Brain Stimulation 10 (2017) 305–314

Contents lists available at ScienceDirect

Brain Stimulation

journal homepage: http://www.journals.elsevier.com/brain-stimulation

Cortical excitability after pediatric mild traumatic brain injury

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ARTICLE INFO

Article history:
Received 30 June 2016
Received in revised form
15 November 2016
Accepted 18 November 2016
Available online 19 November 2016

Keywords:
Transcranial magnetic stimulus
Mild traumatic brain injury
Pediatrics
Cortical silent period
Long interval intracortical inhibition

ABSTRACT

Introduction: Mild traumatic brain injury (mTBI) outcomes are variable, and 10–15% may suffer from prolonged symptoms beyond 3 months that impair the child's return to normal activities. Neurophysiological mechanisms of mTBI are incompletely understood, particularly in children, but alterations in cortical excitability have been proposed to underlie post-concussion syndrome. Improved understanding is required to advance interventions and improve outcomes.

Objective/Hypothesis: To determine if cortical excitability is altered in children with mTBI, and its association with clinical symptoms.

Methods: This was a cross-sectional controlled cohort study. School-aged children (8–18 years) with mTBI were compared to healthy controls. Cortical excitability was measured using multiple TMS paradigms in children with (symptomatic) and without (recovered) persistent symptoms one-month post-injury. Primary outcome was the cortical silent period (cSP), a potential neurophysiological biomarker of GABAergic inhibition. Secondary outcomes included additional TMS neurophysiology, safety and tolerability. Associations between neurophysiology parameters and clinical symptoms were evaluated.

Results: Fifty-three children with mTBI (55% male; mean age 14.1 SD: 2.4 years; 35 symptomatic and 27 asymptomatic participants) and 28 controls (46% male; mean age 14.3 SD: 3.1 years) were enrolled. cSP duration was similar between groups ($F(2, 73) = 0.55$, $p = 0.582$). Log_{10} long interval intracortical inhibition (LICI) was reduced in symptomatic participants compared to healthy controls ($F(2, 59) = 3.83$, $p = 0.027$). Procedures were well tolerated with no serious adverse events.

Conclusions: TMS measures of cortical excitability are altered at one month in children with mTBI. Long interval cortical inhibition is decreased in children who remain symptomatic at one month post-injury.

1. Introduction

Mild traumatic brain injury (mTBI) is a significant public health concern as it is both common, occurring in 350–799 per 100,000 per year [1–4], and 11–31% of children mTBIs have symptoms which last longer than 1 month: defined as post-concussion syndrome (PCS) [5,6]. PCS is a constellation of physical, emotional, and cognitive symptoms following mTBI [7] that significantly impacts the quality of life of the child and family [8]. The mechanisms underlying the pathophysiology of PCS are poorly understood [9–11], which significantly impedes the development of better diagnostic tools and treatments.

Traumatic brain injury results in dysregulated neurotransmitter release, altered receptor expression, and injury to interneurons and microcircuits, potentially leading to disruption in the functional balance between cortical excitation and inhibition. This is supported by both murine models of TBI [12,13], and adult human research [14–17]. Initially, TBI results in an uncontrolled glutamate release and a disruption of ionic balance across neuronal membranes, the extent of which is dependent on the severity of the injury [18,19]. Subsequent alterations in receptor expression occur, such as early changes in n-methyl-d-aspartate (NMDA) receptor subunit composition [20] and later shifts in γ-aminobutyric acid (GABA) subtype receptor subunits ratios [21,22]).

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http://dx.doi.org/10.1016/j.brs.2016.11.011
1935-861X/

Cortical excitation and inhibition can be interrogated *in vivo* in humans using transcranial magnetic stimulation (TMS) [23,24]. Using TMS methodologies, cortical inhibition has been found to be increased both acutely [25] and chronically in adult athletes recovering from mTBI (e.g., increased cortical silent period (cSP) [26,27] and long interval intracortical inhibition (LICI) [27,28]). Whether such alterations in cortical inhibition occur in children, who have shorter cSP [29], different physiological responses to injury, and different recovery profiles [30,31], is unknown. Nor is it known how these physiological changes relate to clinical symptoms.

We explored cortical excitability following mTBI in children and its relationship with clinical symptoms to better understand mechanisms of symptom persistence and the variability in subject recovery. Specifically, we asked whether children with early versus late recovery differed in their neurophysiological parameters of cortical excitation and inhibition when compared to healthy controls of similar age and sex.

2. Methods

This prospective controlled cohort study was performed as part of PLAY GAME, a randomized controlled trial of melatonin for the treatment of PCS following childhood mTBI [32] (https://clinicaltrials.gov/ct2/show/NCT01874847). This study was approved by the University of Calgary Conjoint Health Research Ethics Board (REB13-0372).

2.1. Participants

Children and adolescents (ages 8–18 years) presenting to the Alberta Children's Hospital with an mTBI were eligible. Mild TBI was defined as an impact to the head or body with a Glasgow Coma Score of 13–15 resulting in at least one of the following: an observed loss of consciousness less than 30 min, or at least one acute symptom suggesting neurological dysfunction attributable to the injury (e.g., headache, confusion, vomiting, amnesia, balance problems) [8,33]. Concussion was considered part of the mTBI spectrum [34]. Exclusion criteria were: suspected child abuse; alcohol or drug use at the time of injury; inability to complete questionnaires; significant past medical or psychiatric history requiring medication; contraindications to TMS [35]; previous mTBI within 3 months or failure to recover from a previous mTBI; and/or use of neuroactive drugs. Untreated Attention Deficit Disorders (ADHD) or mild learning disorders were not excluded. Typically developing children (ages 8–18 years) were eligible if they satisfied exclusion criteria and had no history of TBI (healthy controls).

Children with mTBI were identified from a tertiary care pediatric Emergency Department (n = 761) and eligible children with mTBI were contacted by telephone at 4 weeks post-injury (n = 294). The recruitment process is shown in Fig. 1. Parental consent and participant assent were obtained. The Post-Concussion Symptom Inventory (PCSI) was used to document symptoms. Participants who had clinically recovered were selected to be similar in age and sex to the symptomatic group. Controls were recruited from friends or siblings of the mTBI participants. Outcome was assessed at 4–6 weeks post-injury before enrolment into the treatment trial.

2.2. Clinical outcome measures

2.2.1. Post-concussion symptom inventory

This age-appropriate, standardized questionnaire provides ratings for 26 symptoms (Guttman scale: 0 to 6) and an overall rating

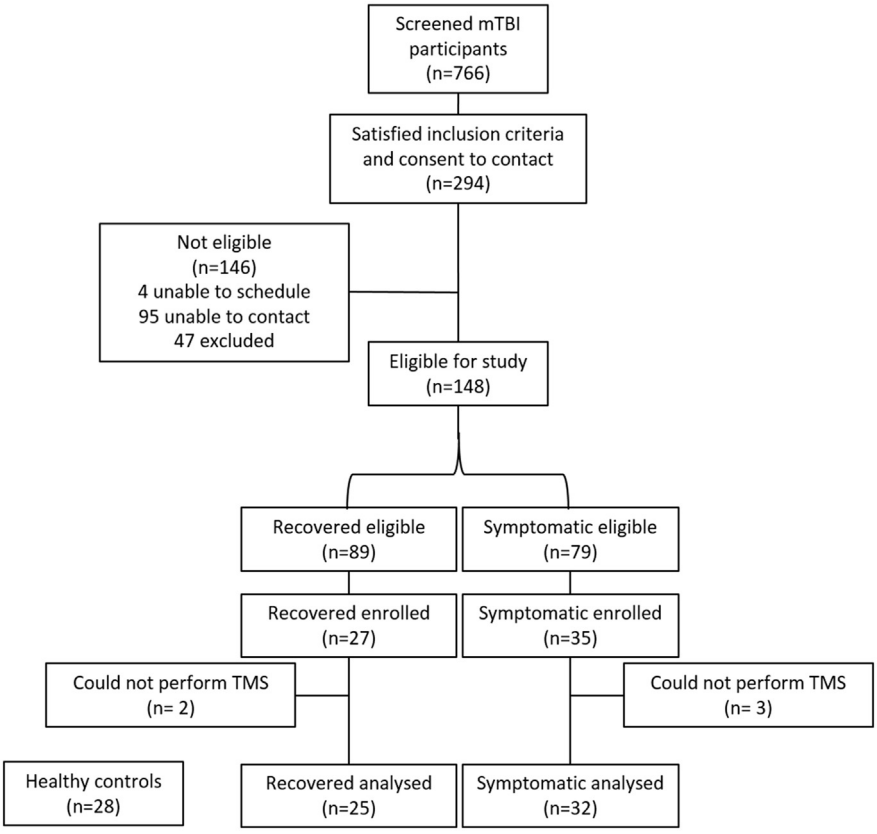

Fig. 1. Participant recruitment flow. A flow chart of the recruitment of participants through each step in screening and final samples. Analysed participants are those whose thresholds permitted at least one TMS paradigm to be performed.