



UNIVERSITÀ DEGLI STUDI DI PADOVA

Dipartimento di Psicologia Generale

**Corso di laurea in Scienze Psicologiche Cognitive e
Psicobiologiche**

Elaborato finale

**Neuroanatomical and functional substrates underlying
contralateral transfer of motor learning**

**Substrati neuroanatomici e funzionali alla base del trasferimento
controlaterale dell'apprendimento motorio**

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Anno accademico 2023/2024

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Abstract (Eng)

Motor learning refers to the process of acquiring new motor skills through repeated interactions with the environment. Recent studies have shown that motor practice enhances the same motor skills of the contralateral, unpracticed hand beyond improving unilateral motor skills. Interhemispheric transcallosal connections are believed to be the underlying mechanisms behind this phenomenon, termed “contralateral learning transfer” (CLT), yet physiological evidence is still sparse and lacks perturbational and electrophysiological approaches.

Here, we investigated behaviorally the outcome of motor learning on both hands. In parallel, we used transcranial magnetic stimulation (TMS) to index the transcallosal connectivity between primary motor cortices by assessing the ipsilateral silent period (iSP) to investigate whether CLT might be explained.

Two experiments were conducted. In experiment 1, twenty-five right-handed participants were trained in a modified version of the Nine-Hole Peg Test (mNHPT). Before the training, iSP was evaluated with TMS. The results showed that the extent of the contralateral behavioral improvement for each participant was predicted by the iSP value, with an explained variance of nearly 40%. These results indicate that transcallosal connections between brain motor structures play a fundamental role in mediating the occurrence and proficiency of CLT.

In the second experiment, we enrolled twenty right-handed participants performing the same training but with the contralateral hand. Our findings showed that at the behavioral level, the performance was similar to that of the previous group, indicating the symmetrical nature of CLT with a transfer of learning from the non-dominant to the dominant hand and vice versa.

Beyond revealing how our motor system operates during everyday activities, these notions may also impact clinical contexts where physiological monitoring like iSP could be envisioned for tailoring neuro-rehabilitative treatments.

Abstract (Ita)

L'apprendimento motorio si riferisce al processo di acquisizione di nuove abilità motorie attraverso interazioni ripetute con l'ambiente. Studi recenti hanno dimostrato che oltre a migliorare le abilità motorie unilaterali, la pratica motoria aumenta anche le stesse abilità motorie della mano controlaterale, non allenata. Le connessioni interemisferiche transcallosali sembrano sottendere a questo fenomeno, chiamato "trasferimento dell'apprendimento controlaterale" (CLT), tuttavia le evidenze fisiologiche sono ancora scarse e mancano approcci perturbazionali ed elettrofisiologici.

In questo studio abbiamo investigato l'esito dell'apprendimento motorio su entrambe le mani a livello comportamentale. Parallelamente abbiamo utilizzato la stimolazione magnetica transcranica (TMS) per analizzare la connettività transcallosale tra le cortecce motorie primarie valutando il periodo silenzioso ipsilaterale (iSP) al fine di investigare se il CLT potesse essere spiegato da esso.

Abbiamo svolto due esperimenti. Nel primo, 25 soggetti destrimani sono stati sottoposti ad una versione modificata del Nine Hole Peg Test (mNHPT). Prima dell'addestramento, l'iSP è stato valutato con TMS. I risultati hanno mostrato che la magnitudine del miglioramento comportamentale controlaterale per ciascun partecipante era predetta dal valore di iSP, con una varianza spiegata quasi al 40%. Questi risultati indicano che le connessioni transcallosali tra le strutture motorie cerebrali svolgono un ruolo fondamentale nella mediazione del CLT.

Nel secondo esperimento, abbiamo indagato comportamentalmente la possibile bidirezionalità del CLT. Venti partecipanti destrimani hanno svolto lo stesso compito, ma con la mano controlaterale. I nostri risultati suggeriscono che il CLT, a livello comportamentale, è di natura simmetrica con un trasferimento dell'apprendimento dalla mano dominante a quella non dominante e viceversa.

Oltre a rivelare come il nostro sistema motorio operi durante le attività quotidiane, queste nozioni potrebbero avere un impatto anche in contesti clinici dove il monitoraggio fisiologico di indici come l'iSP potrebbe essere considerato per personalizzare i trattamenti riabilitativi neurologici.

1. Introduction

1.1 Motor training and learning

Motor learning can be conceptualized as both skill acquisition and skill maintenance. Skill acquisition pertains to the process by which an individual rapidly and appropriately identifies a movement goal within a specific task framework and then provides a suitable response based on sensory, bodily, and environmental cues, ultimately executing the precise movement. Conversely, skill maintenance involves preserving proficiency in a previously mastered motor skill across different contexts.

Furthermore, motor learning allows to expand the motor repertoire through various mechanisms, including the adaptation process, sequence learning, motor acuity, and De Novo learning. The adaptation process enables the modification or adjustment of selected actions according to changes in the environment or bodily conditions (e.g., limb position) while maintaining the initial goal of the motor task. Sequence learning refers to the ability to quickly - and often implicitly - retrieve from memory multiple actions in the correct sequence, as demonstrated by the seamless and accurate finger movements required for typing on a keyboard. Motor acuity denotes the ability to perform actions with increased precision, typically achieved through repetition. De Novo learning involves acquiring new skills in response to novel stimuli, often necessitating changes in the mechanisms underlying action selection and execution.

Moreover, De Novo learning can be categorized as either explicit or implicit. Explicit De Novo learning occurs through motor training, which involves the voluntary and repeated practice of the same action. This process entails an initial trial-and-error stage aimed at understanding the appropriate movement, followed by a consolidation phase characterized by intensive repetition, which is carried out to reiterate the correct motor strategy. Implicit De Novo learning is achieved through different paradigms such as action observation (Bazzini et al., 2022; John W. Krakauer et al., 2019; Rizzolatti et al., 2021).

The objective of motor learning varies across different stages of life. During childhood, motor learning serves as a mean through which children can explore and engage with the environment. In adulthood, the focus shifts towards acquiring specific motor skills applicable in professional settings or recreational purposes, such as sports and music. Later in life, motor learning becomes essential for adapting to the changing

physical abilities associated with aging (Bazzini et al., 2022).

Enhancements in motor abilities are associated with neuroplastic changes occurring at various levels of the central nervous system. These changes predominantly involve the functional reorganization of the primary motor cortex (M1) (Nuara et al., 2023). However, they also encompass a broad network of motor-related cortices, including the prefrontal cortex (PFC), the dorsal (dPMC) and ventral premotor cortex (vPMC), the supplementary motor area (SMA), the primary somatosensory cortex (S1) and the superior parietal lobule (PPC). Additionally, subcortical regions including the thalamus, basal ganglia, and cerebellum, are involved (**Fig 1**), (Hardwick et al., 2013)

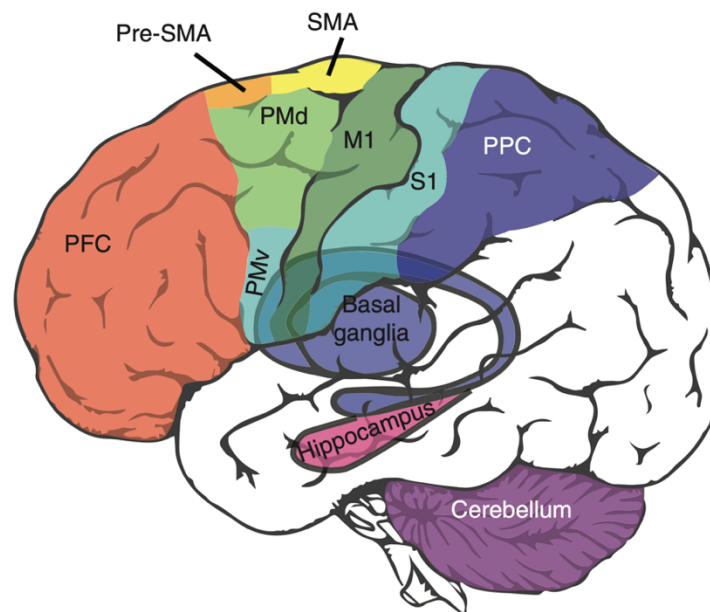


Fig 1- neuroanatomical basis of motor learning

Brain regions contributing to motor learning. PFC: prefrontal cortex; SMA: supplementary motor area; pre-SMA: pre-supplementary motor area; PMd: dorsal premotor cortex; PMv: ventral premotor cortex; M1: primary motor cortex; S1: primary somatosensory cortex; PPC: posterior parietal cortex; hippocampus; cerebellum; basal ganglia. From Krakauer et al., (2019)

1.2 Transcranial Magnetic Stimulation

In 1985, Transcranial Magnetic Stimulation (TMS) was introduced as a non-invasive method to stimulate the human brain (Barker et al., 1985). TMS induces currents in the brain via Faraday's principle of electromagnetic induction¹ (Sauv & Crowther,

¹“A magnetic field that is in motion relative to a conductor brings about a current in said conductor. Hence, a changing magnetic field induces a flow of electric current in nearby conductors that, include human tissue, [...] thus allowing for electrical stimulation of neurons within the brain in a non- invasive fashion” Sauv & Crowther (2014).

2014). A coil generates a strong but short magnetic field that induces a current through the brain, depolarizing cerebral neurons and triggering action potentials. When the coil is positioned above M1 and the descending cortical volleys are sufficiently strong to surpass the firing threshold, they prompt the release of glutamate in cortico-motoneuronal synapses. Subsequently, an action potential propagates along the peripheral motor axons, eliciting a muscle response. A single pulse to M1 elicits a response in the muscle receiving the cortical input, resulting in a motor-evoked potential (MEP), a spike in muscle activity due to the activation of corticospinal neurons, recorded with electromyography. Therefore, MEPs directly measure cortical and spinal motoneuron excitability (Hupfeld et al., 2020).

TMS combines a relative easiness of administration with a richness of information. Depending on the pattern of stimulation, it provides high spatial and high temporal resolution data. Additionally, TMS enables a causative approach, applicable in both research involving healthy individuals and patients, as well as other fields such as neuropsychology and medicine (e.g. for neuromuscular disorders and multiple sclerosis) (Làdavas Elisabetta & Berti Anna, 2020). However, it is important to note that TMS may cause mild side effects such as headaches or, in rare cases, seizures. It is not recommended for individuals with a history of epilepsy, neurological diseases or psychiatric conditions (Rossi et al., 2021).

TMS can be administered through various paradigms of stimulation. It can be delivered using two pulse forms: monophasic (unidirectional voltage with a single polarity) or biphasic (both positive and negative phases). Based on the aim of the study, the paradigm can include single-pulse paradigms, paired-pulse paradigms, or repetitive TMS (rTMS). Single-pulse paradigms involve isolated stimulations applied to specific cortical regions to explore cortical reactivity. The functional connectivity is assessed using a paired-pulse paradigm consisting of two pulses delivered in close succession, either at the same or different locations. Finally, rTMS employs trains of pulses to induce cortical effects outlasting the stimulation period (see Rotenberg et al. (2014)).

In addition, the shape of the TMS coil can vary depending on its intended use. The most common one is the figure-of-8 coil, also known as the ‘butterfly’ coil, developed in the mid-1990s to enhance penetration depth and focality. It consists of two adjacent circular coils housed within a single encasement, allowing currents with the same

direction to combine below the junction, thereby maximizing their effect (Charles M. Epstein et al., 2008; Hupfeld et al., 2020).

1.2.1 Motor execution and interhemispheric inhibition

The ability to mirror movements with opposite limbs appears to be a basic function of the sensorimotor system, especially in upper limb actions (Swinnen, 2002). Interhemispheric networks require precise tuning to control unilateral movement and coordination between the two hemi-bodies effectively. TMS can be utilized to investigate the interactions between the two hemispheres, particularly by analyzing neural activity in the two M1s responsible for motor functions and coordination. One of the relevant indices is interhemispheric inhibition (IHI), which assesses the inhibition of a test MEP following a conditioning stimulus (i.e., a TMS pulse applied on M1 with a variable interstimulus interval prior to the test pulse) (Charles M. Epstein et al., 2008). Various experiments have investigated bilateral interaction, particularly the connections between M1s during unilateral actions. Findings suggest that interhemispheric inhibition occurs from the ‘active’ M1 to the M1 ipsilateral to the moving limb, probably to prevent mirror activity (Gueugneau et al., 2016). In addition, similar interactions have been observed during mental actions (i.e., imagining) (Giovannelli et al., 2009). Furthermore, research has highlighted the role of transcallosal circuits in the lateralization of motor outputs necessary to perform both unimanual and bimanual tasks (Carson, 2005; Kuo et al., 2017).

1.2.2 Ipsilateral silent period (iSP)

When applying a single-pulse TMS paradigm to the hand representation in M1, a MEP is elicited in the contralateral hand. However, it can also result in a brief suppression of the voluntary tonic motor output (i.e. tonic contraction of the muscle) in the ipsilateral hand (Hupfeld et al., 2020). This effect, known as the ipsilateral silent period (iSP), is detected through electromyography (EMG) as a momentary silence in muscle activity (see **Fig 2**).

iSP is sampled from the EMG signal by identifying an onset, which is the point where EMG activity decreases below the baseline with a minimum duration of 10 ms, and an offset, which is the first point after the onset where EMG returns to the baseline value (Nuara et al., 2023). iSP can be quantified by its duration (the length of time that

the EMG signal is disrupted), its area (the EMG area between iSP onset and offset), and its normalized area (compared to the pre-stimulus EMG signal) (Kuo et al., 2017)

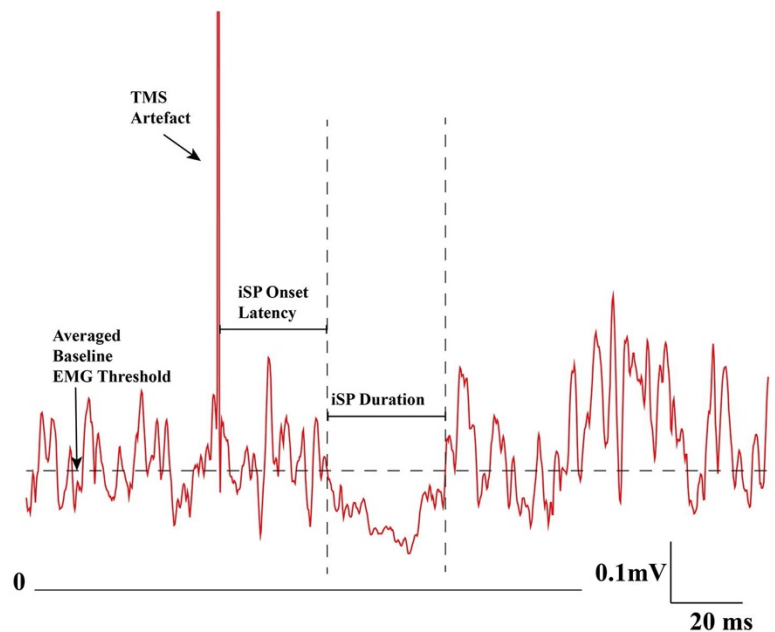


Fig.2 – example of iSP

Example of a rectified ipsilateral silent period (iSP) in a healthy subject. EMG is recorded from the abductor pollicis brevis muscle. iSP onset and offset are indicated by the vertical dashed lines and the horizontal dashed line represents the mean baseline EMG level before TMS. From Chen et al. (2022)

The mechanism for iSPs proposed by Hupfeld et al. (2020) is as follows: a TMS pulse stimulating M1 results in excitatory (glutamatergic) transcallosal motor fibers synapsing on inhibitory (GABAergic) interneurons in the contralateral primary motor cortex. This interaction leads to a net inhibitory effect and a brief depression in the descending corticospinal activity that supports the tonic muscle contraction, resulting in the visible silent period on the EMG recording (**Fig 3**). This process is considered to have cortical origin without involving spinal contributions (Wassermann et al., 1991).

iSP serves as a direct measure of interhemispheric inhibition, providing information about the transcallosal inhibition of the voluntary motor output from the non-stimulated contralateral M1, potentially mediated by GABAB receptors (Gueugneau et al., 2016). Multiple lines of evidence support the notion that the corpus callosum is at the basis of iSP. First, iSPs are absent or delayed in patients with agenesis² or lesions of the

² Congenital cerebral malformation that leads to complete or partial absence of the corpus callosum (M Das & Geetha, 2024)

posterior corpus callosum (Meyer et al., 1998) and callosal infarction³ (Li et al., 2013). Additionally, in patients with callosal pathologies such as multiple sclerosis, iSP is abnormal (Llufriu et al., 2012). Furthermore, iSP is absent in children with an incompletely developed corpus callosum, who typically exhibit more prevalent mirroring (Hupfeld et al., 2020).

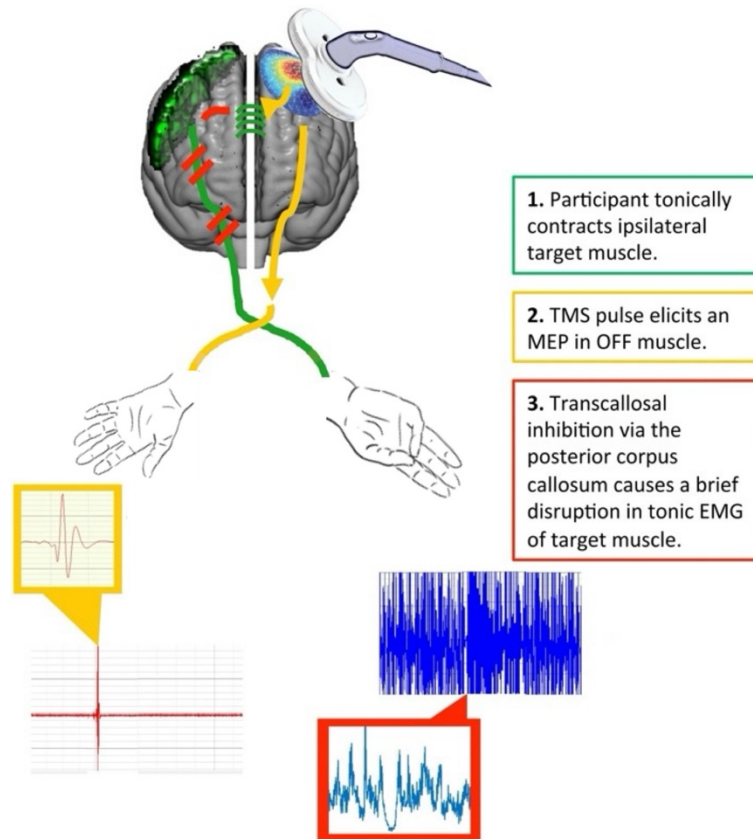


Fig 3 – iSP pathways

Frontal view of the brain. Stimulation with TMS on left M1 with positive projections through the corpus callosum, inhibitory interneurons that transmit to descendent pathways. MEP on the right hand resulting from stimulation of left M1 and ipsilateral silent period of an EMG registration of contracted muscle. Modified from (Hupfeld et al., 2020)

Recent studies using TMS and electroencephalogram (EEG) have identified two components of TMS-evoked potentials (TEP) as indexes of transcallosal communication during iSP registration. These components, occurring 15 ms after motor area stimulation are M1-P15 (positive evoked potential from M1 stimulation) and dPMC-P15 (positive evoked potential from dorsal premotor cortex stimulation). Of these, only M1-P15

³ Rapture of a blood vessel in the brain resulting in bleeding (i.e. hemorrhagic stroke) (Làdavas Elisabetta & Berti Anna, 2020)

amplitude correlated with the inhibition of the contralateral M1 as measured by iSP. Specifically, the larger the TEP was, the greater the iSP normalized area. These results suggest that transcallosal inhibition is highly specific to the primary motor cortex (Bortoletto et al., 2021; Zazio et al., 2022).

1.3 Contralateral Learning Transfer (CLT)

Research on humans and animals has demonstrated that knowledge acquired with one hand transfers to the other, a phenomenon known as contralateral learning transfer (CLT) (Japikse et al., 2003). This ability is a crucial aspect of the motor system. It has been observed in different tasks including prism adaptation (Edward Taub & Israel A. Goldberg, 1973), inverted or reversed writing (Parlow & Kinsbourne, 1989), figure drawing (Thut et al., 1996) and motor sequence learning (Camus et al., 2009; Grafton et al., 2002). Additionally, Dickins et al. (2015) found that CLT following unilateral dominant hand training does not appear to be affected by age in both simple (i.e., repeated thumb abduction) and complex (i.e., sequential finger-thumb abduction) tasks.

Recent functional imaging studies have revealed that M1 contralateral to the untrained hand (i.e., the hemisphere ipsilateral to the trained hand) is active during sequence learning tasks and implicit motor learning of the trained hand (Camus et al., 2009). Furthermore, interactions between the two hemispheres likely contribute to this intermanual transfer related to procedural knowledge, as evidenced by split-brain (i.e., person with a severed corpus callosum) and acallosal (i.e., individuals without the corpus callosum) patients exhibiting deficits in this domain. Moreover, it has been demonstrated that the transfer of motor skills to the unskilled hand following the learning of a unimanual task is strongly linked to interhemispheric inhibition (IHI) modulation between both hemispheres (Camus et al., 2009; Kuo et al., 2017).

Despite the current findings, some aspects of CLT still require further understating. This study aims to investigate the existence of CLT and assess how inter-hemispheric brain connectivity, measured through iSP, may impact its magnitude.

2. Methods Experiment 1

2.1 Participants

Twenty-five healthy individuals, all right-handed (19 females and six males, 31 ± 8 y.o. [range: 21-50]) were recruited for the study using an internal database. Right-handedness was confirmed using The Edinburgh Handedness Inventory (Oldfield, 1971). Prior to the study, participants were provided with detailed information regarding the experimental procedures and provided written consent in accordance with the Helsinki Declaration. Four participants were subsequently excluded from the analysis because their results were outliers, with more than two degrees of standard deviation from the mean, and their failure to achieve maximal contraction of the left hand during the experimental protocol. The experiment was approved by the local ethical committee “Area Vasta Emilia Nord” (n. 10084, 13.03.2018). The experimental design described in the following paragraphs, is graphically summarized in Figure 4.

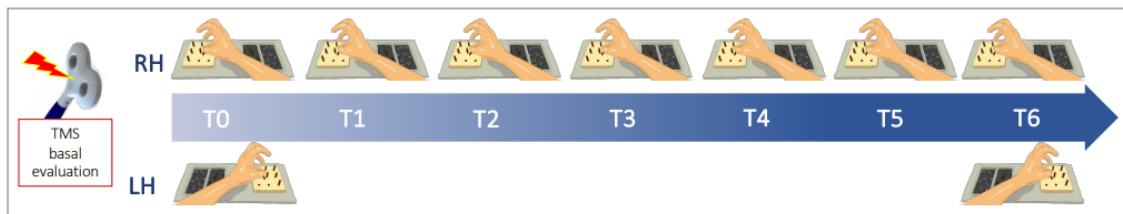


Fig 4 – study design

In the first phase (i.e., baseline evaluation), TMS was used to register ipsilateral silent periods (iSP) while subjects contracted the ipsilateral opponens pollicis muscle (OP). In the second phase (i.e., motor task evaluation) a modified version of the Nine Hole Peg Test (mNHPT) was performed with both dominant and non-dominant hand (T0). In the third stage (i.e., motor training) the motor task was repeated with the dominant hand (T1-T6). The last trial included left-hand execution as well. Modified from (Nuara et al., 2023)

2.2 Experimental procedure

The participants were seated comfortably in an armchair with both arms placed at a 90° angle on a table in front of them. EMG signals were recorded from both hands using Ag-AgCl electrodes. Two electrodes were placed on both the right and left opponens pollicis muscle (R-OP, L-OP) while the grounding electrode was placed on the right pisiform bone. The EMG signals were amplified ($\times 1000$) using a CED1902 amplifier (Cambridge Electronic Design), sampled at 2.5 kHz and filtered with an analogical online

band-pass (20–500 Hz) and a notch (50 Hz) filter. Data acquisition was performed using a CED Micro 1401 interfaced with Spike2 software (Cambridge Electronic Design), and digital markers of the TMS triggers were integrated into the same EMG file. The data was stored for subsequent analyses. TMS was administered using a figure-of-eight coil (70 mm) connected to a Magstim BiStim stimulator (Magstim, Whitland, UK), delivering monophasic pulses inducing current in a posterior-anterior direction on the scalp, with the coil handle rotated 45° from the sagittal plane.

The experimental protocol closely followed the method outlined by Nuara et al. (2023). Initially, a brain template of each subject was created using an optoelectronic neuro-navigation system (visor2, ANT Neuro, Netherlands) registering the individual head landmarks (nasion, ears, scalp surface). Subsequently, using the brain template, the TMS coil was positioned over the hand knob area in the precentral gyrus. TMS pulses were delivered at 35% of the maximal stimulation output within a distance below 2 cm from the initial location. If no MEPs were induced, the TMS intensity was increased incrementally by 5% until MEPs ($> 50 \mu\text{V}$) were elicited. The coil position corresponding to the optimal hotspot for R-OP, where the highest and most reliable MEPs were induced, was then determined and recorded in the neuro-navigation system. A dedicated monitor provided the experimenter with online visual feedback for accurate coil-target placement, ensuring minimal spatial errors during stimulus delivery. The maximum allowed spatial errors for stimulus delivery were as follows: (a) a tilt angle of up to 10° from the target, (b) a rotation angle of up to 10° from the target, and (c) a linear distance of up to 5 mm from the target. All TMS stimuli were accurately delivered, below the error threshold.

The TMS parameters recorded are as follows:

- 1- The resting motor threshold (RMT) is defined as the lowest stimulator output intensity capable of eliciting MEPs greater than 50 μV peak-to-peak amplitude in relaxed R-OP in at least 5 of 10 trials (Nuara et al., 2023).
- 2- 15 MEPs were acquired by delivering 15 single-pulse TMS with an intensity increased by 120% of the RMT. The stimulation was targeted at the hotspot for R-OP with both hands resting on the table.

- 3- 15 ipsilateral silent periods (iSP) were acquired with the same procedure as for MEPs, while the participant maintained a maximal contraction of the L-OP

The voluntary contraction commenced upon the verbal cue from the experimenter, who regulated the delivery of TMS pulses. Participants were instructed to initiate the voluntary contraction at each action onset and relax during the intertrial period. A time gap between successive TMS pulses was considered to prevent rTMS effects.

iSP parameters were derived from the rectified traces of the L-OP EMG signal. iSP onset was identified as the point where EMG activity decreased by at least two standard deviations from the baseline (60-10 ms pre-stimulus), with a minimum duration of 10 ms. iSP offset was determined as the first point after iSP onset, where EMG activity returned to baseline. iSP duration was calculated from onset to offset, while iSP area represented the EMG area between iSP offset and iSP onset. Baseline area was defined as the EMG area between 60 and 10 ms before the TMS stimulus. Subsequently, iSP normalized area was calculated for every participant according to the formula:

$$iSP_{\text{normalized area}} = \left(1 - \frac{iSP_{\text{area}}}{\text{baseline}_{\text{area}}}\right) \times 100$$

(Kuo et al., 2017)

2.3 Motor task

A modified version of the Nine Hole Peg Test (mNHPT), a standardized measure of upper limb function (Oxford Grice et al., 2003), was employed to evaluate motor proficiency. Research indicates that NHPT scores exhibit improvement with repeated administration, suggesting its suitability for assessing motor learning over time (Solari et al., 2005). Participants were seated at a table with a wooden block with nine empty holes on one side and a divided container on the other, containing nine pegs and nine nuts, respectively. Upon receiving a starting cue, participants were instructed to retrieve and place the pegs into the designated holes sequentially, followed by the nuts in the same predetermined order (from left to right, top to bottom). Subsequently, participants removed the nuts and pegs placing them back into the proper container one at a time.

During the initial assessment (T0), both the dominant and non-dominant hands underwent evaluation (see Fig. 4, task performance). The task was then repeated for five times (T1-T5) exclusively with the right hand, with a final repetition using both hands to assess motor proficiency.

Notably, participants were instructed to utilize a pinch grasp (thumb-little finger) throughout the task. This constraint, along with the addition of nuts, was integrated into the modified version of the test, thereby delaying the occurrence of the “ceiling effect” (i.e., reaching maximal proficiency where further improvement becomes undistinguishable) (Meier & Feeley, 2022). The task sessions were video-recorded and subsequently scored offline. The primary outcome measure was the time taken to complete the mNHPT.

2.4 Data analysis

Using Signal software, we imported the EMG data from two channels (positive and negative, capturing signals from both the right and left hand along with grounding) and an additional channel containing digital markers of the TMS triggers. Subsequently, we reviewed the EMG trace sampling to ensure the accurate detection of every MEP and iSP synchronized with the corresponding TMS pulse. Parameters such as iSP duration, area, and normalized area were recorded. However, our analysis primarily focused on iSP normalized area, following the recommendation by Kuo et al., (2017), due to its reduced variability resulting from oscillatory EMG activity and various contraction levels. The motor task videos underwent assessment using VLC with the ‘time’ extension enabling frame-by-frame examination and precise task duration registration. Excel was utilized for data storage and analysis.

Initially, we established a template including subject identifiers, age, sex, RMT, MEP amplitude (peak-to-peak), iSP duration, iSP area, baseline area and task performance scores. Subsequently, iSP normalized area was computed using the formula outlined in section 2.2. After data normalization, we evaluated performance improvement for each subject and hand across every trial, using the following formula:

$$\frac{T0 - T_n}{T0}$$

to express data as a percentage change from baseline. iSP mean and standard deviation calculations were performed for each participant, with outliers exceeding two standard deviations discarded. This led to the exclusion of four subjects, resulting in a final sample size of 21 subjects (18 F, 31 ± 7 y.o. [range: 21-50]). Furthermore, all iSPs were collected and the normality of the sample was verified using a Shapiro test conducted in R programming.

Regarding behavioral analysis, two paired t-test were conducted between T0 and T6 performances in each hand to verify significant performance improvement. ANOVA within subjects with Benjamini-Hochberg correction (BH) was employed for the right hand to evaluate performance improvement across each trial. We also correlated the right-hand improvement and the left one to investigate the relationship between the two variables.

Finally, a simple regression analysis was performed to explore the potential predictive value of iSP normalized area (independent variable) on CLT (dependent value). CLT was assessed using a transfer index ratio calculated by dividing the improvement in the left hand (LH) performance by that of the right hand (RH), according to the following formula:

$$\frac{(T0_{LH} - T6_{LH})/T0_{LH}}{(T0_{RH} - T6_{RH})/T0_{RH}}$$

3. Results Experiment 1

The normality of the sample distribution was verified with a Shapiro test. iSP normalized area spanned from 0.843 to 0.943 with a median of 0.889. The mean and standard deviation were also calculated (0.896 ± 0.03). iSP distribution is shown in Fig 5. iSP duration and area were not used in further analysis, but we calculated the mean and standard deviation of both (iSP duration = 0.023 ± 0.005 , iSP area = 0.004 ± 0.002).

Regarding RMT, we witnessed a bit of variability, with 33 being the lowest threshold registered and 61 the highest ($46 \pm 6,957$).

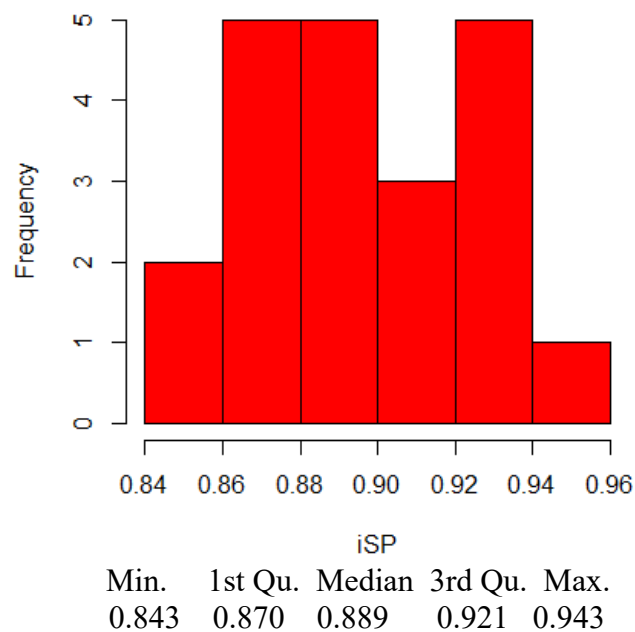


Fig 5 – iSP normalized area distribution
Histogram of iSP normalized area distribution

3.1 Behavioral results

ANOVA within-subjects analysis revealed significant improvement overall and between each training session of the right hand, suggesting that motor learning occurred (T0-T6, $p < 0.001$, $R^2 = 0.48$). Consistent with a typical learning curve, the biggest improvement was found between T0 and T1 ($p < 0.001$), followed by a progressively reduced but still significant improvement between T1 and T3 ($p < 0.01$). Finally, the rate of improvement lessened further from T2 ($p < 0.05$) (see Fig 6).

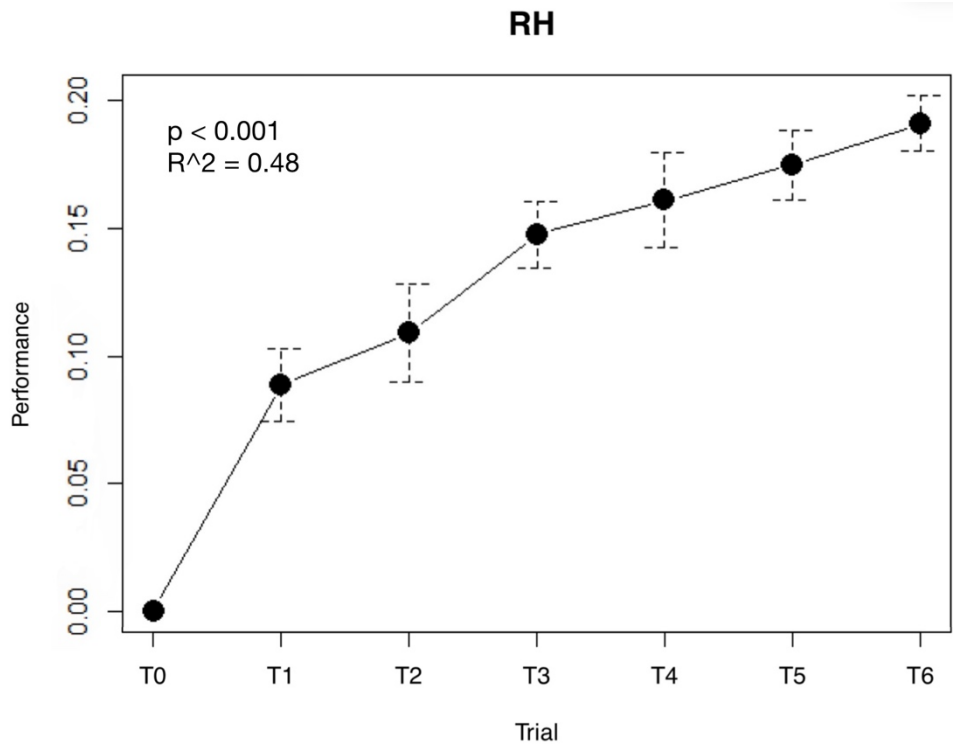


Fig 6 – motor improvement in the right hand

The improvement of the left hand was also significant ($p < 0.001$, $R^2 = 0.77$) (Fig 7). This result indicates learning transfer from the dominant to the non-dominant hand.

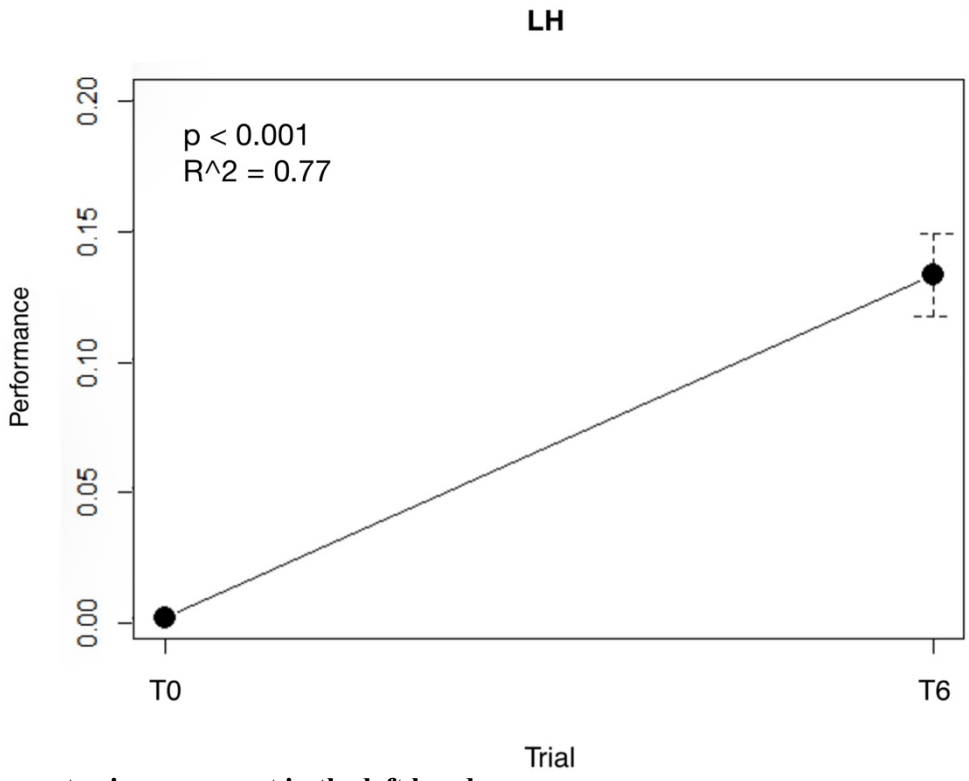


Fig 7 – motor improvement in the left hand

The correlation between the improvements in right and left-hand performance was not statistically significant ($p > 0.05$, $R^2 = 0.14$) even if a positive trend was detectable (see Fig 8).

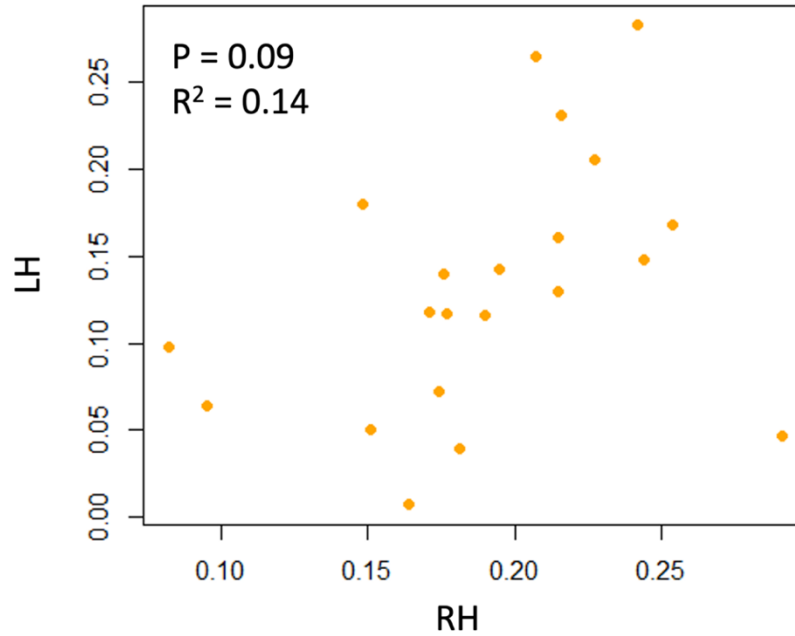


Fig 8 – correlation between improvement in the right and left hand

3.2 Regression analysis

Linear regression analysis (Fig 9) highlighted the predictive value of iSP on CLT ($p = 0.0025$, multiple $R^2 = 0.3882$, Adj. $R^2 = 0.356$). iSP accounted for 38% of the variability of CLT. Moreover, multiple R^2 and the adj R^2 values were very similar suggesting both the reliability of the model and its potential for generalization.

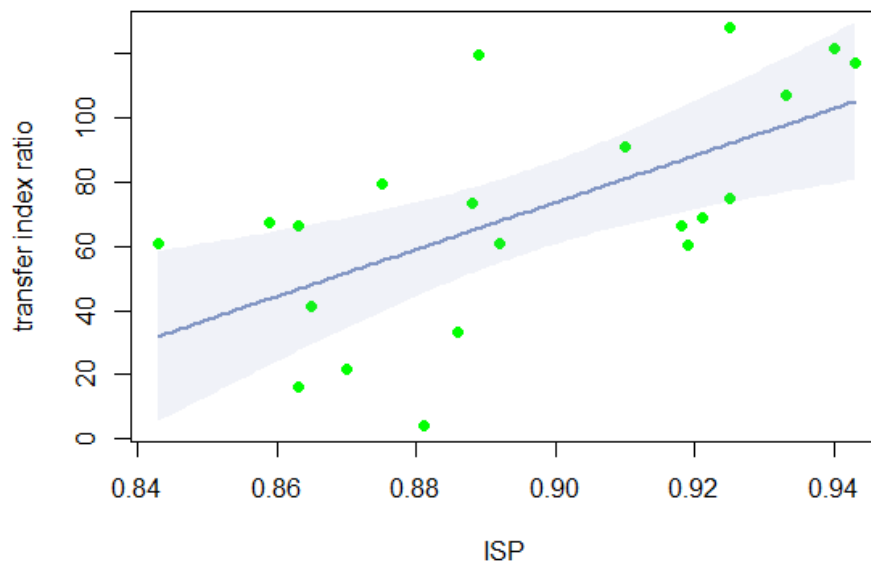


Fig 9 – linear regression analysis

4. Summing up Experiment 1

In the present study, we investigated CLT and the predictive value of iSP. The results show that improvement in task performance is evident following training. While this outcome was expected, an interesting aspect is that, at a behavioral level, we found an improvement in the hand that did not undergo training, indicating a transfer of improvement. Moreover, our results show that the contralateral transfer of motor learning depends on iSP, with an explained variance of nearly 40%.

Starting from these premises, the second experiment aims to investigate whether the training involving the non-dominant hand (i.e., the left hand in right-handed participants) impacts the untrained hand. In other words, we behaviorally investigated the bidirectionality of CTL while maintaining the same experimental setting and testing right-handed participants. In this second experiment, we did not examine the neurophysiological response using TMS.

5. Experiment 2

5.1 Participants

Twenty healthy participants, all right-handed (11 females and 9 males, 31 ± 14 y.o. [range: 20-59]) were recruited for the study using local networks. Right-handedness was confirmed using The Edinburgh Handedness Inventory (Oldfield, 1971). Before the study, subjects received detailed information regarding the experimental procedures and provided written consent as stated in the Helsinki Declaration.

5.2 Motor task

The experiment was conducted as described in paragraph 2.3. The sole difference was the trained hand, that was the non-dominant one (left hand). The initial assessment (T0) was performed by both the dominant and non-dominant hand separately (see Fig. 4, task performance), while the following five repetitions (T1-T5) were performed with the left hand. At the end of the training, the task was conducted with both hands was conducted to assess motor proficiency.

5.3 Data analysis

As described in paragraph 2.4 we evaluated performance improvement for each subject across every trial. Pearson's correlation analysis was conducted to assess the relationship between age and performance for both hands and between handedness and performance. ANOVA withing subjects was employed to examine performance improvement with Benjamini-Hochberg correction (BH). Subsequently, a correlation between the left hand improvement and the right one was performed to investigate potential associations. Moreover, we analyzed CLT using a transfer ratio index (see paragraph 2.4) and compared the results with the first experiment using the Mann-Whitney U test.

6. Results Experiment 2

Participants' age and handedness did not correlate significantly with performance ($p > 0.05$), suggesting that these variables did not influence their performance. Moreover, ANOVA within-subjects on the left hand was statistically significant ($p < 0.001$, $R^2 = 0.29$), indicating that the training of the left hand was effective (Fig 10). Consistent with the results in paragraph 3.2, the improvement was not linear. Between T0 and T1, motor performance was enhanced significantly ($p < 0.01$), whereas from T3, the rate of improvement decreased, though it remained statistically significant ($p < 0.05$).

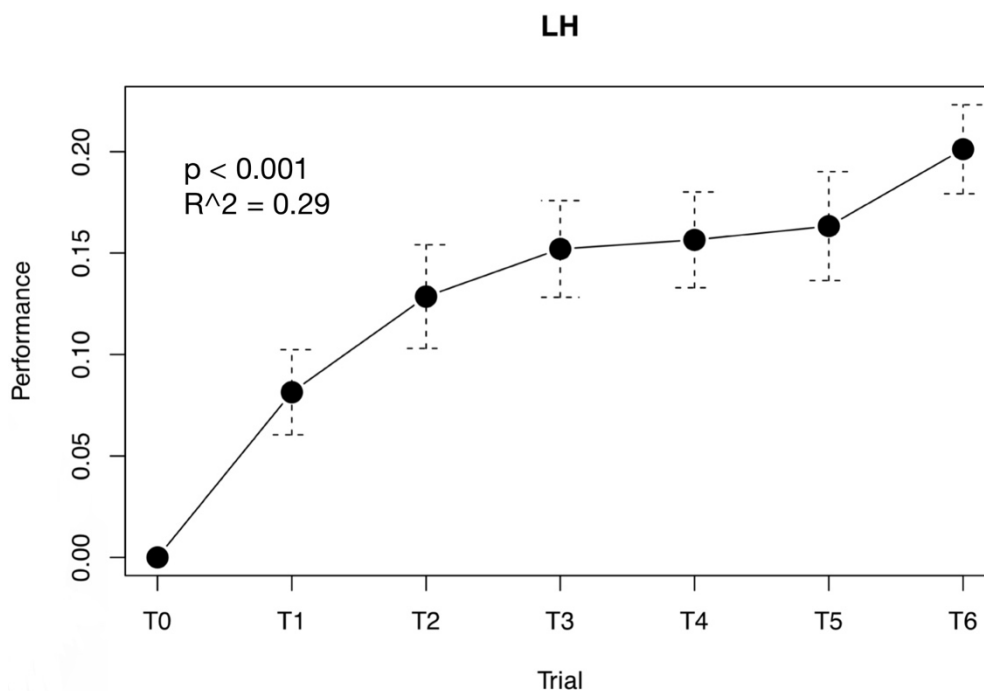


Fig 10 – motor improvement left hand

When analyzing the performance obtained by the contralateral hand, we witnessed a significant difference between T0 and T6 ($p < 0.001$, $R^2 = 0.54$) (see Fig 11). However, the correlation analysis between left and right hand performance improvement was not significant ($p > 0.05$, $R^2 = 0.0253$) (Fig 12).

Subsequently, we calculated the transfer ratio index (0.69 ± 0.87) that was not significantly different from the one of the first sample ($p > 0.05$, $p = 0.2382$).

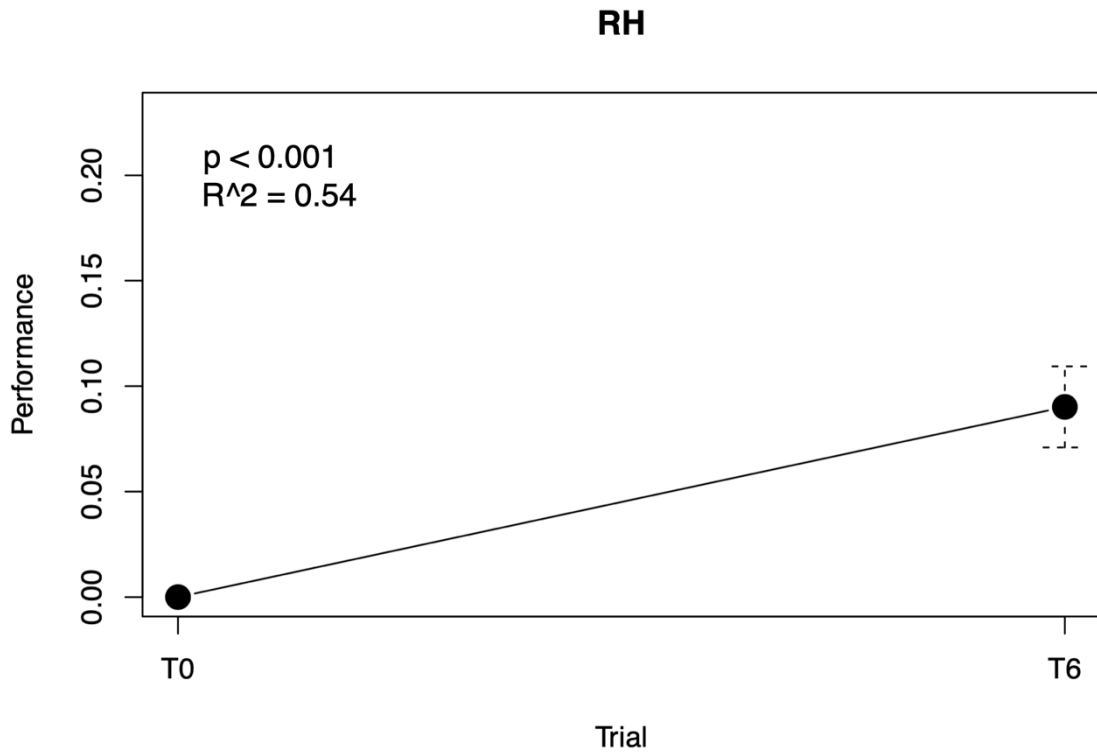


Fig 11 – motor improvement in the right hand

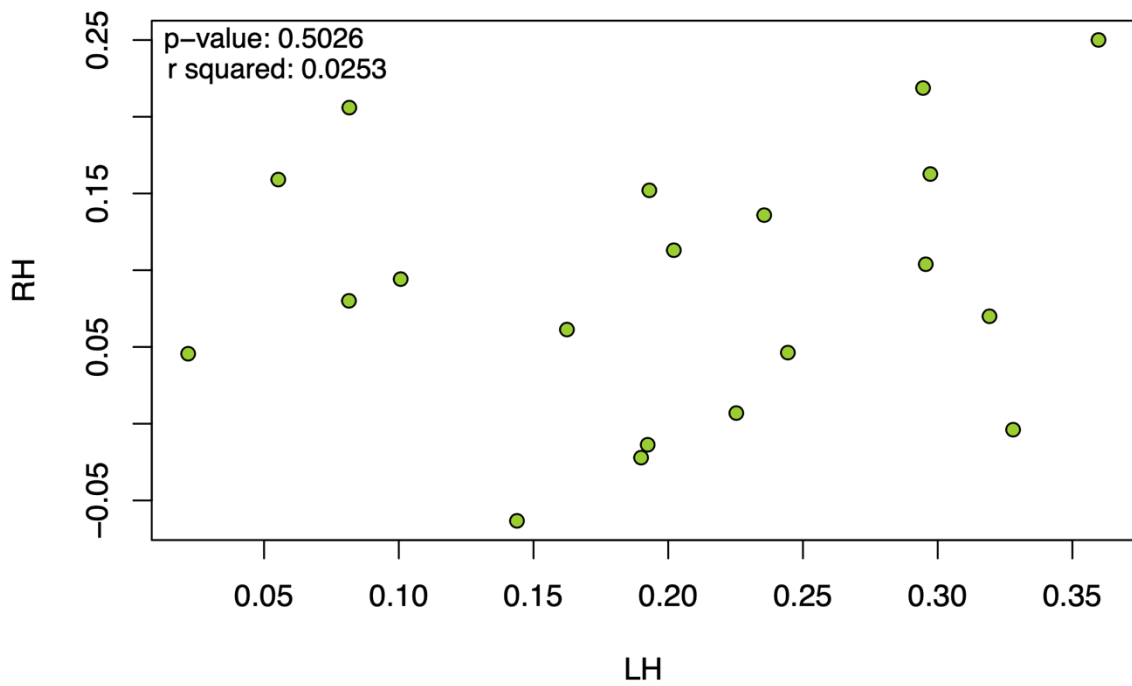


Fig 12 – correlation between left and right hand performance improvement

7. Summing up Experiment 2

The present study aimed at exploring CLT in terms of performance improvement in the non-trained hand. The results showed that the training of the non-dominant (left hand) had an impact on the contralateral one, resulting in a 9% improvement, supporting the notion that CLT is bidirectional.

8. Discussion

8.1 Bidirectional or unidirectional nature of CLT

Our results indicate that following training, performance improvement was evident in the untrained hands regardless the handedness. These results were corroborated by the lack of significant differences between the two experiments indicating the transferability of motor skills from the non-dominant hand and vice versa.

Different studies have investigated the possible symmetry of CLT in literature, but the results are not complete and often contradictory. For instance, Paparella et al. (2023) conducted a TMS research on right-handed individuals performing a visuomotor task while assessing IHI. They observed comparable motor learning in both hands. However, CLT was found exclusively from the dominant to the non-dominant hand. These findings support the asymmetric nature of CLT and its association with the modulation of specific inhibitory interhemispheric connections. In particular, the degree of transfer in the visuomotor task seemed to correlate with the extent of reduced inhibition between hemispheres.

Opposite results are reported by Dirren et al. (2021). In their fMRI experiment subjects trained their non-dominant left hand in a finger tapping. Learning transfer was observed in both hands, independently of the trained hand's performance. Similarly, other studies reported symmetrical CLT regardless of task type, magnitude or direction, unlike the learning rate (Yadav & Mutha, 2020).

Other studies found less polarized results. In the study conducted by Kirsch & Hoffmann, (2010), right-handed subjects underwent training in either their dominant or non-dominant hand. Throughout the training they had to respond to the original sequence of stimuli or the mirrored one. The findings revealed contralateral learning transfer for both hands but with qualitative differences. Training the dominant hand improved the left hand's performance when responding to the original sequence, while training the non-dominant hand enhanced the performance of the right hand for the mirrored stimuli.

In addition, in a study involving right-handed participants, it was discovered that the control mechanisms governing movement speed differed between the dominant and non-dominant arm. Specifically, the right arm varied acceleration amplitude per movement speed, while the left changed acceleration duration (Schaefer et al., 2007).

Similar results were reported by Sainburg et al. (2016) proved in a single-joint task in which reaches were targeted to 4 different distances. While speed and accuracy were similar between both arms, acceleration resulted to be different. In particular, training the dominant arm led to higher acceleration amplitudes in peak velocities in the left arm, while training the non-dominant arm resulted in longer acceleration duration for the right arm. These results suggest that interlimb transfer can enhance performance symmetry between arms and imply that hemispheric specialization influences transfer.

Within the ongoing debate about the nature of CLT, our data provides compelling evidence that the training exerts a bidirectional effect. Specifically, our findings from both experiments indicate a significant improvement in the performance of the untrained hand, suggesting that the benefits are not limited to the hand directly involved in the training. Moreover, the neurophysiological results highlight the predictive value of ISP, offering valuable insights into how training-induced improvements behave.

8.2 Neuroanatomical and functional substrates underlying CLT

Various studies employing different methodologies, such as functional magnetic resonance imaging (fMRI) and EEG have provided insights into the potential areas and mechanisms involved in learning transfer, although these findings are often inconsistent. For instance, Perez et al. (2007) in an fMRI study, investigating CLT using a similar paradigm as ours, found increased activity in the supplementary motor area (SMA) during successful skill transfer. Additionally, they reported that CLT was inhibited when rTMS was applied over SMA without affecting skill acquisition, indicating that SMA may support CLT. Subsequent research conducted by Dirren et al. (2021) corroborated these findings. Using fMRI before and after motor training, they showed that changes in connectivity within the motor network, particularly between trained and untrained M1 and between SMA and the untrained M1, correlated with transfer following training. They proposed that SMA might facilitate the transfer by converting spatial variables of movement representations into motor sequences that the untrained hand can execute. Furthermore, they suggested that the premotor cortex (PMC) could be another region supporting CLT. Specifically, they observed that CLT was linked to increased pre-training functional connectivity between the left PMC and the dorsal attention network.

Collectively, these findings indicate that the transfer process is facilitated by the interaction between attentional, executive, and motor systems, while post-training CLT is linked to enhanced connectivity between trained and untrained M1s, SMA and PMC.

Focusing on the premotor cortex, Gabitov et al. (2016), provided additional evidence for the involvement of this area in learning transfer. They reported a correlation between transfer and changes in the functional connectivity between the two M1 and between the ‘trained’ M1 and the left dorsal premotor cortex (dPMC). However, no correlation was detected between these two pathways, suggesting two independent neural routes for CLT: one connecting the two M1s directly and one involving projections to the dPMC. They hypothesized that dPMC is responsible for recalling sequence-specific knowledge obtained with the ipsilateral hand. In contrast with the two previously mentioned studies, they did not find evidence supporting the contribution of SMA in CLT.

Finally, an EEG study conducted by Veldman et al. (2018) showed that the interplay between the two M1s was solely responsible for CLT. Interhemispheric connectivity between the two M1s and S1 and M1 in the non-practiced hemisphere correlated to CLT consolidation, while increased connectivity from M1 to the dPMC and from dPMC to the SMA correlated with skill acquisition.

9. Conclusion

In conclusion, our study shows the bidirectionality of CLT following the execution of training. It also supports, from a neurophysiological perspective, the idea that the structure mediating this effect is the corpus callosum. Furthermore, it can be concluded that the impact of circuitry within the hemisphere, known to be asymmetric, plays a marginal role. Our data indicates that ISP is a biomarker of transcallosal transmission and thus becomes a predictor of learning capacity not on the contralateral hand but on the ipsilateral hand. This provides further evidence of the involvement of the corpus callosum and represents a potential tool to evaluate, in advance, whether a subject has a good chance of transferring the trained skill to the other hand.

Beyond their physiological value, these data have potential in rehabilitation pathways, considering the individualization of treatments for all those conditions where hemispheric imbalance suggests adopting contralesional training to condition the lesioned hemisphere. If validated in a clinical population, these findings would allow for verifying the effectiveness of the contralesional training approach in clinical settings. Specifically, if our study's results are confirmed through patient trials, they will provide evidence supporting the efficacy of CTL in clinical rehabilitation programs. This training method, which leverages the non-affected hemisphere to condition and enhance the function of the lesioned hemisphere, could thus be established as a beneficial treatment for patients with specific brain injuries or conditions.

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