

# Exploring the role of the left DLPFC in fatigue during unresisted rhythmic movements

Aranza Vila-Villar<sup>1</sup> | Mariña Naya-Fernández<sup>1</sup> | Antonio Madrid<sup>1</sup> |  
 Elena Madinabeitia-Mancebo<sup>1</sup>  | Verónica Robles-García<sup>1</sup> | Javier Cudeiro<sup>1,2</sup> |  
 Pablo Arias<sup>1</sup> 

<sup>1</sup>Department of Physiotherapy, Medicine and Biomedical Sciences and INEF Galicia, Universidade da Coruña, NEUROcom (Neuroscience and Motor Control Group) and Biomedical Institute of A Coruña (INIBIC), A Coruña, Spain

<sup>2</sup>Centro de Estimulación Cerebral de Galicia, A Coruña, Spain

## Correspondence

Pablo Arias, Department of Physiotherapy, Medicine and Biomedical Sciences and INEF Galicia, Universidade da Coruña, NEUROcom (Neuroscience and Motor Control Group) and Biomedical Institute of A Coruña (INIBIC), A Coruña, Spain.  
 Email: [pabloarias.neurocom@udc.es](mailto:pabloarias.neurocom@udc.es)

## Abstract

Understanding central fatigue during motor activities is important in neuroscience and different medical fields. The central mechanisms of motor fatigue are known in depth for isometric muscle contractions; however, current knowledge about rhythmic movements and central fatigue is rather scarce. In this study, we explored the role of an executive area (left dorsolateral prefrontal cortex [DLPFC]) in fatigue development during rhythmic movement execution, finger tapping (FT) at the maximal rate, and fatigue after effects on the stability of rhythmic patterns. Participants ( $n = 19$ ) performed six sets of unresisted FT (with a 3 min rest in-between). Each set included four interleaved 30s repetitions of self-selected (two repetitions) and maximal rate FT (two repetitions) without rest in-between. Left DLPFC involvement in the task was perturbed by transcranial static magnetic stimulation (tSMS) in two sessions (one real and one sham). Moreover, half of the self-selected FT repetitions were performed concurrently with a demanding cognitive task, the Stroop test. Compared with sham stimulation, real tSMS stimulation prevented waning in tapping frequency at the maximal rate without affecting perceived levels of fatigue. Participants' engagement in the Stroop test just prior to maximal FT reduced the movement amplitude during this mode of execution. Movement variability at self-selected rates increased during Stroop execution, especially under fatigue previously induced by maximal FT. Our results indicate cognitive-motor interactions and a prominent role of the prefrontal cortex in fatigue and the motor control of simple repetitive movement patterns. We suggest the need to approach motor fatigue including cognitive perspectives.

## KEYWORDS

DLPFC, fatigue, magnetic stimulation, neuromodulation, repetitive movements

Aranza Vila-Villar and Mariña Naya-Fernández contributed equally to this work.

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## 1 | INTRODUCTION

Task dependency is an accepted principle in the study of human muscle fatigue (Barry & Enoka, 2007; Enoka et al., 2011; Enoka & Duchateau, 2008; Enoka & Stuart, 1992), and their central origins have been explored in depth for isometric muscle contractions (D'Amico et al., 2020; Gandevia, 2001). In contrast, the central components of fatigue induced by unresisted rhythmic or repetitive movements are poorly defined, despite these movements being part of many daily living activities.

During unresisted rhythmic movements performed at the maximal rate, peripheral fatigue develops in muscle fibers, and neuromuscular synapses, which impair the efficiency of muscle contractions (Madrid et al., 2018). However, fatigue in these movements is also characterized by changes in the excitability of spinal and supraspinal structures (Arias et al., 2012; Arias et al., 2015; Bachinger et al., 2019; Madrid et al., 2016; Teo et al., 2012b). At the cortical level, the excitability of primary motor cortex (M1) inhibitory interneurons (likely operating through GABA<sub>B</sub> receptors) increases while the maximal movement rate decreases (Arias et al., 2015; Madrid et al., 2016; Madrid et al., 2018). Remarkably, an increase in M1-GABA<sub>B</sub> excitability appears to be central in origin, and there is no response to the waning of muscle contractility mediated by afferent feedback (Madinabeitia-Mancebo et al., 2021).

One important question that has remained unsolved is whether fatigue-induced changes in M1 excitability emerge at its intrinsic circuitry, or conversely, reflect the “echoes” of activity at some other structures engaged in executive and/or rhythm control. The latter might well be a possibility because changes in spinal excitability and M1 excitatory/inhibitory balance explain little of the waning in tapping rate when performing unresisted finger tapping (FT) at the maximal rate (*maximal FT*) for a couple of minutes (Madinabeitia-Mancebo et al., 2020). Furthermore, changing M1 excitability with transcranial magnetic stimulation (TMS) did not lessen or worsen the fast decline in maximal movement frequency during 30 s of FT (Madinabeitia-Mancebo et al., 2021) but, conversely, it prevented muscle force loss (Madinabeitia-Mancebo et al., 2021).

Based on the above observations, the mechanism of fatigue for unresisted rhythmic movements appears to be dissociable from processes engaged in muscle force fatigability. In agreement with this, fatigue development during unresisted FT does not impair the central drive to the muscle or force loss (Madrid et al., 2018), and some research has suggested that it might engage processes and structures involved in motor rhythm formation. In line with this possibility, fatigue during FT impacts the activation-time sequence of agonist and antagonist muscles, and

when fatigue develops, co-activation increases. This means that the muscles involved in finger displacement in opposite directions increased their simultaneous activation, making movement less fluent (Bachinger et al., 2019; Rodrigues et al., 2009). However, the central loci determinants of such disruption in rhythmic activity remain unclear.

This study explored the possible origins of fatigue during unresisted rhythmic movements upstream of the motor cortex. Among the different structures with a possible role, we selected the dorsolateral prefrontal cortex (DLPFC) as a core node for fatigue development. Our hypothesis is based on different behavioral and neurophysiological observations.

First, beyond the role of the DLPFC in higher order executive functions, especially in the temporal organization of goal-oriented actions (Fuster, 2000, 2001; Koechlin et al., 2003; Miller, 2000; Ott & Nieder, 2019), there is growing evidence of its top-down control over simple motor actions. Thus, Hasan et al. (2013) showed a selective modulation of M1 excitability (time- and muscle-specific) during movement preparation with origin in the DLPFC during instructed finger reaction movements. In the case of simple repetitive movements, such as right-hand FT, brain imaging indicates the existence of functional connectivity between the left DLPFC and sensorimotor cortices (Anwar et al., 2016; Witt et al., 2008). Remarkably, effective connectivity analyses to discern the direction of interactions between the left DLPFC, premotor, and sensorimotor cortices, advocate for DLPFC top-down control over those motor structures; a study performed with FT rates ranging from 2 to 5 Hz (Anwar et al., 2016).

Second, the DLPFC connects with subcortical structures engaged in rhythm formation. When high-frequency repetitive TMS is applied over the left DLPFC, dopamine levels increase in the ipsilateral caudate nucleus of the basal ganglia (Strafella et al., 2001). The basal ganglia is a complex structure with different functions (Lanciego et al., 2012; Obeso et al., 2008; Rodriguez-Oroz et al., 2009); however, it is especially engaged in the temporal organization of motor patterns (Rao et al., 2001). For instance, patients with BG alterations display a characteristic “arhythmkinetic” profile in repetitive movements (Arias et al., 2012; Arias & Cudeiro, 2008; del Olmo et al., 2006; Shimoyama et al., 1990).

Third, the DLPFC has been a candidate for treating pathological fatigue through different brain stimulation techniques (Lefaucheur et al., 2017), such as fibromyalgia (Fitzgibbon et al., 2018) or multiple sclerosis (Chalah et al., 2017).

On the other hand, one approach to explore DLPFC involvement in acute fatigue (i.e., task-induced) is the application of noninvasive brain stimulation techniques to

change its excitability during the fatiguing task. However, the results of neuromodulation studies on repetitive movement fatigue are ambiguous, as shown in a meta-analysis (Machado et al., 2019). This is likely because the tasks explored were also highly demanding for muscle force (e.g., cycling). In such tasks, it is difficult to determine whether force generation capacity, rhythm formation (maximal rate and/or rhythmic movement stability), or their interaction is the most relevant function affected by stimulation. Remarkably, a change in excitability induced by noninvasive brain stimulation techniques might not produce changes in behavior. This is because circuits targeted by stimulation might be different from those responsible for a given behavior (especially if stimulation is applied at rest), just because connectivity between areas varies with different brain functional states (Rothwell, 2011). Therefore, another possible approach to test the role of the DLPFC in fatigue during FT is to engage the structure in a demanding task and observe the immediate effect on motor execution (without allowing rest periods to avoid recovery) during FT.

In this study, we explored the role of the left DLPFC in fatigue that developed during unresisted repetitive rhythmic movements requiring low levels of muscle force. We used FT as the model of unresisted rhythmic movements because it is reliable (Arias et al., 2012) and characterizes rhythmicity control across physiological and pathological populations (Arias et al., 2012; Shimoyama et al., 1990). In addition, it is a model of rhythmic movement commonly used in the field of motor control (Collyer et al., 1994; Freeman et al., 1993; Gill et al., 1986; Jackson, 1953; Jancke et al., 2000; Parks et al., 2003; Shimoyama et al., 1990; Theoret et al., 2001).

Therefore, to test the role of the left DLPFC during fatiguing tasks (unresisted FT at different rates in righthanders), we perturbed this prefrontal area through two experimental conditions, together with controls:

- (i) By applying transcranial static magnetic stimulation (tSMS) for 25 min before the motor task while subjects are at rest and for 30 min during different sets of FT. tSMS changes cortical excitability over the application area but also affects functionally connected remote structures (Aguila et al., 2016; Arias et al., 2017; Carrasco-Lopez et al., 2017; Dileone et al., 2018; Gonzalez-Rosa et al., 2015; Kirimoto et al., 2018; Lozano-Soto et al., 2017; Matsugi & Okada, 2017; Antonio Oliviero et al., 2011; Paulus, 2011; Sheffield et al., 2019). tSMS is safe even when applied for extended periods (Oliviero et al., 2015); therefore, it is used as a probe technique and conceived as an experimental intervention option for disorders of cortical excitability (di Lazzaro et al., 2021).

Magnet mechanisms of action are not fully understood but appear to operate by changes at the synaptic level. Thus, static magnetic fields modify the activation dynamics of membrane channels (Rosen, 1993a, 1993b, 2003a, 2003b; Rosen & Lubowsky, 1987, 1990), perhaps by changing the molecular orientation of their proteins (Cavopol et al., 1995; McLean et al., 1995).

Therefore, observing the changes obtained after real tSMS (compared with the observed behavior during sham tSMS) permits exploration of the role of the stimulated area/network in a given behavior. We also altered the putative role of the left DLPFC on FT by engaging participants in a demanding cognitive task during and immediately before FT. Thus, subjects executed some repetitions of maximal rate FT immediately after executing the Stroop test. The Stroop is a widely used test of executive control (MacLeod, 1991), which is demanding for the left DLPFC (Huang et al., 2020). Therefore, if fatigue during FT emerges in prefrontal networks, we might expect an altered and diminished performance when maximal FT is executed immediately after Stroop. A rhythmicity control distortion (FT frequency and variability) is also expected if motor actions are performed while the DLPFC is engaged in a demanding cognitive task, such as the Stroop task.

This study was designed to explore the hypothesis that tSMS on the left DLPFC modifies fatigue developed by FT at the maximal rate. We also checked the impact of executing a demanding cognitive task on fatigue development during the subsequent performance of maximal FT. Fatigue development will impact FT stability (i.e., variability of participants' self-selected FT patterns); therefore, if the DLPFC plays a prominent role in fatigue generation, movement stability will be further altered by concurrent execution of FT and Stroop.

## 2 | METHOD

The procedures of this double-blind crossover study were in accordance with the Declaration of Helsinki and approved by the University of A Coruña Ethics Committee (CEID17112017). The participants signed informed consent forms.

### 2.1 | Participants

Nineteen healthy participants, recruited through ads, mailing, and word of mouth among students in our

university, completed two scheduled sessions (mean age: 24.5 years; SE: 1.3; 10 females). In a preliminary interview, informed consent was obtained. Participants were also screened for incompatibility with brain stimulation techniques based on ICFN recommendations (Rossini et al., 2015), drug consumption in the last weeks (again asked before each session), color blindness and hand dexterity through self-report, and history of neurocognitive, psychiatric symptoms, or motor impairment. All participants were right-handed according to their self-report. They also were native Spanish speakers with normal or corrected-to-normal vision.

## 2.2 | FT task and instrumentation for its recording

The participants performed FT with the index finger of their dominant hand, as follows: A low-tone auditory cue was the signal to start the FT at a comfortable pace (*self-selected FT*) for 30s. At the end and without rest, the same cue prompted subjects to tap at their maximal rate (*maximal FT*) for another 30s. Next, with no rest, the auditory cue called for the execution of a second *self-selected*

*FT*, also for 30s. Finally, subjects executed a second 30s *maximal FT* in response to the cue, which was presented again at the end of the 30s to complete that sequence. The FT test is valid and reliable for characterizing rhythmicity control across different physiological and pathological populations (Shimoyama et al., 1990). More recently, we have re-examined some properties of the FT test executed at comfort and maximal rates during different sets (Arias et al., 2012).

The whole sequence (*self-selected FT* repetition 1, *maximal FT* repetition 1, *self-selected FT* repetition 2, and *maximal FT* repetition 2) formed a set lasting 2 min. The set was repeated several times during the sessions (as explained below), with intervening periods of rest (Figure 1a). This sequence of repetitions allowed us to check how fatigue developed within repetitions (defined as a reduction in FT frequency or range of motion [ROM] along with the 30s of maximal FT) (Madinabeitia-Mancebo et al., 2020; Madinabeitia-Mancebo et al., 2021; Madrid et al., 2018), and to check if fatigue generated in *maximal FT* repetition 1 remained when executing the 2nd repetition of maximal FT. However, rhythmicity control expressed as the ability to maintain stable rhythmic patterns cannot be tested during maximal FT because its movement frequency wanes but can be tested

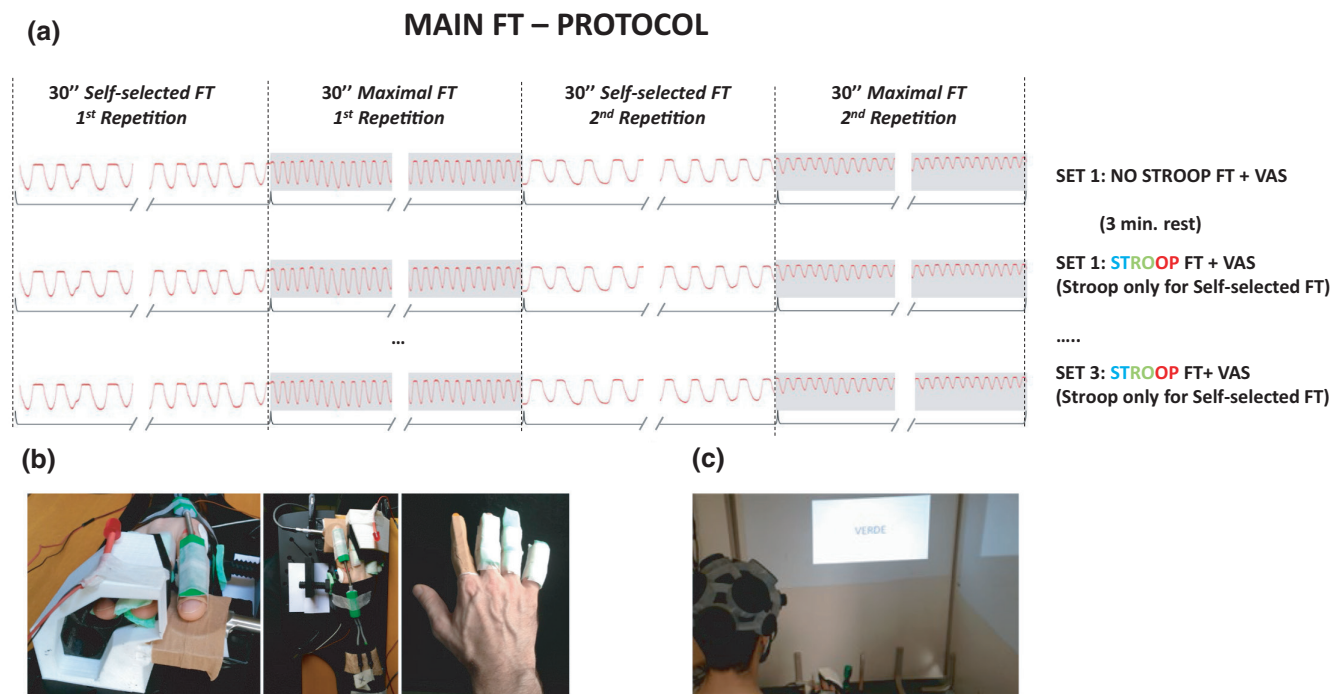


FIGURE 1 (a) Schematic representation of the tapping task and the main FT protocol. A set included a 1<sup>st</sup> repetition of 30 s *self-selected FT*, immediately followed by the 1<sup>st</sup> repetition of 30 s *maximal FT*, immediately followed by a 2<sup>nd</sup> repetition of 30 s *self-selected FT*, and immediately followed by a 2<sup>nd</sup> repetition of 30 s *maximal FT*. After a rest of 3 min, the set was repeated until there were six sets in total. In alternating order, half of the sets were performed with the execution of the Stroop test simultaneously with the two repetitions of the 30 s *self-selected FT*. Immediately at the end of each set, levels of perceived fatigue were acquired (with a visual analogue scale - VAS). (b) A picture of the hand preparation and fixation for the protocol. (c) A participant performing a part of the protocol

during self-selected FT (Arias et al., 2012). Therefore, the effect of fatigue on movement rhythmicity control is evaluated by comparing *self-selected FT* repetition 1 versus repetition 2.

At the beginning of the session, it was explained to the subjects that *self-selected FT* required tapping at their “preferred and most comfortable rate of tapping from the first cue to the following cue, keeping the same rate always.” For *maximal FT*, it was explained that they were to tap “as fast as you can, from the very beginning to the end of the 30 s, both called with the auditory cue,” and they were encouraged. Instructions were repeated before the execution of each set at the end of the rest periods; however, no instructions were given on the FT ROM amplitude.

For FT execution, participants were seated comfortably in a chair with a tablet arm, and the participants' dominant hand and forearm were attached to a 3D fixation system (Madrid et al., 2018). The system fixed the forearm, hand, and all fingers, but the index finger, which was free to move around the metacarpophalangeal joint. A finger splint immobilized the interphalangeal joints of the index finger (Figure 1b). Participants tapped on a small dynamometer (P200 Biometrics Ltd) while a light S100 (Biometrics Ltd) goniometer recorded flexo-extension index movements. The sensors were connected to a K800 amplifier (Biometrics Ltd), which sent signals to a CED1401mkII unit. This unit was controlled with Signal 6.0, which sampled recordings at 10 kHz and stored them on the computer.

### 2.3 | Stimulation of left DLPFC with a static magnetic field (tSMS)

Each subject performed two sessions. The sessions were identical, except for the kind of stimulation applied to the participants' left DLPFC (real or sham). The session order was counterbalanced across participants.

In the real tSMS session, a 60-mm diameter and 30 mm height neodymium magnet (with a nominal strength  $\approx 120$  kg) was applied over the left DLPFC (on F3 according to the EEG 10–20 system). We used a MAGdvp1.1 helmet (Neurek Ltd., Figure 1c) for this purpose. In the sham tSMS session, a nonmagnetic replica replaced the real magnet. Magnet application does not produce any perceivable “cutaneous” sensation or muscle twitches on subjects, unlike other sham protocols (the case of repetitive transcranial magnetic stimulation or, transcranial direct current stimulation). This is because tSMS does not induce electric fields in the body, which makes real and sham tSMS indistinguishable from each other (Oliviero et al., 2011).

### 2.4 | Session structure and Main FT protocol

Each session included a main FT protocol while subjects wore the tSMS helmet. We also performed preliminary tests and procedures to assess baseline parameters of perceived fatigue with a visual analog scale (VAS) before FT, motor system corticomuscular excitability, and one Stroop and FT familiarization trial. Some of these tests were repeated after the main FT protocol. Please see [Supporting Information](#) for the procedures and their objectives.

The main FT protocol comprised six sets of the FT task, while the tSMS helmet was worn, as described previously in Section 2.2. Immediately after each set, the participants' perceived fatigue was rated (using the VAS). In half of the sets, participants executed *self-selected FT* while performing Stroop simultaneously (Figure 1a). A rest period of 3 min was always included between sets.

For FT sets including Stroop, these were performed during the first and second repetitions of *self-selected FT*. Sets with and without Stroop were alternated in their presentation order. Maximal FT was never executed with Stroop, but alone. Nine subjects started the main FT protocol with a set including Stroop during *self-selected FT*, and the other 10 subjects started without Stroop in the two tSMS sessions.

We also performed the Stroop test twice at rest (one before any motor action and again at the very end of the protocol; see [Supporting Information](#) for timeline).

### 2.5 | Stroop test

We used the incongruent modality of the Stroop test in our experiment (Hatukai & Algom, 2017). Items (“rojo,” “azul,” “verde”; Spanish words for red, blue, and green, respectively) were presented on a 1 × 1-m screen in front of participants in red, blue, or green colors (see Figure 1c), and subjects indicated colors as fast as items appeared on the screen. After correctly identifying an item, another item appeared with no delay. Subjects were told to identify as many items as possible. An experimenter (blinded to the tSMS modality applied) controlled the word appearance using a computer keyboard key.

### 2.6 | Data processing and analyzed variables

We calculated FT kinematic variables (inter-tap intervals and ROM amplitude) from dynamometric and

goniometric recordings using customized MATLAB programs, as described in the literature (Madinabeitia-Mancebo et al., 2020; Madrid et al., 2018).

The first five taps were discarded from the *self-selected* tapping computations to avoid calculations that included events during the transition phase from the previous tapping mode or from rest. With the remaining events, we calculated the median FT frequency and ROM amplitude and their coefficient of variation (CV) (%) =  $(SD/mean) \times 100$ .

For *maximal* tapping modes, we considered the median tapping frequency and ROM amplitudes in two 5 s time windows of execution, including the first (PRE) and last (POST) 5 s of the 30 s period. A reduction in the maximal tapping frequency from PRE to POST defined fatigue (Arias et al., 2015; Madrid et al., 2016; Madrid et al., 2018).

Later, offline, individual tapping frequencies and ROM amplitude scores were submitted for a process of intra-subject normalization. For FT frequency, the corresponding scores were divided by the maximal frequency obtained at any of the PRE or POST 5 s time windows defined above for each session (Table 1). Regarding ROM amplitude, the maximal active ROM amplitude recorded at the beginning of the session was used to divide all scores obtained during the FT.

The number of correctly identified items in 30 s defined the Stroop score.

In summary, the analyzed variables were FT frequency (Hz) and ROM amplitude (grades) during *self-selected* and *maximal* FT, FT frequency and ROM amplitude CVs (%; only computed for *self-selected* FT), Stroop score (word/sec), and VAS scores (on a 10-point scale). We also evaluated cortico-motor excitability variables recorded before and after the main FT protocol, described in the Supporting Information.

## 2.7 | Statistical analyses

Variables were analyzed using repeated-measures analysis of variance (ANOVA). Distribution normality was determined using the one-sample Kolmogorov–Smirnov test. If sphericity assumptions were violated (Mauchly's

W test), the ANOVA degrees of freedom were corrected using Greenhouse–Geisser coefficients ( $\epsilon$ ).

Regarding FT kinematics, ANOVA included the following factors: STIM (real and sham tSMS), SET (three levels, one for each set), REPETITION (REP; two levels, one for each of the two repetitions within sets), and COGNITIVE LOAD (CL; with or without Stroop). Note that maximal FT was always performed without simultaneous Stroop execution; however, the CL factor was maintained to differentiate between maximal FT immediately following self-selected FT with/without Stroop.

For the analyses of tapping frequency and ROM amplitude during *maximal* FT, we also performed another ANOVA, including the factor TIME, with PRE, and POST levels. These are the median scores at the 0–5 s and 25–30 s time windows of execution. TIME tests change in tapping profile within repetitions (from the beginning to the end of the 30 s). This was included because the decrease in maximal FT frequency within repetitions denotes fatigue (Arias et al., 2015; Elena Madinabeitia-Mancebo et al., 2020; E Madinabeitia-Mancebo et al., 2021; Madrid et al., 2016; Rodrigues et al., 2009; Teo et al., 2012a; Teo et al., 2012b). Therefore, it was not included in the self-selected FT analyses.

To report ANOVA in the results section, and for simplicity, the different factors related to main effects were indicated by a sub-index at the side of the p-value (i.e., the main effect of the factor TIME was termed “p-value<sub>TIME</sub>”), as well as significant interactions (i.e., the interaction TIME  $\times$  REP was termed “p-value<sub>TIME  $\times$  REP</sub>”).

A paired Student's *t* test was used to check differences between sessions for (i) maximal tapping rate achieved at any testing time point within a session; (ii) maximal active ROM tested at the beginning of each session; and (iii) Stroop performance at rest at the beginning of the protocol.  $p < .05$  was considered statistically significant. Results plotted in graphs are means across subjects and standard errors of the mean (SE).

## 3 | RESULTS

First, we observed that maximal finger ROM at the beginning of the protocol did not differ across sessions; the

	REAL	SHAM	Difference
Maximal active ROM (°)	51.4, SE: 1.9	51.7, SE: 1.8	$t_{18} = 0.2, p = .8$
Stroop score (words/s)	1.00, SE: 0.03	0.94, SE: 0.03	$t_{18} = 1.5, p = .163$
Maximal tapping rate (Hz)	6.5, SE: 0.18	6.4, SE: 0.20	$t_{18} = 1.3, p = .213$

TABLE 1 Normalizing scores in the different sessions

same occurred for Stroop scores recorded at rest before the execution of any other task (Table 1).

Then, we tested whether magnet application on the left DLPFC affected the maximal FT frequency achieved by participants along the protocols and compared the results obtained in the two tSMS sessions (real vs. sham). While receiving tSMS, the maximal frequency attained by participants at any time did not differ across sessions (Table 1). This punctual parameter indicated that real tSMS of the left DLPFC did not affect maximal movement frequency.

The scores served as intra-subject normalization values in each session (Table 1) and were equivalent to y axis units in graphs.

### 3.1 | FT pattern (frequency and ROM amplitude) during maximal execution mode

However, when we looked at how FT progressed along the protocol, fatigue, expressed as waning in maximal FT frequency during the 30s repetitions or across sets, changed in a different manner in the real and sham tSMS sessions, as shown by significant interactions ( $F_{1,18} = 5.2$ ,  $p = .036_{\text{STIM} \times \text{CL} \times \text{TIME}}$  and  $F_{1,18} = 4.4$ ,  $p = .051_{\text{STIM} \times \text{REP}}$ ). We performed independent follow-up ANOVAs for each stimulation mode to understand the differences in behavior.

Maximal FT frequencies in the second repetitions were reduced compared with the first 30s repetitions (suggesting fatigue). With real tSMS, this changed across sets ( $F_{2,36} = 13.3$ ,  $p < .001_{\text{SET} \times \text{REP}}$ ) in a way that second repetitions were significantly slower than first repetitions only in set 1, but not in set 2 or 3 (see Figure 2a for post hoc comparisons). Conversely, in the sham tSMS session, the second repetitions were significantly slower than the first repetitions in all sets ( $F_{2,36} = 3.9$ ,  $p = .030_{\text{SET} \times \text{REP}}$ ; see Figure 2a for post hoc comparisons). These results suggest that real stimulation of the left DLPFC reduces fatigue development.

Next, we checked whether the decrease in maximal FT from repetition 1 to 2 was dependent on the previous execution of Stroop along self-selected FT. For sham tSMS (Figure 2b), the drop in maximal tapping rates from 1st to 2nd repetitions ( $F_{1,18} = 15.8$ ,  $p < .001_{\text{REP}}$ ) did not differ when they followed self-selected FT with Stroop (colored in figures) or without Stroop (black/white in figures) ( $F_{1,18} = 1.5$ ,  $p = .236_{\text{CL} \times \text{REP}}$ ). The second repetition was always slower. However, this was not the case for real tSMS ( $F_{1,18} = 8.4$ ,  $p = .010_{\text{CC} \times \text{REP}}$ ; Figure 2b), which prevented fatigue development for maximal FT when they followed the no-Stroop self-selected FT (post hoc comparisons shown in Figure 2b).

After that, we determined whether ROM amplitude evolved across the protocol. ROM during maximal FT reduced significantly in the maximal FT repetitions executed immediately after self-selected FT with Stroop ( $F_{1,18} = 7.5$ ,  $p = .014_{\text{CL}}$ ; Figure 2c); no other significant interaction was observed for all repetitions (1st and 2nd), sets, and sessions (real and sham tSMS). This indicates that a greater cognitive engagement immediately before maximal FT wanes subsequent motor responses. The effect ( $\approx 1.5\%$ ) appeared to be small, but notably, ROM across all maximal FT trials was 25.2% of the full joint ROM in the two sessions. Therefore, a 1.5% change was approximately equal to 6% of the ROM set during maximal FT.

Supporting Results include some other significant effects (in line with previous literature) that are not essential for testing the current hypothesis.

### 3.2 | FT pattern at self-selected execution rate

The frequency of self-selected FT during the course of the protocol differentially evolved for real and sham tSMS, as shown by significant interactions ( $F_{2,36} = 4.9$ ,  $p = .013_{\text{STIM} \times \text{CL} \times \text{SET} \times \text{REP}}$ ). However, in the two sessions, self-selected FT was approximately one-third faster in Stroop versus no-Stroop trials (real:  $F_{1,18} = 28.1$ ,  $p < .001_{\text{CL}}$ ; sham:  $F_{1,18} = 23.4$ ,  $p < .001_{\text{CL}}$ ) (Figure 3a; asterisks between cognitive levels were omitted for clarity).

For both real ( $F_{1,18} = 15.3$ ,  $p < .001_{\text{CL} \times \text{REP}}$ ) and sham tSMS sessions ( $F_{1,18} = 6.5$ ,  $p = .020_{\text{CL} \times \text{REP}}$ ), cognitive-motor interactions ruled movement frequency in a different way in the absence and presence of fatigue (1st and 2nd repetitions, respectively). Without Stroop, participants reduced their self-selected tapping frequency with fatigue; this behavior was not observed when participants were also engaged in Stroop execution.

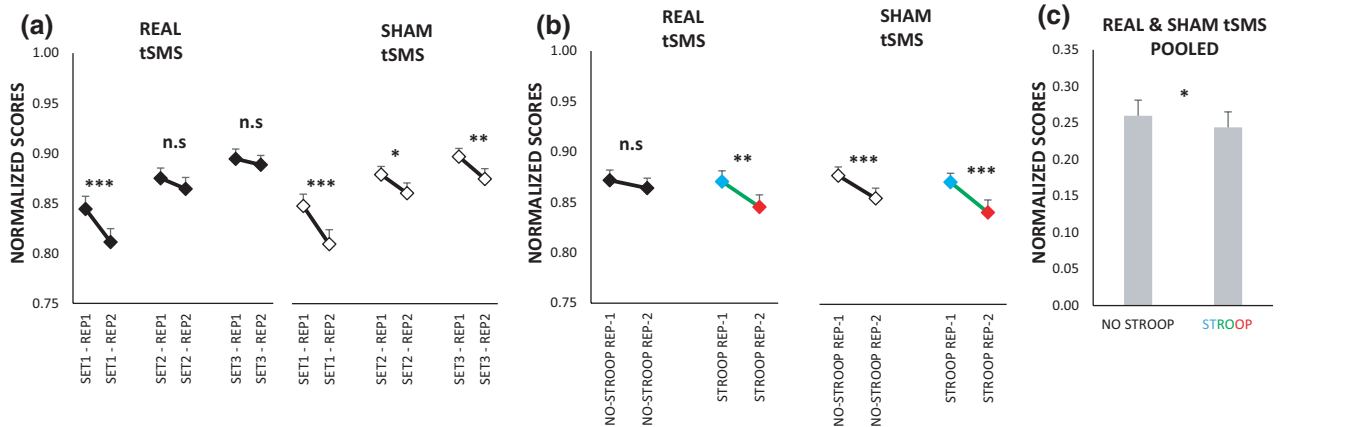
Only for real tSMS ( $F_{2,36} = 4.4$ ,  $p = .020_{\text{CL} \times \text{SET} \times \text{REP}}$ ) did these responses significantly change with set progression (a.1 inset in Figure 3 asterisks omitted for clarity).

On the other hand, we also evaluated putative effects on ROM amplitude during self-selected FT. Changes were few and small (please see Supporting Results).

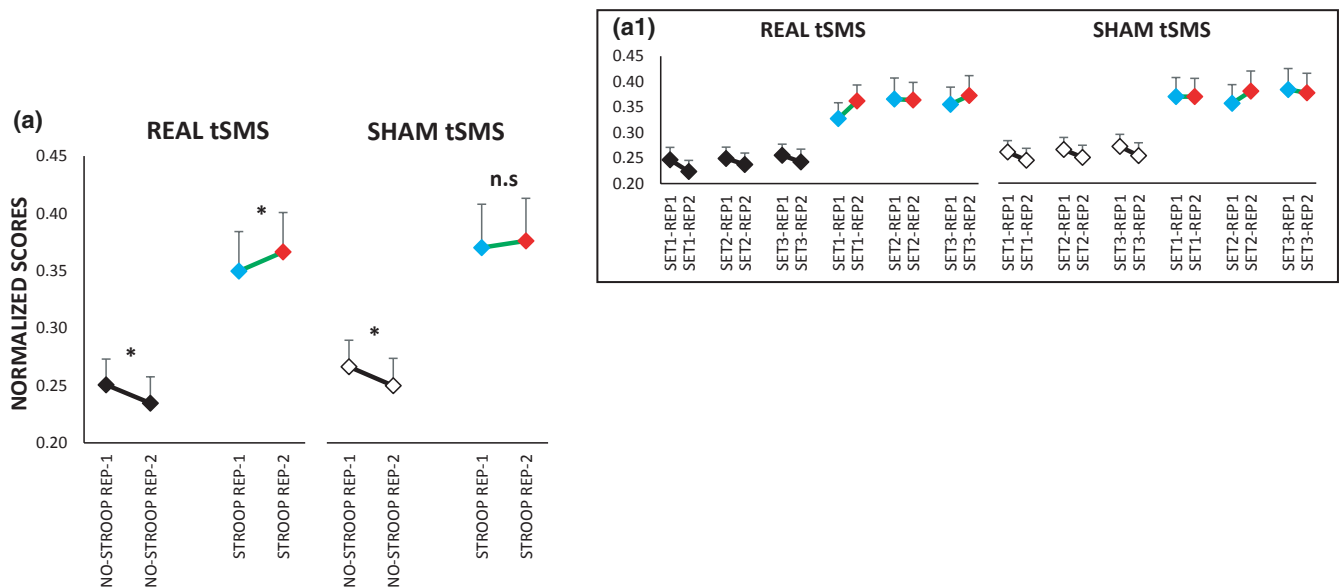
### 3.3 | Tapping variability for self-selected-rate FT

Another relevant question was how fatigue, involvement in a demanding cognitive task, and their interaction altered the stability of rhythmic movements.

The CV of the tapping frequency ( $CV_{\text{FQ}}$ ) differed across the two sessions (real and sham tSMS) in sets and

**FREQUENCY AT MAXIMAL FT**


**FIGURE 2** (a) Frequency of maximal FT increased set after set ( $p < .001_{\text{SET}}$  in the two sessions, asterisks omitted), but reduced significantly from the 1st to the 2nd repetition in all sets with sham tSMS. With real tSMS, this reduction was significant only in set 1, but not in set 2 or 3. (b) The reduction in maximal FT frequency from the 1st to the 2nd repetition (REP) was significant for sets including Stroop and no-Stroop in the sham tSMS session. Real tSMS prevented the significant frequency reduction in maximal FT from repetition 1 to repetition 2 for no-Stroop sets. (c) ROM amplitude during maximal FT significantly reduced in repetitions following the execution of self-selected FT with Stroop compared to those following self-selected FT without Stroop. Gray bars represent responses pooled across real and sham tSMS sessions. \* $p < .05$ ; \*\* $p < .01$ ; \*\*\* $p < .001$

**FREQUENCY AT SELF-SELECTED FT**


**FIGURE 3** (a) Tapping frequencies during self-selected FT increased during Stroop execution ( $p < .001_{\text{CL}}$  for the two sessions; asterisk omitted). In the absence of the Stroop test, tapping frequencies in second repetitions reduced in real and sham tSMS sessions. During Stroop execution, the tapping frequency remained stable from repetition 1 to 2 in the sham tSMS session; conversely, with real tSMS, the tapping frequency increased in a significant way from repetition 1 to 2. The a.1 inset displays behavior split by sets (asterisks omitted). \* $p < .05$

repetitions  $F_{2,36} = 6.4$ ,  $\epsilon = 0.7$ ,  $p = .011$   $\text{STIM} \times \text{CL} \times \text{SET} \times \text{REP}$ . However, in the two sessions,  $\text{CV}_{\text{FQ}}$  was approximately 4% higher in Stroop than in no-Stroop (real magnet session,  $F_{1,18} = 39.2$ ,  $p < .001_{\text{CL}}$ ; sham session,  $F_{1,18} = 31.4$ ,  $p < .001_{\text{CL}}$ ) (Figure 4a).

When participants executed self-selected FT in the presence of fatigue (2nd repetitions) compared with

execution in the absence of fatigue (1st repetitions), the  $\text{CV}_{\text{FQ}}$  of self-selected FT changed in a different way for Stroop and no-Stroop trials, both in real ( $F_{1,18} = 21.0$ ,  $p < .001_{\text{CL} \times \text{REP}}$ ) and sham ( $F_{1,18} = 19.6$ ,  $p < .001_{\text{CL} \times \text{REP}}$ ) tSMS sessions. Participants' variability reduced when fatigued only in no-Stroop trials (both sessions). Conversely, variability was not reduced when subjects were fatigued

FREQUENCY CV AT SELF-SELECTED FT

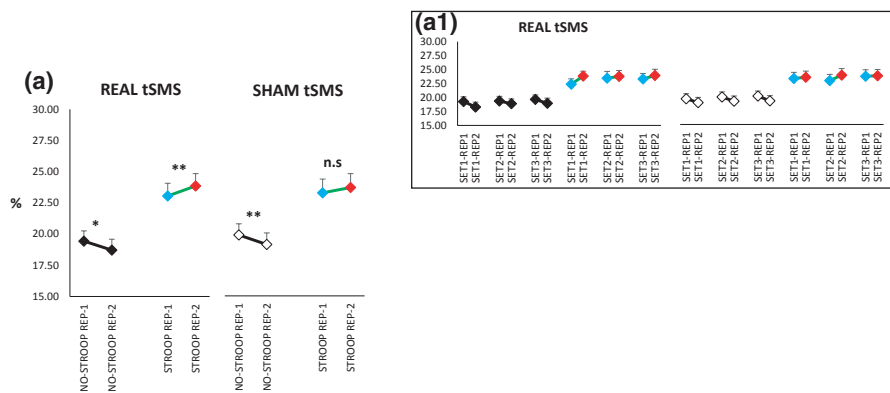
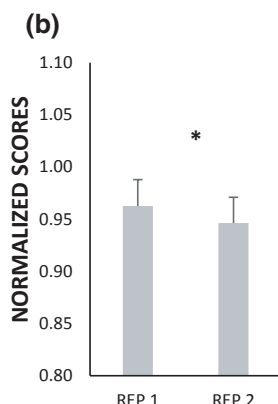
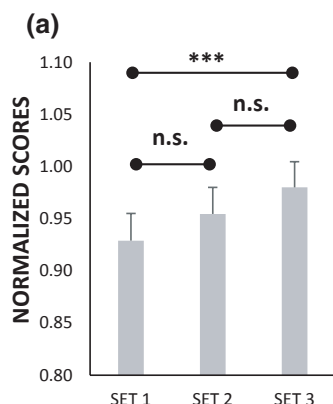


FIGURE 4 (a) CV<sub>FQ</sub> at self-selected FT increased while performing Stroop (vs. no-Stroop) in both sessions ( $p < .001_{CL}$  the two sessions; asterisk omitted). Additionally, again in both sessions, CV<sub>FQ</sub> was reduced in the presence of fatigue (2nd repetition) for no-Stroop FT. For Stroop FT, CV<sub>FQ</sub> increased with fatigue for real tSMS, an effect not observed for sham tSMS. a.1 inset displays behavior split by sets (asterisks omitted). \* $p < .05$ ; \*\* $p < .01$

STROOP SCORES



VAS SCORES

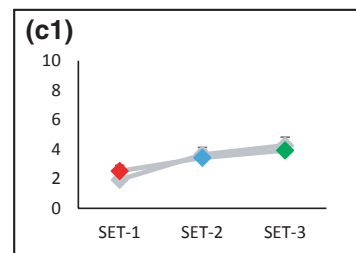
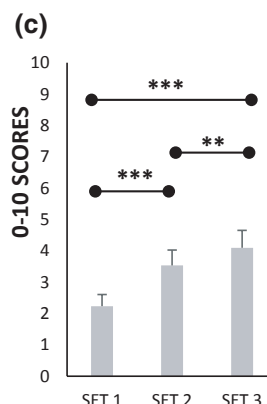


FIGURE 5 (a and b) Stroop scores and (c) VAS scores. None of these effects differed between real and sham tSMS sessions (gray tones represent both stimulation modes pooled). The increase in Stroop performance was significant with repeated practice during FT (a) across sets. However, scores were reduced in the second self-selected FT repetition within sets (b). (c) Fatigue perception increased set after set. Inset c.1 shows the variables for Stroop (colored) and no-Stroop sets (asterisk omitted). \* $p < .05$ ; \*\* $p < .01$ ; \*\*\* $p < .001$

and engaged in the Stroop; however, it increased significantly in the real tSMS session (see Figure 4a for post hoc comparisons).

Only in real tSMS sessions did changes differentially progress across sets ( $F_{2,36} = 4.9_e = 0.6 p = .029_{CL \times SET \times REP}$ ; a1 inset of Figure 4, post hoc comparisons are omitted for clarity).

Changes in tapping variability from 1st to 2nd repetitions were small, whereas changes due to increasing cognitive load during task execution were larger.

CV<sub>ROM</sub> displayed a very similar profile (please see Supporting Results).

3.4 | Stroop scores

We were also interested in cognitive performance as reflected by Stroop scores (number of correctly identified items in time) to understand the possible presence of motor-cognitive bidirectional interactions. First, as regards tSMS, changes in Stroop scores while performing FT never differed between real and sham sessions (i.e., the main effect of STIM and their interactions were non-significant, and Figure 5 shows both tSMS modes pooled).

However, in the two sessions, the Stroop score increased progressively across the FT, set after set ( $F_{2,36} = 14.8$ ,

$p < .001_{\text{SET}}$ ; Figure 5a). This significant change likely reflects learning. However, within sets, fatigue impacted the Stroop performance, and scores reduced in the 2nd repetition of self-selected FT ( $F_{1,18} = 6.8$ ,  $p = .019_{\text{REP}}$ ; Figure 5b). This suggests that fatigue developed during the first maximal FT repetition impacted cognitive performance during the second self-selected FT with Stroop.

Please see Supporting Results for some other significant effects on Stroop scores that were not essential for assessing our current hypothesis.

### 3.5 | Perceived levels of fatigue tested with VAS scores

At the end of each set (i.e., self-selected 1; maximal 1; self-selected 2; maximal 2 FT), we tested fatigue perception. Fatigue perception did not differ between the two sessions (real and sham tSMS over DLPFC), and the main effects of factor STIM and their interactions were not significant. In contrast, fatigue perception progressively increased set after set ( $p < .001_{\text{SET}}$ , Figure 5c), and changes differed between sets, with or without the Stroop test ( $p = .005_{\text{SET} \times \text{CC}}$ ). However, the magnitude of these differences was small, and post hoc comparisons were omitted for clarity in c.1 inset of Figure 5.

### 3.6 | Modulation of cortico-spinal and M1 cortico-cortical excitability by tSMS of DLPFC before and after the execution of the FT tasks

Responses of excitability followed a classic pattern of motor fatigue and did not differ with real and sham stimulation of the DLPFC (please see Supporting Results section).

## 4 | DISCUSSION

We studied the putative role of the left DLPFC in fatigue development during rhythmic repetitive movements and its effects on movement rhythmicity control in healthy right-handers. For this purpose, participants performed FT at maximal and self-selected rates, while their left DLPFC was stimulated with a static magnet (Arias et al., 2017; Carrasco-Lopez et al., 2017; Dileone et al., 2018; Gonzalez-Rosa et al., 2015; Kirimoto et al., 2018; Lozano-Soto et al., 2017; Oliviero et al., 2011; Paulus, 2011). Subjects were also engaged in a cognitive task dependent on left DLPFC activity (Huang et al., 2020) while performing some FT repetitions.

While performing maximal FT, movement frequency decreased over time as a clear sign of fatigue (Arias et al., 2012; Arias et al., 2015; Bachinger et al., 2019; Madinabeitia-Mancebo et al., 2020; Madrid et al., 2016; Madrid et al., 2018; Rodrigues et al., 2009; Teo et al., 2012b) (see Figure S1). Fatigue perception also increased over the course of the protocol.

However, the manner in which the FT changed along the 30 s repetitions differed when the left DLPFC was stimulated with real or sham magnets. Real magnet reduced the drop in frequency in the second repetition of maximal FT along the sets, compared with the sham session. Therefore, this suggests that the left DLPFC is a spot for fatigue development during unresisted repetitive movements. In addition, increasing cognitive demands (Stroop was performed just prior to maximal FT) reduced ROM amplitude during maximal FT, which is another sign of fatigue when maximal FT prolongs (Madinabeitia-Mancebo et al., 2020).

Stroop execution also altered other FT parameters, either in the presence or absence of fatigue. For instance, the self-selected FT rate was higher during “FT + Stroop” than during “FT alone,” and this was observed in the first (un-fatigued) FT self-selected repetition and in the second, when fatigue was present (Figure 3). This indicates a motor-cognitive interaction, which suggests that some of the cognitive resources involved in Stroop execution were also relevant for FT execution. It is important to note that the average self-selected FT rates (1.6 Hz. for no-Stroop and 2.3 Hz. for Stroop) were well above the Stroop rate of response (word production was always lower than 1 Hz), which rules out the possibility of syncope (i.e., rhythmic matching).

Some other tapping features, such as movement variability during self-selected FT, were further impacted when cognitive demands increased in the presence of “motor” fatigue. On the one hand, this suggests a fundamental role of prefrontal circuits in the execution of simple rhythmic movements (Anwar et al., 2016) without the need for reward (Ott & Nieder, 2019), which expands the well-recognized role of the left DLPFC in temporal sequencing of a goal-oriented behavior (Fuster, 2000, 2001; Miller, 2000; Miller & Cohen, 2001). On the other hand, our observation might be relevant at the clinical level when considering the treatment of fatigue; this reflects a complex scenario and the need for an integrative approach, including motor and cognitive domains.

Overall, both ways of interfering with the normal functioning of the left DLPFC during FT (stimulation with a potent magnet or engagement in a demanding cognitive task) support the notion that the prefrontal cortex (PFC) plays a main role in fatigue development during unresisted repetitive movements and in their rhythmicity

control. However, the mechanisms engaged in motor fatigue expressions (affecting rate, ROM amplitude, and variability of FT) might differ just because “magnet” and “Stroop” interventions likely operate by different routes. Perhaps for these reasons, magnet application affected fatigue expressed in avoiding reductions of maximal tapping rate, whereas increasing cognitive demands during self-selected FT impacted ROM amplitude during subsequent execution of maximal FT. In addition, increasing cognitive demands increased the variability of self-selected FT in the presence of fatigue and always increased self-selected FT rates (regardless of fatigue levels).

A detailed description of putative intrinsic mechanisms governing our observations is beyond the scope of this study. We have to consider the profuse interconnection within prefrontal areas and that no single behavior emerges from a single PFC spot (Fuster, 2002). tSMS was placed on F3 (10–20 EEG system) and was therefore located on the left DLPFC (B46). Despite this, the effects observed with the magnet application might engage structures beyond B46. As previously reported, focused interventions on the left DLPFC with noninvasive brain stimulation techniques also change the excitability of other prefrontal regions, such as the medial orbitofrontal cortex (Li et al., 2017), which is interesting in the context of fatigue because the orbitofrontal area appears involved in task failure during fatiguing trials (Hilty et al., 2011). Its engagement may be related to regulating selective attention during motor behavior with “help” from the cingulate cortex (Fuster, 2002). A recent meta-analysis (Huang et al., 2020) also showed that the Stroop task engages the cingulate cortex. For the above discussion, we cannot exclusively attribute our observation to left DLPFC changes but also to a broader prefrontal network.

Among the functions attributed to the PFC, we cannot say which is responsible for the fatigue observed during FT; however, it may be related to its top-down influence during simple finger control (Anwar et al., 2016). In line with this possibility, the DLPFC connects to subcortical networks contributing to temporal sequencing of motor patterns (Strafella et al., 2001), and some other studies have shown that fatigue in these movements impacts the rhythmic activation sequencing of flexor and extensor muscles. Such fine sequencing is essential for the production of fast rhythmic movements because muscles generating movements in opposite directions must not fight against each other to ease finger displacement (Bachinger et al., 2019; Rodrigues et al., 2009).

Suppose prefrontal circuits are key for this form of fatigue. In that case, it is less surprising that we did not detect differences between sham and real tSMS sessions for another “classic” neurophysiological mark of muscle fatigue after isometric muscle contractions: depression

of cortico-spinal excitability after task execution (Brasil-Neto et al., 1993; Brasil-Neto et al., 1994; Samii et al., 1997; Teo et al., 2012b). Excitability did not differ for real and sham tSMS sessions, despite the better performance in the real tSMS session (Figure S6, and Supporting Results & Methods).

Although FT fatigue was affected by interference with the left DLPFC, it is important to mention that the maximal tapping rates achieved throughout the protocol were not affected (Table 1). Therefore, the left DLPFC appears to have a greater role in sustaining maximal performance and not in increasing its peak values. In addition, differences in maximal frequencies of FT between real and sham tSMS focused on the second repetitions of FT but not on first repetitions. Our work cannot answer whether attentional deficits matter to explain this behavior. However, it is worth mentioning that attentional deficits affect the Stroop score (Lansbergen et al., 2007); thus, fatigue might have compromised attention in our work since Stroop scores reduced in the second self-selected repetitions (in the presence of fatigue) compared with the first (in the absence of fatigue) (Figure 5b).

The impact of the real tSMS on reducing maximal FT fatigue (it reduced the rate drop from the first to the second repetition, Figure 2a) became further evident in the last sets. The simplest explanation is the dose-dependent effect because in the last sets, when differences between real and sham tSMS were more evident, the left DLPFC had been subjected to magnet stimulation for a longer period.

Apart from fatigability at maximal FT, motor execution features at self-selected rates are relevant because they are a way of performing movements in daily activity and clinical subjects. First, Stroop execution while FT always increased tapping rates without affecting ROM (assuring no frequency/amplitude trade-off, i.e., reducing ROM permits faster rates, and to increase ROM, we have to reduce the rate). Thus, it appears that the use of executive resources to carry out Stroop altered the concurrent motor performance of self-selected FT. However, our study also showed that movement variability in the presence of fatigue was reduced in agreement with previous studies (Cortes et al., 2014; Helbostad et al., 2007; Kao et al., 2018; Morrison et al., 2016; Nagano et al., 2014) but only without Stroop execution. Conversely, in the presence of fatigue, variability increased when subjects' executive resources were engaged in Stroop. For this reason, we suggest that greater involvement of the left DLPFC is needed in the presence of fatigue, perhaps to ensure more stable rhythmicity during the movement. In this study, such stability in motor control could not be fully achieved because we engaged the left DLPFC in another demanding cognitive task.

Thus far, we have focused our discussion on cognitive-motor interactions in one direction (the study was designed for this purpose); however, we also observed that they were bidirectional: FT execution reduced Stroop scores (Figure S5), and they further decreased with fatigue (Figure 5b). Future studies must check whether similar interactions occur when walking since dysregulation of gait stability correlates with the risk of falls (Hausdorff, 2007; Hausdorff et al., 2007). We also recommend further exploration of motor/cognitive interactions during fatigue.

Finally, the perceived levels of fatigue increased set after set over the course of the protocol. This is a classic parameter for assessing fatigue, which is associated with motor output reduction (Barry & Enoka, 2007; Enoka et al., 2011; Enoka & Stuart, 1992; Gandevia, 2001). However, in our study, the increased levels of fatigue perceived set after set did not match any motor impairment expressed after each set. For instance, maximal FT rates increased with set progression, likely a learning process also reported previously (Madinabeitia-Mancebo et al., 2021). Therefore, we suggest that the relationship between distortions in motor execution and perceived levels of fatigue might depend on motor task features (Taylor & Gandevia, 2008).

#### 4.1 | Study limitation

Participants' cognitive-motor engagement in our protocol lasted several minutes, and their left DLPFC was stimulated for nearly an hour. Thus, the study design had to deal with the recognized issue of metaplasticity in the field of noninvasive brain stimulation techniques. Metaplasticity refers to a change in synaptic function due to previous activity of postsynaptic neurons or a neuronal network (Müller-Dahlhaus & Ziemann, 2015). Thus, inhibitory techniques, such as cathodal tDCS, produced facilitation if applied while subjects performed a motor task (Ataoglu et al., 2017).

For these reasons, we could not predict with certainty whether the effects of tSMS on fatigue would be positive or negative at study conception. Notwithstanding, this does not go against the possibility of using tSMS as a probe technique to test left DLPFC engagement in fatigue (compared to sham tSMS responses). We could have reduced the protocol duration to avoid some of the shortcomings of using tSMS; however, fatigue is time dependent and usually expresses better with longer protocols.

## 5 | CONCLUSIONS

We conclude that the left DLPFC is involved in fatigue development during rhythmic unresisted repetitive

movements performed at the maximal rate in righthanders. This structure could be an important node related to fatigue generation, whose activity is reflected in other cortical areas, such as M1 (Arias et al., 2015; Madinabeitia-Mancebo et al., 2021; Madrid et al., 2016; Madrid et al., 2018), through functional connections and top-down control (Anwar et al., 2016). Our results indicate a fundamental role of prefrontal networks in regulating basic motor movements and expanding their recognized implication in the temporal regulation of goal-oriented actions (Fuster, 2001). At the clinical level, this study reinforces the need for a comprehensive approach to fatigue; fatigue expressions during very simple motor tasks might emerge from “non-motor” structures.

#### AUTHOR CONTRIBUTIONS

**Aranza Vila-Villar:** Data curation; formal analysis; investigation; methodology; writing – review and editing. **Mariña Naya-Fernández:** Data curation; formal analysis; investigation; writing – review and editing. **Antonio Madrid:** Data curation; formal analysis; investigation; methodology; software; writing – review and editing. **Elena Madinabeitia-Mancebo:** Data curation; formal analysis; investigation; writing – review and editing. **Verónica Robles-García:** Data curation; investigation; writing – original draft. **Javier Cudeiro:** Conceptualization; data curation; investigation; writing – review and editing. **Pablo Arias:** Conceptualization; formal analysis; funding acquisition; investigation; methodology; project administration; writing – original draft.

#### ORCID

Elena Madinabeitia-Mancebo  <https://orcid.org/0000-0002-5720-6603>

Pablo Arias  <https://orcid.org/0000-0002-9029-5310>

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

### Appendix S1

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