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Motor learning in unilateral cerebral palsy and the influence of corticospinal tract reorganization

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Abstract:	Cerebral Palsy (CP) is a complex neurological disorder, characterized by congenital motor disability associated with behaviour, perception and cognition disorders. The sensorimotor impairments represent the main hallmark of the disease, significantly impacting the quality of life. So far, few studies have investigated motor learning abilities in CP and their association with the plastic reorganization of the motor system remains largely unknown. The present proof-of-principle study explored explicit motor sequence learning in children with unilateral CP and different patterns of motor system reorganization (bilateral, ipsilateral, contralateral). Children with unilateral CP, and a group of age-matched typically-developing (TD) children, underwent a sequential finger tapping task, performed with the affected hand by children with CP and with the non-dominant hand by TD children. The pattern of corticospinal tract projections in hemiparetic patients was assessed by single-pulse Transcranial Magnetic Stimulation (TMS). The study showed the presence of finger dexterity impairments in children with unilateral CP presenting with a bilateral or an ipsilateral control of the affected (trained) hand, as compared to TD children. Conversely, motor sequence learning was impaired in unilateral CP with ipsilateral or contralateral corticospinal reorganization, but not in the case of a bilateral control of the paretic hand. These preliminary findings, although referred to small clinical samples, suggest that unilateral control of the paretic upper-limb, from the ipsilateral or the contralateral motor cortex, may not be sufficient to develop typical motor learning with the affected hand, which seems to require a bilateral representation in the motor cortex. This evidence has potential implications for fine motor skills rehabilitation in CP.
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HIGHLIGHTS

Disorders of fine motor control and learning in unilateral cerebral palsy

Corticospinal reorganization in cerebral palsy and finger dexterity and learning

Bilateral control of the paretic hand could be beneficial for practice-dependent learning

Abstract

Cerebral Palsy (CP) is a complex neurological disorder, characterized by congenital motor disability associated with behaviour, perception and cognition disorders. The sensorimotor impairments represent the main hallmark of the disease, significantly impacting the quality of life. So far, few studies have investigated motor learning abilities in CP and their association with the plastic reorganization of the motor system remains largely unknown. The present proof-of-principle study explored explicit motor sequence learning in children with unilateral CP and different patterns of motor system reorganization (bilateral, ipsilateral, contralateral). Children with unilateral CP, and a group of age-matched typically-developing (TD) children, underwent a sequential finger tapping task, performed with the affected hand by children with CP and with the non-dominant hand by TD children. The pattern of corticospinal tract projections in hemiparetic patients was assessed by single-pulse Transcranial Magnetic Stimulation (TMS). The study showed the presence of finger dexterity impairments in children with unilateral CP presenting with a bilateral or an ipsilateral control of the affected (trained) hand, as compared to TD children. Conversely, motor sequence learning was impaired in unilateral CP with ipsilateral or contralateral corticospinal reorganization, but not in the case of a bilateral control of the paretic hand. These preliminary findings, although referred to small clinical samples, suggest that unilateral control of the paretic upper-limb, from the ipsilateral or the contralateral motor cortex, may not be sufficient to develop typical motor learning with the affected hand, which seems to require a bilateral representation in the motor cortex. This evidence has potential implications for fine motor skills rehabilitation in CP.

Keywords: motor learning; cerebral palsy; corticospinal tract reorganization; motor cortex; dexterity.

Title: Motor learning in unilateral cerebral palsy and the influence of corticospinal tract reorganization

Running title: Corticospinal plasticity and motor learning

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1. INTRODUCTION

Cerebral palsy (CP) is a complex neurological disorder featured by movement impairments and caused by a non-progressive brain injury, occurring before birth or during the perinatal period. Disturbances of sensation, cognition, communication, perception, and behavior are also common, with significant impact on daily living activities[1,2]. Children with unilateral CP usually present with heterogeneous sensorimotor impairments, including spasticity, muscle contractures and weakness of both upper and lower limbs of the affected side[3,4]. The time of the lesion (i.e., before or early after birth)[5,6], its location and extent, as well as the type of the structural damage (i.e., brain malformations, periventricular or cortico-subcortical lesions), are critical factors affecting motor development and recovery in children with CP[7-10].

So far, few studies have explored motor learning capabilities in children with CP. As in a nonlinear process in which motor performance is extremely variable, motor learning involves the acquisition, consolidation and reinforcement of motor skills along cognitive, associative and autonomous stages[11-14]. At the beginning of the practice, there is a fast improvement of motor performance that primarily relies on explicit, conscious, processes; after long-term practice, sensorimotor maps become stronger and are stored in long-term memory, with a progression from explicit action's control to a more implicit or automatic control[15]. Despite a slower pace, children with CP seem to be capable of explicit learning, while implicit learning may be compromised[16,17]. Indeed, children and adolescents with spastic CP do not show implicit learning in serial reaction time tasks[16], suggesting that CP primarily impacts on the transition to automatic performance, which is less susceptible to attentional and cognitive control and sensory feedback. In fact, sequence memory skills and learning in children with CP seems independent from age and motor severity, being primarily influenced by cognitive abilities[17,18].

Abbreviations: CP= Cerebral Palsy; TD= typically developing; TMS= Transcranial Magnetic Stimulation; CST= Corticospinal tract; FTT= finger tapping task; MEPs= motor evoked potentials; SD= standard deviation; MACS= Manual ability classification system; JTT= Jebsen Taylor Hand Function Test; M1= primary motor cortex; EMG= electromyography; APB= abductor pollicis brevis; MT= motor threshold; MLI= motor learning index; ANOVA= Analysis of Variance.

A still open question about motor learning in unilateral CP concerns the influence of the plastic reorganization of the motor system, which is known to impact on upper limb motor function and recovery[19,20]. During typical motor development, there is a competitive withdrawal shaping the corticospinal tract (CST), by which ipsilateral uncrossed projections gradually weaken and contralateral crossed projections strengthen; this process results in a predominant contralateral control of voluntary upper limb movements[21,22]. Early unilateral injury can cause deviations from such normal CST anatomy, resulting in three main kinds of 'wiring' of the efferent projections from the motor cortex to the affected hand: the affected hand may receive input from crossed CST, originating in the damaged hemisphere (contralateral CST), from uncrossed CST originating in the intact hemisphere (ipsilateral CST), or from both crossed and uncrossed CSTs from damaged and intact hemispheres (bilateral CST)[22,23]. The different reorganizations of CST projections are related to the timing of the damage (according with brain maturation), as well as to the lesion location and extent. Therefore, in patients with periventricular lesions, typically occurring around weeks 24-34 of gestation and directly affecting the CST, the reorganization pattern is mainly related to the extent of the lesion (the larger the lesion, the more likely a complete contralesional shift of motor control); on the other hand, crossed CST projections from the damaged hemisphere are at least partially intact following cortical-subcortical postnatally acquired lesions[22]. Noteworthy, the type of CST wiring pattern impacts on upper-limb motor function and recovery, with better motor control in children with crossed CST projections from the affected hemisphere, as compared to those with ipsilateral and bilateral CST patterns[3,5,24,25].

The present pilot study explored motor sequence learning with the affected hand in children with unilateral CP, comparing them to age-matched typically developing (TD) children. Motor sequence learning refers to the process by which simple and stereotyped movements are performed effortlessly as a unitary sequence through repeated practice; it is assessed through improvements in accuracy and speed performance in motor sequence tasks[26]. Here, motor sequence learning was assessed through a finger tapping task (FTT), in which participants were trained to tap a fixed motor digit sequence. The FTT is a well-established paradigm to probe explicit motor learning, since participants are given a digit sequence to learn, to explicitly remember, and then to perform[27,28]. This task taps the strategic process of learning, by selecting and sequencing the most effective spatial targets of finger movements, at the conscious level[26,28].

However, dexterous finger movements are particularly affected in unilateral CP: hemiparetic children often exhibit diminished ability to move their fingers independently and a reduced capacity to create independent fingertip forces[29-30]. The development of fine motor control is strongly associated with practice and it is necessary for a useful interaction with the environment, as for instance to effectively use tools and perform challenging manipulation tasks, as well as to develop skilled gesture and efficient bimanual coordination[31]. The impairment of manual dexterity has a profound impact on the whole function of the upper limb and on the use of the hand in patients with CP[29]. Therefore, uncovering whether impaired finger dexterity can be improved through learning in unilateral CP is of relevance for the design of appropriate treatments targeting this relevant motor function. Moreover, since the corticospinal tract is the main responsible for the highly skilled finger movements[32,33], it is relevant to explore whether motor learning abilities in CP patients differ according to the CST reorganization. In the present study, CST reorganization was assessed by recording motor evoked potentials (MEPs) in the trained hand (the affected hand in children with unilateral CP) induced by single-pulse Transcranial Magnetic Stimulation (TMS) delivered over the primary motor cortex of both hemispheres[3].

2. MATERIALS AND METHODS

2.1. Participants

Nine children (4 males, mean age=10.9 years, standard deviation, SD=3.5, range=6-17) were enrolled, between June 2016 and June 2017, from a total of 38 patients with unilateral CP followed up at the out-patient clinic of the Developmental Neurology Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta (Milan, Italy). Children were included in the study according to the following criteria: clinical diagnosis of unilateral CP; age between 6-18 years; presence of mild to moderate upper-limb motor impairment (levels I-III of the Manual Ability Classification System); ability to perform independent finger movements, as to allow the administration of the FTT; normal visual functions; cognitive functioning in the normal range, as confirmed by clinical assessment and/or administration of age-specific Wechsler scales; disposability to attend the study. Exclusion criteria were: contraindications to non-invasive brain stimulation accordingly to international safety guidelines of TMS - e.g., active epilepsy in the last two years or intake of antiepileptic medication[34]; moderate to severe cognitive or behavioral disorders that could interfere with the experimental procedure; concomitant enrollment in intensive motor rehabilitation programs; treatment of the upper limb spasticity with botulinum toxin in the last 6 months or upper limb surgery. More frequent causes of exclusion were: age, severity of upper limb impairment, contraindication to TMS (in particular, concomitant epilepsy), inability to perform the motor task or TMS for behavioral/clinical reasons.

Before the experiment, children with CP underwent a clinical and neurophysiological assessment (see below): motor function of the affected hand was assessed through the Manual Ability Classification System and Jebsen-Taylor Hand Function Test, while the CST reorganization was evaluated with single-pulse TMS. Demographic and clinical details of the participants with CP are reported in Table 1.

[---Insert Table 1 about here ---]

Fifteen typically developed (TD) children served as control group. This sample included 8 males and 7 females, with a mean age of 11.7 (SD= 2.4) years (see Table 2). All TD participants had a normal or corrected-to-normal vision and none of them had history or evidence of neurological, psychiatric or other relevant disorders. According to the Oldfield's handedness questionnaire[35], 13 TD children were right-handed and 2 left-handed.

[---Insert Table 2 about here ---]

The study was approved by the Ethics Committees of the IRCCS Istituto Neurologico Carlo Besta (protocol NIBS-BIT, version 3.0) and of the University of Milano-Bicocca (protocol number 352). The study was conducted in accordance with the ethical standards of the Declaration of Helsinki. Parents were informed about the aim of the study and written informed consent was obtained from them.

2.2. Clinical Assessment

Manual ability of children with CP was clinically assessed by administering the following tests (see Table 1):

i) Manual Ability Classification System (MACS)[36]. MACS classifies manual ability based on how children use hands to manipulate objects in activities of daily living. The classification is made through a 5-point ordinal system (Range=I-V), with each level considering the need (or not) of assistance: lower scores indicate better outcomes. For instance, level I codifies children with minor limitations (i.e., able to handle objects easily and successfully), while those classified in level V have more severe functional limitations (e.g., unable to handle objects and having difficulties in performing simple actions).

ii) Jebsen-Taylor Hand Function Test (JTT)[37,38]. The JTT comprises 7 tasks (i.e., writing, turning cards over, picking up small objects, simulated eating, stacking checkers and moving light/heavy cans). Children are asked to perform each activity with their affected hand as quickly and accurate as possible. The JTT has been successfully used to assess hand function in TD children as well as in those with CP[36,39,40]. In the present study, the writing task was excluded since children with CP could not easily perform it with the affected hand. The total time (in seconds) needed to finish all tasks was used as the performance score; thus, lower scores reflect a better motor performance. In accordance with JTT guidelines, in case the child could not perform one or more tasks, a score of 180 seconds was assigned to the activity.

2.3. CST Assessment

All children with unilateral CP underwent the assessment of CST re-organization by measuring MEPs from the affected hand, which were induced by single-pulse TMS applied over the primary motor cortex (M1) of both hemisphere[3,22]. The CST assessment[3] was performed before the administration of the FTT. During the TMS assessment, children with CP comfortably seated on an armchair. Focal TMS pulses to M1 were delivered using a 80 mm figure-of-eight coil (Tonica Elecktronic A/S, Farum, Denmark), which was held tangential to the skull and aligned in the para-sagittal plane with the handle rotated 45° lateral. Online monitoring of the electromyographic activity (EMG) in response to TMS was performed. EMG signals were band-pass filtered (0.5 Hz - 2KHz), digitized, and stored on a computer for offline analysis (Keypoint, Alpine Biomed, Orage County, CA, USA). Ag-AgCl surface electrodes were placed bilaterally over the Abductor Pollicis Brevis (APB) **muscle** of both hands.

Firstly, we determined the motor hotspot, namely, the coil location over the M1 that elicited optimal (i.e. maximum amplitude and shortest latency) MEPs at the lowest stimulation intensity. Then, the resting and active Motor Threshold (MT) were determined for both hemispheres, with respect to contralateral hand muscles (see Table 3). For EMG recording, children were required to keep their hand relaxed during the TMS assessment; muscle activity was visually monitored to confirm the relaxed status before the stimulation. For active MT, children were asked to perform voluntary contractions of their thumbs during the TMS assessment. In both cases, TMS intensity was progressively increased at 5% steps until reliable MEPs were reached in about the 50% of 10-20 consecutive pulses **(i.e. upper threshold method)**[3,**42-43**]. In the affected hemisphere we could determine active and resting MT in 6 out of 9 children, while in 3 children (i.e., P4, P5 and P6) MEPs could not be evoked by stimulating the affected hemisphere, both in the active and in the rest conditions **even at 100% of the maximal TMS output**. The resting MT was higher than 84% (of the stimulator output) in the unaffected hemisphere of two children (i.e. P2 and P6), and in the affected hemisphere of two children (i.e. P2 and P9).

Afterwards, single TMS pulses to M1 of each hemisphere, at an intensity of 120% of the previously determined resting MT, were administered to induce 10 MEPs, following a standard protocol[e.g.3]. When the resting MT was >84% of the stimulator output, in order to obtain MEPs, TMS pulses were delivered at the 100% of the stimulator output (hence this intensity did not reach the theoretical 120% of the MT). MEPs were first selected by visual inspection, in order to exclude any possible artefact, and then averaged (Table 3). Any single MEP with amplitude less than 0.5 mV was excluded from average**: accordingly, we excluded from the mean obtained for the stimulation of the affected hemisphere 1 MEP in P1, 2 MEPs in P2 and 1 MEP IN P7; all MEPs <0.5 mV resulted from the stimulation of the affected hemisphere only.** Using this standard procedure[3], the pattern of CST reorganization (see Figure 1) in children with CP was classified as: (i) bilateral CST pattern, when MEPs in the affected hand were induced by applying TMS pulses over M1 of both hemispheres; (ii) ipsilateral CST pattern, MEPs in the affected hand were induced by TMS of the contralesional M1 only; (iii) contralateral CST pattern, when MEPs in the affected hand were induced by TMS of the ipsilesional M1 only[22,23,41]. According to this classification, our CP sample comprised 3 subgroups, each including 3 participants for each type of CST reorganization.

Worth mentioning, the classification of CST reorganization is TMS intensity-dependent; hence, in principle, it could be theoretically possible that some patients with an ipsilateral pattern could show a bilateral response with TMS pulses at higher intensity**, as by adopting a lower threshold method to define their MT[42-43]**. However, residual responses with very high stimulus intensity are unlikely to have functional significance[3] (for the same reason, we excluded from the analysis all MEPs with an amplitude lower than 0.5 mV, **which are difficult to distinguish MEPs from noise, e.g.[42]**.

[---Insert Figure 1 and Table 3 about here----]

2.4. Finger tapping task

The motor sequence learning task consisted in a modified version of the sequential finger tapping task (FTT)[44], which was adapted for stroke patients with upper-limb hemiparesis[45]; such adaptation was necessary also for our children with CP, who required more time to perform a digit sequence with the affected hand. Similar paradigms have been previously used in children with motor disorders of various origins, including CP[46-49]. During our FTT, children had to perform a sequential pressing of a fixed 5-element sequence (4 1 3 2 4) on a 4-button keyboard. Children with CP had to reproduce the sequence displayed on the computer screen with the corresponding fingers of their affected hand; instead, TD children practiced with their non-dominant hand. For children (both TD, or with CP) using the right hand, the following correspondence between fingers and numbers was used[44]: index=1, middle finger=2, ring finger=3, little finger=4. Conversely, for children using the left hand, the following correspondence was used: little=1, ring=2, middle=3, and index finger=4. In this way, the digits order was the same, and thus comparable, regardless of the used hand (right or left). The FTT requires to learn and then reproduce correctly the entire 5-element sequence; consequently, the reproduced sequence is considered wrong even if it contains a single incorrect press.

The task comprised 3 blocks of practice, each lasting 3 minutes, with 2 minutes of break between blocks. Participants were instructed to perform the motor activity as quickly and accurately as possible. In case of errors, they were asked not to correct, but to continue the task. An asterisk mark appeared after each button press (below the corresponding number) regardless of the correctness of the response. No feedback regarding **the correctness of responses** was provided.

Before administering the 3 experimental blocks, participants underwent a training session during which they were exposed to the 5-element sequence in order to ensure the understanding of the task and the knowledge of the requested motor sequence.

During the experimental session, children were invited to report whenever they felt tired, or if they wanted a longer break between blocks. None of the children complained of muscle fatigue during the task, nor they required longer breaks between blocks or asked to suspend the task.

The FTT was administered through a PC software (E-prime 2.0 Psychology Software Tools).

2.5. Statistical analyses

Statistical, non-parametric, analyses were performed using the IBM SPSS Statistics (Version 25). For each participant, the number of **correct sequences performed** and the overall total number of sequences reproduced (but regardless of their correctness) in each block of the FTT were considered[42]. Firstly, Friedman ANOVAs were used to detect differences between blocks of trials (improvements with practice, i.e. learning effect) in each group. Then, Kruskal-Wallis tests by ranks were used to compare, in each FTT block, the performance of each CP group with that of TD children. Significance was set at *alpha*=.05.

A further, exploratory, analysis (Kruskal-Wallis test by ranks) was run on a motor learning index (MLI), computed as a percentage as follows: [(number of correct reproduced sequences in the last block of practice - B3) *minus* (number of correct sequences in the first block of practice - B1)], *divided* by the number of correct sequences in B1, *multiplicated* by 100. The MLI takes into account the high between-participants variability at FTT and it reflects the rate of improvement at the task normalized on the 'starting' level of accuracy of each participant (for a similar approach see[50,51]). Additionally, Spearman's rank correlations were used to explore the association between the MLI and the manual ability of children with CP (JTT score and MACS level).

3. RESULTS

3.1. Correct sequences reproduced

Friedman ANOVAs showed a significant **improvement** across blocks of practice in TD children (χ^2 = 14.93, p< .0006), and in children with CP and bilateral CST reorganization (χ^2 = 6, p= .049), while performance did not change during the training in children with CP and ipsilateral (χ^2 = 2.6, p= .27) or contralateral (χ^2 = 1.27, p= .53) CST reorganization. In the first bock of practice (H= 12.825, p= .005), only **the number of correct sequences performed by** children with CP and contralateral CST reorganization was comparable to that of TD children (p= .9), while a significant worse performance was shown by children with CP and with bilateral (p= .034) or ipsilateral (p= .043) CST pattern, as compared to TD children. Similar results were found with respect to the second (H= 13.514, p= .003) and third (H= 14.34, p= .002) block of practice: the **number of correct sequences performed by** TD children was higher than that of hemiparetic children with bilateral (Block 2, p= .043; Block 3, p= .047) or ipsilateral (Block 2, p= .021, Block 3, p= .012) CST reorganization; children with CP and contralateral CST reorganization did not differ from TD children (Blocks 2 and 3, p= .9) (see Figure 2).

[---Insert Figure 2 about here---]

3.2. Total (correct plus incorrect) sequences

The analyses showed a significant increase of the total number of reproduced sequences, regardless of their accuracy, across blocks of practice only in TD children (χ^2=24.034, p<.0001). Instead, each CP group did not show any difference between blocks of practice: bilateral CST (χ^2 = 4.67, p= .097), ipsilateral CST (χ^2 = .8, p= .67), contralateral CST (χ^2 = 2, p= .37) (see Figure 3). The total number of sequences reproduced by children with CP with contralateral and bilateral CST projections were comparable to that of TD children in every FTT block (all ps>.07), while CP children with ipsilateral CST always differed from TD children (all ps<.01): Block 1 (H= 11.81, p= .008), Block 2 (H= 12.53, p= .005), Block 3 (H= 14.12, p= .002) (see Figure 3).

[---Insert Figure 3 about here----]

3.3. Motor Learning Index (MLI)

The analyses of MLI showed differences between the four experimental groups (H= 7.69, p= .05). However, although further multiple comparisons **(even without correction)** did not show significant differences between groups, likely due to the small samples, pairwise comparison with the Mann-Whitney Test indicates a larger motor learning effect in children with CP and bilateral CST projections (Z= 1.96, p= .049) at least as compared to children with contralateral CST, but not in comparison with children with ipsilateral CST (Z= 1.75, p= .083), or TD children (Z= 1.72, p= .085) (see Figure 4).

There was no correlation between the MLI and the JTT (r_s= .07, p= .86) and MACS (r_s= .009, p= .98) scores, suggesting that motor sequence learning is not straightforwardly associated to the level of manual ability in children with CP (Figure 4).

[---Insert Figure 4 about here----]

4. DISCUSSION

The present study shows that the pattern of CST reorganization in unilateral CP differently affects fine motor control and learning with the affected hand. Indeed, our findings show that finger dexterity and explicit motor learning of a digit sequence are dissociable in unilateral CP, and differently associated to the type of CST wiring. Finger dexterity is closely linked to motor control, namely the planning and execution of finger movements; motor skill learning instead refers to the increased spatial and temporal movements accuracy with practice[28]. In our sample, as compared to TD children, impaired finger dexterity was found in children with congenital hemiparesis presenting with ipsilateral or bilateral control of the affected hand, while children with hemiparesis and preserved crossed projections from the lesioned hemisphere performed the FTT with the same level of accuracy of TD children. Despite that, only hemiparetic children with a bihemispheric control of the affected hand showed motor learning at the FTT similar to that of TD children. With respect to the total amount of reproduced sequences, but regardless of their correctness, children with CP and ipsilateral CST projections from the intact hemisphere showed the worst performance in each FTT block; all CP subgroups did not show any increase in the number of reproduced sequences, at variance with TD children.

In particular, our children with unilateral CP and bilateral CST pattern show an increased ability to correctly perform, with the affected hand, the digit sequence to be learnt across blocks of practice (a marker of explicit motor learning in FTT paradigms[26]), as TD children do. The improved accuracy is not associated with a more general increase of the total number of performed digit movements, indexing that the accuracy improvement is strictly related to the learning of the trained digit sequence. Conversely, children with CP and an ipsilateral or a contralateral CST pattern do not show any accuracy improvement with practice, at least with respect to the online (during practice) component of explicit motor sequence learning tested here. Moreover, the magnitude of motor learning, net of the level of accuracy in the first block practice (i.e. MLI), of children with CP and bilateral CST **tend to be** larger than that of children with CP and ipsilateral or contralateral CST, as well as of TD children. This finding suggests that impaired fine motor control does not preclude the chance of learning, although the amount of learning depends on the starting level: a nearly optimal performance reduces the room for improvement, as found here in TD children who, by practicing with an healthy hand, cannot show a vast amelioration as in the case of practicing with an impaired hand.

By using different paradigms, previous literature has provided some evidence of impaired motor learning in CP, but without taking into consideration the role of corticospinal circuit plasticity. For instance, Hung and Gordon (2013) showed that children with unilateral CP are able to improve their performance in a bimanual speed task, but their rate of learning is lower than that of TD children[52]. Gagliardi and colleagues (2011) showed impaired sequence learning skills in children with CP (i.e. they required more trials to complete the task, making more spatial errors), as compared to TD controls; in line with our findings, such learning difficulties were unrelated to the severity of the hand motor disorder, measured with the Gross Motor Function Classification System[53]. So far, there is no evidence regarding the development of motor learning abilities in children with CP according to their pattern of CST reorganization. The majority of previous studies assessing CST reorganization in CP have investigated its influences on hand function recovery[9,54,58] or the efficacy of different rehabilitation protocols, such as constraint-induced movement therapy[55] or intensive bimanual training[56,57]. For instance, Rich and colleagues (2017) showed that children with CP and ipsilateral CST reorganization had the worst motor performance at the JTT, as compared to children with CP and contralateral motor control; in their study, children with CP and bilateral CST reorganization were not tested[58]. The link between ipsilateral/contralateral motor control and upper limb motor disorders is also in line with the present results: children with CP and uncrossed CST projections from the intact hemisphere have the worst performance at the FTT (lower rate of reproduced sequences, regardless of their correctness), beyond the lack of a motor learning effect; they also performed poorly the JTT. Instead, children with crossed CST projections from the lesioned hemisphere do not differ from TD children with respect to the number of reproduced motor sequences (correct and/or incorrect) at the FTT, although they do not show learning effects.

The main, novel, contribution of the present study to the knowledge of motor learning in children with CP is offering a new, hypothesis-generating, view of the potential modulatory role of atypical CST projections, reorganized as consequence of an early acquired brain injury, to the development of motor learning functions. Our results suggest that children with CP and bilateral CST reorganization may present a ‘normal’ motor sequence learning, showing improvements in accuracy with practice. Instead, children with ipsilateral or contralateral CST projections to the paretic (trained) hand did not show the typical pattern of learning-related improvement found in TD children. The learning effect in children with bilateral CST suggests that the paretic hand may improve with an explicit learning paradigm only if it is controlled by both hemispheres. The unilateral control by either the contralateral (damaged) or the ipsilateral (healthy) motor cortex seems not sufficient to promote motor learning; somewhat, this process in CP seems to require the recruitment of both motor cortices. Bilateral CST wiring may allow integrating motor programs from both the affected and healthy motor cortices to sustain learning with the paretic hand. In other words, a bilateral control of the affected hand could provide the substrate for a more efficient transmission, in parallel pathways, of a larger amount of sensorimotor information necessary for learning with a paretic hand. This hypothesis is in line with studies showing the existence of parallel pathways mediating manual dexterity in the macaque[59]: the transmission of sensorimotor information by neuron populations functioning in parallel, across which the transfer of similar but not identical information is distributed, may support the neuronal processing underlying the recovery of manual dexterity by learning. Accordingly, it has been shown that impaired dextrous finger movements in congenital hemiplegia correlate with the corticospinal tract dysgenesis, as estimated with the cerebral peduncle asymmetry[32]. Moreover, in adults with congenital hemiparesis, the temporary disruption of the contralesional (intact) motor cortex, by means of repetitive TMS, impairs the ability of performing sequential finger movements with the paretic hand, even in the case of preserved crossed CST projections from the injured hemisphere[60]. Neuroimaging evidence in healthy humans also shows a bilateral recruitment of the motor system during the initial stage of the motor learning process[15], along with an enhanced neural efficiency in sensorimotor activity and connectivity[61]. Our findings suggest that these 'normal', bilateral, activations may become more relevant when learning with a paretic hand in face of a dysfunctional, weak, crossed CST, as suggested by the present findings.

In conclusion, our study provides evidence that children with CP who have developed bilateral CST projections to the affected hand may present a normal practice-dependent motor sequence learning, while children with CP exhibiting ipsilateral or contralateral CST reorganization seem unable to improve their motor performance with practice. Such effects seem unrelated to finger dexterity, which was found to be impaired in children with unilateral CP and both ipsilateral and bilateral control of the paretic hand.

Within a clinical perspective, the present findings are promising since they suggest a potential link between CST reorganization and motor learning disorders in CP, as well the importance of assessing motor learning abilities along with the evaluation of dexterity, since they may dissociate in CP. A better understanding of how CST reorganization patterns may impact on motor learning could help guide the personalization of treatments based on principles of motor learning. For instance, with respect to the role of CST reorganization in the clinical efficacy of constraint-induced movement (CIMT) and bimanual therapies in children with CP, mixed results have been found[55-57,62-63]; assessing the presence of motor learning deficit may offer a new framework to understand such inconsistencies. Our results also indicate that finger dexterity deficit in hemiparetic children can benefit of learning-based practice. Despite the importance of finger dexterity to activities of daily living, so far, the impact of finger dexterity on hand rehabilitation in CP has received little attention. A final clinical implication: an essential central concept that has emerged from therapeutic non-invasive brain stimulation studies is the need to augment motor learning-induced plasticity[64]. It follows that knowing which motor system (ipsilesional, contralesional, or both) is recruited by a given therapy is essential to optimize the use of brain stimulation as add-on intervention to motor learning therapies, whose application has been, until now, primarily driven by the model of interhemispheric imbalance in both adult and child rehabilitation. However, this model neglects the potential supportive role of the intact motor cortex in some motor processes, as suggested by the present study for motor learning.

The main limitation of the present study that needs to be entertained is surely the small sample size, **whose CST reorganization pattern was defined following a specific TMS procedure**, which does not allow to draw inference at the population level considering the high variability of unilateral CP; studies including larger samples of children with CP and different CST patterns, by having more statistical power, are necessary to corroborate the present results. Increasing the sample size will also allow to better characterize the performance of children with unilateral CP by exploring which factors primarily impact on explicit learning of fine motor skills, beyond and/or in conjunction to the type of CST wiring. Indeed, motor sequence task demands several non-motor processes (i.e. visuo-spatial processing, attention, cognitive control and planning, memory), which are often compromised in CP. Other factors that can affect motor learning in CP include deficits of sensation, muscle strength and coordination[26-28]. **Future research is also needed to explore the effect of CST reorganization on motor learning with whole hand tasks, as well as with tasks requiring more proximal control, which would also allow the inclusion of more patients, here excluded on the basis of stringent criteria based on the upper limb impairment.**

There are also methodological aspects that need to be considered. Firstly, no retention or follow-up assessments were performed, so the interpretation of the results is confined to online (during practice) motor sequence learning. Our FTT procedure does not allow to discern which stage of motor learning is damaged, or to detect difference between explicit and explicit motor learning processes. It would be of great relevance to extend the present findings exploring whether the type of CST reorganization has different effects on explicit processes during the early phase of the acquisition of motor skills, and/or on the emergence of implicit automatic control. The adoption of a serial reaction time paradigm, in which, at variance of our FTT, motor sequences vary trial-by-trial in a probabilistic fashion, would be useful to disentangle explicit and implicit learning deficits in CP. Finally, it would be important to verify whether a longer, and more intensive, practice may further increase the learning rate of children with bilateral CST reorganization, maybe allowing even the emergence of learning in children with ipsilateral and contralateral CST projections.

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Conflict of Interest

All authors declare no conflict of interest

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References

1. Riva D, Franceschetti S, Erbetta A, et al. Congenital brain damage: cognitive development correlates with lesion and electroencephalographic features. *J Child Neurol.* 2013; 28: 446-454.
2. Bax M, Goldstein M, Rosenbaum P, et al. Proposed definition and classification of cerebral palsy. *Dev Med Child Neurol*. 2005; 47: 571-576.
3. Baranello G, Sebastiano DR, Pagliano E, et al. Hand function assessment in the first years of life in unilateral cerebral palsy: correlation with neuroimaging and cortico-spinal reorganization. *European Journal of Paediatric Neurology*. 2016; 20: 114-124.
4. Rose J, McGill KC. The motor unit in cerebral palsy. *Dev Med Child Neurol*. 1998; 40: 270-277.
5. Staudt M, Gerloff C, Grood W, et al. Reorganization in congenital hemiparesis acquired at different gestational ages. *Ann Neurol*. 2004; 56: 854-863.
6. Steinlin M, Good M, Martin E, et al. Congenital hemiplegia: morphology of cerebral lesions and pathogenetic aspects from MRI. *Neuropediatrics*. 1993; 24: 224-229.
7. Feys H, Eyssen M, Jaspers, et al. Relation between neuroradiological findings and upper limb function in hemiplegic cerebral palsy. *European Journal of Paediatric Neurology*. 2010; 14: 169-177.

8. Krägeloh-Mann I, Horber V. The role of magnetic resonance imaging in elucidating the pathogenesis of cerebral palsy: a systematic review. *Dev Med Child Neurol.* 2007; 49: 144-151.
9. Mackey A, Stinear C, Stott S, Byblow WD. Upper limb function and cortical organization in youth with unilateral cerebral palsy. *Frontiers in Neurology*. 2014; 5: 117.
10. Wiklund LM, Uvebrant P. Hemiplegic cerebral palsy: correlation between CT morphology and clinical findings. *Dev Med Child Neurol*. 1991; 33: 512-523.
11. Anderson JR. Acquisition of cognitive skill. *Psychol Rev*. 1982; 89: 369.
12. Fitts, PM. Perceptual-motor skill learning. In AW Melton (Ed.), *Categories of human learning.* San Diego, CA: Academic Press, 1964, pp.243-285.
13. Krakauer JW, Mazzoni P. Human sensorimotor learning: adaptation, skill, and beyond. *Curr Opin Neurobiol*. 2011; 21: 636-644.
14. Logan GD. Toward an instance theory of automatization. *Psychol Rev*. 1988; 95: 492.
15. Halsband U, Lange RK. Motor learning in man: a review of functional and clinical studies. *J Physiol Paris*. 2006; 99: 414-424.
16. Gofer-Levi M, Silberg T, Brezner A, Vakil E. Deficit in implicit motor sequence learning among children and adolescents with spastic cerebral palsy. *Res Dev Disabil. 2013; 34: 3672-3678.*
17. van der Kamp J, Steenbergen B, Masters RS. Explicit and implicit motor learning in children with unilateral cerebral palsy. *Disabil Rehabil*. 2018; 40: 2790-2797.
18. Gagliardi C, Tavano A, Turconi AC, Borgatti R. Sequence memory skills in Spastic Bilateral Cerebral Palsy are age independent as in normally developing children. *Disabil Rehabil*. 2013; 35: 506-512.
19. Cioni G, D'Acunto G, Guzzetta A. Perinatal brain damage in children: neuroplasticity, early intervention, and molecular mechanisms of recovery. *Prog Brain Res*. 2011: 139-154.

20. Kirton A. Modeling developmental plasticity after perinatal stroke: defining central therapeutic targets in cerebral palsy. *Pediatr Neurol*. 2013; 48: 81-94.

21. Eyre J, Taylor J, Villagra F, Smith M, Miller S. Evidence of activity-dependent withdrawal of corticospinal projections during human development. *Neurology*. 2001; 57: 1543-1554.

22. Jaspers E, Byblow WD, Feys H, Wenderoth N. The corticospinal tract: a biomarker to categorize upper limb functional potential in unilateral cerebral palsy. *Frontiers in paediatrics*. 2016; 3: 112.

23. Staudt M. Reorganization after pre and perinatal brain lesions. *J Anat*. 2010; 217: 469-474.

24. Guzzetta A, Bonanni P, Biagi L, et al. Reorganisation of the somatosensory system after early brain damage. *Clinical Neurophysiology*. 2007; 118: 1110-1121.

25. Zewdie E, Damji O, Ciechanski P, Seeger T, Kirton A. Contralesional corticomotor neurophysiology in hemiparetic children with perinatal stroke: developmental plasticity and clinical function. *Neurorehabilitation and neural repair*. 2017; 31: 261-271.

26. Doyon J, Gabitov E, Vahdat S, Lungu O, Boutin A. Current issues related to motor sequence learning in humans. *Current opinion in behavioural sciences*. 2018; 20: 89-97.

27. Steenbergen B, van der Kamp J, Verneau M, Jongbloed-Pereboom M, Masters RS. Implicit and explicit learning: applications from basic research to sports for individuals with impaired movement dynamics. *Disabil Rehabil*. 2010; 32: 1509-1516.

28. Willingham DB. A neuropsychological theory of motor skill learning. *Psychol Rev*. 1998; 105: 558.

29. Lang CE, Beebe JA. Relating movement control at 9 upper extremity segments to loss of hand function in people with chronic hemiparesis. *Neurorehabil. Neural Repair* 2007; 21: 279-291.

30. Duff SV, Aaron DH, Gogola GR, Valero-Cuevas FJ. Innovative evaluation of dexterity in pediatrics. *J Hand Ther*. 2015; 28 (2): 144-150.

31. Golubović Š, Slavković S. Manual ability and manual dexterity in children with cerebral palsy. *Hippokratia*. 2014; 18: 310.

32. Duque J, Thonnard JL, Vandermeeren Y, et al. Correlation between impaired dexterity and corticospinal tract dysgenesis in congenital hemiplegia. *Brain* 2003; 126: 732-747.

33. Porter, R and Lemon, R. *Corticospinal function and voluntary movement.* Oxford: Clarendon Press, 1993, pp. 427.

34. Rossi S, Hallett M, Rossini PM, et al. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clinical Neurophysiology*. 2009; 120: 2008-2039.

35. Oldfield RC. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia*. 1971; 9: 97-113.

36. Eliasson AC, Krumlinde-Sundholm L, Rösblad B, et al. The Manual Ability Classification System (MACS) for children with cerebral palsy: scale development and evidence of validity and reliability. *Dev. Med. Child Neurol*. 2006; 48: 549-554.

37. Jebsen RH, Taylor N, Trieschmann R, Trotter MJ, Howard LA. An objective and standardized test of hand function. *Arch. Phys. Med. Rehabil*. 1969; 50: 311-319.

38. Taylor N, Sand P, Jebsen R. Evaluation of hand function in children. *Arch. Phys. Med. Rehabil*. 1973; 54: 129-135.

39. Klingels K, Feys H, De Wit L, et al. Arm and hand function in children with unilateral cerebral palsy: a one-year follow-up study. *Eur. J. Paed. Neurol*. 2012; 16: 257-265.

40. Reedman SE, Beagley S, Sakzewski L, Boyd RN. The Jebsen Taylor test of hand function: a pilot test-retest reliability study in typically developing children. *Physical and Occupational therapy in paediatrics*. 2016; 36: 292-304.

41. Carr L, Harrison L, Evans A, Stephens J. Patterns of central motor reorganization in hemiplegic cerebral palsy. *Brain.* 1993; 116: 1223-1247.

42. Groppa S, Oliviero A, Eisen A, et al.A practical guide to diagnostic transcranial magnetic stimulation: report of an IFCN committee. *Clin Neurophysiol*. 2012; 123:858–882.

43. Mills KR, Nithi KA. Corticomotor threshold to magnetic stimulation: normal values and repeatability. *Muscle Nerve*. 1997; 20 (Suppl.): 570-6.

44. Karni A, Meyer G, Rey-Hipolito C, et al. The acquisition of skilled motor performance: fast and slow experience-driven changes in primary motor cortex. *Proc Natl Acad Sci USA*. 1998; 95: 861-868.

45. Zimerman M, Heise KF, Hoppe J, et al. Modulation of training by single-session transcranial direct current stimulation to the intact motor cortex enhances motor skill acquisition of the paretic hand. *Stroke*. 2012; 43: 2185-2191.

46. Alves-Pinto A, Ehrlich S, Cheng G, et al. Effects of short-term piano training on measures of finger tapping, somatosensory perception and motor-related brain activity in patients with cerebral palsy. *Neuropsychiatric disease and treatment*. 2017; 13: 2705.

47. Kara OK, Yardimci BN, Livanelioglu A, Soylu AR. Examination of touch-coordinate errors of adolescentes with unilateral spastic cerebral palsy at an aiming-tapping task. *Journal of back and musculoskeletal rehabilitation*. 2019: 1-9.

48. Hervey N, Khan B, Shagman L, et al. Motion tracking and electromyography-assisted identification of mirror hand contributions to functional near-infrared spectroscopy images acquired during a finger-tapping task performed by children with cerebral palsy. *Neurophotonics*. 2014; 1: 025009.

49. Steenbergen B, Veringa A, de Haan A, Hulstijn W. Manual dexterity and keyboard use in spastic hemiparesis: a comparison between the impaired hand and the 'good' hand on a number of performance measures. *Clin Rehabil*. 1998; 12: 64-72.

50. Bolognini N, Spandri V, Ferraro F, et al. Immediate and sustained effects of 5-day transcranial direct current stimulation of the motor cortex in phantom limb pain. *The Journal of Pain*. 2015; 16: 657-665.
51. Mercier C, Sirigu A. Training with virtual visual feedback to alleviate phantom limb pain. *Neurorehabilitation and neural Repair*. 2009; 23: 587-594.
52. Hung YC, Gordon AM. Motor learning of a bimanual task in children with unilateral cerebral palsy. *Res Dev Disabil*. 2013; 34: 1891-1896.
53. Gagliardi C, Tavano A, Turconi AC, Pozzoli U, Borgatti R. Sequence learning in cerebral palsy. *Pediatr Neurol*. 2011; 44: 207-213.
54. Holmström L, Vollmer B, Tedroff K, et al. Hand function in relation to brain lesions and corticomotor-projection pattern in children with unilateral cerebral palsy. *Dev Med Child Neurol*. 2010; 52: 145-152.
55. Islam M, Nordstrand L, Holmström K, et al. Is outcome of constraint-induced movement therapy in unilateral cerebral palsy dependent on corticomotor projection pattern and brain lesion characteristics? *Dev Med Child Neurol*. 2014; 56: 252-258.
56. Bleyenheuft Y, Dricot L, Gilis N, et al. Capturing neuroplastic changes after bimanual intensive rehabilitation in children with unilateral spastic cerebral palsy: a combined DTI, TMS and fMRI pilot study. *Res Dev Disabil*. 2015; 43: 136-149.
57. Smorenburg AR, Gordon AM, Kuo HC, et al. Does corticospinal tract connectivity influence the response to intensive bimanual therapy in children with unilateral cerebral palsy? *Neurorehabilitation and neural repair*. 2017; 31: 250-260.
58. Rich TL, Menk JS, Rudser KD, Feyma T, Gillick BT. Less-affected hand function in children with hemiparetic unilateral cerebral palsy: a comparison study with typically developing peers. *Neurorehabilitation and neural repair*. 2017; 31: 965-976.
59. Darian-Smith I, Burman K, Darian-Smith C. Parallel pathways mediating manual dexterity in the macaque. *Exp Brain Res*. 1999; 128: 101-108.

60. Lotze M, Sauseng P, Staudt M. Functional relevance of ipsilateral motor activation in congenital hemiparesis as tested by fMRI-navigated TMS. *Exp Neurol*. 2009; 217: 440-443.
61. Karim HT, Huppert TJ, Erickson KI, et al. Motor sequence learning-induced neural efficiency in functional brain connectivity. *Behav Brain Res*. 2017; 319: 87-95.
62. Juenger H, Kuhnke N, Braun C, et al. Two types of exercise-induced neuroplasticity in congenital hemiparesis: a transcranial magnetic stimulation, functional MRI, and magnetoencephalography study. *Dev Med Child Neurol*. 2013; 55: 941-951.
63. Kuhnke N, Juenger H, Walther M, et al. Do patients with congenital hemiparesis and ipsilateral corticospinal projections respond differently to constraint-induced movement therapy? *Dev Med Child Neurol*. 2008; 50: 898-903.
64. Bolognini N, Pascual-Leone A, Fregni F. Using non-invasive brain stimulation to augment motor training-induced plasticity. *Journal of neuroengineering and rehabilitation*. 2009; 6: 8.

Captions to figures

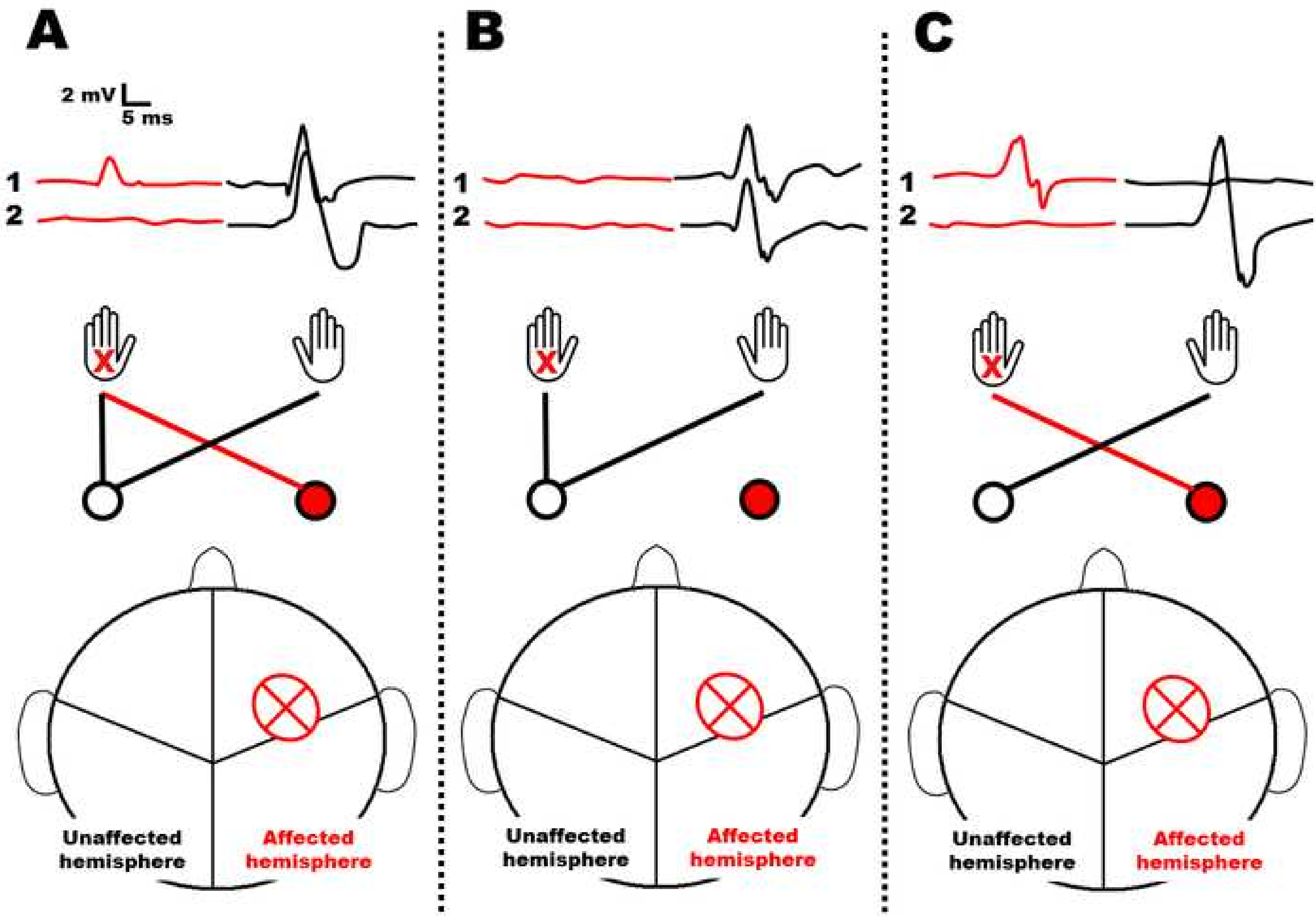
Figure 1. Representation of CST reorganization as assessed with TMS. In (A) bilateral, (B) ipsilateral and (C) contralateral CST wiring patterns are schematically represented. The **upper** part of the figure shows representative MEPs traces recorded in children with CP (A corresponds to P3, B to P4, C to P7). The traces obtained by stimulation of the affected motor cortex are shown in red, those induced by the stimulation of the unaffected motor cortex are shown in black. The traces acquired from the affected hand are shown in the line ‘1’; those from the unaffected hand in line ‘2’.

Figure 2. Number of correct sequences at FTT. The upper panel (A) shows the mean number of **correct** digit sequences performed in each FTT block by TD children, and by children with unilateral CP and bilateral, ipsilateral or contralateral CST patterns, whose individual performance is also shown in the lower panel (B). The brace with the asterisk indicates a significant improvement across blocks of practice; the circle indicates a difference, with respect to the performance of TD children, at the block of the FTT. Error bars= standard error (SE). In panel B, performance of CP children with bilateral CST is represented by dotted black lines (P1-3), with ipsilateral CST is represented by gray lines (P4-6), with contralateral CST is represented by black lines (P7-P9).

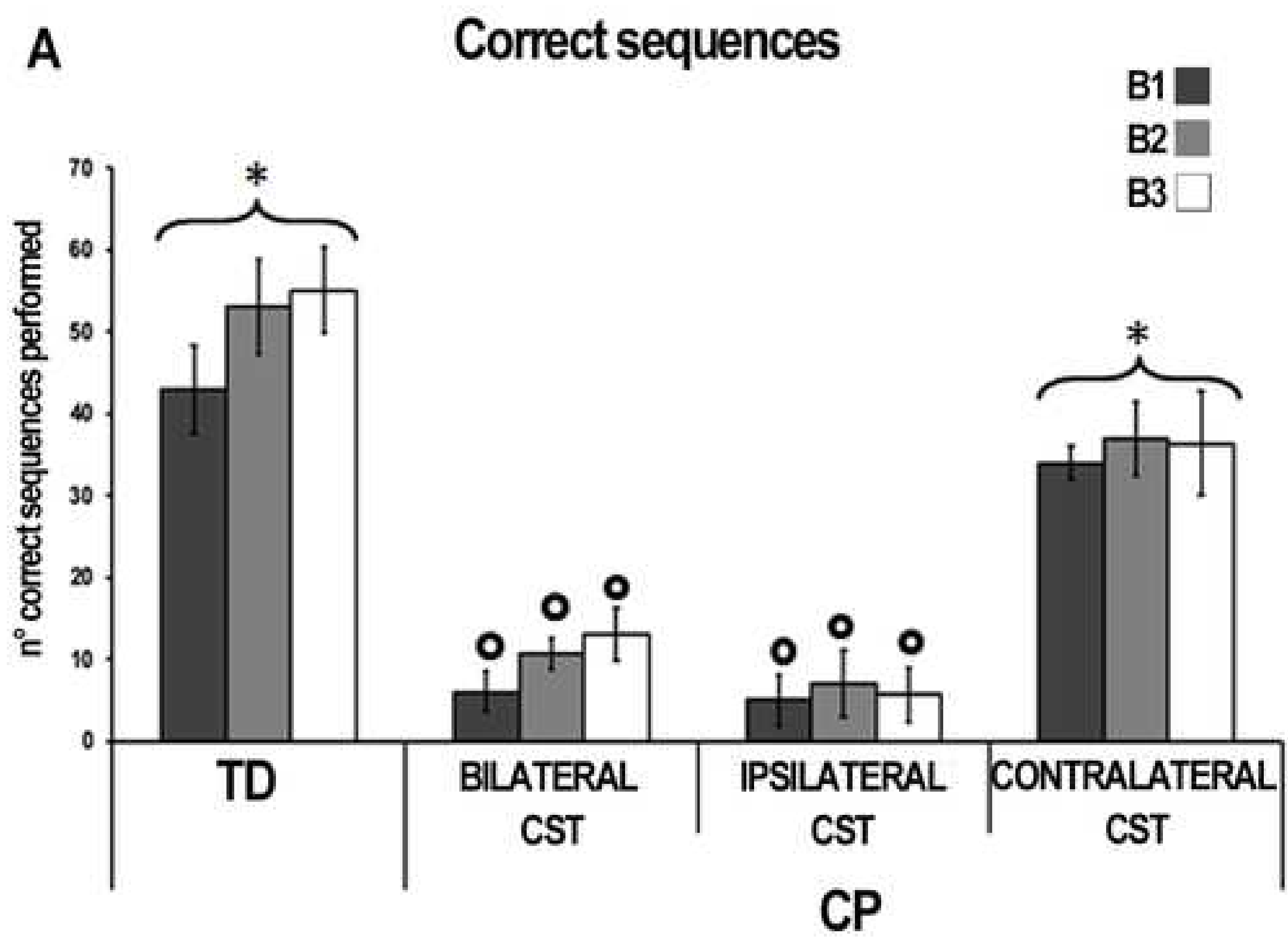
Figure 3. Total number of sequences at the FTT. The upper panel (A) shows the mean total number of motor sequences, regardless of their correctness, performed in each FTT block by TD children, and by children with CP and bilateral, ipsilateral or contralateral CST patterns, whose individual performance is also shown in the lower panel (B). The brace with the asterisk indicates a significant improvement across blocks of practice; the circle indicates a difference, with respect to the performance of TD children, at the block of the FTT. Error bars= SE. In panel B, performance of

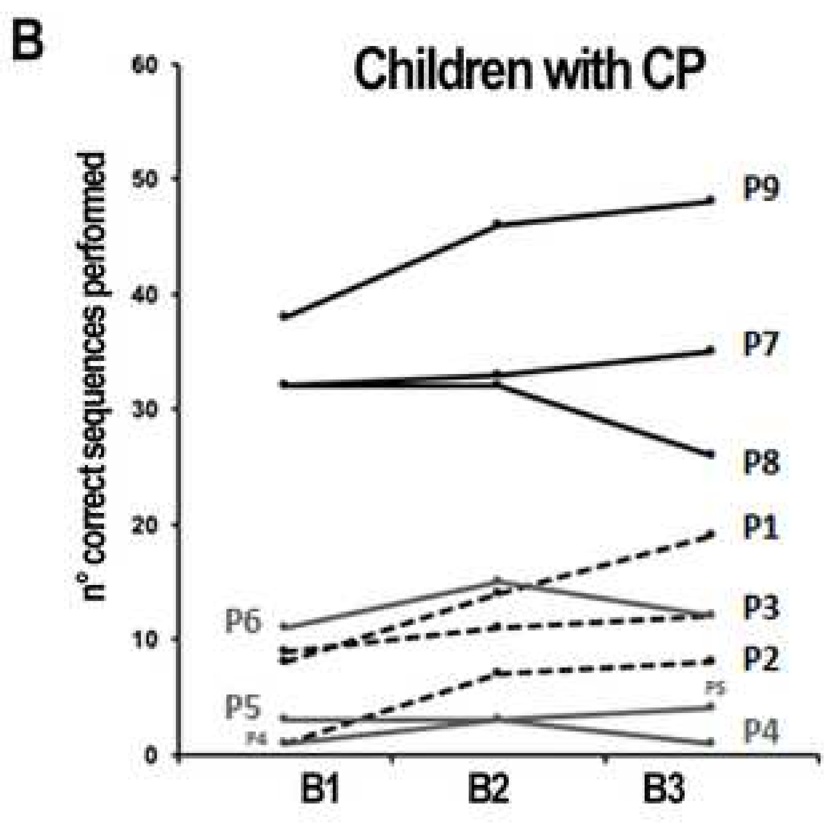
CP children with bilateral CST is represented by dotted black lines (P1-3), with ipsilateral CST is represented by gray lines (P4-6), with contralateral CST is represented by black lines (P7-P9).

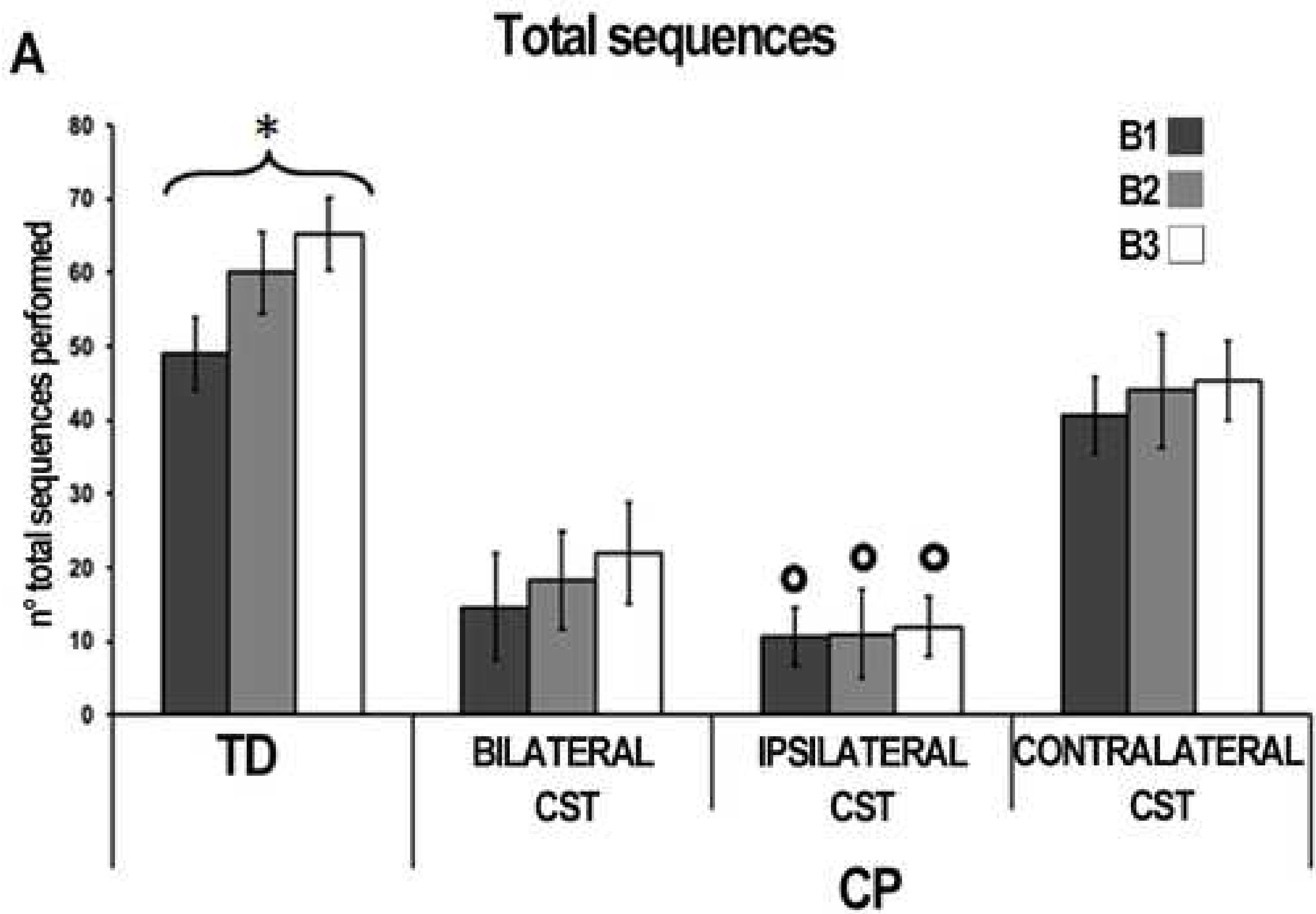
Figure 4. Upper panel (A): mean Motor Learning Index (MLI, %) of TD children (white bar), and individual values for CP group (black bars); error bars= SE. Lower panel (B): correlations between the MLI and JTT score (left-sided graph) and MACS level (right-sided graph) for children with CP.

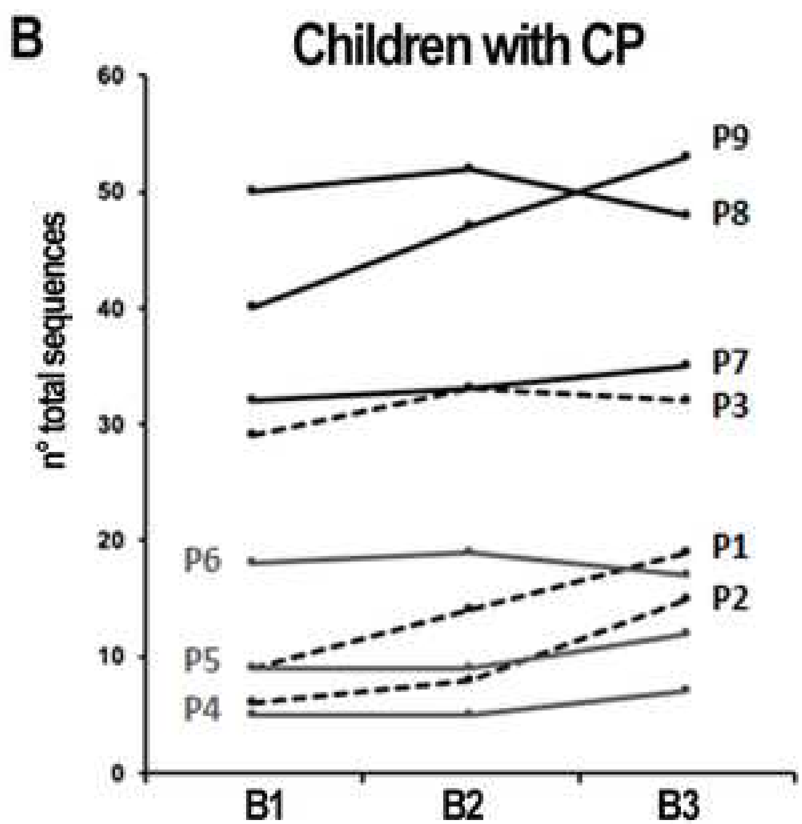

A
B
C
2 mV
5 ms
1
2
1
2
1
2
X
X
X
Unaffected hemisphere
Affected hemisphere
Unaffected hemisphere
Affected hemisphere
Unaffected hemisphere
Affected hemisphere

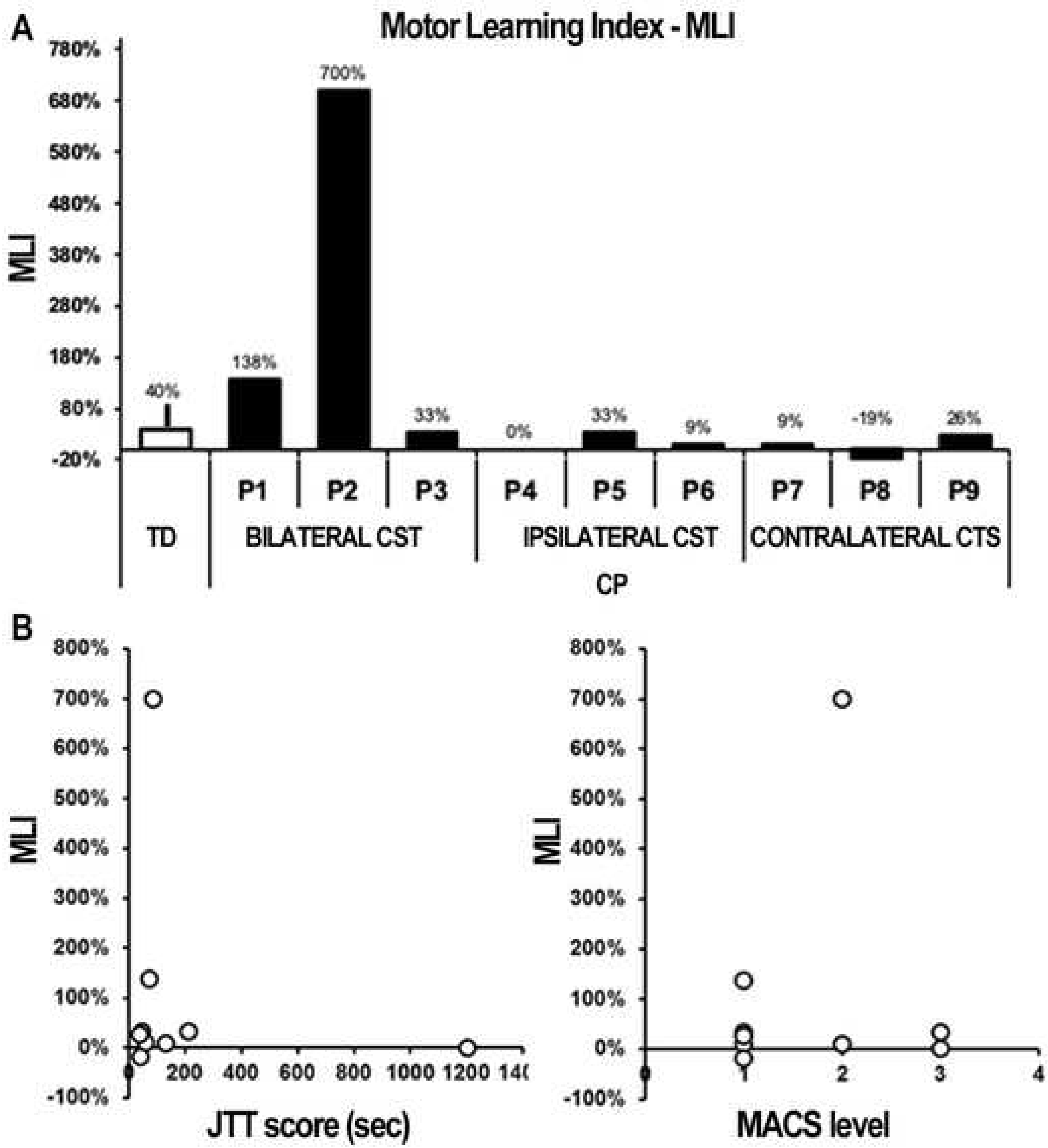
Figure


A
Correct sequences
B1
B2
B3
n° correct sequences performed
0
10
20
30
40
50
60
70
*
*
TD
BILATERAL CST
IPSILATERAL CST
CONTRALATERAL CST
CP


B
Children with CP
n° correct sequences performed
0
10
20
30
40
50
60
P9
P7
P8
P1
P3
P2
P4
P6
P5
B1
B2
B3


A
Total sequences
n° total sequences performed
0
10
20
30
40
50
60
70
80
*
B1
B2
B3
TD
BILATERAL CST
IPSILATERAL CST
CONTRALATERAL CST
CP


B
Children with CP
n° total sequences
0
10
20
30
40
50
60
P9
P8
P7
P3
P6
P1
P2
P5
P4
B1
B2
B3


A
Motor Learning Index - MLI
MLI
780%
680%
580%
480%
380%
280%
180%
80%
-20%
40%
138%
700%
33%
0%
33%
9%
9%
-19%
26%
P1
P2
P3
P4
P5
P6
P7
P8
P9
TD
BILATERAL CST
IPSILATERAL CST
CONTRALATERAL CTS
CP
B
MLI
800%
700%
600%
500%
400%
300%
200%
100%
0%
-100%
0
200
400
600
800
1000
1200
JTT score (sec)
MLI
800%
700%
600%
500%
400%
300%
200%
100%
0%
-100%
0
1
2
3
4
MACS level

Declaration of interests

☒ 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.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: