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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.

1. Introduction

The safety of repetitive transcranial magnetic stimulation (rTMS) applications in adult stroke has been supported (Carey et al., 2008; Khedr, Ahmed, Fathy, & Rothwell, 2005; Liepert, Zittel, & Weiller, 2007), and recent investigations of rTMS in

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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, Stinear, Barber, & Byblow, 2012; Cheeran et al., 2008; Maeda, Keenan, Tormos, Topka, & Pascual-Leone, 2000; Senićw 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 or an 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, Sancho, Bautista, Escudero, & Lopez-Trigo, 1998; Kirton, Deveber, Gunraj, & Chen, 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 hemisphere ensues (Eyre, Taylor, Villagra, Smith, & Miller, 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, Harrison, Evans, & Stephens, 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 $\pm$ 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° 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.