



Asymmetric relationship between transcallosal inhibition and contralateral learning transfer of hand motor skills

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Dear Editor,

Beyond improving the dexterity of the actively practiced hand, unilateral motor practice also improves the motor skills of the contralateral one - a phenomenon known as Contralateral Learning Transfer (CLT) [1]. The corpus callosum plays a crucial role in mediating this effect, as demonstrated by studies indicating that disrupted callosal connectivity markedly hinders CLT in both humans [2] and non-human primates [3]. Transcranial magnetic stimulation (TMS) studies further suggest that post-training reductions in interhemispheric inhibition are associated with the contralateral transfer of visuomotor skills [1] and shorter response times in the untrained hand [4]. Here, a critical question is whether CLT can be reliably predicted before training begins. Addressing this would have substantial theoretical and practical implications, particularly in rehab and training environments, where exercise lateralization is often central to achieving clinical and performance goals. Indeed, stratifying individuals by their proneness to transfer motor skills could enable the design of targeted, physiologically driven interventions.

With this aim in mind, here we tested whether the pre-training ipsilateral silent period (ISP) – a TMS measure of transcallosal inhibition – predicts subsequent CLT.

The ISP is a brief reduction in muscular activity triggered by a suprathreshold single-pulse to the primary motor cortex (M1) ipsilateral to the recorded muscle. This effect is mainly mediated by trans-callosal excitatory (glutamatergic) motor fibers that synapse onto inhibitory (GABAergic) interneurons in the contralateral M1 [5].

All participants provided written informed consent prior to participating in the study, in accordance with the Helsinki Declaration. The experimental procedures were approved by the local ethics committee "Area Vasta Emilia Nord" (approval number 10084, 13/03/2018). We recruited two groups of 30 healthy, right-handed [6] individuals (Group1: 11 M, 19 F, mean age = 30.77 ± 7.25 ; Group2: 12 M, 18 F, mean age = 26.67 ± 2.85). ISP was collected by stimulating the dominant M1 in Group1, and the non-dominant M1 in Group2, with surface EMG recording activity from the Opponens Pollicis (OP) muscle

ipsilateral to the stimulated hemisphere. TMS was applied at 120 % of the resting motor threshold, and each participant underwent 15 trials. Then, we computed the ISP relative amplitude, duration, and area reduction (ISP_{AR}) (see supplementary materials for methodological details). Both amplitude and duration indicated stronger inhibition from the dominant to the non-dominant hemisphere, in line with a marginally yet significantly larger ISP_{AR} in Group1 ($88.5 \% \pm 3.2$) than Group2 ($86.5 \% \pm 2.7$; $p = 0.011$; Cohen's $d = 0.67$; see [Supplementary Fig. 1](#)).

Following ISP collection, participants were involved in a motor learning paradigm based on a modified version of the Nine-Hole-Peg Test [7]. Participants of Group1 were asked to perform the motor task as fast and accurately as possible with their right hand for 7 consecutive times (T0-T6). At T0 and T6, the performance of the left (untrained) hand was also assessed. Participants of Group2 underwent the same procedure, but involving the left hand as the trained one (see [Fig. 1](#), panel A).

Both groups exhibited a similar T0-T6 improvement in the trained hand (Group1: $18.8 \pm 5.9 \%$, Group2: $18.5 \pm 6.3 \%$), and comparable gains in the untrained hand (Group1: $11.0 \pm 7.7 \%$; Group2: $8.4 \pm 6.8 \%$). Likewise, the CLT – quantified as the ratio between untrained and trained hand improvement – did not significantly differ between groups (Group1: $59.2 \pm 38.2 \%$; Group2: $47.7 \pm 35.8 \%$; $p = 0.27$; see [Supplementary Fig. 1](#)). However, a striking hemispheric difference emerged in the relationship between ISP_{AR} and CLT: pre-training ISP_{AR} strongly predicted CLT from the dominant to the non-dominant hand (linear regression model, $R^2 = 0.48$, $p < 0.001$), explaining nearly 50 % of the variance. In contrast, no predictive relationship was observed in the opposite direction ($R^2 = 0.008$, $p = 0.63$, see [Fig. 1](#), panel B).

Positing the directional specificity of the relationship between ISP_{AR} and CLT as our main finding, we cannot attribute this effect solely to the corpus callosum, given its well-established bidirectional and anatomically symmetrical structure. A more compelling explanation centers on the functional asymmetry in motor cortex recruitment during manual tasks. Specifically, movements performed with the non-dominant hand elicit more bilateral activation of higher-order motor areas (e.g., pre-motor and supplementary motor areas) compared to movements with

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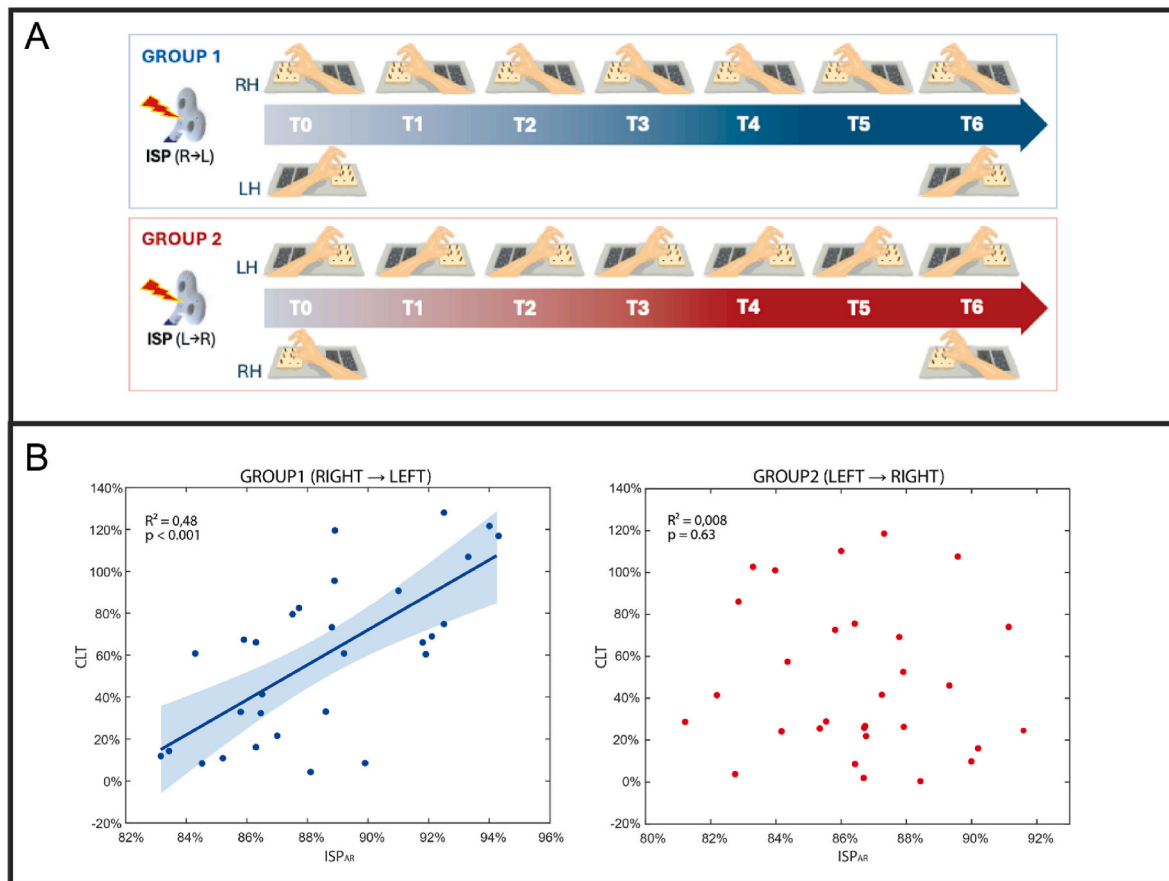


Fig. 1. **Panel A.** Study design: following ISP collection (Group1: left M1; Group2: right M1), the modified Nine Hole Peg test was performed for seven consecutive times (T0–T6) with the ‘trained’ hand (Group1: right hand; Group2: left hand), with the first (T0) and the last (T6) timepoint also including the ‘untrained’ hand performance. **Panel B.** Scatterplots representing the relationship between Ipsilateral Silent Period (ISP_{AR}) and Contralateral Learning Transfer (CLT), for each group (left of the panel: Group1; right of the panel: Group2).

the dominant hand [8]. In this context, training with the dominant hand may rely primarily on the corpus callosum to convey information to the ipsilateral (non-dominant) M1. In contrast, during non-dominant hand training, interhemispheric information flow may be integrated with parallel cortico-cortical processes, thereby diminishing the predictive value of ISP_{AR} for CLT in the non-dominant-to-dominant direction.

While the mechanisms discussed above involve inter-areal dynamics at a global scale, local neurochemical factors, such as the excitation/inhibition balance, may also contribute to the ISP_{AR} –CLT relationship. In right-handed individuals, the dominant M1 typically exhibits reduced intracortical inhibition compared to the non-dominant hemisphere [9], likely reflecting differences in GABAergic tone. GABAergic activity, a key neurophysiological substrate of ISP, plays a critical role in the fine-tuning and stabilization of motor engrams. The lower inhibitory tone in the dominant hemisphere may limit its ability to incorporate new motor engrams. Conversely, the non-dominant M1—characterized by higher local inhibition—may provide a more favorable substrate for integrating transcallosally transmitted motor information.

In summary, the predictive power of ISP on CLT observed exclusively following dominant hand training can be explained by both global and local factors, highlighting how hemispheric asymmetries shape the directionality and efficacy of interlimb transfer of learning. Notably, ISP_{AR} provides a comprehensive indicator of transcallosal inhibition that integrates information from both ISP duration and relative amplitude, whose respective contributions to CLT variability can be disentangled. As shown in [Supplementary Table 1](#), ISP relative amplitude is already a robust predictor of CLT in Group1 ($R^2 = 0.46$, $p < 0.001$). In contrast, ISP duration shows a weaker association ($R^2 = 0.19$, $p = 0.016$),

suggesting that both factors contribute to the amount of motor learning transfer, with the former playing a particularly key role in the process.

These insights underscore the pivotal role of hemispheric dominance, a fundamental and uniquely human trait underlying motor learning and skill specialization, in shaping interhemispheric communication.

Beyond their theoretical significance, our findings have important translational implications. ISP could serve as a biomarker for motor cross-education, potentially enabling personalized interventions for both healthy individuals (e.g., athletes, musicians) and clinical populations (e.g., patients with unilateral orthopedic injuries or Parkinson’s disease). Stronger pre-training ISP in the intact, dominant hemisphere may indicate greater susceptibility to cross-education, whereas weaker ISP might signal the need for alternative or complementary therapeutic strategies. Importantly, the ability to predict CLT responsiveness should not be regarded as a static constraint. Studying expert populations characterized by naturally enhanced interhemispheric symmetry, such as elite musicians [10], could provide causal evidence that atypical ISP profiles underlie exceptional CLT capabilities. In parallel, emerging evidence suggests that interhemispheric inhibition is a modifiable feature of brain function [11], opening the possibility that non-invasive brain stimulation techniques, such as TMS, could enhance CLT by selectively modulating transcallosal interactions.

CRediT authorship contribution statement

A. Nuara: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **A.**

Mancuso: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Data curation, Conceptualization, Formal analysis. **M.C. Bazzini:** Writing – review & editing, Writing – original draft, Investigation, Data curation. **L. Ferrari:** Writing – review & editing, Investigation, Data curation. **T. Petti:** Writing – review & editing, Methodology. **M. Fabbri-Destro:** Writing – review & editing, Supervision, Methodology, Formal analysis. **P. Avanzini:** Writing – review & editing, Supervision, Methodology, Conceptualization, Formal analysis.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.brs.2025.06.002>.

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