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Letter to Editor Open Access

Modulation of Developmental Plasticity with Non-Invasive Brain Stimulation in Cerebral Palsy

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By definitions both historical and modern, cerebral palsy is considered a static disease. Such assumptions of an inability to change are not unreasonable given the complex and often severe nature of the underlying perinatal brain injuries. However, the same assumptions contradict the long suspected and increasingly understood ability for the developing brain to change. Our ability to measure and understand such plasticity in human children has expanded enormously in recent years, thanks in particular to technological progress in advanced neuroimaging and non-invasive brain stimulation. While complimentary to each other, only the latter carries the additional exciting possibility of actually modulating this plasticity to improve function.

Perinatal stroke probably represents the ideal human model of developmental motor plasticity following early brain injury. By definition, these are specific focal cerebrovascular diseases affecting cerebral arteries or veins resulting in regional brain injury occurring between 20 weeks gestation and 28 days of life [1]. Modern neuroimaging with MRI permits the accurate classification of perinatal stroke into specific disease states, the most common of which are ischemic and include large arterial lesions acquired near term and isolated subcortical venous strokes acquired prematurely [2,3]. Such specific, well circumscribed lesions of defined timing and mechanism in what is usually an otherwise healthy brain represent a very appealing model for the study of human developmental plasticity and neurorehabilitation in children.

You will not incur a more focused period of risk for ischemic stroke than the week you are born [4]. The pathophysiology of perinatal stroke is poorly understood with most cases being idiopathic [4]. As a result, no treatment or prevention strategies exist, suggesting perinatal stroke-induced disability will persist in the population. Combined with a common occurrence of >1:2500 live births, [4,5] the global burden is substantial. Most survivors of perinatal stroke suffer lifelong neurological disability and motor deficits are most common [6,7]. Much of term cerebral palsy is hemiparetic [8] and stroke is the leading cause [9,10]. Motor deficits typically emerge in the first year but evolve throughout development and are likely the single greatest contributor to decreased quality of life. Our ability to understand and treat such congenital hemiparesis is limited but improving.

Despite these many reasons to consider perinatal stroke as the perfect disease state to understand and improve function in cerebral palsy, evidence based rehabilitation strategies for motor deficits are lacking. Although there are still no clinical trials focused on perinatal stroke, exciting evidence is emerging for multiple motor rehabilitation therapies in children with hemiparetic cerebral palsy, many of whom presumably have perinatal stroke. The best studied is constraint induced movement therapy (CIMT) which promotes functional use of an impaired limb by physical constraint of the less-impaired limb coupled with repetitive motor practice [11-15]. In the presumably less plastic brains of adults with stroke, two weeks of CIMT can generate gains in upper extremity motor function lasting years [14,15]. Multiple pediatric trials support similar CIMT effectiveness in hemiparetic cerebral palsy [16-25]. These studies likely include a high proportion of perinatal stroke but their results likely remain clouded by the inevitable disease heterogeneity created in otherwise unspecified cerebral palsy samples. CIMT limitations include a modestly invasive nature, particularly for young children, and the exclusion of bimanual learning. CIMT trials dedicated to specific perinatal stroke diseases are now in progress (clinicaltrials. gov/NCT01189058) and promise to offer more specific indications and predictors of success as well as improved modeling to understand CIMT effects on plasticity and motor learning.

Hand-Arm Intensive Bimanual Therapy (HABIT) [20] has also been shown to improve function in hemiparetic cerebral palsy clinical trials [26,27]. The absence of constraint facilitates functional bimanual motor learning and removes the complications of casting. The safety, validity and effectiveness in enhancing motor learning are increasingly well established in children with hemiparesis [20,27-30] though applications to specific brain injuries such as stroke are still required. A recent comparison of CIMT and HABIT found comparable benefits but greater achievement of self-directed goals with HABIT [27]. Beyond this evidence for CIMT and HABIT, few other avenues to enhance function are available. Consensus-based pediatric stroke guidelines support early initiation of multimodal rehabilitation therapy [31,32]. The role of botulinum toxin injections in both upper and lower extremities is increasingly defined in cerebral palsy and may be particularly amendable to the more focal tone issues typical of perinatal stroke [24,33,34]. What virtually all of these reasonable approaches to rehabilitation are lacking is a fundamental understanding of the underlying central nervous system physiology and targets of intervention and the means by which they might be altered when therapy is "effective".

Fortunately, recent progress has advanced new understandings of developmental plasticity in perinatal stroke-induced hemiparetic cerebral palsy. Combining animal studies with modern advanced neuroimaging and brain stimulation in children has generated new models of motor developmental plasticity [35]. At the root of this model is the relative balance of cortical motor control between the ipsilateral and contralateral hemispheres. Excessive control of an affected upper extremity by the ipsilateral (i. e. non-lesioned) hemisphere likely represents an example of maladaptive developmental plasticity in perinatal stroke [36]. Such ipsilateral projections are normal at birth but the majority are typically withdrawn in early development, persisting to a mild degree in some individuals but often becoming prominent following contralateral injury. This model has been developed by combining elegant animal work [37] with transcranial magnetic stimulation (TMS) studies [38,39] in human children. TMS

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delivers focused magnetic fields to discrete functional regions of cortex, inducing localized electrical currents that depolarize upper motor neurons to generate motor evoked potentials measureable in target muscles with surface EMG. TMS can define bilateral corticospinal inputs while characterizing cortical neurophysiology. This in turn has defined the normal evolution of corticospinal control whereby ipsilateral connections present at birth are gradually withdrawn during early development [40]. More sophisticated methods can quantify complex cortical neurophysiology. Safety and tolerability of TMS in children is now well established (Rajapakse, Trnds neurosci 2013, in press).

This exciting progress has generated not only an increased understanding of disease-specific neurophysiology but has identified real central therapeutic targets and possible means by which they might be affected [35]. Specifically, interventions that enhance motor control and learning within the lesioned hemisphere, or discourage control by the unlesioned hemisphere, would be expected to encourage a more favorable balance of motor control. If such modulation could occur in combination with motor skill training (e.g. occupational therapy) during susceptible timeframes in motor development, perhaps enhanced functional improvements could be realized. Consistent with the plasticity model outlined above, preliminary functional imaging studies suggest that effective CIMT shifts motor function toward the lesioned hemisphere [41-45]. Similar CIMT-induced cortical reorganization has been demonstrated in adults with functional MRI [42,46-48] and TMS [41,49-55] and small studies of children with hemiparetic cerebral palsy [44,45,56]. What is required therefore are other means of modulating such cortical control systems.

Can non-invasive brain stimulation modulate cortical motor systems to enhance function in children with cerebral palsy? Brain stimulation given repeatedly can produce lasting changes in brain function with potential therapeutic effects. Repetitive TMS (rTMS) studies have established this principle in health and disease over the past two decades [57-59]. High frequency rTMS (>5-10 Hz) stimulates cortex which both animal [60-62] and adult [58] stroke studies suggest can facilitate motor function. In contrast, low frequency rTMS (~1 Hz) inhibits cerebral cortex [63,64].

Additional appealing features of rTMS include a well established safety profile and excellent tolerability, including recent evidence in children. (Rajapakse, Trans Neurosci 2013, inpress) rTMS is amenable to randomized, sham-controlled clinical trials [65]. Repetitive (rTMS) studies report no significant adverse events [66-68]. Daily rTMS administered for weeks in animals [69] as well as adults with stroke [70-74] and our recent pediatric stroke trials [75,76] also appear safe. Evidence from our group and others has also shown no adverse effects of non-lesioned motor cortex inhibitory rTMS on normal hand function [75,77].

Substantial evidence suggests rTMS can modulate neural networks [78] to enhance motor function in chronic adult stroke [70,79]. A recent meta-analysis provides an excellent summary [80]. Despite both the high burden of motor disability and probable greater brain plasticity in children, interventional stimulation studies have been extremely limited. We completed the first small pediatric rTMS randomized trial where 8 days of non-lesional inhibitory rTMS appeared to improve hand function in children with chronic subcortical stroke [75]. We are currently executing the PLASTIC CHAMPS study [76], a factorial randomized trial of contralesional rTMS and CIMT to enhance motor learning in children with perinatal stroke (www. clinicaltrials. gov/ NCT01189058). Interim safety analysis (n=38) confirms excellent safety, tolerability, and feasibility with no adverse events or drop-outs. The same trial has also provided important safety data, suggesting that contralesional inhibitory rTMS does not adversely influence affected hand function in children with prominent ipsilateral corticospinal projections. These trials have also confirmed the feasibility of measuring complex plastic neurophysiology with TMS and neuroimaging to determine both baseline and post-interventional changes in children with hemiparesis. Collectively, evidence supports the feasibility and potential efficacy of non-invasive stimulation trials in children with perinatal stroke-induced hemiparesis.

Potential limitations of rTMS include very focal administration and burdensome, immobile hardware that prevents simultaneous rehabilitation and co-activation of endogenous motor learning systems. New non-invasive brain stimulation technologies are emerging that may overcome some of these disadvantages. Transcranial Direct Current Stimulation (TDCS) applies two simple scalp electrodes (anode and cathode) to generate weak direct currents (1-2mA) that induce polarity-dependent changes in brain excitability [81]. TDCS induces regional, transient modulation of resting membrane potential and cortical neuronal excitability [82]. Anodal stimulation increases cortical excitability while cathodal stimulation decreases it, much like high and low frequency rTMS respectively. Modern commercial TDCS systems are painless, inexpensive, safe, and portable, allowing patients to remain mobile during active rehabilitation. TDCS is amenable to sham blinded clinical trials [83] and safety and tolerability in adults is well established with thousands tested and published guidelines [84-86].

Published consensus statements endorse the ability of TDCS to enhance motor learning in healthy and diseased adults [87]. TDCS can enhance motor learning in both animals and healthy adults when administered briefly over the motor cortex [88-91]. Adult studies have not only demonstrated enhanced motor skill learning with contralateral anodal or ipsilateral cathodal TDCS but are also elucidating the mechanisms of neuroplasticity involved [88,89]. The duration of effect clearly outlasts TDCS interventions by hours to days in a dose dependent fashion, confirming a therapeutic potential [92-95]. Recent trials provide Class I evidence that TDCS can enhance motor recovery in adults with chronic stroke [92,96-100]. Though fundamental mechanisms may differ, the same approach outlined above - stimulating the lesioned or inhibiting the unlesioned hemisphere (or both) [96] – enhances motor function. Despite such substantial evidence of feasibility, safety, and potential efficacy, TDCS is yet to be applied to the above model of plasticity following perinatal stroke.

It appears that cerebral palsy definitions that continue to suggest permanent, unmodifiable brain dysfunction may need to be revised to reflect a rapidly emerging understanding of developmental plasticity following early injury. Current models have defined real cortical therapeutic targets while modern technologies and therapies may provide the means to modulate them. With focal injury of defined timing and mechanism in an otherwise healthy brain, perinatal stroke provides the ideal human example. Whether the earliest windows of development provide the best opportunity for such intervention remains to be determined, but the proven ability to modulate elderly adult brains suggests children of all ages with cerebral palsy are an ideal population.

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