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Changes in spectroscopic biomarkers after transcranial direct current stimulation in children with perinatal stroke

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ABSTRACT

Background: Perinatal stroke causes lifelong motor disability, affecting independence and quality of life. Non-invasive neuromodulation interventions such as transcranial direct current stimulation (tDCS) combined with intensive therapy may improve motor function in adult stroke hemiparesis but is under-explored in children. Measuring cortical metabolites with proton magnetic resonance spectroscopy (MRS) can inform cortical neurobiology in perinatal stroke but how these change with neuromodulation is yet to be explored.

Methods: A double-blind, sham-controlled, randomized clinical trial tested whether tDCS could enhance intensive motor learning therapy in hemiparetic children. Ten days of customized, goal-directed therapy was paired with cathodal tDCS over contralesional primary motor cortex (M1, 20 min, 1.0 mA, 0.04 mA/cm^2) or sham. Motor outcomes were assessed using validated measures. Neuronal metabolites in both M1s were measured before and after intervention using fMRI-guided short-echo 3T MRS.

Results: Fifteen children [age(range) = 12.1(6.6–18.3) years] were studied. Motor performance improved in both groups and tDCS was associated with greater goal achievement. After cathodal tDCS, the non-lesioned M1 showed decreases in glutamate/glutamine and creatine while no metabolite changes occurred with sham tDCS. Lesioned M1 metabolite concentrations did not change post-intervention. Baseline function was highly correlated with lesioned M1 metabolite concentrations (*N*-acetyl-aspartate, choline, creatine, glutamate/glutamine). These correlations consistently increased in strength following intervention. Metabolite changes were not correlated with motor function change. Baseline lesioned M1 creatine and choline levels were associated with clinical response.

Conclusions: MRS metabolite levels and changes may reflect mechanisms of tDCS-related M1 plasticity and response biomarkers in hemiparetic children with perinatal stroke undergoing intensive neurorehabilitation.

Introduction

Perinatal stroke causes lifelong motor disability, typically hemiparetic cerebral palsy, affecting independence and quality of life [1]. Perinatal strokes are common, focal, vascular brain injuries occurring between 20 weeks gestation and 28 days of life [2,3].

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There are no prevention strategies, resulting in a large, ongoing burden. As an isolated, unilateral injury of defined timing, perinatal stroke represents an ideal human model of developmental plasticity [4]. Modern neuroimaging has defined specific perinatal stroke disease states [5]. Periventricular venous infarctions (PVI) are small subcortical strokes affecting periventricular white matter occurring *in utero* prior to 32–34 weeks [5]. In contrast, arterial ischemic strokes (AIS) of the middle cerebral artery typically occur near term and damage large cortical and subcortical structures [6]. Such arterial strokes can present acutely at birth (neonatal arterial ischemic stroke, NAIS) or later in infancy (arterial presumed perinatal ischemic stroke, APPIS). Both AIS and PVI typically injure one or more components of the motor system, resulting in contralateral hemiparetic cerebral palsy. Emerging animal [7] and human [4,8,9] models are defining how the motor system develops following such early injury. Integrity of both the lesioned and contralesional motor cortices, and the balance between them, are essential determinants of function. These models have identified potential cortical targets for therapeutic neuromodulation [10].

Non-invasive neuromodulation technologies such as transcranial direct current stimulation (tDCS) combined with intensive motor therapy have shown promise in chronic hemiparesis after adult stroke [11,12]. During tDCS, a weak electrical current is applied to the scalp, altering cortical plasticity. Trends include relative increases in excitability with anodal stimulation and decreased excitability with cathodal stimulation [13,14] though exceptions are increasingly recognized [15–17]. When paired with task learning or rehabilitation, lasting changes in performance have been demonstrated [12,18]. tDCS also lends itself to blinded clinical trials with effective sham techniques [19]. Anodal tDCS over damaged primary motor cortex (paired with intensive motor therapy) may improve motor function by increasing perilesional cortical excitability [20]. Conversely, cathodal tDCS over the intact hemisphere may have effects by altering transcallosal inhibition [12]. Both the lesioned and contralesional M1 are the main targets of such neuromodulation but molecular mechanisms are almost entirely unknown.

Emerging evidence suggests similar potential of non-invasive neuromodulation in children with perinatal stroke and hemiparesis. Two controlled trials of repetitive transcranial magnetic stimulation (rTMS) have suggested efficacy and safety [21,22]. That tDCS can safely produce marked enhancement of motor learning in healthy school-aged children has also now been established [18]. A recent phase 1/2 controlled clinical trial of contralesional M1 tDCS combined with 2 weeks of intensive motor therapy suggested potential efficacy for children with hemiparesis after perinatal stroke [23].

The mechanisms of non-invasive neuromodulation are poorly understood but amenable to investigation with pre- and post-interventional neuroimaging [24,25]. Most studies to date have focused on changes in functional connectivity, task-based functional MRI activation patterns or white matter structure rather than neurochemistry. Measuring cortical metabolite concentrations with proton magnetic resonance spectroscopy (MRS) can provide information on neuronal health (*N*-acetyl-aspartate [NAA]), cell membrane health (choline compounds [Cho]), energy metabolism (creatine compounds [Cre]), health of glial cells (*myo*-Inositol [Ins]), metabolic activity and excitatory neurotransmitter concentrations (glutamate [Glu]) among others [26,27]. Limited evidence supports specific neurochemical changes after tDCS in adults. Increased glutamate and glutamine (Glx) under the stimulating anode with smaller changes in contralateral homologous regions may occur and correlate with changes in motor behaviour [28]. Metabolite increases after anodal tDCS have also been demonstrated for total NAA [28] and *myo*-inositol [29] whereas decreases may occur in γ-Aminobutyric acid (GABA) [30]. During cathodal tDCS, decreases in both Glx and GABA have been reported [30]. Using fMRI-guided MRS, we recently demonstrated specific neurochemical alterations in bilateral M1 in children with perinatal stroke that correlated with degree of hemiparesis [31].

Therefore, MRS represents a novel means by which mechanisms of therapy and modulation-induced changes in cortical function might be explored in disabled children. Our aim here was to examine intervention-induced metabolic changes in the motor cortex in children with perinatal stroke and hemiparesis within a tDCS neuromodulation clinical trial [23]. We hypothesized that Glx concentration would decrease under cathodal stimulation in the non-lesioned M1 with the degree of change correlating with change in clinical function.

Methods

Population

Participants with perinatal stroke were recruited via the Alberta Perinatal Stroke Project (APSP), a population-based research cohort [32]. Inclusion criteria were: (1) unilateral, MRI-confirmed perinatal stroke syndrome according to previously validated criteria [5] including neonatal arterial ischemic stroke (NAIS), arterial presumed perinatal ischemic stroke (APPIS), or periventricular venous infarction (PVI), (2) current age 6–19 years and term birth (>36 weeks), and (3) symptomatic hemiparetic cerebral palsy (HCP) [Pediatric Stroke Outcome Measure (PSOM) score >0.5 [33] and Manual Ability Classification System (MACS) score I-IV [34] and perceived functional limitations by child and parent]. Children with additional neurodevelopmental or psychiatric conditions, clinical or imaging evidence of bilateral or more diffuse injury (e.g. premature white matter injury), unstable epilepsy, or hemiparesis intervention (e.g. orthopedic surgery, botulinum toxin) within 12 months were excluded. Children with NAIS and APPIS were combined into a single group (AIS) due to a similar mechanism of injury (arterial ischemic stroke).

Typically developing control (TDC) volunteers were recruited through an established healthy controls program. TDC participants were right handed, aged 6–19 years, and had no MRI contraindications, neurodevelopmental or psychiatric conditions. TDC participants were gender and age (±1 year) balanced with stroke cases. TDC children did not undergo tDCS or attend the motor learning therapy camp.

Written parental informed consent and participant assent was obtained for all participants. This study was approved by the Conjoint Health Research Ethics Board, University of Calgary.

Interventions

Motor learning therapy

Stroke patients participated in a two week (10 consecutive weekdays) after-school, goal-directed motor learning therapy camp at the Alberta Children's Hospital (ACH), the details and clinical results of which are described elsewhere [23]. Participants set their own goals according to the Canadian Occupational Performance Measure (COPM) [35]. They were grouped with peers to maximize social benefits. Sessions were facilitated by experienced occupational therapists (OT). Typical camp activities included sports, therapeutic arts, music, horticulture, creative gaming, and activities of daily living. Individualized therapy (90 min) was complemented with group activities (30 min) for a total of 120 min per day. For the first five weekdays, constraint-induced movement therapy (CIMT) [36] was applied with the higher-functioning limb restrained using a soft, removable cast. For the second five weekdays, Hand-arm Intensive Bimanual Therapy (HABIT) was utilized, an evidence-

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