HHS Public Access

Author manuscript

Res Dev Disabil. Author manuscript; available in PMC 2016 December 01.

Published in final edited form as:

Res Dev Disabil. 2015 December ; 47: 154–164. doi:10.1016/j.ridd.2015.09.010.

Ipsilesional Motor-Evoked Potential Absence in Pediatric Hemiparesis Impacts Tracking Accuracy of the Less Affected Hand

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Abstract

This study analyzed the relationship between electrophysiological responses to transcranial magnetic stimulation (TMS), finger tracking accuracy, and volume of neural substrate in children with congenital hemiparesis. Nineteen participants demonstrating an ipsilesional motor-evoked potential (MEP) were compared with eleven participants showing an absent ipsilesional MEP response. Comparisons of finger tracking accuracy from the affected and less affected hands and ipsilesional/contralesional (I/C) volume ratio for the primary motor cortex (M1) and posterior limb of internal capsule (PLIC) were done using two-sample *t*-tests. Participants showing an ipsilesional MEP response demonstrated superior tracking performance from the less affected hand ($p = 0.016$) and significantly higher I/C volume ratios for M1 ($p= 0.028$) and PLIC ($p = 0.005$) compared to participants without an ipsilesional MEP response. Group differences in finger tracking accuracy from the affected hand were not significant. These results highlight differentiating factors amongst children with congenital hemiparesis showing contrasting MEP responses: less affected hand performance and preserved M1 and PLIC volume. Along with MEP status, these factors pose important clinical implications in pediatric stroke rehabilitation. These findings may also reflect competitive developmental processes associated with the preservation of affected hand function at the expense of some function in the less affected hand.

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The authors declare that they have no conflict of interest.

Keywords

stroke; transcranial magnetic stimulation; pediatrics; corticospinal tract; motor-evoked potential; hemiparesis

1.Introduction

The safety of repetitive transcranial magnetic stimulation (rTMS) applications in adult stroke has been supported (Carey et al., 2008; Khedr et al., 2005; Liepert et al., 2007), and recent investigations of rTMS in children with congenital hemiparesis from stroke and periventricular leukomalacia have also demonstrated safety (Gillick et al., 2015; Kirton et al., 2008). Supporting the efficacy of rTMS in adult and pediatric stroke rehabilitation, however, is challenging. First, individual variability in responsiveness to non-invasive brain stimulation exists in both healthy individuals and in those with stroke, thus adding to the complexity of formulating accurate conclusions and refining stimulation parameters (Bradnam et al., 2012; Cheeran et al., 2008; Maeda et al., 2000; Seniów et al., 2012). Second, stringent enrollment criteria aimed at achieving optimal homogeneity often yield small sample sizes that compromise statistical power and generalizability of findings to larger stroke populations. In particular, studies employing rTMS interventions and/or TMS-based outcome measures frequently require a resting oran active motor-evoked potential (MEP) from the ipsilesional primary motor cortex area (M1). The MEP is the muscle response measured with electromyography(EMG) following a TMS pulse to the motor region of the brain. Yet, MEPs from the ipsilesional hemisphere are often absent in individuals with stroke (Escudero et al., 1998; Kirton et al., 2010; Stinear et al., 2007), thus hindering patient recruitment.

An ipsilesional MEP depends on he integrity of the contralateral (crossed) corticospinal tract (CST) projections, with influence from the size and location of the lesion (Staudt et al., 2002). The MEP (or lack thereof) is also dependent on central nervous system maturation (Koh & Eyre, 1988; Nezu et al., 1997). During typical development, an activity-dependent withdrawal of ipsilateral (uncrossed) CST projections from the hemisphereensues (Eyre et al., 2001; Martin & Lee, 1999). When an early-onset of neurological injury such as congenital stroke occurs, these ipsilateral projections can persist and even enlarge, rather than withdraw, and eventually predominate over surviving contralateral projections from the ipsilesional hemisphere (Eyre et al., 2001, 2007; Martin & Lee, 1999). Such adaptation may be important to preserving a modicum of function in the affected hand amidst major unilateral brain damage. Previous investigations of MEPs in children and in young adults with congenital hemiplegia have confirmed the utility of MEPs in determining CST organization and resultant motor function (Carr et al., 1993; Holmström et al., 2010). Elicitable MEPs may therefore contribute valuable insight to pediatric stroke and subsequent rehabilitation.

In our previous study investigating a combined rTMS and constraint-induced movement therapy (CIMT) intervention in participants with congenital hemiparesis, 19 of the 36(53%) originally enrolled children screened onsite qualified to participate (Gillick et al., 2014). Of

the 17 children excluded after enrollment, 11 children (65%) could not participate secondary to absent ipsilesional MEPs. The purpose of this current observational study was to analyze the relationship between elicitable MEPs, finger tracking accuracy, and volume of neural substrate in cortical and subcortical regions of interest on magnetic resonance images (MRI) in children with congenital hemiparesis. Finger tracking is a complex task encompassing multiple systems. Akin to MEP status, finger tracking may also elucidate valuable information related to CST maturation (Fietzek et al., 2000; Heinen et al., 1998). We hypothesize that children with an ipsilesional MEP will demonstrate significantly higher tracking performance from the affected hand and significantly higher amounts of PLIC and M1.

2.Methods

2.1 Participants

Thirty children (13 females) with a mean ± SD age of 10.4 ± 2.79 years enrolled in a previous rTMS/CIMT study (Gillick et al., 2014) were included in this investigation. Of these 30 children, 19 were included in the initial study and comprised the MEP group in this investigation. The remaining 11 children were excluded from the initial study due to the absence of a resting or an active ipsilesional MEP determined during initial TMS testing. These 11 participants formed the no-MEP group in this study. Inclusion criteria for all children were congenital hemiparesis due to ischemic stroke that occurred within one year of birth or periventricular leukomalacia validated by MRI, at least 10 degrees of active flexion and extension at the metacarpophalangeal (MCP) joint of the affected index finger, and aged between 8 and 17 years. Exclusion criteria for all children were seizure within the previous two years, neoplasm, metabolic disorders, hemorrhage, receptive aphasia, pregnancy, disorders of cellular migration and proliferation, indwelling metal or medical devices contraindicated with MRI and TMS, claustrophobia, and gross visual field cuts that would hinder task performance during functional MRI (fMRI). All children and their legally authorized representatives assented/consented to participation.

2.2 Neuroimaging

All participants completed an anatomical MRI to confirm stroke and to assess stroke characteristics. Anatomical images were acquired using a 3-Tesla magnet (Magnetom Trio, Siemens, Munich, Germany). Fluid attenuated inversion recovery images were collected and assessed by a pediatric neurologist to specify location, type of stroke and cortical and/or subcortical involvement. Additional detail regarding MRI protocol and data acquisition is stated in previous work (Gillick et al., 2014). Diffusion tensor imaging (DTI) was attempted, but excessive head motion in essentially all participants prevented group-level analysis. fMRI was attempted while participants performed a finger tracking task, as done previously in adults with stroke (Carey et al., 2002), but this also was not successful because of excessive head motion and mirroring activity between the two hands. These movement-related issues that hinder brain imaging validity do not diminish the value of the finger tracking tasks in measuring manual control inside the MRI scanner.

2.3 Defining Regions of Interest

A team of trained investigators blinded to MEP status used Brain Voyager (Brain Innovation B.V., Maastricht, Netherlands) software to manually define two regions of interest: 1) M1 and 2) posterior limb of the internal capsule (PLIC). M1 was defined as the grey matter encompassing the posterior half of the precentral gyrus (Dassonville et al., 2001) including the motor hand-knob region (Yousry et al., 1997) beginning with the appearance of the central sulcus and ending with the disappearance of the central sulcus. PLIC borders were defined as: 1) anterior: genu of internal capsule, 2) posterior: posterior edge of globus pallidus and onset of corona radiata, 3) medial: thalamus, 4) lateral: globuspallidus, 5) rostral: lentiform nucleus, and 6) caudal: anterior commissure (Schaechter et al., 2008). Investigators performed a volumetric analysis (voxel count) for ipsilesional and contralesional M1 and PLIC regions, and constructed volume symmetry ipsilesional/contralesional (I/C) ratios for each region. If the lesion intruded the ROI boundaries, only the area around but not within the lesion was included. We included the full volume of the ROI on the contralesional hemisphere.

2.4 Finger Tracking

For the fMRI performance task, participants wore custom-made electrogoniometers with potentiometers (ETI Systems Inc., Carlsbad, CA) positioned at the MCP joint of both index fingers while performing a finger tracking task separately with each hand. The tracking task occurred in the MRI scanner with children positioned in supine while performing active finger flexion and extension movements. A mirror attached to the head coil reflected a 21.5 cm high target waveform image to a 43 cm high by 49 cm wide screen approximately 30.5 cm from the participant. The task included 30-second alternating blocks of rest (7 blocks), affected finger tracking (3 blocks), and less affected finger tracking (3 blocks). Past work has shown improvement in tracking performance in healthy children after several hours of tracking training (Gauthier et al., 1988). Because participants in this study completed only one practice trial to ensure comprehension of visual cues, it is unlikely that training or learning effects occurred. However, to control for potential learning, participants were randomized to one of two block sequences with the first non-rest block beginning with either affected finger tracking or less affected finger tracking. Accuracy index (AI) scores of the tracking performance in each hand were computed using the following formula:

$$AI = 100\,(\mathrm{P} - \mathrm{E})\,/\mathrm{P}$$

where P is the root-mean-square (RMS) difference between the sine wave and a midline separating the upper and lower phases of the sine wave and E is the RMS error between the subject's response and the target waveform (Carey et al., 2002). AI scores were normalized to the participant's available MCP joint range of motion to account for variation in excursion amongst participants. Maximum AI scores equal 100%. Negative scores are possible and indicate a poor tracking response as described previously (Carey et al., 2002, 1990). This finger tracking paradigm has been shown to be reliable and valid in people with stroke (Carey et al., 1998, 1990), and it has been used repeatedly to study both manual and ankle

control in people with stroke in MRI scanners (Bhatt et al., 2007; Carey et al., 2002, 2007; Deng et al., 2012; Kimberley et al., 2004).

2.5 TMS Assessment of Ipsilesional Corticospinal Excitability

Participants sat in a reclining chair, donning earplugs for safety and a Lycra swimcap that enabled investigators to mark points for stimulation. Surface electrodes (Cadwell Laboratories, Kennewick, WA) were attached over the extensor digitorummuscle on the affected hand and connected to a Cadwell Sierra II EMG machine to monitor muscle activity. Single TMS pulses were delivered through a 70 mm figure-eight coil connected to a Magstim Rapid-200 stimulator (Magstim Company Limited, Dyfed, UK). The coil was positioned over the potential motor "hotspot" with the coil handle aligned in a 45-degree posterolateral direction from the sagittal line. Pulses were delivered at 0.1 Hz beginning at an intensity of 50% of maximum machine output. The intensity and position of the coil were adjusted until a resting motor threshold, defined as the lowest intensity that produced MEPs ≥ 50μV peak-to-peak amplitude in 3 of 5 trials, was found. If MEPs could not be found at rest, the participant was instructed to perform a mild voluntary contraction of their affected extensor digitorum muscle during TMS pulse delivery. This active motor threshold was defined as the intensity required toevoke an active MEP with a peak-to-peak amplitude ≥ 100 μV in 3 of 5 trials (Kirton et al., 2010). If neither resting nor active ipsilesional MEPs were found, the child was discontinued; however, the AI scores and I/C volume ratios of this "no-MEP group" were compared to those who did have an ipsilesional MEP ("MEP group").

2.6 Statistical Analysis

Group (MEP vs. no-MEP) comparisons of primary outcome measures entailing AI scores from the affected and less affected hands and M1 and PLIC I/C volume ratios were performed using two-sample *t*-tests. Prior to the main group comparisons, potential group differences in age, sex, mirroring, and stroke hemisphere were completed using two-sample *t*-tests for continuous data and Fisher Exact Tests for categorical data. Associations between AI scores, I/C volume ratios, and Assisting Hand Assessment (AHA) logit-based scores (Krumlinde-Sundholm, 2012) were assessed using Pearson correlation coefficients. The AHA is a bimanual hand function test (Krumlinde- Sundholm et al., 2007). If a violation of normality occurred as indicated by the Shapiro-Wilk test, the corresponding non-parametric test (i.e. Mann Whitney U) was performed. A p-value ≤ 0.05 indicated significance. Consistent with reasoning provided by Pocock(1997), use of the Bonferroni correction for a smaller-sized exploratory study likely over-corrects for Type I error possibly hindering future study and advancement in the field. Therefore, we did not correct for multiple comparisons. Due to the exploratory nature of this study, formal power and sample size assessments were not done.

3.Results

A summary of participant demographics and their corresponding anatomical MRIs are provided in Table 1 and Figure 1, respectively. Affected and less affected hand tracking scores were not available for one no-MEP participant. Affected hand tracking performance

was not available for one MEP participant. The MEP group demonstrated significantly higher I/C volume ratios for M1 ($p = 0.028$) and PLIC ($p = 0.005$) and superior less affected hand finger tracking accuracy ($p = 0.016$) than the no-MEP group. Affected hand finger tracking accuracy, age, sex, mirroring, and stroke hemisphere did not significantly differ between groups (Table 2). Figure 2 illustrates representative examples of less affected hand finger tracking from participants in the MEP and no-MEP groups. No major adverse events occurred during TMS testing. Additional detail concerning safety is available (Gillick et al., 2015).

As part of a subanalysis, we examined associations between finger tracking performance and M1 and PLIC I/C volume ratios. All correlation coefficients were statistically non-significant – affected hand AI and M1 I/C ratio: $r = 0.207$, $p = 0.282$; less affected hand AI and M1 I/C ratio:$\rho = 0.056$, $p = 0.778$; affected hand AI and PLIC I/C ratio: $r = 0.128$, $p = 0.508$; and less affected hand AI and PLIC I/C ratio: $\rho = 0.158$, $p = 0.423$. An identical analysis performed exclusively on the MEP group also showed non-significant associations between affected hand AI and M1 I/C ratio: $r = 0.090$, $p = 0.715$; less affected hand A1 and M1 I/C ratio:$\rho = -0.237$, $p = 0.345$; affected hand AI and PLIC I/C ratio: $r = 0.182$, $p = 0.455$; and less affected hand AI and PLIC I/C ratio: $\rho = -0.014$, $p = 0.958$.

Participants in the MEP group who qualified for the aforementioned larger CIMT/rTMS study completed additional hand function testing involving the AHA (Table 1). A significant correlation was observed for logit-based AHA scoresand affected hand AI scores ($r = 0.715$, $p < 0.001$). The correlation between logit-based AHA scores and less affected hand AI scores was not significant ($\rho = 0.316$, $p = 0.201$).

4.Discussion

This study compared finger tracking performance and anatomical regions of interest in children with congenital hemiparesis with an elicitable vs. non-elicitable ipsilesional MEP. The important main finding was that finger tracking performance from the less affected hand, but not the affected hand, was significantly lower in participants with no MEP. Additionally, the M1 and PLIC I/C volume ratios were significantly lower in participants with no MEP.

The finger tracking task in our study required participants to visually process a target trajectory and coordinate finger extension/flexion motion to match the trajectory. We chose this task over other dexterity tasks because it is an fMRI compatible task that probes sensorimotor regions of interest (Carey et al., 2002; Deng et al., 2012; Kimberley et al., 2004; Plow et al., 2009). Previous studies have examined finger tracking ability along with other motor tests including auditory reaction time, velocity of ballistic arm movements, finger tapping, and diadochokinesis in healthy children to study motor development with respect to CST maturation assessed with TMS (Fietzek et al., 2000; Heinen et al., 1998). Investigators found that the most robust period of finger tracking development occurred within the first ten years of life, continuing beyond CST maturation and adolescent timeframes, later plateauing in early adulthood. Significant intra-individual effects for handedness (i.e. dominant vs. non-dominant hand) were also discovered (Fietzek et al.,

2000). This study was the first to compare tracking performance in children with congenital hemiparesis on the basis of MEP presentation. Our unexpected yet intriguing finding was the significant difference in tracking performance of the less affected hand favoring participants with an MEP over participants with no MEP.

One potential explanation is that participants with no ipsilesional MEP relied more heavily on contralesional M1 to control the affected hand via ipsilateral CST pathways. As previously mentioned, the activity-dependent withdrawal of ipsilateral CST projections during typical development leads to contralateral motor control organization. A neurological injury like stroke may disrupt this withdrawal process thereby promoting ipsilateral motor control (Eyre et al., 2001; Martin & Lee, 1999). The possibility exists that with substantial stroke damage to the PLIC substrate, through which the CST projections descend, a favorable adaptation for the affected hand follows. The postulated adaptation in individuals with still developing nervous systems is that rather than ipsilateral CST projections from contralesional M1 withdrawing, they persist and enlarge to form a substrate for preserving at least a modicum of ipsilateral sensorimotor control of the affected hand. Indeed, even participants with the largest infarcts (Fig. 1) demonstrated at least 10 degrees of finger extension, as this was an inclusion criterion. We must surmise that because of the near total loss of cortical tissue in the stroke hemisphere in some participants (e.g. participant 24), that the observed motion in the more affected hand was likely due to ipsilateral control from the contralesional hemisphere. Unfortunately, because of excessive head movements in nearly all of the participants that invalidated their fMRI, we cannot confirm this postulate and so it remains speculative, but very worthy of future study.

In a longitudinal study combining neuroimaging and TMS to study CST developmentin infants and children, Eyre et al.(2007) found ipsilesional MEP responses in infants with unilateral lesions that later disappeared by 12 months in approximately half. Corresponding imaging revealed significantly greater growth in diameter of ipsilateral CST projections from the contralesional hemisphere compared to healthy age-matched individuals and to those with bilateral lesions. Importantly, the ipsilateral CST projections from the contralesional hemisphere in the individuals with unilateral lesions who had no ipsilesional MEP were significantly larger than the corresponding projections of the individuals with unilateral lesions who did have an ipsilesional MEP. Thus, this stroke-induced alteration in CST anatomy may reflect an ipsilateral motor control adaptation with the contralesional hemisphere contributing to voluntary movements of the affected extremities in individuals with substantial unilateral stroke damage (Eyre et al., 2007).

However, based on our finding of reduced tracking performance in the less affected hand of participants with no MEP, it appears that the postulated favorable adaptation for the more affected hand concomitantly has a maladaptive corollary consistent with the assertion by Cramer et al.(2011) that neuroplasticity can sometimes have negative consequences. The tradeoff in preserving some affected hand function may be the relinquishment of neural substrate initially dedicated to less affected hand function.

The term “crowding”, introduced by Juenger et al. (2013), refers to the competition arising when one hemisphere contains motor representations of both sides of the body. Crowding

may account for the differences in tracking performance observed from the less affected hand between MEP and no-MEP groups. In those participants with an ipsilesional MEP response and a greater PLIC I/C volume ratio, there may be greater contralesional CST substrate available to control the less affected hand because of no adaptive need for "crowding" to preserve function in the more affected hand. We acknowledge that additional investigation of activity-dependent competition between corticospinal systems, specifically between the ipsilateral and contralateral fiber volumes descending from contralesional M1, is necessary to substantiate our theory.

Notably, our findings did not support our original hypothesis of significant between-group differences in affected hand finger tracking performance. In contrast, prior work has demonstrated significant relationships between corticospinal organization and the severity of affected hand impairment (Bleyenheuft, et al., 2007; Mackey et al., 2014; Rickards et al., 2014; Weinstein et al., 2013). A lack of significance may be partially explained by the multiple systems involved in tracking, and considerable uncertainty exists in the degree of motor system contribution to tracking. Hence, finger-tracking accuracy may not be as robust of a motor measure compared to other more commonly utilized upper-extremity motor tests. Despite the significant correlation between affected finger tracking and AHA, a more purely motor-based task may have better captured affected hand discrepancies between groups.

Relatedly, participants with MEPs showed increased M1 and PLIC I/C volume ratios, consistent with the literature (Duque et al., 2003; Holmström et al., 2011; Kuhnke et al., 2008; Staudt et al., 2002). However, no significant associations between I/C volume and finger tracking performance were found even after isolating the MEP group and repeating the analysis. Several studies that assessed CST and/or PLIC integrity in children using DTI technology found significant correlations with upper-extremity motor function (Bleyenheuft et al., 2007; Mackey et al., 2014; Rickards et al., 2014; Weinstein et al., 2013). The capability of these DTI measures in predicting rehabilitative gains and overall outcome requires additional investigation (Friel et al., 2014; Kirton et al., 2007; Kuhnke et al., 2008; Mackey et al., 2014; Rickards et al., 2014). The small sample size and resulting low power of this study may have prohibited the detection of significant relationships between tracking performance and volume of preserved neural substrate. Other white matter regions may also depict stronger correlations with motor function. Previous studies have found significant associations between cerebral peduncle (Bleyenheuft et al., 2007; Duque et al., 2003; Friel et al., 2014), corpus callosum (Weinstein et al., 2013), corticofugal fiber (Holmström et al., 2011) and sensorimotor thalamic projections (Rose et al., 2011) integrity with upper-extremity function. Lastly, it is possible that our I/C volume ratio method is a less sensitive measure compared to DTI. Bleyenheuft et al. (2007) measured cerebral peduncle cross-sectional area using conventional MRIs and DTI to compute asymmetry indices. Investigators discovered significant associations between these measures and with upper-extremity function, but they found that the conventional MRI method strongly underestimated the degree of CST dysgenesis (Bleyenheuft et al., 2007).

Collectively, the clinical implication of this work is that judicious consideration of the individual is key when determining post-stroke rehabilitative therapies. Based on our finger tracking results, participating in an intervention study involving low-frequency rTMS to

suppress contralesional M1 excitability may be detrimental to participants with no ipsilesional MEP since it is likely that their contralesional hemisphere controls both contralateral (less affected) and ipsilateral (affected) hand function. Therefore, suppressing contralesional M1 may hinder, not enhance, affected hand function. Additionally, contralesional M1 may not be the optimal therapeutic target for rTMS delivery, aimed at suppressing cortical excitability, for participants with no MEP; thus, discouraging the "one size fits all" approach to rTMS intervention (Bradnam et al., 2012). Fittingly, the proposed bimodal-balance recovery model by Di Pino et al. (2014) emphasizes *structural reserve* (e.g. CST and M1 preservation) when predicting the type of brain reorganization likely shaping an individual's post-stroke recovery. Though, we recognize that the term *reorganization* is not applicable in congenital stroke because the nervous system is not fully mature at the time of insult. In our participants, structural reserve was contingent on MEP responses which provided a partial representation of CST integrity. MEP responses, therefore, have the potential to help guide the development of treatment parameters, therapeutic targets, and delivery while serving as potentially useful predictors of intervention responsiveness. Future studies should embrace the heterogeneity in MEP responses in stroke by focusing on effective therapeutic targets and interventions specifically for individuals showing absent ipsilesional MEPs. Combining neuroimaging with TMS testing will provide valuable insight to individual brain (re)organization following stroke that will ultimately strengthen the clinical-decision making process necessary for the skilled delivery of interventions including rTMS.

4.1 Limitations

We acknowledge a number of limitations in our study. We previously discussed how movement artifact prohibited DTI and BOLD signal examination. We believe that our methodology of using PLIC and M1 volumes from anatomical MRIs, however, is a valuable clinical measure based on similar methodology used in previous studies (Bleyenheuft et al., 2007; Duque et al., 2003). Though DTI is fast-becoming a standard tool in stroke research and may be worthwhile in the clinic setting especially in children with CP with normal-appearing MRIs (Benini et al., 2013) or combined with other measures (Shiran et al., 2014), DTI is not without its own limitations (Cheng et al., 2012).

Our study population exhibited heterogeneity in lesion size, location, and hemisphere. We also enrolled subjects with congenital hemiparesis resulting from ischemic stroke occurring before, during, or one year after birth. Such a wide developmental timeframe, encompassing gestational and postnatal periods, pose varying organizational strategies and functional outcomes dependant on the time of infarct (Staudt et al., 2002). Also, due to the observational nature of this study, participants with no MEP did not complete additional testing that included the Canadian Occupational Performance Measure, AHA, Manual Abilities Classification Scale, and stereognosis testing. Despite finding significant correlations between the affected hand finger tracking AI scores with AHA performance, an examination of finger tracking with validated unimanual dexterity tests like the Box and Block (Mathiowetz et al., 1985) and the 9-Hole Peg Test (Smith & Hong, 2000) is needed.

A comparison of finger tracking AI scores between our participants with healthy age-matched controls would provide additional insight. Former work from our lab examined this identical tracking task in 76 right-handed healthy children aged 8-9 years (Carey et al., 2003). AI scores from these children compared to our participants were greater, thus, underscoring the effect of impairment on tracking performance. Yet, tracking performance from the less affected hand in participants with an MEP was greater than tracking performances from the dominant and non-dominant hands in the healthy cohort, which may represent an age effect in tracking since our sample was, on average, older. Direct comparisons between these studies are difficult considering the discrepancies in age range, sample size, and experimental conditions related to participant positioning (sitting vs. supine in an MRI coil) and screen size, for example.

This study was part of a larger study that applied 6 Hz primed 1 Hz rTMS with behavioral therapy (CIMT) in children with congenital hemiparesis (Gillick et al., 2014). The initial approved protocol did not permit any additional pre-test TMS stimulation beyond ipsilesional M1 since study exclusion was based on the absence of an ipsilesional MEP response. Thus, an absent ipsilesional MEP does not directly correspond to ipsilateral motor organization. A bilateral MEP response from contralesional M1 would justify ipsilateral motor control organization. However, we are confident that in those children with absent ipsilesional M1 responses, affected hand function is likely subserved by other motor and/or motor-related substrates as all participants without an MEP displayed some magnitude of voluntary movement in their affected MCP joint.

4.2 Conclusion

We observed that for our sample of children with congenital hemiparesis, specifically participants with no ipsilesional MEP compared to those with an ipsilesional MEP, a reduction in finger tracking performance from the less affected hand and I/C volume ratio of M1 and PLIC. Past studies have shown activity-dependent competition in the visual (Wiesel & Hubel, 1963) and motor (Nudo, 1996) systems. We speculate that diminished tracking performance from the less affected hand may be a consequence of competition between various motor and motor-related tracts driven by both the neural injury and by maturation of the nervous system. Specifically, in more severely injured developing brains, some CST substrate from the contralesional hemisphere normally destined for the contralateral less affected hand, may be competitively redistributed to the ipsilateral more affected hand to preserve some function there, but at the expense of some function in the less affected hand. These findings suggest careful attention to the amount of neural substrate preservation when determining the optimal rTMS delivery approach to promote recovery of hand function following stroke.

Acknowledgements

This project received support from the National Institute of Health (1RC1HD063838-01) and from the National Center for Research Resources to the University of Minnesota Clinical and Translational Science Institute (CTSI) (1UL1RR033183). Drs. Cassidy and Gillick received support from the Foundation for Physical Therapy. Dr. Gillick received additional support from the American Academy of Cerebral Palsy. We further extend our gratitude to William Thomas, PhD and doctoral physical therapy graduate students Brian Battista, Chris Brown, Jaime Calmes, and Jaime Cupit. We are especially grateful for the dedicated children and families involved in our research.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Highlights

- Superior finger tracking in less affected hand seen in children with vs. without an ipsilesional motor-evoked potential (MEP) response.
- Finger tracking performance from the affected hand did not differ amongst children with vs. without an ipsilesional MEP response.
- Greater M1 and PLIC preservation found in children with an ipsilesional MEP response compared to those without.
- Finger tracking scores were not related to neural substrate preservation.

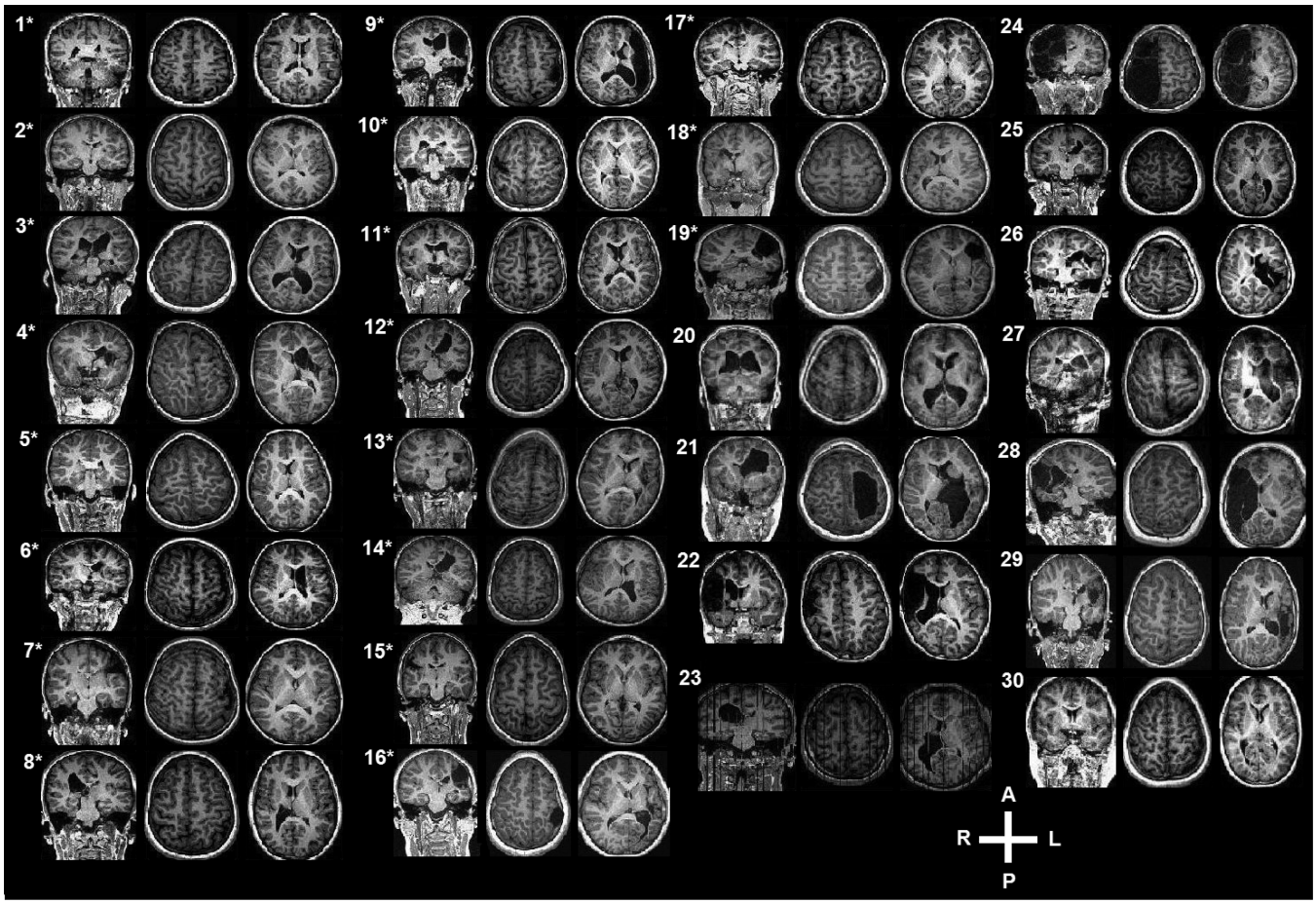

Fig. 1.

One coronal and two transverse views of anatomical magnetic resonance images depicting damage to primary motor cortex and/or posterior limb of internal capsule of participants with an ipsilesional primary motor cortex motor-evoked potential (denoted by asterisk) and those participants without a motor-evoked potential.

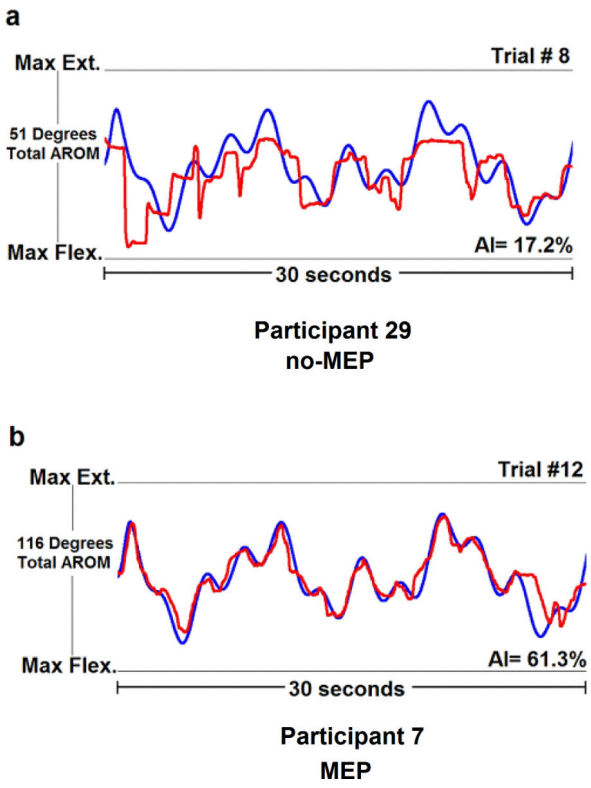

Fig. 2.

Demonstration of two 30-second trials of finger tracking from the less affected hand in a representative participant from the no motor-evoked potential group (no-MEP, a) and the MEP group (b). The blue line represents the target waveform with the participant's corresponding tracking responses denoted by the red line. Accuracy Index (AI) scores were normalized to each participant's maximum flexion (Max Flex.) and extension (Max Ext.) active range of motion at the metacarpophalangeal joint of the affected (not shown) and less affected index fingers. Higher positive AI scores (maximum AI score = 100%) indicate better tracking performance.

Table 1

Participant Demographics

Participant	Group	Threshold Type	Motor Threshold (% of Machine Output)	Sex	Age (y)	GMFCS	MACS	Stroke Hemisphere	Stroke Location
1	MEP	RMT	39	F	15	1	1	R	PVWM
2	MEP	RMT	42	F	15	1	2	L	LV, BG
3	MEP	RMT	72	M	8	1	2	L	T, P, posterior/anterior IC
4	MEP	RMT	65	M	8	1	2	L	T, P, BG, anterior IC,
5	MEP	RMT	79	M	8	1	1	L	MCA, CS, parietal/occipital/ frontal WM
6	MEP	AMT	79	M	8	1	2	L	T, P, BG, anterior IC
7	MEP	AMT	74	M	8	1	2	L	PFL
8	MEP	AMT	66	M	12	1	2	R	CS, BG, T
9	MEP	RMT	69	F	12	1	2	L	BG, MCA, PFL T
10	MEP	AMT	78	F	8	1	2	R	CR, PFL
11	MEP	AMT	60	M	9	1	2	L	IC, T, P, LN,CR
12	MEP	AMT	85	M	11	1	2	L	FPC, IC, T, BG
13	MEP	AMT	52	F	8	1	2	L	C, CS, IC, T, PFL
14	MEP	RMT	84	M	15	1	2	L	CR, T, BG
15	MEP	AMT	52	M	15	1	1	R	MCA
16	MEP	AMT	81	F	10	1	3	L	MCA
17	MEP	RMT	63	F	10	1	2	R	PFL
18	MEP	RMT	68	F	14	1	1	R	PFL
19	MEP	RMT	46	F	13	1	2	L	PFL, parietal/occipital lobes, BG, T
20	no-MEP	none	none	F	8	1	NA	L	PVWM, parieto-occipal cortex
21	no-MEP	none	none	F	8	1	NA	L	LV
22	no-MEP	none	none	M	9	1	NA	R	MCA
23	no-MEP	none	none	M	16	1	NA	R	BG, C, PFL
24	no-MEP	none	none	M	13	1	NA	R	R hemisphere rostral to midbrain
25	no-MEP	none	none	F	10	1	NA	L	CR, T, PFL
26	no-MEP	none	none	M	9	1	NA	L	MCA
27	no-MEP	none	none	M	8	1	NA	L	parietal/occipital lobes
28	no-MEP	none	none	F	9	1	NA	R	BG, CS, FL, T

Participant	Group	Threshold Type	Motor Threshold (% of Machine Output)	Sex	Age (y)	GMFCS	MACS	Stroke Hemisphere	Stroke Location
29	no-MEP	none	none	M	8	1	NA	L	BG, CS, MCA, FPC, IC, T
30	no-MEP	none	none	M	8	2	NA	L	CS, FPC

Participant	Group	M1 I/C Volume Ratio	PLIC I/C Volume Ratio	AI (%) Affected	AI (%) Less Affected	AHA Score (Logit-Based)	Mirroring
1	MEP	0.863	0.995	68.23	73.33	100	No
2	MEP	0.839	0.889	57.10	64.07	86	No
3	MEP	0.918	0.831	−41.03	−40.07	48	Yes
4	MEP	0.829	0.403	−13.67	40.83	35	Yes
5	MEP	0.986	0.980	43.50	64.10	90	No
6	MEP	0.830	0.415	27.30	48.43	63	Yes
7	MEP	0.462	0.898	66.23	65.10	67	No
8	MEP	0.870	0.681	53.13	70.87	66	Yes
9	MEP	0.301	0.488	−64.30	73.10	46	Yes
10	MEP	0.640	0.789	46.40	29.23	67	No
11	MEP	0.858	1.110	−15.63	54.00	54	No
12	MEP	0.820	0.778	7.77	68.63	59	No
13	MEP	0.578	1.022	−52.37	36.23	57	Yes
14	MEP	1.070	0.777	1.40	42.60	66	Yes
15	MEP	0.416	0.753	57.83	78.47	55	Yes
16	MEP	0.526	0.632	−17.72	43.00	45	Yes
17	MEP	1.070	0.707	42.33	64.20	71	Yes
18	MEP	1.130	0.722	−3.83	MD	48	No
19	MEP	0.516	0.763	53.67	72.53	73	No
20	no-MEP	0.761	0.649	−8.67	−25.17	NA	No
21	no-MEP	0.106	0.161	2.07	21.03	NA	Yes
22	no-MEP	0.373	0.139	−0.27	6.30	NA	Yes
23	no-MEP	0.675	0.536	44.37	72.76	NA	Yes
24	no-MEP	0.000	0.137	−49.70	27.23	NA	Yes
25	no-MEP	0.847	0.581	39.63	49.53	NA	Yes
26	no-MEP	0.579	0.051	31.87	49.97	NA	No
27	no-MEP	0.436	0.564	MD	MD	NA	MD
28	no-MEP	0.228	0.032	36.13	40.90	NA	No

Participant	Group	M1 I/C Volume Ratio	PLIC I/C Volume Ratio	AI (%) Affected	AI (%) Less Affected	AHA Score (Logit-Based)	Mirroring
29	no-MEP	0.554	0.597	−54.27	−7.90	NA	No
30	no-MEP	0.983	1.058	−6.63	−10.07	NA	No

AMT active motor threshold, BG basal ganglia, C caudate, CR corona radiata, CS centrum semiovale, F female, FL frontal lobe, FPC frontoparietal cortex, GMFCS Gross Motor Function Classification Scale, GP globus pallidus, IC internal capsule, L left, LN lentiform nucleus, LV adjacent to lateral ventricle, M male, MACS Manual Abilities Classification Scale, MCA middle cerebral artery distribution, MEP ipsilesional motor-evoked potential, NA not available, no-MEP absent ipsilesional motor-evoked potential, P putamen, PFL posterior frontal lobe, PVWM periventricular white matter, R right, RMT resting motor threshold, T thalamus, WM white matter, y years

AHA Assisting Hand Assessment (Logit-Based Scores), AI accuracy index, I/C ipsilesional/contralesional, M1 primary motor cortex, MD missing data, MEP motor-evoked potential, NA not available, no-MEP absent ipsilesional motor-evoked potential, PLIC posterior limb of internal capsule

Table 2

Group Comparisons

Measure	MEP *(n= 19)*	no-MEP *(n= 11)*	*p*
Age (years)	10.9 (2.87)	9.6 (2.58)	0.240
Sex (M/F)	(10/9)	(7/4)	0.708
Stroke Hemisphere (R/L)	(6/13)	(4/7)	1.000
Mirroring during fMRI (yes/no)	(10/9)	(5/5)	1.000
Ipsilesional/Contralesional Volume Ratio			
Primary Motor Cortex	0.764 (0.240)	0.504 (0.310)	**0.028**
Posterior Limb of Internal Capsule	0.770 (0.195)	0.410 (0.326)	**0.005**
Finger Tracking Accuracy Index Scores (%)			
Affected Hand	16.64 (42.19)	3.45 (35.41)	0.407
Less Affected Hand	52.70 (27.46)	22.45 (31.45)	**0.016**

Values presented as mean (standard deviation).