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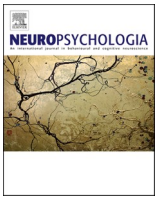

The acute effects of motor imagery and cervical transcutaneous electrical stimulation on manual dexterity and neural excitability

Antonio Capozio *, Ronaldo Ichiyama, Sarah L. Astill

School of Biomedical Sciences, University of Leeds, United Kingdom

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ABSTRACT

Transcutaneous electrical stimulation (TCES) of the spinal cord induces changes in spinal excitability. Motor imagery (MI) elicits plasticity in the motor cortex. It has been suggested that plasticity occurring in both cortical and spinal circuits might underlie the improvements in performance observed when training is combined with stimulation. We investigated the acute effects of cervical TCES and MI delivered in isolation or combined on corticospinal excitability, spinal excitability and manual performance. Participants (N = 17) completed three sessions during which they engaged in 20 min of: 1) MI, listening to an audio recording instructing to complete the purdue pegboard test (PPT) of manual performance; 2) TCES at the spinal level of C5–C6; 3) MI + TCES, listening to the MI script while receiving TCES. Before and after each condition, we measured corticospinal excitability via transcranial magnetic stimulation (TMS) at 100% and 120% motor threshold (MT), spinal excitability via single-pulse TCES and manual performance with the PPT. Manual performance was not improved by MI, TCES or MI + TCES. Corticospinal excitability assessed at 100% MT intensity increased in hand and forearm muscles after MI and MI + TCES, but not after just TCES. Conversely, corticospinal excitability assessed at 120% MT intensity was not affected by any of the conditions. The effects on spinal excitability depended on the recorded muscle: it increased after all conditions in biceps brachii (BB) and flexor carpi radialis (FCR); did not change after any conditions in the abductor pollicis brevis (APB); increased after TCES and MI + TCES, but not after just MI in the extensor carpi radialis (ECR). These findings suggest that MI and TCES increase the excitability of the central nervous system through different but complementary mechanisms, inducing changes in the excitability of spinal and cortical circuits. MI and TCES can be used in combination to modulate spinal/cortical excitability, an approach particularly relevant for people with limited residual dexterity who cannot engage in motor practice.

1. Introduction

The motor system demonstrates a remarkable capacity for adaption in response to experience and external stimuli (Hallett, 1999). This mechanism, which has been labelled as use-dependent plasticity, provides the neural substrates which motor learning and recovery of motor function are based upon (Mawase et al., 2017; Lynskey et al., 2008). In addition, neuromodulatory approaches making use of external stimulation to promote neural plasticity are based on the same mechanisms which are activated during movement and motor learning (Iddings et al., 2021). One recently developed technique that uses the principles of neuromodulation is transcutaneous electrical stimulation (TCES) (Gerasimenko et al., 2015). TCES is a non-invasive technique in which electrical stimulation can be applied to the spinal cord via adhesive electrodes placed directly on the skin at the spinal segment of interest (Gerasimenko et al., 2015). TCES has been successfully employed to improve clinical outcomes in a variety of patient groups such as people with spinal cord injury (Inanici et al., 2018), multiple sclerosis (Hofstoetter et al., 2021; Gad et al., 2021). For example, when combined with physical therapy, TCES applied at the cervical level of the spinal cord has been reported to improve grip strength and hand functions in people with a cervical spinal cord injury (SCI) (Inanici et al., 2018, 2021; Gad et al., 2018). These findings suggest that TCES is a promising non-invasive techniques for upper limb rehabilitation (Inanici et al., 2021).

Despite the increasing number of papers that used TCES to explore and improve movement outcomes across multiple clinical populations, relatively little is known about the neurophysiological mechanisms

* Corresponding author. Manton 6.87, School of Biomedical Sciences, University of Leeds, Leeds, LS2 9JT, United Kingdom.
E-mail address: a.capozio@leeds.ac.uk (A. Capozio).

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activated by spinal stimulation which might underlie the recovery of function (Milosevic et al., 2019). Computational modelling first indicated that TCES activates spinal networks via dorsal root afferents (Parazzini et al., 2014), and experimental findings later confirmed that stimulation activates spinal motoneurons transsynaptically through activation of Ia afferents (Milosevic et al., 2019). Regarding the effects of TCES once stimulation is turned off, Benavides and colleagues (Benavides et al., 2020) assessed changed in the excitability of cortical and subcortical motor circuits occurring before and after cervical TCES delivered continuously for 20 min in healthy and cervical SCI participants. Subcortical but not cortical potentials were found to be increased up to 74 min after the end of the stimulation in both groups, suggesting that TCES can elicit neural plasticity at the spinal but not cortical level (Benavides et al., 2020). It has been suggested that plasticity occurring in both cortical and spinal circuits might underlie the additional functional improvements observed when training is combined with TCES (Iddings et al., 2021). For example, spinal stimulation has been employed as a means to augment the beneficial effects of functional task training (Inanici et al., 2021). Functional task training induces plastic changes in corticospinal excitability as assessed by motor-evoked potentials (MEPs) evoked upon transcranial magnetic stimulation (TMS) (Beekhuizen and Field-Fote, 2008). Therefore, the pairing of a neuromodulatory technique affecting spinal excitability with another technique that predominantly targets cortical excitability could potentially bring about further changes in neural plasticity and additional improvements in performance (Iddings et al., 2021).

One such behavioural technique which has been used to support motor training in sport (Mizuguchi et al., 2012) as well as clinical settings (Mulder, 2007) is motor imagery (MI). MI can be defined as the mental process of internal rehearsal of a movement or a task without the overt production of the corresponding movement (Decety, 1996). In a typical MI study, clear instructions on what to imagine are listened by participants in the form of an imagery script which could be verbally recited or played on audio recordings (Bovend'Eerdt et al., 2012). MI can support recovery of grasp after stroke (Page et al., 2001) and cervical SCI (Mateo et al., 2015) and is also effective in improving behavioural outcome in participants who completely lack motor functions below the level of the lesion (Cramer et al., 2007). With respect to the neural mechanisms mediating the effects of MI, research suggests that the timing and extent of cortical activation elicited during MI are similar to the ones observed during task execution (Grezes and Decety, 2001). During MI, descending corticospinal volleys modulate the excitability of spinal motoneurons without their direct activation (Grosprêtre et al., 2016). However, intracortical and neuroimaging data demonstrate that movement production activates more cortical areas and to a greater extent than MI (Amador and Fried, 2004; Lacourse et al., 2004), a difference which might depend on the lack of sensory feedback during MI (Ruffino et al., 2017). The effects of MI on the excitability of the motor cortex seem to depend on the properties of the imagined movement (Stinear et al., 2006). Two main kind of strategies can be employed when designing MI scripts: visual MI, in which the participants see themselves performing movements from a third person perspective; kinaesthetic MI in which participants imagine themselves performing the movements from a first person perspective and also imagine the sensory consequences of the movements (Mulder, 2007). While brain stimulation studies revealed that kinaesthetic MI induces both short and long-term plasticity in the motor cortex (Stinear et al., 2006; Pascual--Leone et al., 1995), to our knowledge no study to date has investigated the effects of combining motor imagery with non-invasive spinal stimulation on skilled behaviour and corticospinal/spinal excitability.

Given the above, the aims of this study were as follows: (1) compare the effects of a single session of MI, TCES and MI + TCES on manual performance; (2) compare the effects of a single session of MI, TCES and MI + TCES on corticospinal excitability; (3) compare the effects of a single session of MI, TCES and MI + TCES on spinal excitability. Manual performance was measured using the Purdue Pegboard Test (PPT) of manual dexterity. Corticospinal and spinal excitability were assessed, respectively, by comparing MEPs and spinal responses recorded from arm muscles before and after the three conditions.

2. Material and methods

2.1. Participants

Eighteen healthy participants (M ± SD = 23.8 ± 3.20; females = 7) with no known history of neurological disorders volunteered for the study. Participants were included in the study if right-handed, as assessed by the Edinburgh Handedness Questionnaire (M ± SD) = 78.8 ± 28.80, scores between 50 and 100 indicate right-handedness) (Oldfield, 1971). The total sample size was chosen according to an a priori power analysis calculated using the R package pwrss. The expected effect size was based on effect size estimates (partial eta squared) derived from data given in Ruffino et al. (2019) (Group*Muscle interaction, $\eta p^2 = 0.11$) of the acute effects of motor imagery on corticospinal excitability. The sample size calculation was determined using the following parameters: $\eta p^2 = 0.11$; number of groups = 3; $\alpha = 0.05$; 1- $\beta = 0.8$; rm. corr = 0.6. The total number of participants required was estimated to be 54 (18 per group). Due to circumstances unrelated to the testing protocol, one person completed only the first session. Seventeen participants completed three experimental sessions scheduled at the same time of the day to control for potential influences of circadian rhythms and separated by at least 7 days to avoid the influence of carry-over effects of stimulating the brain (Sale et al., 2007; Nitsche et al., 2008). The order of allocation to conditions was pseudo-randomised and counterbalanced across participants. Motor performance improvements after MI are influenced by the individuals' ability to form vivid mental images (Ruffino et al., 2017). Therefore, at the beginning of the first session, participants completed the Vividness of Movement Imagery Questionnaire-2 (VMIQ-2) (Roberts et al., 2008), which assess the vividness with which participants are able to imagine movements from the first-person (Internal visual imagery) and third-person (External) perspective. In addition, participants are asked to rate how well they can imagine the sensations associated with a movements (Kinaesthetic imagery) (Roberts et al., 2008). Each of the twelve movements is scored on a five-point scale (1 = perfectly clear and vivid as normal vision to 5 = no image at all). VMIQ scores showed that all participants had at least "clear and reasonably vivid" (score 2 out of 5) MI ability in all subscales (internal, 1.87 ± 0.63; external, 2.36 ± 0.90; kinaesthetic, 2.00 ± 0.70) on the first session. All participants gave written informed consent to experimental procedures approved by the Faculty of Biological Sciences Ethical Review Committee (BIOSCI 20-020) at the University of Leeds and conformed to the Declaration of Helsinki.

2.2. Electromyography (EMG) measures

Surface EMG activity was recorded from the following muscles and positions on the right arm: abductor pollicis brevis (APB), electrode at the midpoint between the first metacarpophalangeal joint and carpometacarpal joint (Perotto, 2011); flexor carpi radialis (FCR), electrode at one-third of the distance from the medial epicondyle to radial styloid (Christie et al., 2005); extensor carpi radialis longus (ECRL), electrode at one-sixth of the distance from the lateral epicondyle to radial styloid (Riek et al., 2000); biceps brachii (BB), electrode at one-third of the distance from cubital fossa to medial acromion (Madeleine and Arendt-Nielsen, 2005). EMG were recorded using parallel-bar wireless sensors (3.7 × 2.6 cm) (Trigno, Delsys Inc., Natick, MA, USA) for BB, FCR and BB and a parallel-bar wireless mini sensor (Trigno, Delsys Inc., Natick, MA, USA) for APB. Raw EMG recordings were pre-105 amplified (gain = 909) with a 20–450 Hz bandwidth and digitized at 2 kHz using data 106 acquisition software (Spike2, Cambridge electronics Design, Cambridge, UK).

2.3. TMS

Magnetic stimulation was applied to the left primary motor area (M1) by means of a Magstim Rapid stimulator and a flat alpha coil (D70 Alpha Flat Coil, Magstim Company, Whitland, Dyfed, UK) being held by a support stand (Magstim AFC Support Stand, Magstim Company, Whitland, Dyfed, UK), at a rate of 0.2 Hz. Participants wore sound-attenuating headphones while receiving stimulation in order to reduce the confounding effects of sound on the excitability of the corticospinal tract (Capozio et al., 2021a). The coil was oriented at ~45°, inducing a posterior-to-anterior current flow perpendicular to the central sulcus (Janssen et al., 2015). The optimal coil position to evoke MEPs in APB was found by moving the coil over the scalp while delivering stimulation and marking the position at which MEPs could be elicited at the lowest stimulation intensity. The position was marked with a non-permanent marker to ensure consistency of recordings over the session. The position and orientation of the coil was monitored continuously, and if necessary, adjusted to align with the scalp markings (Capozio et al., 2021b). During all the interventions, the stimulation was controlled through Spike2 (Cambridge Electronic Design, Cambridge, UK) software. Resting motor threshold (MT) was defined as the smallest intensity of stimulation (in % of maximal stimulator output, MSO) necessary to elicit peak-to-peak MEP amplitudes between 50 and 100 μV in at least 5 out of 10 trials in the APB muscle plus 1, following the relative frequency method (Rossini et al., 1994). Once the MT was estimated, ten MEPs were recorded and averaged at the MT intensity for each time, participant, and session. Given that stimulation at the optimal site to induce MEPs in the APB also elicit activity in the FCR muscle (Triggs et al., 1999), we simultaneously measured MEPs in both muscles. In addition, to measure the effects of TMS when delivered at higher stimulation intensities, ten MEPs were recorded and averaged at 120% MT intensity for each time, participant and session (Cavaleri et al., 2017).

2.4. Single-pulse TCES

TCES was delivered by means of a 5-channels constant-current spinal stimulator (BioStim-5, Cosyma, Moscow, Russia). Stimulation was delivered through two self-adhesive electrodes (Axelgaard, ValuTrode Cloth): a 5 × 9 cm electrode placed over the left iliac crest as anode; a 3.2 cm round electrode placed at the midline between C5 and C6 spinous processes as cathode (Benavides et al., 2020). In order to elicit spinal responses, TCES pulses were delivered using 1ms biphasic square-wave pulses delivered every 5 s (Hofstoetter et al., 2021). Spinal responses were recorded simultaneously from the right APB, FCR, ECR and BB muscles. The stimulation amplitude was determined for each participant by increasing the current until spinal responses of amplitudes >50 μV could be observed in each of the four muscles (Wecht et al., 2021). The stimulation intensity was then increased twice by 10% of the threshold value (110%, 120% of threshold) to characterise the recruitment curve of muscles at higher stimulation intensities (Wecht et al., 2021). Upon every increase of intensity, participants were asked to rate their perceived pain level from 0 to 10 using a visual analogue scale for pain, with 0 defined as "no discomfort at all" and 10 as "unbearable pain". Stimulation was halted immediately if discomfort reached level 8 out of 10.

Five responses were recorded at each intensity of stimulation (Benavides et al., 2020).

2.5. Purdue pegboard test (PPT)

Manual performance was measured with the Purdue pegboard test (PPT) (Tiffin and Asher, 1948). The test is composed of a board with two parallel rows, one on the left and one on the right, of 25 holes. Cylindrical metallic pegs are located in a container at the top of the board. Participants are instructed to pick up the pegs with their right hand, one by one, and place them in the holes on the right side of the board (Desrosiers et al., 1995). The experimenter demonstrated the movement and then allowed participants to practice the trial three times (Desrosiers et al., 1995), following the three-trials administration method commonly employed to assess manual dexterity in clinical populations (Radomski and Latham, 2008). The number of pegs correctly placed in the holes within 30 s was taken as measure of manual performance. The experimenter informed participants on when to start and stop the task using a stopwatch.

2.6. Experimental design

Each experimental session was divided in three phases: Baseline (approx. 40 min), during which TMS, single-pulse TCES and the PPT test were administered according to the methods described above; Condition (20 min), in which one of the following three experimental conditions was completed; Post (approx. 40 min), to assess changes in TMS, single-pulse TCES and the PPT test measures (Fig. 1, *A*). Since some of the outcome measures employed in this study can potentially alter the measurement of the other parameters collected at a later point, inducing an order effect (Kumru et al., 2021a), the order of measures was pseudo-randomised across time, participants and sessions.

2.6.1. MI

Participants listened to a pre-recorded MI script delivered through wireless headphones (HD 4.4O BT, Sennheiser, Germany) (Fig. 1, *B*). Participants listened to a native English speaker instructing them to close their eyes and to imagine themselves completing the PPT test from the first-person perspective (internal MI) (Callow et al., 2013). Instructions included: "take your right arm, straightening your elbow, towards the container at the top of the pegboard"; "open your fingers and thumb as the hand approaches the container"; "then grasp the peg gently between your finger and thumb". Additionally, the script incorporated kinaesthetic elements such as "feel the edge of the pegboard" and "feel the pressure on the peg". Kinaesthetic MI includes imagining the sensations associated with a specific task and has been proved to modulate the excitability of the motor cortex (Stinear et al., 2006). The total duration of MI practice was set at 20 min, since a meta-analysis showed that after 20 min of practice the effects of MI on performance become less beneficial (Driskell et al., 1994). MI was delivered in a distributed fashion by interleaving the imagery trials with rest periods of equal length since distributed practice (the amount of rest between trials is equal of greater than the amount of training) has greater effects on motor performance compared to massed practice (the amount of rest between trials is less than the amount of practice) (Bovend'Eerdt et al., 2012). Thus the MI script lasted for 2 min and was followed by 2 min of rest (Bovend'Eerdt et al., 2012) both repeated 5 times for a total length of 20 min.

2.6.2. TCES

For continuous TCES, the cathode electrode was located at the midline between C5 and C6 spinous processes (Fig. 1, *B*). Stimulation was delivered using biphasic blocks of pulses at a frequency of 30 Hz. Each block contained 5 pulses of 200 μs length (modulating frequency of 5 kHz) (Benavides et al., 2020). Continuous TCES lasted for 2 min and was followed by 2 min of rest, both repeated 5 times for a total length of 20 min. The stimulus intensity was individually chosen based on the threshold values calculated during the baseline phase. On the first stimulation cycle, intensity started at 20 mA and was ramped up in steps of 3 mA until reaching 90% of the threshold value (Kumru et al., 2021b). Participants were asked again to rate their perceived pain level from 0 – to 10 using the visual analogue scale.

2.6.3. MI + TCES

Participants listened to the pre-recorded MI script delivered through wireless headphones (HD 4.4O BT, Sennheiser, Germany) while

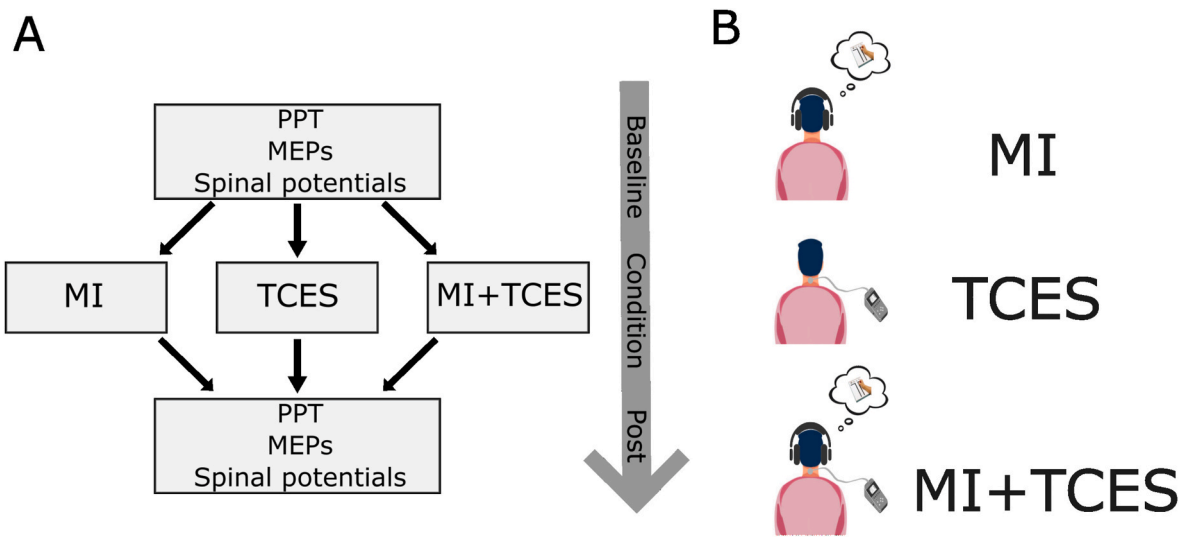

Fig. 1. Experimental design. (*A*) Time course of the experimental sessions and (*B*) graphical depiction of the three experimental conditions.

simultaneously receiving stimulation at the midline between C5 and C6 spinous processes according to the above described protocol (Fig. 1, *B*). Therefore, this condition was identical to MI apart from the introduction of TCES while participant listened to the MI script.

2.7. Data analyses

The number of pegs correctly placed within 30 s on each session/phase (PPT score) was used as a measure of manual performance. A linear mixed-effects model fit by maximum likelihood was run (SPSS software; Version 26.0) with an a priori significance level of 0.05. Participant was included as a random factor, with Condition (MI, TCES, MI + TCES) and Time (Pre, Post) included as fixed factors. The Levene's test showed no violation of the assumption of homoscedasticity (Condition $p = 0.219$, Time, $p = 0.606$).

We calculated the peak-to-peak amplitude for each MEP and averaged the 10 MEPs recorded at MT and 120% MT. Given that TMS amplitude data often reveal skewed distributions and deviations from normality (Nielsen, 1996), logarithmic transformations were carried out on the MT and 120% MT data. Given that the assumption of homoscedasticity across different intensities ($p < 0.001$), and muscles ($p = 0.006$) was violated we ran separate linear mixed-effects models fit by maximum likelihood (SPSS software; Version 26.0) for the MT and 120% MT data, both with an a priori significance level of 0.05. Participant was included as a random factor, with Condition (MI, TCES, MI + TCES) Time (Pre, Post) and Muscle (FCR, APB) included as fixed factors. For the MT data, three outliers (1.4% of the 204 data points) were removed to meet the assumption of homogeneity of variance assessed via Levene's test (Condition $p = 0.796$, Time, $p = 0.056$, Muscle, $p = 0.718$). For the 120% MT data, the Levene's test showed no violation of the assumption of homoscedasticity (Condition $p = 0.248$, Time, $p = 0.874$, Muscle, $p = 0.407$).

For the TCES data, we calculated the peak-to-peak amplitude for each spinal response and averaged the 5 spinal responses recorded at each intensity. A logarithmic transformation was carried out to reduce right skewness (skewness = 2.297). Given that the assumption of homoscedasticity across different muscles was violated ($p < 0.001$), we ran separate linear mixed-effects models for each of the four muscles (APB, FCR, ECR, BB). All GLM analyses included Participant as a random factor and Condition (MI, TCES, MI + TCES) Time (Pre, Post) and Intensity (100%, 110%, 120%) as fixed factors. The Levene's test showed no violation of the assumption of homoscedasticity for APB (Time, $p = 0.725$; Condition, $p = 0.210$; Intensity, $p = 0.753$), FCR (Time, $p = 0.647$; Condition, $p = 0.379$; Intensity $p = 0.966$) and ECR (Time, $p = 0.797$; Condition, $p = 0.702$; Intensity $p = 0.945$). For BB, the Levene's test showed no violation of the assumption of homoscedasticity for Time ($p = 0.354$) and Intensity ($p = 0.918$), but the assumption was violated for Condition ($p = 0.001$). Nevertheless, since linear mixed-effects models were shown to be robust to violation of homoscedasticity (Schielzeth et al., 2020), we run a GLM analysis on TCES data collected from this muscle including Participant as a random factor and Condition (MI, TCES, MI + TCES) Time (Pre, Post) and Intensity (100%, 110%, 120%) as fixed factors. The distributions of residuals were plotted to check for any violation of the assumption of normality.

3. Results

3.1. Manual performance

The linear mixed-effects analysis revealed that the interaction between Condition and Time on the PPT scores was not significant [$F(2, 48) = 0.375$, $p = 0.689$, $\eta^2 = 0.02$]. Similarly, the factors Condition [$F(2, 48) = 0.049$, $p = 0.952$, $\eta^2 = 0.001$] and Time [$F(1, 48) = 0.347$, $p = 0.559$, $\eta^2 = 0.001$] did not significantly affect PPT scores (Fig. 2). The

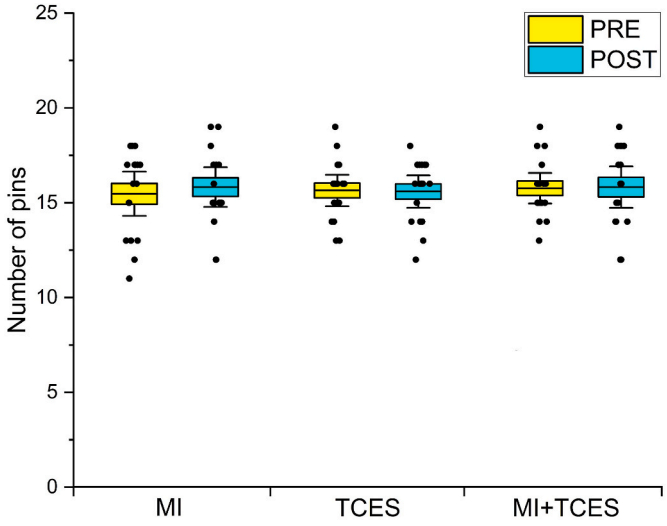

Fig. 2. Behavioural results. Mean number of pins correctly placed during the PPT test across time and conditions. Boxes represent the associated standard error (SE) and whiskers represent the associated 95% confidence interval.

plotted distribution of residuals did not show substantial variations from normality.

3.2. Corticospinal excitability

Mean and SD of the MT values across all participants were 67 ± 6% MSO. The linear mixed-effects analysis run on the MEPs at MT intensity revealed a significant interaction between Condition and Time [F (2, 93) = 4.406, $p = 0.015$, $\eta^2 = 0.09$]. Pairwise comparisons showed a significant effect of Time on MEPs for MI [F (1, 93) = 8.046, $p = 0.006$, $\eta^2 = 0.08$] and MI + TCES [F (1, 93) = 4.869, p = 0.030, $\eta^2 = 0.05$], but not TCES [F (1, 93) = 1.151, $p = 0.286$, $\eta^2 = 0.01$] conditions (Fig. 3, *A*). The effect of Muscle was significant [F (1, 95) = 40.209, $p < 0.001$, $\eta^2 = 0.46$], which shows that MEPs recorded from APB were significantly higher (MI: Pre = 0.08 ± 0.03, Post = 0.15 ± 0.09; TCES: Pre = 0.09 ± 0.04, Post = 0.09 ± 0.05; MI + TCES: Pre = 0.08 ± 0.04, Post = 0.16 ± 0.11) than the ones recorded from FCR (MI: Pre = 0.05 ± 0.04, Post = 0.07 ± 0.06; TCES: Pre = 0.04 ± 0.02, Post = 0.03 ± 0.02; MI + TCES: Pre = 0.04 ± 0.02, Post = 0.05 ± 0.04). All the other interactions and main effects are reported in Table 1. The plotted distribution of residuals did not show substantial variations from normality. Data recorded from

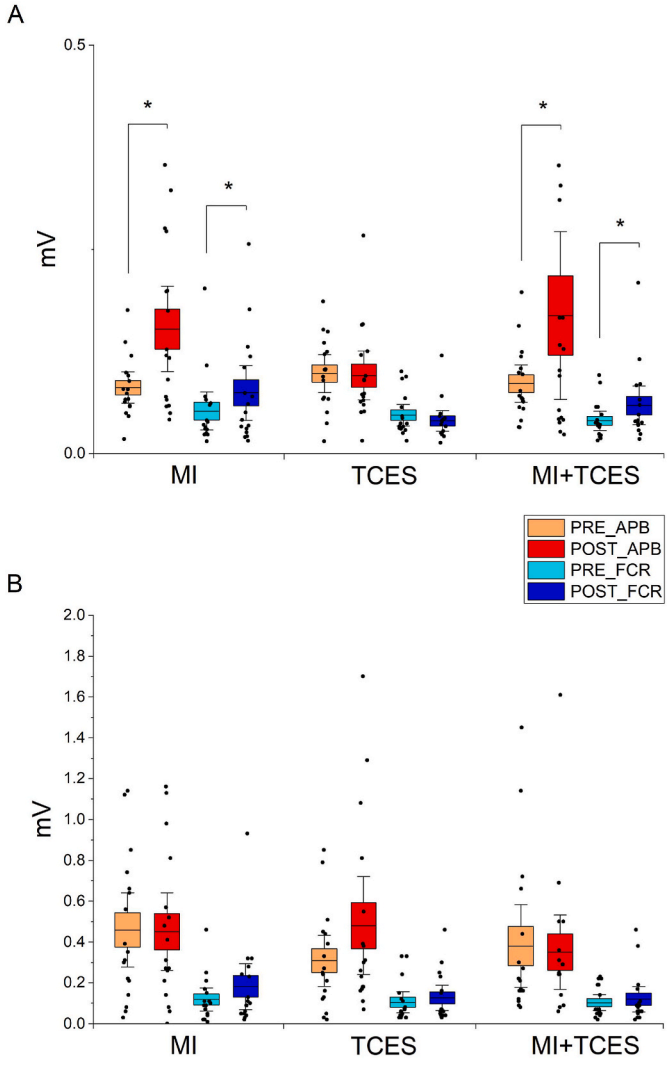

Fig. 3. Brain stimulation results. Mean amplitude values of the MEPs recorded from APB and FCR muscles at MT intensity *(A)* and 120% MT intensity *(B)* across time and conditions. Boxes represent the associated standard error (SE) and whiskers represent the associated 95% confidence interval. Asterisks denote a statistically significant ($p < 0.05$) effect.

Table 1
Fixed-effects table for the linear mixed model run on the MEPs collected at MT intensity.

Parameter	Numerator df	Demominator df	*F*	Sig.	$\eta 2$
Time	1	93	5.255	0.024	0.05
Condition	2	95	1.077	0.345	0.02
Muscle	1	95	40.209	<0.001	0.46
Time*Condition	2	93	4.406	0.015	0.09
Time*Muscle	1	93	0.616	0.434	0.01
Muscle*Condition	2	95	0.180	0.836	0.001
Time*Condition* Muscle	2	93	0.984	0.378	0.02

the other muscles (BB, ECR) were not included in the analysis because stimulating the APB hotspot did not induce activity in these muscles.

The linear mixed-effects analysis run on the MEPs at 120% MT intensity revealed no significant interaction between Condition and Time [F (2, 96) = 1.625, $p = 0.202$, $\eta^2 = 0.03$]. Similarly, no significant effect of Time [F (1, 96) = 3.227, $p < 0.076$, $\eta^2 = 0.03$] or Condition [F (1, 96) = 0.383, $p < 0.683$, $\eta^2 = 0.01$] were observed (Fig. 3, *B*). The main effect of Muscle was significant [F (1, 96) = 43.319, $p < 0.001$, $\eta^2 = 0.31$]. All the other interactions and main effects are reported in Table 2. The plotted distribution of residuals did not show substantial variations from normality.

3.3. Spinal excitability

Mean and SD of the threshold intensity for TCES across all participants were 87 ± 18 mA. TCES data were analysed separately for each muscle. For the APB, the interaction between Condition and Time was non-significant [F (2, 144) = 0.387, $p = 0.680$, $\eta^2 = 0.01$]. The main effect of Time [F (1, 144) = 2.403, $p = 0.123$, $\eta^2 = 0.02$], Condition [F (2, 144) = 0.092, $p = 0.912$, $\eta^2 = 0.001$] and Intensity [F (2, 144) = 0.739, $p = 0.479$, $\eta^2 = 0.01$] were non-significant (Fig. 4, *A*. Data points were collapsed across all three stimulation intensities to help data visualisation). For FCR, the interaction between Condition and Time was non-significant [F (2, 144) = 2.103, $p = 0.126$ $\eta^2 = 0.03$]. The main effect of Time was significant [F (1, 144) = 7.711, $p = 0.006$, $\eta^2 = 0.05$] (Fig. 4, *B*). The main effect of Condition [F (1, 144) = 0.561, $p = 0.572$, $\eta^2 = 0.001$] and Intensity [F (2, 144) = 0.330, $p = 0.719$, $\eta^2 = 0.001$] were not significant. For ECR, the interaction between Condition and Time was significant [F (2, 141) = 3.993, $p = 0.021$, $\eta^2 = 0.05$]. Pairwise comparisons showed that spinal responses increased from Pre to Post for the MI + TCES [F (1, 141) = 5.853, $p = 0.017$, $\eta^2 = 0.04$] and TCES [F (1, 141) = 6.341, $p = 0.013$, $\eta^2 = 0.04$] conditions but not for MI [F (1, 141) = 0.943, $p = 0.333$, $\eta^2 = 0.01$] (Fig. 4, *C*). The main effect of Intensity was not significant [F (2, 144) = 0.417, $p = 0.660$, $\eta^2 = 0.01$]. Finally, for BBthe interaction between Condition and Time was non-significant [F (2, 143) = 0.463, $p = 0.648$, $\eta^2 = 0.01$]. The main effect of Time was significant [F (1, 143) = 7.926, $p = 0.006$, $\eta^2 = 0.10$] while the effects of Condition [F (2, 144) = 0.090, $p = 0.914$, $\eta^2 = 0.001$] and Intensity [F (2, 144) = 0.436, $p = 0.648$, $\eta^2 = 0.01$] were non-significant

Table 2
Fixed-effects table for the linear mixed model run on the MEPs collected at 120% MT intensity.

Parameter	Numerator df	Demominator df	*F*	Sig.	$\eta 2$
Time	1	96	3.227	0.076	0.03
Condition	2	96	0.383	0.683	0.01
Muscle	1	96	43.319	<0.001	0.31
Time*Condition	2	96	1.625	0.202	0.03
Time*Muscle	1	96	0.443	0.507	0.001
Muscle*Condition	2	96	0.020	0.980	0.001
Time*Condition* Muscle	2	96	1.784	0.173	0.04

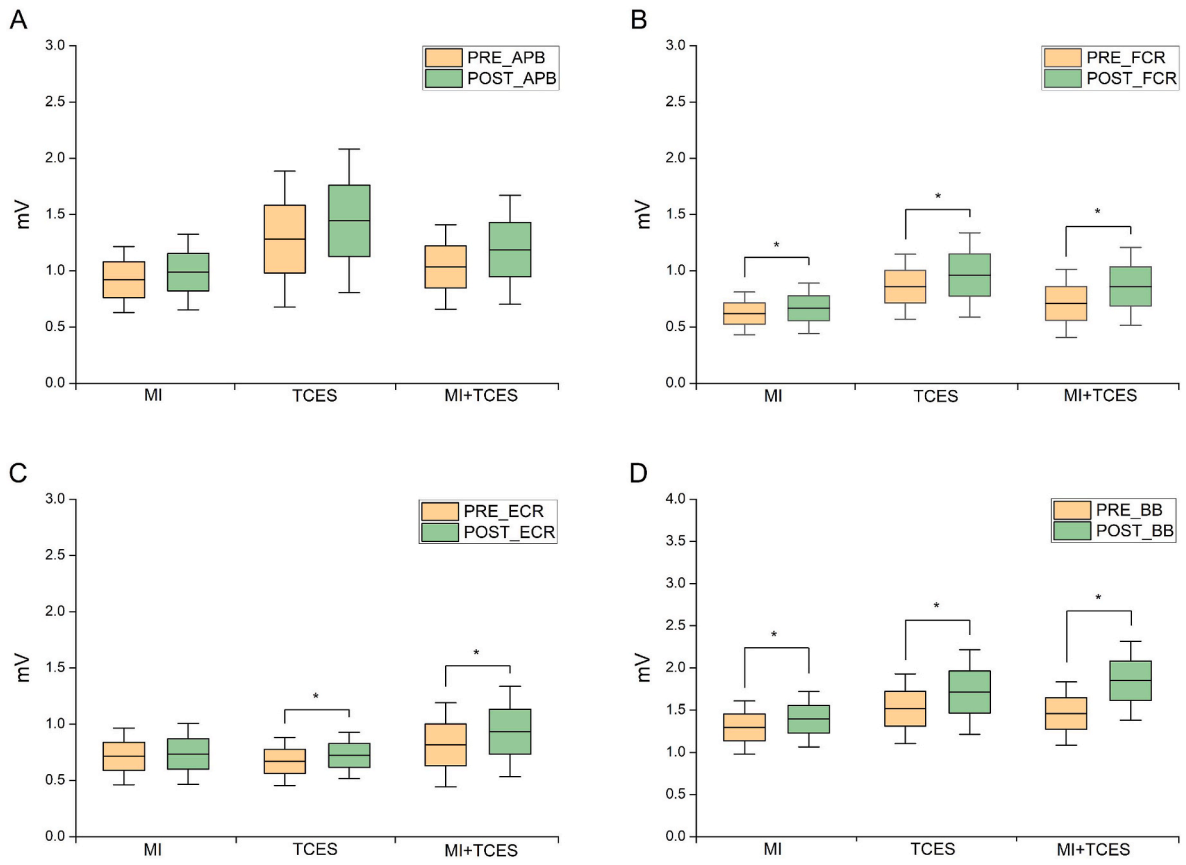

Fig. 4. Spinal stimulation results. Mean amplitude values of the spinal responses recorded at all three intensities from APB (*A*), FCR (*B*), ECR (*C*) and BB (*D*) muscles across time and conditions. Boxes represent the associated standard error (SE) and whiskers represent the associated 95% confidence interval. Asterisks denote a statistically significant ($p < 0.05$) effect.

(Fig. 4, *D*). Data collected at each stimulation intensities and individual data points can be found in the Supplementary material (Fig. S1) together with examples MEPs (Fig. S2) and spinal-evoked potentials (Fig. S3) traces from a representative participant.

4. Discussion

The aim of this study was to investigate the acute (e.g. within-session) effects of TCES and MI delivered alone and in combination with MI on: (1) Manual performance, (2) corticospinal excitability and (3) spinal excitability were measured before and after 20-min of TCES, MI or MI + TCES. We did not observe any changes in manual performance after any of the three conditions. Regarding corticospinal excitability, MEPs collected from FCR and APB muscles increased after the MI and MI + TCES conditions, but not after the TCES conditions. The effects of each condition on spinal excitability differed according to the muscle from which spinal-evoked potentials were recorded: no effects were observed for the APB muscle after any of the condition; increased excitability was observed after all conditions in the FCR muscle; increased excitability was observed after TCES an MI + TCES conditions in the ECR muscle; increased excitability was observed after TCES conditions in the BB muscle (Fig. 4).

4.1. Effects on manual performance

This study is the first to investigate the acute effects of TCES and MI on PPT scores. Our findings show that manual performance did not significantly improve after any of the conditions employed, suggesting that single sessions of cervical TCES and MI are not sufficient to improve PPT scores. Contrarily, multiple studies have reported within-session improvements in PPT performance after delivery of transcranial direct current stimulation (tDCS) (Kidgell et al., 2013; Karok et al., 2017)). There are, however, important discrepancies between methods used to quantify performance in these studies and the one we employed. Kidgell and colleagues (Kidgell et al., 2013) measured the average time taken to complete one side of the board (25 pegs) over three trials. Karok and colleagues averaged scores across two 30-s trials, with the possibility to practice with 5 pins (Karok et al., 2017). Conversely, in the current study, participants were allowed 3 trials of practice before completing the test trial and only performance in the latter was included in the analysis to control for the effects of task familiarisation (Tiffin and Asher, 1948). We chose to include practice trials because effects of practice on the PPT scores showed that performance increases from the first to the fourth and fifth practice trials even in the absence of any experimental manipulation (Noguchi et al., 2006). Our findings suggest that PPT scores measured from a single trial after practice might not be sensitive enough to detect acute changes in manual dexterity in healthy individuals (Bastani and Jaberzadeh, 2014).

4.2. Effects on corticospinal excitability

The three experimental conditions affected the excitability of the motor cortex, assessed via MEPs recorded upon brain stimulation from APB and FCR muscles, in different ways. MI significantly increased corticospinal excitability in both the APB and FCR muscles. This finding is in line with the exhaustive evidence that shows that a single session of MI induces plasticity in the cortical representations of hand and upper arm muscles (Pascual-Leone et al., 1995; Leung et al., 2013; Volz et al., 2015). To note, demonstrating that an experimental manipulation affects the amplitude of TMS-induced MEPs does not necessarily imply a

change in cortical excitability, since MEP amplitudes depend on both the strength of the descending volley and the excitability of the spinal motor neuron pool (Burke and Pierrot-Deseilligny, 2010). Nevertheless, together with the finding that MI did not affect TCES amplitudes recorded from APB and therefore spinal excitability, we conclude that MI exerted its effect by modulating the cortical drive to spinal motoneurons.

Cortical excitability was not significantly affected by 20 min of cervical TCES delivered in a distributed fashion (10 min of stimulation and 10 min of rest). Similar lack of cortical effects were reported by Sasaki and colleagues (Sasaki et al., 2021), who delivered electrical stimulation between C7 and T1 spinal processed for 10 min, and Kumru and colleagues (Kumru et al., 2021a), who stimulated two cervical sites (C3–C4 and C6–C7) for 20 s followed by 80-s rests for a total time of 30 min (6 min of stimulation). Importantly, the lack of changes in TMS-induced responses does not necessarily imply that the stimulation has no effect on cortical circuits. Multiple pathways such as intracortical connections to pyramidal neurons or circuits mediating presynaptic inhibition of Ia afferents modulate movement and cannot be evaluated via TMS-evoked MEPs (Burke and Pierrot-Deseilligny, 2010). Nevertheless, our results may suggest that TCES alone does not affect the pyramidal drive to motoneurons.

Experimental evidence suggests that higher intensities of stimulation recruit different neural populations and with different temporal patterns compared to stimulation at threshold intensity (Lazzaro et al., 1998). For example, while threshold stimulation activates the monosynaptic component of the corticospinal tract, higher intensities induce additional descending volleys thought to originate from intracortical circuits (Di Lazzaro et al., 2012). Thus, to further characterise the effect of TCES on corticospinal excitability we explored the use of higher stimulation intensities with MEPs also being collected at the suprathreshold intensity of 120% MT (Kumru et al., 2021a). Our data supports that of Kumru and colleagues (Kumru et al., 2021a) in that TCES did not modulate the amplitudes of MEPs recorded at 120% MT, suggesting that TCES does not modulate the excitability of intracortical circuits.

This is the first study investigating corticospinal excitability after combining MI and TCES. Our data show that combining MI and TCES for 20 min significantly increased MEP amplitudes in both the APB and FCR muscles. When cervical transcutaneous stimulation was paired with hand training to assess acute changes in neural excitability (Kumru et al., 2021a), the authors observed increased recruitment curve amplitudes recorded from APB upon cortical stimulation after combined TCES and hand training, but not after stimulation nor hand training alone. The different effects of hand training and MI on MEPs amplitudes within the present study can be explained by differences in the nature of the task employed. Indeed, sustained muscle contractions such as the ones employed during strength training might lead to a transient decrease in corticospinal excitability (Pitcher and Miles, 2002). To note, the only difference between the MI and MI + TCES conditions was the addition of spinal stimulation while participants listened to the MI script.

In the present study, the magnitude of the MEPs increase after MI + TCES was similar to the one observed after MI, which suggest that the effects of the combinatorial strategy on cortical excitability are dependent on the modulation brought upon by MI rather than on an additive effect of the two modalities (Saito et al., 2013).

4.3. Effects on spinal excitability

No significant differences in the amplitude of spinal responses evoked from cervical stimulation were observed after 20 min of MI in APB, ECR and BB. However, a facilitating effect on spinal excitability was observed in the FCR. The FCR muscle is involved in flexion and radial deviation of the wrist and is strongly activated during PPT task completion (Carroll et al., 2005; Matsuura et al., 2017). Since the MI script instructed participants to imagine completing the PPT test, it is possible that the MI condition was more effective in modulating excitability of this muscle. Nevertheless, spinal excitability did not change in a muscle heavily involved in precision grip such as the APB (Cooney et al., 1985). This difference might depend on the spinal stimulation site (C5–C6) employed and the different innervation of the two muscles (C6–C7 for the FCR, C8-T1 for the APB (Harvey, 2008)). The majority of studies investigating spinal effects during MI employed as outcome measure the Hoffmann's reflex (H-reflex) evoked from posterior tibial nerve stimulation in the soleus muscle (Oishi et al., 1994; Hale et al., 2003). The only study we are aware of employing the technique of TCES to evoke spinal responses during MI (Nakagawa et al., 2018) reported spinal facilitation in lower muscles during motor imagery of upper and lower limb movements. Importantly, none of the aforementioned studies assessed the after effects (e.g. after stimulation is turned off) of MI on spinal excitability. While spinal responses were not recorded during MI administration in the present study, our findings indicate that the after-effects of MI on upper limb spinal excitability differ across muscles.

In the present study, the effects of TCES differed according to the specific muscle. First, we confirmed the finding (Sasaki et al., 2021) that spinal responses evoked from APB did not change after stimulation. This findings partially contradicts the effects observed in the first dorsal interosseous (FDI) muscle by Benavides et al. (2020). This discrepancy can be explained by the different methods employed to measure spinal stimulation between the two studies: first, Benavides et al. (2020) recorded responses from electrical stimulation at the cervicomedullary junction; second, the authors tested responses in APB separately from the other muscles by optimising stimulation parameters to this muscle rather than recording from all muscles simultaneously as done in the present study. Nevertheless, TCES alone increased the amplitude of responses evoked from FCR, ECR and BB muscles. These findings and those of similar studies employing delivery of sub-threshold TCES (Kumru et al., 2021a; Hofstoetter et al., 2014) argues against the notion that higher intensities are necessary to induce a neuromodulating effect. Additionally, we demonstrated that 10 min of spinal stimulation delivered in a distributed fashion interwoven with period of rests are sufficient to alter spinal excitability.

The present study is the first to assess the effects of MI delivered in combination with TCES on spinal excitability. We observed increases in spinal excitability measured via single-pulse TCES in FCR and ECR after 20 min of MI + TCES. This suggests that the additional effects on spinal excitability observed in the MI + TCES condition (e.g. increases in ECR and BB excitability) compared to the MI condition can be attributable to TCES. In contrast, Kumru and colleagues did not report changes in spinal responses evoked from TCES at the cervical level (C3–C4 and C6–C7) in multiple muscles (Kumru et al., 2021a) after a single session of cervical TCES paired with hand strength training. The authors acknowledged that the strength training protocol used, involving maximal hand grip contractions for 20 s, might have induced fatigue at the peripheral/central level (Kumru et al., 2021a). Thus the decrease in spinal excitability observed after fatiguing contractions can therefore have counteracted a potential increase observed after the combination condition (TCES + strength training) (Duchateau and Hainaut, 1993). Nonetheless, spinal excitability was not affected after the stimulation-only condition in which participants were at rest, a finding inconsistent with our results and those of Benavides et al. (2020). Thus, an alternative explanation is that the longer amount of total stimulation time in the present study (10 min rather than 6) induced the effects observed in the TCES and MI + TCES conditions.

4.4. Limitations

There are several limitations to be considered in the present study. First, while after-effects of each condition are reported, the outcomes measures were not reassessed after a follow-up to assess persistence of the effects (Kumru et al., 2021a). Future studies might address this limitation by measuring the long-term neural and behavioural effects of

MI + TCES after multiple sessions and after follow-up periods in which no intervention is provided. While a dissociation between changes in neural plasticity and motor improvements have been reported (Pascual-Leone et al., 1995; Mason et al., 2020) and changes in performance after MI can be observed over multiple training sessions even in the absence of acute effects (Pascual-Leone et al., 1995), a study employing multiple sessions of MI, TCES and MI + TCES might shade light on the plastic mechanisms occurring and would be more ecologically valid for translation of these techniques to rehabilitation protocols. To note, while we assessed spinal excitability by measuring responses evoked upon cervical TCES, it is important to note that this method is not selective enough to evaluate the excitability of spinal interneuronal circuits mediating movements (Pierrot-Deseilligny and Burke, 2005). Additional techniques such as H-reflex conditioning are required in order to fully characterise the effects of MI and spinal stimulation on spinal pathways (Grosprêtre et al., 2016).

Coritcospinal excitability was assessed by stimulating the motor cortex at two intensities based on the MT (100% and 120% MT). We employed a limited range of intensities due to the time constraint of having to also assess spinal excitability and manual dexterity (the after-effects induced by a single session of motor imagery were shown to last only up to 30 min after training (Ruffino et al., 2019)). In the future, further studies might address this limitation by employing recruitment curves to characterise the input-output properties of corticospinal pathways (Carson et al., 2021). In addition, TMS and TCES were delivered at increasingly higher intensities rather than in a randomised order, method which might induce order effects (Pearce et al., 2013). While it has been shown that the order of stimulation does not affect MEPs collected upon TMS (Pearce et al., 2013), to our knowledge no study so far has investigated order effects of spinal-evoked potentials evoked upon TCES. None of our participants reported high levels of pain (bigger than 7 out of 10) during TCES, but it remains the possibility that pain might mediate the neuromodulating effect of TCES as it has been shown that experimentally induced pain can affect corticospinal/spinal excitability (Sanderson et al., 2021).

As previously discussed, our findings suggest that practicing the PPT with the dominant hand might induce ceiling effects of performance, therefore rendering the test non sensitive enough to detect acute changes in manual dexterity in healthy individuals. This limitation can be addressed in the future by measuring manual dexterity with test such as the Minnesota Manual Dexterity test, whose scoring system is based on time to task completion rather than number of items (Desrosiers et al., 1997). Finally, a further limitation of the study is the relatively small sample size which might limit the validity of our findings. However, the total sample size is in line with other studies investigating the effects of motor imagery (N = 12 in (Avanzino et al., 2015); N = 12 in (Ruffino et al., 2019)) or spinal stimulation (N = 17 in (Benavides et al., 2020); N = 10 in (Sasaki et al., 2021)) on neural excitability.

5. Conclusions

This study investigated the effects of MI and TCES delivered alone and in combination on manual performance and neural excitability. While none of the conditions increased manual performance, change in neural excitability at the brain and spinal levels were observed when MI and TCES were delivered together compared to MI and TCES alone. We suggest that the two techniques might activate separate mechanisms which can synergically induce plasticity in cortical and spinal circuits. The results of this study need to be extended over multiple sessions of intervention and to be replicated in clinical populations affected by motor impairments, and can potentially guide the design of upper-limb rehabilitation strategies.

Credit authorship contributions statement

Antonio Capozio: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing. **Ronaldo Ichiyama:** Conceptualization, Writing – review & editing, Supervision, Funding Acquisition. **Sarah L Astill:** Conceptualization, Writing – review & editing, Supervision, Funding acquisition; Project administration.

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Declaration of competing interest

None.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuropsychologia.2023.108613.

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