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Noninvasive Stimulation of Contralateral Primary Motor Cortex Reduces the Amount of Skill Generalization to the Untrained Arm

Goldy Yadav | Manon Chauvaux | Julie Duque

Institute of Neuroscience, Université Catholique de Louvain, Brussels, Belgium

Correspondence: Goldy Yadav (goldy.yadav@uclouvain.be)

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ABSTRACT

Successfully learned motor skills can generalize or transfer to the untrained arm. The neural substrate underlying such intermanual/interlimb generalization of newly acquired skill memory is unclear. Here, we focused on contralateral primary motor cortex (cM1), which is considered a key brain area for skill learning and memory consolidation. We probed the causal role of cM1 in intermanual skill generalization in a 2-day study involving right-handed young individuals ($n = 31$) who learned a novel motor skill reaching task. Immediately following (right-arm) learning, we delivered low-frequency (1 Hz, 1800 pulses) repetitive transcranial magnetic stimulation (rTMS) to target left cM1 in one group of individuals ($n = 15$), whereas another group ($n = 16$) served as an active control in which ipsilateral M1 (iM1) was targeted. On the same day, we measured corticospinal excitability (CSE) to assess learning-induced and rTMS-induced neuroplastic changes occurring in the targeted M1s. Next day after 24-h, both groups were tested for intermanual skill generalization (left arm), followed by a brief test of intralimb retention (right arm). Our results show that stimulating cM1, versus iM1, reduced the amount of generalization to the untrained arm on the next day, without affecting its (re)learning ability or the follow-up retention performance of the trained arm. Further, low frequency rTMS stimulation in our study surprisingly induced a net facilitation in CSE—with higher facilitation tending to correlate to lower generalization in a subset of high learners in the cM1 group. Taken together, this study highlights the role of cM1 in skill generalization such that it seems to mediate the early transfer of learning to the untrained arm.

1 | Introduction

Human motor skill behaviour is dependent on formation and stabilization of motor memories resulting from successful learning. Such motor memories are deemed robust and especially beneficial when they can generalize to untrained contexts, for instance, the untrained arm. This form of generalization is known as intermanual generalization (also known as

Abbreviations: ANOVA, analysis of variance; cM1, contralateral primary motor cortex; CSE, corticospinal excitability; DLPFC, dorsolateral prefrontal cortex; EMG, electromyography; FDI, first dorsal interosseous; iM1, ipsilateral primary motor cortex; LTD, long-term depression; M1, primary motor cortex; MEP, motor evoked potential; rMT, resting motor threshold; RMT, root mean square; rTMS, repetitive transcranial magnetic stimulation; SE, standard error; SMA, supplementary motor area; TMS, transcranial magnetic stimulation.

cross-education or interlimb transfer), and, given its relevance for clinical rehabilitation, it is a widely studied topic in the domain of motor neuroscience (Ghahramani et al. 1996; Krakauer et al. 2000; Hwang et al. 2003; Shadmehr 2004; Farthing et al. 2009; Magnus et al. 2010; Ausenda and Carnovali 2011; Pearce et al. 2013; Green and Gabriel 2018; Kumar et al. 2020; Yadav and Mutha 2020; Yadav, Pal, et al. 2025). In the domain of reaching movements, most research studies have shown that a newly learned reaching movement can generalize to the untrained arm in healthy individuals. Yet these studies have used different motor learning paradigms leading to quite heterogenous findings when it comes to characterizing such interlimb generalization. For example, studies using motor adaptation paradigms have shown that such generalization is mostly unidirectional or asymmetrical, that is, left arm to the right arm only and not from right to the left arm (Wang and Sainburg 2003, 2004; Kumar et al. 2018; Kumar et al. 2020). Such generalization has been shown to be influenced by factors such as training speed (Lefumat et al. 2015) and contextual similarity of the training and task space (Hwang et al. 2003; Wang and Sainburg 2006). Other studies using nonadaptation paradigms such as training for ballistic movements (Hinder et al. 2011; Hinder et al. 2013; Stöckel et al. 2016) have reported that interlimb generalization can occur from right to left arm and vice versa. There seems to be heterogeneity in these findings concerning the directionality of generalization (Wong et al. 2024), which is often attributed to hand dominance (Farthing 2009). Finally, our work focusing on de novo skill learning showed that newly acquired motor skills characterized by improved movement speed and accuracy (Yadav and Duque 2023) can generalize from dominant right arm to the left nondominant arm following long training (Yadav, Pal, et al. 2025), as well as from nondominant to the dominant arm (Yadav and Mutha 2020).

In contrast to this significant amount of research exploring behavioural aspects of interlimb generalization of reaching movements, the neural basis of this generalization of newly learned motor skills is unclear. The current paper aims to address this gap in knowledge, and, as a first step, we focus on elucidating the role of primary motor cortex (M1) as the neural substrate mediating interlimb skill generalization. It is widely known that M1 is a critical brain region in the network that drives motor skill learning (Floyer-Lea and Matthews 2005; Halsband and Lange 2006; Doyon et al. 2009; Dayan and Cohen 2011; Cantarero et al. 2013; Narayana et al. 2014; Kawai et al. 2015). More specifically, studies have shown that damage to M1 can lead to pronounced contralesional impairments of fine motor skills (Canning et al. 2000; Balasubramanian 2015; Buetefisch et al. 2018; Gerardin et al. 2024). Further, noninvasive stimulation of the contralateral M1 (cM1) in healthy individuals has been shown to enhance online and offline skill performances (Reis et al. 2009) as well as learning related changes in motor excitability (Yadav, Vassiliadis, et al. 2025). On the other hand, repetitive transcranial magnetic stimulation (rTMS) over cM1 can disrupt skill acquisition (Kobayashi et al. 2009). In addition, Kantak, Sullivan, et al. (2010) showed the causal involvement of cM1 in memory consolidation of a newly learned skill (skilled reaching movements to predictable target) such that rTMS over cM1 immediately after training impaired retest performance of the trained arm at 24 h. Parallelly, there is converging evidence for cM1 involvement in enhancing memory of newly learned motor sequences (Hussain et al. 2021) as well as value-based motor decisions (Derosiere, Vassiliadis, et al. 2017; Derosiere, Zénon, et al. 2017). Further, a recent work by Paparella et al. (2023) using a visuomotor task showed neuroplastic change occurring in the trained M1 (contralateral to training arm) irrespective of the hand used to perform the task.

Taken together, it is evident that cM1 undergoes significant plastic changes during skill training to support memory formation and consolidation processes that can influence future motor performances. On the other hand, as mentioned earlier, skill generalization is contingent on factors that influence training performance and processes that develop during training. Thus, it is possible that training induced neuroplastic changes occurring within cM1 are also driving generalization of the learned skill from trained to the untrained arm. To causally probe this idea, we recruited 34 young healthy individuals (31 included in the final analysis) who trained on a novel motor skill in a predictable training condition (known to specifically engage cM1) with their right (dominant) arm. Immediately following training, we applied rTMS to disrupt M1, contralateral to the trained arm in the test group (cM1 Group rTMS over left M1) or ipsilateral to the trained arm in an active control group (iM1 Group rTMS over right M1). Finally, we tested the untrained left arm of all individuals 24-h later for intermanual skill generalization. We also tested the trained right arm for intramanual skill retention performance to assess if rTMS to cM1 or iM1 following Day 1 training impaired the follow-up retention performance on Day 2. We hypothesized that rTMS to cM1, as compared to iM1, would result in significant impairment in intermanual skill generalization. Additionally, we expected that intramanual retention at 24 h will be impaired in the cM1 but not iM1 Group because such noninvasive stimulation of cM1 can disrupt memory representations that start to develop and consolidate immediately following skill training. We believe that causally probing the role of cM1 in this manner in the current study will have direct implications for motor rehabilitation wherein generalization of skills from one limb to another as well as within-limb retention are highly desirable goals.

2 | Materials and Methods

Thirty-one (out of the recruited 34, see Section 2.2) right-handed young individuals (25 females; 23.09 ± 2.80 years old; normal or corrected vision) successfully completed the entire study. Sample size calculation was based on our prior data set (Yadav and Mutha 2020). A one-way ANOVA was performed with the dependent variable reflecting the net change in performance (right arm on Day 1 and left arm on Day 2) across two groups. Accounting for a potential 10% difference in performance revealed that 13 individuals per group were required. The current study spanned over two consecutive days and involved behavioural assessments (motor skill learning, generalization and retention) and neurophysiological procedures involving transcranial magnetic stimulation (TMS) and electromyography (EMG) recording. Prior to participating in the study, all individuals completed a handedness questionnaire (adapted from Hull 1936), as well as a TMS risk assessment questionnaire to rule out any contraindications. None of the participants reported any neurological or psychiatric disorder or had any history of drug/alcohol abuse. All Individuals provided written informed consent and were financially compensated for participating in the study. The study was conducted in accordance with the Ethics Committee of the University and the principles of the Declaration of Helsinki.

2.1 | Experimental Design

2.1.1 | Motor Skill Task

2.1.1.1 | Apparatus. The task setup comprised of a graphic tablet (Huion, Graphics Technology [HK] Limited) placed horizontally on a tabletop connected to a vertical computer screen (Figure 1A). Participants were required to make planar reaching movements on the tablet with a stylus affixed to their index finger, which provided real-time position coordinates data during the movement. Finger position data were sampled at 60 Hz. The task was displayed on the computer screen and designed using MATLAB with Psychtoolbox (Brainard and Vision 1997).

2.1.1.2 | Task Procedure. The skill task (a modified version of skill task used in Yadav, Pal, et al. 2025) started with positioning the hand inside a green start circle (1-cm diameter) at the centre of the tablet. After 500 ms of staying within the start circle, a blue target circle (1-cm diameter) appeared on the screen (at a distance of 15 cm) along with an audio 'go' cue. Subjects were instructed to make fast and accurate movements from the start position (green circle on the screen) to the target (blue) circle in 750 ms, within a specified path—a 1-cm-wide yellow path connecting the green and blue circles (Figure 1A). Performance feedback was given at the end of each trial—temporal error was indicated by a red square denoting hand position at 750 ms after movement onset, whereas spatial error was indicated by a red line displaying parts of the movement falling outside the specified yellow path. In addition to these visual cues (see Figure 1A), participants were also provided with a numeric score indicating 'motor error' (in mm), which was a sum of temporal and spatial errors (a measure used in our previous work of Yadav and Mutha 2016, 2020 and Yadav, Pal, et al. 2025; and detailed later in Section 2.2.1). Participants were instructed to reduce this motor error over the course of training by performing fast and accurate movements to the target circle. On each trial, one target circle appeared at one of the eight locations on the screen (target location was clockwise in order and thus predictable). Each trial lasted 2 s (movement time), and the performance feedback (visual cues with numeric motor error score) was presented for an additional 2 s on the screen.

All participants first received a brief familiarization on the motor skill task (eight trials each with right and left arm,

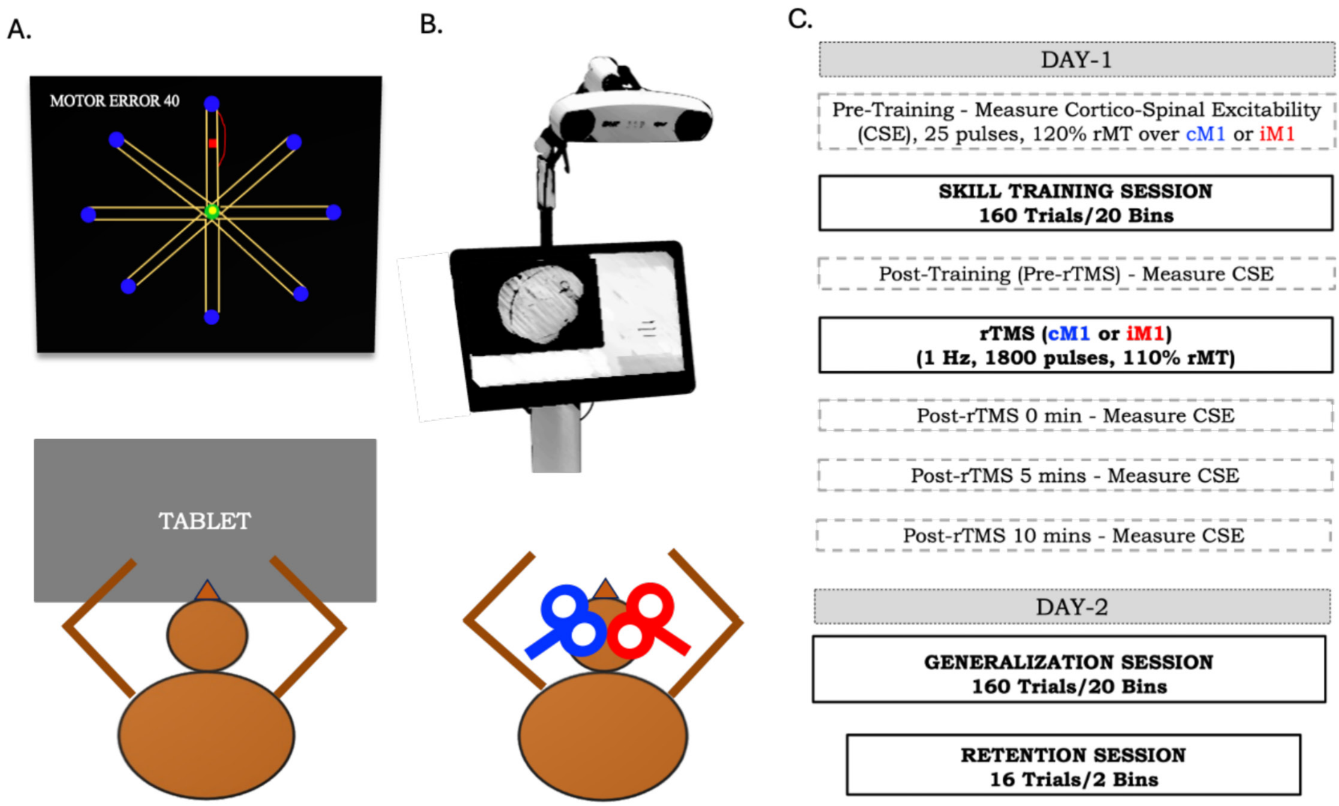

FIGURE 1 | Experimental design. (A) Motor skill task in which right-handed participants ($n = 31$) were required to make fast and accurate movements on a digitizing tablet to one of the eight target circles (blue colour) presented clockwise on a computer screen (shown on top) with a goal to reduce 'motor error' (numeric score computed based on movement time and accuracy). (B) TMS procedures over left/contralateral M1 (cM1 test group in blue, $n = 15$) or the right/ipsilateral M1 (iM1 control group in red, $n = 16$) were performed using Neuronavigation (shown on top). (C) Study design flow depicting TMS procedures and skill training session for Day 1 involving CSE measurements pre-training and post-training (also serving as pre-rTMS in our case), as well as at 0-, 5- and 10-min post-rTMS. Next, on Day 2, we tested all participants for interlimb skill generalization and intralimb retention.

respectively). Next, during the 'skill training session' on Day 1, they performed a total of 160 trials (8 trials corresponding to the eight target directions and repeated over 20 blocks) to learn the skill task with the right hand. Immediately, after training on that day, all subjects received repetitive TMS (rTMS) over M1 (see Figure 1B and following section for more details). Next, on Day 2 during the '*generalization session*', all subjects performed 160 trials (20 blocks) with their left untrained hand to test intermanual skill generalization. Based on the results of our prior work (Yadav and Mutha 2020; Yadav, Pal, et al. 2025), we decided to test for right to left hand generalization in the current study because this test condition allows us to capture skill transfer from dominant to the nondominant hand. Thus, it helps us better understand how the nondominant 'bad' hand is benefitted from the training of the dominant 'good' hand. We think that testing for this condition allows for future translational work with individuals with unilateral stroke in whom generalization/transfer from the unimpaired/good to the impaired/bad limb is the main goal. Finally, immediately following the '*generalization session*' on Day 2, we also briefly had subjects perform 16 trials (two blocks) with their trained right hand to evaluate intramanual skill retention performance at 24 h ('retention session'; see Figure 1C).

2.1.2 | Transcranial Magnetic Stimulation (TMS)

2.1.2.1 | TMS Procedure With Neuronavigation. As mentioned in the introduction, our main objective was to assess the causal role of contralateral (left) M1 in interlimb generalization of newly learned motor skill in young right-handed individuals. To probe this brain region, we used a figure-of-eight TMS coil (MCF-B70 connected to MagPro X100 stimulator, Magventure) along with a neuronavigation system (visor2 ANT Neuro). Participants were randomly divided into two groups in the beginning of the experiment on Day 1. In one group, TMS pulses were delivered to the region of interest, that is, left contralateral M1 (cM1 Group, $n = 15$), whereas in the second group, TMS pulses were delivered to the right ipsilateral M1 (iM1 Group, $n = 16$), which served as an active control in this study (Figure 1B).

Participants wore a fitted headcap (Electro-cap, Electro-Cap International, United States) onto which neuronavigation trackers were attached to precisely coregister head position with respect to the TMS coil. TMS coil was placed tangentially at 45° angle from the midline on the scalp. TMS pulses were delivered over cM1 or iM1 (depending on the group) to identify the optimal scalp position where a single pulse of TMS consistently produced the best detectable motor-evoked potential (MEP, recorded using EMG detailed in next section) in the contralateral first dorsal interosseous (FDI of the right or left hand, respectively), an agonist muscle for our skill task. This 'hot spot' was registered in the neuronavigation system for each participant (onto a default MRI) and used as reference throughout the experiment. Next, we proceeded to determine resting motor threshold (rMT) at the hotspot for each participant, which refers to the minimal TMS intensity required to evoke MEPs of ~50-μV peak to peak in the target muscle (right or left FDI) in at least 5 out of 10 consecutive pulses.

TMS was used on Day 1 only. The hotspot and rMT were established before the *skill training session* in all individuals of both groups (mean rMT of group cM1 = 53.33%; iM1 = 53.17% of maximum stimulator output). Our study design also allowed us to probe changes in corticospinal excitability (CSE) as a consequence of training on our skill task. To do so, we applied single biphasic TMS pulses on the registered M1 hotspot (cM1/iM1 depending on the group) at an intensity of 120% of the individual's rMT. Twenty-five pulses with interpulse interval of 4–4.3 s were delivered to obtain reliable MEPs in the right (trained hand for cM1 group) or left (untrained hand for iM1) FDI muscle (depending on the group) before and after the *skill training session* (see Figure 1C). Next, central to our research question, we applied rTMS to probe the causal role of cM1 in interlimb generalization of motor skill learning. To do so, we employed a widely studied low frequency rTMS (1 Hz) neuromodulation protocol, considered to have an inhibitory effect on the stimulated region possibly via long-term depression (LTD) like mechanisms (Hess and Donoghue 1996; Chen et al. 1997; Boroojerdi et al. 2001; Fitzgerald et al. 2002; Kantak, Sullivan, et al. 2010; Kantak, Fisher, et al. 2010). We delivered 1800 pulses of 1 Hz rTMS (lasting about 30 min) at an intensity of 110% of rMT. This rTMS intervention was applied over cM1 (test group) or iM1 (control group). To assess rTMS-induced changes in CSE associated with this neuromodulation intervention, we delivered single-pulse TMS to obtain resting MEPs immediately before, as well as at three different time points after the intervention-at 0, 5 and 10 min following rTMS offset. As mentioned earlier, 25 pulses (interpulse interval of 4–4.3 s at 120% of rMT) were delivered again to obtain the resting MEPs at each of these time points following rTMS.

2.1.2.2 | Electromyography (EMG) Recording and Processing. EMG was recorded to measure peak-to-peak MEP amplitude using surface bipolar electrodes targeting the FDI—one electrode was placed on the belly of the muscle; a second electrode was placed on the proximal interphalangeal joint of the index finger; and a ground electrode was placed on the ulnar styloid of the wrist. Note that EMG electrodes were attached to both left and right hands of all individuals (regardless of the group) to avoid any confounding effect of electrode placement on skill performance, which was always with the right arm only. In other words, this ensured that both cM1 and iM1 groups performed the skill task with electrodes placed over their right training hand. However, EMG was recorded and assessed from one hand (FDI) only, depending on the group type (right hand for cM1 and left hand for iM1 group). The raw EMG signal recorded from the target FDI muscle was amplified (1-K gain), band-pass filtered (10–500 Hz, Neurolog; Digitimer), notch-filtered (50 Hz) (Digitimer D360, Hertfordshire, United Kingdom) and digitized at a sampling rate of 2 kHz (CED and Signal 6 software) for off-line analysis (similar to Yadav, Vassiliadis, et al. 2025). Data extraction and offline analyses were performed using Signal 6 and MATLAB (Mathworks) software.

2.2 | Statistical Analyses

For statistical analyses, we used JMP software (Version Pro 17.1, SAS Institute Inc.). For all statistical tests, significance level was set at 0.05, and post hoc Tukey test was conducted following a significant main effect in the ANOVA. Partial eta-squared ($\eta^2 p$) measure for effect size reported along the test results with data expressed as mean ± standard error (SE) throughout the manuscript.

2.2.1 | Motor Skill Performance Assessments: Learning, Interlimb Generalization and Intralimb Retention

As described above in Section 2.1, participants were required to learn a reaching skill task by making fast and accurate movements to reduce the motor error (in mm) during the training session (comprising 20 blocks of eight-trial each). Trials on which participants failed to initiate a movement from the start circle in 750 ms (expected time to reach the target circle, as mentioned earlier) were excluded from our analyses (2.23% of the total trials). To quantify learning on this task in both groups on Day 1, we assessed change in their mean motor errors over 20 blocks of the training session. Motor error was the main variable of interest for assessing skill performance in this study—sum of temporal error (measured as distance [in mm] of the hand at 750 ms from the target circle) and spatial error (measured as distance [in mm] of the hand path falling outside the specified path connecting the start and target circles). Participants who exhibited a reduction in the motor error on Block 20 as compared to Block 1 were included for the remainder of data analyses in this study (a total of 31 participants out of the 34 that were recruited). Next, related to the central question of our study, we statistically examined and compared the extent of skill generalization on Day 2 following skill training and rTMS intervention on Day 1 in both groups. To do so, we performed a two-way repeated-measures ANOVA with group (cM1 and iM1) and block (first block training, last block training, first block generalization and last block generalization) as between- and within-subject factors, respectively, to compare the motor errors. To assess whether intramanual retention performance of the trained right arm on Day 2 was impacted by rTMS following end of training on Day 1, we performed a two-way ANOVA with group (cM1 and iM1) and block (last block training, first block retention and last block retention) as factors to compare the motor errors.

2.2.2 | CSE Measurements in Relation to Motor Skill Learning and rTMS Intervention

We extracted root mean square (RMS) of EMG activity of the FDI muscle in the 200-ms time window preceding a TMS pulse and peak-to-peak MEP amplitude in the 10- to 60-ms time window after the TMS pulse using Signal software. This was done to obtain resting MEPs corresponding to the five time points of CSE measurement (see Figure 1C), that is, pre-training, post-training (also Pre-rTMS), post-rTMS 0 min, post-rTMS 5 min and post-rTMS 10 min. We removed the first MEP of each time point, as well as any MEP preceded by a significant muscular activity (based on RMS threshold set at 0.02 mV), as done previously (see methods section of Yadav, Vassiliadis, et al. 2025). Next, we removed outlying trials (±2.5 SD of mean of each time point), as also typically done in our lab (see, for instance, Quoilin et al. 2019). As a result, a total of 6.4% of all trials were removed, leaving at least 21 MEPs (out of 25 pulses delivered) for each TMS time point for each participant. Finally, we calculated the mean MEP amplitude for each of these five TMS time points.

First, we assessed the consequence of de novo motor skill learning on CSE by analysing MEPs with a two-way ANOVA with group (cM1 and iM1) and TMS timing (pre-training and post-training) as factors. Remember that cM1 MEPs were recorded from the trained right arm, whereas iM1 MEPs were recorded from the untrained left arm. Therefore, the factor 'group' in this analysis reflects differences in CSE not only across subject groups but also across different arms with respect to training. Then, in a further analysis, we linked training-related CSE changes, that is, $\Delta CSE_{training}$ (post-training minus pre-training MEPs) to motor error changes (first-training minus last-training blocks) to explore any association between the amount of skill learning on our task and underlying CSE changes. A positive correlation would indicate that a greater training-induced CSE increase is associated with greater learning. Finally, we assessed the effect of the 1-Hz rTMS on CSE. To do so, we compared MEPs obtained after the training session but immediately before the rTMS intervention (in other words, pre-rTMS), with post-rTMS (0, 5 and 10 min) time points (see Figure 1C). To compare MEPs obtained at these four different time points, we performed a two-way ANOVA with group (cM1 and iM1) and rTMS timing (pre, post–0 min, post–5 min and post–10 min) as factors. Based on this finding in which we observed net facilitation in CSE, we performed further correlations to explore any underlying relationship between CSE changes following rTMS, that is, ΔCSE_{rTMS} (post-rTMS 10 min minus pre-rTMS MEPs) and intermanual generalization performance, that is, *ΔGeneralization* (motor errors on first-training minus first-generalization blocks) of our test group participants (cM1). Here, a negative correlation would indicate that a greater rTMS-induced CSE facilitation is followed by an attenuated generalization on the next day.

3 | Results

3.1 | Skill Behaviour

3.1.1 | Learning and Intermanual Generalization

The overall training, generalization and retention performances of cM1 and iM1 groups are depicted in Figure 2. As evident from the left panel of this figure, both groups learned the skill task on Day 1 by reducing their motor errors over the 20 blocks of training session. We, therefore, proceeded to statistically examine the intermanual skill generalization in these two groups resulting from the skill training and rTMS procedure (see Figure 3). Our two-way ANOVA revealed a significant effect of block ($F_{3,\,87} = 117.8091$, $p < 0.0001$, $\eta^2_p = 0.8024$) and a block x group interaction ($F_{3,\,87} = 3.0002$, $p = 0.0349$, $\eta^2_p = 0.0937$) with no main effect of group ($F_{1,\,29} = 1.1076$, $p = 0.3013$, $\eta^2_p = 0.0755$). As expected, Tukey post hoc tests revealed significant differences in mean motor errors on the first and last blocks of the training session on Day 1 in both cM1 ($p < 0.0001$) and iM1 ($p < 0.0001$) groups. We observed that the mean motor errors reduced in both groups over the first (cM1: 93.7 ± 3.69 mm; iM1: 83.7 ± 3.57 mm) and last training blocks (cM1: 30.5 ± 3.69 mm; iM1: 30.4 ± 3.57 mm), with no significant difference between the groups on the first ($p = 0.5273$) or last training ($p = 1.00$) blocks.

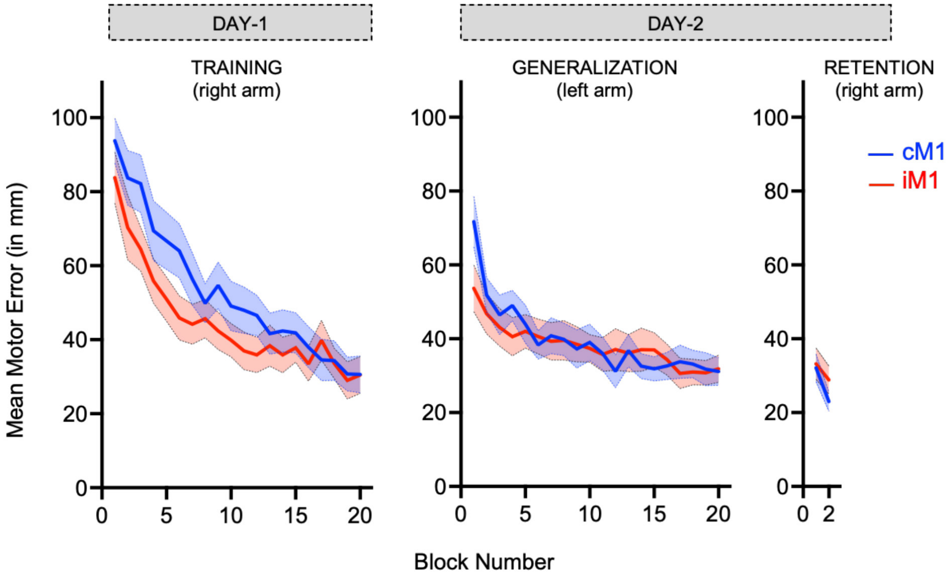

FIGURE 2 | Mean motor error across training, generalization and retention sessions. Left panel: skill performance on Day 1. Both groups (cM1 in blue, $n = 15$; iM1 in red, $n = 16$) learned the motor task with their right arm by reducing mean motor errors (in mm) over the 20 blocks during the training session. Middle panel: generalization session on Day 2. cM1 test group started with larger motor errors as compared to iM1 control group, on the first block of generalization session with their untrained left arm. Right panel: ensuing retention session on Day 2. Comparable skill performance observed in the two groups when tested for intramanual retention with their trained right arm. Shaded error bands on the figure denote SE.

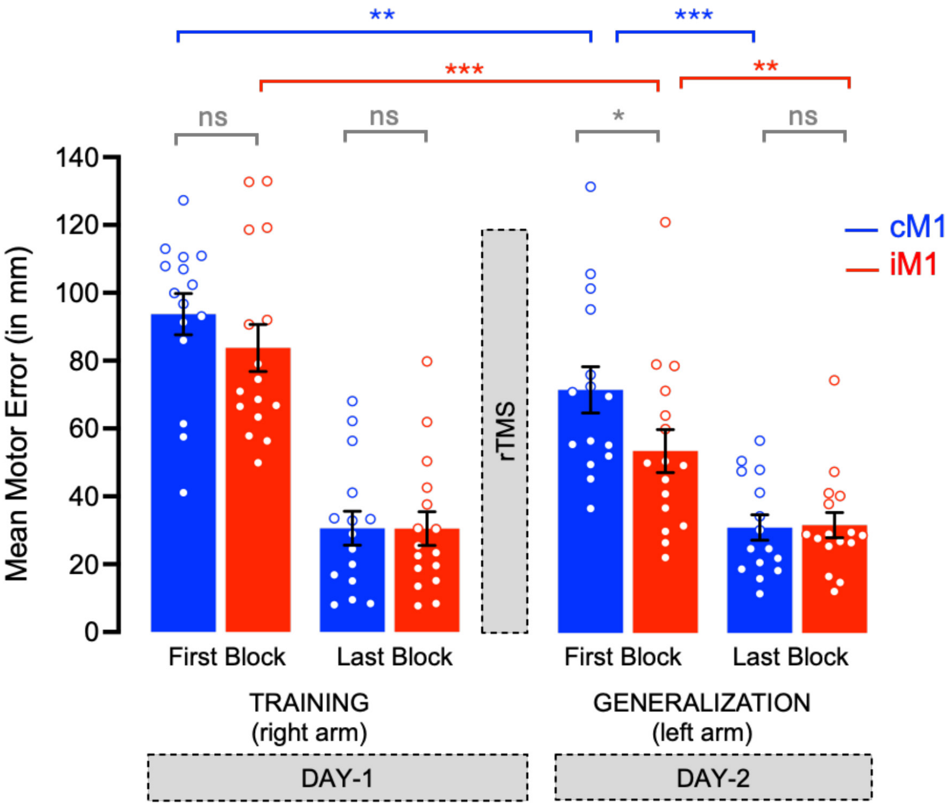

FIGURE 3 | Intermanual skill generalization. Left panel: lower motor errors observed in both cM1 (in blue, $n = 15$) and iM1 (in red, $n = 16$) groups at the end of Day 1 suggesting comparable level of skill learning. Right panel: when tested on Day 2, both groups exhibited reduced motor errors on the first generalization block as compared to first training block; a signature of intermanual skill generalization. However, cM1 test group (who received rTMS over contralateral M1 at the end of training) exhibited significantly larger motor errors on the first block of generalization session, as compared to iM1 control group (who received rTMS over ipsilateral M1 at the end of training), indicating reduced amount of skill generalization in this group. Both groups further improved performance of their left untrained arm and reached a comparable level by the last block of this session. Error bars on the figure denote SE. Coloured circles denote individual participants. *$p < 0.05$, **$p < 0.001$, and ***$p < 0.0001$. ns, nonsignificant.

This suggests that both groups were able to successfully learn the motor skill task in our study with lower motor errors evident by the end of the training session on Day-1 (see Figures 2 and 3, left panels).

Next, upon examining intermanual generalization by comparing first training (on Day 1) and first generalization blocks (on Day 2, as we have done previously in Yadav and Mutha 2020; Yadav, Pal, et al. 2025), the post hoc test revealed a significant difference in motor errors between these blocks corresponding to the right/trained and the left/untrained arm in both cM1 ($p=0.0015$) and iM1 ($p<0.0001$) groups, respectively. Interestingly, however, a direct comparison of motor errors on the first block of generalization (see Figure 2 middle panel and Figure 3 right panel) between cM1 and iM1 revealed a significant difference between the two groups ($p=0.0157$) with higher motor errors observed in cM1 group (71.7 ± 3.69 mm) as compared to iM1 (53.6 ± 3.57 mm). These findings indicate that although both groups exhibited significant skill generalization to their untrained arm (on Day 2) thus, benefiting from training of the first arm (on Day 1), it was less prominent in the cM1 group. This suggests that rTMS over cM1 following skill training may have caused this reduced amount of skill generalization observed on the first block of generalization session in this group compared to the iM1 group, as we had hypothesized in the introduction of this paper. However, this impairing effect of rTMS on skill generalization in the cM1 group did not last for the entire session, as we did not find any significant difference between the two groups on the last block of the generalization test ($p=1.0000$ [cM1: 31.1 ± 3.69 mm and iM1: 31.8 ± 3.57 mm]). And we found that irrespective of the group type, the untrained left arm exhibited significant reduction in the motor errors over the first and last generalization blocks (cM1: $p<0.0001$ and iM1: $p=0.0011$). This reflects (re)learning by the untrained arm on Day 2, thus reaching a performance level that was comparable to the end of Day 1 training arm performance (last training and last generalization blocks not significantly different for cM1 [$p=1.00$] or iM1 [$p=1.00$]).

Overall, these results suggest that a newly learned skill task in our study was generalized to the untrained arm when tested on Day 2 in the two groups. However, the amount of skill generalization (as evident on the first block of generalization test) was reduced in the group that received rTMS over cM1 immediately following training on Day 1. Further, this rTMS induced impairment was possibly quashed by any relearning processes, thus resulting in overlapping performances observed in the two groups by the end of the generalization session (Block 20). This could imply that cM1 rTMS possibly disrupted underlying skill memory consolidation processes that impaired transfer without perturbing online (re)learning in the untrained arm.

3.1.2 | Intramanual Retention After 24 h on Day 2

Finally, related to the intramanual retention session, we assessed and compared the trained right arm performances of the two groups at the end of training (just prior to rTMS intervention on Day 1) with that on Day 2 (which immediately followed the generalization session; see Figure 4). Our group (cM1 and iM1) x block (last training, first retention and last retention) ANOVA

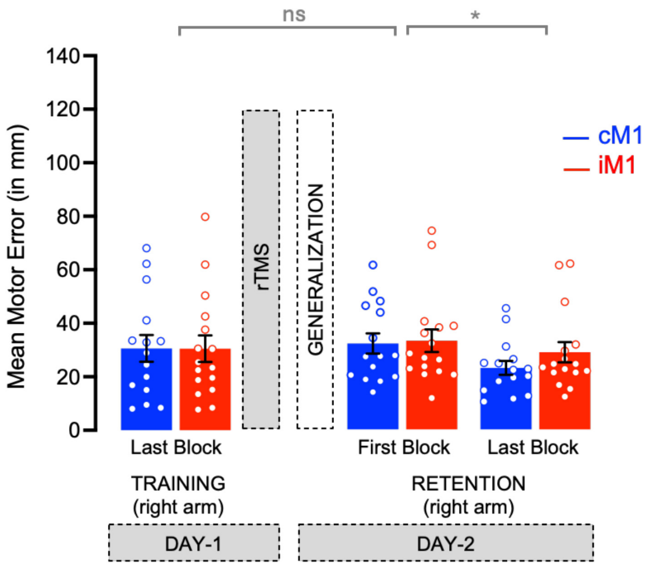

FIGURE 4 | Intramanual skill retention. Left panel: mean motor error in last training block on Day 1. Right panel: same for first and last retention blocks on Day 2. Note the similar amount of motor errors when comparing last training and first retention blocks, in both the cM1 (in blue, $n=15$) and iM1 (in red, $n=16$) groups, suggesting similar level of skill retention across 2 days in both groups. Moreover, both groups further improved performance of their right trained arm over the two blocks of this session on Day 2 with no group differences. Error bars on the figure denote SE. Coloured circles denote individual participants.

revealed a significant effect of block ($F_{2,\ 58}=4.5351$, $p=0.0148$, $\eta^2_p=0.1352$) only, with no group ($F_{1,\ 29}=0.1868$, $p=0.6688$, $\eta^2_p=0.0250$) or group X block interaction ($F_{2,\ 58}=0.9645$, $p=0.3872$, $\eta^2_p=0.0321$). Tukey post hoc tests revealed that the only significant difference for motor errors was that between the first and last retention blocks ($p=0.0127$), regardless of the group. Errors were comparable between the first retention and last training blocks ($p=0.6245$) as well as between the last retention and last training blocks ($p=0.1172$). This suggests that rTMS intervention following training on Day 1 did not cause any group differences in retention performance of the trained arms when tested on Day 2.

Taken together, our behavioural results show that applying 1-Hz rTMS over contralateral M1, as compared to ipsilateral M1 at the end of skill training, led to reduced interlimb generalization of the newly acquired skill to the untrained arm, without affecting the subsequent retention performance of the trained arm.

3.2 | Motor Neurophysiology

3.2.1 | Learning-Induced Changes in CSE

We were curious to know whether learning on our skill task induced excitability changes in the primary motor cortex, as reported in previous research using different motor tasks (Uehara et al. 2018; Spampinato et al. 2019; Yadav, Vassiliadis, et al. 2025). We explored whether CSE changed within contralateral and ipsilateral M1 due to skill training in our study by comparing the MEPs obtained in right FDI of cM1 and left FDI of iM1 groups,

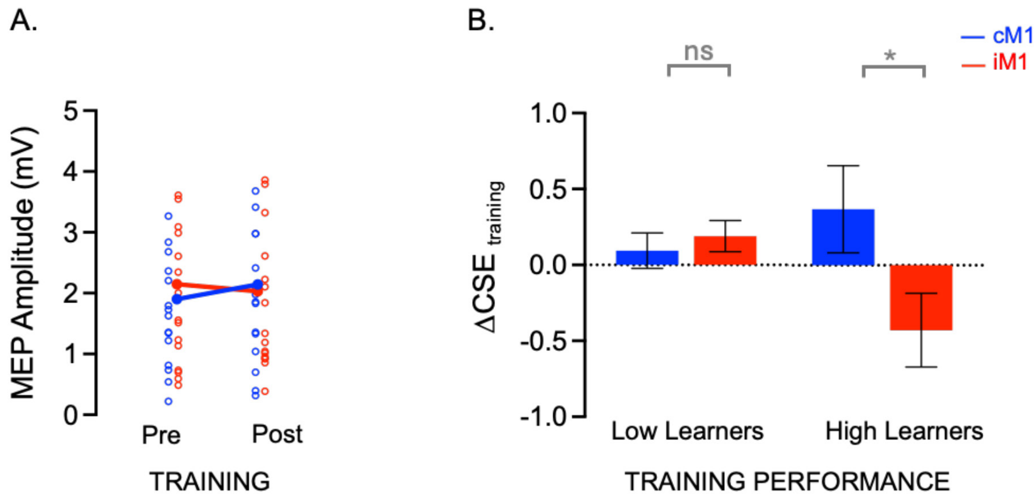

FIGURE 5 | CSE changes related to skill training. (A) Pre-training and post-training MEP amplitudes. No significant change in CSE as a result of training in the two groups. (B) CSE changes in low and high learners of cM1 and iM1 groups. A median-split based on learning revealed significant differences in training-related changes in CSE ($\Delta CSE_{training}$: post-training minus pre-training) between cM1 (in blue) and iM1 (in red), only in high learners of the two groups, but not for low learners. Error bars on the figure denote SE. Coloured circles denote individual participants.

before and after the training session (see Figure 5A). Our analysis revealed no significant group ($F_{1,\ 29}=0.3557$, $p=0.5555$, $\eta^2_p=0.0121$), timing ($F_{1,\ 29}=0.3093$, $p=0.5824$, $\eta^2_p=0.0105$) or group x timing interaction ($F_{1,\ 29}=2.6737$, $p=0.1128$, $\eta^2_p=0.0844$).

However, upon performing some exploratory analyses, we noticed heterogeneity in the amount of learning across subjects. We, therefore, categorized subjects into 'high' and 'low' learners based on group wise median split of their training motor error data (first training – last training blocks) to evaluate any effect of learner-type on CSE changes induced by training ($\Delta CSE_{training}$: post-training – pre-training MEPs). Our two-way ANOVA on this $\Delta CSE_{training}$ with group (cM1 and iM1) and learner type (high and low) as factors revealed a significant group x learner-type interaction ($F_{1,\ 27}=4.5834$, $p=0.0415$, $\eta^2_p=0.1451$). The Tukey post hoc test showed a significant difference in ΔCSE for 'high' learners of the two groups ($p=0.0485$; ΔCSE for cM1: 0.36 ± 0.20 mV and iM1: −0.42 ± 0.20 mV). These results suggest that in high learners, skill training resulted in a larger increase in CSE (i.e., higher post-training MEPs as compared to pre-training MEPs) when measured on the trained side (TMS over contralateral M1) than on the untrained side (TMS over ipsilateral M1; Figure 5B). On the other hand, such difference was not found for low learners ($p=0.9885$ [ΔCSE for cM1: 0.09 ± 0.21 mV and iM1: 0.18 ± 0.20 mV]). These results suggest that learning induces greater increases in CSE on the trained side than on the untrained one, but this effect is only apparent in individuals showing greater learning. However, please note that these analyses were conducted on small samples and should therefore be considered preliminary, aiming to generate hypotheses and guide future investigations rather than establish strong conclusions.

3.2.2 | rTMS Related Changes in CSE

Finally, related to the 1-Hz rTMS intervention used in our study, we examined MEPs using a two-way ANOVA with group (cM1 and iM1) and rTMS timing (pre, 0 min, 5 min and 10 min) as factors. This analysis revealed a significant effect of rTMS timing ($F_{3,\ 87}=3.3029$, $p=0.0240$, $\eta^2_p=0.1022$) but no group ($F_{1,\ 29}=0.0007$, $p=0.9791$, $\eta^2_p=0.0000$) or timing x group interaction ($F_{3,\ 87}=0.4285$, $p=0.7331$, $\eta^2_p=0.0145$). Surprisingly, related to the rTMS timing effect, the post hoc test revealed a significant increase in MEP amplitudes between pre- and the post-rTMS 10-min timing ($p=0.0490$ [pre-rTMS: 2.08 ± 0.11 mV and post-rTMS 10 min: 2.50 ± 0.11 mV]). We did not find any significant change in MEP amplitudes between pre-rTMS and 0 min ($p=0.9224$) or pre-rTMS and 5-min time points ($p=0.0959$). This suggests that, irrespective of whether the 1-Hz rTMS was applied on (left) cM1 or (right) iM1, it produced a significant increase in MEP amplitudes for the FDI of the opposite hand at 10 min following the end of the neuromodulation intervention. Hence, here, rTMS seems to have increased rather than decreased CSE associated with the stimulated M1 (see Figure 6A). This finding of ours contrasts with the anticipated inhibition effect based on past research (Wassermann et al. 1996; Chen et al. 1997; Touge et al. 2001; Fitzgerald et al. 2002; Chouinard et al. 2003; Lang et al. 2006). Instead, our data add to the literature that is suggestive of mixed findings including no change in CSE or facilitation especially at higher intensities, which we discuss later in the discussion section (Pascual-Leone et al. 1994; Siebner et al. 1999; Siebner et al. 2004; Fitzgerald et al. 2006; Lang et al. 2006; Hoogendam et al. 2010; Veldema et al. 2023).

With significant CSE facilitation observed at 10 min following rTMS, we wanted to examine whether there was any correlation between the strength of this CSE increase and the reduced amount of interlimb generalization observed in cM1 group in our study. To do this, we performed a linear correlation between the rTMS-related CSE change (ΔCSE_{rTMS} = post-rTMS 10 min – pre-rTMS) and interlimb generalization performance ($\Delta Generalization$ = motor errors on first training block – first generalization block) for the cM1 group (Figure 6B). Our results revealed no significant correlation between ΔCSE_{rTMS} and $\Delta Generalization$ ($R^2=0.049$, $p=0.4294$). Further, upon performing an exploratory analysis on this correlation based

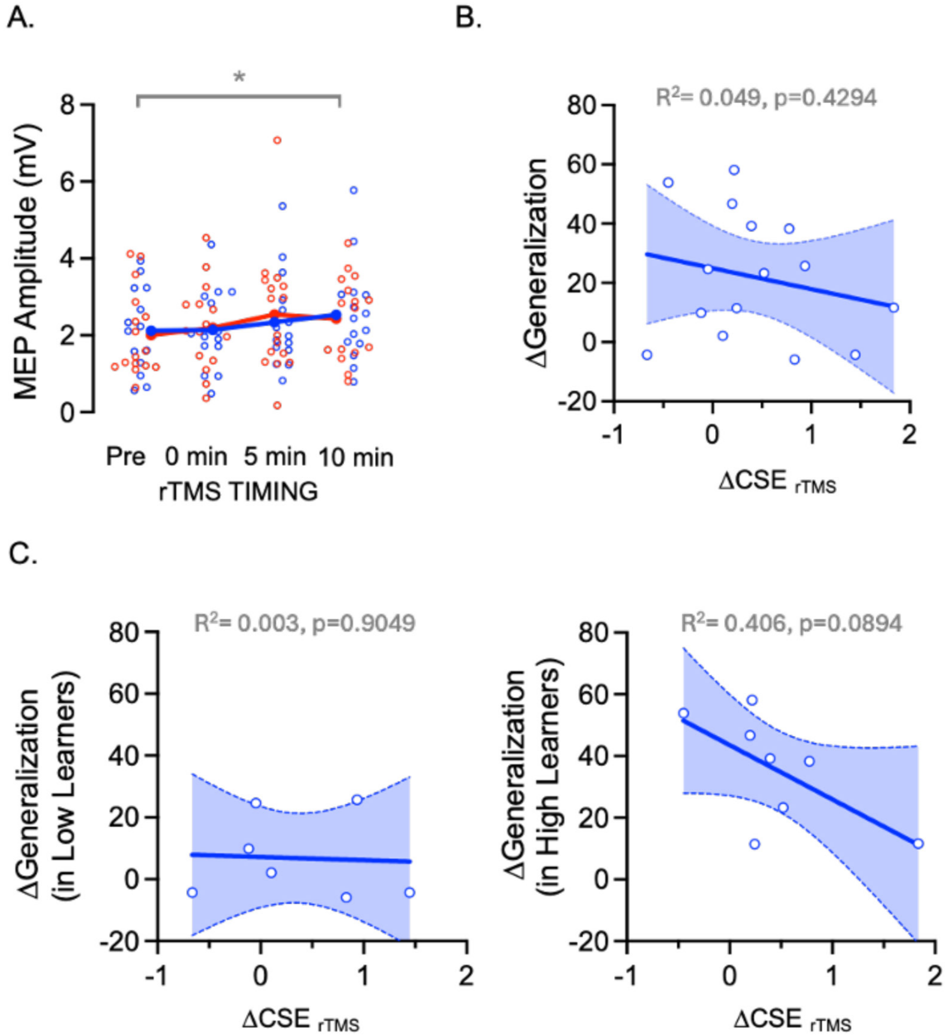

FIGURE 6 | CSE changes related to the rTMS intervention. (A) MEP amplitudes across rTMS timings. rTMS induced a significant increase in MEP amplitudes (mV) for post-rTMS 10 min compared to pre-rTMS, irrespective of group type (cM1 in blue and iM1 in red). (B) Correlation with generalization in cM1 group. For cM1 test group (in blue), who exhibited reduced interlimb skill generalization between first training and first generalization blocks (ΔGeneralization: lower values mean lower generalization), no significant correlation was found between their generalization performance and rTMS induced CSE changes (ΔCSE_{rTMS}: post-rTMS 10 min compared to pre-rTMS). (C) Same correlation in low (left panel) and high learners (right panel) of cM1 group. A near significant correlation was noted for the high learners of this group but not for the low learners. These results are of course to be taken with caution given the small size of each subgroup. Error bands on the figure denote SE. Coloured circles denote individual participants.

on learner-type (high vs. low learners as described earlier), we noted a marginally significant correlation between ΔCSE_{rTMS} and *ΔGeneralization* for high-learners of the cM1 group ($R^2 = 0.406$, $p = 0.0894$) with no significant correlation for low learners ($R^2 = 0.003$, $p = 0.9049$) (see Figure 6C). These preliminary findings suggest that the rTMS-induced facilitation of cM1 may have negatively affected generalization in high learners: The stronger the facilitation, the weaker the generalization. Our observation here supports the notion that the rTMS can induce opposite effects on motor behaviour and excitability changes (Hoogendam et al. 2010; Veldema et al. 2023).

4 | Discussion

In this study, we primarily set out to probe the causal role of contralateral primary motor cortex (cM1) in intermanual skill generalization by testing the untrained nondominant left arm at 24 h following right hand training. As hypothesized, we found that noninvasively stimulating cM1 (vs. iM1) using rTMS intervention did impair skill generalization to the untrained arm. Despite this reduction in the amount of generalization in the cM1 group, compared to iM1 group, overall, both groups still benefitted from prior training: The naïve nondominant untrained (left) arm performance on Day 2 was significantly better than that of the naïve trained (right) arm on Day 1. And contrary to our hypothesis, rTMS to cM1 in our study did not impact intramanual skill retention of the trained arm, which was tested at the end of Day 2. Behaviourally, these findings suggest that intermanual generalization of skill memory following de novo motor learning can be hampered if cM1 is targeted immediately following skill learning. Next, we noted that in the subset of participants who exhibited higher learning, CSE changes measured in the trained hand (assessed with cM1 TMS) were larger (i.e., an increase in training-induced MEPs) as compared to CSE changes in untrained hand (assessed with iM1 TMS). Finally, and somewhat unexpectedly, our rTMS intervention produced a facilitation of CSE, which tended to correlate negatively with the degree of intermanual generalization on Day 2 in high learners of cM1 group: The more cM1 rTMS induced CSE facilitation on Day 1, the lower the intermanual generalization on Day 2.

Our current findings build upon our prior work in which we investigated whether it is possible for the untrained arm to access newly acquired fine motor skill memory from training of the other arm, and if yes, then what are the underlying mechanisms driving this phenomenon in young healthy individuals? We have previously reported (Yadav and Mutha 2020; Yadav, Pal, et al. 2025) that the phenomenon of intermanual skill generalization to the untrained arm (1) is robust following successful acquisition of novel skill memory representations and (2) is negatively impacted when individuals engaged in a secondary task immediately following training, suggesting that post-training skill memory consolidation/stabilization processes operating endogenously also impact the amount of generalization. In this study, we took the next obvious step to explore the neural substrate involved in mediating these processes and focused on cM1—a key brain region for skill learning and consolidation (Floyer-Lea and Matthews 2005; Doyon et al. 2009; Narayana et al. 2014; Kawai et al. 2015; Gerardin et al. 2024), specifically in the context of predictable skill reaching movements (Kantak, Sullivan, et al. 2010). Thus, we noninvasively stimulated cM1 (with iM1 serving as an active control group) immediately after learning with the aim to perturb the newly acquired skill memory and found that it negatively affected the untrained left arm performance on the next day. However, the overall skill performance of the untrained arm in both groups was significantly better as compared to the naïve training arm (when comparing first generalization and first training blocks), thereby suggesting that the untrained arm still benefitted from the trained arm learning despite the stimulation intervention. Moreover, the untrained arms of both groups further (re)learned on Day 2 and reached the prestimulation performance level of the trained arm (comparable performance on Block 20 of Day 2, as indicated in Section 3.1 and Figure 3).

Additionally, perturbing the newly acquired memory with cM1 (or iM1) stimulation did not impact intralimb retention: Trained arm tested on Day 2 maintained its prestimulation performance levels. It is of note that this intact retention could possibly be attributed to our study design, which allowed the right trained arm to not only benefit from its original training on Day 1 but also from the left untrained arm test performance that occurred just before on Day 2. This could have resulted in another instance of intermanual skill generalization (left to right arm in this case on Day 2), thus potentially obscuring the effect of cM1 stimulation on intramanual retention that we had expected. Thus, although stimulation of cM1 reduced skill generalization to the untrained arm, it did not prevent further learning in this arm or impair subsequent test performance of the trained arm on Day 2. In other words, although cM1 neuromodulation weakened generalization, it did not prevent some generalization from occurring. These observations could imply the following: (1) involvement of additional brain regions that participate in skill learning and memory consolidation and thereby impact future motor skill performances such as generalization; (2) 1-Hz rTMS intervention could not efficiently perturb the offline memory consolidation processes operating within cM1 (as shown by Psurek et al. 2021 for motor sequence learning); and (3) variability observed in the amount of skill learning on our task and differential rTMS effects on high versus low learners. Based on our behavioural and neurophysiology data, we have reflected on these points in the coming section along with the limitations posed by a noninvasive brain stimulation approach such as rTMS for probing human skill behaviour.

First, we would like to understand the underlying neural bases for the skill behaviour observed in our study. We found that three main frameworks can be identified from the broader motor learning literature that may help us uncover how sharing or transfer of movement related information in the brain and between limbs (such as arms) facilitates motor behaviour. The first framework for cross-limb transfer of learned movements is referred to as 'callosal access hypothesis', and according to this, skill memory representations formed following learning reside in the trained contralateral hemisphere, which in turn can be accessed by the untrained hemisphere/arm system through corpus callosum (Taylor and Heilman 1980; Anguera et al. 2007; Ruddy and Carson 2013). Second framework for intermanual transfer of motor learning is known as 'cross-activation hypothesis' (Parlow and Kinsbourne 1989; Ruddy and Carson 2013), which posits that extensive unilateral training generates cortical activity not only in the contralateral hemisphere but also the ipsilateral hemisphere. This ipsilateral activity in turn facilitates performance benefits to the untrained arm (Anguera et al. 2007; Lee and Carroll 2007). Lee et al. (2010), for instance, showed that rTMS to the untrained hemisphere reduced the amount of intermanual generalization of ballistic movements, providing support to the view that cortical processes in the hemisphere ipsilateral to the trained arm can contribute to transfer.

In our case, however, rTMS to cM1, and not iM1, led to an impairment in skill generalization to the untrained arm, thus favouring the *callosal access hypothesis* as opposed to the *cross-activation hypothesis*. However, our findings also show that the naïve untrained arm tested on Day 2 still benefitted from the training arm even after rTMS intervention (lower motor errors on the later blocks of the generalization session). This indicates that skill learning and memory consolidation related neuroplastic changes that could drive such generalization are possibly not strictly restricted to cM1. Consistently, a number of neuroimaging findings have highlighted the involvement of a wide number of brain regions in addition to M1, such as the somatosensory cortices, SMA, DLPFC, posterior parietal cortex, basal ganglia and cerebellum that participate in skill learning (Hikosaka et al. 2002; Doyon et al. 2002; Floyer-Lea and Matthews 2005; Doyon and Benali 2005; Dayan and Cohen 2011; Vassiliadis et al. 2024). Furthermore, brain region such as the SMA has been shown to be involved in transfer of motor performance to the untrained hand (Perez et al. 2008; Andrushko et al. 2023). The seat(s) of skill memory representation in the brain, thus, has a lot of implications for intermanual skill generalization and should be further investigated in future work focusing on skilled reaching tasks. This brings us to a third framework, namely, the 'bilateral access hypothesis' (which Ruddy and Carson 2013 have merged together with the 'callosal access' framework).

This model of intermanual generalization acknowledges that learning related neuroplastic changes not only involve cM1, as implied by the callosal access hypothesis, but also additional brain areas that participate in skill learning and memory consolidation. Skill representation developing or consolidating in these additional brain regions, in turn, can be bilaterally accessed by the untrained or trained hemisphere/arm whenever the task is performed again. Our current data with overall significant skill transfer (though with initial reduction in the group that received cM1 stimulation) as well as intact intralimb retention lend support to this framework hinting participation of additional brain regions. Future work targeting some of these above-mentioned areas involved in skill learning (such as DLPFC or SMA that could potentially be involved in skill task such as ours) can help elucidate regions in addition to cM1 that are facilitating skill generalization and retention.

Finally, we would like to briefly comment about the role of rTMS in our study, its variable effects and other potential limitations that should be kept in mind while interpreting our results. First, we noted a facilitatory effect of rTMS on CSE in both our groups as opposed to the traditionally expected inhibitory effect induced by low-frequency stimulation (1 Hz) reported earlier (Chen et al. 1997; Boroojerdi et al. 2001; Fitzgerald et al. 2006; Kantak, Sullivan, et al. 2010; Kantak, Fisher, et al. 2010; Psurek et al. 2021). Our findings, on the other hand, are consistent with other work who report mixed effects of rTMS on excitability (Pascual-Leone et al. 1994; Siebner et al. 1999; Fitzgerald et al. 2006; Lang et al. 2006; Hoogendam et al. 2010; Siebner et al. 2022; Veldema et al. 2023). Taken together, this shows heterogeneity in how rTMS modulates underlying cortical activity. Furthermore, our data show an interesting effect with cM1 rTMS facilitating CSE while impairing generalization, an effect that was specific to high learners based on our preliminary results. This shows a dissociation between TMS induced underlying excitability changes and its effect on behaviour, which has been reported by others as well (Jäncke et al. 2004; Schramm et al. 2019; Kim et al. 2021; Psurek et al. 2021; Veldema et al. 2023). This indicates a potential nonlinear relationship between rTMS effects on excitability and behaviour. We would also like to highlight that although training-induced facilitation of CSE could be seen as a marker of adaptive plasticity, rTMS-induced facilitation of CSE with reduced amount of generalization in our case could surprisingly be a case of maladaptive plasticity. However, we reiterate that the analyses comparing high and low learners were based on relatively small subgroups. These results should therefore be considered exploratory and interpreted with caution. Alternatively, the effects of a long session of rTMS (1800 pulses, which lasted approximately 30 min in our study) on CSE could potentially have been impacted by the underlying homeostatic processes that set in to restore normality in the brain tissue (Anil et al. 2023). Thus, the traditional view of rTMS having an overall 'knock out' effect needs further detailed investigation. Moreover, we think such variability seen in studies investigating neurophysiology measures and behaviour can be attributed to many factors. These include differences in stimulation parameters across studies (Maeda et al. 2000; Kantak, Fisher, et al. 2010; Anil et al. 2023), such as the intensity of stimulation (we used 110% of rMT for rTMS as compared to a subthreshold intensity of 90%) and its duration (we applied 1800 pulses, a maximum deemed safe for efficient brain stimulation). The type of machine and coil used could also matter (Lang et al. 2006). Moreover, timing of measurement (such as at 0-, 5- and 10-min poststimulation) and endogenous brain state while applying rTMS (i.e., different learning levels) could also influence the pattern of findings. Each of these factors requires a separate detailed investigation with a larger sample size in order to fully establish the efficacy of this noninvasive brain stimulation procedure for studying human behaviour.

Lastly, our study involved two groups of subjects who received rTMS—one being the test group that received TMS over cM1 and another one being the active control group with TMS over iM1. This means that both groups might have been affected by TMS-specific side effects, including coil-related sensory stimulation. Note though that performance in iM1 group is quite consistent with our past work assessing intermanual skill generalization without any stimulation (Yadav and Mutha 2020; Yadav, Pal, et al. 2025), suggesting that these TMS-specific effects were likely limited. However, future work assessing underlying neural bases may benefit from including a sham group to account for any TMS induced sensory effects. To conclude, our current study employs rTMS with an active control group to elucidate the role of cM1 in human skill generalization of de novo learning and extends previous literature showing its involvement in human motor learning, plasticity and memory consolidation.

Author Contributions

Goldy Yadav: conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, visualization, writing – original draft, writing – review and editing. **Manon Chauvaux:** data curation, formal analysis, methodology. **Julie Duque:** conceptualization, funding acquisition, investigation, project administration, resources, supervision, validation, visualization, writing – review and editing.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Dataset used in this study is available online (https://doi.org/10.17605/OSF.IO/5FXQJ).

Peer Review

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