financial interests to declare.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/ejn.15867.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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