Evaluating the Feasibility of Transcranial Direct Current Stimulation as an Adjunct to Physiotherapy in Children and Youth with Acquired Brain Injury

by

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Abstract

Background: Children and youth with subacute moderate to severe acquired brain injury (ABI) experience plateaus in gross motor recovery toward the end of inpatient rehabilitation. Thus, novel treatment adjuncts may be used to enhance recovery. The primary objective of this dissertation was to evaluate the feasibility of transcranial direct current stimulation (tDCS) as an adjunct to inpatient physiotherapy in school-aged children and youth with ABI.

Methods: A chart review was conducted to establish the gross motor change associated with inpatient ABI. A systematic review was undertaken to determine if motor evoked potentials (MEP) are an appropriate neural outcome for tDCS protocols involving motor intervention in healthy individuals. A tDCS feasibility trial was conducted at the author's pediatric rehabilitation centre where participants were randomized to receive either 20 minutes of sham or active anodal tDCS immediately prior to their existing inpatient physiotherapy sessions for up to 16 sessions.

Results: The chart review provided an estimate of gross motor change for inpatient ABI rehabilitation with two of the outcome measures implemented in the feasibility study. The systematic review revealed that MEP outcomes varied considerably across tDCS studies and

were therefore not measured in the feasibility study. Feasibility study eligibility and retention were lower than the *a priori* targets. Over 21 months, six children were eligible for the study, four enrolled in the study, three commenced the study protocol, and one completed all study sessions. Symptom ratings before and after each tDCS session suggest that the participants tolerated tDCS. Physiotherapy session documentation and analysis detailed the motor learning strategies content of the physiotherapy sessions accompanying tDCS.

Conclusions: This dissertation established gross motor outcomes associated with inpatient pediatric ABI rehabilitation and identified the limitations of MEPs as a neural outcome. While eligibility and retention were barriers to tDCS study feasibility, our study processes (including differentiating between ABI symptoms and tDCS side effects, analyzing the physiotherapy session content paired with the tDCS, and evaluating gross motor outcomes with a complementary set of outcome measures) were feasible and can be applied in future tDCS research in pediatric ABI.

Acknowledgments

"Alone we can do so little. Together we can do so much."

Helen Keller

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Chapter 1

1 Background and rationale

1.1 Introduction

Inpatient physiotherapy for children and youth with moderate to severe acquired brain injury (ABI) focuses on the relearning and refinement of functional gross motor skills with the goal of independent mobility and participation in meaningful activities (Dumas et al., 2004a; Lee et al., 2017; Levac et al., 2012; Spivak et al., 2021). While children with ABI typically make substantial physical gains with inpatient rehabilitation, their recovery tends to plateau leaving them with residual motor challenges (Dumas et al., 2004a; Galvin et al., 2010a; Galvin et al., 2010b; Tailor et al., 2013). Intervention during the subacute stage of recovery is critical because it is associated with increased neuroplasticity and significant functional gains (Anderson & Catroppa, 2006; Chen et al., 2010; Dromerick et al., 2021; Zeiler & Krakauer, 2013). Given the high potential for recovery and the likelihood of persistent motor deficits, clinicians and researchers are interested in adjuncts to traditional interventions that will maximize motor outcomes during this critical recovery period. However, evidence supporting motor learning-based technologies in pediatric ABI is limited and their feasibility within existing rehabilitation programs is unknown.

Transcranial direct current stimulation (tDCS) is a treatment adjunct that has been linked with improved motor learning outcomes when paired with motor practice in adults with stroke (Navarro-López et al., 2021; Vaz et al., 2019) and children with cerebral palsy (CP) (Elbanna et al., 2019; Salazar Fajardo et al., 2022; Saleem et al., 2019a) but has yet to be studied in pediatric ABI. To determine if tDCS enhances gross motor outcomes in children with subacute ABI, it is imperative to first establish the gross motor outcomes associated with traditional inpatient physiotherapy and determine whether a tDCS protocol can be integrated into an existing inpatient physiotherapy program. The first chapter of this thesis begins with an overview of pediatric ABI, neural control of movement, motor learning and neural plasticity, and tDCS as an adjunct therapy, and concludes by outlining the thesis objectives and rationale. Chapters 2 through 5 address the thesis objectives in four independent manuscripts. Finally, Chapter 6

provides a general discussion, integrates the main findings, details limitations, and outlines directions for future research.

1.2 Pediatric acquired brain injury

1.2.1 Etiology and incidence of pediatric ABI

Pediatric ABI refers to a brain injury that occurs during childhood or adolescence caused by trauma, infection, non-infectious disorder (e.g., hypoxia, ischemia, epilepsy), vascular abnormality, or tumour (Galvin et al., 2010b; Johnson et al., 2009). Moderate to severe ABI in children is associated with persistent motor and cognitive deficits that affect functional independence and social interactions (Galvin et al., 2010a; Hebert et al., 2016; Johnson et al., 2009). The extent of chronic disability after ABI is correlated with injury severity and age where increased severity and younger age at onset intensifies long-term physical, cognitive, emotional, and behavioural challenges (Anaby et al., 2012; Dumas et al., 2004a; Galvin et al., 2010b; Johnson et al., 2009). In contrast, sex has been inconsistently associated with the extent of disability after inpatient ABI rehabilitation (Bedell, 2008; Galvin et al., 2010b). Return to community-based activities is particularly challenging for children with ABI because of the need to quickly adapt motor, cognitive, and social responses to unpredictable situations that arise in daily life (Galvin et al., 2010a). As such, children with moderate to severe ABI are less likely to participate in physical activities (e.g., sports) than children with mild ABI within the first year after ABI, and their participation further declines beyond that first year (Anaby et al., 2012).

Due to variability in pediatric ABI classification, etiology, and reporting, the overall incidence of pediatric ABI is difficult to estimate (IPBIS, 2016; Knight et al., 2019). The incidence of traumatic brain injury (TBI) in children varies between 47 and 280 per 100,000 internationally with approximately 20% of TBIs classified as moderate to severe (Dewan et al., 2016), whereas the incidence of pediatric ischemic and hemorrhagic stroke (types of non-traumatic ABI) is 1.8 and 1.59 per 100,000, respectively. (Krishnamurthi et al., 2015). However, diagnostic and reporting of pediatric stroke varies considerably and, as such, the incidence of childhood onset stroke is thought to be underreported (Agrawal et al., 2009; Krishnamurthi et al., 2015). In Ontario, Canada, data for pediatric ABI excluding stroke and TBI (e.g., brain tumour, encephalitis, anoxia, meningitis) has an incidence of 82.3 per 100,000 with an average acute care

stay of 13.4 days, 35% of admissions going to intensive care units, and 15% of acute care admissions requiring further inpatient rehabilitation (Chan et al., 2016).

1.2.2 Pathophysiology and neurophysiology of ABI

ABI is often associated with three patterns of brain damage that affect: 1) the outer grey matter, 2) the white matter tracts, and/or 3) the deep brain structures (e.g., basal ganglia, thalamus) (Giustini et al., 2013). ABI also involves focal and/or diffuse brain damage depending on etiology (Brown et al., 2008; Giustini et al., 2013; Messacar et al., 2018; Tsze & Valente, 2011). Whether blood or oxygen supply is disrupted, mechanical injury occurs, or a virus crosses the blood-brain barrier, an insult to the brain leads to a cascade of events involving vascular, cellular, and molecular changes that damage brain tissue (Andriessen et al., 2010; Messacar et al., 2018; Sekerdag et al., 2018). The inflammation induced by these changes supports angiogenesis (i.e., formation of new blood vessels) and synaptogenesis (i.e., formation of new neural connections), but can also lead to cell death (McGinn & Povlishock, 2015; Sekerdag et al., 2018). Neuron death can be productive or deleterious in nature and usually occurs due to imbalanced ion concentrations (e.g., calcium, potassium, sodium) at synaptic junctions that disrupt synaptic transmission (Andriessen et al., 2010; Elmore, 2007; Sekerdag et al., 2018). The over- or under-firing of these neurons triggers changes in cell membrane composition and ultimately leads to cell death (Andriessen et al., 2010; Sekerdag et al., 2018) with the location and extent of damage influencing clinical presentation (Giustini et al., 2013; Overman & Carmichael, 2014).

TBI differs from non-traumatic ABI because of the mechanical forces involved. Focal injuries usually consist of cerebral contusions, localized haemorrhaging, or ischaemic lesions that occur when the brain strikes the inside of the skull (Brown et al., 2008). However, injury severity increases depending on the extent of diffuse injury (Giustini et al., 2013). While diffuse injury can occur in non-traumatic ABI due to hypoxia or inflammation, diffuse axonal injury is unique to TBI and occurs when axons are overstretched due to the rapid accelerations and rotational forces on the brain (Andriessen et al., 2010; Brown et al., 2008; Giustini et al., 2013; McGinn & Povlishock, 2015). Diffuse axonal injury leads to widespread white matter damage affecting the brainstem, corpus callosum, and cerebral hemispheres with the severity depending on the involvement of each of these structures; the least severe is widespread axonal damage without

evidence of focal injury and the most severe involves widespread axonal damage accompanied by focal abnormalities, often in the corpus callosum, and brainstem injury (Giustini et al., 2013; Jang, 2009). Motor impairment after TBI is either due to focal injury affecting specific motor areas within the brain or diffuse axonal injury affecting the corticospinal tract (Andriessen et al., 2010; Jang, 2009).

Recovery from ABI involves the reactivation of damaged neural pathways and the formation of new neural pathways in non-injured areas of the brain (Gordon & di Maggio, 2012; Nudo, 2013; Popernack et al., 2015). In addition to the automatic cellular responses that contribute to natural recovery, experience-dependent neural plasticity is integral to recovery after ABI (Katušić, 2011; Overman & Carmichael, 2014). Specific areas of the motor cortex are responsible for the movement of each body part (i.e., somatotopic organization) and neural reorganization is affected by a person's exposure to and practice of various movement patterns (Jones, 2017; Kandel et al., 2013; Overman & Carmichael, 2014). When an ABI affects the motor cortical representation of a particular part of the body and/or the descending pathways associated with that representation, movement of that body part will be impaired. Compensation for this impairment in motor function may involve relying on unaffected body parts to perform a particular movement which leads to neural reorganization with expanded representations of the overused body parts within the motor cortex and diminished representations of the less used, or impaired, body parts (Jones, 2017; Nudo, 2013). However, attempting to use the affected body part creates an important opportunity to reestablish its cortical representation and promote functional recovery (Jones, 2017; Nudo, 2013).

The neural changes in the motor cortex affected by ABI are also accompanied by changes in the unaffected motor cortex due to imbalances in interhemispheric inhibition (Gerges et al., 2022). In the uninjured brain, each cerebral hemisphere is thought to equally inhibit the other hemisphere (Boddington & Reynolds, 2017). However, an imbalance in interhemispheric inhibition after a unilateral stroke decreases inhibition of the unaffected hemisphere which, in turn, increases inhibition of the affected hemisphere and limits the potential for neural plasticity (Boddington & Reynolds, 2017). However, research evaluating the role of interhemispheric inhibition in stroke recovery focuses on upper extremity function (Gerges et al., 2022), and its impact on lower extremity function and gait is unclear due to the need for bilateral activation of the trunk and

lower extremities, as well as the need for interlimb coordination in gait (Charalambous et al., 2016; Lee & Kim, 2021).

1.2.3 The impact of moderate to severe ABI on gross motor function

Gross motor skills are fundamental movements that involve postural control (i.e., stability), locomotion (e.g., walking, crawling), or object manipulation (e.g., lifting, throwing) (Hadders-Algra, 2018; Veldman et al., 2019). Most typically developing children have sufficient strength and postural control to sit, crawl, stand, and walk by one year of age (Hadders-Algra, 2018; Payne & Isaacs, 2017). These gross motor skills allow children to interact with their environment which positively affects their cognitive and psychological development (Anderson, 2018; Veldman et al., 2019). Early gait is inefficient and uncoordinated because postural instability leads to coactivation of antagonist muscle groups, variable stepping patterns, a wide base of support with decreased step length, foot flat initial contact with the ground, and arms held in a high guard position (Hadders-Algra, 2018; Kraan et al., 2017; Payne & Isaacs, 2017). As postural control develops, the child's gait pattern matures with decreased step variability, increased step length, reduced step width, heel strike initial contact, push off at terminal stance, and a reciprocal arm swing (Hadders-Algra, 2018; Kraan et al., 2017; Payne & Isaacs, 2017). However, even once a child attains a mature gait pattern, usually between six and eight years old, they are more prone to deterioration in gait quality than adolescents or adults due to their decreased capacity to process cognitive information, and thus multi-task, during gait (Kraan et al., 2017; Payne & Isaacs, 2017). As postural control improves, children also develop more advanced gross motor skills (e.g., running, jumping, hopping) which require increased balance, coordination, strength, and power compared to walking (Payne & Isaacs, 2017). Notably, adolescents demonstrate immature postural stabilization strategies compared to young adults (Barlaam et al., 2012; Cignetti et al., 2013) which suggests the continued refinement of advanced gross motor skills throughout adolescence.

Depending on the areas of the brain affected by ABI, children may present with a combination of impaired balance, strength, coordination, endurance, and/or muscle tone, which ultimately affects gross motor function (Baque et al., 2016; Galvin et al., 2010a; Kuhtz-Buschbeck et al., 2003; Popernack et al., 2015). The child's stage of gross motor development at the time of injury

also has implications for recovery, as theoretically, it is easier to relearn a skill after ABI rather than learn it for the first time (Babikian et al., 2015; Giza et al., 2009). Independent ambulation is often the primary gross motor goal during inpatient rehabilitation for children with ABI due to the role of ambulation in functional independence (Dumas et al., 2004a). However, even after independent ambulation is achieved, children with severe ABI have increased step variability and decreased gait speed due to decreased postural control (Katz-Leurer et al., 2011). As a result, these children also have difficulty changing gait speed and experience decreased stability when required to walk slower than their preferred speed (Katz-Leurer et al., 2011). Ambulatory children with ABI also often lack the balance, postural control, coordination, speed, agility, and strength required for high level gross motor skills (Baque et al., 2016) which limits their progression from independent ambulation to their pre-injury level of function. Additionally, the combination of gross motor challenges with cognitive difficulties contributes to children's decreased participation in physical activities after ABI (Anaby et al., 2012; Galvin et al., 2010a; Lee et al., 2017).

1.3 Neural control of gross motor function

1.3.1 Voluntary movement

Movement involves a complex sequence of neural commands transmitted from the central to peripheral nervous system (Kandel et al., 2013; Scott, 2004). Voluntary movement begins with a motor plan, or an internal representation of the desired movement, generated in the premotor area of the cerebral cortex (Cisek, 2005; Kandel et al., 2013). This plan is transmitted to the primary motor cortex before descending via the corticospinal tract through the brain stem and spinal cord and synapsing with neurons in the peripheral nervous system that innervate the muscles responsible for executing the movement (Cisek, 2005; Kandel et al., 2013; Scott, 2004). The actual motor output differs from the internalized motor plan due to a multitude of factors, including discrepancies between the internal representation of the motor plan and the environmental circumstances, or fluctuations in neural transmission affecting the accuracy and precision of muscle activation (Cisek, 2005; Gallivan et al., 2018; Kandel et al., 2013; Scott, 2004). After the movement is executed, sensory feedback regarding these discrepancies is relayed via ascending pathways back to the cerebral cortex where the existing motor plan is updated and the movement is adapted to meet the current external demands (Cisek, 2005;

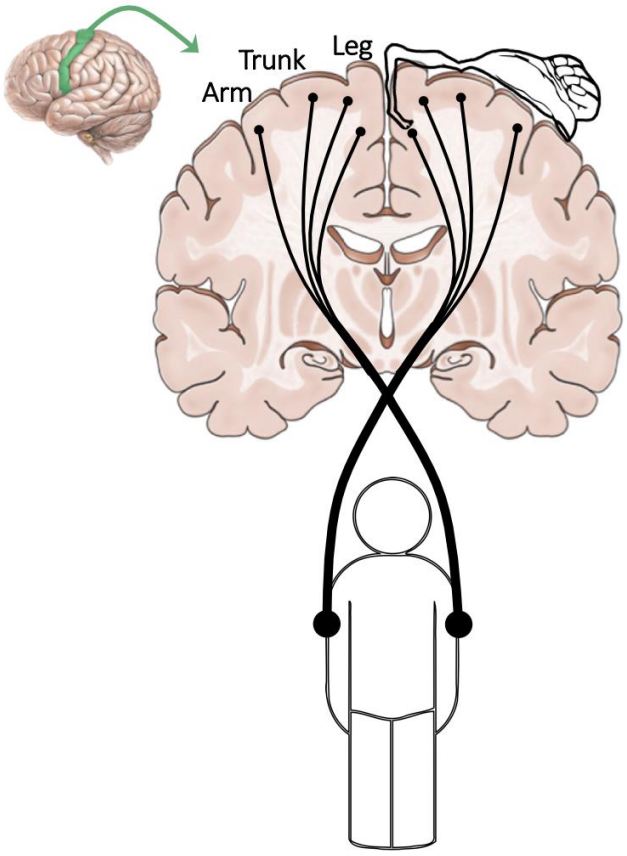
Gallivan et al., 2018; Hirashima & Nozaki, 2012; Kandel et al., 2013; Scott, 2004). Thus, the motor representations and neural connections continually adapt based on individual experience (Cisek, 2005; Cordani et al., 2022; Hamano et al., 2021; Hirashima & Nozaki, 2012; Nakagawa et al., 2020; Nudo, 2013).

The primary motor cortex, located on the precentral gyrus of the frontal lobe, is organized somatotopically with the upper motor neurons controlling the lower extremity located medially and descending into the longitudinal fissure between the cerebral hemispheres, and the motor neurons controlling the trunk, arm, hand, and face extending laterally along the precentral gyrus (Kandel et al., 2013; Kwon et al., 2014) (Figure 1.1). Upper motor neurons descend from the primary motor cortex via the corticospinal tract which decussates (i.e., crosses midline) in the brainstem before descending into the spinal cord and synapsing directly with spinal motor neurons and interneurons at the level of the upper or lower extremity (Kandel et al., 2013; Welniarz et al., 2017). The primary motor cortex contributes to approximately 30-40% of the projections within the corticospinal tract, with the supplementary motor area and the premotor cortex providing additional contributions (Chenot et al., 2019; Kumar et al., 2009; Seo & Jang, 2013). At birth, the corticospinal tract begins with large, nonspecific, bilateral connections to the spinal cord that are refined throughout development with experience-dependent learning leading to a reduction in ipsilateral projections (Eyre et al., 2001; Welniarz et al., 2017). Motor neurons in the corticospinal tract descend from the cerebral cortex through the internal capsule to the brainstem where most neurons cross the midline in the medulla prior to entering the spinal cord (Jang, 2014; Nathan & Smith, 1955). This decussation is responsible for each cerebral hemisphere controlling the sensorimotor function of the contralateral extremity (Kandel et al., 2013; Welniarz et al., 2017).

To a lesser extent, there are projections from the primary motor cortex that descend via the corticoreticular tract and synapse with the reticulospinal tract in the reticular formation within the brainstem (Jang et al., 2013; Mendoza & Foundas, 2008). In addition to sending projections to the primary motor cortex, the premotor cortex influences proximal extremity movement and postural stability via the reticulospinal tract (Jang & Lee, 2019). The reticulospinal tract descends mainly ipsilaterally and is thought to contribute to both automatic processes (e.g., postural muscle tone, locomotor rhythm) and voluntary muscle activation in the trunk, shoulder,

and hip (Jang et al., 2013; Jang & Lee, 2019; Mendoza & Foundas, 2008). However, while postural control and proximal extremity movement is typically associated with the cortico-reticulospinal tract (Jang et al., 2013), the primary motor cortex also plays a role in proximal extremity movement (Jaeger et al., 2014; Yeo et al., 2013) with bilateral activation of the medial primary motor cortices (i.e., lower extremity representations) observed during gait (Miyai et al., 2001; Takakusaki, 2013).

Figure 1. 1. Somatotopic organization of the primary motor cortex and corticospinal tract (Hilderley, 2018).



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1.3.2 Automatic processes underlying voluntary movement

The automatic processes underlying voluntary movement involve aspects of postural control and multi-limb coordination (MacKinnon, 2018; Takakusaki, 2017). These involuntary components of movement occur subcortically (e.g., thalamus, basal ganglia), as well as in the brainstem, cerebellum, and spinal cord (MacKinnon, 2018; Takakusaki, 2017). One automatic process that plays an important role in postural control and gait is the spinal reflex where stereotyped movements occur in response to stimulation of peripheral receptors (Kandel et al., 2013; Takakusaki, 2017). Another process that is responsible for automatic postural responses is muscle synergies that are thought to originate in the reticular formation (i.e., brainstem) (Kandel et al., 2013; Zaaimi et al., 2018). Finally, there are automatic processes involving the cerebellum, visual, and vestibular systems that provide input regarding orientation and balance (Dijkstra et al., 2020; Kandel et al., 2013; MacKinnon, 2018).

While these processes are involuntary, they can be modified by cognitive processes and central motor commands (Gallivan et al., 2018; Kandel et al., 2013; Zaaimi et al., 2018). For example, postural control is attained through subconscious (i.e., postural reflexes and regulation of postural muscle tone) and conscious (i.e., cognitive responses where the individual learns a motor skill or reacts to unfamiliar circumstances) processes (Takakusaki, 2017). Postural control involves a combination of postural orientation (i.e., aligning the trunk and head with respect to gravity, support surfaces, visual surroundings, and internal references) and postural equilibrium (i.e., movement strategies that provide stability after a balance disturbance) that is required for both stability and mobility (Horak, 2006; Nam et al., 2017). Whether a person is moving or stationary, postural control involves the use of anticipatory and reactive movement strategies that rely on the somatosensory, visual, and vestibular systems to control the body's centre of mass and maintain awareness of the body's orientation in space (Horak, 2006; Nam et al., 2017; Takakusaki, 2013).

1.3.3 The impact of neural damage on motor function

Given the proximity of the neural tracts responsible for motor function in the motor cortex and their convergence at the brainstem, ABI often affects multiple neural tracts (e.g., both the corticospinal and cortico-reticulospinal pathways) (Jang & Lee, 2019). Damage to the

corticospinal tract causes weakness, apraxia, and decreased coordination (Jang, 2014; Kandel et al., 2013). The corticospinal tract is also heavily involved in proactive and reactive gait adaptations such as navigating obstacles or adjusting to changes in ground surface (Barthélemy et al., 2011; Takakusaki, 2013), with damage substantially affecting balance, gait, and lower extremity function (Handelzalts et al., 2019; Seo et al., 2014). While the corticospinal tract is primarily thought to be responsible for distal extremity motor control (e.g., ankle, knee), stroke research comparing adults with hemiparesis with and without corticospinal tract damage emphasizes the additional role of primary motor cortex and corticospinal tract in proximal limb function and postural control by demonstrating that stroke-induced corticospinal damage also influences hip function (Seo et al., 2014). Residual ipsilateral projections from the uninjured corticospinal tract may also contribute to improved lower extremity function and gait after stroke (Kim et al., 2020; Lee & Kim, 2021). Cerebellar injury or damage to the cortico-pontine-cerebellar pathways also affects all types of motor function from speech and ocular movements to coordination of the trunk and extremities (Ilg & Timmann, 2013; Marsden & Harris, 2011). Cerebellar injury leads to a reduction in postural muscle tone, decreased coordination of the extremities, and oculomotor dysfunction which contributes to gait and balance impairments (Marsden & Harris, 2011; Takukasaki, 2017).

1.4 Motor learning and neural plasticity

Motor learning refers to the relatively permanent acquisition of a motor skill that occurs with practice or experience (Nudo, 2013; Schmidt & Lee, 2014). Fitts & Posner (1967) proposed three behavioural stages of motor learning: cognitive, associative, and autonomous. The cognitive stage is the preliminary stage of motor learning where performance is highly variable and the learner uses a substantial amount of conscious effort to attend to task requirements (Schmidt & Lee, 2014; Zwicker & Harris, 2009). With progression to the associative stage, the skill is refined and performance is more consistent (Schmidt & Lee, 2014; Zwicker & Harris, 2009). Once the autonomous stage is reached, little cognitive effort is required to execute the skill allowing the learner to engage in other cognitive tasks while performing the motor skill (Schmidt & Lee, 2014; Zwicker & Harris, 2009). On a neural level, motor learning is thought to be accompanied by increased efficiency of signal transmission within the corticospinal tract (Reid et

al., 2017) and is associated with differing areas of brain activation depending on the stage of learning (Dayan & Cohen, 2011; Tavor et al., 2020).

Motor learning can also be categorized as fast (i.e., rapid improvement, possibly occurring within a single practice session) or slow (i.e., gradual improvement that occurs over multiple practice sessions) with the duration of each stage depending on skill complexity (Dayan & Cohen, 2011). Regardless of the stage, the primary motor cortex is integral to motor learning with varying degrees of activation depending on the level of skill proficiency (Dayan & Cohen, 2011; Lohse et al., 2014). Fast motor learning begins with increased activation of the anterior regions of the brain including the dorsolateral prefrontal cortex, pre-supplementary motor cortex, supplementary motor cortex, premotor area, and primary motor cortex which highlights the cognitive demand during early learning (Dayan & Cohen, 2011; Ma et al., 2010). During early learning, cerebellar projections to the premotor and primary motor cortex that provide feedback related to errors are also highly active due to increased performance variability (Doyon et al., 2003; Lohse et al., 2014; Tavor et al., 2020). Substantial reorganization of the primary motor cortex occurs throughout fast motor learning with an initial expansion of the motor representation in the early stages of practice followed by a return to the baseline levels of activation as the skill and neural connections are refined (Dayan & Cohen, 2011; Lohse et al., 2014; Ma et al., 2010). This reorganization is accompanied by increased activity in the premotor cortex, supplementary motor cortex, parietal regions, striatum, and cerebellum (Dayan & Cohen, 2011; Lohse et al., 2014) with the connection between the supplementary motor area and the primary motor cortex considered integral to motor memory consolidation (Tanaka et al., 2010; Veldman et al., 2018).

The progression from fast to slow motor learning involves a shift in brain activity from the associative/premotor areas of the brain to the sensorimotor regions of the brain (i.e., anterior to posterior) as the skill becomes more automatic (Dayan & Cohen, 2011; Lohse et al., 2014; Veldman et al., 2018). Even within the subcortical and cerebellar regions of the brain, there are changes in brain activation patterns indicative of increased automaticity (Lohse et al., 2014). Slow motor learning involves smaller and more gradual changes in activation with increased activity in the primary motor cortex, somatosensory cortex, and putamen (Dayan & Cohen, 2011; Lohse et al., 2014). These cortical changes are accompanied by a shift from rostral (i.e.,

cognitive) to caudal (i.e., sensorimotor) activity in the putamen, as well as a shift from cerebellar cortex (i.e., cognitive) to deep nuclei (i.e., sensorimotor) in the cerebellum (Dayan & Cohen, 2011; Doyon et al., 2003; Lehéricy et al., 2005; Lohse et al., 2014). Even once the performance of a skill has stabilized, there are ongoing changes in neural activity (e.g., weakening of connections between the prefrontal cortex and primary motor cortex, strengthening of connections between the basal ganglia and primary motor cortex) indicative of increased automaticity (Ma et al., 2010; Tavor et al., 2020; Veldman et al., 2018).

1.4.1 Motor skills-based physiotherapy for children with ABI

Acquiring gross motor skills is fundamental to children's physical, cognitive, and social development, and is closely linked to their level of physical activity and participation in social, recreational, and academic activities (Lucas et al., 2016). While motor learning (or relearning) goals are common in most neurorehabilitation settings (Kleynen et al., 2017; Valvano, 2004; Winstein et al., 2014), motor learning in pediatric ABI differs from adults with ABI because children with ABI are relearning previously mastered skills as well as having to learn new developmentally applicable motor skills (Anderson & Catroppa, 2006; Giza et al., 2009). As such, children with ABI are faced with a phenomenon known as "growing into the injury" where there is delayed manifestation of injury sequelae and the possibility of new deficits emerging as the child develops, with younger children being more susceptible to this phenomenon due to the disruption of critical early brain development (Giza et al., 2009). While children with ABI tend to recover motor function more quickly than cognitive skills, motor recovery plateaus toward the end of subacute ABI and long-term deficits persist (Dumas et al., 2004a; Dumas et al., 2004b; Galvin et al., 2010a; Tailor et al., 2013). Further, cognitive and motor function are not mutually exclusive. The overlay of cognitive deficits associated with ABI also influences motor recovery and has implications for return to meaningful physical activities such as community mobility and recreational sports (Baque et al., 2016; Dumas et al., 2004b; Galvin et al., 2010a).

Physiotherapy for children with ABI targets goals that involve the learning and relearning of gross motor skills required for functional independence and participation in daily activities (Baque et al., 2016; Dumas et al., 2004b; Levac et al., 2012; Popernack et al., 2015). Motor skills-based physiotherapy for children with ABI should be meaningful, engaging, age

appropriate, and progressively adapted to promote independence (Hebert et al., 2016; Lucas et al., 2016). Advanced gross motor skills goals, such as running and jumping, are addressed once children have acquired basic gross motor skills such as sitting, standing, and walking (Baque et al., 2016). Physiotherapists use individualized goal setting and task-specific training to address the balance, postural control, coordination, strength, and endurance challenges associated with ABI (ABIKUS, 2007; Hebert et al., 2016; Levac et al., 2012; Popernack et al., 2015; Ustinova et al., 2015). They also facilitate the integration of vestibular, visual, and proprioceptive feedback during functional gross motor skills to promote independent mobility and optimize motor control (ABIKUS, 2007; Hebert et al., 2016; Popernack et al., 2015; Ustinova et al., 2015). On a neurological level, these interventions involve targeting specific motor skills that influence the formation, strength, and direction of specific synaptic connections, which ultimately leads to improvements in the execution and coordination of functional motor tasks (Gordon & di Maggio, 2012; Nudo, 2013). Dumas et al. (2004b) found that the intensity of inpatient physiotherapy for children with subacute ABI is positively associated with the extent of mobility gains made during admission.

There is growing evidence in pediatric rehabilitation to support the use of motor learning strategies (MLS) in motor skills-based interventions to promote motor learning in children with neuromotor conditions (Bar-Haim et al., 2010; Cameron et al., 2017; Khamis et al., 2020; McKechnie et al., 2020; Morgan et al., 2016; Pierce et al., 2021; Prado et al., 2017). MLS are therapeutic actions that involve the selection, manipulation, and application of motor learning variables based on child- and task-specific factors to promote motor skill acquisition (Levac et al., 2011). There are a wide range of MLS that can be categorized as therapist verbalizations (e.g., feedback, instructions), therapist actions (e.g., demonstration, physical guidance), and practice organization (e.g., progressive, whole, random practice) (Levac et al., 2011; Spivak et al., 2021). Several studies have evaluated the effectiveness of single MLS. Cameron et al. (2017) demonstrated that the Cognitive Orientation to Occupational Performance (i.e., a therapist verbalization that uses asking to promote problem solving) led to improved motor outcomes compared to traditional occupational therapy intervention. Serrano-Gonzalez et al. (2022) used action observation (i.e., demonstration) to improve hand function in children after brain tumour resection. Prado et al. (2017) found that the random practice order (i.e., a practice organization

MLS) of a computerized maze task led to improved performance in a transfer test in children with CP compared to constant practice. In contrast, other studies have used combinations of MLS such as Bar-Haim et al. (2010) who found that a motor learning coaching program involving intentional verbal and non-verbal instructions, feedback related to results, and task variability led to improved retention and transfer of motor skills in school-aged children with CP compared to a conventional neurodevelopmental treatment. Successful MLS application depends on physiotherapists' ability to adapt MLS use on an ongoing basis depending on the child's stage of learning and cognition, as well as the child's motivation and the practice environment (Bar-Haim et al., 2010; Larin, 1998; Ryan et al., 2020; Valvano, 2004). They use multiple MLS during a single treatment session and transition between MLS depending on the learner's performance (Kleynen et al., 2017; Ryan et al., 2020).

While MLS application is associated with improved retention of gross motor skills and increased transfer of skills beyond the therapeutic environment (Bar-Haim et al., 2010), the optimal combination of MLS has yet to be determined (MacWilliam et al., 2021; Spivak et al., 2021; Valvano, 2004). Lab-based motor learning research involving typically developing children or healthy adults is often more conducive to isolating and evaluating a specific MLS. This standardized approach to motor learning research becomes more difficult in clinical interventions where physiotherapists address individualized motor learning goals and also continually adapt MLS application to meet the learner's needs (Kleynen et al., 2015; Kleynen et al., 2017; Ryan et al., 2020; Valvano, 2004), meaning that there are an increased number of confounding variables to consider when conducting motor learning research in pediatric neurorehabilitation.

1.4.2 Evaluating gross motor outcomes in pediatric ABI

Pediatric PTs measure gross motor progress using a variety of standardized outcome measures. The following section describes the gross motor outcome measures considered for this dissertation's tDCS feasibility study. The accepted standard for measuring change in gross motor function in children with moderate to severe ABI is the Gross Motor Function Measure (GMFM-88) (Kuhtz-Buschbeck et al., 2003; Linder-Lucht et al., 2007; Russell et al., 2021; Storm et al., 2020; Thomas-Stonell et al., 2006). This 88-item outcome measure is divided into five dimensions: 1) lying and rolling, 2) sitting, 3) crawling and kneeling, 4) standing, 5) walking,

running & jumping (Russell et al., 2021). While a shorter version, the GMFM-66, is available, the 88-item version more accurately detects change in children with TBI than the GMFM-66 which was designed specifically for the developmental trajectories of children with cerebral palsy (Linder-Lucht et al., 2007). A minimal clinically important change for the GMFM-88 in children with TBI is approximately 5% (Linder-Lucht et al., 2007). However, the GMFM-88 has a ceiling effect for children who have difficulty with advanced gross motor skills (Alotaibi et al., 2014; Ibey et al., 2010; Vos-Vromans et al., 2005) and, because it does not evaluate quality of movement, it often underestimates improvements in functionally important gross motor skill refinement (Russell et al., 1989).

When the GMFM-88 reaches its ceiling, physiotherapists usually administer more advanced outcome measures to identify physiotherapy goal areas and detect change (Ibey et al., 2010; Wright et al., 2010). The Community Balance and Mobility Scale (CB&M) (Howe et al., 2006) is a 13-item outcome measure developed for ambulatory adults with TBI that was subsequently validated in children with ABI (Wright et al., 2010). The CB&M evaluates both quantitative and qualitative aspects of static and dynamic balance (Howe et al., 2006). In addition to assessing functional gross motor skills like walking, running, and descending stairs, the CB&M incorporates aspects of multitasking, sequencing movement components, and complex motor skills that challenge the precision and fluidity of movement (Howe et al., 2006). However, the Acquired Brain Injury Challenge Assessment (ABI-CA) is likely a better overall indication of advanced gross motor function because it was specifically developed to expand upon the "walking, running, & jumping" dimension of the GMFM-88 and assesses elements of advanced gross motor skills (e.g., strength, agility, coordination) not covered in the CB&M (Ibey et al., 2010; Wong et al., 2014). Like the CB&M, the ABI-CA evaluates both quantitative and qualitative aspects of performance (Ibey et al., 2010; Wong et al., 2014).

The Pediatric Evaluation of Disability Inventory (PEDI) is norm-referenced measure that evaluates function in Daily Activities, Mobility, and Social/Cognitive domains (Haley et al., 2010). The PEDI has been validated in many pediatric clinical populations, including inpatient ABI (Dumas et al., 2002; Kothari et al., 2003). PEDI change scores are used to evaluate intervention effectiveness (Haley et al., 2010) and highly correlated with GMFM change scores in children with CP (Lewis et al., 2020; Wright et al., 2008). The computer adaptive version of

the PEDI, the PEDI-CAT, uses item response theory to adjust the items presented based on responses to previous items such that content is tailored to the child's functional abilities (Haley et al., 2011) and is responsive to change in inpatient pediatric rehabilitation (Fragala-Pinkham et al., 2016). The PEDI-CAT asks the therapist, parent, or child to indicate the ease with which the child completes a variety of functional tasks in Daily Activities, Mobility, and Social/Cognitive domains (Fragala-Pinkham et al., 2016; Haley et al., 2011). When used as a parent-reported outcome, the PEDI-CAT provides additional information about the child's functional ability beyond a clinical setting and minimizes the assessment demands on the child (Lewis et al., 2020).

Given the focus on ambulation-based goals in inpatient ABI rehabilitation (Dumas et al., 2004a), ambulation-specific outcome measures are also used to evaluate change. The 6-Minute Walk Test (6MWT) is a self-paced assessment of walking endurance that is frequently used in pediatric ABI (Storm et al., 2020). Despite its widespread use in many pediatric clinical populations, children typically have difficulty sustaining a self-set pace without ongoing encouragement which then has implications for test validity (Bartels et al., 2013). In contrast, the 10-metre Fast Walk Test (10mFWT) takes far less time to complete and, as such, decreases the reliance on the need to sustain attention. While the 10mFWT does not evaluate the endurance aspect of ambulation, it represents the minimum distance required for functional ambulation (Thompson et al., 2008).

Individualized goals are central to outcome evaluation in pediatric rehabilitation because they address child and/or parent priorities and measure progress at a level tailored to each child's abilities (Cusick et al., 2006; Pritchard-Wiart et al., 2019). Further, by being involved in the goal-setting process, children are more likely to be motivated to work towards a specific and, thus, more engaged in the intervention (Pritchard-Wiart et al., 2019; Ziviani, 2015). GAS and COPM are individualized goal-setting measures frequently used in pediatric rehabilitation research (Cusick et al., 2006). Goal attainment scaling (GAS) (Kiresuk & Sherman, 1968) is a method for quantifying goal achievement that is highly adaptable to individual needs and, as such, is frequently used in rehabilitation (Schlosser, 2004; Turner-Stokes, 2009). At baseline, the child's current level of function for a particular goal is set at '-2' (Schlosser, 2004; Turner-Stokes, 2009). The therapist then establishes criteria for incremental improvements on a scale of

-2 to +2 where 0 is the extent of improvement the therapist expects to observe within a specified time frame (Schlosser, 2004; Turner-Stokes, 2009). Goals are reassessed at the end of the time frame and assigned a score between -2 and +2 where -2 is 'much less than expected', -1 is 'less than expected', 0 is 'expected', +1 is 'more than expected', +2 is 'much more than expected' (Schlosser, 2004; Turner-Stokes, 2009). The personalized nature of GAS avoids the floor and ceiling effects, as well as the lack of sensitivity, frequently encountered with standardized rehabilitation outcome measures (Turner-Stokes, 2009).

The Canadian Occupational Performance Measure is another method for standardizing individualized goals and involves a semi-structured interview where the client identifies performance areas that they would like to improve upon (Law et al., 1990). The client then assigns a weight to each goal and indicates their current level of performance out of 10, as well as their satisfaction with their performance out of 10 (Law et al., 1990). In pediatric rehabilitation, COPM goals are developed with children and/or parents and are an effective way of establishing meaningful goals in therapeutic intervention (Cusick et al., 2006; Law et al., 1997; Verkerk et al., 2006). GAS and COPM goals often complement each other due to their differing attributes. While the child and/or parent rate satisfaction and performance for COPM goals, either the therapist and/or child/parent can score GAS goals depending on the nature of the goals (Cusick et al., 2006; Schlosser, 2004). Further, the goal setting process for COPM is more standardized while GAS permits a more flexible administration process (Cusick et al., 2006). When used in research, GAS and COPM are frequently designed to measure different constructs (Cusick et al., 2006) which permits a well-rounded evaluation of study outcomes.

1.4.3 Using rehabilitation technologies to optimize motor learning

The rapid influx of rehabilitation technologies over the last decade in particular, has led to increased use of these technologies in clinical settings with the goal of enhancing motor outcomes (Spiess et al., 2018). Some modalities (e.g., robotic assisted gait training, virtual reality) influence change on a behavioural level by increasing exposure to motor learning opportunities within the intervention. For example, robotic-assisted gait training capitalizes on repetition and physical guidance to familiarize the learner with an efficient gait pattern (Lefmann et al., 2017; Mikolajczyk et al., 2018) while virtual reality creates an enriched training

environment that provides enhanced feedback and motivates the individual (Levac et al., 2019; Levin et al., 2015). Conversely, other rehabilitation technologies (e.g., functional electrical stimulation, non-invasive brain stimulation) may influence motor learning on a physiological level. For example, functional electrical stimulation targets the timing and magnitude of muscle activation at the neuromuscular junction during functional tasks (Everaert et al., 2010; Pool et al., 2015) while non-invasive brain stimulation modulates synaptic transmission within the cerebral cortex (Elbanna et al., 2019; Stagg & Nitsche, 2011).

While implementing rehabilitation technologies in a clinical setting may be appealing, their feasibility must be considered (Aprile et al., 2019; Feldner et al., 2019). Challenges associated with implementing technologies often include high cost or decreased ease of use (Banerjee-Guénette et al., 2020; Feldner et al., 2019; Ferche et al., 2015; Mikolajczyk et al., 2018). Cost not only refers to the purchase and maintenance of the equipment itself but also the investment in training staff to effectively administer the technology (Feldner et al., 2019; Ferche et al., 2015). Additionally, the time required to set up and use the device can be a barrier to implementation (Feldner et al., 2019; Glegg et al., 2017). As such, clinicians must perceive that a technology has increased benefits compared to traditional intervention and the properties of the technology must align with the patient's abilities and goals (Aprile et al., 2019; Banerjee-Guénette et al., 2020; Feldner et al., 2019; Ferche et al., 2015; Glegg et al., 2017). The technology also needs to be tolerated and acceptable from a patient perspective with the potential benefits outweighing the possible risks (Andrade et al., 2014; Aprile et al., 2019; Gillick et al., 2015).

1.5 Transcranial direct current stimulation

Transcranial direct current stimulation (tDCS) is a form of non-invasive brain stimulation that temporarily modulates neural activity in a targeted area of the brain and is used with the goal of inducing neuroplasticity and influencing behavioural change (Stagg et al., 2011; Wessel et al., 2015; Woods et al., 2016). When motor learning is the intended outcome, tDCS involves delivering a small subthreshold current (1.0 to 2.0 mA) to a specific motor region of the brain, usually the primary motor cortex (Stagg & Nitsche, 2011; Woods et al., 2016). The subthreshold nature of the electrical current means that tDCS does not directly induce neuronal firing, rather it increases or decreases the likelihood of membrane depolarization (i.e., synaptic transmission)

when accompanied by a motor task, making the elements of task practice that accompany the tDCS integral to motor learning outcomes (Stagg & Nitsche, 2011). tDCS-induced neuromodulation generally lasts for up to 90 minutes after stimulation and, as such, motor practice should occur during this window of altered cortical excitability (Ciechanski & Kirton, 2016; Stagg & Nitsche, 2011).

1.5.1 Electrode montages

The most common tDCS electrode montage is a dual electrode montage with the anode positioned over the neural target (e.g., the primary motor cortex) to increase cortical excitability (i.e., shift resting membrane potential of underlying neurons toward depolarization) and the cathode is placed over a remote region of the brain (Ciechanski & Kirton, 2016; Stagg & Nitsche, 2011). Conversely, the cathode is placed over the neural target if the goal is to suppress cortical activity (i.e., hyperpolarize the resting membrane potentials of underlying neurons) (Stagg & Nitsche, 2011). Given the somatotopic organization of the primary motor cortex (Kandel et al., 2013), electrode position can be adjusted to target the motor representation of a specific body part (e.g., hand, leg). If improving right hand function is the desired outcome, the anode is placed over the hand region of the left primary motor cortex and the cathode is placed over the right forehead. Given the proximity of the leg and foot regions of the primary motor cortex, electrode placement may be adjusted closer to midline when targeting lower extremity motor goals (Figure 1.2). Locating a specific neural target can be accomplished using several methods: the International 10-20 System for electrode placement, neuronavigation (e.g., magnetic resonance imaging [MRI]), or single pulse transcranial magnetic stimulation (TMS) to elicit contraction of the target muscle group (Woods et al., 2016).

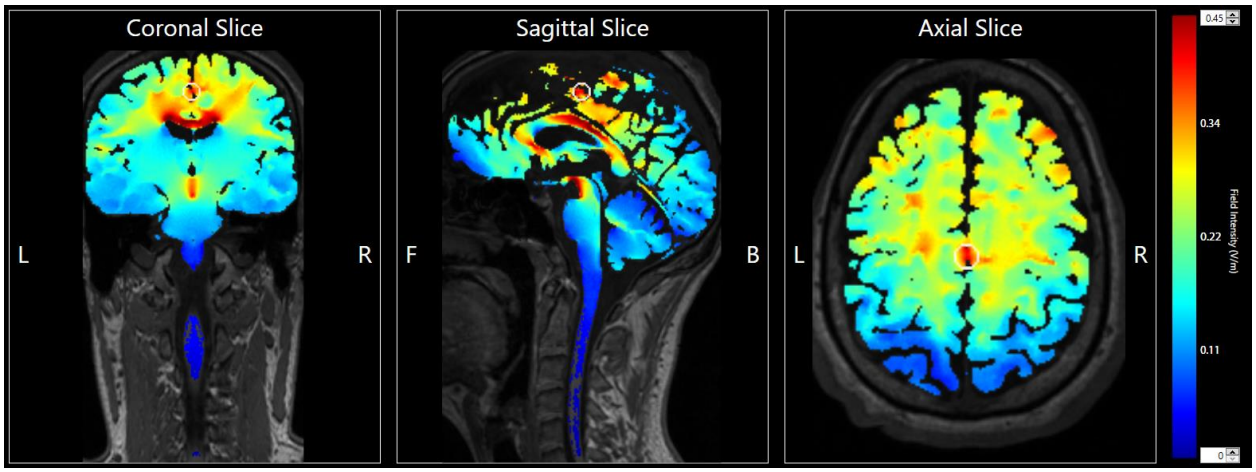
Figure 1. 2. Anodal tDCS montage targeting bilateral lower extremities (a) and associated electrical fields (b).

a.

Anode: Cz (i.e., centre top of head), cathode: Fpz (i.e., middle of forehead).

(Note: parent informed consent and child assent obtained to use photograph.)

b.



Electrical fields for the electrode placement shown in (a), created using Soterix Medical HD-Explore ™ modeling software on a standard adult head where red indicates increased field intensity.

1.5.2 tDCS safety, tolerance, and ease of use

tDCS is safe and tolerable among adults and children in both clinical and non-clinical populations (Bikson et al., 2016; Buchanan et al., 2021; Zewdie et al., 2020). A common transient side effect associated with tDCS is itching or tingling under the electrode sites, while a burning sensation under the electrodes, fatigue, nausea, dizziness, or headache is less common (Ambrus et al., 2012; Bikson et al., 2016; Buchanan et al., 2021; Ciechanski & Kirton, 2016; Russo et al., 2017; Wood et al., 2016; Zewdie et al., 2020). Unlike TMS that induces synaptic transmission on its own, tDCS is unlikely to cause seizures due to the subthreshold nature of stimulation (Russo et al., 2017; Woods et al., 2016). Contraindications to tDCS include metal implants in the head or neck, pacemakers, cranial defects, wounds under the electrode site, pregnancy, cochlear implants, and brain tumours (Ciechanski & Kirton, 2016; Russo et al., 2017; Woods et al., 2016). In addition to being the most inexpensive form of neuromodulation, tDCS is also the most portable (Woods et al., 2016). The recent increase in use of wireless tDCS devices allows people to be more physically active during tDCS treatments (Bulteau et al., 2022; Salazar Fajardo et al., 2022). Additionally, there are studies in adult clinical populations (e.g., pain, dementia, stroke, depression) evaluating tDCS use in the home with remote supervision (Palm et al., 2018).

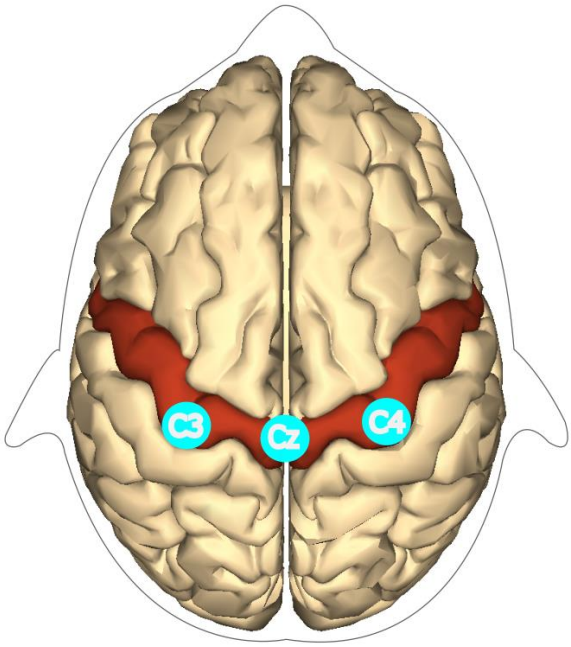
1.5.3 tDCS protocols involving motor intervention in clinical populations

The combination of tDCS and motor interventions has been studied extensively in adults with stroke, with over 20 systematic reviews published since 2016. While fewer systematic reviews have been specific to gross motor function in adults with stroke, these reviews found evidence of improved gait (e.g., Six-Minute Walk Test, the 10-metre Walk Test, spatiotemporal gait parameters), balance (e.g., Berg Balance Scale, rate of falls), and lower extremity motor outcomes (e.g., Fugl-Meyer) when anodal tDCS was paired with various gross motor interventions (e.g., conventional stroke physiotherapy, robotic-assisted gait training, treadmill training) (Navarro-López et al., 2021; Vaz et al., 2019). There have been far fewer tDCS studies in adults with TBI compared to stroke, with most tDCS studies in adults with TBI focusing on cognitive interventions (e.g., cognitive training) and/or outcomes (e.g., errors, apathy, attention, consciousness) (Zaninotto et al., 2019). Of the few studies that evaluated the impact of tDCS on motor function after TBI, one case study with a single participant evaluated upper extremity

function but did not provide an accompanying intervention (Chiang et al., 2022), one proof-of-concept pilot study evaluated tDCS with an upper extremity intervention in two participants with TBI (Middleton et al., 2014), and the remaining studies evaluated the effects of tDCS on dysphagia (Momosaki et al., 2016). Accordingly, review papers have commented on the paucity of motor-based tDCS research in TBI and called for more research in this area (Kim et al., 2019; Rudroff & Workman, 2021; Zaninotto et al., 2019).

Across adult stroke and TBI, tDCS studies have been conducted in the acute, subacute, and chronic stages of recovery (Bornheim et al., 2022; Navarro-López et al., 2021; Vaz et al., 2019; Zaninotto et al., 2019). For tDCS protocols targeting the primary motor cortex, the anode electrode position has varied with the motor representation for the tibialis anterior being a prominent neural target when TMS was used to locate the muscle 'hotspot' and C3/C4 (i.e., unilateral hand/arm regions of the primary motor cortex) or Cz (i.e., bilateral lower extremity regions of the primary motor cortex) targeted when the 10-20 system for electrode placement was used (Bornheim et al., 2022; Middleton et al., 2014; Vaz et al., 2019) (Figure 1.3). The systematic reviews specific to gross motor tDCS studies indicated that the multi-session treatment protocols were between seven and 30 sessions and involved individual tDCS sessions lasting between 10 and 20 minutes with current intensities of 1.0 to 2.0 mA (Navarro-López et al., 2021; Vaz et al., 2019).

Figure 1. 3. Location of tDCS neural targets on the primary motor cortex according to the 10-20 system (Seeck et al., 2017) for electrode placement.



Legend: Superior view of the primary motor cortices (red); Cz: bilateral lower extremity representations; C3: right upper extremity representation, C4: left upper extremity representation

In pediatric clinical populations, motor learning tDCS protocols have focused predominantly on children with cerebral palsy (CP) with protocols that involve gross motor intervention having positive gait, balance, and mobility outcomes (Elbanna et al., 2019; Salazar Fajardo et al., 2022; Saleem et al., 2019a). Study protocols most frequently involved 10 sessions over two weeks with each tDCS session lasting 20 minutes (Saleem et al., 2019a). Current intensities were all 1.0 mA with the anode most frequently positioned over the primary motor cortex (Elbanna et al., 2019). The outcome measures used in these studies included various gait parameters (e.g., velocity, cadence, step length), walking endurance (i.e., 6MWT), motor function (i.e., GMFM-88, PEDI), and balance (i.e., Pediatric Balance Scale) (Elbanna et al., 2019; Salazar Fajardo et al., 2022; Saleem et al., 2019a). While tDCS is currently being explored in children with severe ABI with disorders of consciousness (Saleem et al., 2019b), there is only one published tDCS study in pediatric ABI that involves motor intervention (based on a review of results from MEDLINE search: “transcranial direct current stimulation” AND [“brain injuries” OR “stroke”] restricted to 0-18 years old) and no registered clinical trials on ClinicalTrials.gov. The published study is a

single participant case report that involved a 17-year old girl who sustained an arterial ischemic stroke at the age of six and presented with hemiparesis of the right upper extremity (Ciechanski et al., 2020). She underwent a 10-day treatment protocol over two weeks where each session involved 60 minutes of goal-directed occupational therapy with 20 minutes of cathodal tDCS (1.5 mA) over the contra-lesional (i.e., right hemisphere) hand region of the primary motor cortex (Ciechanski et al., 2020). She experienced clinically significant changes in upper extremity functional outcomes (e.g., Jebsen Taylor Hand Function Test, COPM) that were maintained six months post-intervention (Ciechanski et al., 2020). These positive preliminary motor outcomes in childhood onset stroke (Ciechanski et al., 2020) along with similar results in children with CP (Elbanna et al., 2019; Salazar Fajardo et al., 2022; Saleem et al., 2019a) suggest that tDCS combined with gross motor interventions has strong potential to be effective in children with ABI.

1.5.4 Evaluating neural outcomes in tDCS research

Behavioural outcomes in motor learning research are evaluated based on the time required to complete the task, task accuracy, and/or movement variability (Dayan & Cohen, 2011). In addition to evaluating behavioural outcomes, there is a need to understand the neural changes accompanying behavioural change. As such, the neurophysiological effects of tDCS are frequently explored using TMS, electroencephalography, and functional MRI (Horvath et al., 2015). MEP measurement in selected muscles is the most common neural outcome when tDCS is used to target the primary motor cortex (Bastani & Jaberzadeh, 2012; Horvath et al., 2015). MEPs are a measure of corticospinal tract excitability that involves single pulse TMS eliciting a muscle contraction in a targeted muscle group (Bestmann & Krakauer, 2015). For example, when the anode is placed over the motor representation for the tibialis anterior in the primary motor cortex, tDCS is expected to increase excitability of the underlying motor neurons responsible for ankle dorsiflexion. By measuring the change in MEP amplitude or MEP latency in the tibialis anterior pre-post tDCS treatment, researchers can determine if tDCS has influenced activation of this muscle.

To date, there are few pediatric tDCS studies that have measured MEP outcomes (Gillick et al., 2015; Moliadze et al., 2015; Rich et al., 2018). Early safety and feasibility work in children

involved measuring first dorsal interosseus (FDI) MEPs pre and post tDCS without an accompanying motor intervention (Gillick et al., 2015; Moliadze et al., 2015). Gillick et al. (2015) randomized 13 children ages 7 to 18 years with congenital hemiparesis to receive 10 minutes of either active (up to 1.5 mA) or sham tDCS where the anode was positioned over the FDI (i.e., hand representation) of the lesioned hemisphere and the cathode over the FDI of the non-lesioned hemisphere. They observed no difference MEPs between the sham and active tDCS groups and noted that several children reported discomfort during TMS (Gillick et al., 2015). Moliadze et al. (2015) evaluated the impact of different tDCS intensities of FDI MEPs measured every 10 minutes up to 60 minutes after the tDCS session in typically developing children and youth. Their crossover protocol involved single sessions of 1.0 mA of anodal and cathodal tDCS for 10 minutes in 19 children and youth with a follow-up crossover study where 10 of the original 19 participants received additional sessions with 0.5 mA of anodal and cathodal tDCS (Moliadze et al., 2015). Interestingly, the 1.0 mA current led to significantly increased MEP amplitudes up to 60-minutes post-tDCS for both anodal and cathodal conditions, while 0.5 mA decreased MEP amplitude in the cathodal condition and had no effect in the anodal condition (Moliadze et al., 2015).

The only pediatric study to evaluate MEP outcomes in a tDCS study involving motor intervention involved eight children and young adults (7-21 years) with unilateral CP who participated in 10 cathodal tDCS sessions to the non-lesioned hemisphere concurrent with bimanual training (Rich et al., 2018). In addition to functional outcomes and other TMS outcomes, FDI MEPs in the non-lesioned hemisphere were measured one week before and one week after the treatment protocol (Rich et al., 2018). While MEP amplitude in the non-lesioned hemisphere decreased (i.e., reduced excitability) in five of eight participants, other measures TMS outcomes suggested increased excitability in the same hemisphere (Rich et al., 2018). The authors attributed this inter- and intra-individual variability to anatomical differences among children with CP, including differences in lesion location and corticospinal circuitry (i.e., contralateral versus bilateral), as well as variable interference from the motor intervention depending on each participant's functional ability (Rich et al., 2018).

Given the limited pediatric studies along with the potential neuroanatomic differences between congenital and childhood onset ABI, consideration of adult tDCS studies was required to

determine the merit of measuring MEPs as a neural outcome in tDCS research involving motor intervention. To date tDCS protocols involving gross motor interventions in adults with stroke have had mixed MEP outcomes. When evaluated MEPs in adults with stroke with mixed results in protocols targeting gross motor function. Chang et al. (2015) found that 10 sessions of anodal tDCS with conventional physiotherapy in adults with stroke improved tibialis anterior MEPs (i.e., increased amplitude, decreased latency) and lower limb function compared to sham tDCS with conventional physiotherapy.

In contrast, Madhavan et al. (2011) found that a single session of anodal tDCS during an ankle tracking task in adults with stroke led to significant improvements in task performance (compared to sham tDCS combined with task practice) but no difference in MEP outcomes between tDCS conditions. Madhavan et al. (2016) went on to look at the impact of anodal tDCS targeting the leg region of the lesioned primary motor cortex and high intensity interval treadmill training on MEPs where adults with chronic stroke participated in two 40-minute treadmill sessions, one with 15 minutes of anodal tDCS (1.0 mA) prior to treadmill training and one with treadmill training alone. While there were no significant changes in MEPs immediately following the intervention treadmill training alone, tDCS with treadmill training increased MEPs in the hemiparetic tibialis anterior and decreased MEPs in the nonparetic tibialis anterior, and neither group had improved gait speed following the limited number of training sessions (Madhavan et al., 2016).

Madhavan et al. (2020) built upon their preliminary work by evaluating the impact of tDCS and high intensity treadmill training in 81 adults with chronic stroke over a four-week period (40 minutes, three days per week). This study also involved an ankle tracking task where participants were assigned to one of four treatment groups: no intervention prior to treadmill training, ankle tracking prior to treadmill training, tDCS prior to treadmill training, or ankle tracking and tDCS prior to treadmill training (Madhavan et al., 2020). Notably, MEPs in the paretic tibialis anterior were present in only 35 of the 81 participants, generally those with improved lower extremity function, and nine participants did not tolerate MEPs measurement due to discomfort (Madhavan et al., 2020). They found that the tDCS and ankle tracking group had greater changes in MEPs that were retained at the three-month follow assessment, but all groups experienced similar increases in walking speed post-intervention (Madhavan et al., 2020).

Most recently, Sivaramakrishnan & Madhavan (2021) conducted a crossover study where adults with stroke participated in three single sessions of anodal tDCS (1.0 mA for 20 minutes targeting paretic tibialis anterior), aerobic exercise (on a recumbent stepping machine) with sham tDCS, and tDCS with aerobic exercise. MEPs could not be elicited in the paretic tibialis anterior in two of the 25 participants (Sivaramakrishnan & Madhavan, 2021). They found that MEPs were reduced in the aerobic exercise only condition compared to the tDCS and tDCS with aerobic exercise conditions, and none of the conditions improved reaction time of the paretic limb (Sivaramakrishnan & Madhavan, 2021).

This variability between motor and MEP outcomes across tDCS studies that involve motor intervention suggests that the benefits of MEP outcomes within the context of tDCS combined with motor practice are unclear. The movement associated with motor practice is thought to interfere with the tDCS-induced changes in MEPs (Antal et al., 2007; Horvath et al., 2014) but the extent of this interference may vary (Antal et al., 2007; Bestmann & Krakauer, 2015). While a systematic review of tDCS without motor practice in healthy adults suggests that MEPs are the most reliable method of evaluating tDCS-induced neurophysiological outcomes, they noted that recent studies had variable results (Horvath et al., 2015). Given the variability in MEP results and the limited tDCS studies in clinical populations that include a motor intervention and evaluate MEPs, a review of tDCS protocols that measure MEPs and involve motor function in healthy individuals may clarify the role of MEPs in detecting the neural change associated with tDCS.

1.6 Rationale and objectives

The primary objective of this dissertation was to evaluate the feasibility of tDCS as an adjunct to an existing inpatient physiotherapy program for children and youth with moderate to severe ABI. While feasibility studies are not powered to determine treatment effect, they play an important role in testing study processes and provide an estimation of treatment effect which informs the decision to conduct a definitive (i.e., appropriately powered) clinical trial (Thabane et al., 2010). Prior to conducting a feasibility study, the need to investigate a novel treatment approach should be established and, in this case, was accomplished by reviewing the current state of inpatient ABI gross motor outcomes. Once the need is identified, an integral aspect of feasibility study

design is selecting the outcome measures capable to detecting change associated with the intervention. Given the ongoing need to understand the neural changes underlying motor learning, the inclusion of a neural outcome was also explored.

This manuscript-style thesis contains four independent manuscripts (Chapters 2 through 5) that address the following objectives:

Objective 1. Estimate the gross motor change associated with inpatient ABI rehabilitation for school-aged children with moderate to severe subacute ABI using standardized clinical outcome measures. By establishing the gross motor change that occurs during traditional inpatient ABI rehabilitation (Chapter 2), this work demonstrates the strong potential for change during the subacute stage of rehabilitation, the outstanding gross motor challenges that children with ABI contend with beyond inpatient rehabilitation, and the need to enhance motor learning outcomes during this stage using a novel technology like tDCS as an adjunct to traditional physiotherapy intervention. It also provides an estimate of gross motor change associated with physiotherapy intervention that can be used as a benchmark comparator for studies where novel technologies are applied as adjuncts to physiotherapy.

Objective 2. Determine whether evaluating MEPs in a tDCS protocol that involves motor performance provides an accurate indication of the neural changes associated with clinical motor outcomes. By summarizing the impact that the combination of tDCS and motor intervention/assessment have on MEPs in healthy individuals (Chapter 3), this thesis explores the suitability of using MEPs as a neural indicator of change in motor learning tDCS protocols. These findings informed whether MEPs were included as an outcome measure in the feasibility study protocol that evaluated tDCS as an adjunct to inpatient physiotherapy in children with ABI.

Objective 3. Evaluate the feasibility of tDCS as an adjunct to inpatient physiotherapy in children with moderate to severe ABI. By evaluating study feasibility (Chapter 4) and detailing specific aspects of the study protocol in a case report (Chapter 5), this thesis will inform the design of future motor learning tDCS studies for children with ABI.

Chapter 2

Gross motor change after intensive rehabilitation for children and youth with ABI: A 10-year retrospective review

This chapter was published in its entirety as:

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2 Gross motor change after intensive rehabilitation for children and youth with ABI: A 10-year retrospective review

2.1 Abstract

Aim: Estimate gross motor change in inpatient school-aged children with subacute acquired brain injury (ABI), identify factors associated with gross motor change, and describe inpatient physiotherapy focus.

Method: This retrospective chart review involved inpatient children (5-18 years) with subacute ABI who had either two Gross Motor Function Measure (GMFM-88) assessments or one GMFM-88 with another pre/post gross motor outcome measure. Outcome change scores and Goal Attainment Scaling (GAS) T-scores were calculated. Regression analyses examined factors predicting gross motor change. GAS goal areas were analyzed to determine physiotherapy focus.

Results: Of the 546 charts screened, 266 (118 female) met study criteria. The GMFM-88 was generally administered first, followed by other measures. GMFM-88 (n=202), Community Balance and Mobility Scale (n=89), and Six-Minute Walk Test (6MWT) (n=98) mean change scores were 18.03% (SD=19.34), 17.85% (SD=10.77), and 142.3m (SD=101.8), respectively. The mean GAS T-score was 55.06 (SD=11.50). Lower baseline scores and increased time between assessments were most predictive of greater GMFM-88 change ($|r| \geq 0.40$). Twenty-five percent of GAS goals were ambulation-based.

Interpretation: Appropriate outcome measure selection is integral to detecting gross motor change in pediatric inpatient ABI rehabilitation. Mean change score estimates can be used to compare standard inpatient rehabilitation with new treatment approaches.

2.2 Introduction

The ultimate goal for most children with moderate to severe acquired brain injury (ABI) is returning to pre-injury activities at home, school, and in the community (Galvin et al., 2010a; Gordon & di Maggio, 2012; Lee et al., 2017). Since functional ability plays an integral role in participation, inpatient ABI rehabilitation typically focuses on relearning the skills necessary for resuming age-appropriate activities (Galvin et al., 2010b; Rast & Labruyère, 2020). Changes in mobility are often greatest during the subacute stage of recovery and are influenced by injury severity and physiotherapy intensity (Dumas et al., 2004a; Dumas et al., 2004b). Physiotherapy for children with ABI usually involves task-specific practice that addresses individualized goals related to restoring motor and postural control, maximizing functional mobility, and relearning previously mastered gross motor skills (Baque et al., 2016; Dumas et al., 2004a; Levac & DeMatteo, 2009; Levac et al., 2012). Despite substantial physical gains with intensive physiotherapy during this stage, recovery typically plateaus and long-term motor deficits often persist (Anderson & Catroppa, 2006; Galvin et al., 2010b; Lee et al., 2017).

While novel treatment adjuncts offer hope for enhancing paediatric rehabilitation outcomes (Beretta et al., 2018; Gordon & di Maggio, 2012), clinical trials in subacute ABI are constrained by diagnostic heterogeneity (Gordon & di Maggio, 2012) and time-intensive rehabilitation schedules (Anderson & Catroppa, 2006). Thus, researchers may use early single group trials without a control group to focus solely on the new treatment approach (Beretta et al., 2018), or feasibility randomized control trials that are not, by design, powered to detect a treatment response (Eldridge et al., 2016; Thabane et al., 2010). Because the extent of gross motor change associated with traditional physiotherapy using standardized assessments is not well-documented (Johnson et al., 2009; Popernack et al., 2015), there are limits to understanding the preliminary treatment effects in these early trials. However, the treatment effect associated with traditional interventions can be estimated using routinely collected health data where change score estimates for standardized outcomes serve as preliminary reference points for comparing traditional physiotherapy with new treatment approaches (Eldridge et al., 2016).

Given the emphasis on function during inpatient rehabilitation (Dumas et al., 2004a; Galvin et al., 2010b), outcome measures are often situated within the activities (i.e., task execution)

domain of the International Classification of Function, Disability, and Health (ICF) (Rast & Labruyère, 2020; World Health Organization, 2001). Physiotherapists evaluate a range of gross motor abilities in paediatric ABI, from fundamental skills that are precursors to functional mobility (e.g., lifting head in supine, sitting hands-free) to advanced gross motor skills (e.g. hopping, walking backwards) that may influence participation in sport (Haley et al., 2010; Ibey et al., 2010; Linder-Lucht et al., 2007). The Gross Motor Function Measure (GMFM-88) contains five domains (lying & rolling; sitting; crawling & kneeling; standing; walking, running & jumping), and is validated for children with ABI (Linder-Lucht et al., 2007; Russell et al., 1989). While sensitive to change in children of varying abilities, the GMFM-88 does not evaluate movement quality and has a ceiling effect (Ibey et al., 2010; Russell et al., 1989; Wright et al., 2010). Additional standardized outcomes may be required to further evaluate balance and advanced motor skills.

Physiotherapists in our hospital's inpatient ABI program routinely use the GMFM-88 to document gross motor change in school-aged children and youth with ABI. The GMFM-88 is completed by most children upon admission, as cognition, behaviour, and tolerance permit, due to the breadth of skills it evaluates. Then, based on GMFM-88 performance, other assessments are administered to evaluate aspects of gross motor function beyond the GMFM-88; the Six-Minute Walk Test (6MWT) to measure walking endurance (Storm et al., 2020; Thompson et al., 2008), Community Balance and Mobility Scale (CB&M) to evaluate high level balance and mobility with an emphasis on movement quality and coordination (Wright et al., 2010), and Goal Attainment Scaling (GAS) to address skills not covered by other standardized measures and/or create change increments that better align with the child's needs (Harpster et al., 2019). These capacity-based measures are valid, reliable, and responsive to change in pediatric rehabilitation (Harpster et al., 2019; Ko & Kim, 2013; Steenbeek et al., 2011; Steenbeek et al., 2010; Storm et al., 2020; Thompson et al., 2008; Wright et al., 2010). They quantify the extent of gross motor progress during inpatient rehabilitation and provide an indication of the extent that gross motor function will influence participation in community-based activities upon discharge (Rast & Labruyère, 2020).

Given the importance of quantifying gross motor change and the availability of these clinical data, we conducted a retrospective review of gross motor change in our hospital's inpatient

pediatric ABI program. Our primary objective was to obtain clinical estimates of gross motor change in school-aged children with subacute ABI using the GMFM-88, CB&M, and 6MWT. An estimation of GMFM-88 change was the priority because of its widespread recognition as an appropriate gross motor outcome in subacute ABI (Gmelig Meyling et al., 2021; Linder-Lucht et al., 2007; Storm et al., 2020) and frequent use in our program. Secondary objectives were to: 1) explore differences in gross motor change based on age, sex, diagnosis, and baseline motor function, and 2) summarize physiotherapy GAS goal areas relative to the child's gross motor function to understand the foci of inpatient physiotherapy intervention.

2.3 Methods

This study was a retrospective review of health data for children admitted for intensive inpatient ABI rehabilitation at our hospital. Admission requirements include: 0-18 years with moderate to severe ABI, level four (i.e., confused-agitated) or higher on the Rancho Los Amigos Scale, need two or more clinical services (e.g., physiotherapy, occupational therapy, speech language pathology). The ABI aetiologies within the program can be categorized as: traumatic, stroke (ischaemic or haemorrhagic), brain tumour (i.e., post tumour resection), epilepsy (e.g., post hemispherectomy or grid surgery for intractable seizures), post-infectious (e.g., acute necrotizing encephalitis, meningitis, cerebellitis), neuroinflammatory (e.g., anti-NMDA encephalitis), hypoxia (secondary to cardiac arrest or asphyxia). Children receive up to one hour of physiotherapy per day, five days per week. Physiotherapy intervention focuses on increasing independence and efficiency of various gross motor skills with the goal of performing these skills in daily activities. The specific content of each physiotherapy session is guided by the child's physical presentation, cognition, individualized goals, and motivation. The Ethics Boards at our hospital and University of Toronto approved the study protocol.

2.3.1 Participants

Study inclusion criteria were: 5-18 years old at admission, moderate to severe ABI sustained ≤6 months before admission, and hospital admission between January 1, 2009 and December 31, 2019. Charts also had to meet one of the following conditions: 1) two GMFM-88 assessments, or 2) one GMFM-88 plus two CB&M, 6MWT, or GAS assessments. Charts were excluded if: length of stay <6 weeks, readmitted to acute care during rehabilitation for >14 days cumulative,

or participation in the hospital's robotic-assisted gait trainer (Lokomat®) feasibility study during their admission.

Hospital administration provided first author (JR) a random order list of charts that met admission time frame, age, and diagnostic inclusion criteria. JR screened these charts for the remaining eligibility criteria.

2.3.2 Data abstraction

Data were abstracted by two reviewers (JR, CZ) using a study-specific abstraction manual. Both reviewers independently abstracted data from the first three charts, meeting after each chart to establish initial consensus. An interrater threshold for percent agreement (i.e., the number of agreed upon items divided by the total number of possible agreements) (Portney & Watkins, 2020) ≥0.90 in the first 15 charts was required before proceeding with data abstraction. JR assigned the remaining charts in the order provided with the goal of CZ abstracting 30% and JR abstracting 70%. After all charts were abstracted, senior author (VW) randomly selected five of JR's chart for CZ to abstract. These five charts, in combination with the initial 15 charts, were used to estimate overall interrater reliability.

2.3.3 Statistical analysis

Analysis was conducted using MedCalc Statistical Software (version 20.027; MedCalc Software, Ostend, Belgium). Descriptive statistics were calculated for the GMFM-88, CB&M, and 6MWT baseline, discharge and change scores. Change score distribution normality was assessed using the D'Agostino-Pearson test (Jakobsen et al., 2017). As the primary outcome, GMFM-88 mean change scores were calculated for children with two GMFM-88 scores, and repeated using imputations (i.e., the same score for baseline and discharge for a conservative estimate of change) (Jakobsen et al., 2017) to include children with one only GMFM-88.

When two scores were available, scatterplots were created for baseline/change scores for each outcome measure. Correlations between outcome data (e.g., baseline, change scores) and other independent variables (e.g., age, sex, time between assessments, mobility status) were evaluated using Pearson's or Spearman's correlation coefficients depending on normality. *P* values <0.05 and |r|>0.40 were used as the threshold for clinically relevant associations (Wright et al., 2008).

A stepwise multiple regression analysis was conducted for the GMFM-88 change score with baseline assessment score, time between assessments, sex, age, and diagnosis (stroke, brain tumour, TBI, epilepsy, post-infectious, neuroinflammatory, hypoxia) as independent variables (G*Power version 3.1.9.4 requires >123 charts with 11 predictors for alpha 0.05, power 0.80). Stepwise regression analyses were repeated for CB&M and 6MWT change scores without diagnosis variables due to fewer charts with these measures (>85 charts required with 4 predictors, alpha 0.05, power 0.80). Variance inflation factor (VIF) was calculated for each variable in the regression analyses to establish if multicollinearity (i.e., redundancy) existed between variables (Portney & Watkins, 2020).

GAS goal areas were summarized using categories created by JR (e.g., functional 'strength' goals such as planks, push-ups, bridges were divided into core, upper extremity, lower extremity categories; 'hopping' and 'jumping' goals were combined into 'hopping/jumping'), and goals per category were tallied. When setting GAS goals, a final score of 0 is the desired outcome (Kiresuk & Sherman, 1968). Scores of -2 or -1 indicate "less than expected" progress while scores of +1 or +2 indicate "better than expected" progress (Kiresuk & Sherman, 1968). As final scores of +2 (i.e., "much better than expected") may indicate that the goal or timeframe for re-evaluation was inappropriate, the following calculations were completed: mean post-intervention raw T-score, percentage of goals that scored ≥0, and percentage of goals scoring 0 or +1 (to eliminate goals of insufficient challenge) (Harpster et al., 2019). Baseline goal areas were plotted against baseline GMFM-88 scores to visually analyze goal setting patterns relative to gross motor ability.

Interrater reliability for the 20 charts abstracted by both reviewers was estimated by: 1) kappa statistic for categorical variables (e.g., mobility status, sex), 2) intraclass correlation coefficients (ICCs) for continuous variables (e.g., outcome measure scores, time between assessments), and 3) percent agreement (i.e., not corrected for chance) for nominal variables (e.g., primary diagnosis, GAS goal areas) (Portney & Watkins, 2020).

2.4 Results

Of 546 charts screened, 266 (48.72 %) were eligible for abstraction with 202 (75.94%) having two GMFM-88 assessments. Reasons for exclusion (n=280 charts) were: admission <6 weeks (n=108), ABI onset >6 months after admission (n=10), no GMFM-88 (n=90), one GMFM-88 but

no other outcomes (n=40), readmitted to acute care >14 days (n=11), Lokomat study participant (n=18), or other (n=3). Documented reasons for not completing a GMFM-88 were: unable to follow directions (n=30), weight bearing or activity restrictions (n=18), very high functioning (n=15), or unexpected discharge (n=5). JR and CZ independently abstracted 174 and 92 charts, respectively, including the 20 charts abstracted by both reviewers. Interrater reliability varied from 0.88 (goal areas) to 1.00 (sex, GMFM-88) (Table 2.1).

Table 2. 1. Interrater agreement for the 20 charts abstracted by both reviewers.

	Type of Agreement*	**Agreement [95% CI]****
Time between assessments	ICC	0.97 [0.95 – 0.98]
Primary Diagnosis	PA	1.00
Activity Restrictions	PA	0.95
Mobility Status	Kappa	0.90 [0.80 – 0.99]
Sex	Kappa	1.00
GMFM-88	ICC	1.00
CB&M	ICC	0.98 [0.93 – 0.99]
6MWT	ICC	0.97 [0.92 – 0.99]
GAS areas	PA	0.88
GAS scores	Kappa	0.99 [0.96 – 1.00]

*ICC, kappa statistic, or percent agreement (PA) depending on type of variable.
**95% confidence interval only relevant to ICC and kappa statistic

Table 2.2 outlines child demographics of the eligible charts. The mean age was 11 years 9 months (standard deviation [SD]=3 years 9 months), and mean length of stay was 75 days (SD=41). On admission, 169 (63.53%) children used a wheelchair as their primary method of mobility, 19 (7.14%) ambulated with assistance, and 78 (29.32%) ambulated independently. By discharge, 30 (11.28%) children used a wheelchair as their primary method of mobility, 26 (9.88%) ambulated with assistance, and 210 (79.95%) ambulated independently. GMFM-88 data were not normally distributed ($p<0.001$). Data were normally distributed for 6MWT and CB&M baseline scores ($p>0.05$), but their change scores were not ($p<0.05$). Normality of change score percentages was also rejected after log and arcsine transformations (Kleinbaum et al., 2013).

Table 2. 2. Children/youth by diagnostic, sex, and age group.

Diagnosis	Total	Female	Total by Age Group		
			5-8 years	9-12 years	13-18 years
Stroke	84	37	16	29	39
Brain Tumour	63	30	15	24	24
TBI	42	13	10	4	28
Epilepsy	33	16	8	10	15
Post-infectious	18	7	8	7	3
Neuroinflammatory	15	11	2	2	11
Hypoxia	11	4	0	6	5
Total	**266**	**118**	**59**	**82**	**125**

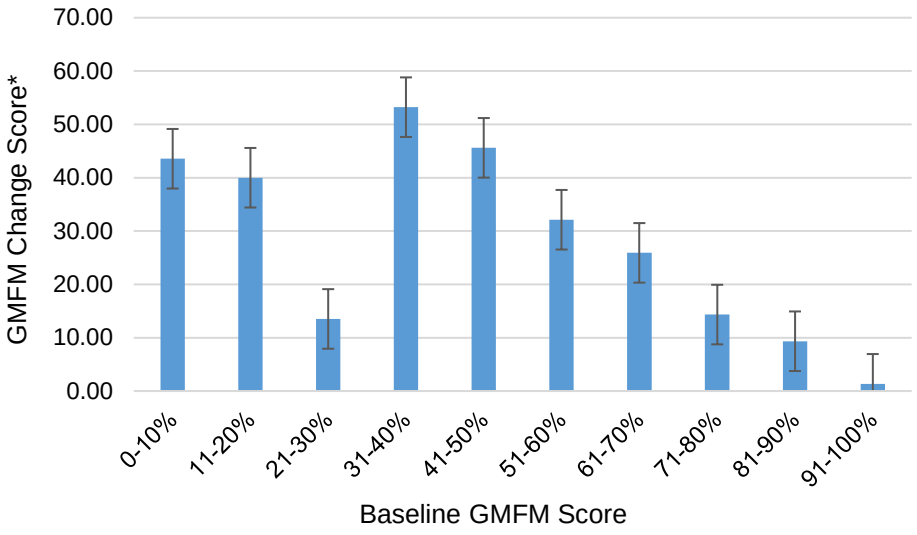
The baseline GMFM-88 mean score was 76.73% (SD=28.19) (Table 2.3) with 88 of 251 children scoring ≥95.00% on admission. The mean score for the 217 children who completed the GMFM-88 at discharge was 90.51% (SD=15.47) with 177 children scoring ≥95.00%. The overall GMFM-88 mean change scores was 18.03% (SD=19.34) without imputations (n=202) and 13.49% (SD=18.71) with imputations (n=266). GMFM-88 change scores varied widely depending on baseline GMFM-88 (Figure 2.1) and mobility status: wheelchair users =19.88% (SD=20.56), ambulates with assistance =5.80% (SD=5.86), and ambulates independently =1.52% (SD=5.00).

Table 2. 3. Outcome baseline, discharge, and change scores

	GMFM-88 [%]		CB&M [%]		6MWT [m]	
	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
Baseline	251	76.73 (28.19)	95	65.12 (16.35)	121	370.4 (138.8)
Discharge	217	90.51 (15.47)	128	78.76 (15.76)	141	468.5 (146.8)
Mean Change Scores*						
All ages†	202	**18.03 (19.34)**	89	**17.85 (10.77)**	98	**142.3 (101.8)**
5-8 years	56	20.05 (20.27)	5	21.50 (14.23)	9	99.5 (94.7)
9-12 years	61	16.33 (16.18)	30	17.99 (10.22)	31	122.5 (96.0)
13-18 years	85	17.91 (20.83)	54	17.34 (10.84)	58	159.3 (103.6)

n: Number of charts with data for the outcome measure
*Only charts with baseline and discharge scores for each outcome were included
†Mean days between admission and discharge GMFM-88, CB&M, 6MWT were 60(32), 41(17), and 43(18) respectively.

Figure 2. 1. GMFM-88 change scores for the entire sample (n=266) based on baseline GMFM-88 score.



*Imputed scores if admission or discharge GMFM-88 score not available.

The CB&M mean change was 17.85% (SD=10.77) for the subsample (n=89) with admission and discharge assessments. A layered approach of administering the GMFM-88 and the CB&M was observed with 37 of the 88 children who scored ≥95.0% on the GMFM-88 at admission completing the CB&M within two weeks of the GMFM-88 with a mean CB&M score of 72.42% (SD=11.44). Thirty-two of these 37 children completed a discharge CB&M with a mean change of 14.14% (SD=9.34). For children scoring <95.0% on their admission GMFM-88, 22 completed two CB&Ms during their admission with a mean 17 days (SD=20) between baseline GMFM-88 and CB&M, and a CB&M mean change of 20.67% (SD=11.38).

Ninety-eight children with admission and discharge 6MWTs had a mean change of 142.3m (SD=101.8). Ninety-three children completed a baseline GMFM-88 and 6MWT within two weeks of each other. Seventy-three of these children went on to complete a 6MWT at discharge with a mean change of 145.9m (SD=102.8). GMFM-88, CB&M, and 6MWT change scores were negatively correlated with their respective baseline scores (r=-0.88, -0.59, -0.41 respectively, p<0.001; Figure 2.2). GMFM-88 change scores were positively correlated with length of stay, time between assessments, and baseline mobility status (r=0.58, 0.55, 0.52 respectively, p<0.001; Table 2.4).

Figure 2. 2. Outcome change scores plotted against respective baseline scores.

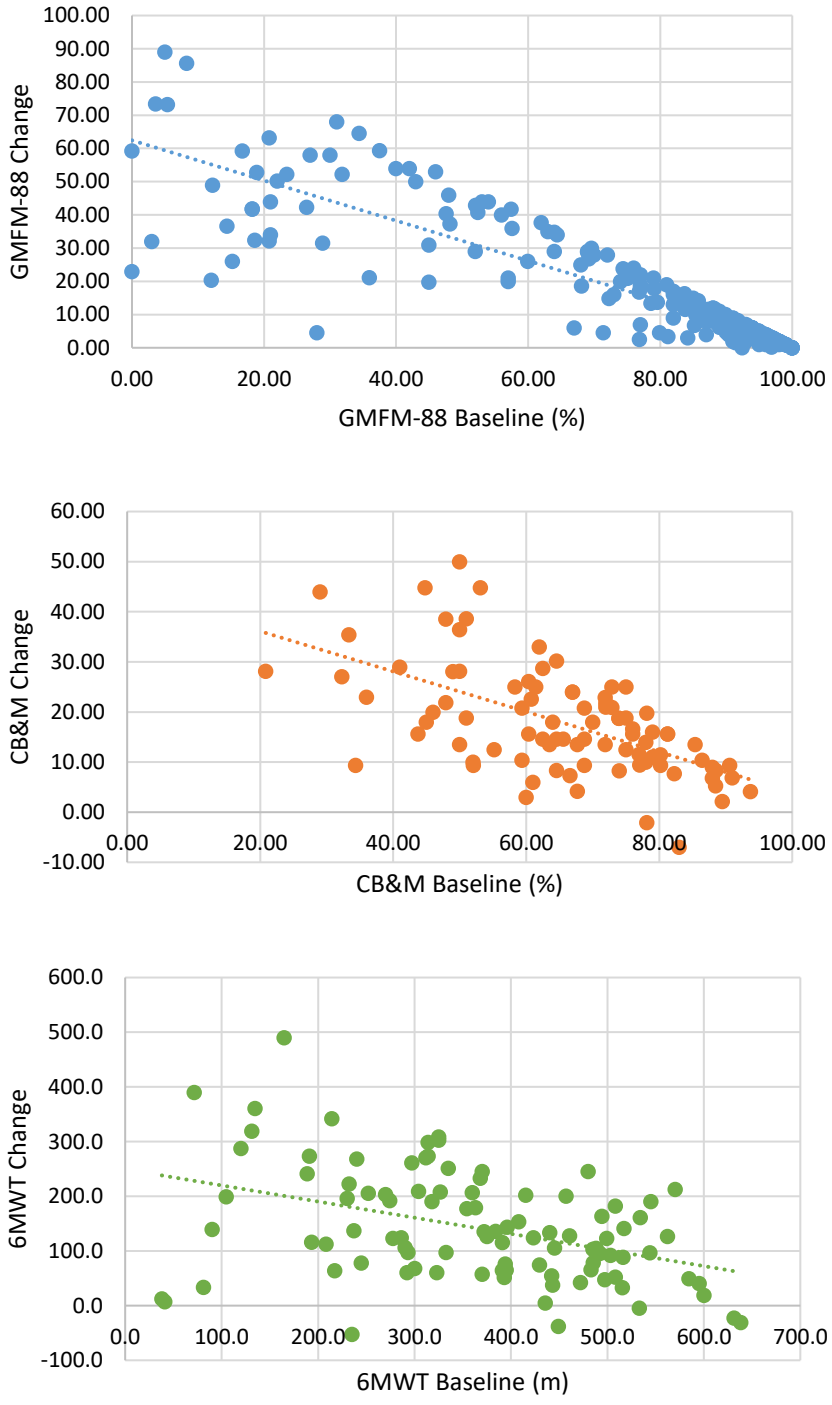


Table 2. 4. Correlations for outcome measure baseline, change, and discharge scores.

	Outcome† baseline	Outcome† DC	Time Between Assessments	Length of Stay	Baseline Mobility Status	Age	Sex
GMFM-88 Baseline	-	**0.78***	**-0.49***	**-0.54***	**0.52***	0.10	0.03
GMFM-88 Change	**-0.88***	**-0.47***	**0.55***	**0.58***	**-0.58***	-0.07	-0.03
6MWT Baseline	-	**0.72***	-0.24	**-0.53***	**0.56***	-0.06	0.09
6MWT Change	**-0.41***	0.26	0.40*	0.29*	-0.22	0.31*	0.15
CB&M Baseline	-	**0.70***	-0.05	-0.14	0.27*	0.25*	0.01
CB&M Change	**-0.59***	0.07	0.20	0.17	-0.11	0.05	0.04

†Outcome corresponds with the outcome measure listed in the left column; $|r| > 0.40$ bolded, $*p < 0.05$

Regression analyses indicated that 74% of the variation in GMFM-88 change score variation was explained by baseline assessment score ($p<0.001$), time between assessments ($p<0.001$), age, sex, and diagnosis ($p_{stroke}=0.001$, $p_{post\text{-}infectious}=0.030$) (Table 2.5).[1] Thirty-nine percent of variation in CB&M and 6MWT change was explained by baseline assessment ($p<0.001$), time between assessments ($p_{6MWT}<0.001$), sex ($p_{6MWT}=0.021$), and age ($p_{6MWT}=0.009$). VIFs between 1.01 and 1.52 indicated no redundancy among variables across all three regression analyses except for the brain tumour dummy variable ($VIF>10^4$) in the GMFM-88 stepwise regression which was then removed from the equation. Regression analyses with change score log and arcsine transformations did not improve model fit.

[1] Addendum to the published manuscript- Regression models for each outcome measure:

- **GMFM-88 change** = 41.63 - 0.50 * (baseline GMFM-88) + 0.11 * (time between GMFM-88s in days) + 6.35 * (stroke: yes = 1, no = 0) + 6.13 (post-infectious ABI: yes = 1, no = 0)
- **CB&M change** = 35.55 – 0.43 * (baseline CB&M)
- **6MWT change** = 12.56 - 0.23 * (baseline 6MWT) + 2.14 * (time between 6MWTs in days) + 6.89 * (Age in years) + 40.62 * (sex: female = 0, male = 1)

Table 2. 5. Results of stepwise multiple regression analyses for outcome measure change scores.

GMFM-88: R^2 = 0.72 (n = 202)					
Independent Variables	**Coefficient**	**Std. Error**	**t**	***P***	**VIF**
Baseline GMFM-88	-0.50	0.03	-15.98	**<0.001**	1.52
Time between GMFM-88s (days)	0.11	0.03	3.88	**<0.001**	1.52
Age (years)	0.21	0.19	1.08	0.231	1.08
Sex*	0.24	1.47	0.16	0.872	1.03
Stroke	6.35	1.93	3.28	**0.001**	1.55
TBI	2.31	2.40	0.97	0.336	1.38
Epilepsy	1.06	2.50	0.43	0.670	1.32
Post-Infectious	6.13	2.80	2.19	**0.030**	1.24
Neuroinflammatory	3.91	3.74	1.05	0.297	1.16
Hypoxic	1.22	3.94	0.31	0.757	1.15
Brain Tumour	*Not included in model due to multicollinearity*				$>10^4$
CB&M: R^2 = 0.39 (n = 89)					
Independent Variables	**Coefficient**	**Std. Error**	**t**	***P***	**VIF**
Baseline CB&M	-0.43	0.06	-7.06	**<0.001**	1.10
Time between CB&Ms (days)	0.06	0.06	1.12	0.265	1.04
Age (years)	0.56	0.35	1.62	0.110	1.12
Sex*	-0.02	1.90	-0.01	0.992	1.00
6MWT: R^2 = 0.39 (n = 98)					
Independent Variables	**Coefficient**	**Std. Error**	**t**	***P***	**VIF**
Baseline 6MWT	-0.23	0.06	-3.66	**<0.001**	1.10
Time between 6MWTs (days)	2.14	0.49	4.33	**<0.001**	1.14
Age (years)	6.89	2.59	2.66	**0.009**	1.01
Sex*	40.62	17.24	2.36	**0.021**	1.04

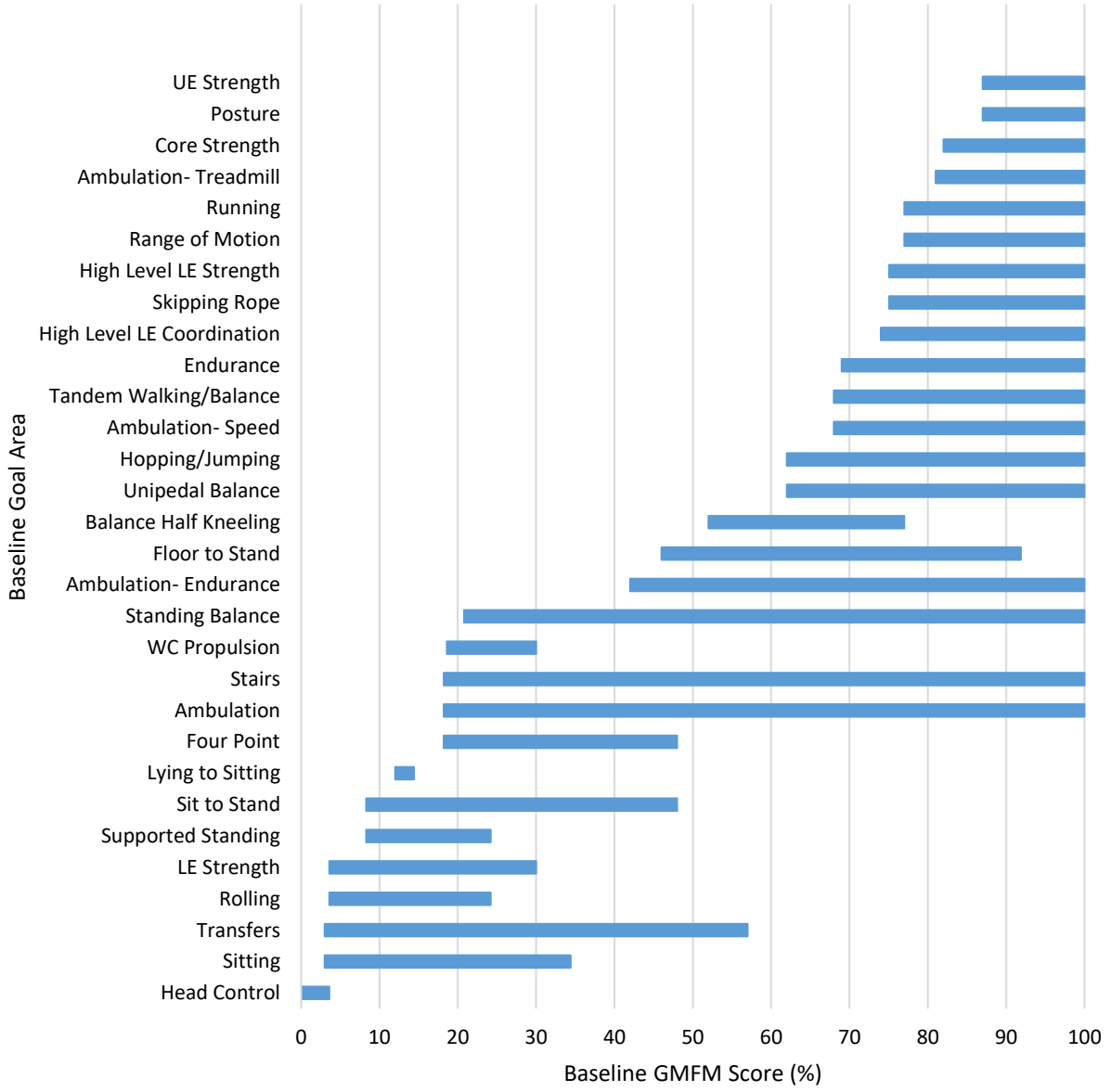
*Sex was assigned 0 for female and 1 for male in the regression analyses
Bolded values indicate statistical significance (p <0.05)
VIF: variance inflation factor

There were 694 scored GAS goals in 209 charts with a mean post-intervention T-score of 55.06 (SD=11.50). Fifty-eight charts (21.80%) had multiple sets of GAS. GAS scores were ≥0 in 547 of 694 goals (78.82%) with 388 goals (55.91%) scoring 0 or +1. The GAS goal areas were documented in the chart according to factors influencing motor function (e.g., balance, strength, endurance, coordination, range of motion, posture) or specific gross motor skills (e.g., sitting,

standing, ambulation, transfers, floor to stand). Ambulation was the most frequent goal area (25% of all goals set) and targeted walking with/without support, speed, endurance (e.g., walking throughout the day), and quality (e.g., heel strike). Stairs and balance were the second most frequent goal areas (13% each). Sitting, head control, posture, and range of motion were the least frequent goal areas (≤2% each).

When the baseline GMFM-88 was <50%, admission goals often focused on foundational skills (e.g., head control, rolling, sitting, transfers, supported standing, four-point) (Figure 2.3). Goals related to standing balance, stairs, floor to stand transitions, and ambulation spanned a wide range of GMFM-88 scores (18.2–100%). More advanced gross motor skills (e.g., unipedal balance, running, jumping/hopping skipping rope) began at GMFM-88 >60%. Goals focusing on advanced strength, posture, range of motion, and coordination began at GMFM-88 >75%.

Figure 2. 3. Baseline GAS goal areas relative to the range of baseline GMFM-88 scores for each goal area (n=209).



LE =lower extremity; UE =upper extremity

2.5 Discussion

During their admission, school-aged children with moderate to severe ABI experienced change on the GMFM-88, CB&M and 6MWT (18.03%, 17.85%, and 142.3m) that surpasses the published minimal clinically important differences for children with ABI (5.3% (Storm et al.,

2020), 13.5% (Wright et al., 2010), and 38m (Storm et al., 2020), respectively). These improvements, along with GAS goal achievement, highlight the strong potential for recovery during the subacute stage of ABI. This GMFM-88 change score can serve as a reference point for gross motor change associated with traditional inpatient ABI rehabilitation. Our study identifies variables associated with gross motor change and emphasizes the importance of taking a layered approach to physiotherapy assessment where performance on one outcome measure informs the use of subsequent measures.

GMFM-88, CB&M, and 6MWT changes were predicted by their respective baseline scores where lower scores were associated with greater change. GMFM-88 and 6MWT change was also predicted by time between assessments where more time was associated with greater change. These findings are explained by children with extensive motor challenges having more room for improvement and requiring longer admissions (with more time between pre/post assessments) to attain their goals. Having a stroke or post-infectious ABI appeared to predict larger GMFM-88 change scores than other diagnoses. However, fewer charts in some diagnostic groups limit the conclusions drawn from this data. While age and sex did not predict GMFM-88 or CB&M change, being older and male predicted greater 6MWT change. This finding aligns with typically developing youth where older males have higher 6MWT scores than their female or younger male counterparts based on height difference (Geiger et al., 2007). Given that ABI does not generally affect height, male adolescents with ABI should also have greater room for walking speed improvements.

Ambulation is often the primary focus of inpatient physiotherapy for children with ABI (Beretta et al., 2018; Dumas et al., 2004a; Kuhtz-Buschbeck et al., 2003; Levac et al., 2012; Rast & Labruyère, 2020). After completing a baseline GMFM-88, ambulatory children were frequently evaluated with other measures (e.g., CB&M, 6MWT), presumably to identify additional balance and mobility challenges. This layered approach allowed physiotherapists to identify advanced mobility challenges (e.g., endurance, quality of movement, high level balance), detect clinically important change, and develop individualized GAS goals. However, the physiotherapists' process for determining when to administer measures beyond the GMFM-88 was not explored.

As gross motor function extends beyond ambulation to skills such as bed mobility, floor to stand transitions, and standing balance (Dumas et al., 2004b; Russell et al., 1989; Wright et al., 2010), physiotherapy goals for children with ABI addressed multiple areas of functional mobility. In this review, GMFM-88 item scores appeared to guide GAS goal development. The individualized nature of GAS makes it applicable to all inpatient ABI admissions regardless of functional ability. The physiotherapists structured GAS goals to capture qualitative aspects of performance (e.g., extent of assistance required to roll, use of equilibrium reactions in unipedal stance, achieving heel strike during gait) and quantitative aspects of gross motor function (e.g., time spent walking throughout the day, consecutive times jumping rope, distance travelled dribbling a basketball) not captured by the GMFM-88 with input from the child and/or parent. For example, when a child indicates they want to climb stairs independently at home, the physiotherapist constructs GAS goal increments based on environmental constraints (e.g., number of steps, railing location) and the child's abilities (e.g., reciprocal versus non-reciprocal stepping, holding railing versus hands-free). Notably, the documented goal area for stairs tasks varied across charts, either corresponding with an activity label (e.g., gross motor, stairs) or based on the primary underlying body structure or function affecting independence on the stairs (e.g., "strength" for a child with hemiparesis, "balance" for a child with ataxia, "coordination" for a child with motor planning challenges). While GAS addressed multiple aspects of function, goal areas appeared to increasingly address movement quality as GMFM-88 scores increased.

Several factors should be considered when interpreting our results: 1) our analysis refers to association between variables and is not intended to imply causation; 2) the eligible population was a subgroup of children with ABI capable of participating in standardized assessment and admitted for inpatient rehabilitation with gross motor goals; 3) our review was limited to children aged five years and up as the GMFM-88 is not consistently administered on admission in younger children with subacute ABI at this hospital, due to decreased tolerance to standardized assessment at this early stage of recovery; and 4) exploring change based on diagnosis was exploratory and did not take injury location or severity into consideration. While physiotherapy intervention in this ABI program is typically 60-minute sessions up to five days per week, use of the electronic health record prevented exact calculation of physiotherapy dose as intervention dates and durations were not consistently recorded. Finally, this chart review does not

differentiate between the role of inpatient rehabilitation and natural recovery. However, this limitation is unavoidable even in prospective research due to the ethical concerns of withholding standard care (i.e., intensive rehabilitation) for children with subacute ABI.

This chart review summarized the gross motor changes that school-aged children with moderate to severe ABI make during inpatient rehabilitation and demonstrates the value of using routinely collected health data to inform research and clinical practice. These clinically derived change scores can now be used to estimate sample size in studies exploring gross motor treatment approaches in pediatric subacute ABI and evaluate the preliminary effect of novel treatment approaches in feasibility trials where a control group is not feasible. With our identification of goal areas for inpatient ABI physiotherapy, the goal setting process and its role in engaging children with subacute ABI in physiotherapy can be explored prospectively. Further research is also required to understand how physiotherapists select appropriate outcome measures and the relative timing of their administration, explore gross motor change in children with limited ability to participate in standardized assessment, and evaluate how injury severity and location influences recovery.

2.5.1 Acknowledgements

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Chapter 3

Using motor evoked potentials to measure the neural impact of transcranial direct current stimulation on the primary motor cortex in healthy participants: A systematic review of studies involving motor behaviour

At the time of thesis submission, this chapter was under peer review for separate publication.

3 Using motor evoked potentials to measure the neural impact of transcranial direct current stimulation on the primary motor cortex in healthy participants: A systematic review of studies involving motor behaviour

3.1 Abstract

Background: Motor evoked potentials (MEPs) are a measure of corticospinal excitability frequently used to evaluate neural change in response to transcranial direct current stimulation (tDCS) targeting the primary motor cortex (M1). A subset of these studies involves motor behaviour (i.e., motor practice and/or evaluating motor performance).

Methods: To understand the role of MEPs as an indication of neural change in tDCS studies involving motor behaviour and explore the association between changes in motor performance and MEPs, this systematic review summarized unilateral M1-targeted tDCS studies in healthy individuals that involved motor behaviour and measured change in MEP amplitude. We executed our search strategy across four bibliographic databases. Two reviewers independently screened abstracts from all search results using Covidence systematic review management software and extracted data from eligible manuscripts. Quality assessment was completed using the Revised Cochrane Risk of Bias Assessment.

Results: Twenty-two manuscripts were eligible (five that evaluated motor performance with no motor practice, five with motor practice but did not evaluate motor performance, 12 with motor practice that evaluated motor performance). Treatment parameters varied widely across studies. MEP outcomes varied considerably and did not always align with changes in motor performance.

Conclusion: While anodal tDCS combined with motor practice frequently increased MEP amplitude, study findings should be interpreted with caution based on risk of bias assessment results. Because MEP outcomes did not necessarily align with changes in motor performance, MEPs may not be the most appropriate indicator of neural change in tDCS studies that aim to improve motor performance.

3.2 Introduction

Transcranial direct current stimulation (tDCS) targeting the primary motor cortex (M1) has been regularly studied in healthy and clinical populations for several decades with the goal of promoting neural reorganization and changing motor behaviour (Stagg & Nitsche, 2011). tDCS alters cortical excitability by delivering subthreshold electrical currents to targeted cortical neurons (Brunoni et al., 2012; Stagg & Nitsche, 2011). In dual electrode montages (i.e., one anode, one cathode), *anodal tDCS* refers to placing the anode directly over the neural target which causes temporary excitation of the proximate grey matter by predisposing axonal resting membrane potentials toward depolarization (Nitsche & Paulus, 2000; Stagg & Nitsche, 2011). *Cathodal tDCS* involves placing the cathode over the neural target and is theoretically associated with decreased cortical excitability or hyperpolarization of axonal resting membrane potentials in proximate grey matter (Nitsche & Paulus, 2000; Stagg & Nitsche, 2011). Task practice during these periods of altered cortical activity is thought to promote neural reorganization by strengthening existing neural pathways and forming new neural connections, and is associated with improved motor behaviour (Stagg & Nitsche, 2011).

Motor behaviour encompasses motor learning and performance (Schmidt & Lee, 2014). Motor learning refers to the acquisition and retention of a motor skill that occurs with practice or experience, whereas motor performance refers to the ability to execute a motor skill at a single point in time which varies considerably depending on individual and environmental factors (Schmidt & Lee, 2014). While motor performance is measured at a single timepoint, motor learning is inferred by evaluating performance at multiple time points and usually involves a retention test that occurs after a period without practice (Schmidt & Lee, 2014). M1 is frequently the neural target in studies evaluating the impact of tDCS on motor behaviour (Stagg & Nitsche, 2011) as M1 is responsible for the initiation of voluntary movement and plays an important role in motor learning and performance (Dayan & Cohen, 2011; Karni et al., 1998). The somatotopic organization of M1 allows researchers to target a specific muscle by positioning electrodes on the scalp such that current is directed toward (i.e., anodal) or away (i.e., cathodal) from the underlying cortical representation of the muscle or body part of interest (Stagg & Nitsche, 2011). M1-targeted tDCS aiming to improve motor behaviour often involves repeated practice of an upper or lower extremity task either during or immediately following stimulation (Bastani &

Jaberzadeh, 2012). Motor practice provides exposure to a specific motor skill and should ultimately improve speed (e.g., timed serial reaction tasks), accuracy (e.g., visuomotor tracking), strength (e.g., isolated joint movement at a percentage of the maximum voluntary contraction), or endurance (e.g., cycling). Augmenting motor practice with tDCS is thought to increase the rate and amount of motor learning that occurs compared to practice on its own (Stagg et al., 2011).

M1-targeted tDCS studies often assess motor performance to evaluate the impact of tDCS on strength, endurance, speed, and/or accuracy. Equally important is the evaluation of neural outcomes for identifying the neural processes associated with changes in motor performance. Motor evoked potentials (MEPs) are the most frequently studied neural outcome in M1-targeted tDCS research (Bastani & Jaberzadeh, 2012; Horvath et al., 2015). MEP amplitude is a measure of corticospinal excitability where single pulse transcranial magnetic stimulation (TMS) delivered to a targeted region of M1 induces a contraction in the associated muscle (Bestmann & Krakauer, 2015). While MEP amplitude is expected to temporarily change after tDCS with an increase in amplitude for the muscle whose M1 representation is under the anode and a decrease for those under the cathode (Nitsche & Paulus, 2000), evidence of prolonged MEP changes and their association with motor behaviour is unclear (Bestmann & Krakauer, 2015). MEPs change throughout the various stages of motor practice with the extent and timing of change dependent on the speed, precision, and force required for a particular movement or task (Bestmann & Krakauer, 2015; Cinelli et al., 2019; Kidgell et al., 2010; Pearce & Kidgell, 2010). MEPs also vary considerably based on individual (e.g., resting state, anatomical differences) and experimental factors (e.g., timing of tDCS relative to motor practice, TMS parameters) (Ammann et al., 2020; Goldsworthy et al., 2016; Wiethoff et al., 2014). Furthermore, muscle activation during motor practice is thought to limit the extent that tDCS induces change in MEPs (Antal et al., 2007; Horvath et al., 2014), and introduces the question of whether MEPs are in fact a suitable indicator of temporary and/or lasting neural change.

Given the frequency that MEPs are used as a neural outcome in tDCS studies and the lack of clarity regarding the impact that motor behaviour has on tDCS-induced change in MEPs, a review of recent M1-targeted tDCS studies involving motor behaviour in healthy individuals is required. To our knowledge, no systematic review to date has focused solely on tDCS protocols

that involve both motor behaviour (i.e., motor practice and/or evaluating change in motor performance) and MEP measurement in healthy individuals (Bastani & Jaberzadeh, 2012; Dissanayaka et al., 2017; Hassanzahraee et al., 2018; Horvath et al., 2015). Thus, the primary objective of this review was to determine whether tDCS with or without motor practice induces change in MEP amplitude pre/post intervention in healthy individuals by synthesizing data from tDCS studies involving motor behaviour. The secondary objectives were to explore: 1) the duration of change in MEP amplitude, 2) the impact of tDCS on motor performance, and 3) how changes in MEPs relate to changes in motor performance.

3.3 Methods

3.3.1 Literature search

Systematic reviews are conducted to establish the appropriateness or effectiveness of a specific practice (Munn et al., 2018) and, as such, this methodology was the ideal for addressing our research objectives. We conducted this systematic review according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al., 2021). Our protocol was registered on Open Science (https://doi.org/10.17605/OSF.IO/XV3JA). We executed our search strategy across four databases: MEDLINE, EMBASE, PsycINFO, and CINAHL. A health sciences research librarian developed the initial search strategy for MEDLINE (see Appendix A) in consultation with the first author and translated it into the appropriate terms for the other three databases. The search strategy involved two major concepts: tDCS and MEPs. The preliminary MeSH terms used were “transcranial direct current stimulation”, “potentials, motor evoked”, and “motor cortex” and then synonyms and other keywords were generated. The search was limited to human subjects, articles written in English, and articles published since 2011 to summarize current trends in this area of study.

3.3.2 Study Selection

Search results from the four databases were uploaded into Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org) which automatically removes duplicates. The remaining articles were screened independently by two reviewers (J Ryan, E Eng). Study titles and abstracts were

screened and articles that did not meet study eligibility criteria were excluded. If eligibility could not be ascertained by the title and abstract, the article underwent a full text review. Screening discrepancies between reviewers were discussed and resolved at the screening and full text review stages, consulting the senior author (D Beal) when reviewers could not reach consensus.

3.3.3 Eligibility Criteria

The inclusion criteria were: original peer-reviewed research studies published between Jan 1, 2011 and Dec 31, 2021; healthy participants of any age; any tDCS electrode montage targeting one M1; protocols involving motor behaviour (i.e., motor practice and/or measurement of change in motor performance; and pre-post MEPs were measured. The exclusion criteria were: case studies; drug trials; participants with orthopedic or neurological conditions; treatment protocols involving other types of non-invasive brain stimulation, peripheral nerve stimulation, imagery, visual perturbations or sensory stimulation; MEP measurement or motor task practice ipsilateral to the M1 stimulated by tDCS; bihemispheric or dual hemisphere stimulation of M1; or stimulation of other cortical areas (e.g., premotor cortex, supplemental motor area).

3.3.4 Data Extraction

One reviewer was designated the primary reviewer and the other was the secondary reviewer for each eligible manuscript. Once the data were extracted by the primary reviewer, the secondary reviewer confirmed that all pertinent data were accurately entered.

3.3.5 Quality Assessment

A quality assessment was completed via the same two-step review process described in the Data Extraction section using the Revised Cochrane Risk of Bias Tool for Randomized Trials (RoB 2), with or without the ‘Additional considerations for crossover trials’ document depending on study design (Sterne et al., 2019). The RoB 2 scores studies as *low risk*, *some concerns*, or *high risk* in six domains for parallel group trials (randomization, effect of assignment to intervention, effect of adhering to intervention, missing outcome data, measurement of the outcome, selection of the reported result) and in an additional seventh domain for crossover trials (period and carryover effects) (Sterne et al., 2019). An overall risk of bias rating is determined based on the ratings in each domain (Sterne et al., 2019).

3.3.6 Results Synthesis

The appropriateness of conducting a meta-analysis was determined by appraising study heterogeneity, and given our primary objective, the availability of MEP change scores (mean and standard deviation). Heterogeneity was appraised based on tDCS parameters, the type of motor skill, and the timing of tDCS relative to motor practice. If a meta-analysis could not be conducted due to study heterogeneity and/or the absence of numerical MEP change scores, we planned to use Campbell et al.'s (2020) Synthesis Without Meta-analysis (SWiM) reporting guidelines to conduct a narrative synthesis for studies with overall ROB 2 ratings of *some concerns* or *low risk*. This synthesis involved grouping based on the presence or absence of motor practice within the protocol and, within motor practice, establishing subgroups based on the type of motor practice before reporting on effect direction for MEP amplitude and motor performance (e.g., increased, decreased, nil). The timing of MEP assessment and duration of changes were also discussed.

3.4 Results

Of the 4266 articles generated from the search (1039 MEDLINE, 1662 EMBASE, 771 PsycINFO, 796 CINAHL), 1346 were duplicates, 2591 were eliminated by screening study title and abstracts, and 307 were removed after screening the full article (Figure 3.1). Twenty-two articles met the eligibility criteria and were included in the systematic review. All studies involved adult participants. Participants were either randomized to a treatment group in parallel trials (n=5) or to an order of treatment conditions in crossover trials (n=17). Sample size varied from 11 to 60 participants with treatment group sizes of 7 to 20 participants (Figure 3.2). Eighteen studies involved tDCS targeting the upper extremity region of M1 and four targeted the lower extremity region of M1. Five studies measured change in motor performance without a motor practice component (Table 3.1). Seventeen studies involved motor practice: strength/endurance (n=7), speed/accuracy (n=8), or repetitive (n=2) tasks (Table 3.2). Of the 17 studies involving motor practice, 10 studies measured change in motor performance.

Figure 3. 1. PRISMA flow diagram (Page at al., 2021).

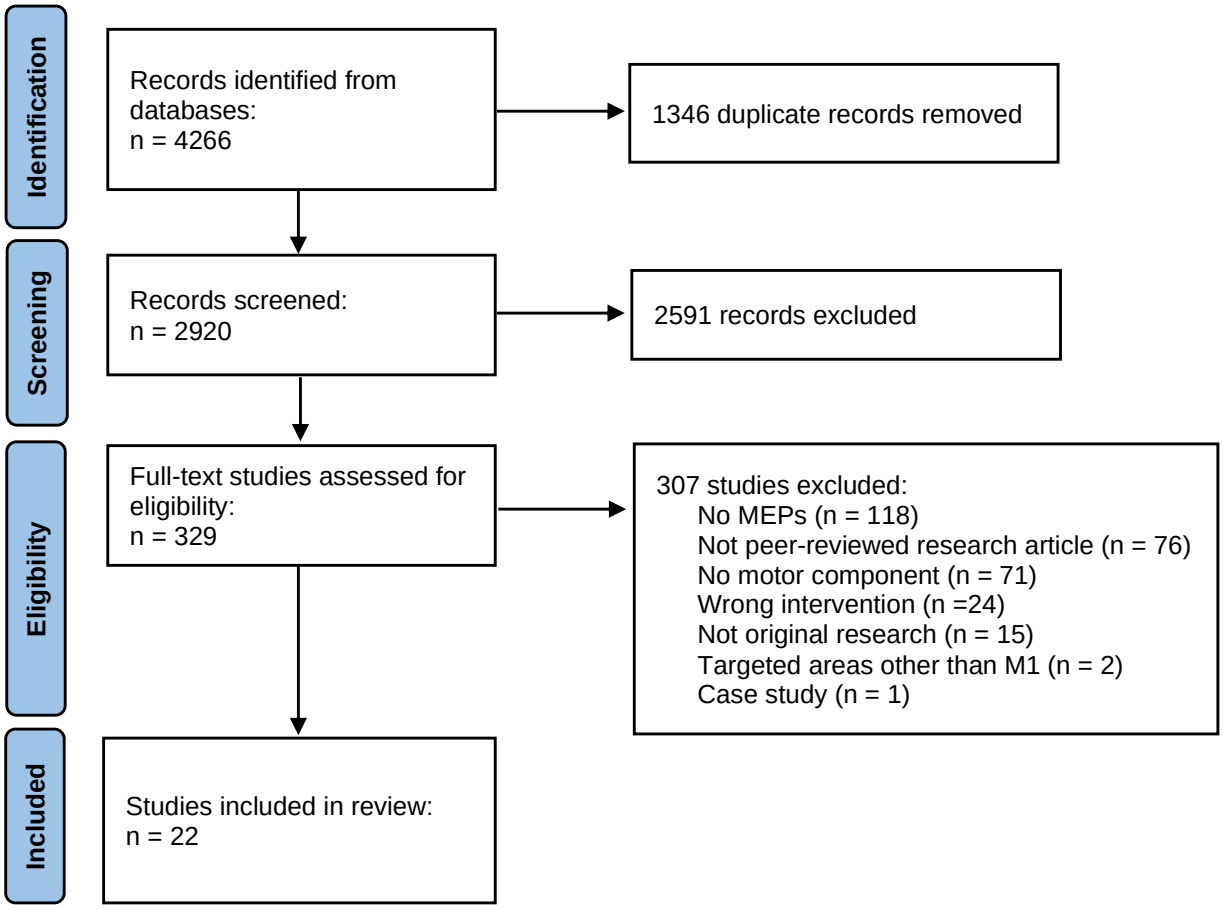
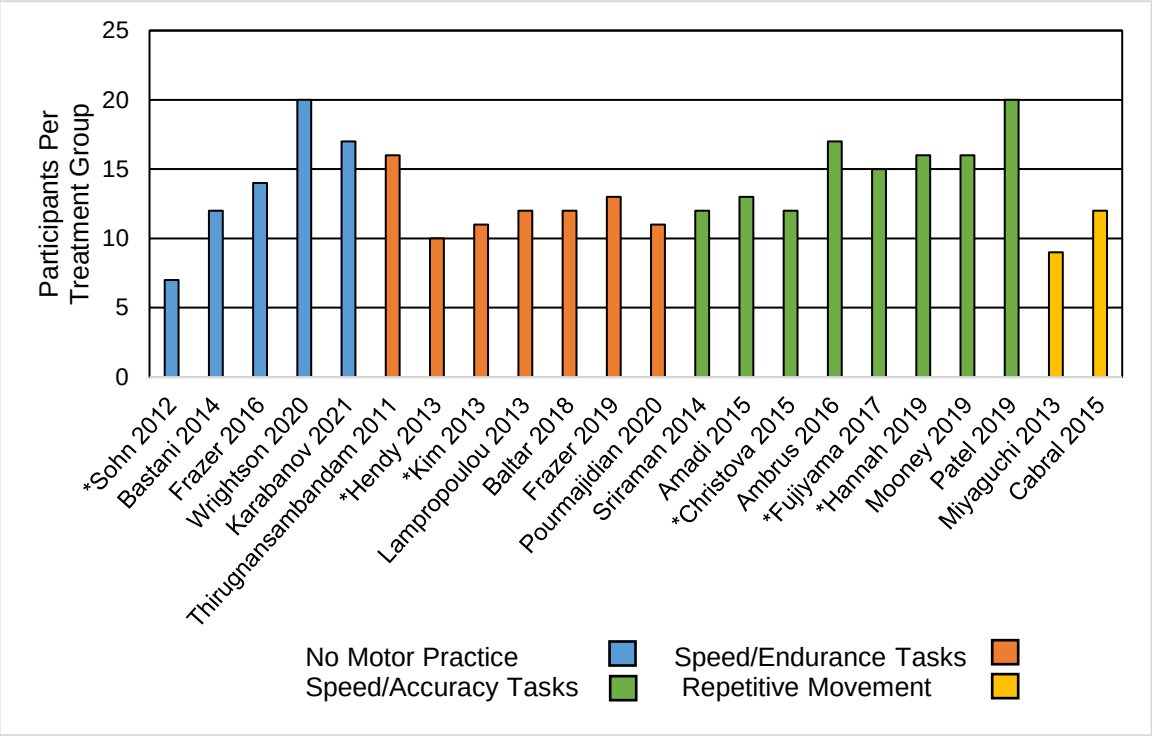


Figure 3. 2. Number of participants allocated to each treatment group.



(Note: For crossover studies, participants per treatment group is the entire sample size. For parallel group study designs*, the total sample is divided by the number of treatment groups. Fujiyama et al. (2017) and Mooney et al. (2019) were further divided into age subgroups.)

Table 3. 1. Studies that evaluated change in motor performance but did not involve motor practice.

Study (first author, year)	**Study Design & RoB**	**Motor Assessment**	**Study Description**	**Stimulation Electrode**	**tDCS type**	**tDCS Duration** / **tDCS Intensity**	**Impact on MEP***	**Impact on Motor****
Sohn, 2012	Parallel group; double blind ⊖	Jebsen-Taylor hand function Test	One session of: 1) A-tDCS (ND), 2) C-tDCS (ND), 3) S-tDCS (ND), or 4) A-tDCS (D). MEP Ax: timing not indicated Motor Ax: pre-tDCS (ND hand), post-tDCS (both hands)	APB	A,C,S	15 min / 1.0 mA	A: ↑ (ND) ↓ (D) C: ↓ (ND)	A: ↑ (ND) nil (D) C: nil (ND)
Bastani, 2014 (experiment 1)	Crossover, single blind ⊖	Purdue Pegboard Test	One session of each combination of conditions‡: 1, 2, or 3 tDCS intervals with 5 or 25-min breaks. MEP Ax: after each tDCS interval, 0-120 min post-tDCS Motor Ax: pre-tDCS, post-tDCS (final interval only)	FDI	A	10 / 0.2	↑	↑
Frazer, 2016	Crossover, double blind ⊕	Maximum Voluntary Contraction (MVC)	4 sessions on consecutive days of each condition‡ MEP Ax: timing not indicated Motor Ax: Wrist flexor and extensor strength before 1st and after final tDCS session in each condition	FCR	A,S	20 / 2.0	↑	↑
Wrightson, 2020	Crossover, double blind ⊕	MVC	One session of each condition‡ MEP Ax: 0 min post-tDCS Motor Ax: isometric knee extension to failure post-tDCS	VL	A,S	10 / 1.0, 2.0	nil	nil
Karabanov, 2021	Crossover, double blind ⊕	Tracking Error (joystick operated by finger abduction/ adduction)	One session of each tDCS condition‡ MEP Ax: 0-60 min post-tDCS Motor Ax: visuomotor assessment tDCS	FDI	A,S	20 / 0.75	nil	nil

RoB = risk of bias (⊖ = some concerns; ⊕ = high risk); ND = non-dominant, D = dominant; tDCS type: A= anodal, C= cathodal, S=sham; Ax= assessment; ‡treatment conditions in crossover studies separated by ≥ 48h – 1 week minimum; APB: abductor pollicis brevis; FDI: first dorsal interosseus; FCR: flexor carpi radialis; VL: vastus lateralis; *Impact on MEP refers to amplitude (↑= increase, nil = no impact, ↓= decrease); **Impact on Motor refers to motor assessment (↑= improvement, nil = no impact, ↓= decreased performance)

Table 3. 2. Studies involving motor practice.

Study (first author, year)	**Study Design & RoB**	**Motor Component**	**Study Description**	**Target Muscle**	**tDCS type**	**tDCS Duration** / **tDCS Intensity**	**Impact on MEP***	**Impact on Task****
STRENGTH/ENDURANCE TASKS								
Thirugnanasam-bandam, 2011	Crossover, single blind ⊖	Ax: NA Rx: voluntary muscle contraction (VMC) 20% of 1-repetition max [RM] x 120s	One session of each condition‡: 1) A-tDCS, 2) C-tDCS, 3) S-tDCS, 4) A-tDCS+VMC, and 5) C-tDCS+VMC Motor Rx: after tDCS MEP Ax: 0 min post-tDCS	FDI	A,C,S	20 min 1.0 mA	A: ↑ C: ↓ (A+VMC < A)	NA
Hendy, 2013	Parallel group, double blind ⊖	Ax: strength testing Rx: wrist extension (4 sets of 6-8 reps at 70% 1-RM)	Nine sessions of: 1) S-tDCS + strength, 2) A-tDCS + strength, or 3) control (no strength or tDCS). Motor Rx: during tDCS MEP and Motor Ax:48-72 hours after final session.	ECRL	A,S	30 2.0	A: ↑	A↑ = S↑
Kim, 2013	Parallel group, double blind ⊖	Ax: NA Rx: grip exercise	One session of: 1) S-tDCS, 2) A-tDCS, 3) S-tDCS + grip exercise, or 4) A-tDCS + grip exercise. Motor Rx: during tDCS (final 30s) MEP Ax: 0 min post-tDCS	FDI	A,S	20 2.0	A+grip ↑ (compared to A or S+grip)	NA
Lampropoulou, 2013	Crossover, double blind ⊖	Ax: NA Rx: isometric elbow flexion with visual feedback at 30,50,70,100% maximum voluntary contraction (MVC)	One session of each condition‡. Motor Rx: Elbow flexion task 35 and 15 min before tDCS, then 5, 25, and 45 min post-tDCS. MEP Ax: 1,20,40 min post-tDCS.	BB, BR	A,C,S	10 1.5	nil	NA
Baltar, 2018 (experiment 2)	Crossover, double blind ⊖	Ax: NA Rx: treadmill training (TT)	One session of each tDCS/motor combination‡: A-tDCS, C-tDCS, S-tDCS Motor Rx: low or high intensity TT, after tDCS MEP Ax: 0 min post-tDCS, 0-90 min post-TT	TA	A,C,S	20 2.0	nil	NA
Frazer, 2019	Crossover, double blind ⊖	Ax: isometric strength (MVC) Rx: elbow flexor strength training (4 sets of 6-8 reps 80% 1RM)	One session of each condition‡: A-tDCS, S-tDCS Motor Rx: after tDCS MEP Ax: 0 min post-tDCS	BB	A,S	20 2.0	Nil	A↓ = S↓

Study (first author, year)	**Study Design & RoB**	**Motor Component**	**Study Description**	**Target Muscle**	**tDCS type**	**tDCS Duration** / **tDCS Intensity**	**Impact on MEP***	**Impact on Task****
Pourmajidian, 2020	Crossover, double blind ⊖	Ax: NA Rx: low intensity cycling	One session of each condition‡: 1) C-tDCS prime + A-tDCS, 2) S-tDCS prime + A-tDCS Motor Rx: during A-tDCS MEP Ax: 0-10 min pre and post a-tDCS.	FDI	A, Prime: S or C	10 / 2.0	↑ (with C-tDCS priming)	NA
SPEED/ACCURACY TASKS								
Sriraman, 2014	Crossover, blinding not indicated ⊕	Ax: tracking accuracy Rx: ankle plantar/dorsi-flexion tracking task	One session of each condition‡: 1) A-tDCS before task, 2) A-tDCS during task, 3) S-tDCS during task. Motor Ax: 10,25 min, and 24h post-tDCS MEP Ax: 0,25 min post-tDCS.	TA	A,S	15 / 1.0	nil	↑
Amadi, 2015	Crossover, blinding not indicated ⊕	Ax: reaction time Rx: visuomotor button-pressing task	One session of each condition‡: 1) A-tDCS then rest, 2) A-tDCS then task, 3) A-tDCS during task then rest, 4) S-tDCS then S-tDCS during task. Motor Ax: during practice MEP Ax: mid-point, end of each session.	FDI	A,S	20 / 1.0	↑ (a-tDCS only vs a-tDCS before task), Nil (a-tDCS during task)	↓ (a-tDCS before task)
Christova, 2015	Parallel groups, single blind ⊕	Ax: Grooved Pegboard Test Rx: Grooved Pegboard (4 blocks of 4 trials)	One session of: 1) S-tDCS prime + S-tDCS, 2) S-tDCS prime + A-tDCS, or 3) C-tDCS prime + A-tDCS. Motor Rx: during A-tDCS Motor Ax: during practice and 14 days post MEP Ax: after priming tDCS, 0-60 min post-tDCS	APB	A,S, Prime: S or C	20 / 1.0	↑ (a-tDCS vs sham), Priming with a-tDCS: ↑	↑ (a-tDCS vs sham), Priming ↑ offline
Ambrus, 2016	Crossover, single blind ⊕	Ax: Serial Reaction Time Task (SRTT) Rx: 8 blocks of SRTT (pressing buttons with 1 of 4 fingers)	One session of each tDCS condition‡ Motor Rx: during tDCS MEP and Motor Ax: during, 15 min post-tDCS	FDI	A,C,S	14 / 1.0	A: ↑ C: nil	nil
Fujiyama, 2017	Parallel groups; double blind ⊖	Ax: skill index (isometric abduction) Rx: isometric abduction of little finger based on instructions from computer	Younger, older adults randomized to one session of 1) C-tDCS prime + A-tDCS, or 2) S-tDCS prime + A-tDCS. Motor Rx: pre A-tDCS, during A-tDCS, post A-tDCS MEP and Motor Ax: 0,20,40min, 24 hours post-tDCS	FDI	A, Prime: S or C	20 / 1.5	↑ with cathodal priming (no effect of age); nil at 24h	↑ in both age groups (older < younger), priming: nil at 24h

Study (first author, year)	**Study Design & RoB**	**Motor Component**	**Study Description**	**Target Muscle**	**tDCS type**	**tDCS Duration** / **tDCS Intensity**	**Impact on MEP***	**Impact on Task****
Hannah, 2019	Parallel groups, double blind ⊖	Ax: accelerometry (ballistic thumb abduction) Rx: ballistic thumb abduction task	One session of PA-tDCS, AP-tDCS, or S-tDCS Motor Rx: during tDCS Motor Ax: change during practice, then return next day for retention test (no tDCS) MEP Ax: 5 min post-tDCS	APB	PA,AP, S	12 1.0	AP: nil PA: ↓	AP: ↓ PA: nil
Mooney, 2019	Crossover, double blind ⊖	Ax: speed accuracy function for sequential isometric force task Rx: visual isometric wrist extension task	One tDCS session for each condition‡ Motor Rx: during tDCS Motor Ax: 0 min, 24 hours, 7 days post-tDCS MEP Ax: 0 min post-tDCS Analysis in two groups: younger and older	ECR	A,S	20 1.0	↑	A ↑ = S ↑
Patel, 2019	Crossover, blinding not indicated ⊕	Ax: accuracy index of ankle dorsiflexion Rx: visuomotor ankle dorsiflexion task	One session of each tDCS condition‡ Motor Rx: during tDCS Motor Ax: 0 min post-tDCS MEP Ax: 10, 30 min post-tDCS	TA	A,AP	15 1.0	nil	A: ↑ only in responders
REPETITIVE MOVEMENT								
Miyaguchi, 2013	Crossover, blinding not indicated ⊖	Ax: NA Rx: repetitive passive or active finger abduction/ adduction movement	One session of each condition‡: 1) A-tDCS, 2) no tDCS + active movement, 3) no tDCS + passive movement, 4) A-tDCS + active movement, 5) A-tDCS + passive movement MEP Ax: 2,10 min post-tDCS	FDI	A	10 2.0	tDCS only: ↑, Passive/active only and tDCS + active: ↓, tDCS + passive: nil	NA
Cabral, 2015	Crossover, double blind ⊖	Ax: NA Rx: repetitive thumb abduction/adduction	One session of each condition‡: 1) S-tDCS before motor task, 2) A-tDCS before motor, 3) A-tDCS after motor, 4) A-tDCS during motor. MEP Ax: 0 min post-tDCS.	FDI	A,S	13 1.0	↑ when tDCS before motor training	NA

RoB = risk of bias (⊖ = some concerns; ⊕ = high risk); Ax = assessment, Rx = treatment; VMC = voluntary muscle contraction; 1-RM = one-repetition maximum; MVC= maximum voluntary contraction; TT = treadmill training; NA = not applicable (because motor assessment did not occur); ‡treatment conditions in crossover studies separated by ≥ 48h – 1 week minimum; APB: abductor pollicis brevis; ADM: adductor digiti minimi; BB: biceps brachii; BR: brachioradialis; ECR(L): extensor carpi radialis (longus); FCR: flexor carpi radialis; FDI: first dorsal interosseus; TA: tibialis anterior; tDCS type: A= anodal, C= cathodal, S=sham, AP= current flow anterior-to-posterior with electrodes equal distance from M1, PA= current flow posterior-to-anterior with electrodes equal distance from M1; *Impact on MEP refers to amplitude (↑= increase, nil = no impact, ↓= decrease); **Impact on Motor refers to motor assessment (↑= improvement, nil = no impact, ↓= decreased performance)

3.4.1 tDCS Parameters

All studies used tDCS montages with two electrodes between 3.14 and 57.75 cm^2 (35 cm^2 electrodes were used in 15 studies). The most frequently targeted region of M1 was the first dorsal interosseus (n=10). Twenty-one studies involved anodal tDCS, five involved cathodal tDCS, three involved cathodal priming tDCS (i.e., cathodal tDCS prior to anodal tDCS), and two involved non-traditional electrode montages (i.e., electrodes centred around M1). Nineteen studies had a sham tDCS control condition. tDCS durations were 10 to 30 minutes with most studies (n=9) using a 20-minute duration. tDCS intensities were 0.2 to 2.0 mA; 11 studies used 1.0 mA and eight studies used 2.0 mA. All but two studies (Frazer et al., 2016; Hendy & Kidgell, 2013) involved a single tDCS session per treatment condition.

3.4.2 MEP Measurement

MEP change scores were reported numerically in two studies, and illustrated using graphs in 19 studies. Fourteen studies measured MEPs using resting motor thresholds, six used active motor thresholds, and two did not indicate the type of motor threshold (Table 3.3). Nineteen studies measured MEP amplitude within five minutes of tDCS completion, while only five of those studies also measured MEPs ≥ 60 minutes after tDCS. MEP measurement immediately upon tDCS completion (i.e., at 0 min post-tDCS) was the most frequently measured timepoint (n=14). The number of MEPs averaged at each timepoint varied between 8 and 30 (mean=15.37, SD=7.14). The timing of MEP measurement relative to motor outcomes varied among studies (see Study Description column in Table 3.2).

Table 3. 3. TMS parameters for MEP measurement.

Study	Target Muscle	TMS settings	MEPs/ Timepoint	Post-tDCS MEP Timepoints (minutes)
Thirugnanasam-bandam, 2011	FDI	AMT; AMT= min SI to evoke MEP ≥ 100μV in 5 of 10 trials at 15% MVC	20	0
Sohn, 2012	APB	120% RMT; RMT= minimum stimulator intensity (min SI) to evoke MEP ≥ 50μV in 5 of 10 trials	NI	0
Hendy, 2013	ECRL	AMT; AMT= min SI to evoke MEP ≥ 200μV in 5 of 10 trials at 5% MVC	10	0
Kim, 2013	FDI	120% RMT; RMT= min SI to evoke MEP ≥ 50μV in 5 of 10 trials	10	0
Lampropoulou, 2013	BB, BR	120% RMT; RMT= min SI to evoke MEP ≥ 50μV in 5 of 10-12 trials	15	1,20,40
Miyaguchi, 2013	FDI	RMT; RMT= min SI to evoke MEP 1 mV in ≥ 50% of 10 stimuli	12	2,10
Bastani, 2014	FDI	120% RMT; RMT= min SI to evoke MEP ≥ 50μV in 5 of 10 trials	12	10,20,30,45,60,90,120 (and between tDCS intervals)
Sriraman, 2014	TA	120% AMT; AMT= min SI to evoke MEP ≥ 0.4mV in 50% of trials	10	0,25
Amadi, 2015	FDI	RMT; RMT= min SI to evoke MEP approx. 1mV in 10/10 trials	30	0 (after each modulation period- 2 per session)
Cabral, 2015	FDI	1 mV	NI	0
Christova, 2015	APB	110, 130, 150% RMT; RMT= min SI to evoke MEP ≥ 0.05 mV in 5 of 10 trials	8	After priming tDCS and 0,60
Ambrus, 2016	FDI, FF	RMT; RMT= min SI to evoke MEP ≥ 0.05 mV in 3 of 6 trials	20; 10 per task block	15 (and 8 times during task)
Frazer, 2016	FCR	110, 130, 150, 170, 190, 210% AMT; AMT= min SI to evoke MEP ≥ 200μV in 5 of 10 trials during 2% MVC	NI	0
Fuijyama, 2017	FDI	90, 110, 130% RMT; RMT= min SI to evoke MEP ≥ 50μV in 3 of 5 trials	8	After priming tDCS and 0,20,40, and 24h
Baltar, 2018	TA	0.4 mV	20	Post tDCS- 0, post treadmill- 0,10,20,30,60,90
Frazer, 2019	BB	90, 110, 130, 150, 170, 190% AMT; AMT= min SI to evoke MEP ≥ 200μV in 5 of 10 trials	10	0
Hannah, 2019	APB	RMT; RMT= min SI to evoke MEP ≥ 0.5mV in 5 of 10 trials	30	5
Mooney, 2019	ECR	120% RMT; RMT= min SI to evoke MEP ≥ 50μV	24	0
Patel, 2019	TA	80-140% AMT; AMT= min SI to evoke MEP ≥ 0.4 mV in 50% of trials	8	10,30
Pourmajidian, 2020	FDI	RMT; RMT= min SI to evoke MEP ≥ 50μV in 5 of 10 trials	15	After priming: 3 blocks in 10 min; post a-tDCS: 3 in 10 min
Wrightson, 2020	VL	120% RMT	10	0
Karabanov, 2021	FDI	RMT; RMT= min SI to evoke MEP of 0.5mV	20	2,60

RMT= resting motor threshold; AMT= active motor threshold; NI= not indicated; MVC= maximum voluntary contraction; APB: abductor pollicis brevis; ADM: adductor digiti minimi; BB: biceps brachii; BR: brachioradialis; ECR(L): extensor carpi radialis (longus); FCR: flexor carpi radialis; FDI: first dorsal interosseus; FF: finger flexors; TA: tibialis anterior

3.4.3 Quality Assessment

The RoB 2 indicated that no studies were *low risk*, 14 studies had *some concerns*, and eight studies were *high risk* (Table 3.4). While every study indicated that participants were randomized either to treatment group or order, the ‘randomization’ domain had *some concerns* in all but one study (Baltar et al., 2018) because studies did not specify if the randomized allocation sequence was concealed until participants were assigned to interventions (Sterne et al., 2019). None of the studies detailed the type of randomization (e.g., simple, blocked) or how the allocation sequence was concealed (e.g., sealed opaque envelopes). The ‘effect of assignment to intervention’ domain had *some concerns* in 15 of the 22 studies because they did not indicate if there was missing data. There were *some concerns* in the ‘measurement of the outcome’ domain in 10 studies because assessors were not blinded to the intervention received or assessor blinding was not indicated. In all crossover trials but one (Wrightson et al., 2020), the ‘period and carryover effects’ were accounted for and detailed in the manuscript.

Table 3. 4. Quality assessment results.

	Randomization	Period and Carryover Effects	Effect of Assignment to Intervention	Effect of Adhering to Intervention	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Result	OVERALL RISK OF BIAS*
Thirugnanasambandam, 2011	⊖	○	○	○	○	○	○	⊖
Sohn, 2012	⊖	NA	⊖	○	○	○	○	⊖
Hendy, 2013	⊖	NA	○	○	○	○	○	⊖
Kim, 2013	⊖	NA	⊖	○	○	○	○	⊖
Lampropoulou, 2013	⊖	○	○	○	○	○	○	⊖
Miyaguchi, 2013	⊖	○	⊖	○	○	○	○	⊖
Bastani, 2014	⊖	○	○	○	○	⊖	○	⊖
Fujiyama, 2014	⊖	○	○	○	○	⊖	○	⊖
Sriraman, 2014	⊖	○	⊖	○	○	⊖	○	⊕
Amadi, 2015	⊖	○	⊖	○	○	⊖	○	⊕
Cabral, 2015	⊖	○	⊖	○	○	○	○	⊖
Christova, 2015	⊖	NA	⊖	○	○	⊖	○	⊕
Ambrus, 2016	⊖	○	⊖	○	○	⊖	○	⊕
Frazer, 2016	⊖	○	⊖	○	○	⊖	○	⊕
Baltar, 2018	○	○	⊖	○	○	○	○	⊖
Frazer, 2019	⊖	○	⊖	○	○	○	○	⊖
Hannah, 2019	⊖	NA	⊖	○	○	○	○	⊖
Mooney, 2019	⊖	○	○	○	○	○	○	⊖
Patel, 2019	⊖	○	⊖	○	○	⊖	○	⊕
Pourmajidian, 2020	⊖	○	○	○	○	⊖	○	⊖
Wrightson, 2020	⊖	⊖	⊖	○	○	○	○	⊕
Karabanov, 2021	⊖	○	⊖	○	○	⊖	○	⊕

○ Low risk ⊖ Some concerns ⊕ High risk

*Overall RoB Ratings: Low Risk must have ‘low risk’ ratings for all domains; Some Concerns has ‘some concerns’ rating in at least one domain; High Risk has ‘some concerns’ in multiple domains (Sterne et al., 2019)

3.4.4 Narrative Synthesis

Given the lack of numerically reported MEP change scores (i.e., only two of 22 studies) and the heterogeneity of study protocols, a meta-analysis was not conducted. The following synthesis of results pertains to the 14 studies with a ROB 2 rating of *some concerns* (i.e., excludes 'high risk' studies).

3.4.4.1 MEP Outcomes

Anodal tDCS was associated with increased MEP amplitude in 10 studies and had no effect in three studies. Both studies without motor practice observed an increase in MEP amplitude with anodal tDCS (Bastani et al., 2014; Sohn et al., 2012). However, Sohn et al. (2012) only observed this increase in participants' non-dominant hand and observed a decrease when tDCS and task practice targeted the dominant hand. Bastani et al. (2014) did not have a sham comparison but found that more intervals of anodal tDCS with longer breaks between intervals led to increased MEP amplitude. While Sohn et al. (2013) did not indicate the timing of MEP assessment post-tDCS, Bastani et al. (2014) measured MEPs up to two hours post-tDCS (Table 3.3).

When motor practice involved strength/endurance tasks, four of seven studies observed an increase in MEP amplitude with anodal tDCS (Hendy et al., 2013; Kim et al., 2013; Pourmajidian et al., 2020; Thirugnanasambandam et al., 2011). Hendy et al. (2013) found that nine sessions of anodal tDCS combined with wrist strengthening increased MEPs at 48-72 hours post-tDCS compared to anodal tDCS or strengthening alone. Kim et al. (2013) found that a single session of anodal tDCS combined with grip strengthening increased MEPs immediately following tDCS (compared to strengthening, sham tDCS, or anodal tDCS on their own) but did not measure MEPs at any later timepoints. Pourmajidian et al. (2020) used sham or cathodal tDCS priming prior to anodal tDCS combined with cycling and found that MEPs increased immediately following tDCS for the cathodal priming condition but did not measure MEPs at any later timepoints. Of the three strength/endurance protocols that did not observe a change in MEPs, one measured MEPs immediately following tDCS (Frazer et al., 2019) while the others measured MEPs up to 40 minutes (Lampropoulou et al., 2013) and 90 minutes (Baltar et al., 2018) following intervention.

Both studies with speed/accuracy tasks had increased MEPs (Fujiyama et al., 2017; Mooney et al., 2019). Fujiyama et al.'s (2017) protocol involved priming tDCS (i.e., cathodal or sham) prior to anodal tDCS with task practice immediately prior to, during, and after the anodal tDCS with MEP measurement up to 24 hours post-tDCS. In contrast, Mooney et al.'s (2019) protocol involved task practice during anodal (or sham) tDCS and only reassessed MEPs immediately post-tDCS.

While both studies with repetitive movement tasks showed an increase in MEPs with anodal tDCS, the treatment conditions differed considerably and MEPs were only measured immediately following tDCS (Cabral et al., 2015; Miyaguchi et al., 2013). Miyaguchi et al. (2013) observed an increase in MEPs with anodal tDCS alone compared to active repetitive finger movement on its own or the active movement in combination with tDCS. They also found that passive repetitive movement with and without tDCS increased MEPs more than the active repetitive movements with and without tDCS (Miyaguchi et al., 2013). Cabral et al. (2015) specifically studied the impact of the timing of an active thumb movement relative to tDCS and found that tDCS prior to the movement was the only condition that increased MEPs.

Cathodal tDCS decreased MEP amplitude in the only study without task practice (Sohn et al., 2012). Of the three strength/endurance protocols that involved cathodal tDCS only one had an effect on MEPs. Thirugnanasambandam et al. (2011) observed a decreased in MEP amplitude immediately following the 'no practice' and 'practice after cathodal tDCS' conditions. Aside from being used as primer for anodal tDCS by Fujiyama et al. (2017), cathodal tDCS was not evaluated in any other task type.

Hannah et al. (2019) evaluated a non-traditional electrode configuration with the anode and cathode centred around the primary motor cortex. They found that an anteroposterior current had no effect on MEPs and a posteroanterior current decreased MEPs immediately following tDCS (Hannah et al., 2019).

3.4.4.2 Motor Performance

Both studies without motor practice had improved motor performance and corresponding increases in MEP amplitude after anodal tDCS (Bastani & Jaberzadeh, 2014; Sohn et al., 2012).

However, Sohn et al. (2014) only observed these coinciding improvements in the non-dominant hand. Of the 12 studies with motor practice, only five evaluated motor performance (Frazer et al., 2019; Fujiyama et al., 2017; Hannah et al., 2019; Hendy et al., 2013; Mooney et al., 2019). For strength/endurance tasks, Hendy et al. (2013) observed equal increases in strength at 48-72 hours post-tDCS between the anodal and sham tDCS groups with increased MEPs only after anodal tDCS. In contrast, Frazer et al., (2019) observed equal decreases in strength and no change in MEPs immediately following tDCS.

For protocols involving speed/accuracy tasks, the interventions differed considerably. While Fujiyama et al.'s (2017) found that cathodal priming prior to anodal tDCS increased MEP amplitude (compared to sham priming), both treatment groups experienced improvements in motor performance up to 40 minutes following intervention but not at 24 hours post-tDCS. Mooney et al. (2013) only evaluated MEPs immediately after tDCS and found that anodal tDCS increased in MEPs. However, they observed increased performance in both the anodal and sham tDCS conditions immediately following tDCS and at seven days post-tDCS (Mooney et al., 2019). The effects of Hannah et al.'s (2019) non-traditional electrode montages were only evaluated immediately after tDCS with MEP and motor results differing; no change in MEPs coincided with a decrease in motor performance for the anteroposterior montage and a decrease in MEPs coincided with no change in motor performance for the posteroanterior montage.

3.5 Discussion

This systematic review summarized a decade of unilateral M1-targeted tDCS studies involving motor behaviour in healthy individuals where MEP outcomes were evaluated. While most studies in this review concluded that anodal tDCS increased MEP amplitude, there were also several studies with and without motor practice where tDCS had no impact on MEPs. Across all studies involving motor practice, practice timing and type differed, and changes in MEPs were not always accompanied by changes in motor performance. Together these studies highlight the challenges of using MEPs as an outcome in tDCS research involving motor behaviour, the complexity of tDCS study design when motor behaviour is involved, and the intricacies of interpreting changes in motor performance. Finally, our quality assessment identified areas where the methodological quality of future tDCS studies can be improved.

3.5.1 MEPs as a neural outcome

While MEP amplitude is a widely accepted measure of corticospinal excitability (Horvath et al., 2015; Sivaramakrishnan & Madhavan, 2020), its utility in measuring the impact of tDCS in protocols that involve motor practice may be limited by interference from motor activity (Horvath et al., 2014). This finding was supported by several studies in the narrative synthesis that did not observe changes in MEPs post-tDCS (Baltar et al., 2018; Frazer et al., 2019; Lampropoulou & Nowicky, 2013) and was further supported by the studies that observed greater change in the tDCS-only condition compared to conditions that combined tDCS and motor practice (Miyaguchi et al., 2013; Thirugnanasambandam et al., 2011). However, there were also studies that observed a change in MEPs when tDCS and motor practice were combined (Cabral et al., 2015; Fujiyama et al., 2017; Hendy & Kidgell, 2013; Kim & Ko, 2013; Mooney et al., 2019; Pourmajidian et al., 2020), indicating that additional factors influence MEPs.

MEP amplitude is dependent upon the net excitatory and inhibitory input on spinal motor neurons and does not differentiate between the relative contributions to M1 activation, such as feedback from the cerebellum, cognitive input from the prefrontal cortex, (Bestmann & Krakauer, 2015; Cinelli et al., 2019), or tDCS-induced activation. Functional magnetic resonance imaging, in contrast, is more conducive to identifying the various intracortical (e.g., cognitive, perceptual, and motor) contributions to motor behaviour (Albouy et al., 2012; Tseng et al., 2020) and, in doing so, may provide greater insight to their relative activity at the various stages of motor learning. Additionally, the wide range of factors that influence MEPs can lead to substantial inter- and intra-individual variability in MEP measurement (Cinelli et al., 2019; Horvath et al., 2015; Sivaramakrishnan & Madhavan, 2020) and has the potential to obscure tDCS-induced changes in corticospinal excitability if variability is not appropriately accounted for in the assessment protocol. While researchers may attempt to limit variability by controlling for study session time of day, restricting caffeine or alcohol intake, and excluding smokers (Li et al., 2015), these details were not consistently addressed by studies in this review. Other recommendations for reducing variability in MEP measurement are averaging a minimum of 20 MEPs at each timepoint (Li et al., 2015; Sivaramakrishnan & Madhavan, 2020) and using a low-level of voluntary muscle contraction during MEP measurement (i.e., active motor threshold) (Darling et al., 2006; Sivaramakrishnan & Madhavan, 2020). However, studies in this review

measured a mean of 15.37 MEPs per timepoint with only 6 of 22 studies using active motor thresholds. Thus, trial-to-trial variability may have obscured tDCS-induced changes in MEPs. Additionally, most studies in this review only measured MEPs immediately post-tDCS which does not provide sufficient information about the prolonged impact of tDCS on MEPs and does little to establish whether change in MEP amplitude is an appropriate indication of lasting neural change.

3.5.2 tDCS study design

Study design is particularly important when developing a tDCS protocol involving motor practice. Crossover studies are useful because each participant acts as their own control and the required sample size is less than parallel group studies (Krogh et al., 2019). However, crossover designs may have increased dropouts and carryover effects depending on the time required for each study condition and the time between each condition (Krogh et al., 2019). The crossover studies in this review limited the potential for attrition related to time commitment by using a single practice session per treatment condition, and all but one study (Wrightson et al., 2020) clearly delineated an appropriate amount of time between treatment conditions to eliminate carryover effects. An additional but crucial consideration in crossover studies is the reporting of results, as the data required to conduct a meta-analysis is frequently omitted from crossover study publications (Krogh et al., 2019). Unfortunately, most studies in this review did not provide numerical data (i.e., mean and standard deviation) for post-intervention MEPs or MEP change scores, opting to present data graphically instead, which was a barrier to meta-analysis.

When designing tDCS studies that involve motor practice, a systematic approach should be used to evaluate the impact of different treatment variables on MEPs. Most studies in this review used the same task and timing of practice across treatment groups to compare different types of stimulation (e.g., anodal, cathodal, sham tDCS). Because none of the studies manipulated tDCS intensity or duration within a single protocol, the combined impact of tDCS dose and motor practice on MEPs remains unknown. While the motor practice condition was typically constant within each study, two studies used task variations to evaluate their impact on MEPs. Miyaguchi et al. (2013) used combinations of anodal tDCS and/or active/passive finger movement and found that both passive and active movement alone decreased MEP amplitude, and that active

abduction in combination with tDCS interfered with MEPs but passive movement in combination with tDCS did not. Although Baltar et al. (2018) used a similar approach to evaluate tDCS in combination with high/low intensity treadmill training, their results differed with none of the treatment conditions having an impact on MEP amplitude. Together these two studies demonstrate how task type and the muscles involved can have vastly different effects on MEPs.

3.5.3 Interpreting motor outcomes

This review confirms that MEP and motor changes are not necessarily linked to one another, with few studies detecting change in both MEPs and motor outcome (Bastani & Jaberzadeh, 2014; Christova et al., 2015; Frazer et al., 2016; Fujiyama et al., 2017; Sohn et al., 2012), and endorses previous findings that motor learning is more likely over the course of multiple tDCS sessions (Hashemirad et al., 2016). The limited impact of a single tDCS session on motor behaviour in healthy individuals may be due to participants' baseline proficiency with simple motor tasks (Cuypers et al., 2013; Hashemirad et al., 2016; Kimura & Nakano, 2019; Seidel & Ragert, 2019; Xiao et al., 2020; Zhou et al., 2018) or the need for multiple practice sessions to consolidate learning for more complex tasks (Dayan & Cohen, 2011; Karni et al., 1998). In this review, Sohn et al. (2012) highlighted the impact of baseline task proficiency on tDCS study outcomes with simultaneous induced changes in MEPs and motor performance in the non-dominant hand but not in the dominant hand.

The studies in this review that involved less functional tasks (i.e., isolated movements or isometric contractions at a single joint) did not observe improvements in motor performance (Hannah et al., 2019; Karabanov et al., 2021; Mooney et al., 2019; Patel & Madhavan, 2019; Wrightson et al., 2020). The simplicity of these tasks may have meant that participants had a baseline level of task proficiency that limited the potential for further tDCS-induced improvement. Complex motor tasks involve the coordination of a greater number of muscle groups (Flament et al., 1993; Tseng et al., 2020) and have increased cognitive demands (Cinelli et al., 2019; Stuhr et al., 2018). Because improved performance in these types of tasks often occurs incrementally over multiple practice sessions, the motor learning benefits of an intervention involving a more functional or complex motor skill can be overlooked if the treatment protocol only involves one practice session (Karni et al., 1998; Schmidt & Lee, 2014)

which limits the applicability of these studies to people with neurological conditions who frequently turn to new rehabilitation technologies with the goal of enhancing motor learning. Additionally, tDCS-induced improvements in strength and/or endurance outcomes occur more often in whole body tasks rather than tasks isolated to a single joint (Alix-Fages et al., 2019).

The motor learning benefits of an intervention can also be overlooked when motor performance is only re-evaluated immediately following motor practice due to the impact of mental and physical fatigue on performance (Kimura & Nakano, 2019; Schmidt & Lee, 2014). Providing a period of rest between practice and reassessment of motor outcomes eliminates the noise associated with fatigue and allows for a more accurate measure of change (Kimura & Nakano, 2019; Schmidt & Lee, 2014) and was supported by improved motor outcomes in studies that had motor assessments ≥ 40 minutes post-tDCS (Christova et al., 2015; Fujiyama et al., 2017; Hendy & Kidgell, 2013; Sriraman et al., 2014).

3.5.4 Risk of bias

The RoB 2 ratings indicate that study results should be interpreted with caution, particularly in the 'no motor' practice and 'speed/accuracy task' subgroups where most studies were *high risk*. The quality of future tDCS studies can be improved by addressing the following concerns identified in the risk of bias assessment: 1) detail the randomization process such as the randomization schedule (e.g., simple, blocked), the people with access to the randomization schedule (especially whether the person obtaining consent), how participants are allocated to treatment group (e.g., sealed envelopes), and when the study team members and/or participant become aware of a participant's treatment allocation (e.g., before/after informed consent); 2) specify which members of the research team are blinded (e.g., assessors, staff administering the treatment protocol); and 3) indicate whether data is available at all timepoints for each participant (Chan et al., 2013; Sterne et al., 2019).

3.5.5 Limitations

Results synthesis was limited by the heterogeneity of study protocols. While we attempted to minimize heterogeneity by grouping studies according to the presence and/or absence of motor practice and dividing the motor practice studies into subgroups based on the type of motor

practice, substantial differences within these subgroups (e.g., upper versus lower extremity tasks) may have obscured other results.

3.6 Conclusion

The studies in this review had vastly different treatment protocols focusing on a variety of motor tasks, practice timing, and tDCS parameters. While movement interferes with tDCS-induced MEPs, this systematic review suggests that unilateral M1-targeted anodal tDCS in combination with motor practice in healthy individuals tends to temporarily increase MEP amplitude after a single treatment session. However, few studies evaluated MEP amplitude beyond 30 minutes post-tDCS. The studies in this review confirm that changes in MEP amplitude are not necessarily accompanied by similar changes in motor performance, suggesting that MEPs are not the optimal outcome measure for tDCS studies evaluating the neural changes associated with motor learning and performance. Because the goal of M1-targeted tDCS is usually to improve motor outcomes and motor learning is more likely to occur with an increased practice dose, future tDCS treatment protocols in healthy individuals should involve multiple treatment sessions, more complex tasks, follow-up assessment of motor performance and neural outcomes beyond the immediate post-tDCS period, and neural outcomes that differentiate between the relative intracortical contributions to motor output.

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Chapter 4

Evaluating the feasibility of transcranial direct current stimulation as an adjunct to inpatient physiotherapy in pediatric acquired brain injury: A randomised feasibility trial

At the time of thesis submission, this chapter was under peer review for separate publication.

4 Evaluating transcranial direct current stimulation as an adjunct to inpatient physiotherapy in pediatric acquired brain injury: A randomised feasibility trial

4.1 Abstract

Background: Children and youth with moderate to severe acquired brain injury (ABI) make substantial improvements in gross motor function in the first six months after their injury. However, they also experience plateaus in recovery that affect their long-term physical function. To improve upon motor outcomes, rehabilitation technologies are frequently explored as adjuncts to traditional physiotherapy intervention. When transcranial direct current stimulation (tDCS) is paired with physiotherapy, children with cerebral palsy have experienced improved motor outcomes. However, the use of tDCS to promote motor learning has not been evaluated in the early stages of childhood onset ABI. Thus, we evaluated the feasibility of tDCS as an adjunct to inpatient physiotherapy in children and youth with ABI.

Methods: This randomised feasibility trial was conducted in children (5-18 years) with moderate to severe ABI. Participants were allocated (dynamic blocked randomization), to receive either 20 minutes of active or sham anodal tDCS immediately prior to 16 of their existing inpatient physiotherapy sessions. Participants, physiotherapists, assessors, and primary investigators were blinded to treatment allocation. The following feasibility outcomes were evaluated against *a priori* targets: eligibility, recruitment, retention, tolerance, preliminary treatment effect.

Results: Of 232 children admitted over 21 months, six children were eligible (2.6%) and four were recruited (66.7%). One participant completed the entire study protocol, two were withdrawn for unrelated changes in medical stability (after five and seven study sessions, respectively), and one did not commence the study due to COVID-19 restrictions. Three participants were allocated to sham tDCS and one was allocated to active tDCS. Pre/post tDCS session tracking indicated that participants tolerated active/sham tDCS with sub-electrode itchiness being the primary transient side effect in both treatment groups. Tracking symptoms pre/post tDCS allowed researchers to differentiate between tDCS side effects and ABI symptoms.

Conclusions: While the study lacked feasibility from eligibility and retention perspectives, study procedures (e.g., assessment, treatment, side effect tracking, physiotherapy session documentation) were successfully implemented and should be applied in guide future pediatric tDCS studies.

4.2 Background

Children with moderate to severe acquired brain injury (ABI) participate in inpatient physiotherapy during the subacute stage of recovery to relearn and refine the gross motor skills affected by their injury (Dumas et al., 2004a; Ryan et al., 2022). Depending on injury location, children can experience altered motor control, strength, balance, endurance, and coordination, leading to varying levels of mobility challenges from complete dependence for care to advanced gross motor deficits (Kelly et al., 2015; Popernack et al., 2015; Ryan et al., 2022). Motor function involves multiple complex networks of neural pathways within the brain, with the primary motor cortices being responsible for voluntary movement (Nishiyori et al., 2016; Nudo, 2013).

Motor learning, or 'relearning' in neurorehabilitation settings, refers to the acquisition and retention of a motor skill achieved through practice or experience (Nudo, 2013). The functional changes associated with motor learning are thought to be accompanied by cortical reorganization within the brain (Nishiyori et al., 2016; Nudo, 2013). Physiotherapists (PTs) aim to promote motor learning by using specific, individualized therapeutic actions based on child- and task-specific factors called motor learning strategies (MLS) that involve verbalizations (e.g., instructions, feedback), actions (e.g., demonstration, physical guidance), or treatment session organization (e.g., whole skill practice, random order practice) (Levac et al., 2011; Ryan et al., 2019).

While children with ABI experience substantial improvements in gross motor function with inpatient rehabilitation (Dumas et al., 2004a; Ryan et al., 2022; Tailor et al., 2013), their recovery tends to plateau toward the end of the subacute stage of recovery, and long-term motor deficits may persist (Haley et al., 2003; Kuhtz-Buschbeck et al., 2003). As such, novel treatment approaches, often with limited evidence, may be implemented on their own or in combination

with physiotherapy to enhance recovery. However, without a direct evaluative comparison between traditional and novel approaches, it is impossible to determine whether the novel approach further improves motor skill recovery.

Transcranial direct current stimulation (tDCS) is a safe form of non-invasive brain stimulation that facilitates adaptive patterns of neural activity and suppresses maladaptive patterns, and can be paired with physiotherapy to try to enhance the gains associated with motor skill practice (Stagg & Nitsche, 2011). tDCS temporarily modulates cortical excitability by delivering small subthreshold currents to targeted areas of the brain (e.g., the primary motor cortex when the individual has motor learning goals (Stagg & Nitsche, 2011). The effects of tDCS last beyond the stimulus duration with evidence of approximately 90 minutes of altered cortical excitability that is thought to prime the brain for the formation of new cortical networks when accompanied by motor skill practice (Stagg & Nitsche, 2011).

There are many unanswered questions regarding tDCS feasibility and efficacy in pediatric clinical populations (Palm et al., 2016) with most research conducted in children with cerebral palsy (CP) (Elbanna et al., 2019; Saleem et al., 2019a). Preliminary motor learning outcomes in tDCS studies involving gait and balance training in children with CP have been positive (Grecco et al., 2014; Grecco et al., 2015), but had not incorporated aspects of individualized physiotherapy intervention in their protocol until Salazar Fajardo et al. (2022) demonstrated that the combination of tDCS and an individualized physiotherapy program led to greater improvements in gross motor function than physiotherapy alone. With the increased potential for neural recovery in the early stages of a neurological condition, there is demand for more tDCS studies to be conducted in the subacute stage of ABI (Bornheim et al., 2020; Ulam et al., 2015), an area of study that has yet to be explored in pediatric rehabilitation. Given that the motor deficits caused by ABI are detrimental to children's development, mobility, and participation in physical activity, and the enhanced ability to promote motor recovery during the subacute stage (Anaby et al., 2012; Fragala et al., 2002; Galvin et al., 2010b; Haley et al., 2003), there is a need to determine if tDCS can be used to augment the motor outcomes associated with traditional inpatient physiotherapy for children with ABI. However, the feasibility of incorporating tDCS into an existing intensive ABI rehabilitation program needs to be evaluated before its effectiveness can be determined.

4.3 Aim

The primary objective of this study was to evaluate the feasibility of using tDCS as an adjunct to an existing inpatient physiotherapy in children and youth with ABI. The secondary objective was to document the MLS content of inpatient physiotherapy for children with subacute ABI as a preliminary way of understanding how PTs promote motor learning.

4.4 Methods

4.4.1 Study design

Feasibility studies are small scale studies that evaluate study procedure before determining whether the protocol can or should be used in a larger scale investigation with process indicators often addressing eligibility, recruitment, retention, and adherence, and scientific indicators addressing treatment safety, dose, and an estimation of treatment effect (Lancaster et al., 2004; Thabane et al., 2010). This randomised feasibility trial (Eldridge et al., 2016; Lancaster et al., 2004) (ClinicalTrials.gov Identifier: NCT04422886) involved children/youth with moderate to severe ABI admitted as inpatients for ABI rehabilitation at Holland Bloorview Kids Rehabilitation Hospital, Toronto, Canada. Using a parallel group design, participants received either active or sham (control) anodal tDCS intervention immediately prior to their existing inpatient physiotherapy treatment sessions for up to 16 sessions over four weeks. This study protocol was approved by research ethics boards at Holland Bloorview Kids Rehabilitation Hospital and the University of Toronto. Written informed consent was obtained from participants (or participant assent with parent consent when participants did not demonstrate the capacity to provide consent).

4.4.2 Participants

Study inclusion criteria were:

- moderate to severe ABI confirmed with diagnostic imaging,
- 5-18 years of age,
- admitted for first intensive inpatient bout of ABI rehabilitation (i.e., subacute stage of recovery) at Holland Bloorview,

- medically stable,
- receiving active motor learning-based physiotherapy to address ABI-specific gross motor goals,
- length of stay permits at least three weeks of study intervention,
- tolerates 45 minutes of physiotherapy,
- sits independently at the edge of the bed for 5 seconds,
- cognitively and behaviorally capable of completing standardized physiotherapy assessment, and
- accurately communicates discomfort (verbally or non-verbally).

Study exclusion criteria were:

- pre-existing seizure disorder (i.e., prior to ABI),
- anti-seizure medication use if seizure(s) occurred during acute care admission,
- brain tumour,
- neurodegenerative diagnosis,
- metal implants in the head,
- cranial bone flap removed,
- stitches/staples on the head,
- wounds or unhealed incisions at tDCS electrode sites,
- experience with tDCS (as this could affect participant blinding),
- diagnosed with another neurological disorder(s) affecting gross motor function (e.g., cerebral palsy, spinal cord injury),
- lower extremity weight bearing restrictions at the time of study enrollment, or
- physiotherapy sessions with ≥ 15 minutes of non-motor learning content (e.g., behavioural redirection, passive range of motion).

In 2017-2018 (two years prior to the launch of the tDCS study), 338 children were admitted for ABI rehabilitation at this hospital, 223 of whom were 5-18 years of age. Based on a recent unrelated feasibility study with similar primary eligibility criteria in our inpatient ABI program involving physiotherapy (Wright et al., 2018), we estimated that up to 20% of admissions would be eligible for the tDCS feasibility study and 50% of eligible children would ultimately enroll in

the study (i.e., 22 children per year). We planned to enroll up to 30 participants over a 24-month period, a pragmatic determination consistent with the design parameters for feasibility studies as they have no specific sample size (power) requirements (Thabane et al., 2010).

4.4.3 Recruitment

The first author screened inpatient program admissions on a weekly basis. Any child who met the age and preliminary diagnostic criteria (i.e., moderate to severe ABI unrelated to brain tumour or epilepsy) underwent further screening. The child's clinical PT was consulted to confirm physiotherapy-related eligibility criteria. Children who met these criteria underwent medical screening by the study physician who consulted with the child's physician in the program. Eligible children and their legal guardian(s) were then approached by their clinical PT to determine if they were interested in learning about the study. The study research manager met with families to explain the study and obtain written informed consent if they were interested in participating.

4.4.4 Randomization and blinding

After baseline assessment, an independent research assistant (RA) assigned each child to 'sham' or 'active' tDCS groups using a computer-generated blocked randomization schedule developed by the RA. Randomization was stratified by the child's primary method of mobility (i.e., ambulation or wheelchair) to ensure similar levels of baseline physical ability between treatment groups. Only the independent RA was aware of the randomization schedule. The two study team members who administered tDCS and the independent RA were aware of each participant's treatment allocation, while participants, assessing/treating PTs, and other study investigators were blinded.

4.4.5 Intervention

4.4.5.1 tDCS

Study treatment sessions were scheduled by the participant's treating PT in their weekly inpatient rehabilitation schedule. All treatment sessions except the first were 90 minutes in duration, with the first 30 minutes allocated to tDCS and the final 60 minutes allocated to

physiotherapy. The first study treatment session was 120 minutes with 60 minutes allocated to tDCS measurements and setup. Depending on allocation, a trained research assistant provided either 20 minutes of active or sham anodal tDCS (Soterix 1×1 LTE tDCS Device Limited Total Energy tDCS For Susceptible Subjects) immediately prior to each physiotherapy sessions for up to 16 sessions. While the goal was to complete study treatment over a four-week period, treatment was permitted to take up to six weeks to make up for missed sessions related to illness or medical appointments.

Participants were given the option of sitting in bed or their wheelchair (i.e., a supported sitting position) on the inpatient unit during tDCS intervention. Using a dual-electrode montage and the 10-20 system for electrode placement, 5x5cm electrodes were positioned over Cz (anode) to target the lower extremity region of bilateral primary motor cortices and the central supraorbital (Fpz) area of the forehead (cathode) (Seeck et al., 2017). tDCS current intensities typically range from 1.0 to 2.0 mA (Buchanan et al., 2021; Stagg & Nitsche, 2011). The first tDCS session began with tDCS intensity ramping up to 1.0 mA of stimulation over the first minute for both the sham and active tDCS groups. The active tDCS group's stimulation then continued at 1.0 mA for the remaining 19 minutes while the sham tDCS ramped down and turned off with the electrodes remaining in place for the remainder of the session (Ambrus et al., 2012; Kessler et al., 2012). The sham group continued to receive 1.0 mA for the first minute for all sessions while the tDCS intensity for active group was titrated upward by 0.5mA per session to a maximum of 2.0 mA depending on participant tolerance.

tDCS causes a tingling or itching sensation that fades over time (Kessler et al., 2012). This sensory adaptation in combination with sham treatment protocol was expected to prevent participants from accurately determining whether they were receiving active or sham tDCS (Ambrus et al., 2012; Kessler et al., 2012). To promote participant blinding, both treatment groups were told they may not feel the stimulation throughout the entire treatment, as their bodies adapted to the sensation.

4.4.5.2 Physiotherapy

The physiotherapy intervention immediately following tDCS involved the typical intervention that children receive in this inpatient ABI program consisting of four to five sessions of motor

learning-based physiotherapy per week, provided by a combination of PT and/or PT assistant, depending on the child's goals and gross motor ability. Physiotherapy sessions are intended to promote motor learning by focusing on functional tasks related to the child's individualized functional goals. Therapists individualize the intervention by adapting the tasks, instructions, feedback, and challenge based on the child's needs. In the study, therapists were free to choose the tasks and MLS they felt were appropriate for the child. However, to ensure all therapists had the same baseline level of MLS knowledge, they completed the MLS Online Training Program (Ryan, 2017) prior to the study. Following each study session, the therapist documented the functional tasks completed, along with task duration and focus (i.e., selected primary and secondary foci from a menu of common physiotherapy intervention foci: stability/balance, coordination, strength, motor skills, fitness/endurance, education, practice outside of therapy, other).

4.4.6 Outcomes

Eligibility, recruitment, retention, adherence, tolerance, and treatment outcomes were used to evaluate the feasibility of the study protocol (Table 4.1). Screening data were collected to determine the proportion of eligible admissions and document reasons for exclusion. Because anodal tDCS increases cortical excitability for up to 90 minutes after receiving tDCS and motor practice should ideally occur during this period of enhanced excitability (Stagg & Nitsche, 2011), the start/stop times and duration of the tDCS and physiotherapy sessions were documented.

Table 4. 1. Study feasibility outcomes.

TYPE	INDICATOR	TARGET	DESCRIPTION
Eligibility	Eligibility rate	20%	Children/youth admitted for inpatient ABI rehabilitation who meet eligibility criteria
	Eligibility criteria	n/a	Diagnosis, age, and reasons for exclusion for all admissions
Recruitment	Recruitment rate	70%	Eligible admissions who enroll
Retention	Treatment sessions completed	75%	Completed ≥ 12 treatment sessions
Adherence	Time between tDCS and physiotherapy	< 15 minutes	Mean time between tDCS completion and physiotherapy commencement (to ensure motor practice occurs during period of enhanced cortical excitability)
	Session duration	n/a	Mean time (in minutes) of tDCS sessions and physiotherapy sessions
	Completion of Reassessment 1	95%	Completed ≤ 7 days after final treatment session
	Completion of Reassessment 2	80%	Completed three months (+/- 2 weeks) after treatment protocol
Scientific	tDCS tolerance	80%	Tolerated ≥ 1.0 mA for ≥ 10 minutes of every tDCS session
		n/a	Subjective report of tDCS experience
	tDCS side effects	n/a	Pre/post session report rating of symptoms/side effects using five-point scale
	Gross motor change	5 points	GMFM-88 mean change score difference (active > sham)
	Goal change score	2 points	COPM mean change score difference (active > sham)
	Physiotherapy session content	n/a	Intervention logs that document task order, focus, duration
			MLSRI-22 rating of two video-recorded sessions

GMFM-88: Gross Motor Function Measure (Russell et al., 2021); COPM: Canadian Occupational Performance Measure (Law et al., 2014); MLSRI-22: Motor Learning Strategies Rating Instrument (Levac et al., 2011; Spivak et al., 2021)

To evaluate tDCS tolerance, participant symptoms were tracked before and after each tDCS session using study-specific standardized reporting forms (Appendices B and C). Before each session, participants were asked if they had experienced any new health concerns, seizures, syncope, or skin irritation/redness at electrodes sites, fatigue, headaches, upset stomach, or dizziness since the previous tDCS session. If they were currently experiencing fatigue,

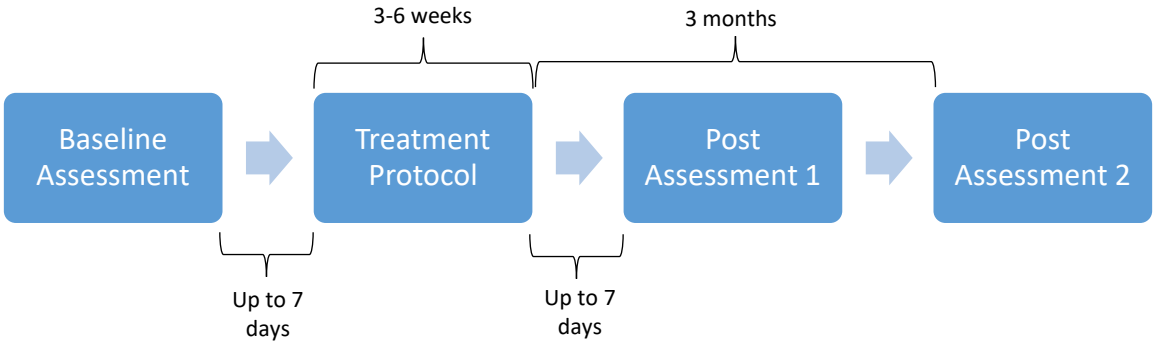
headaches, upset stomach, or dizziness, participants were then asked to rate the extent of each symptom on a five-point rating scale (e.g., 0 = 'not at all', 1 = 'a little bit', 2 = 'a bit more', 3 = 'even more', 4 = 'a whole lot') that was accompanied by images of facial expressions for each rating.

After each tDCS session (just prior to physiotherapy), participants used the same scale to rate fatigue, upset stomach, headache, dizziness again. They also rated additional side effects (itchy, tingly, hot, weird taste in mouth) that were unlikely to persist beyond the tDCS session and were therefore not part of the pre-session ratings. REB-approved monitoring rules required that if participants rated headache, upset stomach, or dizziness as "4" post-tDCS, the research assistant would notify their ABI nurse, contact the principal investigators, and complete an adverse event form. If a seizure or syncope occurred at any time during study participation, the entire study would have been put on hold until the participant was evaluated by their ABI physician and the adverse event was reviewed by the feasibility study DSMB. There was also an open comment section on the post-session tDCS tolerance form to capture additional participant-specific challenges encountered during the tDCS treatment (e.g., decreasing tDCS current due to persistent symptoms, difficulties rating symptoms, behavioural concerns).

Overall tDCS tolerance was evaluated using a modified version of Garvey et al.'s (2001) pediatric non-invasive brain stimulation questionnaire where, at baseline, participants identified one most enjoyable activity and one least enjoyable activity that they had experienced in the last month. They then separately ordered seven pre-determined activities from most enjoyable to least enjoyable, and their self-identified most and least enjoyable activities were added at the beginning and end of the ordered list of pre-determined activities (Garvey et al., 2001). At the post-intervention assessment, participants were asked to rate their experience with tDCS relative to their pre-intervention list (Garvey et al., 2001). The questionnaire was modified by having participants answer the following questions: 1) Would you say yes to having tDCS again? 2) Would you tell other kids to try tDCS? 3) What did you like best about the tDCS? 4) Do you think you received a lot or a little bit of tDCS? 5) How sure are you of your answer above? 6) Did you have any side effects?

Physiotherapy assessments were conducted by a blinded independent PT without access to previous assessment results and occurred according to the timeline outlined in Figure 4.1. The co-primary outcome measures were the Gross Motor Function Measure (GMFM-88) (Russell et al., 2021), an assessment of gross motor function, and Canadian Occupational Performance Measure (COPM) (Law et al., 2014), where the child and/or parent/guardian set three to five gross motor goals pre-randomization. Secondary outcome measures were the ABI-Challenge Assessment (ABI-CA) (an assessment of advanced gross motor skills) (Ibey et al., 2010), 10m fastest walk test (10mFWT), and parent-reported 'Daily Activity' and 'Mobility' domains of the Pediatric Evaluation of Disability Inventory (Haley et al., 2011). Goal Attainment Scaling (Kiresuk et al., 2014) goals for the four-week study duration were created and evaluated by the child's treating PT. In addition to documenting physiotherapy session content, two physiotherapy sessions were video recorded for each study participant and the MLS content was measured using the Motor Learning Strategies Rating Instrument (MLSRI-22) (Spivak et al., 2021).

Figure 4. 1. Assessment timeline.



4.4.7 Changes to trial design

Study process was monitored, and iterative adaptations made to the protocol to address challenges encountered. Initially, eligibility was restricted to children with cerebral stroke or traumatic brain injury (TBI) in the preceding six months. Due to low eligibility rates in the first nine months of the study, we expanded the inclusion criteria to any child with an ABI participating in their first bout of inpatient rehabilitation. We also eliminated the exclusion

criterion that prevented children who could balance greater than 5s on their most affected leg from enrolling.

After the first participant, adaptations were also made to include baseline tracking of ABI symptoms to differentiate between ABI symptoms and tDCS side effects. To this end, the study team introduced a modified version of the Safety Monitoring Uniform Reporting Form (SMURF) (Coates et al., 2018) to document the pattern, severity, duration, and factors contributing to any symptoms the participant experienced in the period leading up to the study treatment and thus provide a point of comparison for the study investigators and the DSMB when reviewing an adverse event. Symptom tracking before each session was also updated. Initially, any pre-session symptoms were only documented as present or absent. However, to better track symptom changes pre/post tDCS, the five-point rating scale used post-tDCS was implemented pre-tDCS to rate the extent of fatigue, headache, upset stomach, or dizziness.

4.4.8 Data analyses

Feasibility study analyses should be descriptive and address specific objectives (Lancaster et al., 2004). Accordingly, descriptive statistics were used to describe group characteristics and summarize the feasibility indicators outlined in Table 4.1. In feasibility studies, feasibility indicators along with the primary outcome measure mean change scores are used to determine if next stage research is warranted (Eldridge et al., 2016; Thabane et al., 2010). If warranted, comparative magnitude change scores and standard deviation of change for the primary outcome measures are of particular interest when calculating the sample size for a next stage randomised control trial (Eldridge et al., 2016; Thabane et al., 2010).

Each gross motor outcome was reviewed to determine its appropriateness. To examine physiotherapy session content, data from participants were pooled. Descriptive statistics were used to summarize task duration and focus. The plan was to visually compare MLSRI-22 individual item scores between weeks one and four for each participant, followed by a graphic summary of MLSRI-22 item scores for weeks one and four, respectively.

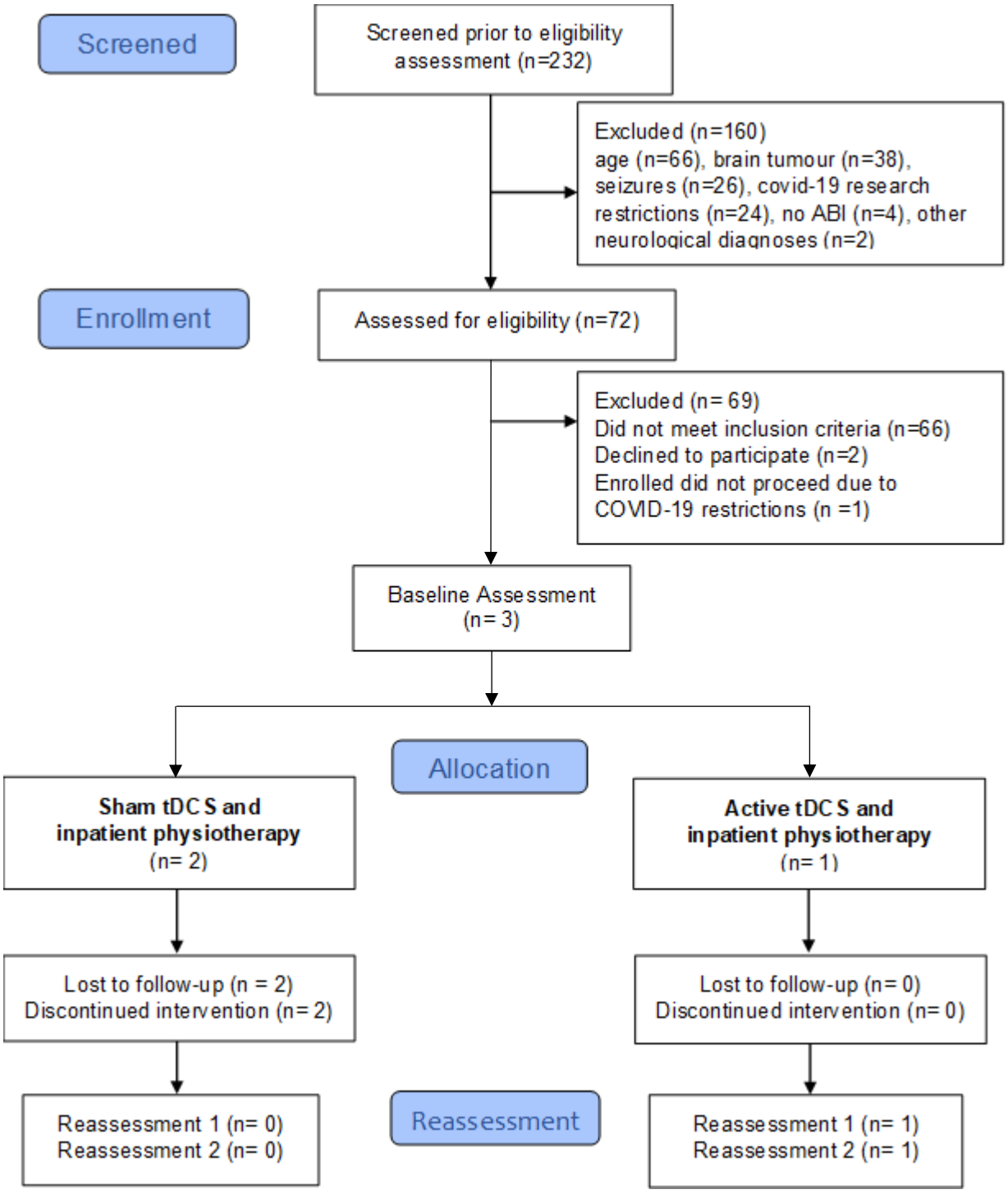
4.5 Results

Of 232 children admitted to the inpatient ABI program over 21 months (Table 4.2), six were eligible for the study and four (two with traumatic brain injury, two with stroke) enrolled (Figure 4.2). Three participants were primary wheelchair users and one participant was ambulatory. One participant (wheelchair user) was allocated to the active tDCS group and three participants (two wheelchair users, one ambulatory) were allocated to receive sham tDCS. One participant completed the entire study protocol, two were withdrawn from the study after five and eight sessions, respectively, for unrelated medical reasons (as determined by the DSMB in collaboration with the participant's ABI physician) that required readmission to acute care, and one (the ambulatory participant) was unable to commence the baseline assessment due to early COVID-19 restrictions on research at our hospital (i.e., clinical trials were put on hold for six months). During this research hold, admissions were not screened for eligibility. Once research activities resumed, the age and diagnosis of admissions during that six-month period were retroactively obtained but further clinician screening was not completed due to the likelihood for inaccurate recall post-discharge. Finally, given the low eligibility and retention rates, we discontinued study enrollment three months earlier than the planned 24 months.

Table 4. 2. Program admissions between January 1, 2020 and September 30, 2021 by age and diagnosis.

	0-4 years	**5-8 years**	**9-12 years**	**13+ years**	**TOTAL**
Stroke	12	4	6	20	**42**
Traumatic brain injury	16	7	8	22	**53**
Brain Tumour	12	10	15	13	**50**
Neuroinflammatory	2	6	6	14	**28**
Post-infectious	4	2	2	4	**12**
Epilepsy	19	9	6	6	**40**
Hypoxia	1	1	3	2	**7**
TOTAL	**66**	**39**	**46**	**81**	**232**

Figure 4. 2. Study flow diagram.

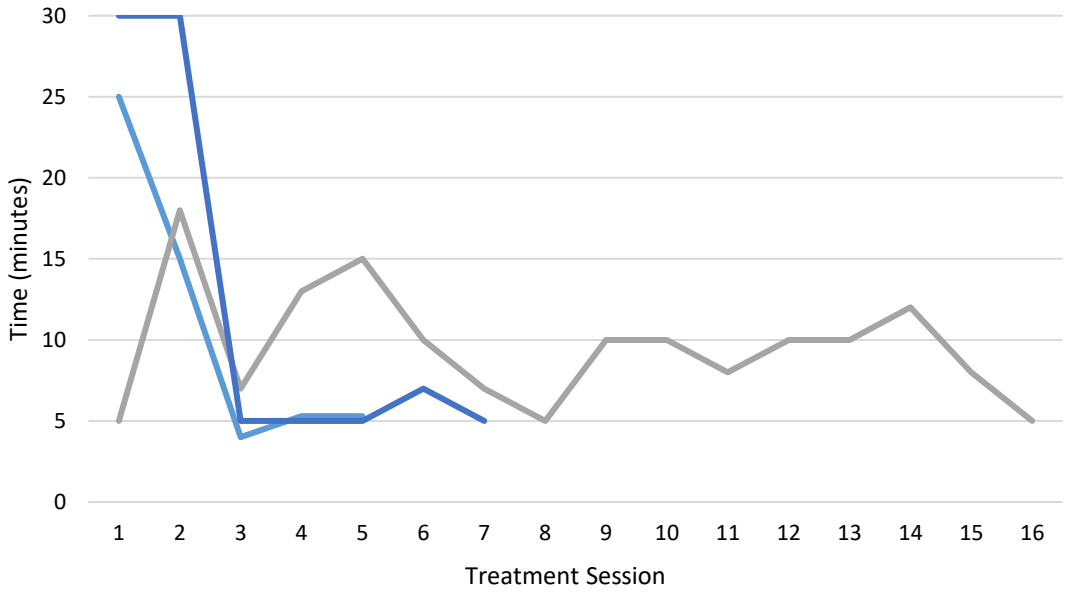


4.5.1 Feasibility outcomes

The eligibility rate (2.6%) was well below the *a priori* target (20%). Exclusions were due to: age (n=66), brain tumour (n=38), seizures (n=26), short admission (n=12), behavioural challenges (n=8), decreased tolerance to physiotherapy (n=8), physiotherapy goals unrelated to ABI (n=7), bone flap removed (n=5), communication challenges (n=5), scalp wounds/incisions (n=4), not receiving active physiotherapy (n=4), ABI not confirmed (n= 4), chronic ABI (n=4), decreased medical stability (n=3), weight bearing restrictions (n=3), other neurological diagnoses (n=2), pacemaker (n=1), metal fragments in head (n=1).

The recruitment rate (66.7%) of eligible admissions was close to the *a priori* target (70%). The *a priori* target for completed treatment sessions was 75%. Only one participant surpassed that target, completing all 16 treatment sessions, while the other two participants withdrawn from the study for medical reasons completed five (31.25%) and seven (43.75%) tDCS sessions, respectively. The participant who completed the treatment protocol, did the first reassessment in less than seven days after his final tDCS session and reassessment two in the three-month timeline. The two participants withdrawn from the study did not complete the reassessments but their baseline assessments and tDCS session data were included in the analysis. The mean tDCS setup time was 7.36 minutes (SD=4.04) and the mean tDCS duration was 20 minutes (i.e., participants completed every tDCS they started). The mean time between tDCS completion and physiotherapy commencement was 10.50 minutes (SD=7.31) with a maximum of 30 minutes and minimum of 4 minutes between sessions (Figure 4.3).

Figure 4. 3. Time between tDCS completion and physiotherapy session commencement by participant.



The *a priori* target for tDCS tolerability was 80%. While all three participants (100%) who received tDCS (active or sham) tolerated 20-minutes of tDCS in every session that they attended, only one participant was allocated to the active tDCS treatment. Pre/post tDCS session tracking indicated that participants reported itchiness under the electrodes in both sham and active groups (Table 4.3). No challenges were documented in the open comments section of the tDCS post-session tolerance form. Only one participant (allocated to active tDCS), completed Garvey's tDCS Tolerability Questionnaire post-intervention which is detailed in a separate case report (Chapter 5). Three adverse event forms were filed during the feasibility study: two for participants being readmitted to acute care, and one for a participant reporting hair loss. The Data Safety Monitoring Board (DSMB) reviewed these events with the participants' ABI physician, and all were deemed unrelated to study participation.

Table 4. 3. Mean (standard deviation) pre- and post-tDCS session tracking of side effects, rated from 0 to 4.

		Sham tDCS* (n=2)	Active tDCS (n=1)
Pre-session	**Tired**	0	2.44 (1.03)
	Headache	0	0.69 (0.60)
	Upset stomach	0.13 (0.35)	0.31 (0.70)
	Dizzy	0.13 (0.35)	0.19 (0.54)
Post-session	**Tired**	0	2.31 (1.25)
	Headache	0.38 (0.51)	0.31 (0.60)
	Upset stomach	0.15 (0.38)	0
	Dizzy	0	0
	Itchy	0.92 (0.76)	2.06 (1.29)
	Tingling	0.31 (0.48)	0.38 (0.72)
	Hot	0.38 (0.77)	0.19 (0.75)
	Weird taste	0.08 (0.28)	0

*Pre-session rating only available for one participant in sham group due to protocol change

4.5.2 Gross motor assessment

Because only one participant completed reassessments one and two, mean change scores were not calculated. However, baseline physiotherapy assessments for the three participants provided insight into their level of physical function upon study enrollment. All three participants used a wheelchair as their primary method of mobility at baseline. They each completed the GMFM-88 (mean: 35.49%, standard deviation (SD): 21.22) at baseline. Two participants were unable to complete the 10mFWT (one was non-ambulatory, one required substantial therapist assistance to take steps) while the third completed it with a two-wheeled walker. None of the participants achieved the requisite level of gross motor function to complete the ABI-CA (i.e., they could not independently walk a short distance without a gait device).

All three participants' parents completed the Daily Activities (scaled score range: 43-52, where scores can be a minimum of 20 and a maximum of 80) and Mobility (scaled score range: 38-52) sections of the PEDI-CAT, and participants (with parent input) created four to five mobility-based COPM goals with guidance from the PT assessor. Examples of COPM goals included: walk again on my own, improve sitting balance, improve standing balance, go to the washroom on my own, use the stairs on my own, transfer in and out of bed on my own. While some GAS

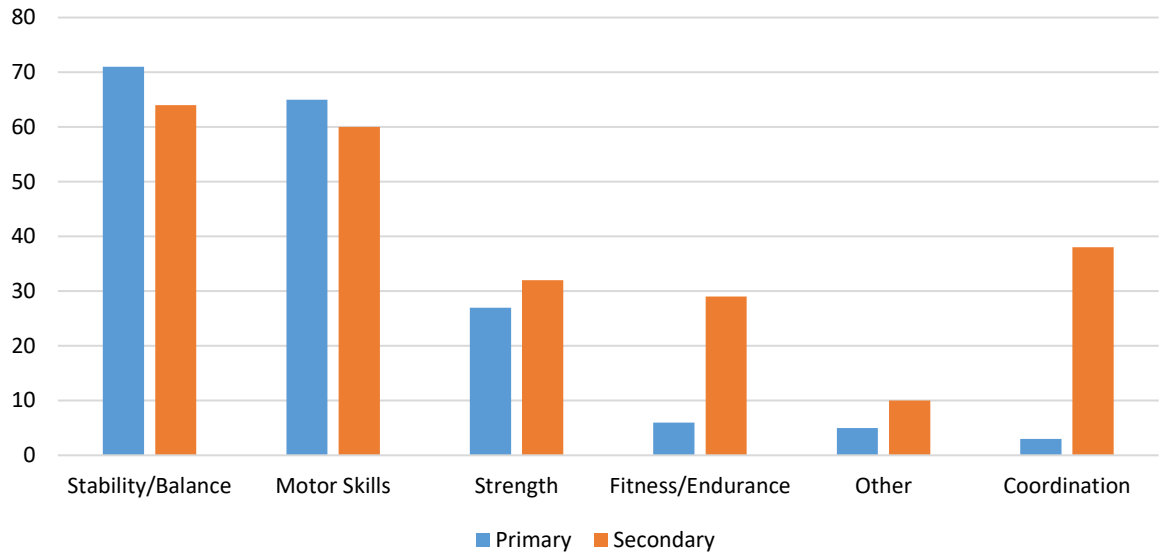
goals (all of which were created by the treating PT) overlapped the COPM goals (e.g., sliding board transfers, sitting balance, standing balance, ambulation), there were additional goal areas not identified by the child or parent, including rolling, stepping over obstacles, and sit to stand transition.

The one participant who completed the reassessments had the highest baseline scores for all outcome measures. From baseline to the first reassessment, this participant improved by 33.05% points on the GMFM-88, 4.31s on the 10mFWT, 2 and 6 scaled score points on the Mobility and Daily Activities domains of the PEDI-CAT (see Chapter 5 for details).

4.5.3 Physiotherapy session content

The physiotherapy intervention logs were completed by the treating therapists for all study sessions. The mean duration of physiotherapy sessions in the study was 56.55 (SD=6.42) minutes, with a mean of 5.93 (SD=1.70) tasks per session and 8.26 (SD=3.23) minutes spent on each task varying from 2 to 30 minutes per task. Of the 178 tasks occurring across 30 physiotherapy sessions, PTs provided education on 12 and recommended practice outside of the session for seven. ‘Stability/balance’ and ‘motor skills’ were the most frequent primary and secondary task focus (Figure 4.4). ‘Coordination’ was the least frequent primary focus and ‘other’ was the least frequent secondary focus. The ‘other’ category included foci such as vision, range of motion, assessment, and proprioceptive awareness.

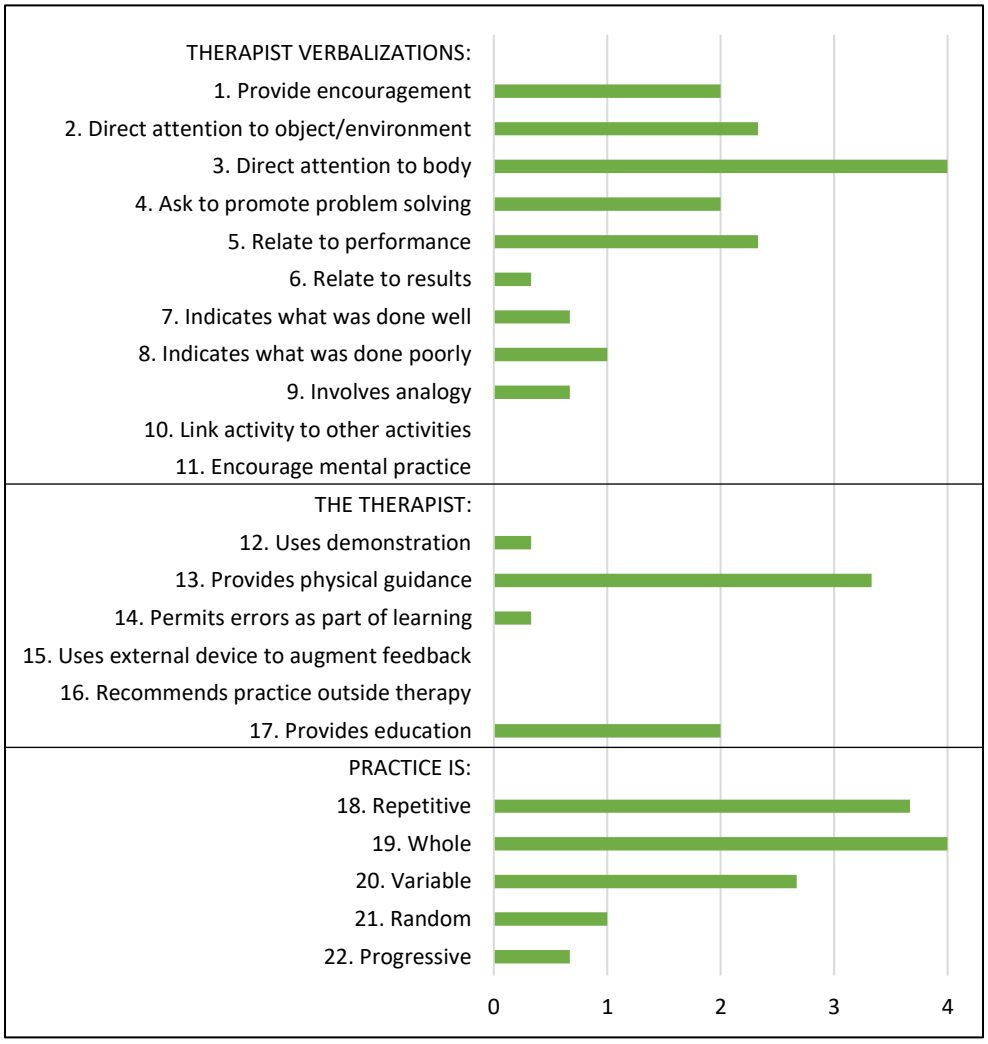
Figure 4. 4. Task focus* across all physiotherapy sessions.



*Tasks had one primary focus but could have multiple secondary foci.

For all three participants, several clinicians were present during the video-recorded physiotherapy sessions (e.g., occupational therapist, PT assistant, PT student). Figure 4.5 outlines the mean MLSRI-22 item scores for the video-recorded session in the first week of the tDCS protocol. Week four mean MLSRI-22 item scores could not be calculated due to participant withdrawal nor could within participant visual comparisons between weeks one and four be completed. Comparisons of videos from weeks one and four are detailed in a separate case report (Chapter 5).

Figure 4. 5. Mean MLSRI-22 item scores for the videos recorded (n=3 participants) in the first week of the tDCS protocol.



Scores are the extent that each MLS was observed (e.g., 0 = very little [0-5%], 1 = somewhat [6-24%], 2 = often [25-49%], 3 = very often [50-75%], 4 = mostly [76-100%]) (Spivak et al., 2021).

4.6 Discussion

Despite drawing upon our experience conducting a previous intervention study in this ABI program and reviewing admission trends, eligibility was the primary limiting factor to study feasibility. While it is impossible to definitively determine, the COVID-19 pandemic appeared to also have an impact on program admissions and eligibility. Specifically, several children were

excluded from the study due to decreased medical stability possibly because of earlier transfer to rehabilitation based on bed shortages in acute care. Conversely, several children (predominantly those with TBI) with high level balance and mobility concerns had decreased lengths of rehabilitation stay, possibly due to families opting to minimize the time spent in hospital during the pandemic.

Unfortunately, expanding diagnostic eligibility criteria beyond stroke or TBI mid-trial did not improve the eligibility rate. Participants who enrolled in this study either had a stroke or TBI suggesting that children with other diagnoses were affected by other exclusion criteria. While expanding eligibility to children with balance greater than five seconds on their most affected leg included children with important advanced balance and mobility goals, these children were likely the same children who had reduced lengths of stay since a high level of mobility increases the likelihood of being safely discharged from an inpatient setting. While a shorter treatment protocol may have been suitable for these children, the logistics of screening, consenting, assessing, and treating participants in a more condensed timeframe could be still be a barrier to feasibility. Thus, an outpatient tDCS protocol shortly after discharge may have been more feasible.

Individual medical circumstances (e.g., medication adjustments to address ABI symptoms, recovery from acute care interventions) also often led to study exclusion. In these situations, an outpatient tDCS protocol after this subacute phase may have been more suitable as medical issues often resolve or improve over the course of an inpatient admission. For instance, children with TBI and orthopedic injuries often have weight bearing restrictions throughout most of their inpatient admission which limit participation in a motor learning focused physiotherapy program and standardized physiotherapy assessment. Additionally, children with stroke or TBI may have a bone flap removed post-decompressive craniectomy which is a contraindication to tDCS. Decreased tolerance to physiotherapy assessment and treatment, as well as inconsistent communication, is often more prevalent earlier in rehabilitation and would have prevented participants from following study protocol. The medical acuity of children with subacute ABI was further evident in the two participants withdrawn from the study due to changes in their medical stability despite being stable at the time of study screening.

Conversely, recruitment rates were within acceptable limits and demonstrated the willingness of eligible children (and their parents) to use tDCS during inpatient rehabilitation. The 90-minute treatment session duration provided ample time to administer tDCS in the participant's room on the inpatient unit and transition to the physiotherapy gym. It is imperative that physiotherapy intervention occurs during the tDCS-induced cortical excitability to optimize the motor learning potential of the treatment protocol (Stagg & Nitsche, 2011). While there was more variability in time between tDCS and physiotherapy in the first two treatment sessions across participants, the timing was still within acceptable limits, and became more consist over subsequent sessions, likely as the participant and RA established a routine.

The study also demonstrated that tracking tDCS side effects pre/post-tDCS is an effective way of differentiating between ABI symptoms and tDCS side effects, and is critical to evaluating tDCS tolerance. Participants in both treatment groups reported symptoms pre- and post-tDCS, suggesting that some symptoms may be attributable to their ABI rather than tDCS and/or that tDCS did not exacerbate ABI symptoms. Further, the reports of itching and tingling post-tDCS in both treatment groups indicated that the sham protocol mimicked the itching and tingling sensations of active tDCS. While the lack of challenges documented in the open comments section of the tDCS post-session tolerance form suggest that participants did not encounter challenges during the tDCS sessions, future iterations of this form should include more specific questions to ensure that nothing is overlooked. For example, a "yes/no" question indicating if the participant needed parent/RA assistance with symptom rating, followed by an open text area to elaborate on the assistance provided, would identify whether younger children or children with cognitive difficulties require an adapted version of the rating scale.

While mean change scores could be not calculated for co-primary outcomes as only one participant completed the protocol, this study allowed our team to determine the suitability of the primary and secondary gross motor outcome measures for these children. With a mean baseline of 35.49% on the GMFM-88, there was substantial room to detect improvement on this co-primary outcome. While only one participant could complete the 10mFWT at baseline, its inclusion as a secondary outcome remains useful for detecting functional changes in walking speed. The Daily Activities and Mobility domains of the PEDI-CAT were also easily administered with the parent completing the questionnaire while the participant completed other

gross motor assessments. While none of the participants met the minimum ability threshold for completing the ABI-CA, its use in future study protocols will be particularly beneficial for detecting change in children and youth with ABI who have advanced mobility goals (Ibey et al., 2010), as these children would likely reach the ceiling of the GMFM-88 at baseline. Participants and parents created meaningful mobility based COPM goals that complemented the GAS goals developed by the treating PT. This combination of tracking goal areas, documenting physiotherapy session content (i.e., tasks and task foci), and evaluating MLS content was not only viable but critical to understanding the ingredients of motor learning interventions for children and youth with ABI.

While it is unclear whether the eligibility challenges we encountered would generalize to other inpatient pediatric rehabilitation hospitals, our experiences can inform the design of future tDCS studies in children with ABI. Based on our experiences, we have several recommendations for future tDCS studies in children and youth with ABI. As administering the treatment protocol itself was feasible and there is still potential for tDCS to enhance motor learning after ABI, future studies embedded in a clinical setting should: 1) allocate 30 minutes to tDCS and 60 minutes to physiotherapy sessions, 2) document tDCS parameters, 3) track symptoms pre- and post-tDCS, 4) administer the complement of gross motor outcome measures used in this study to ensure that change is detected at all levels of functional ability, 5) individualize physiotherapy intervention based on child-specific abilities and goals, and 6) document and analyze physiotherapy session content to support exploration of how it may have contributed to motor learning. Based on the challenges encountered in this trial, future studies should consider the following options to increase enrollment: 1) conduct a multi-center study, 2) reduce treatment protocol duration to two weeks for inpatient children with advanced gross motor goals, and 3) develop outpatient protocols for children who either have reduced lengths of stay or may only meet eligibility criteria after discharge from inpatient rehabilitation.

4.7 Conclusions

While implementing tDCS as an adjunct to inpatient physiotherapy may enhance gross motor outcomes in children and youth with ABI and may be of particular benefit in subacute ABI due to the increased potential to influence neuroplasticity early in recovery, our study protocol was

not feasible from both eligibility and retention perspectives. As such, a definitive randomised control trial is not warranted at this time. However, our study procedures (e.g., assessment, treatment, side effect tracking, physiotherapy session documentation) were feasible and should be used to inform the design of future tDCS feasibility protocols in children and youth with ABI.

4.7.1 Funding

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4.7.2 Acknowledgements

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Chapter 5

Integrating transcranial direct current stimulation into an existing inpatient physiotherapy program to enhance motor learning in an adolescent with traumatic brain injury: A case report

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5 Integrating transcranial direct current stimulation into an existing inpatient physiotherapy program to enhance motor learning in an adolescent with traumatic brain injury: A case report

5.1 Abstract

Purpose: Describe how transcranial direct current stimulation (tDCS) was incorporated into an inpatient physiotherapy program for an adolescent with severe traumatic brain injury (TBI), detail the motor learning focus of the physiotherapy sessions, and summarize gross motor progress.

Method: This case report describes an adolescent who received 20 minutes of anodal tDCS immediately prior to 16 physiotherapy sessions over four weeks. Potential side effects were tracked pre/post tDCS. Gross motor outcomes were measured pre-intervention, post-intervention, and three months post-intervention. Physiotherapy session content was analyzed using therapist documentation and the Motor Learning Strategies Rating Instrument.

Results: The youth tolerated tDCS well. The primary side effect was itchiness under the electrodes during tDCS sessions. His mobility progressed from wheelchair use pre- 'tDCS + physiotherapy' to ambulation with a walker post-intervention. His Gross Motor Function Measure score increased 33.1% points pre/post intervention. Session tasks often had several foci (e.g., skill acquisition, strength, and balance) with task focus changing as the youth progressed. Various motor learning strategies were layered within tasks to support performance and learning.

Conclusions: tDCS was successfully integrated into an existing inpatient physiotherapy program for an adolescent with TBI. This protocol provides a structure for implementing, monitoring, and measuring tDCS + physiotherapy in pediatric rehabilitation.

5.2 Introduction

Acquired brain injury (ABI) can be traumatic or non-traumatic (e.g., stroke, encephalitis, tumour) in nature (Giustini et al., 2013). Children and youth with moderate to severe acquired brain injury (ABI) experience physical and cognitive challenges that affect their development and participation (Anderson & Catroppa, 2006; Braga et al., 2005; Galvin et al., 2010a). Because the subacute stage of ABI is a critical period for neural recovery, children are often admitted to inpatient rehabilitation where they receive intensive multidisciplinary intervention to address functional goals (Anderson & Catroppa, 2006; Dumas et al., 2004a). Inpatient physiotherapy after ABI focuses on relearning and refining a range of gross motor skills while simultaneously addressing strength, endurance, balance, and coordination deficits (Dumas et al., 2004b; Ryan et al., 2022). Physiotherapists (PTs) often employ individualized therapeutic actions based on child- and task-specific factors called motor learning strategies (MLS) to promote skill acquisition and refinement (Levac et al., 2011). These strategies consist of verbalizations (e.g., instructions, feedback), actions (e.g., demonstration, physical guidance), and practice organization (e.g., whole versus part practice, random versus blocked practice) (Spivak et al., 2021).

Ambulation is a common inpatient physiotherapy goal for children with ABI (Ryan et al., 2022) due to its association with independence and community access (Dumas et al., 2004a). While experts agree upon the importance of functional mobility and task-specific practice in children with ABI, there is no consensus regarding the optimal content of physiotherapy intervention (Baque et al., 2016; Dumas et al., 2004b). Children with ABI typically make substantial gross motor progress during inpatient rehabilitation (Dumas et al., 2004a; Ryan et al., 2022), followed by a plateau in recovery with persisting functional deficits (Braga et al., 2005; Galvin et al., 2010a; Gordon & di Maggio, 2012). Because of the long-term sequelae associated with pediatric ABI, new treatment approaches are often explored to determine if superior outcomes can be achieved (Anderson & Catroppa, 2006; Gordon & di Maggio, 2012). The influx of technology in neurorehabilitation has led to therapists increasingly adopting its use as an adjunct to traditional intervention when they anticipate a therapeutic benefit and are supported in its implementation (Hamilton et al., 2019; Bower et al., 2021). Some technologies influence motor learning on a behavioural level by augmenting feedback (e.g., active video gaming, robotic-assisted gait training) while other technologies target change on a physiological level (e.g., functional

electrical stimulation, non-invasive brain stimulation) (Gordon & di Maggio, 2012; Takeuchi & Izumi, 2013).

Transcranial direct current stimulation (tDCS) is a form of non-invasive brain stimulation that temporarily modulates neural activity by delivering small subthreshold currents to a targeted region of the brain via electrodes placed on the scalp (Stagg & Nitsche, 2011). When motor learning is the goal, tDCS electrodes are typically positioned over the primary motor cortex (Stagg & Nitsche, 2011). tDCS alters cortical activity for approximately 90 minutes after a treatment session by hyperpolarizing (i.e., excitation) the resting membrane potential of neurons located beneath the anode and hypopolarizing (i.e., suppression) neurons beneath the cathode (Stagg & Nitsche, 2011). This altered neural state is thought to prime the brain to form new cortical networks, and strengthen existing networks, when motor practice is introduced (Stagg & Nitsche, 2011; Takeuchi & Izumi, 2013). However, the subthreshold influence on cortical activity means that tDCS likely does not enhance motor learning on its own (Stagg & Nitsche, 2011). As such, the motor learning content of the practice accompanying the tDCS is integral to its effectiveness.

While tDCS safety is well-established (Bikson et al., 2016; Zewdie et al., 2020), there are many unanswered questions regarding its feasibility and efficacy. tDCS is well-tolerated among children with cerebral palsy (CP) and youth with concussion (Zewdie et al., 2020). Pediatric motor skills-based tDCS research has predominantly occurred in children with CP with positive gross motor outcomes after treadmill training (Grecco et al., 2014), virtual reality balance training (Lazzari et al., 2017), and neurodevelopmental treatment (Salazar Fajardo et al., 2022). However, the exact motor learning content of these interventions is unclear. Additionally, the effect of tDCS on motor learning in children and youth with ABI has yet to be explored. Further tDCS research is also required in the subacute stage of neurological recovery when the potential to influence neuroplasticity is increased (Bornheim et al., 2020).

When exploring a novel intervention, case reports permit an in-depth examination of a single participant's experience and can be used to inform future stages of research (Nissen & Wynn, 2014). Given the novelty of tDCS in pediatric subacute ABI and the limited information about physiotherapy session content in these children, the aims of this case report were to demonstrate:

1) the incorporation of tDCS into an existing pediatric inpatient ABI physiotherapy program, 2) the motor learning and treatment session content of the physiotherapy intervention paired with the tDCS, and 3) the process for evaluating gross motor progress and skill retention using a complementary set of outcome measures.

5.3 Methods

5.3.1 Case description

This case report involved a participant who took part in a feasibility randomized control trial (RCT) (ClinicalTrials.gov Identifier: NCT04422886) evaluating tDCS as an adjunct to an existing inpatient physiotherapy program for children and youth with ABI. The protocol was approved by the hospital's research ethics board (REB). Within the feasibility RCT, children and youth ages 5 to 18 years with ABI (i.e., traumatic or non-traumatic) received either active or sham anodal tDCS immediately prior to 16 physiotherapy sessions. Participants, assessors, and PTs were blinded to treatment allocation. While feasibility RCT results are reported in a separate manuscript (i.e., Chapter 4), this case report provides a more detailed account of study protocol nuances for an adolescent with traumatic brain injury (TBI).

5.3.2 Case report participant

Ethan (pseudonym) is an adolescent who was admitted to inpatient rehabilitation six weeks after sustaining a severe TBI. In addition to receiving one hour of physiotherapy five days per week throughout his admission, Ethan participated in occupational therapy and speech language pathology interventions up to five days per week, and he attended school within the hospital between therapy sessions. On admission, Ethan's primary method of mobility was a manual tilting wheelchair. He had a right hemiparesis and hypertonia. Ethan was capable of following verbal directions in physiotherapy sessions. He took steps with moderate assistance from two people and his Gross Motor Function Measure (GMFM-88) (Russell et al., 2021) total score was 22.6%. Ethan had vocal cord paralysis on admission and was fed via gastrostomy tube. When he started the tDCS treatment protocol, in the final month of his three-month admission, he was verbal, ate orally, and walked indoors with a two-wheeled walker. After completing the

feasibility RCT, Ethan provided written informed consent to describe his participation in the feasibility RCT within this case report.

5.3.3 tDCS Treatment

Treatment sessions were 90 minutes in duration with the first 30 minutes allocated to tDCS, including 10 minutes for equipment set-up and administering tDCS symptom questionnaires, followed by 60 minutes of physiotherapy. tDCS protocols either provide tDCS immediately prior to (Bornheim et al., 2020) or during behavioural intervention (Salazar Fajardo et al., 2022). In this case, tDCS occurred before physiotherapy to maintain electrode positioning and prevent tDCS equipment from interfering with gross motor tasks. tDCS sessions were conducted by a tDCS-trained research assistant on the inpatient unit where Ethan opted to sit in bed rather than in a chair with armrests or his wheelchair. tDCS training involved practical and didactic training under the supervision of the second author who is certified in its use.

Ethan was allocated to the treatment group that received active tDCS. He received 20 minutes of anodal tDCS (Soterix 1×1 LTE tDCS Device Limited Total Energy tDCS For Susceptible Subjects) immediately prior to 16 physiotherapy sessions. Using the electroencephalography 10-20 system for electrode placement (Seeck et al., 2017), our dual electrode tDCS montage (5x5cm electrodes) positioned the anode over Cz (i.e., the lower extremity region of bilateral primary motor cortices) and the cathode over Fpz (i.e., centre of the forehead) (Figure 5.1). Each tDCS treatment began with the current ramping up over the first minute to the target current that was then maintained for 18 minutes. In the final minute, the current ramped down and turned off. tDCS current intensities generally vary between 1.0 and 2.0 milliamperes (mA) (Stagg & Nitsche, 2011). The starting current intensity was incrementally increased over the first three tDCS sessions (i.e., 1.0 mA in the first session, 1.5 mA in the second session) with the goal of reaching 2.0 mA by the third session; 2.0 mA was used for the remaining sessions. The research assistant documented the time that tDCS finished and the PT documented the time that the physiotherapy session started to determine if physiotherapy occurred during the period of enhanced cortical excitability.

Figure 5. 1. Study tDCS electrode montage.

Side effects were tracked immediately before and after each tDCS session using study-specific standardized reporting forms. Before each session, Ethan reported any new health concerns, seizures, syncope, skin irritation/redness at electrode sites, fatigue, headaches, upset stomach, or dizziness since the previous tDCS session. If he reported fatigue, headache, upset stomach, or dizziness, Ethan was asked to rate the extent of the side effect(s) on a five-point rating scale (e.g., 0 = 'not at all', 1 = 'a little bit', 2 = 'a bit more', 3 = 'even more', 4 = 'a whole lot'). After each tDCS session (prior to physiotherapy), he used the same scale to rate fatigue, upset stomach, headache, dizziness again. He also rated additional side effects (itchy, tingly, hot, weird taste in mouth) that were unlikely to persist beyond the tDCS session and were therefore not part of the pre-session ratings. REB-approved monitoring rules dictated that headache, upset stomach, or dizziness ratings of "4" post-tDCS required the study team to notify the participant's nurse and complete an adverse event form. Seizure or syncope at any time during the study protocol would have led to a study hold until the participant was evaluated by their ABI physician and the adverse event was reviewed by the Data Safety and Monitoring Board.

5.3.4 Physiotherapy intervention

The content of the individualized physiotherapy sessions paired with the tDCS was at the discretion of Ethan's treating PT in the inpatient ABI program. Physiotherapy intervention in this inpatient ABI program focuses on increasing independence and efficiency of various gross motor skills with the goal of transferring these skills to meaningful activities. Physiotherapy session content is guided by individual physical function, cognition, and goals. Children/youth in the program receive up to five 60-minute physiotherapy sessions Monday to Friday provided by a combination of PT, a PT assistant (PTA), and/or PT with the PTA, depending on the level of assistance required. While there is inherently a motor learning focus within the inpatient ABI program, all PTs and PTAs in the program completed the MLS Online Training Program (Ryan et al., 2017) to ensure a minimum level of MLS knowledge prior to providing treatment in the study. The online program consists of four modules with skill testing questions at the end of each module and takes approximately four hours to complete (Ryan et al., 2017). It describes various motor learning concepts (e.g., factors that influence motor learning, implicit versus explicit motor learning), defines 22 MLS, and provides multiple video examples of how to apply MLS in various clinical scenarios (Ryan et al., 2017).

The PT/PTA documented the tasks completed in each physiotherapy session, in the order performed, on a study-specific intervention log. For each task, they recorded task duration and variations and selected primary and secondary task foci from a menu of pre-determined physiotherapy principles: stability/balance, coordination, strength, motor skill, endurance/fitness, other. They also indicated if they provided task-specific education or recommended practice outside physiotherapy. Two physiotherapy sessions were video recorded, one at the beginning of the study and one near the end to capture changes in session content and MLS use based on progress over the study intervention period. The first author, a practicing PT with 16 years of clinical experience in pediatric ABI and Motor Learning Strategies Rating Instrument (MLSRI-22) (Levac et al., 2011; Spivak et al., 2021) certification, analyzed the MLS content of these video-recorded sessions using the MLSRI-22. The MLSRI-22 documents the frequency and extent that 22 MLS are observed in a video-recorded physiotherapy session for children/youth with ABI (Levac et al., 2011; Spivak et al., 2021). MLSRI-22 items are divided into three

categories: *therapist verbalizations* (items #1-11), *the therapist* (i.e., therapist actions) (items #12-17), and *practice is* (i.e., session organization) (items #18-22) (Spivak et al., 2021).

5.3.5 Outcome measures

The same independent PT assessor, blinded to treatment group and previous scores, completed study assessments pre-intervention, post-intervention, and three months post-intervention. Outcome change from pre-intervention to post-intervention evaluated change associated with the combined tDCS and physiotherapy program. Change scores for post-intervention to three months post-intervention provided insight into progression and/or retention of skills beyond the inpatient admission. The pre-intervention assessment occurred eight weeks into Ethan's admission. The post-intervention assessment occurred the week that he was discharged (i.e., four weeks after the pre-intervention assessment).

The following outcome measures evaluated a breadth gross motor skills with input from the parent and youth. The co-primary outcome measures were the: Gross Motor Function Measure (GMFM-88) (Russell et al., 2013), that evaluates five dimensions (A: lying and rolling, B: sitting, C: crawling and kneeling, D: standing, E: walking, running, jumping), and Canadian Occupational Performance Measure (COPM) (Carswell et al., 2004), where the participant set four gross motor goals in collaboration with the assessing PT and parent. The GMFM-88 is a reliable and responsive outcome measure (Ko & Kim, 2013) that has been validated for children with ABI (Linder-Lucht et al., 2007). The COPM is also a reliable and valid outcome measure that has demonstrated responsiveness in pediatric rehabilitation research (Carswell et al., 2004; Cusick et al., 2007). The minimum clinically important difference for the GMFM-88 and COPM are 5% (Storm et al., 2020) and 2 points (Law et al., 2014), respectively.

The following secondary outcome measures were also evaluated: 10-metre Fast Walk Test (10mFWT) (Thompson et al., 2008), and the parent-reported Pediatric Evaluation of Disability Inventory (PEDI-CAT; Speedy versions of the 'Daily Activity' and 'Mobility' domains), where scaled scores range from a minimum of 20 to a maximum of 80 points (Haley et al., 2011). The PEDI has been validated for use in pediatric ABI (Ziviani et al., 2002) and is responsive to change during inpatient rehabilitation (Fragala-Pinkham et al., 2016). The 10mFWT is reliable in children with CP, with 10m representing the minimum distance that a child must walk

independently to be considered a functional ambulator (Thompson et al., 2008). The treating PT also used Goal Attainment Scaling (Kiresuk et al., 2014) to create three individualized functional goals specifically for the study treatment period (Table 5.1), following the same process the PTs in this program regularly use in their clinical practice (Ryan et al., 2022a). In general, GAS is valid, reliable, and sensitive to functionally meaningful change (Cusick et al., 2006; Schlosser, 2004).

Table 5. 1. Ethan's study-specific GAS goals.

	Walking*	**Stepping Over Obstacles**	**Standing Balance**
Starting level (-2)	Walks on the [inpatient] unit with two-wheeled** walker, uses wheelchair throughout the hospital	Unable to step over obstacles of any height	Stands > 10 seconds with left foot on 8-inch step
Slightly Less Than Expected (-1)	Walks full days [in the hospital] with a two-wheeled walker with supervision	Steps over 2- to 3-inch obstacle with one arm support	Stands > 10 seconds with left foot on large foam roll
Expected Level (0)	Walks full days [in the hospital] using a rollator walker*** with supervision	Steps over 2- to 3-inch obstacle (hands free) with close supervision	Stands > 10 seconds with left foot on soccer ball
Slightly Better Than Expected (+1)	Walks full days [in the hospital] with a cane with supervision	Steps over an obstacle at mid-calf height with close supervision	Right foot unipedal stance 3 to 5 seconds
Much Better Than Expected (+2)	Walks full days [in the hospital], unaided, with supervision	Steps over an obstacle at knee height with close supervision	Right foot unipedal stance > 5 seconds

*The inpatient unit is where patients eat, bathe, and sleep. Thus, walking on the inpatient unit would consist of walking short distances sporadically at times when not in school or therapy. Walking full days involved walking to therapy appointments or school which are on different floors of the hospital.

**A two-wheeled walker is a suitable for indoor use only. It has small, non-swivel wheels.

*** A rollator walker is suitable for community mobility. It has four wheels that swivel and hand brakes to control speed.

At the pre-intervention assessment, Ethan completed the baseline of an adapted version of Garvey et al.'s (2001) questionnaire that documents children's subjective reactions to transcranial magnetic stimulation where he identified his own most and least enjoyable activities

in the last month and then separately ordered Garvey's seven pre-determined activities from most enjoyable to least enjoyable. At the post-intervention assessment, Ethan then rated his experience with tDCS relative to the ordered list of activities he provided pre-intervention and answered questions about his tDCS experience (Table 5.2).

5.4 Findings

5.4.1 tDCS sessions

To ensure that Ethan's tDCS sessions could be incorporated into his busy inpatient schedule, all treatment sessions were scheduled by his treating PT prior to the first study session. Ethan completed 16 tDCS sessions over 23 days as scheduled. He did not receive treatment on weekends as physiotherapy was not offered in the program at those times. tDCS duration and progression of current intensity proceeded as planned. Every tDCS treatment was 20 minutes with a mean (standard deviation) set up time of 6.31 (3.09) minutes. The mean time between tDCS completion and physiotherapy session commencement was 9.56 (3.65) minutes. Ethan's highest mean pre-session symptom was fatigue which remained the same post-session (Table 5.2). The only side effects rated "4" post-tDCS were: itchy (one session), tired (two sessions). There were no seizures or syncope. Ethan rated his enjoyment of tDCS between 'going to the dentist' and 'getting a needle' (Table 5.2).

Table 5. 2. Ethan's tDCS session symptom ratings and tolerability questionnaire.

Symptom Rating[a]			tDCS Tolerability Questionnaire[d]		
	Pre-Session[b]	**Post-Session[b]**	MOST ENJOYABLE	*Talking with friends**	1. Would you say yes to having tDCS again? *Yes*
Tired	2.4 (1.0)	2.3 (1.3)		Playing a (video) game†	2. Would you tell other kids to try tDCS? *Yes, if it is needed*
Headache	0.6 (0.6)	0.3 (0.6)		Long car ride†	3. What did you like best about the tDCS? *Sitting in bed during the tDCS*
Upset stomach	0.4 (0.7)	0		Watch TV†	4. Do you think you received a lot or a little bit of tDCS? *A lot*
Dizzy	0.2 (0.7)	0		Go to a birthday party†	5. How sure are you of your answer above? *Very sure*
Itching[c]	n/a	2.1 (1.3)		Go to the dentist†	6. Did you have any side effects? *No*
Tingling[c]	n/a	0.4 (0.7)		***tDCS*‡**	
Hot[c]	n/a	0.2 (0.8)		Get a needle†	
Weird taste in mouth	n/a	0	LEAST ENJOYABLE	Throw up†	
				*Pain at gastric-tube site***	

a- Completed at each tDCS session

b- Mean (SD). Ratings are on a five-point scale where 0 = not at all, 1 = a little bit, 2 = a bit more, 3 = even more, 4 = a whole lot

c- Refers to symptoms under electrode sites

n/a- Symptoms were only rated post-session

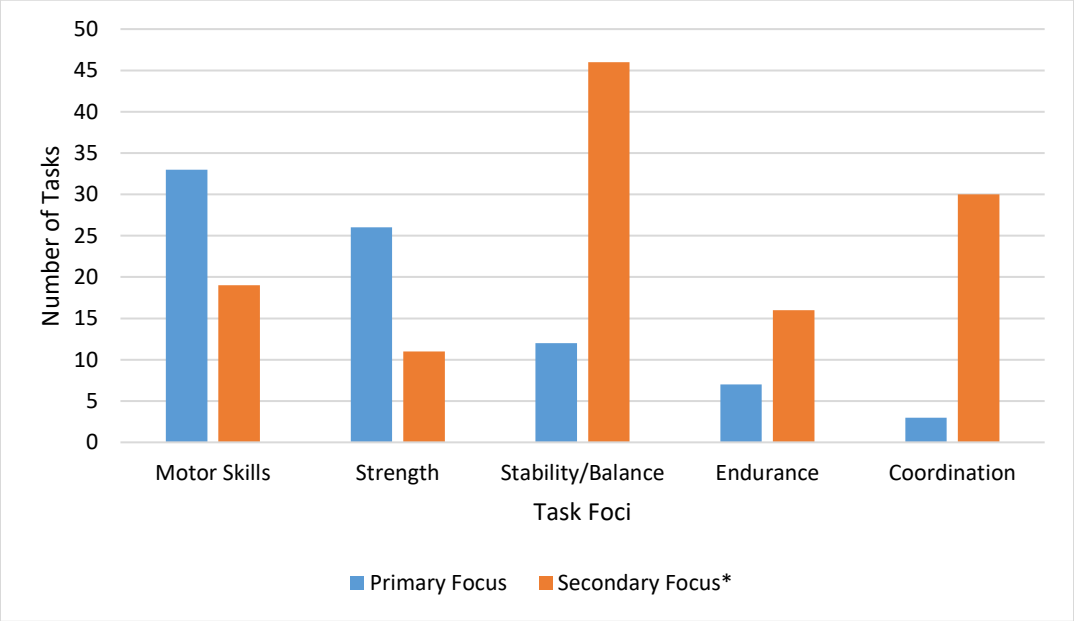
d- Adapted from Garvey (2001). Prior to the first tDCS session, Ethan generated his own *most** and *least*** enjoyable activities in the last month. He then separately ordered Garvey's seven pre-determined activities† from most enjoyable to least enjoyable. For reassessment, the researchers added the *most* and *least* enjoyable activities to the beginning and end of Ethan's ordered list of pre-determined activities. At the post-intervention assessment, Ethan rated his enjoyment of ***tDCS*‡** relative to this ordered list of activities.

5.4.2 Physiotherapy intervention

Ethan spent a mean of 46.38 (6.0) minutes per physiotherapy session actively participating in tasks with a mean of 4.94 (1.1) tasks per session and 9.67 (3.6) minutes spent on each task. The time spent on each task varied from 2 to 35 minutes. Across all study sessions, the most frequent primary task focus was *motor skills* (1.9 [1.1] tasks per session), and *stability/balance* was the most frequent secondary task focus (2.8 [1.1] tasks per session). *Coordination* was the least frequent primary task focus (0.2 [0.4] tasks per session) and *strength* was the least frequent secondary task focus (0.7 [0.8] tasks per session). Figure 5.2 presents these data as cumulative task performance numbers across sessions. The PT documented 'recommending practice outside

physiotherapy' for only two walking tasks (primary focus: *motor* skills, secondary focus: *fitness*/endurance) across all sessions and did not document any instances of 'providing education' related to the tasks practiced during the sessions.

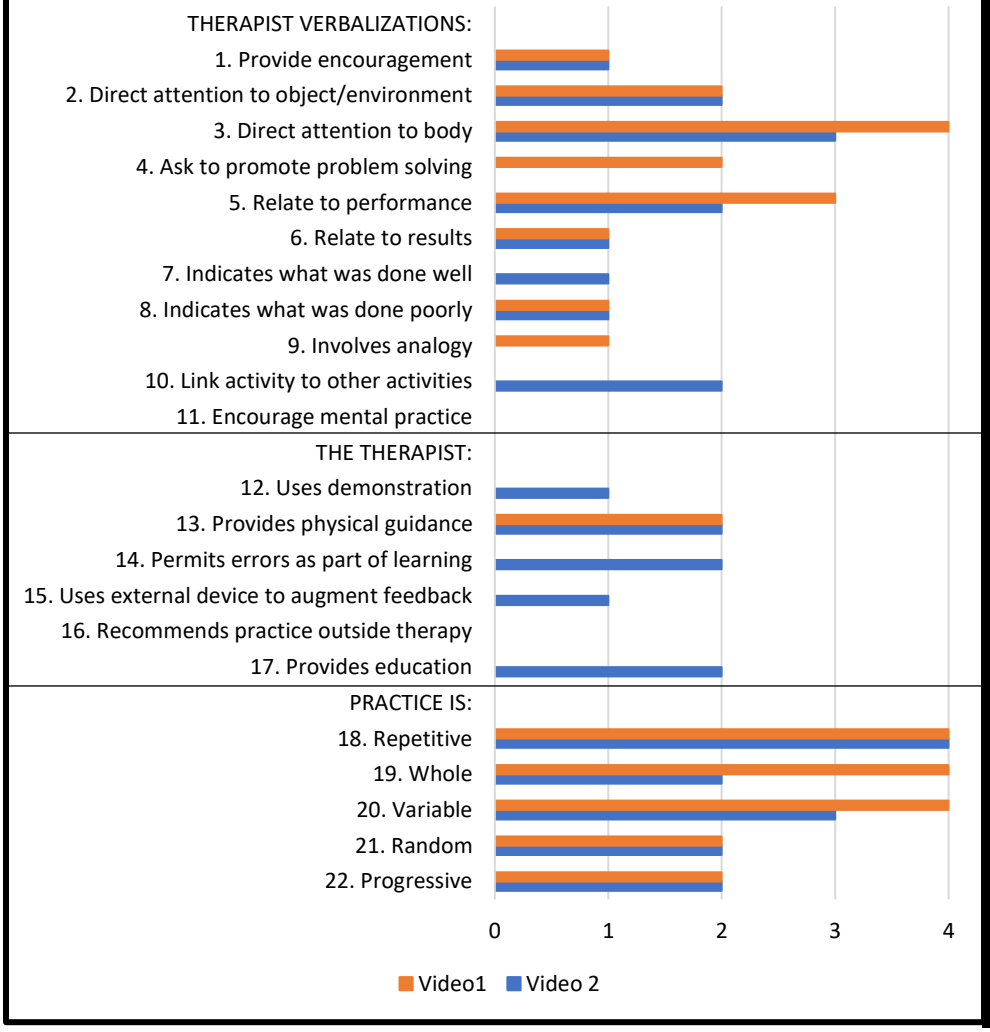
Figure 5. 2. Task foci across all physiotherapy sessions.



*Tasks could have multiple secondary foci.

In the first video, Ethan used a two-wheeled walker with minimal assistance to walk within the physiotherapy gym. Figure 5.3 details the tasks (in order) and MLSRI-22 item scores. The primary task foci in video one were: strength (squats, step-ups), motor skills (walking, stride stance), stability/balance (standing + upper extremity [UE] activity). Coordination was the secondary focus for four tasks: standing + UE activity, stride stance, step-ups, treadmill walking. Additional secondary foci were: motor skill (step-ups), stability/balance (stride stance), fitness/endurance (treadmill walking).

Figure 5. 3. MLS content documented using the MLSRI-22 for the video-recorded physiotherapy sessions.



VIDEO 1	
#	**Tasks**
1	Squats (pick up darts + throw)
2	Standing + upper extremity activities
3,6	Walking (parallel bars, treadmill)
4	Stride stance activities (weight shift onto affected leg)
5	Step-ups
VIDEO 2	
#	**Tasks**
1	Stationary bike (intervals)
2	Bridging (unweight less affected foot)
3,5	Hip hiking (standing on affected leg)
4,6	Stride stance (weight shift onto affected leg)
7	Step-ups
8	Walking (in the hall)

Scores are the extent that each MLS was observed (e.g., 0 = very little (0-5%), 1 = somewhat (6-24%), 2 = often (25-49%), 3 = very often (50-75%), 4 = mostly (76-100%)) (Spivak et al., 2021). Tasks and the order (#) that the tasks occurred in the session are provided for each video.

(Note: task order informs scoring for item 21.)

In the second video, Ethan walked hands-free between tasks with the PT providing minimal support using a gait belt. The primary task foci in video two were: stability/balance (stride stance), fitness/endurance (stationary bike), strength (bridging, hip hike, step-ups), motor skill (walking). Stability/balance was the secondary focus for four tasks: stationary bike, bridging, hip

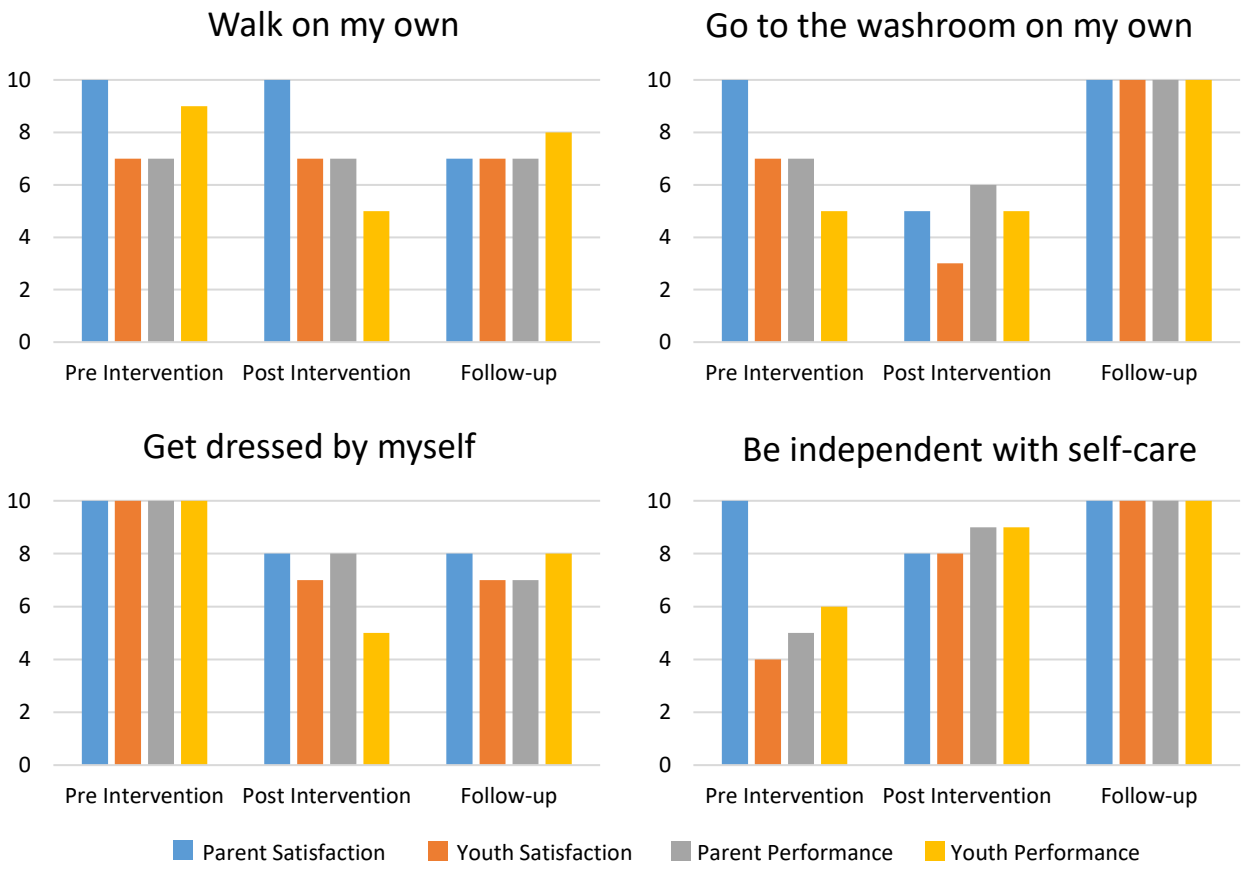
hike, step-ups, walking. The following were additional secondary foci: motor skill (stride stance), coordination (walking), fitness/endurance (walking).

Across the two video-recorded sessions, the most used MLS by MLSRI-22 category were: *therapist verbalizations* 'direct attention to the body' (item #3), *the therapist* 'provides physical guidance' (#12), and *practice is* 'repetitive' (#18). The least used MLS by MLSRI-22 category were: *therapist verbalizations* 'encourage mental practice' (#12), *the therapist* 'recommends practice outside of therapy' (#16), and *practice is* 'random' (#21) and 'progressive' (#22).

5.4.3 Gross motor outcomes

Ethan's GMFM-88 total score at pre-intervention, post-intervention, and three-month follow-up were 50.9%, 84.0%, and 86.1%, respectively. His GMFM-88 goal totals (i.e., the average of dimensions D and E) (Russell et al., 2021) were 33.5%, 69.4%, and 72.3%, respectively. His four COPM goals listed in self-reported order of importance were: walk on my own, go to the washroom on my own, get dressed by myself, and be independent with self-care. Ethan's performance ratings at pre-intervention, post-intervention, and three-month follow-up varied considerably: walking on my own (9, 5, 8), going to the washroom on my own (5, 5, 10), getting dressed by myself (10, 5, 8), and being independent with self-care (6, 9, 10) (Figure 5.4).

Figure 5. 4. COPM goals with parent and youth ratings of satisfaction and performance.



Pre-intervention, Ethan completed the 10mWT in 7.7s using a two-wheeled walker and wearing a right ankle foot orthosis (AFO). Post-intervention, he walked 10m in 3.4s using a rollator walker and wearing the AFO. At the three-month follow-up, he walked 10m in 6.0s without a gait aid or AFO. Ethan achieved the expected level ('0') for all three GAS goals (T-score = 50.0) (Table 5.1). PEDI-CAT scaled scores at pre-intervention, post-intervention, and three-month follow-up were: Daily Activities- 50, 56 and 56, respectively; Mobility- 52, 54 and 62, respectively.

5.5 Discussion

PTs have an opportunity to optimize functional outcomes and enhance neuroplasticity in pediatric subacute ABI by integrating rehabilitation technologies into their interventions. By demonstrating how tDCS can be incorporated into an existing inpatient physiotherapy program

for a youth with TBI and providing preliminary evidence that tDCS can be tolerated during this early stage of recovery, this case report provides a structure for future tDCS research conducted in clinical settings. Further, this case emphasizes the importance of differentiating between TBI symptoms and tDCS side effects. Given the influence that the motor practice portion of tDCS protocols has on optimizing motor learning outcomes, this case report also highlights the need to analyze the motor learning content of the physiotherapy paired with tDCS as a precursor to evaluating treatment protocol effectiveness. Finally, by summarizing Ethan's gross motor progress, we demonstrate the benefits of a complementary set of outcome measures to detect gross motor change (and skill retention) associated with tDCS and individualized motor skills-based physiotherapy.

Scheduling tDCS sessions within a busy inpatient schedule requires advanced planning and regular communication between the clinical and research teams. To optimize the motor learning potential of tDCS, motor practice should occur during a period of tDCS-induced cortical excitability and therefore must be scheduled appropriately. With less than 10 minutes between tDCS and physiotherapy sessions in this case, research and clinical staff demonstrated that it is possible to efficiently transition between the two components of the intervention in an inpatient setting. This process was aided by including the tDCS sessions on the youth's clinical schedule, as well as having a consistent location for all tDCS sessions (i.e., the youth's room on the inpatient unit) and a designated waiting area for all physiotherapy appointments. Finally, having a parent or nurse escort the youth between locations ensured timely transitions.

Because fatigue (Crichton et al., 2018), headaches (Blume et al., 2012), and dizziness (Maskell et al., 2006) are symptoms associated with pediatric TBI, and possible transient side effects of tDCS (Bikson et al., 2016; Stagg & Nitsche, 2011), the systematic tracking of side effects before and after tDCS sessions was integral to differentiating between TBI symptoms and tDCS side effects in our analysis. Ethan's fatigue, headaches, and dizziness ratings were higher prior to tDCS than immediately following tDCS, indicating that tDCS did not exacerbate his TBI symptoms. We surmise that sitting in bed during the tDCS sessions contributed to the reduction in Ethan's fatigue, headaches, and dizziness post-tDCS due to the cognitive and physical break from his rehabilitation schedule. While Ethan rated his enjoyment of tDCS as relatively low, he indicated that he would be willing to do it again. Together, the pre/post-session symptom ratings

(i.e., individual session tolerance) and the tDCS Tolerability Questionnaire (i.e., tolerance across the entire protocol) indicated that Ethan tolerated tDCS treatment. These metrics for evaluating tDCS tolerance provide important context to tDCS safety and acceptability that can be implemented in future tDCS protocols for children and youth with any type of ABI.

Given the motor learning emphasis of neurorehabilitation (Takeuchi & Izumi, 2013), it was not surprising that the primary focus of most tasks in Ethan's physiotherapy sessions was acquiring and refining motor skills (Figure 2). However, because sensorimotor cortex damage directly affects the muscle strength, postural stability, and intralimb coordination that underlies gross motor function (Lima et al., 2011), these areas of concern were often secondary foci. And when strength, balance, or coordination was the primary task focus, *motor skill* was usually listed as a secondary focus, which further emphasizes the need to address multiple factors contributing to motor function. While the focus of some tasks remained the same across both video-recorded sessions (e.g., *motor skill* for walking), the foci of other tasks shifted as Ethan's gross motor function improved. For example, the primary focus of the stride stance task was the motor skill in video one with coordination and stability/balance being secondary foci. However, in video two, the primary focus became stability/balance while *motor skill* became a secondary focus. These changing foci suggest that stability/balance only became a priority once Ethan had learned the requisite components of the movement (e.g., weight shifting over his hemiparetic leg).

Documenting MLS use is integral to ultimately establishing the effective components of any motor learning focused intervention (Levac et al., 2011). The video-recorded physiotherapy sessions in this case demonstrated that within each task, the PT used overlapping MLS from all three MLSRI-22 categories. The most frequently used *therapist verbalization* MLS in both videos was MLSRI-22 item #3 'direct attention to the body'. While motor learning research recommends using an external focus of attention (i.e., #2 'direct attention to object/environment') (Pourazar et al., 2017), PTs use an internal focus of attention (i.e., #3 'direct attention to body') more often (Durham et al., 2009; Johnson et al., 2013). Although enhanced education regarding focus of attention may influence PTs' practice, an external focus may not always be practical in clinical scenarios, particularly in subacute ABI when there is often an emphasis on movement refinement. Similar to Spivak et al. (2021) who analyzed the MLS content of robotic-assisted treadmill training in inpatient pediatric ABI, the least used

therapist verbalization in this case report was #11 ‘encourage mental practice’. While motor imagery ability can be impaired in children with ABI (Caeyenberghs et al., 2009), the potential benefits of combining mental and physical practice in neurorehabilitation (Alashram et al., 2020; Souto et al., 2020) should not be overlooked. When fatigue and safety limit the physical practice of certain gross motor skills, particularly in early stages of ABI inpatient rehabilitation, mental practice may provide an opportunity to increase practice dose.

The most used *therapist action* MLS was #13 ‘provides physical guidance’, while #17 ‘recommends practice outside of therapy’ was not observed in either video. Physical guidance is frequently used neurorehabilitation and can be beneficial in pediatric ABI when processing verbal information is a challenge. It can also be used concurrently with verbalizations, as was observed frequently in the video-recorded sessions. Physical guidance not only reduces falls risk but also provides learners with the spatial and temporal feedback necessary for movement refinement (Wulf et al., 1998). However, practice outside of therapy sessions is equally important because it promotes the transfer of a motor skill to a functional and meaningful environment, and increases practice dose (Braga et al., 2005). While the video-recorded physiotherapy sessions did not include recommending practice outside therapy, study intervention logs indicated that the PT recommended task practice outside physiotherapy in other study sessions. Thus, Ethan had an opportunity to practice gross motor skills in a meaningful context and was an integral part of his physiotherapy intervention.

All five *practice organization* MLS were applied in each video-recorded physiotherapy session, illustrating how these MLS can be layered within a single treatment session. Repetitive practice is frequently used in neurorehabilitation because of its link with neuroplasticity (Lee et al., 1991) and was, indeed, a foundation for both video-recorded sessions. Within those repetitions, variable practice was observed when Ethan worked on walking in the parallel bars, on the treadmill, throughout the physiotherapy gym, and in the hallway. Within each task, the PT also progressed the level of difficulty by reducing support or increasing step distance. Given the complexity of ambulation and Ethan’s ability to follow directions and coordinate movement, ambulation was addressed through a combination of whole and part practice, with part practice used to refine specific components of gait before working on the skill in its entirety. For example, the stride stance task targeted efficient weight transfer onto Ethan’s more affected leg.

Following stride stance, the PT then emphasized the same weight transfer while Ethan walked across the gym. Random practice (i.e., interspersing the practice of one task among other tasks) (Lage et al., 2015) was also incorporated into the session. The contextual interference created by random practice increases cognitive demands and is considered essential to skill retention and generalization to real-life situations (Lage et al., 2015). By returning to walking, step-ups, and stride stance tasks within the same session, the PT intentionally challenged Ethan's ability to retain a motor plan after introducing other tasks that involved different motor plans which mimics the contextual interference occurring in daily activities.

The outcome measures documenting Ethan's gross motor progress demonstrated the strong potential for gross motor recovery during inpatient ABI rehabilitation. While a single case cannot determine whether tDCS augmented the effect of physiotherapy, Ethan's GMFM-88 change score after four weeks of tDCS intervention (33.05% points) surpassed the reference mean of 18.03% points (19.34) (Ryan et al., 2022) for inpatient children and youth with moderate to severe ABI over an entire admission. This improvement coincided with an increase in walking speed and PEDI-CAT Daily Activities and Mobility domain scores.

COPM goal satisfaction and performance ratings fluctuated between assessments, possibly due to changing parent and youth expectations during the rehabilitation process. These changing expectations highlight how the uncertainty of recovery, individual experiences, and the desire to return to pre-ABI level of function influence perceptions of progress throughout rehabilitation (Holliday et al., 2007). For example, Ethan rated his walking performance higher pre-intervention than post-intervention despite an increase in walking speed on the 10mFWT, attainment of his GAS walking goals, and a 36.91% increase on the dimensions D and E of the GMFM-88 (i.e., standing, walking, running, jumping). We speculate that this decreased performance rating may have been due to Ethan's changing expectations regarding his recovery and/or increased awareness of his mobility challenges with exposure to new ambulation opportunities during his admission.

While improvements observed between discharge and three-month follow-up can be attributed to community-based therapies and/or natural recovery rather than the tDCS intervention alone, change during this timeframe demonstrate the benefits of using a complementary set of outcome

measures to detect gross motor progress throughout recovery. Ethan's GMFM-88 total score changed by only 2.10% points between post-intervention and three-month follow-up, and his PEDI-CAT Daily Activities score and several COPM ratings plateaued which is indicative of skill retention rather than progress. However, Ethan's PEDI-CAT Mobility score changed the most (8 points) during the same period. The difference between GMFM-88 and PED-CAT Mobility change score patterns is likely due to the environmental context of PEDI-CAT items (e.g., getting on/off a school bus) and increased exposure to community-based gross motor activities after discharge. This interplay among correlated outcome measures demonstrates the value of employing a battery of complementary assessments to detect change at different points in the rehabilitation process.

While this case is not intended to infer intervention effectiveness, it illustrates the process and experience of incorporating tDCS into an inpatient motor learning-based physiotherapy program for a youth with ABI and provides structure for future research involving tDCS and pediatric motor skills-based interventions. Like the individualized physiotherapy intervention detailed in this case report, research-based motor learning interventions in pediatric ABI should be adapted to each child's physical and cognitive abilities and address meaningful goals to provide a true indication of the intervention's motor learning potential. By detailing the content of these individualized interventions, including MLS use, researchers will not only have an opportunity to determine the motor learning ingredients of effective interventions, but they will also increase the likelihood of replicating effective interventions in clinical practice.

5.6 Acknowledgements

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Chapter 6

6 General discussion and conclusion

6.1 Summary of findings

The primary aim of this thesis was to evaluate the feasibility of tDCS as an adjunct to inpatient physiotherapy for school-aged children and youth with moderate to severe ABI. However, prior to conducting the feasibility study, the gross motor change associated with traditional inpatient physiotherapy in children and youth with ABI had to be established and the decision of whether to evaluate neural outcomes alongside gross motor outcomes had to be determined. This chapter summarizes the key findings and implications from each manuscript, describes the dissertation's strengths and limitations within the context of advancing pediatric rehabilitation research, and proposes ideas for future research in children with ABI.

6.1.1 Study 1: Change in gross motor function with intensive rehabilitation for children and youth with ABI: A 10-year retrospective review

School-aged children and youth with moderate to severe subacute ABI who participate in inpatient physiotherapy make substantial gross motor progress during their admission (Dumas et al., 2004a). However, until this retrospective chart review, the documentation of gross motor change using standardized physiotherapy outcome measures in the literature was limited. Because the GMFM-88 is validated for and frequently used in pediatric ABI (Linder-Lucht et al., 2007; Storm et al., 2020), it was the primary outcome of interest in this review. Other outcomes frequently administered in the inpatient ABI program at Holland Bloorview Rehabilitation Hospital are the 6MWT, CB&M, and GAS, and were therefore secondary outcomes in this review.

This chart review involved health record data from 266 children (118 female) ages 5 to 18 years with subacute ABI who had either two GMFM-88 assessments or one GMFM-88 with another pre/post gross motor outcome measure in their chart. The mean GMFM-88 was 76.73% (SD=28.19) at baseline and 90.51% (SD=15.47) at discharge. There were 202 charts that had two GMFM-88 assessments with a mean change score of 18.03% (SD=19.34). The 6MWT (n=98)

and CB&M (n=89) mean change scores were 17.85% (SD=10.77) and 142.3m (SD=101.8), respectively. The baseline outcome measure score and the time between assessments explained most of the change score variation for each outcome measure. The mean GAS T-score was 55.06 (SD=11.50). While the most frequent goal area was ambulation (25% of all goals set), PTs set a variety of goals targeting gross motor skills, balance, strength, coordination, and endurance. Goals for children with greater gross motor limitations (i.e., low baseline GMFM-88) often targeted foundational gross motor skills such as head control, sitting, or supported standing, while goals for children with fewer gross motor limitations (i.e., high baseline GMFM-88) focused on advanced gross motor skills and refining aspects of posture, balance, and coordination.

6.1.1.1 Implications of study 1

This review indicates that children with subacute ABI make substantial improvements in gross motor function during inpatient rehabilitation but are often discharged with outstanding mobility challenges that have implications for their long-term development and participation. Subacute ABI is a critical period for neuroplasticity (Anderson & Catroppa, 2006; Giza et al., 2009) and, as such, may be the optimal time to introduce novel treatment approaches that enhance gross motor outcomes. While feasibility studies are frequently conducted in pediatric ABI, the very nature of their design means that they are underpowered and, thus, insufficient for determining treatment effectiveness. However, evaluating feasibility study change scores are an important factor when deciding whether a full-scale clinical trial is warranted. Comparing feasibility change scores with the mean change score estimates from this chart review can provide a preliminary indication of whether a novel treatment approach may improve gross motor outcomes compared to standard inpatient ABI physiotherapy. As there is no single outcome measure that adequately detects gross motor change across the range of functional abilities in pediatric ABI, this review also highlights the need to select a complementary set of standardized outcome measure capable of collectively detecting change across the spectrum of gross motor abilities.

6.1.2 Study 2: Using MEPs to measure the neural impact of tDCS on the primary motor cortex in healthy participants: A systematic review of studies involving motor behaviour

While studies evaluating M1-targeted tDCS in healthy individuals frequently use MEPs as a measure of neural change, tDCS research in clinical populations focuses predominantly on motor outcomes. Given the need to understand the neural changes that accompany changes in motor function in pediatric ABI and the absence of tDCS research evaluating MEPs in clinical populations, we conducted a systematic review of M1-targeted tDCS involving motor behaviour (i.e., motor practice and/or evaluation of motor performance) in healthy individuals that evaluated MEPs. Of the 22 manuscripts eligible for review, five evaluated motor outcomes with no motor practice, five involved motor practice but did not evaluate motor outcomes, and 12 involved motor practice and evaluated outcomes. Treatment parameters and MEP outcomes varied widely among studies. Eight studies were excluded from narrative synthesis due to a high risk of bias rating. Of the 13 studies in the narrative synthesis that evaluated anodal tDCS, 10 studies observed changes in MEPs. However, only four studies evaluated MEPs beyond 60 minutes post-tDCS which limits conclusions regarding prolonged change in MEPs. Five studies in the narrative synthesis evaluated change in motor performance. While four of these studies observed a change MEP amplitude that coincided with a change in motor performance, two studies observed similar changes in motor performance after sham tDCS. Overall, anodal tDCS combined with motor practice had a tendency toward increasing MEP amplitude. However, because MEP outcomes do not necessarily correlate with motor outcomes, MEPs may not be the most appropriate indicator of neural change in tDCS studies aiming to enhance motor performance.

6.1.2.1 Implications of study 2

Given the variability in results among the studies in this systematic review, MEPs do not appear to be the ideal neural outcome for tDCS studies involving motor practice. As such, we opted not to evaluate MEPs as part of our feasibility study evaluating tDCS as an adjunct to physiotherapy for children and youth with ABI. One of the primary challenges with MEPs is that they do not differentiate between the various cortical contributions to gross motor function, of which there are many. While other neural outcomes were not explored as part of this thesis, the use of MRI in

future tDCS studies for children with ABI should be considered, as MRI provides an opportunity to evaluate changes in brain structure, function, and connectivity (Turner, 2016) and has successfully detected the neural changes associated with motor learning (Frizzell et al., 2022; Hamano et al., 2021; Kraeutner et al., 2021).

6.1.3 Study 3: Evaluating the feasibility of tDCS as an adjunct to inpatient physiotherapy in pediatric ABI: A randomised feasibility trial

This blinded feasibility RCT allocated children ages 5 to 18 years with moderate to severe ABI receiving inpatient rehabilitation to receive 20 minutes of active or sham anodal tDCS immediately prior to 16 of their existing inpatient physiotherapy sessions. Feasibility was evaluated using the following indicators: eligibility, recruitment, retention, tolerance, preliminary treatment effect. Of 232 children admitted over 21 months, six were eligible (2.6%) which was far below the targeted 20% eligibility rate. However, four of the six eligible participants enrolled (66.7%) which was close to our recruitment target of 75%. One participant completed the entire study protocol, two were withdrawn midway for unrelated medical reasons, and one did not commence the study due to COVID-19 restrictions. The primary reasons for exclusion (age: n=66, brain tumour: n=38, seizures: n= 26) were expected based on past admission trends. However, the cumulation of other exclusion criteria (e.g., short admission, behavioural challenges, physiotherapy goals unrelated to ABI, bone flap removed, scalp wounds/incisions, decreased medical stability) was unexpected and not something we could have extrapolated from previous admission trends or the retrospective chart review. Pre/post tDCS session tracking indicated that the three participants tolerated the 20-minute active/sham tDCS with sub-electrode itchiness being the primary transient side effect. Tracking participant-reported symptoms pre/post tDCS allowed differentiation between tDCS side effects and ABI symptoms.

6.1.3.1 Implications of study 3

While the study was not feasible from eligibility and retention perspectives, study procedures (e.g., assessment, treatment, side effect tracking, physiotherapy session documentation) were successfully implemented and can be applied to future pediatric tDCS studies. Our feasibility results suggest that children and youth with ABI are often not medically ready to for tDCS during their inpatient admission. However, a tDCS and physiotherapy intervention may be

appropriate after inpatient rehabilitation when many medical concerns (e.g., bone flap removal, scalp incisions, decreased tolerance, decreased medical stability, weight bearing restrictions) have resolved.

To improve enrollment, future tDCS studies in children and youth with ABI should be multi-centre and the feasibility of an outpatient protocol should be explored. While similar tDCS parameters should be used (i.e., up to 2.0 mA for 20 minutes prior to physiotherapy), the frequency, number, and timing of treatment sessions will likely need to be adjusted to address feasibility challenges that are more often encountered in an outpatient protocol (e.g., travel, school schedule). From a process perspective, our study protocol was feasible and demonstrated the need for a designated research coordinator to act as a liaison between the clinical team, the child/family, and tDCS personnel. On a preliminary level, study participants tolerated the active/sham tDCS but needs to be evaluated in more children/youth to definitively conclude that it is tolerated in children with ABI. The established process for tracking symptoms and/or side effects before and after tDCS is an important contribution to tDCS research involving clinical populations with underlying symptoms that may overlap with tDCS side effects (e.g., fatigue, headache, dizziness).

6.1.4 Study 4: Integrating tDCS into an existing inpatient physiotherapy program to enhance motor learning in an adolescent with TBI: A case report

To complement the feasibility study results, this case report described how tDCS was incorporated into an inpatient physiotherapy program for an adolescent with severe TBI, detailed the content of his physiotherapy sessions, and summarized how gross motor progress was evaluated. The youth was allocated to the active tDCS treatment group and received 20 minutes of anodal tDCS immediately prior to 16 physiotherapy sessions over four weeks. He completed all tDCS sessions as planned with the primary side effect being itchiness under the electrodes during the tDCS sessions. Tasks in his individualized physiotherapy session often had several foci (e.g., skill acquisition, strength, and balance) with focus changing as the youth progressed. MLS were layered within tasks to support performance and learning. His GMFM-88 score increased by 33.05% points over the four-week intervention period. The three-month follow-up assessment indicated that his GMFM-88 gains were retained but did not progress substantially.

However, his functional mobility (i.e., PEDI-CAT mobility score) progressed predominantly after discharge home. This case also identified some challenges with using the COPM to evaluate mobility goals during the study and as the youth transitioned from an inpatient to community setting. The youth and parent reported decreased performance and satisfaction related to walking despite other outcomes (i.e., GMFM-88, GAS, PEDI-CAT mobility domain, 10mFWT) indicating substantial improvement. This discrepancy may have been due to changing expectations and increased awareness of mobility limitations throughout inpatient rehabilitation and after discharge.

6.1.4.1 Implications of study 4

While the feasibility of tDCS use in one inpatient pediatric ABI program was limited by eligibility and retention, delving into the single case experience demonstrated how tDCS can be successfully integrated into an existing inpatient physiotherapy program when a participant meets study eligibility criteria. By detailing symptom tracking pre/post tDCS sessions, this case demonstrated how it was possible to differentiate between ABI symptoms and tDCS side effects in a youth who experienced considerable fatigue. The content of the behavioural intervention paired with tDCS is critical to motor learning. Thus, a descriptive analysis of task and MLS progression during the study protocol provided insight into how the physiotherapy portion of the intervention promoted motor learning. This analysis was not only beneficial for the feasibility study but is also an indication of how physiotherapists create opportunities for motor learning during inpatient ABI rehabilitation. Finally, detailing how a complementary set of outcome measures was used to detect gross motor progress at various points in recovery exemplifies how certain measures may detect more change at different points in rehabilitation than others. It also demonstrates potential challenges with patient-reported outcomes when used across a continuum of care. The details of this case report combined with the feasibility study results provide structure for implementing, monitoring, and measuring outcomes in future tDCS research in pediatric rehabilitation.

6.2 Thesis strengths and contributions

6.2.1 Identifying a set of clinical outcome measures for gross motor research in pediatric ABI

A common thread throughout this dissertation is the need for a set of complementary outcome measures capable of detecting the gross motor changes associated with an intervention, particularly in a heterogeneous clinical population like pediatric ABI. While pediatric rehabilitation research publications and our team's clinical experience was the foundation for the initial selection of outcomes for the feasibility study, the chart and systematic reviews further supported this set of outcome measures. The chart review provided empirically derived estimates of gross motor change associated with inpatient rehabilitation for school-aged children and youth with subacute ABI using several clinically relevant outcome measures. The mean change scores for the GMFM-88, CB&M, and 6MWT can now be used as benchmarks in clinical care during the sub-acute stage of rehabilitation as well as in future gross motor research in inpatient pediatric ABI. In particular, the regression models derived from the chart review (p. 40) can be used to estimate gross motor change that occurs with inpatient ABI rehabilitation, with the GMFM-88 model having greater predictive value compared to the CB&M and 6MWT models.

In addition to individualizing interventions, clinicians and researchers should use individualized goal setting to detect meaningful change in function (Cusick et al., 2007; Law et al., 1997; Schlosser, 2004). Both GAS and the COPM are individualized outcomes capable of detecting significant within (and between) group change in pediatric rehabilitation research (Cusick et al., 2006) and, as such, were included in the feasibility study. The chart review results supported the use of GAS, particularly when more standardized measures did not evaluate a specific gross motor skill or did not include scoring increments suitable for the child's level of function. While the COPM was not used by the clinical PTs in the chart review, its frequent and successful use in pediatric clinical research evaluating motor interventions (Hilderley et al., 2020; Hilderley et al., 2016; Kirton et al., 2017; Komar et al., 2016; Morgan et al., 2016; Schnackers et al., 2018) supported its use in the feasibility study to gain a parent and child perspective on aspects of mobility and participation. Although both measures are individualized, their unique properties make them complementary when used in combination. The COPM involves the child and/or parent specifying their own goals in a semi-structured interview with the therapist, but evaluation

of performance and satisfaction is entirely child/parent-reported (Cusick et al., 2006; Law et al., 1990). For GAS, the child/parent may work with the therapist to identify goal areas, but the therapist constructs the appropriate levels for each scoring increment based on their clinical expertise and scores the goals at reassessment (Cusick et al., 2006).

The benefit of using both individualized measures is obtaining perspectives from the child/parent and physiotherapist. In the feasibility study, children and parents identified more generalized goals (e.g., "to walk again on my own") while the GAS goals created by the physiotherapist were more detail-oriented (e.g., "to walk half days in the hospital using a rollator walker") with more concrete differences in scoring levels. However, while the case report participant met his GAS goals, his COPM scores were more variable with his walking scores declining over time despite objective improvements in walking speed (i.e., 10mFWT) and walking-specific items on the GMFM-88. Similar to studies involving COPM goals in children with CP (Kang et al., 2020; Rich et al., 2016), this discrepancy highlights some of the challenges of using the same COPM goals over a prolonged period of time during which child and/or parent priorities and perceptions may change.

The PEDI-CAT is another outcome measure that is frequently and successfully used in pediatric rehabilitation research (Grecco et al., 2017; Pin et al., 2019; Vidal et al., 2021). This measure solicits parent input about their child's functional abilities beyond what is observed in a therapy session with the parent reporting the ease with which the child performs a set of tasks within the context of their daily activities (Haley et al., 2011; Haley et al., 2010). Six to 15 points of change on the PEDI-CAT represents the minimum clinically important change during inpatient rehabilitation with children with TBI typically changing a mean of 8.1 points throughout their admission (Iyer et al., 2003). The combined use of the GMFM-88 and the PEDI-CAT in the case report demonstrated the complementary nature of these two measures and the benefits of using two outcome measures to detected change in gross motor skills at different points in recovery where the GMFM-88 evaluates gross motor skills within a standardized clinical context and the PEDI-CAT provides an indication of gross motor skills within the context of daily life. The youth experienced substantial improvement on the GMFM-88 during the four-week study protocol (33%) but not on the PEDI-CAT mobility domain (2 points), followed by substantial gains on the PEDI-CAT mobility domain three months post-intervention (8 points) with limited

change on the GMFM-88 (2%). Had only one of these measures been used, we may have mistakenly concluded that either the youth made no change during the study intervention (i.e., if the PEDI-CAT was the sole measure) or he made no gains after discharge from inpatient rehabilitation (i.e., if the GMFM-88 was the sole measure), neither of which would have accurately represented his gross motor progress.

Timed walk tests of various durations or distances are a measure of walking ability frequently used to evaluate response to an intervention with mixed success (Kane et al., 2016). While the 6MWT is frequently used in pediatric clinical care (Chapter 2) and research (Storm et al., 2020), children often have difficulty sustaining their effort during longer tasks (Bartels et al., 2013) and, as such, the 6MWT may not provide the most accurate measurement of the farthest distance a child can walk in six minutes. In contrast, distraction or disengagement are less likely to occur during a brief task like the 10mFWT. Ten metres is the minimum distance a person must be able to walk without PT assistance to be deemed a functional ambulator (Thompson et al., 2008) and is an attainable distance for individuals who have recently regained the ability to walk after ABI (Watson, 2002). Thus, we decided to use the 10mFWT instead of the 6MWT in the feasibility study. Unlike the 6MWT, the 10mFWT does not evaluate walking endurance. However, the chart review and the case report indicated that PTs frequently use GAS to evaluate walking endurance, thus ensuring that multiple aspects of ambulation were assessed with the set of outcome measures featured in the feasibility study.

While the GMFM-88 aligned with the gross motor abilities of the participants in the feasibility study, children with more advanced gross motor challenges would have required an additional gross motor measure to evaluate both quantitative and qualitative changes in advanced motor skills. The decision to use the ABI-CA to complement the GMFM-88 was informed by the chart review that demonstrated the GMFM-88 ceiling effect in children who were ambulatory on admission to the inpatient ABI program. Although the CB&M was the measure used in the chart review once children met the GMFM-88 ceiling, the CB&M only evaluates the balance and mobility aspects of gross motor skills and does not evaluate aspects of strength, agility, and coordination required for advanced gross motor skills (Wong et al., 2014). Due to its high correlation with the CB&M and ability to evaluate multiple aspects of advanced gross motor skills (Wong et al., 2014), the ABI-CA was used in the feasibility study instead of the CB&M.

By providing a requisite level of function (i.e., ability to walk down a hallway unaided) to complete the ABI-CA for the feasibility study, we ensured that the child was challenged at a level that was safe and appropriate for them.

6.2.2 Feasibility study design

Of all study designs, appropriately powered RCTs provide the highest level of evidence (Burns et al., 2011). However, feasibility studies play an integral role in determining the need for a definitive RCT, calculating an appropriate RCT sample size, and refining study processes (El-Kotob & Giangregorio, 2018; Lancaster et al., 2004; Morgan et al., 2018; Thabane et al., 2010). Feasibility studies are, by design, underpowered and, as such, should evaluate *a priori* feasibility targets such as process (e.g., eligibility, retention, adherence, data collection) and scientific indicators (e.g., estimate of treatment effect, safety, dose) rather than calculating statistical significance (Lancaster et al., 2004; Thabane et al., 2010; Eldridge et al., 2016). Our feasibility study demonstrated how to apply CONSORT guideline recommendations for randomized feasibility trials (Eldridge et al., 2016) to pediatric rehabilitation research. The *a priori* targets in this feasibility study were established in part by our recent experience evaluating the feasibility of robotic assisted treadmill training as part of the same inpatient ABI physiotherapy program (Wright et al., 2018). By using a feasibility design, we were able to refine inclusion and exclusion criteria in response to low eligibility after nine months of admission screening and, while eligibility remained the primary barrier to study feasibility, tracking the age, diagnosis, and reasons for exclusion of all inpatient ABI admissions provided valuable information for designing future gross motor studies involving children and youth with ABI.

Thabane et al. (2010) describes the possible outcomes of a pilot or feasibility study as the main study is a) not feasible, b) feasible with modifications, c) feasible with closer monitoring, or c) feasible without modifications. However, our feasibility study's challenges and successes illustrate the multifaceted nature of feasibility itself, where some elements of a study may not be viable while other aspects of the study meet the feasibility targets. For example, the eligibility criteria were not feasible in this inpatient ABI rehabilitation program and retention was a challenge due to unrelated changes in medical stability. In contrast, the tDCS treatments were tolerable, a timely transition between tDCS treatment on the inpatient unit and the physiotherapy

gym was attainable, and the study documentation/assessment processes were manageable for staff and participants. Thus, it is not only important to consider a breadth of feasibility indicators when designing a study, but researchers must also contemplate the weight of each indicator in determining the overall success of the study. While a main study for the current tDCS protocol is not feasible, the success of specific feasibility indicators (e.g., process, tolerance) demonstrate the potential for other avenues of tDCS research in pediatric ABI.

Although feasibility studies do not need to be randomized, a randomized feasibility trial permits testing of the randomization process (Eldridge et al., 2016; Thabane et al., 2010). Our feasibility study demonstrated that participants could be allocated to treatment group using a dynamic blocked randomization process while maintaining blinding of participants, study assessors, treating PTs, and the members of research team conducting data analysis. The active nature of most rehabilitation interventions makes it challenging to blind participants to group allocation (Armijo-Olivo et al., 2017; El-Kotob & Giangregorio, 2018). However, tDCS provides a unique opportunity where participants can be blinded to treatment allocation by using sham tDCS (Ambrus et al., 2012; Palm et al., 2013). A study design where participants are blinded to group allocation also increases the likelihood of similar adherence rates between groups and decreases the potential for performance bias (El-Kotob & Giangregorio, 2018). By adhering to Eldridge et al.'s (2016) extension to the CONSORT statement for randomized feasibility trials, we improved the reporting quality and interpretation of our feasibility study results. Further, by applying these guidelines, we are encouraging this level of rigour in future tDCS feasibility studies in children and youth with ABI.

Tracking the age, diagnosis, sex, and study exclusion criteria for all inpatient ABI admissions over a 21-month period provides valuable information for future gross motor research in this clinical population. From a practical perspective, the minimum age for this study was five years due to the potential challenges associated with younger children adhering to standardized physiotherapy intervention and accurately reporting tDCS symptoms. Tracking data over a 21-month period indicated that 71.6% of inpatient ABI admissions were five years of age or older, which not only supports this threshold from an eligibility perspective but also identifies possibilities for research at this facility in children under the age of five.

Currently, research in inpatient pediatric ABI tends to concentrate on TBI or combines TBI and non-TBI without providing a breakdown of the diagnostic groups within the sample. By identifying the diagnostic makeup of inpatient ABI admissions and considering the clinical presentation(s) associated with a particular diagnosis, there is now further opportunity at our facility to develop and evaluate new treatment approaches geared toward specific diagnoses or clinical presentations. The school-aged ABI admissions (n=166) by diagnostic group were: brain tumour 22.9% (n=38), TBI 22.3% (n=37), stroke 18.1% (n=30), neuroinflammatory 15.7% (n=26), epilepsy 12.7% (n=21), post-infectious 4.8% (n=8), and hypoxia 3.6% (n=6). Given that 77.1% of program admissions were non-traumatic ABIs, the feasibility study emphasizes the need for gross motor research in diagnoses beyond TBI. Specifically, brain tumour and epilepsy were study exclusions that accounted for 64.5% of school-aged program admissions. While children who have had a brain tumour resection or undergone surgery for intractable seizures are often excluded from intervention-based research in the subacute stage of recovery due to concurrent treatments (e.g., radiotherapy) or decreased stability (e.g., unknown seizure status), they also contend with gross motor challenges that necessitate inpatient ABI rehabilitation. As such, it is important to either evaluate new treatments that they can benefit from along with children from other diagnoses within ABI (e.g., circuit training, lower extremity constraint induced movement therapy) or explore new treatment approaches specific to their needs (e.g., a novel approach to balance training for children with ataxia after cerebellar tumour resection).

The feasibility study identified additional exclusion criteria specific to tDCS (n=11; bone flap removed, scalp/wounds/incisions, pacemaker, metal fragments in head) as well as other exclusions that could apply to many rehabilitation interventions (n=60; reduced length of stay, behavioural challenges, communication challenges, not receiving active physiotherapy, ABI not confirmed, chronic ABI, decreased medical stability, weight bearing restrictions, other neurological diagnoses). While each of these exclusions were known possibilities when the feasibility study was developed, the frequency that these exclusions would be encountered was unknown. These data can now be used to inform the design of future gross motor intervention research in pediatric ABI.

6.2.3 Physiotherapy session content

Historically, the active ingredients of rehabilitation interventions in clinical and research settings have not been clearly defined (Hart et al., 2014; Whyte & Hart, 2003; Zanca et al., 2019). While we know that the intensity of inpatient physiotherapy in children and youth with ABI is linked to improved mobility outcomes (Dumas et al., 2004b), there is limited description of what takes place during their physiotherapy sessions. By documenting physiotherapy session content, there is an opportunity to unpack and ultimately identify the effective ingredients of a treatment session or an overarching treatment approach (Whyte & Hart, 2003). However, simply listing the tasks completed in a treatment session overlooks the PT's rationale for selecting each task and how the PT facilitates performance and/or learning. By combining PT documentation from the physiotherapy intervention log (Appendix D) with MLSRI-22 scores in this feasibility RCT, we were able to delve into the PTs' session-specific goals and observe how the PTs applied MLS in an attempt to achieve these goals. The physiotherapy intervention log was an adapted version of the intervention log from Hilderley et al. (2016) where, at the end of each treatment session, the PT documented the tasks practiced in the session (in the order performed), along with the primary and secondary foci of each task, thus, providing information on the physiotherapy principles (i.e., stability/balance, coordination, strength, motor skill, fitness/endurance) they were targeting with each task. The menu of task foci on the intervention log provided an element of standardization to the treatment process within an individualized treatment session and a basis of comparison between treatment sessions and among participants (Hilderley et al., 2016).

Because inpatient physiotherapy for children and youth with ABI typically focuses on relearning and refining motor skills, it is reasonable to surmise that the MLS content of a treatment session is likely an active ingredient of the intervention (Levac et al., 2011). Thus, documenting the extent and type of MLS observed in a treatment session provides insight into how the PT facilitates motor learning (Levac et al., 2011). PTs tend to approach treatment sessions with an intervention plan, such as a list of tasks (and ideas for potential variations or progressions) to address specific session goals, but then adapt their approach within the session based on the child's performance and understanding (Ryan et al., 2020). For example, the PT may have to decrease the level of challenge of a particular task or provide more physical guidance than

planned due to the child's fatigue, or they may demonstrate how to perform a task when the child does not appear to understand the verbal instructions.

While tDCS primes the brain to form new neural pathways and strengthen existing connections (Stagg & Nitsche, 2011), the quality of the motor practice that occurs during this state of altered cortical excitability is also integral to motor learning. As practice quality is associated with MLS application, using the MLSRI-22 to detail the MLS content of the video-recorded physiotherapy sessions in the feasibility RCT provided critical information about the PT's role in promoting motor learning within the intervention paired with tDCS. By comparing MLS application across participants and PTs early in the feasibility study treatment protocol, it was evident that directing attention to the body, physical guidance, repetition, and whole practice are frequently used with the study participants. While we cannot generalize these observations to all children with ABI, this preliminary look at MLS content can be combined with Spivak et al.'s (2021) observations in the same inpatient ABI program to suggest that this combination of MLS may be frequently used during inpatient ABI physiotherapy for children and youth who are not yet capable of independent ambulation.

The case report provided further insight into how MLS application can evolve and/or remain consistent across treatment sessions. To optimize the motor learning benefits of an intervention, it is important to provide an appropriate level of challenge based on the task, task conditions, and the skill of the learner (Guadagnoli & Lee, 2004; Pollock et al., 2014). As such, PTs continually evaluate performance within a particular session and adapt MLS application based on their observations (Ryan et al., 2020). The case identified the MLS used consistently across both video-recorded treatment sessions (e.g., directing attention of object/environment, physical guidance, repetition, progressive practice) and the MLS that changed. We speculate that these changes were to some extent based on the youth's progress (e.g., direct attention to body, errors as part of learning, whole practice) or the tasks presented (e.g., link task to other activities, external device that augments feedback). While these observations highlight the task-specific nature of MLS (Levac et al., 2011), they also emphasize the static (i.e., unchanging child and therapist characteristics) and dynamic (i.e., aspects that gradually change based on the child's progress toward their therapeutic goals) factors associated with MLS application (Ryan et al., 2020). Future directions for MLS research are detailed in section 6.4.

6.3 Limitations

The limitations of each study are detailed in Chapters 2 through 5. However, in its entirety, this dissertation also illustrates several overarching limitations associated with evaluating tDCS as an adjunct to inpatient physiotherapy in pediatric ABI and many of these limitations generalize to other gross motor interventions research in these children. The primary limitation that affects all pediatric ABI research is the heterogeneity within this clinical population. However, there are additional limitations related to isolating the effective components of an intervention, understanding the neural changes that accompany gross motor improvements, and using retrospective clinical data to compare current intervention practices with new treatment approaches.

6.3.1 Heterogeneity of pediatric ABI

The heterogeneity of clinical presentations within any diagnostic group complicates the development of clinical trial protocols in rehabilitation. While defining subgroups within a diagnosis can help to control for heterogeneity, it is not always possible. For example, the Gross Motor Function Classification System (Palisano et al., 1997) can be used in gross motor research in children with CP, but it is not validated in childhood onset ABI (Towns et al., 2018). Heterogeneity is amplified within pediatric ABI due to the numerous diagnoses that fall under this diagnostic umbrella and the variable timing of ABI onset relative to other developmental processes (Bedell, 2008). The variability in medical procedures and stability during subacute ABI further increases heterogeneity and had substantial implications when establishing eligibility criteria, standardizing treatment protocols, and evaluating outcomes in this dissertation. When establishing study eligibility criteria in clinical trials (Portney & Watkins, 2020), researchers aim to minimize confounding variables that could obscure the treatment effect. By expanding our inclusion criteria after the first nine months of the trial in an attempt to increase eligibility, we introduced additional confounding variables (e.g., diagnoses beyond stroke or TBI, increased range of gross motor abilities) that could have obscured a preliminary treatment effect had we recruited more participants. Ultimately, these changes had no impact on our results, as all participants met the original eligibility criteria. Further, when reflecting on our eligibility criteria at the conclusion of the study, we decided that there were no additional changes that we could have made without compromising the scientific rigour of the study or participant safety.

When creating a physiotherapy treatment plan, PTs consider the child's clinical presentation which is shaped by ABI location and severity, developmental age, motivation, and goals (Levac et al., 2012; Ryan et al., 2020). While individualizing therapeutic intervention is necessary for optimizing gross motor outcomes in pediatric ABI (Braga et al., 2005), it creates added challenges when developing a research treatment protocol as implementing a set list of standardized exercises in these children is likely neither feasible nor effective. Thus, rehabilitation researchers need to establish creative ways of comparing individualized interventions. As neurological physiotherapy focuses on restoring movement and function through tasks that target either the functional activity (e.g., walking, running) or the underlying impairment (e.g., balance, strength, coordination) that impedes function (Dumas et al., 2004b; Lennon, 2011), categorizing tasks based on common task foci in neurological physiotherapy (e.g., strength, stability/balance, coordination, motor skills, endurance) permits comparison of individualized interventions. While documenting task foci during the feasibility study sessions according to a menu of physiotherapy foci provided an appropriate basis of comparison, it did not actually standardize the physiotherapy intervention as the PTs were not required to address specific foci as part of the study protocol. The feasibility study design allowed children to receive the motor skills-based physiotherapy approach and intensity already provided through the inpatient ABI program, which ensured that their treatment was individualized, but meant that we had little control over treatment session content. Had a menu been used to outline the extent that each focus was addressed within a physiotherapy session, the intervention would have been slightly more standardized. However, this standardization could have been detrimental to participants' obtaining their individualized goals.

The success of a clinical trial is not only based on the effectiveness of an intervention but is contingent upon researchers selecting the most suitable outcome measures to detect clinically meaningful change in a specific construct (Coster, 2013). Our decision to use the GMFM-88 as a co-primary outcome in the feasibility study was entirely appropriate for the three participants who completed the baseline assessment. However, if children with more advanced gross motor goals had enrolled in the study, the GMFM-88 ceiling effect would have decreased our ability to detect improvements. To account for the range of gross motor abilities within pediatric ABI, we intended to use the ABI-CA as a co-primary outcome instead of the GMFM-88 for participants

capable of walking independently down a hallway at baseline. However, given the sample enrolled, we did not need to implement this option. While substituting the ABI-CA for the GMFM-88 addresses the GMFM-88 ceiling effect in children who are ambulatory upon admission to inpatient rehabilitation would be straightforward in the feasibility study, we would not have had a reference mean change score for the ABI-CA. However, the use of these two measures would have implications for analysis of the treatment effect in a full-scale clinical trial. For example, we would need to determine if a pooled index (Kueper et al., 2020; Collada et al., 2021) that combines GMFM-88 and ABI-CA scores would be beneficial as a primary gross motor outcome rather than evaluating the outcomes separately.

6.3.2 Isolating the effective components of inpatient physiotherapy

The chart review indicated that inpatient ABI physiotherapy focused on relearning motor skills and addressing the underlying impairments (e.g., strength, motor control, tone, balance, coordination, endurance) that contributed to decreased motor function was associated with improved gross motor outcomes. However, treatment effectiveness is likely also associated with the PT's ability to adapt intervention content to address each child's individual needs. Given the variability in PT documentation in the health record, the chart review did not provide sufficient detail for identifying the effective components of physiotherapy intervention beyond stating the focus of intervention based on GAS goal areas. Accordingly, an analysis of the physiotherapy session content beyond health record data was required. As practice and/or experience undoubtedly contributes to a child's motor learning, and research in healthy and clinical populations indicates that MLS also play a role in promoting motor learning, the feasibility study used session documentation and videos to explore the task and MLS content of the physiotherapy sessions paired with tDCS. While documenting session content is the first step toward understanding the active ingredients of physiotherapy intervention, it does not directly indicate how various aspects of an MLS-based intervention contribute to treatment effect.

Unlike laboratory-based motor learning research in nonclinical populations that evaluate the effect of a single MLS applied within a highly standardized process, there are ethical and practical considerations that prevent similar protocols from being implemented in clinical research, particularly in the subacute stage of ABI when the established standard of care involves

individualized physiotherapy intervention where MLS and other treatment choices need to consider the child's characteristics and needs. This dissertation described the physiotherapy session content to demonstrate that standardized session documentation is a necessary precursor to evaluating intervention effectiveness but does not establish the effectiveness of specific MLS. Further, MLSRI item mapping in this thesis, as well as in work from Spivak et al. (2021) and MacWilliam et al. (2021), indicates that therapists often use combinations of MLS that vary based on the clinical situation. This individualization and overlapping of MLS may limit the ability to definitively determine the effectiveness of single MLS in future research. However, ideas for addressing MLS effectiveness are provided in section 6.4 Future directions.

6.3.3 Understanding the link between neural and functional outcomes

Researchers continue to explore the link between functional and neural outcomes with the goal of explaining the mechanisms underlying motor learning and optimizing motor learning interventions in neurorehabilitation. However, our understanding of this link is still in its infancy. There are multiple technologies that evaluate neural outcomes but, like functional outcome measures, each technology has its limitations. Further, the availability of these technologies and the burden of additional assessments can be barriers to administering both neural and functional outcome measures in clinical research. Evaluating change in MEPs seemed like a possible option given our lab's access to TMS, the limited time commitment for participants relative to MRI, and their frequent use as neural outcomes in tDCS research involving healthy participants. However, these advantages were offset by concerns about the validity of MEPs as an indicator of motor learning (Bestmann & Krakauer, 2015), participants' tolerance of TMS (Croarkin et al., 2011), and the ability to elicit an MEP in a child with ABI (Nemanich et al., 2019). While many of these questions could have been evaluated as part of the feasibility study, we had to determine the scientific appropriateness of evaluating change in MEP amplitude as neural outcome which led to our systematic review.

Our decision to conduct a systemic review in a nonclinical population was two-fold: 1) the availability of tDCS studies involving motor behaviour that measured MEPs, and 2) the desire to isolate the effect of MEP results in these tDCS protocols independent of neurological injury. Most tDCS studies in clinical populations focus on functional outcome measures and, for the few

studies in clinical populations that measured MEP outcomes, it is unclear how their results would translate to children with ABI. A limitation of synthesizing research in a nonclinical population was the difficulty isolating the impact of a tDCS treatment protocol on MEPs in an optimally functioning nervous system, particularly when a variety of factors contribute to intraindividual MEP variability. However, on the positive side, the absence of neurological injury limits response variability associated with different injuries and provides a more accurate indication of how tDCS protocols involving motor behaviour influences MEPs. While the systematic review results suggest that a different neural outcome is likely better suited to evaluating the neurophysiological underpinnings of motor learning, exploring additional neural outcomes was beyond the scope and timeframe of this thesis.

6.3.4 Using a chart review as a foundation for the feasibility study

Drawing upon retrospective health data permitted the estimation of gross motor outcomes associated with current inpatient physiotherapy intervention and provided a basis of comparison for the feasibility study results. However, the assessment conditions and documentation accuracy are unknown. Further, change score calculations were limited to the outcome measures used by the PTs in the program. Fortunately, the outcome measures used in this inpatient program (e.g., GMFM-88, CB&M, GAS, 6MWT) are validated for children and youth with ABI and two of the four outcome measures abstracted in the chart review provided valuable reference points for the feasibility study. However, the chart review did not provide a basis of comparison for the COPM, 10mFWT, or ABI-CA.

Given our challenges with feasibility study eligibility, an outstanding question is whether the chart review could have been designed to identify these concerns. The chart review was designed to identify school-aged children who were admitted for inpatient ABI rehabilitation for a minimum of six weeks and capable of participating in standardized physiotherapy assessment at two time points in their admission. This design indicated that 48.7% of school-aged children in the inpatient ABI program met these criteria. However, the chart review was not designed to collect details regarding medical stability, tolerance to physiotherapy intervention, bone flap removal, or scalp incisions. While this information could have theoretically been found somewhere within the health record (i.e., physician, physiotherapist, or nursing progress notes),

there was no guarantee that it would have been documented consistently across charts and, therefore, would probably not provide an accurate picture of participant eligibility. Some exclusion criteria could have been easily identified using admission assessment documentation. For example, a brain tumour diagnosis, bone flap removal, or metal instrumentation would be clearly documented in an admission assessment and would remain unchanged over the course of the admission. Conversely, a child's medical stability, physiotherapy tolerance, and wound healing would be difficult to ascertain from a single note and subject to fluctuations throughout an admission and likely prone to reporting variability depending on the clinicians involved in the child's care.

Further, a 10-year retrospective chart review cannot forecast future admission trends, particularly admissions during the COVID-19 pandemic. While we followed many of Huang et al.'s (2018) recommendations for improving clinical trial recruitment over the course of developing and conducting the feasibility study (e.g., eliminate eligibility criteria not necessary for ensuring patient safety, engage stakeholders in the process, reduce procedures to those related to the scientific question), an environmental scan prior to commencing the study would have likely identified eligibility concerns. Instead, we relied on our recent experience recruiting for a Lokomat robotic treadmill training feasibility study in the inpatient ABI program to estimate recruitment for the tDCS study due to many similarities between the physiotherapy assessment and treatment protocols and adjusted our estimates based on the differences in eligibility criteria (e.g., the Lokomat study had more narrow gross motor criteria, the tDCS study had more restrictions based on cranial defects). Had we formally tracked eligibility criteria of inpatient ABI admissions over a six-month period using the tDCS feasibility tracking document (Appendix E), we would have likely concluded that eligibility would not meet our targets and proceeded with a different plan.

6.4 Future directions

This dissertation led to several recommendations for future gross motor research in pediatric ABI: 1) evaluate the feasibility of an outpatient tDCS and physiotherapy protocol, 2) research gross motor interventions for children often excluded from clinical trials, 3) investigate MLS

effectiveness within physiotherapy interventions, 4) explore the link between neural and functional outcomes, and 5) involve multiple sites to optimize recruitment.

The challenges associated with tDCS protocol eligibility during inpatient ABI rehabilitation suggest that an outpatient protocol may be more feasible. An outpatient protocol could target school-aged children in the subacute stage of recovery who do not require inpatient admission and/or children in the chronic stage of recovery. Either demographic would likely involve children with fewer exclusion criteria (e.g., decreased medical stability, decreased tolerance, bone flap removal, unhealed scalp incisions) which should improve their eligibility potential. However, an outpatient study requires an additional time commitment (i.e., for travel) from children and their families that could adversely affect recruitment and retention. There is also potential to explore tDCS and physiotherapy in children under five years of age, although tDCS parameters as well as tolerability and gross motor assessments would require adaptation to meet the needs of a younger age group. Additionally, a more interdisciplinary approach to tDCS intervention could be explored in pediatric ABI where tDCS is directed toward a neural target that influences both cognitive and motor function and is paired with cognitive and motor intervention (i.e., cognitive intervention during tDCS and motor intervention during the period of altered cortical activity immediately following tDCS). The dorsolateral prefrontal cortex could be one such target as it is active during the early stages of motor learning (Dayan & Cohen, 2011) and is frequently the neural target in cognitive tDCS interventions (Zaninotto et al., 2019).

To optimize physiotherapy assessment and treatment in children with ABI of all ages and abilities, researchers should focus on understudied children to address their rehabilitation needs. Children with brain tumours or epilepsy account for a large proportion of inpatient admissions in this ABI program (a combined total of 36% of charts abstracted in the chart review and 39% of admissions during the feasibility study). While our chart review demonstrates that these children benefit from inpatient physiotherapy, they are often excluded from gross motor research during the subacute stage of recovery due to ongoing medical interventions (e.g., radiotherapy, optimizing seizure medication), decreased medical stability, or technology-specific contraindications. Thus, researchers should consult with key stakeholders within these diagnostic groups (e.g., children, families, community partners, physicians) to determine their specific gross motor needs and explore interventions accordingly. There are also children with ABI who benefit

from inpatient physiotherapy but are excluded from gross motor research due to difficulty participating in standardized physiotherapy assessment for cognitive or behavioural reasons. In clinical practice, PTs frequently adapt assessment and treatment for children who have difficulty following directions which indicates that similar adaptations could also occur in a research setting. Thus, alternative methods of assessment should be considered and validated in these children.

Although implementing novel treatment adjuncts during physiotherapy intervention may enhance motor learning, the physiotherapist's ability to optimize MLS application while using the treatment adjunct is likely essential to the motor learning process (Levac et al., 2012; Ryan et al., 2020; Spivak et al., 2021). However, with little limited evidence of the effectiveness of specific MLS in pediatric ABI, it is difficult to definitively conclude why an intervention promotes motor learning. Thus, the next step in motor learning research for children with ABI is evaluating the effectiveness of specific MLS independent of adjunctive treatments. Some MLS (e.g., mental practice, analogy, random practice) may be easier to isolate within a treatment protocol compared to others (e.g., repetition, promoting errors as part of learning) that are likely optimized when layered with other MLS. Researchers could start by evaluating the MLS that can be isolated in a study design where the MLS is either present or absent from a particular treatment protocol. The MLS needs of younger children with ABI and children with substantial cognitive challenges should also be explored by looking at the MLS content of physiotherapy sessions for children with limited ability to follow directions.

Given the ongoing need to establish the link between functional and neural outcomes, future gross motor research should include neural outcomes. As gross motor function involves a complex network of cortical and subcortical structures with variability in activation depending on the person's skill proficiency, it is important to use neural outcomes that have good spatial resolution and are sensitive to change, with MRI likely being the most suitable option. Differences in recovery patterns based on injury location and severity may provide insight into why a particular treatment approach optimizes gross motor outcomes in children with specific clinical presentations. Recovery should also be explored by observing the areas of brain activation at different stages of motor skill recovery.

Where possible, clinical trials should involve multiple sites to optimize recruitment (as needed in this study) and increase generalizability of results (Swartwout et al., 2019; Weinberger et al., 2001). Multisite clinical trials may be more challenging when research takes place within an existing inpatient ABI program due to varying service delivery models across institutions. However, given that children's functional goals would be similar across institutions and standardized MLS training would ensure that all physiotherapists possess a baseline level of MLS knowledge, multisite trials would be possible when the appropriate environmental scans and stakeholder consultation occurs prior to protocol development. Given the time constraints and medical concerns encountered with some inpatient admissions, outpatient-based clinical trials may be more conductive to multisite design. As multisite research often requires increased coordination and funding, a feasibility trial should precede any definitive clinical trial to refine study processes and ensure that a clinical trial is warranted. However, the eligibility and retention challenges encountered during our inpatient feasibility study would likely persist in other inpatient settings. As such, it makes the most sense to proceed with an outpatient tDCS feasibility trial rather than conducting a multi-site inpatient RCT.

6.5 Concluding remarks

While novel adjuncts to traditional motor skills-based physiotherapy provide an opportunity to enhance the gross motor outcomes associated with inpatient rehabilitation for children and youth with moderate to severe ABI, rigorous evaluation is necessary to determine their effectiveness. To our knowledge, this is the first time that tDCS has been evaluated in the subacute stage of pediatric ABI. Our study involved evaluating the feasibility of integrating tDCS into an existing inpatient physiotherapy program and permitted analysis of clinical physiotherapy session content which has received limited attention in the literature to date. Although few children admitted for inpatient ABI rehabilitation were eligible to participate in the tDCS and physiotherapy protocol, this feasibility study identified a process for tracking ABI symptoms and tDCS side effects and demonstrated both the viability and importance of analyzing the physiotherapy MLS session content that accompanied the tDCS. The GMFM-88 mean change score from our chart review served as a reference point for judging the progress of the participant who completed the entire tDCS study protocol and can now be used as a benchmark for other children with subacute ABI and in future gross motor intervention studies in inpatient pediatric ABI rehabilitation. This

dissertation highlights the importance of evaluating protocol feasibility prior to conducting a full scale clinical trial, the value of using a set of comprehensive outcome measures to evaluate the range of gross motor change that occurs during the subacute stage of recovery in a heterogeneous clinical population, the need to identify viable approaches for exploring the neural reorganization that accompanies gross motor change, and the benefits of evaluating MLS content of physiotherapy interventions for children and youth with moderate to severe subacute ABI.

References

ABIKUS. (2007). *ABIKUS Evidence based recommendations for rehabilitation of moderate to severe acquired brain injury*. https://erabi.ca/wp-content/uploads/2018/12/abikus_aug_07.pdf

Agrawal, N., Johnston, S. C., Wu, Y. W., Sidney, S., & Fullerton, H. J. (2009). Imaging data reveal a higher pediatric stroke incidence than prior US estimates. *Stroke, 40*(11), 3415-3421. doi: 10.1161/strokeaha.109.564633

Alashram, A. R., Annino, G., Al-qtaishat, M., & Padua, E. (2020). Mental practice combined with physical practice to enhance upper extremity functional ability poststroke: a systematic review. *Journal of Stroke Medicine*, *3*(2), 51-61. doi: 10.1177/2516608520943793

Albouy, G., Sterpenich, V., Vandewalle, G., Darsaud, A., Gais, S., Rauchs, G., . . . Balteau, E. (2012). Neural correlates of performance variability during motor sequence acquisition. *Neuroimage, 60*(1), 324-331. doi: 10.1016/j.neuroimage.2011.12.049

Alix-Fages, C., Romero-Arenas, S., Colomer-Poveda, D., Jerez-Martinez, A., Marquez, G., Castro-Alonso, M., . . . Fernandez-Del-Olmo, M. (2019). Short-term effects of anodal transcranial direct current stimulation on endurance and maximal force production. A systematic review and meta-analysis. *Journal of Clinical Medicine*, *8*(4), 536. doi: 10.3390/jcm8040536

Alotaibi, M., Long, T., Kennedy, E., & Bavishi, S. (2014). The efficacy of GMFM-88 and GMFM-66 to detect changes in gross motor function in children with cerebral palsy (CP): a literature review. *Disability and Rehabilitation, 36*(8), 617-627. doi: 10.3109/09638288.2013.805820

Ambrus, G. G., Al-Moyed, H., Chaieb, L., Sarp, L., Antal, A., & Paulus, W. (2012). The fade-in-Short stimulation-Fade out approach to sham tDCS-Reliable at 1 mA for naive and experienced subjects, but not investigators. *Brain Stimulation, 5*(4), 499-504. doi: 10.1016/j.brs.2011.12.001

Ammann, C., Guida, P., Caballero-Insaurriaga, J., Pineda-Pardo, J. A., Oliviero, A., & Foffani, G. (2020). A framework to assess the impact of number of trials on the amplitude of motor evoked potentials. *Scientific Reports*, *10*(1), 1-15. doi: 10.1038/s41598-020-77383-6

Anaby, D., Law, M., Hanna, S., & Dematteo, C. (2012). Predictors of change in participation rates following acquired brain injury: results of a longitudinal study. *Developmental Medicine & Child Neurology, 54*(4), 339-346. doi: 10.1111/j.1469-8749.2011.04204.x

Anderson, D. I. (2018). Motor development: Far more than just the development of motor skills. *Kinesiology Review, 7*(2), 99-114. doi: 10.1123/kr.2018-0011

Anderson, V., & Catroppa, C. (2006). Advances in postacute rehabilitation after childhood-acquired brain injury: a focus on cognitive, behavioral, and social domains. *American Journal of Physical Medicine & Rehabilitation*, *85*(9), 767-778. doi: 10.1097/01.phm.0000233176.08480.22

Andrade, A. C., Magnavita, G. M., Allegro, J. V. B. N., Neto, C. E. B. P., Lucena, R. d. C. S., & Fregni, F. (2014). Feasibility of transcranial direct current stimulation use in children aged 5 to 12 years. *Journal of Child Neurology*, *29*(10), 1360-1365. doi: 10.1177/0883073813503710

Andriessen, T. M., Jacobs, B., & Vos, P. E. (2010). Clinical characteristics and pathophysiological mechanisms of focal and diffuse traumatic brain injury. *Journal of Cellular and Molecular Medicine*, *14*(10), 2381-2392. doi: 10.1111/j.1582-4934.2010.01164.x

Antal, A., Terney, D., Poreisz, C., & Paulus, W. (2007). Towards unravelling task-related modulations of neuroplastic changes induced in the human motor cortex. *European Journal of Neuroscience*, *26*(9), 2687-2691. doi: 10.1111/j.1460-9568.2007.05896.x

Aprile, I., Cruciani, A., Germanotta, M., Gower, V., Pecchioli, C., Cattaneo, D., . . . Gramatica, F. (2019). Upper limb robotics in rehabilitation: an approach to select the devices, based on rehabilitation aims, and their evaluation in a feasibility study. *Applied Sciences*, *9*(18), 3920. doi: 10.3390/app9183920

Armijo-Olivo, S., Fuentes, J., da Costa, B. R., Saltaji, H., Ha, C., & Cummings, G. G. (2017). Blinding in physical therapy trials and its association with treatment effects: a meta-epidemiological study. *American Journal of Physical Medicine & Rehabilitation*, *96*(1), 34-44. doi: 10.1097/PHM.0000000000000521

Babikian, T., Merkley, T., Savage, R. C., Giza, C. C., & Levin, H. (2015). Chronic aspects of pediatric traumatic brain injury: review of the literature. *Journal of Neurotrauma*, *32*(23), 1849-1860. doi: 10.1089/neu.2015.3971

Baltar, A., Nogueira, F., Marques, D., Carneiro, M., & Monte-Silva, K. (2018). Evidence of the Homeostatic Regulation With the Combination of Transcranial Direct Current Stimulation and Physical Activity. *American Journal of Physical Medicine & Rehabilitation*, *97*(10), 727-733. doi: 10.1097/PHM.0000000000000956

Banerjee-Guénette, P., Bigford, S., & Glegg, S. M. N. (2020). Facilitating the implementation of virtual reality-based therapies in pediatric rehabilitation. *Physical & Occupational Therapy In Pediatrics*, *40*(2), 201-216. doi: 10.1080/01942638.2019.1650867

Baque, E., Sakzewski, L., Barber, L., & Boyd, R. N. (2016). Systematic review of physiotherapy interventions to improve gross motor capacity and performance in children and adolescents with an acquired brain injury. *Brain Injury*, *30*(8), 948-959. doi: 10.3109/02699052.2016.1147079

Bar-Haim, S., Harries, N., Nammourah, I., Oraibi, S., Malhees, W., Loeppky, J., . . . Lahat, E. (2010). Effectiveness of motor learning coaching in children with cerebral palsy: a randomized controlled trial. *Clinical Rehabilitation*, *24*(11), 1009-1020. doi: 10.1177/0269215510371428

Barlaam, F., Fortin, C., Vaugoyeau, M., Schmitz, C., & Assaiante, C. (2012). Development of action representation during adolescence as assessed from anticipatory control in a bimanual load-lifting task. *Neuroscience*, *221*, 56-68. doi: 10.1016/j.neuroscience.2012.06.062

Bartels, B., De Groot, J. F., & Terwee, C. B. (2013). The six-minute walk test in chronic pediatric conditions: a systematic review of measurement properties. *Physical Therapy*, *93*(4), 529-541. doi: 10.2522/ptj.20120210

Barthélemy, D., Grey, M. J., Nielsen, J. B., & Bouyer, L. (2011). Involvement of the corticospinal tract in the control of human gait. *Progress in Brain Research*, *192*, 181-197. doi: 10.1016/B978-0-444-53355-5.00012-9

Bastani, A., & Jaberzadeh, S. (2012). Does anodal transcranial direct current stimulation enhance excitability of the motor cortex and motor function in healthy individuals and subjects with stroke: a systematic review and meta-analysis. *Clinical Neurophysiology*, *123*(4), 644-657. doi: 10.1016/j.clinph.2011.08.029

Bastani, A., & Jaberzadeh, S. (2014). Within-session repeated a-tDCS: The effects of repetition rate and inter-stimulus interval on corticospinal excitability and motor performance. *Clinical Neurophysiology*, *125*(9), 1809-1818. doi: 10.1016/j.clinph.2014.01.010

Bedell, G. M. (2008). Functional outcomes of school-age children with acquired brain injuries at discharge from inpatient rehabilitation. *Brain Injury*, *22*(4), 313-324. doi: 10.1080/02699050801978948

Beretta, E., Molteni, E., Biffi, E., Morganti, R., Avantaggiato, P., & Strazzer, S. (2018). Robotically-driven orthoses exert proximal-to-distal differential recovery on the lower limbs in children with hemiplegia, early after acquired brain injury. *European Journal of Paediatric Neurology*, *22*(4), 652-661. doi: 10.1016/j.ejpn.2018.03.002

Bestmann, S., & Krakauer, J. W. (2015). The uses and interpretations of the motor-evoked potential for understanding behaviour. *Experimental Brain Research*, *233*(3), 679-689. doi: 10.1007/s00221-014-4183-7

Bikson, M., Grossman, P., Thomas, C., Zannou, A. L., Jiang, J., Adnan, T., . . . Brunoni, A. R. (2016). Safety of transcranial direct current stimulation: evidence based update 2016. *Brain Stimulation*, *9*(5), 641-661. doi: 10.1016/j.brs.2016.06.004

Blume, H. K., Vavilala, M. S., Jaffe, K. M., Koepsell, T. D., Wang, J., Temkin, N., . . . Rivara, F. P. (2012). Headache after pediatric traumatic brain injury: a cohort study. *Pediatrics*, *129*(1), e31-e39. doi: 10.1542/peds.2011-1742

Boddington, L. J., & Reynolds, J. N. J. (2017). Targeting interhemispheric inhibition with neuromodulation to enhance stroke rehabilitation. *Brain Stimulation, 10*(2), 214-222. doi: 10.1016/j.brs.2017.01.006

Bornheim, S., Croisier, J.-L., Maquet, P., & Kaux, J.-F. (2020). Transcranial direct current stimulation associated with physical-therapy in acute stroke patients-A randomized, triple blind, sham-controlled study. *Brain Stimulation, 13*(2), 329-336. doi: 10.1016/j.brs.2019.10.019

Bornheim, S., Thibaut, A., Beaudart, C., Maquet, P., Croisier, J.-L., & Kaux, J.-F. (2022). Evaluating the effects of tDCS in stroke patients using functional outcomes: a systematic review. *Disability and Rehabilitation, 44*(1), 13-23. doi: 10.1080/09638288.2020.1759703

Braga, L., Da Paz Junior, A., & Ylvisaker, M. (2005). Direct clinician-delivered versus indirect family-supported rehabilitation of children with traumatic brain injury: a randomized controlled trial. *Brain Injury, 19*(10), 819-831. doi: 10.1080/02699050500110165

Brown, A. W., Elovic, E. P., Kothari, S., Flanagan, S. R., & Kwasnica, C. (2008). Congenital and acquired brain injury. 1. Epidemiology, pathophysiology, prognostication, innovative treatments, and prevention. *Archives of Physical Medicine and Rehabilitation, 89*(3), S3-S8. doi: 10.1016/j.apmr.2007.12.001

Brunoni, A., Nitsche, M., Bolognini, N., Bikson, M., Wagner, T., Merabet, L., . . . Ferrucci, R. (2012). Clinical research with transcranial direct current stimulation (tDCS): challenges and future directions. *Brain Stimulation, 5*(3), 175-195. doi: 10.1016/j.brs.2011.03.002

Buchanan, D. M., Bogdanowicz, T., Khanna, N., Lockman-Dufour, G., Robaey, P., & D'Angiulli, A. (2021). Systematic review on the safety and tolerability of transcranial direct current stimulation in children and adolescents. *Brain Sciences, 11*(2), 212. doi: 10.3390/brainsci11020212

Bulteau, S., Laurin, A., Bach-Ngohou, K., Péré, M., Vibet, M. A., Hardouin, J. B., ... & Prié, Y. (2022). Feasibility of combining transcranial direct current stimulation and active fully embodied virtual reality for visual height intolerance: a double-blind randomized controlled study. *Journal of Clinical Medicine, 11*(2), 345. doi: 10.3390/jcm11020345

Burns, P. B., Rohrich, R. J., & Chung, K. C. (2011). The levels of evidence and their role in evidence-based medicine. *Plastic and Reconstructive Surgery, 128*(1), 305. doi: 10.1097/PRS.0b013e318219c171

Cabral, M. E., Baltar, A., Borba, R., Galvao, S., Santos, L., Fregni, F., & Monte-Silva, K. (2015). Transcranial direct current stimulation: Before, during, or after motor training? *NeuroReport, 26*(11), 618-622. doi: http://dx.doi.org/10.1097/WNR.0000000000000397

Caeyenberghs, K., Van Roon, D., Swinnen, S., & Smits-Engelsman, B. (2009). Deficits in executed and imagined aiming performance in brain-injured children. *Brain and Cognition, 69*(1), 154-161. doi: 10.1016/j.bandc.2008.07.001

Cameron, D., Craig, T., Edwards, B., Missiuna, C., Schwellnus, H., & Polatajko, H. J. (2017). Cognitive orientation to daily occupational performance (CO-OP): a new approach for children with cerebral palsy. *Physical & Occupational Therapy in Pediatrics, 37*(2), 183-198. doi: 10.1080/01942638.2016.1185500

Campbell, M., McKenzie, J. E., Sowden, A., Katikireddi, S. V., Brennan, S. E., Ellis, S., . . . Thomas, J. (2020). Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline. *BMJ, 368*. doi: 10.1136/bmj.l6890

Carswell, A., McColl, M. A., Baptiste, S., Law, M., Polatajko, H., & Pollock, N. (2004). The Canadian Occupational Performance Measure: a research and clinical literature review. *Canadian Journal of Occupational Therapy, 71*(4), 210-222. doi: 10.1177/000841740407100406

Chan, A. W., Tetzlaff, J. M., Gøtzsche, P. C., Altman, D. G., Mann, H., Berlin, J. A., . . . Parulekar, W. R. (2013). SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ, 346*, e7586. doi: 10.1136/bmj.e7586

Chan, V., Pole, J. D., Keightley, M., Mann, R. E., & Colantonio, A. (2016). Children and youth with non-traumatic brain injury: a population based perspective. *BMC Neurology, 16*(1), 1-10. doi: 10.1186/s12883-016-0631-2

Chang, M. C., Kim, D. Y., & Park, D. H. (2015). Enhancement of cortical excitability and lower limb motor function in patients with stroke by transcranial direct current stimulation. *Brain Stimulation, 8*(3), 561-566. doi: 10.1016/j.brs.2015.01.411

Charalambous, C. C., Bowden, M. G., & Adkins, D. L. (2016). Motor cortex and motor cortical interhemispheric communication in walking after stroke: the roles of transcranial magnetic stimulation and animal models in our current and future understanding. *Neurorehabilitation and Neural Repair, 30*(1), 94-102. doi: 10.1177/1545968315581418

Chen, H., Epstein, J., & Stern, E. (2010). Neural plasticity after acquired brain injury: evidence from functional neuroimaging. *PM&R, 2*, S306-S312. doi: 10.1016/j.pmrj.2010.10.006

Chenot, Q., Tzourio-Mazoyer, N., Rheault, F., Descoteaux, M., Crivello, F., Zago, L., . . . Mazoyer, B. (2019). A population-based atlas of the human pyramidal tract in 410 healthy participants. *Brain Structure and Function, 224*(2), 599-612. doi: 10.1007/s00429-018-1798-7

Chiang, H. S., Shakal, S., Strain, J. F., Womack, K., Kraut, M., Vanneste, S., & Hart, J. (2022). Reversal of unilateral hand movement dysfunction by high definition transcranial direct current stimulation in a patient with chronic traumatic brain injury. *Brain Stimulation, 15*(2), 283-285. doi: 10.1016/j.brs.2022.01.010

Christova, M., Rafolt, D., & Gallasch, E. (2015). Cumulative effects of anodal and priming cathodal tDCS on pegboard test performance and motor cortical excitability. *Behavioural Brain Research, 287*, 27-33. doi: 10.1016/j.bbr.2015.03.028

Ciechanski, P., Carlson, H. L., Herrero, M., Lane, C., MacMaster, F. P., & Kirton, A. (2020). A case of transcranial direct-current stimulation for childhood stroke hemiparesis: A brief report. *Developmental Neurorehabilitation*, *23*(2), 133-136. doi: 10.1080/17518423.2019.1655678

Ciechanski, P., & Kirton, A. (2016). Transcranial direct current stimulation (tDCS): Principles and emerging applications in children. In A. Kirton & D. L. Gilbert (Eds.) *Pediatric Brain Stimulation: Mapping and Modulating the Developing Brain*. (pp. 85-115). Elsevier.

Cignetti, F., Caudron, S., Vaugoyeau, M., & Assaiante, C. (2013). Body schema disturbance in adolescence: from proprioceptive integration to the perception of human movement. *Journal of Motor Learning and Development*, *1*(3), 49-58.

Cinelli, K. T. M., Green, L. A., & Kalmar, J. M. (2019). The task at hand: Fatigue-associated changes in cortical excitability during writing. *Brain Sciences*, *9*(12), 353. doi: 10.3390/brainsci9120353

Cisek, P. (2005). Neural representations of motor plans, desired trajectories, and controlled objects. *Cognitive Processing*, *6*(1), 15-24. doi: 10.1007/s10339-004-0046-7

Coates, M., Spanos, M., Parmar, P., Chandrasekhar, T., & Sikich, L. (2018). A review of methods for monitoring adverse events in pediatric psychopharmacology clinical trials. *Drug Safety*, *41*(5), 465-471. doi: 10.1007/s40264-017-0633-z

Collada, J. M., Trives, L., & Castrejón, I. (2021). The importance of outcome measures in the management of inflammatory rheumatic diseases. *Open Access Rheumatology: Research and Reviews*, *13*, 191. doi: 10.2147/OARRR.S276980

Cordani, C., Preziosa, P., Gatti, R., Castellani, C., Filippi, M., & Rocca, M. A. (2022). Mapping brain structure and function in professional fencers: A model to study training effects on central nervous system plasticity. *Human Brain Mapping*. doi: 10.1002/hbm.25854

Coster, W. J. (2013). Making the best match: selecting outcome measures for clinical trials and outcome studies. *The American Journal of Occupational Therapy*, *67*(2), 162-170. doi: 10.5014/ajot.2013.006015

Crichton, A., Anderson, V., Oakley, E., Greenham, M., Hearps, S., Delzoppo, C., . . . Boutis, K. (2018). Fatigue following traumatic brain injury in children and adolescents: a longitudinal follow-up 6 to 12 months after injury. *The Journal of Head Trauma Rehabilitation*, *33*(3), 200-209. doi: 10.1097/htr.0000000000000330

Croarkin, P. E., Wall, C. A., King, J. D., Kozel, F. A., & Daskalakis, Z. J. (2011). Pain during transcranial magnetic stimulation in youth. *Innovations in Clinical Neuroscience*, *8*(12), 18.

Cusick, A., Lannin, N. A., & Lowe, K. (2007). Adapting the Canadian Occupational Performance Measure for use in a paediatric clinical trial. *Disability and Rehabilitation*, *29*(10), 761-766. doi: 10.1080/09638280600929201

Cusick, A., McIntyre, S., Novak, I., Lannin, N., & Lowe, K. (2006). A comparison of goal attainment scaling and the Canadian Occupational Performance Measure for paediatric rehabilitation research. *Pediatric Rehabilitation*, *9*(2), 149-157. doi: 10.1080/13638490500235581

Cuypers, K., Leenus, D. J. F., van den Berg, F. E., Nitsche, M. A., Thijs, H., Wenderoth, N., & Meesen, R. L. J. (2013). Is motor learning mediated by tDCS intensity? *PloS One*, *8*(6), e67344. doi: 10.1371/journal.pone.0067344

Darling, W. G., Wolf, S. L., & Butler, A. J. (2006). Variability of motor potentials evoked by transcranial magnetic stimulation depends on muscle activation. *Experimental Brain Research*, *174*(2), 376-385. doi: 10.1007/s00221-006-0468-9

Dayan, E., & Cohen, L. G. (2011). Neuroplasticity subserving motor skill learning. *Neuron*, *72*(3), 443-454. doi: 10.1016/j.neuron.2011.10.008

Dewan, M. C., Mummareddy, N., Wellons Iii, J. C., & Bonfield, C. M. (2016). Epidemiology of global pediatric traumatic brain injury: qualitative review. *World Neurosurgery*, *91*, 497-509. doi: 10.1016/j.wneu.2016.03.045

Dijkstra, B. W., Bekkers, E. M. J., Gilat, M., de Rond, V., Hardwick, R. M., & Nieuwboer, A. (2020). Functional neuroimaging of human postural control: A systematic review with meta-analysis. *Neuroscience & Biobehavioral Reviews*, *115*, 351-362. doi: 10.1016/j.neubiorev.2020.04.028

Dissanayaka, T., Jaberzadeh, S., Zoghi, M., Egan, G. F., & Farrell, M. (2017). Does transcranial electrical stimulation enhance corticospinal excitability of the motor cortex in healthy individuals? A systematic review and meta-analysis. *European Journal of Neuroscience*, *46*(4), 1968-1990. doi: http://dx.doi.org/10.1111/ejn.13640

Doyon, J., Penhune, V., & Ungerleider, L. G. (2003). Distinct contribution of the cortico-striatal and cortico-cerebellar systems to motor skill learning. *Neuropsychologia*, *41*(3), 252-262. doi: 10.1016/s0028-3932(02)00158-6

Dromerick, A. W., Geed, S., Barth, J., Brady, K., Giannetti, M. L., Mitchell, A., . . . Newport, E. L. (2021). Critical period after stroke study (CPASS): A phase II clinical trial testing an optimal time for motor recovery after stroke in humans. *Proceedings of the National Academy of Sciences*, *118*(39), e2026676118. doi: 10.1073/pnas.2026676118

Dumas, H. M., Haley, S. M., Carey, T. M., & Ni, P. S. (2004). The relationship between functional mobility and the intensity of physical therapy intervention in children with traumatic brain injury. *Pediatric Physical Therapy*, *16*(3), 157-164. doi: 10.1097/01.pep.0000136004.69289.01

Dumas, H. M., Haley, S. M., Ludlow, L. H., & Carey, T. M. (2004). Recovery of ambulation during inpatient rehabilitation: physical therapist prognosis for children and adolescents with traumatic brain injury. *Physical Therapy*, *84*(3), 232-242.

Dumas, H. M., Haley, S. M., Ludlow, L. H., & Rabin, J. P. (2002). Functional recovery in pediatric traumatic brain injury during inpatient rehabilitation. *American Journal of Physical Medicine & Rehabilitation*, *81*(9), 661-669. doi: 10.1097/01.CCM.0000026918.24522.10

Durham, K., Van Vliet, P. M., Badger, F., & Sackley, C. (2009). Use of information feedback and attentional focus of feedback in treating the person with a hemiplegic arm. *Physiotherapy Research International*, *14*(2), 77-90. doi: 10.1002/pri.431

El-Kotob, R., & Giangregorio, L. M. (2018). Pilot and feasibility studies in exercise, physical activity, or rehabilitation research. *Pilot and Feasibility Studies*, *4*(1), 1-7. doi: 10.1186/s40814-018-0326-0

Elbanna, S. T., Elshennawy, S., & Ayad, M. (2019). Noninvasive Brain Stimulation for Rehabilitation of Pediatric Motor Disorders Following Brain Injury: Systematic Review of Randomized Controlled Trials. *Archives of Physical Medicine and Rehabilitation*, *100*(10), 1945-1963. doi: 10.1016/j.apmr.2019.04.009

Eldridge, S. M., Chan, C. L., Campbell, M. J., Bond, C. M., Hopewell, S., Thabane, L., & Lancaster, G. A. (2016). CONSORT 2010 statement: extension to randomised pilot and feasibility trials. *BMJ*, *355*(i5239). doi: 10.1186/s40814-016-0105-8

Elmore, S. (2007). Apoptosis: a review of programmed cell death. *Toxicologic Pathology*, *35*(4), 495-516. doi: 10.1080/01926230701320337

Everaert, D. G., Thompson, A. K., Chong, S. L., & Stein, R. B. (2010). Does functiona10.12753/2066-026X-15-073l electrical stimulation for foot drop strengthen corticospinal connections? *Neurorehabilitation and Neural Repair*, *24*(2), 168-177. doi: 10.1177/1545968309349939

Eyre, J. A., Taylor, J. P., Villagra, F., Smith, M., & Miller, S. (2001). Evidence of activity-dependent withdrawal of corticospinal projections during human development. *Neurology*, *57*(9), 1543-1554. doi: 10.1212/wnl.57.9.1543

Feldner, H. A., Howell, D., Kelly, V. E., McCoy, S. W., & Steele, K. M. (2019). "Look, your muscles are firing!": a qualitative study of clinician perspectives on the use of surface electromyography in neurorehabilitation. *Archives of Physical Medicine and Rehabilitation*, *100*(4), 663-675. doi: 10.1016/j.apmr.2018.09.120

Ferche, O. M., Moldoveanu, A., Moldoveanu, F., Voinea, A., Asavei, V., & Negoi, I. (2015). Challenges and issues for successfully applying virtual reality in medical rehabilitation. *eLearning & Software for Education*, (1). doi: 10.12753/2066-026X-15-073

Fitts, P. M., & Posner, M. I. (1967). *Learning and skilled performance in human performance*. Brooks/Cole.

Flament, D., Goldsmith, P., Buckley, C. J., & Lemon, R. N. (1993). Task dependence of responses in first dorsal interosseous muscle to magnetic brain stimulation in man. *The Journal of Physiology*, *464*(1), 361-378. doi: 10.1113/jphysiol.1993.sp019639

Fragala, M. A., Haley, S. M., Dumas, H. M., & Rabin, J. P. (2002). Classifying mobility recovery in children and youth with brain injury during hospital-based rehabilitation. *Brain Injury*, *16*(2), 149-160. doi: 10.1080/02699050110103328

Fragala-Pinkham, M. A., Dumas, H. M., Lombard, K. A., & O'Brien, J. E. (2016). Responsiveness of the Pediatric Evaluation of Disability Inventory-Computer Adaptive Test in measuring functional outcomes for inpatient pediatric rehabilitation. *Journal of Pediatric Rehabilitation Medicine*, *9*(3), 215-222. doi: 10.3233/prm-160382

Frazer, A., Williams, J., Spittles, M., Rantalainen, T., & Kidgell, D. (2016). Anodal transcranial direct current stimulation of the motor cortex increases cortical voluntary activation and neural plasticity. *Muscle & Nerve*, *54*(5), 903-913. doi: 10.1002/mus.25143

Frazer, A. K., Kidgell, D. J., Howatson, G., Ahtiainen, J. P., Avela, J., & Rantalainen, T. (2019). Priming the motor cortex with anodal transcranial direct current stimulation affects the acute inhibitory corticospinal responses to strength training. *Journal of Strength and Conditioning Research*, *33*(2), 307-317. doi: 10.1519/JSC.0000000000002959

Frizzell, T. O., Phull, E., Khan, M., Song, X., Grajauskas, L. A., Gawryluk, J., & D'Arcy, R. C. N. (2022). Imaging functional neuroplasticity in human white matter tracts. *Brain Structure and Function*, *227*(1), 381-392. doi: 10.1007/s00429-021-02407-4

Fujiyama, H., Barzideh, A., Van de Vijver, C., Badache, A. C., Manrique-C, M. N., Levin, O., . . . Swinnen, S. P. (2017). Preconditioning tDCS facilitates subsequent tDCS effect on skill acquisition in older adults. *Neurobiology of Aging*, *51*, 31-42. doi: 10.1016/j.neurobiolaging.2016.11.012

Gallivan, J. P., Chapman, C. S., Wolpert, D. M., & Flanagan, J. R. (2018). Decision-making in sensorimotor control. *Nature Reviews Neuroscience*, *19*(9), 519-534. doi: 10.1038/s41583-018-0045-9

Galvin, J., Froude, E. H., & McAleer, J. (2010a). Children's participation in home, school and community life after acquired brain injury. *Australian Occupational Therapy Journal*, *57*(2), 118-126. doi: 10.1111/j.1440-1630.2009.00822.x

Galvin, J., Lim, B. C. J., Steer, K., Edwards, J., & Lee, K. J. (2010b). Predictors of functional ability of Australian children with acquired brain injury following inpatient rehabilitation. *Brain Injury*, *24*(7-8), 1008-1016. doi: 10.3109/02699052.2010.489793

Garvey, M. A., Kaczynski, K. J., Becker, D. A., & Bartko, J. J. (2001). Subjective reactions of children to single-pulse transcranial magnetic stimulation. *Journal of Child Neurology*, *16*(12), 891-894. doi: 10.1177/088307380101601205

Geiger, R., Strasak, A., Treml, B., Gasser, K., Kleinsasser, A., Fischer, V., . . . Stein, J. I. (2007). Six-minute walk test in children and adolescents. *The Journal of Pediatrics*, *150*(4), 395-399. doi: 10.1016/j.jpeds.2006.12.052

Gerges, A. N., Hordacre, B., Di Pietro, F., Moseley, G. L., & Berryman, C. (2022). Do adults with stroke have altered interhemispheric inhibition? A systematic review with meta-analysis. *Journal of Stroke and Cerebrovascular Diseases*, *31*(7), 106494. doi: 10.1016/j.jstrokecerebrovasdis.2022.106494

Gillick, B. T., Feyma, T., Menk, J., Usset, M., Vaith, A., Wood, T. J., . . . Krach, L. E. (2015). Safety and feasibility of transcranial direct current stimulation in pediatric hemiparesis: randomized controlled preliminary study. *Physical Therapy*, *95*(3), 337-349. doi: 10.2522/ptj.20130565

Giustini, A., Pistarini, C., & Pisoni, C. (2013). Traumatic and nontraumatic brain injury. *Handbook of Clinical Neurology*, *110*, 401-409. doi: 10.1016/B978-0-444-52901-5.00034-4

Giza, C. C., Kolb, B., Harris, N. G., Asarnow, R. F., & Prins, M. L. (2009). Hitting a moving target: Basic mechanisms of recovery from acquired developmental brain injury. *Developmental Neurorehabilitation*, *12*(5), 255-268. doi: 10.3109/17518420903087558

Glegg, S. M. N., Holsti, L., Stanton, S., Hanna, S., Velikonja, D., Ansley, B., . . . Brum, C. (2017). Evaluating change in virtual reality adoption for brain injury rehabilitation following knowledge translation. *Disability and Rehabilitation: Assistive Technology*, *12*(3), 217-226. doi: 10.3109/17483107.2015.1111944

Gmelig Meyling, C., Verschuren, O., Rentinck, I. R., Engelbert, R. H. H., & Gorter, J. W. (2021). Physical rehabilitation interventions in children with acquired brain injury: a scoping review. *Developmental Medicine & Child Neurology*, *64*(1):40-48. doi: 10.1111/dmcn.14997

Goldsworthy, M. R., Hordacre, B., & Ridding, M. C. (2016). Minimum number of trials required for within-and between-session reliability of TMS measures of corticospinal excitability. *Neuroscience*, *320*, 205-209. doi: 10.1016/j.neuroscience.2016.02.012

Gordon, A. L., & di Maggio, A. (2012). Rehabilitation for children after acquired brain injury: current and emerging approaches. *Pediatric Neurology*, *46*(6), 339-344. doi: 10.1016/j.pediatrneurol.2012.02.029

Grecco, L. A. C., de Almeida Carvalho Duarte, N., Mendonca, M. E., Cimolin, V., Galli, M., Fregni, F., & Santos Oliveira, C. (2014). Transcranial direct current stimulation during treadmill training in children with cerebral palsy: a randomized controlled double-blind

clinical trial. *Research in Developmental Disabilities*, *35*(11), 2840-2848. doi: 10.1016/j.ridd.2014.07.030

Grecco, L. A. C., de Almeida Carvalho Duarte, N., Mendonca, M. E., Galli, M., Fregni, F., & Oliveira, C. S. (2015). Effects of anodal transcranial direct current stimulation combined with virtual reality for improving gait in children with spastic diparetic cerebral palsy: A pilot, randomized, controlled, double-blind, clinical trial. *Clinical Rehabilitation*, *29*(12), 1212-1223. doi: 10.1177/0269215514566997

Grecco, L. A. C., Oliveira, C. S., Duarte, N. d. A. C., Lima, V. L. C., Zanon, N., & Fregni, F. (2017). Cerebellar transcranial direct current stimulation in children with ataxic cerebral palsy: A sham-controlled, crossover, pilot study. *Developmental Neurorehabilitation*, *20*(3), 142-148. doi: 10.3109/17518423.2016.1139639

Guadagnoli, M. A., & Lee, T. D. (2004). Challenge point: a framework for conceptualizing the effects of various practice conditions in motor learning. *Journal of Motor Behavior*, *36*(2), 212-224. doi: 10.3200/JMBR.36.2.212-224

Hadders-Algra, M. (2018). Early human motor development: From variation to the ability to vary and adapt. *Neuroscience & Biobehavioral Reviews*, *90*, 411-427. doi: 10.1016/j.neubiorev.2018.05.009

Haley, S. M., Coster, W. J., Dumas, H. M., Fragala-Pinkham, M. A., Kramer, J., Ni, P., . . . Ludlow, L. H. (2011). Accuracy and precision of the Pediatric Evaluation of Disability Inventory computer-adaptive tests (PEDI-CAT). *Developmental Medicine & Child Neurology*, *53*(12), 1100-1106. doi: 10.1111/j.1469-8749.2011.04107.x

Haley, S. M., Coster, W. J., Kao, Y.-C., Dumas, H. M., Fragala-Pinkham, M. A., Kramer, J. M., . . . Moed, R. (2010). Lessons from use of the Pediatric Evaluation of Disability Inventory (PEDI): Where do we go from here? *Pediatric Physical Therapy*, *22*(1), 69-75. doi: 10.1097/PEP.0b013e3181cbfbf6

Haley, S. M., Dumas, H. M., Rabin, J. P., & Ni, P. (2003). Early recovery of walking in children and youths after traumatic brain injury. *Developmental Medicine and Child Neurology*, *45*(10), 671-675. doi: 10.1097/pep.0b013e3181cbfbf6

Hamano, Y. H., Sugawara, S. K., Fukunaga, M., & Sadato, N. (2021). The integrative role of the M1 in motor sequence learning. *Neuroscience Letters*, *760*, 136081. doi: 10.1016/j.neulet.2021.136081

Handelzalts, S., Melzer, I., & Soroker, N. (2019). Analysis of brain lesion impact on balance and gait following stroke. *Frontiers in Human Neuroscience*, *13*, 149. doi: 10.3389/fnhum.2019.00149

Hannah, R., Iacovou, A., & Rothwell, J. C. (2019). Direction of TDCS current flow in human sensorimotor cortex influences behavioural learning. *Brain Stimulation*, *12*(3), 684-692. doi: 10.1016/j.brs.2019.01.016

Harpster, K., Sheehan, A., Foster, E. A., Leffler, E., Schwab, S. M., & Angeli, J. M. (2019). The methodological application of goal attainment scaling in pediatric rehabilitation research: a systematic review. *Disability and Rehabilitation*, *41*(24), 2855-2864. doi: 10.1080/09638288.2018.1474952

Hart, T., Ferraro, M., Myers, R., & Ellis, C. A. (2014). Opening the black box: lessons learned from an interdisciplinary inquiry into the learning-based contents of brain injury rehabilitation. *Archives of Physical Medicine and Rehabilitation*, *95*(1), S66-S73. doi: 10.1016/j.apmr.2013.03.033

Hashemirad, F., Jaberzadeh, S., Zoghi, M., & Fitzgerald, P. B. (2016). The effect of anodal transcranial direct current stimulation on motor sequence learning in healthy individuals: A systematic review and meta-analysis. *Brain and Cognition*, *102*, 1-12. doi: 10.1016/j.bandc.2015.11.005

Hassanzahraee, M., Jaberzadeh, S., & Zoghi, M. (2018). How different priming stimulations affect the corticospinal excitability induced by noninvasive brain stimulation techniques: A systematic review and meta-analysis. *Reviews in the Neurosciences*, *29*(8), 883-899. doi: http://dx.doi.org/10.1515/revneuro-2017-0111

Hebert, D., Lindsay, M. P., McIntyre, A., Kirton, A., Rumney, P. G., Bagg, S., . . . Garnhum, M. (2016). Canadian stroke best practice recommendations: stroke rehabilitation practice guidelines, update 2015. *International Journal of Stroke*, *11*(4), 459-484. doi: 10.1177/1747493016643553

Hendy, A. M., & Kidgell, D. J. (2013). Anodal tDCS applied during strength training enhances motor cortical plasticity. *Medicine and Science in Sports and Exercise*, *45*(9), 1721-1729. doi: 10.1249/MSS.0b013e31828d2923

Hilderley, A. J. (2018). *Exploring functional neuroplasticity and the associations with outcomes of advanced gross motor interventions for children with cerebral palsy* [Doctoral dissertation, University of Toronto]. TSpace Repository. https://tspace.library.utoronto.ca/handle/1807/89805

Hilderley, A. J., Fehlings, D., Chen, J. L., & Wright, F. V. (2020). Comparison of sports skills movement training to lower limb strength training for independently ambulatory children with cerebral palsy: a randomised feasibility trial. *Disability and Rehabilitation*, 1-9. doi: 10.1080/09638288.2020.1851779

Hilderley, A. J., Fehlings, D., Lee, G. W., & Wright, F. V. (2016). Comparison of a robotic-assisted gait training program with a program of functional gait training for children with cerebral palsy: design and methods of a two group randomized controlled cross-over trial. *SpringerPlus*, *5*(1), 1886. doi: 10.1186/s40064-016-3535-0

Hirashima, M., & Nozaki, D. (2012). Distinct motor plans form and retrieve distinct motor memories for physically identical movements. *Current Biology*, *22*(5), 432-436. doi: 10.1016/j.cub.2012.01.042

Holliday, R. C., Ballinger, C., & Playford, E. D. (2007). Goal setting in neurological rehabilitation: patients' perspectives. *Disability and Rehabilitation*, *29*(5), 389-394.

Horak, F. B. (2006). Postural orientation and equilibrium: what do we need to know about neural control of balance to prevent falls? *Age and Ageing*, *35*(suppl_2), ii7-ii11. doi: 10.1093/ageing/afl077

Horvath, J. C., Carter, O., & Forte, J. D. (2014). Transcranial direct current stimulation: five important issues we aren't discussing (but probably should be). *Frontiers in Systems Neuroscience*, *8*(2), 1-8. doi: 10.3389/fnsys.2014.00002

Horvath, J. C., Forte, J. D., & Carter, O. (2015). Evidence that transcranial direct current stimulation (tDCS) generates little-to-no reliable neurophysiologic effect beyond MEP amplitude modulation in healthy human subjects: A systematic review. *Neuropsychologia*, *66*, 213-236. doi: 10.1016/j.neuropsychologia.2014.11.021

Howe, J. A., Inness, E. L., Venturini, A., Williams, J. I., & Verrier, M. C. (2006). The Community Balance and Mobility Scale-a balance measure for individuals with traumatic brain injury. *Clinical Rehabilitation*, *20*(10), 885-895. doi: 10.1177/0269215506072183

Huang, G. D., Bull, J., McKee, K. J., Mahon, E., Harper, B., & Roberts, J. N. (2018). Clinical trials recruitment planning: a proposed framework from the clinical trials transformation initiative. *Contemporary Clinical Trials*, *66*, 74-79. doi: 10.1016/j.cct.2018.01.003

Ibey, R. J., Chung, R., Benjamin, N., Littlejohn, S., Sarginson, A., Salbach, N. M., . . . Wright, V. (2010). Development of a challenge assessment tool for high-functioning children with an acquired brain injury. *Pediatric Physical Therapy*, *22*(3), 268-276.

Ilg, W., & Timmann, D. (2013). Gait ataxia- specific cerebellar influences and their rehabilitation. *Movement Disorders*, *28*(11), 1566-1575. doi: 10.1002/mds.25558

IPBIS. (2016). *Paediatric acquired brain injury: A global challenge*. https://ipbis.org/a_global_challenge.html

Iyer, L. V., Haley, S. M., Watkins, M. P., & Dumas, H. M. (2003). Establishing minimal clinically important differences for scores on the Pediatric Evaluation of Disability Inventory for inpatient rehabilitation. *Physical Therapy*, 83(10), 888-898.

Jaeger, L., Marchal-Crespo, L., Wolf, P., Riener, R., Michels, L., & Kollias, S. (2014). Brain activation associated with active and passive lower limb stepping. *Frontiers in Human Neuroscience*, *8*, 828. doi: 10.3389/fnhum.2014.00828

Jakobsen, J. C., Gluud, C., Wetterslev, J., & Winkel, P. (2017). When and how should multiple imputation be used for handling missing data in randomised clinical trials – a practical guide with flowcharts. *BMC Medical Research Methodology*, *17*(1), 162. doi: 10.1186/s12874-017-0442-1

Jang, S. H. (2009). Review of motor recovery in patients with traumatic brain injury. *NeuroRehabilitation*, 24(4), 349-353. doi: 10.3233/NRE-2009-0489

Jang, S. H. (2014). The corticospinal tract from the viewpoint of brain rehabilitation. *Journal of Rehabilitation Medicine, 46*(3), 193-199. doi: 10.2340/16501977-1782

Jang, S. H., Chang, C. H., Lee, J., Kim, C. S., Seo, J. P., & Yeo, S. S. (2013). Functional role of the corticoreticular pathway in chronic stroke patients. *Stroke*, *44*(4), 1099-1104. doi: 10.1161/STROKEAHA.111.000269

Jang, S. H., & Lee, S. J. (2019). Corticoreticular tract in the human brain: a mini review. *Frontiers in Neurology*, *10*, 1188. doi: 10.3389/fneur.2019.01188

Johnson, A. R., DeMatt, E., & Salorio, C. F. (2009). Predictors of outcome following acquired brain injury in children. *Developmental Disabilities Research Reviews*, *15*(2), 124-132. doi: 10.1002/ddrr.63

Johnson, L., Burridge, J. H., & Demain, S. H. (2013). Internal and external focus of attention during gait re-education: an observational study of physical therapist practice in stroke rehabilitation. *Physical Therapy*, *93*(7), 957-966. doi: 10.2522/ptj.20120300

Jones, T. A. (2017). Motor compensation and its effects on neural reorganization after stroke. *Nature Reviews Neuroscience*, *18*(5), 267-280. doi: 10.1038/nrn.2017.26

Kandel, E. R., Schwartz, J. H., Jessell, T. M., Siegelbaum, S., & Hudspeth, A. J. (2013). *Principles of Neural Science* (5th ed.). McGraw-Hill Education.

Kane, K. J., Lanovaz, J., Bisaro, D., Oates, A., & Musselman, K. E. (2016). Preliminary study of novel, timed walking tests for children with spina bifida or cerebral palsy. *SAGE Open Medicine*, *4*, 2050312116658908. doi: 10.1177/2050312116658908

Kang, M., Smith, E., Goldsmith, C. H., Switzer, L., Rosenbaum, P., Wright, F. V., & Fehlings, D. (2020). Documenting change with the Canadian occupational performance measure for children with cerebral palsy. *Developmental Medicine & Child Neurology*, 62(10), 1154-1160. doi: 10.1111/dmcn.14569

Karabanov, A. N., Shindo, K., Shindo, Y., Raffin, E., & Siebner, H. R. (2021). Multimodal assessment of precentral anodal tDCS: individual rise in supplementary motor activity scales with increase in corticospinal excitability. *Frontiers in Human Neuroscience*, *15*, 639274. doi: 10.3389/fnhum.2021.639274

Karni, A., Meyer, G., Rey-Hipolito, C., Jezzard, P., Adams, M. M., Turner, R., & Ungerleider, L. G. (1998). The acquisition of skilled motor performance: fast and slow experience-driven changes in primary motor cortex. *Proceedings of the National Academy of Sciences*, *95*(3), 861-868. doi: 10.1073/pnas.95.3.861

Katušić, A. (2011). Early brain injury and plasticity: reorganization and functional recovery. *Translational Neuroscience, 2*(1), 33-42. doi: 10.2478/s13380-011-0006-5

Katz-Leurer, M., Rotem, H., Keren, O., & Meyer, S. (2011). The effect of variable gait modes on walking parameters among children post severe traumatic brain injury and typically developed controls. *NeuroRehabilitation, 29*(1), 45-51. doi: 10.3233/nre-2011-0676

Kelly, G., Mobbs, S., Pritkin, J. N., Mayston, M., Mather, M., Rosenbaum, P., . . . Forsyth, R. (2015). Gross Motor Function Measure-66 trajectories in children recovering after severe acquired brain injury. *Developmental Medicine & Child Neurology, 57*(3), 241-247. doi: 10.1111/dmcn.12592

Kessler, S. K., Turkeltaub, P. E., Benson, J. G., & Hamilton, R. H. (2012). Differences in the experience of active and sham transcranial direct current stimulation. *Brain Stimulation, 5*(2), 155-162. doi: 10.1016/j.brs.2011.02.007

Khamis, A., Novak, I., Morgan, C., Tzannes, G., Pettigrew, J., Cowell, J., & Badawi, N. (2020). Motor learning feeding interventions for infants at risk of cerebral palsy: a systematic review. *Dysphagia, 35*(1), 1-17. doi: 10.1007/s00455-019-10016-x

Kidgell, D. J., Stokes, M. A., Castricum, T. J., & Pearce, A. J. (2010). Neurophysiological responses after short-term strength training of the biceps brachii muscle. *The Journal of Strength & Conditioning Research, 24*(11), 3123-3132. doi: 10.1519/jsc.0b013e3181f56794

Kim, G. W., & Ko, M. H. (2013). Facilitation of corticospinal tract excitability by transcranial direct current stimulation combined with voluntary grip exercise. *Neuroscience letters, 548*, 181-184. doi: 10.1016/j.neulet.2013.05.037

Kim, D. H., Kang, C. S., & Kyeong, S. (2020). Robot-assisted gait training promotes brain reorganization after stroke: A randomized controlled pilot study. *NeuroRehabilitation, 46*(4), 483-489. doi: 10.3233/NRE-203054

Kim, W. S., Lee, K., Kim, S., Cho, S., & Paik, N. J. (2019). Transcranial direct current stimulation for the treatment of motor impairment following traumatic brain injury. *Journal of NeuroEngineering and Rehabilitation, 16*(1), 14. doi: 10.1186/s12984-019-0489-9

Kimura, T., & Nakano, W. (2019). Repetition of a cognitive task promotes motor learning. *Human Movement Science, 66*, 109-116. doi: 10.1016/j.humov.2019.04.005

Kiresuk, T. J., & Sherman, R. E. (1968). Goal attainment scaling: A general method for evaluating comprehensive community mental health programs. *Community Mental Health Journal, 4*(6), 443-453. doi: 10.1007/BF01530764

Kiresuk, T. J., Smith, A., & Cardillo, J. E. (2014). *Goal attainment scaling: Applications, theory, and measurement*. Psychology Press.

Kirton, A., Ciechanski, P., Zewdie, E., Andersen, J., Nettel-Aguirre, A., Carlson, H., . . . Mineyko, A. (2017). Transcranial direct current stimulation for children with perinatal stroke and hemiparesis. *Neurology, 88*(3), 259-267. doi: 10.1212/wnl.0000000000003518

Kleinbaum, D. G., Kupper, L. L., Nizam, A., & Rosenberg, E. S. (2013). *Applied regression analysis and other multivariable methods* (5th ed.). Cengage Learning.

Kleynen, M., Braun, S. M., Rasquin, S. M., Bleijlevens, M. H., Lexis, M. A., Halfens, J., . . . Beurskens, A. J. (2015). Multidisciplinary views on applying explicit and implicit motor learning in practice: An international survey. *PloS One*, *10*(8), e0135522. doi: 10.1371/journal.pone.0135522

Kleynen, M., Moser, A., Haarsma, F. A., Beurskens, A. J., & Braun, S. M. (2017). Physiotherapists use a great variety of motor learning options in neurological rehabilitation, from which they choose through an iterative process: a retrospective think-aloud study. *Disability and Rehabilitation*, *39*(17), 1729-1737. doi: 10.1097/NPT.0000000000000046

Knight, S., Takagi, M., Fisher, E., Anderson, V., Lannin, N. A., Tavender, E., & Scheinberg, A. (2019). A systematic critical appraisal of evidence-based clinical practice guidelines for the rehabilitation of children with moderate or severe acquired brain injury. *Archives of Physical Medicine and Rehabilitation*, *100*(4), 711-723. doi: 10.1016/j.apmr.2018.05.031

Ko, J., & Kim, M. (2013). Reliability and responsiveness of the gross motor function measure-88 in children with cerebral palsy. *Physical Therapy*, *93*(3), 393-400. doi: 10.2522/ptj.20110374

Komar, A., Ashley, K., Hanna, K., Lavallee, J., Woodhouse, J., Bernstein, J., . . . Reed, N. (2016). Retrospective analysis of an ongoing group-based modified Constraint-Induced Movement Therapy program for children with acquired brain injury. *Physical & Occupational Therapy in Pediatrics*, *36*(2), 186-203. doi: 10.3109/01942638.2015.1076557

Kothari, D. H., Haley, S. M., Gill-Body, K. M., & Dumas, H. M. (2003). Measuring functional change in children with acquired brain injury (ABI): comparison of generic and ABI-specific scales using the Pediatric Evaluation of Disability Inventory (PEDI). *Physical Therapy*, *83*(9), 776-785. doi: 10.1093/ptj/83.9.776

Kraan, C. M., Tan, A. H. J., & Cornish, K. M. (2017). The developmental dynamics of gait maturation with a focus on spatiotemporal measures. *Gait & Posture*, *51*, 208-217. doi: 10.1016/j.gaitpost.2016.10.021

Kraeutner, S. N., Rubino, C., Rinat, S., Lakhani, B., Borich, M. R., Wadden, K. P., & Boyd, L. A. (2021). Resting state connectivity is modulated by motor learning in individuals after stroke. *Neurorehabilitation and Neural Repair*, *35*(6), 513-524. doi: 10.1177/15459683211006713

Krishnamurthi, R. V., Deveber, G., Feigin, V. L., Barker-Collo, S., Fullerton, H., Mackay, M. T., . . . Lo, W. (2015). Stroke prevalence, mortality and disability-adjusted life years in children and youth aged 0-19 years: data from the global and regional burden of stroke 2013. *Neuroepidemiology*, *45*(3), 177-189. doi: 10.1159/000441087

Krogh, H. B., Storebø, O. J., Faltinsen, E., Todorovac, A., Ydedahl-Jensen, E., Magnusson, F. L., . . . Simonsen, E. (2019). Methodological advantages and disadvantages of parallel and crossover randomised clinical trials on methylphenidate for attention deficit hyperactivity disorder: a systematic review and meta-analyses. *BMJ Open*, *9*(3), e026478. doi: 10.1136/bmjopen-2018-026478

Kueper, J. K., Lizotte, D. J., Montero-Odasso, M., Speechley, M., & Alzheimer's Disease Neuroimaging Initiative. (2020). Cognition and motor function: The gait and cognition pooled index. *PloS One*, *15*(9), e0238690. doi: 10.1371/journal.pone.0238690

Kuhtz-Buschbeck, J. P., Hoppe, B., Gölge, M., Dreesmann, M., Damm-Stünitz, U., & Ritz, A. (2003). Sensorimotor recovery in children after traumatic brain injury: analyses of gait, gross motor, and fine motor skills. *Developmental Medicine & Child Neurology*, *45*(12), 821-828. doi: 10.1017/s001216220300152x

Kumar, A., Juhasz, C., Asano, E., Sundaram, S. K., Makki, M. I., Chugani, D. C., & Chugani, H. T. (2009). Diffusion tensor imaging study of the cortical origin and course of the corticospinal tract in healthy children. *American Journal of Neuroradiology*, *30*(10), 1963-1970. doi: 10.3174/ajnr.a1742

Kwon, H. G., Yang, J.-H., Park, J. B., Kim, M. H., Choi, S. H., & Yang, D. S. (2014). Anatomical location and somatotopic organization of the corticospinal tract in the corona radiata of the normal human brain: a diffusion tensor tractography study. *NeuroReport*, *25*(9), 710-714. doi: 10.1097/WNR.0000000000000170

Lage, G. M., Ugrinowitsch, H., Apolinário-Souza, T., Vieira, M. M., Albuquerque, M. R., & Benda, R. N. (2015). Repetition and variation in motor practice: a review of neural correlates. *Neuroscience & Biobehavioral Reviews*, *57*, 132-141. doi: 10.1016/j.neubiorev.2015.08.012

Lampropoulou, S. I., & Nowicky, A. V. (2013). The effect of transcranial direct current stimulation on perception of effort in an isolated isometric elbow flexion task. *Motor Control*, *17*(4), 412-426. doi: 10.1123/mcj.17.4.412

Lancaster, G. A., Dodd, S., & Williamson, P. R. (2004). Design and analysis of pilot studies: recommendations for good practice. *Journal of Evaluation in Clinical Practice*, *10*(2), 307-312. doi: 10.1111/j..2002.384.doc.x

Larin, H. M. (1998). Motor learning: a practical framework for paediatric physiotherapy. *Physiotherapy Theory and Practice*, *14*(1), 33-47.

Law, M., Baptiste, S., Carswell, A., McColl, M. A., Polatajko, H., & Pollock, N. (2014). *Canadian Occupational Performance Measure* (5th ed.). Canadian Association of Occupational Therapists.

Law, M., Baptiste, S., McColl, M., Opzoomer, A., Polatajko, H., & Pollock, N. (1990). The Canadian Occupational Performance Measure: an outcome measure for occupational

therapy. *Canadian Journal of Occupational Therapy*, *57*(2), 82-87. doi: 10.1177/000841749005700207

Law, M., Russell, D., Pollock, N., Rosenbaum, P., Walter, S., & King, G. (1997). A comparison of intensive neurodevelopmental therapy plus casting and a regular occupational therapy program for children with cerebral palsy. *Developmental Medicine & Child Neurology*, *39*(10), 664-670. doi: 10.1111/j.1469-8749.1997.tb07360.x

Lazzari, R. D., Politti, F., Belina, S. F., Collange Grecco, L. A., Santos, C. A., Dumont, A. J. L., . . . Santos Oliveira, C. (2017). Effect of transcranial direct current stimulation combined with virtual reality training on balance in children with cerebral palsy: a randomized, controlled, double-blind, clinical trial. *Journal of Motor Behavior*, *49*(3), 329-336. doi: 10.1080/00222895.2016.1204266

Lee, H. A., & Kim, D. H. (2021). Brain Connectivity Affecting Gait Function after Unilateral Supratentorial Stroke. *Brain Sciences*, *11*(7), 870. doi: 10.3390/brainsci11070870

Lee, T., Norton, A., Hayes, S., Adamson, K., Schwellnus, H., & Evans, C. (2017). Exploring parents' perceptions and how physiotherapy supports transition from rehabilitation to school for youth with an ABI. *Physical & Occupational Therapy in Pediatrics*, *37*(4), 444-455. doi: 10.1080/01942638.2016.1261980

Lee, T. D., Swanson, L. R., & Hall, A. L. (1991). What is repeated in a repetition? Effects of practice conditions on motor skill acquisition. *Physical Therapy*, *71*(2), 150-156. doi: 10.1093/ptj/71.2.150

Lefmann, S., Russo, R., & Hillier, S. (2017). The effectiveness of robotic-assisted gait training for paediatric gait disorders: systematic review. *Journal of Neuroengineering and Rehabilitation*, *14*(1), 1-10. doi: 10.1186/s12984-016-0214-x

Lehéricy, S., Benali, H., Van de Moortele, P.-F., Pélégrini-Issac, M., Waechter, T., Ugurbil, K., & Doyon, J. (2005). Distinct basal ganglia territories are engaged in early and advanced motor sequence learning. *Proceedings of the National Academy of Sciences*, *102*(35), 12566-12571. doi: 10.1073/pnas.0502762102

Lennon, S. (2011). The theoretical basis for evidence-based neurological physiotherapy'. In M. Stokes & E. Stack (Eds.), *Physical Management for Neurological Conditions* (3rd ed., pp. 235-242). Elsevier.

Levac, D., & DeMatteo, C. (2009). Bridging the gap between theory and practice: dynamic systems theory as a framework for understanding and promoting recovery of function in children and youth with acquired brain injuries. *Physiotherapy Theory and Practice*, *25*(8), 544-554. doi: 10.3109/09593980802667888

Levac, D., Miller, P., & Missiuna, C. (2012). Usual and virtual reality video game-based physiotherapy for children and youth with acquired brain injuries. *Physical & Occupational Therapy in Pediatrics*, *32*(2), 180-195. doi: 10.3109/01942638.2011.616266

Levac, D., Missiuna, C., Wishart, L., DeMatteo, C., & Wright, V. (2011). Documenting the content of physical therapy for children with acquired brain injury: Development and validation of the Motor Learning Strategy Rating Instrument. *Physical Therapy, 91*(5), 689-699. doi: 10.2522/ptj.20100415

Levac, D. E., Huber, M. E., & Sternad, D. (2019). Learning and transfer of complex motor skills in virtual reality: a perspective review. *Journal of Neuroengineering and Rehabilitation, 16*(1), 1-15. doi: 10.1186/s12984-019-0587-8

Levin, M. F., Weiss, P. L., & Keshner, E. A. (2015). Emergence of virtual reality as a tool for upper limb rehabilitation: incorporation of motor control and motor learning principles. *Physical Therapy, 95*(3), 415-425. doi: 10.2522%2Fptj.20130579

Lewis, J., Scott, K., Pan, X., & Heathcock, J. (2020). The relationship between parent-reported PEDI-CAT mobility and gross motor function in children with cerebral palsy: brief report. *Developmental Neurorehabilitation, 23*(2), 140-144. doi: 10.1080/17518423.2019.1687601

Li, L. M., Uehara, K., & Hanakawa, T. (2015). The contribution of interindividual factors to variability of response in transcranial direct current stimulation studies. *Frontiers in Cellular Neuroscience, 9*, 181. doi: 10.3389/fncel.2015.00181

Lima, F. P. S., Lima, M. O., Leon, D., Lucareli, P. R. G., Falcon, C., Cogo, J. C., . . . Junqué, C. (2011). fMRI of the sensorimotor cortex in patients with traumatic brain injury after intensive rehabilitation. *Neurological Sciences, 32*(4), 633-639. doi: 10.1007/s10072-011-0604-6

Linder-Lucht, M., Othmer, V., Walther, M., Vry, J., Michaelis, U., Stein, S., . . . Mall, V. (2007). Validation of the Gross Motor Function Measure for use in children and adolescents with traumatic brain injuries. *Pediatrics, 120*(4), e880-e886. doi: 10.1542/peds.2006-2258

Lohse, K. R., Wadden, K., Boyd, L. A., & Hodges, N. J. (2014). Motor skill acquisition across short and long time scales: a meta-analysis of neuroimaging data. *Neuropsychologia, 59*, 130-141. doi: 10.1016/j.neuropsychologia.2014.05.001

Lucas, B. R., Elliott, E. J., Coggan, S., Pinto, R. Z., Jirikowic, T., McCoy, S. W., & Latimer, J. (2016). Interventions to improve gross motor performance in children with neurodevelopmental disorders: a meta-analysis. *BMC Pediatrics, 16*(1), 1-16. doi: 10.1186/s12887-016-0731-6

Ma, L., Wang, B., Narayana, S., Hazeltine, E., Chen, X., Robin, D. A., . . . Xiong, J. (2010). Changes in regional activity are accompanied with changes in inter-regional connectivity during 4 weeks motor learning. *Brain Research, 1318*, 64-76. doi: 10.1016/j.brainres.2009.12.073

MacKinnon, C. D. (2018). Sensorimotor anatomy of ait, balance, and falls. *Handbook of Clinical Neurology, 159*, 3-26. doi: 10.1016/B978-0-444-63916-5.00001-X

MacWilliam, K. R., Giancola, J. R., Wright, F. V., & Ryan, J. L. (2021). Use of Motor Learning Strategies in Occupational Therapy for Children and Youth with Acquired Brain Injury. *Physical & Occupational Therapy In Pediatrics*, *42*(1), 30-45. doi: 10.1080/01942638.2021.1923612

Madhavan, S., Cleland, B. T., Sivaramakrishnan, A., Freels, S., Lim, H., Testai, F. D., & Corcos, D. M. (2020). Cortical priming strategies for gait training after stroke: a controlled, stratified trial. *Journal of NeuroEngineering & Rehabilitation*, *17*(1), 1-14. doi: 10.1186/s12984-020-00744-9

Madhavan, S., Stinear, J. W., & Kanekar, N. (2016). Effects of a single session of high intensity interval treadmill training on corticomotor excitability following stroke: implications for therapy. *Neural Plasticity*, *2016*. 1686414, 1-8. doi: 10.1155/2016/1686414

Madhavan, S., Weber, K. A., 2nd, & Stinear, J. W. (2011). Non-invasive brain stimulation enhances fine motor control of the hemiparetic ankle: implications for rehabilitation. *Experimental Brain Research*, *209*(1), 9-17. doi: 10.1007/s00221-010-2511-0

Marsden, J., & Harris, C. (2011). Cerebellar ataxia: pathophysiology and rehabilitation. *Clinical Rehabilitation*, *25*(3), 195-216. doi: 10.1177/0269215510382495

Maskell, F., Chiarelli, P., & Isles, R. (2006). Dizziness after traumatic brain injury: overview and measurement in the clinical setting. *Brain Injury*, *20*(3), 293-305. doi: 10.1080/02699050500488041

McGinn, M. J., & Povlishock, J. T. (2015). Cellular and molecular mechanisms of injury and spontaneous recovery. *Handbook of Clinical Neurology*, *127*, 67-87. doi: 10.1016/B978-0-444-52892-6.00005-2

McKechnie, J., Ahmed, B., Gutierrez-Osuna, R., Murray, E., McCabe, P., & Ballard, K. J. (2020). The influence of type of feedback during tablet-based delivery of intensive treatment for childhood apraxia of speech. *Journal of Communication Disorders*, *87*, 106026. doi: 10.1016/j.jcomdis.2020.106026

Mendoza, J. E., & Foundas, A. L. (2008). The spinal cord and descending tracts. In *Clinical Neuroanatomy: A Neurobehavioral Approach* (pp. 1-22). Springer. doi: 10.1007/978-0-387-36601-2_1

Messacar, K., Fischer, M., Dominguez, S. R., Tyler, K. L., & Abzug, M. J. (2018). Encephalitis in US children. *Infectious Disease Clinics*, *32*(1), 145-162. doi: 10.1016/j.idc.2017.10.007

Middleton, A., Fritz, S. L., Liuzzo, D. M., Newman-Norlund, R., & Herter, T. M. (2014). Using clinical and robotic assessment tools to examine the feasibility of pairing tDCS with upper extremity physical therapy in patients with stroke and TBI: a consideration-of-concept pilot study. *NeuroRehabilitation*, *35*(4), 741-754. doi: 10.3233/nre-141178

Mikolajczyk, T., Ciobanu, I., Badea, D. I., Iliescu, A., Pizzamiglio, S., Schauer, T., . . . Berteanu, M. (2018). Advanced technology for gait rehabilitation: An overview. *Advances in Mechanical Engineering*, *10*(7), 1687814018783627. doi: 10.1177/1687814018783627

Miyaguchi, S., Onishi, H., Kojima, S., Sugawara, K., Tsubaki, A., Kirimoto, H., . . . Yamamoto, N. (2013). Corticomotor excitability induced by anodal transcranial direct current stimulation with and without non-exhaustive movement. *Brain Research, 1529*, 83-91. doi: https://dx.doi.org/10.1016/j.brainres.2013.07.026

Miyai, I., Tanabe, H. C., Sase, I., Eda, H., Oda, I., Konishi, I., . . . Kubota, K. (2001). Cortical mapping of gait in humans: a near-infrared spectroscopic topography study. *Neuroimage, 14*(5), 1186-1192. doi: 10.1006/nimg.2001.0905

Moliadze, V., Schmanke, T., Andreas, S., Lyzhko, E., Freitag, C. M., & Siniatchkin, M. (2015). Stimulation intensities of transcranial direct current stimulation have to be adjusted in children and adolescents. *Clinical Neurophysiology*, *126*(7), 1392-1399. doi: 10.1016/j.clinph.2014.10.142

Momosaki, R., Kinoshita, S., Kakuda, W., Yamada, N., & Abo, M. (2016). Noninvasive brain stimulation for dysphagia after acquired brain injury: a systematic review. *Journal of Medical Investigation*, *63*(3-4), 153-158. doi: 10.2152/jmi.63.153

Mooney, R. A., Cirillo, J., & Byblow, W. D. (2019). Neurophysiological mechanisms underlying motor skill learning in young and older adults. *Experimental Brain Research*, *237*(9), 2331-2344. doi: http://dx.doi.org/10.1007/s00221-019-05599-8

Morgan, B., Hejdenberg, J., Hinrichs-Krapels, S., & Armstrong, D. (2018). Do feasibility studies contribute to, or avoid, waste in research? *PloS One*, *13*(4), e0195951. doi: 10.1371/journal.pone.0195951

Morgan, C., Novak, I., Dale, R. C., Guzzetta, A., & Badawi, N. (2016). Single blind randomised controlled trial of GAME (Goals Activity Motor Enrichment) in infants at high risk of cerebral palsy. *Research in Developmental Disabilities*, *55*, 256-267. doi: 10.1016/j.ridd.2016.04.005

Munn, Z., Peters, M. D. J., Stern, C., Tufanaru, C., McArthur, A., & Aromataris, E. (2018). Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach. *BMC Medical Research Methodology*. *18*(143) doi: 10.1186/s12874-018-0611-x

Nakagawa, K., Takemi, M., Nakanishi, T., Sasaki, A., & Nakazawa, K. (2020). Cortical reorganization of lower-limb motor representations in an elite archery athlete with congenital amputation of both arms. *Neuroimage: Clinical*, *25*, 102144. doi: 10.1016/j.nicl.2019.102144

Nam, H.-S., Kim, J.-H., & Lim, Y.-J. (2017). The effect of the base of support on anticipatory postural adjustment and postural stability. *The Journal of Korean Physical Therapy*, *29*(3), 135-141. doi: 10.18857/jkpt.2017.29.3.135

Nathan, P. W., & Smith, M. C. (1955). Long descending tracts in man: I. Review of present knowledge. *Brain*, *78*(2), 248-303. doi: 10.1093/brain/78.2.248

Navarro-López, V., Molina-Rueda, F., Jiménez-Jiménez, S., Alguacil-Diego, I. M., & Carratalá-Tejada, M. (2021). Effects of transcranial direct current stimulation combined with physiotherapy on gait pattern, balance, and functionality in stroke patients. a systematic review. *Diagnostics*, *11*(4), 656. doi: 10.3390/diagnostics11040656

Nemanich, S. T., Chen, C.-Y., Chen, M., Zorn, E., Mueller, B., Peyton, C., . . . Gillick, B. (2019). Safety and feasibility of transcranial magnetic stimulation as an exploratory assessment of corticospinal connectivity in infants after perinatal brain injury: an observational study. *Physical Therapy*, *99*(6), 689-700. doi: 10.1093/ptj/pzz028

Nishiyori, R., Bisconti, S., Meehan, S. K., & Ulrich, B. D. (2016). Developmental changes in motor cortex activity as infants develop functional motor skills. *Developmental Psychobiology*, *58*(6), 773-783. doi: 10.1002/dev.21418

Nissen, T., & Wynn, R. (2014). The clinical case report: a review of its merits and limitations. *BMC Research Notes*, *7*, 264. doi: 10.1186/1756-0500-7-264

Nitsche, M. A., & Paulus, W. (2000). Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. *The Journal of Physiology*, *527*(3), 633-639. doi: 10.1111/j.1469-7793.2000.t01-1-00633.x

Nudo, R. J. (2013). Recovery after brain injury: mechanisms and principles. *Frontiers in Human Neuroscience*, *7*, 887. doi: 10.3389/fnhum.2013.00887

Overman, J. J., & Carmichael, S. T. (2014). Plasticity in the injured brain: more than molecules matter. *The Neuroscientist*, *20*(1), 15-28. doi: 10.1177/1073858413491146

Page, M. J., Moher, D., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., . . . Brennan, S. E. (2021). PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ*, *372*. doi: 10.1136/bmj.n71

Palisano, R., Rosenbaum, P., Walter, S., Russell, D., Wood, E., & Galuppi, B. (1997). Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Developmental Medicine & Child Neurology*, *39*(4), 214-223. doi: 10.1111/j.1469-8749.1997.tb07414.x

Palm, U., Reisinger, E., Keeser, D., Kuo, M.-F., Pogarell, O., Leicht, G., . . . Padberg, F. (2013). Evaluation of sham transcranial direct current stimulation for randomized, placebo-controlled clinical trials. *Brain Stimulation*, *6*(4), 690-695. doi: 10.1097/PHM.0000000000000521

Palm, U., Kumpf, U., Behler, N., Wulf, L., Kirsch, B., Wörsching, J., ... & Padberg, F. (2018). Home use, remotely supervised, and remotely controlled transcranial direct current stimulation: a systematic review of the available evidence. *Neuromodulation: Technology at the Neural Interface*, *21*(4), 323-333. doi: 10.1111/ner.12686

Palm, U., Segmiller, F. M., Epple, A. N., Freisleder, F.-J., Koutsouleris, N., Schulte-Körne, G., & Padberg, F. (2016). Transcranial direct current stimulation in children and adolescents: a comprehensive review. *Journal of Neural Transmission*, *123*(10), 1219-1234. doi: 10.1007/s00702-016-1572-z

Patel, R., & Madhavan, S. (2019). Comparison of transcranial direct current stimulation electrode montages for the lower limb motor cortex. *Brain Sciences*, *9*(8), 189. doi: 10.3390/brainsci9080189

Payne, V. G., & Isaacs, L. D. (2017). *Human Motor Development: A Lifespan Approach*. Routledge.

Pearce, A. J., & Kidgell, D. J. (2010). Comparison of corticomotor excitability during visuomotor dynamic and static tasks. *Journal of Science and Medicine in Sport*, *13*(1), 167-171. doi: 10.1016/j.jsams.2008.12.632

Pierce, S. R., Skorup, J., Alcott, M., Bochnak, M., Paremski, A. C., & Prosser, L. A. (2021). The use of dynamic weight support with principles of infant learning in a child with cerebral palsy: a case report. *Physical & Occupational Therapy In Pediatrics*, *41*(2), 166-175. doi: 10.1080/01942638.2020.1766638

Pin, T. W., Butler, P. B., & Purves, S. (2019). Use of whole body vibration therapy in individuals with moderate severity of cerebral palsy-a feasibility study. *BMC Neurology*, *19*(1), 1-7. doi: 10.1186/s12883-019-1307-5

Pollock, C. L., Boyd, L. A., Hunt, M. A., & Garland, S. J. (2014). Use of the challenge point framework to guide motor learning of stepping reactions for improved balance control in people with stroke: a case series. *Physical Therapy*, *94*(4), 562-570. doi: 10.2522/ptj.20130046

Pool, D., Valentine, J., Bear, N., Donnelly, C. J., Elliott, C., & Stannage, K. (2015). The orthotic and therapeutic effects following daily community applied functional electrical stimulation in children with unilateral spastic cerebral palsy: a randomised controlled trial. *BMC Pediatrics*, *15*(1), 1-10. doi: 10.1186/s12887-015-0472-y

Popernack, M. L., Gray, N., & Reuter-Rice, K. (2015). Moderate-to-severe traumatic brain injury in children: complications and rehabilitation strategies. *Journal of Pediatric Health Care*, *29*(3), e1-e7. doi: 10.1016/j.pedhc.2014.09.003

Portney, L. G., & Watkins, M. P. (2020). *Foundations of Clinical Research: Applications to Evidence-based Practice* (4th ed.). FA Davis Company.

Pourazar, M., Mirakhori, F., Bagherzadeh, F., & Hemayattalab, R. (2017). Effects of External and Internal Focus of Attention in Motor Learning of Children Cerebral Palsy. *International Journal of Sport and Health Sciences*, *11*(6), 361-366.

Pourmajidian, M., Sidhu, S. K., & Lauber, B. (2020). Preconditioning cathodal transcranial direct current stimulation facilitates the neuroplastic effect of subsequent anodal

transcranial direct current stimulation applied during cycling in young adults. *Neuroscience Letters*, *714*, 134597. doi: 10.1016/j.neulet.2019.134597

Prado, M. T. A., Fernani, D. C. G. L., da Silva, T. D., Smorenburg, A. R., de Abreu, L. C., & de Mello Monteiro, C. B. (2017). Motor learning paradigm and contextual interference in manual computer tasks in individuals with cerebral palsy. *Research in Developmental Disabilities*, *64*, 56-63. doi: 10.1016/j.ridd.2017.03.006

Pritchard-Wiart, L., Thompson-Hodgetts, S., & McKillop, A. B. (2019). A review of goal setting theories relevant to goal setting in paediatric rehabilitation. *Clinical Rehabilitation*, *33*(9), 1515-1526. doi: 10.1177/0269215519846220

Rast, F. M., & Labruyère, R. (2020). ICF mobility and self-care goals of children in inpatient rehabilitation. *Developmental Medicine & Child Neurology*, *62*(4), 483-488. doi: 10.1111/dmcn.14471

Reid, L. B., Sale, M. V., Cunnington, R., Mattingley, J. B., & Rose, S. E. (2017). Brain changes following four weeks of unimanual motor training: Evidence from fMRI-guided diffusion MRI tractography. *Human Brain Mapping*, *38*(9), 4302-4312. doi: 10.1002/hbm.23514

Rich, T. L., Nawshin, T., Nemanich, S., Gillick, B. T., Chen, M., Friel, K., . . . Meekins, G. (2018). Transcranial direct current stimulation (tDCS) paired with occupation-centered bimanual training in children with unilateral cerebral palsy: A preliminary study. *Neural Plasticity*, *2018*, 9610812. doi: 10.1155/2018/9610812

Rich, T. L., Menk, J., Krach, L. E., Feyma, T., & Gillick, B. T. (2016). Repetitive transcranial magnetic stimulation/behavioral intervention clinical trial: long-term follow-up of outcomes in congenital hemiparesis. *Journal of Child and Adolescent Psychopharmacology*, *26*(7), 598-605. doi: 10.1089/cap.2015.0157

Rudroff, T., & Workman, C. D. (2021). Transcranial Direct Current Stimulation as a Treatment Tool for Mild Traumatic Brain Injury. *Brain Sciences*, *11*(6). doi: 10.3390/brainsci11060806

Russell, D. J., Rosenbaum, P. L., Cadman, D. T., Gowland, C., Hardy, S., & Jarvis, S. (1989). The gross motor function measure: a means to evaluate the effects of physical therapy. *Developmental Medicine & Child Neurology*, *31*(3), 341-352. doi: 10.1111/j.1469-8749.1989.tb04003.x

Russell, D. J., Wright, M., Rosenbaum, P. L., & Avery, L. M. (2021). *Gross Motor Function Measure (GMFM-66 & GMFM-88) User's Manual* (3rd edition ed.). MacKeith Press.

Russo, C., Carneiro, M. I. S., Bolognini, N., & Fregni, F. (2017). Safety review of transcranial direct current stimulation in stroke. *Neuromodulation: Technology at the Neural Interface*, *20*(3), 215-222. doi: 10.1111/ner.12574

Ryan, J. L., Zhou, C., Levac, D. E., Fehlings, D. L., Beal, D. S., Hung, R., & Wright, F. V. (2022). Gross motor change after intensive rehabilitation for children and youth with

ABI: A 10-year retrospective review. *Developmental Medicine & Child Neurology. 00,* 1-8. doi: org/10.1111/dmcn.15471

Ryan, J. L., Levac, D. E., & Wright, F. V. (2019). Reliability of the Motor Learning Strategies Rating Instrument in physiotherapy intervention for children with cerebral palsy. *Developmental Medicine & Child Neurology*, *61*(9), 1061-1066. doi: 10.1111/dmcn.14177

Ryan, J. L., Wright F. V., & Levac, D. E. (2017). *Motor Learning Strategies Online Training Program*. https://hollandbloorview.dualcode.com

Ryan, J. L., Wright, F. V., & Levac, D. E. (2020). Exploring physiotherapists' use of motor learning strategies in gait-based interventions for children with cerebral palsy. *Physical & Occupational Therapy in Pediatrics*, *40*(1), 79-92. doi: 10.1080/01942638.2019.1622623

Salazar Fajardo, J. C., Kim, R., Gao, C., Hong, J., Yang, J., Wang, D., & Yoon, B. (2022). The effects of tDCS with NDT on the improvement of motor development in cerebral palsy. *Journal of Motor Behavior*, 1-10. doi: 10.1080/00222895.2021.2016572

Saleem, G. T., Crasta, J. E., Slomine, B. S., Cantarero, G. L., & Suskauer, S. J. (2019a). Transcranial direct current stimulation in pediatric motor disorders: a systematic review and meta-analysis. *Archives of Physical Medicine and Rehabilitation*, *100*(4), 724-738. doi: 10.1016/j.apmr.2018.10.011

Saleem, G. T., Ewen, J. B., Crasta, J. E., Slomine, B. S., Cantarero, G. L., & Suskauer, S. J. (2019b). Single-arm, open-label, dose escalation phase I study to evaluate the safety and feasibility of transcranial direct current stimulation with electroencephalography biomarkers in paediatric disorders of consciousness: a study protocol. *BMJ Open*, *9*(8), e029967. doi: 10.1136/bmjopen-2019-029967

Schlosser, R. W. (2004). Goal attainment scaling as a clinical measurement technique in communication disorders: a critical review. *Journal of Communication Disorders*, *37*(3), 217-239. doi: 10.1016/j.jcomdis.2003.09.003

Schmidt, R., & Lee, T. (2014). *Motor learning and performance* (5th ed.). Human Kinetics.

Schnackers, M., Beckers, L., Janssen-Potten, Y., Aarts, P., Rameckers, E., van der Burg, J., . . . Group, C. F. (2018). Home-based bimanual training based on motor learning principles in children with unilateral cerebral palsy and their parents (the COAD-study): rationale and protocols. *BMC Pediatrics*, *18*(1), 139. doi: 10.1186/s12887-018-1110-2

Scott, S. H. (2004). Optimal feedback control and the neural basis of volitional motor control. *Nature Reviews Neuroscience*, *5*(7), 532-545. doi: 10.1038/nrn1427

Seeck, M., Koessler, L., Bast, T., Leijten, F., Michel, C., Baumgartner, C., . . . Beniczky, S. (2017). The standardized EEG electrode array of the IFCN. *Clinical Neurophysiology*, *128*(10), 2070-2077. doi: 10.1016/j.clinph.2017.06.254

Seidel, O., & Ragert, P. (2019). Effects of transcranial direct current stimulation of primary motor cortex on reaction time and tapping performance: A comparison between athletes and non-athletes. *Frontiers in Human Neuroscience, 13*. doi: 10.3389/fnhum.2019.00103

Sekerdag, E., Solaroglu, I., & Gursoy-Ozdemir, Y. (2018). Cell death mechanisms in stroke and novel molecular and cellular treatment options. *Current Neuropharmacology, 16*(9), 1396-1415. doi: 10.2174/1570159X16666180302115544

Seo, J. P., Do, K. H., Jung, G. S., Seo, S. W., Kim, K., Son, S. M., . . . Jang, S. H. (2014). The difference of gait pattern according to the state of the corticospinal tract in chronic hemiparetic stroke patients. *NeuroRehabilitation, 34*(2), 259-266. doi: 10.3233/nre-131046

Seo, J. P., & Jang, S. H. (2013). Different characteristics of the corticospinal tract according to the cerebral origin: DTI study. *American Journal of Neuroradiology, 34*(7), 1359-1363.

Serrano-González, P., Cuesta-García, C., Girol-López, E., & Cuenca-Martínez, F. (2022). Action observation training to improve activities of daily living and manipulation skills in children with acquired brain injury secondary to an oncologic process: a prospective case series clinical study. *Physical Therapy Research, 25*(1), 41-48. doi: 10.1298/ptr.e10134

Sivaramakrishnan, A., & Madhavan, S. (2020). Stimulus intensity affects variability of motor evoked responses of the non-paretic, but not paretic tibialis anterior muscle in stroke. *Brain Sciences, 10*(5), 297. doi: 10.3174/ajnr.a3389

Sivaramakrishnan, A., & Madhavan, S. (2021). Combining transcranial direct current stimulation with aerobic exercise to optimize cortical priming in stroke. *Applied Physiology, Nutrition, and Metabolism, 46*(5), 426-435. doi: 10.1139/apnm-2020-0677

Sohn, M. K., Kim, B. O., & Song, H. T. (2012). Effect of Stimulation Polarity of Transcranial Direct Current Stimulation on Non-dominant Hand Function. *Annals of Rehabilitation Medicine, 36*(1), 1-7. doi: 10.5535/arm.2012.36.1.1

Souto, D. O., Cruz, T. K. F., Coutinho, K., Julio-Costa, A., Fontes, P. L. B., & Haase, V. G. (2020). Effect of motor imagery combined with physical practice on upper limb rehabilitation in children with hemiplegic cerebral palsy. *NeuroRehabilitation, 46*(1), 53-63. doi: 10.3233/NRE-192931

Spiess, M. R., Steenbrink, F., & Esquenazi, A. (2018). Getting the best out of advanced rehabilitation technology for the lower limbs: minding motor learning principles. *PM&R, 10*(9), 165-173. doi: 10.1016/j.pmrj.2018.06.007

Spivak, M. R., Chan, J. R., Cooper, M. S., Petrucci, C., Sheridan, A. M., Tang, T. Y., . . . Ryan, J. L. (2021). Reliability of the revised Motor Learning Strategies Rating Instrument and its role in describing the motor learning strategy content of physiotherapy sessions in paediatric acquired brain injury. *Physiotherapy Canada, 73*(4), 381-390. doi: 10.3138/ptc-2020-0014

Sriraman, A., Madhavan, S., & Oishi, T. (2014). Timing-dependent priming effects of tDCS on ankle motor skill learning. *Brain Research*, *1581*, 23-29. doi: 10.1016/j.brainres.2014.07.021

Stagg, C. J., Jayaram, G., Pastor, D., Kincses, Z. T., Matthews, P. M., & Johansen-Berg, H. (2011). Polarity and timing-dependent effects of transcranial direct current stimulation in explicit motor learning. *Neuropsychologia*, *49*(5), 800-804. doi: 10.1016/j.neuropsychologia.2011.02.009

Stagg, C. J., & Nitsche, M. A. (2011). Physiological basis of transcranial direct current stimulation. *The Neuroscientist*, *17*(1), 37-53. doi: 10.1177/1073858410386614

Steenbeek, D., Gorter, J. W., Ketelaar, M., Galama, K., & Lindeman, E. (2011). Responsiveness of Goal Attainment Scaling in comparison to two standardized measures in outcome evaluation of children with cerebral palsy. *Clinical Rehabilitation*, *25*(12), 1128-1139. doi: 10.1177/0269215511407220

Steenbeek, D., Ketelaar, M., Lindeman, E., Galama, K., & Gorter, J. W. (2010). Interrater reliability of goal attainment scaling in rehabilitation of children with cerebral palsy. *Archives of Physical Medicine and Rehabilitation*, *91*(3), 429-435. doi: 10.1016/j.apmr.2009.10.013

Sterne, J. A. C., Savović, J., Page, M. J., Elbers, R. G., Blencowe, N. S., Boutron, I., . . . Eldridge, S. M. (2019). RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*, *366*. doi: http://dx.doi.org/10.1136/bmj.l4898

Storm, F. A., Petrarca, M., Beretta, E., Strazzer, S., Piccinini, L., Maghini, C., . . . Reni, G. (2020). Minimum clinically important difference of gross motor function and gait endurance in children with motor impairment: A comparison of distribution-based approaches. *BioMed Research International, 2794036*. doi: 10.1155/2020/2794036

Stuhr, C., Hughes, C. M. L., & Stöckel, T. (2018). Task-specific and variability-driven activation of cognitive control processes during motor performance. *Scientific Reports*, *8*(1), 1-9. doi: 10.1038/s41598-018-29007-3

Swartwout, E., El-Zein, A., Deyo, P., Grant, P., Fogle, M., Laughon, D., & Goodwin, D. (2019). Innovative collaborative partnerships to conduct multisite research: Strategies for success. *The Journal of Nursing Administration*, *49*(5), 242-248. doi: 10.1097/NNA.0000000000000745

Tailor, Y. I., Suskauer, S. J., Sepeta, L. N., Ewen, J. B., DeMatt, E. J., Trovato, M. K., ... & Slomine, B. S. (2013). Functional status of children with encephalitis in an inpatient rehabilitation setting: a case series. *Journal of Pediatric Rehabilitation Medicine, 6*(3), 163-173. doi: 10.3233/PRM-130248

Takakusaki, K. (2013). Neurophysiology of gait: from the spinal cord to the frontal lobe. *Movement Disorders*, *28*(11), 1483-1491. doi: 10.1002/mds.25669

Takakusaki, K. (2017). Functional neuroanatomy for posture and gait control. *Journal of Movement Disorders, 10*(1), 1. doi: 10.14802/jmd.16062

Takeuchi, N., & Izumi, S. I. (2013). Rehabilitation with poststroke motor recovery: a review with a focus on neural plasticity. *Stroke Research and Treatment, 2013*. 128641. doi: 10.1155/2013/128641

Tanaka, S., Honda, M., Hanakawa, T., & Cohen, L. G. (2010). Differential contribution of the supplementary motor area to stabilization of a procedural motor skill acquired through different practice schedules. *Cerebral Cortex, 20*(9), 2114-2121. doi: 10.1093/cercor/bhp276

Tavor, I., Botvinik-Nezer, R., Bernstein-Eliav, M., Tsarfaty, G., & Assaf, Y. (2020). Short-term plasticity following motor sequence learning revealed by diffusion magnetic resonance imaging. *Human Brain Mapping, 41*(2), 442-452. doi: 10.1002/hbm.24814

Thabane, L., Ma, J., Chu, R., Cheng, J., Ismaila, A., Rios, L. P., . . . Goldsmith, C. H. (2010). A tutorial on pilot studies: the what, why and how. *BMC Medical Research Methodology, 10*(1), 1. doi: 10.1186/1471-2288-10-1

Thirugnanasambandam, N., Sparing, R., Dafotakis, M., Meister, I. G., Paulus, W., Nitsche, M. A., & Fink, G. R. (2011). Isometric contraction interferes with transcranial direct current stimulation (tDCS) induced plasticity- evidence of state-dependent neuromodulation in human motor cortex. *Restorative Neurology and Neuroscience, 29*(5), 311-320. doi: 10.3233/rnn-2011-0601

Thomas-Stonell, N., Johnson, P., Rumney, P., Wright, V., & Oddson, B. (2006). An evaluation of the responsiveness of a comprehensive set of outcome measures for children and adolescents with traumatic brain injuries. *Pediatric Rehabilitation, 9*(1), 14-23. doi: 10.1080/13638490500050097

Thompson, P., Beath, T., Bell, J., Jacobson, G., Phair, T., Salbach, N. M., & Wright, F. (2008). Test–retest reliability of the 10-metre fast walk test and 6-minute walk test in ambulatory school-aged children with cerebral palsy. *Developmental Medicine & Child Neurology, 50*(5), 370-376. doi: 10.1111/j.1469-8749.2008.02048.x

Towns, M., Rosenbaum, P., Palisano, R., & Wright, F. V. (2018). Should the Gross Motor Function Classification System be used for children who do not have cerebral palsy? *Developmental Medicine & Child Neurology, 60*(2), 147-154. doi: 10.1111/dmcn.13602

Tseng, S.-C., Chang, S.-H., Hoerth, K. M., Nguyen, A.-T. A., & Perales, D. (2020). Anodal transcranial direct current stimulation enhances retention of visuomotor stepping skills in healthy adults. *Frontiers in Human Neuroscience, 14*. doi: 10.3389/fnhum.2020.00251

Tsze, D. S., & Valente, J. H. (2011). Pediatric stroke: a review. *Emergency Medicine International, 2011*. doi: 10.1155/2011/734506

Turner, R. (2016). Uses, misuses, new uses and fundamental limitations of magnetic resonance imaging in cognitive science. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *371*(1705), 20150349. doi: 10.1098/rstb.2015.0349

Turner-Stokes, L. (2009). Goal attainment scaling (GAS) in rehabilitation: a practical guide. *Clinical Rehabilitation*, *23*(4), 362-370. doi: 10.1177/0269215508101742

Ulam, F., Shelton, C., Richards, L., Davis, L., Hunter, B., Fregni, F., & Higgins, K. (2015). Cumulative effects of transcranial direct current stimulation on EEG oscillations and attention/working memory during subacute neurorehabilitation of traumatic brain injury. *Clinical Neurophysiology*, *126*(3), 486-496. doi: 10.1016/j.clinph.2014.05.015

Ustinova, K. I., Chernikova, L. A., Dull, A., & Perkins, J. (2015). Physical therapy for correcting postural and coordination deficits in patients with mild-to-moderate traumatic brain injury. *Physiotherapy Theory and Practice*, *31*(1), 1-7. doi: 10.3109/09593985.2014.945674

Valvano, J. (2004). Activity-focused motor interventions for children with neurological conditions. *Physical & Occupational Therapy in Pediatrics*, *24*(1-2), 79-107. doi: 10.1300/J006v24n01_04

Vaz, P. G., Salazar, A. P. d. S., Stein, C., Marchese, R. R., Lukrafka, J. L., Plentz, R. D. M., & Pagnussat, A. S. (2019). Noninvasive brain stimulation combined with other therapies improves gait speed after stroke: a systematic review and meta-analysis. *Topics in Stroke Rehabilitation*, *26*(3), 201-213. doi: 10.1080/10749357.2019.1565696

Veldman, M. P., Maurits, N. M., Nijland, M. A. M., Wolters, N. E., Mizelle, J. C., & Hortobágyi, T. (2018). Spectral and temporal electroencephalography measures reveal distinct neural networks for the acquisition, consolidation, and interlimb transfer of motor skills in healthy young adults. *Clinical Neurophysiology*, *129*(2), 419-430. doi: 10.1016/j.clinph.2017.12.003

Veldman, S. L. C., Santos, R., Jones, R. A., Sousa-Sá, E., & Okely, A. D. (2019). Associations between gross motor skills and cognitive development in toddlers. *Early Human Development*, *132*, 39-44. doi: 10.1016/j.earlhumdev.2019.04.005

Verkerk, G. J. Q., Wolf, M. J. M. A. G., Louwers, A. M., Meester-Delver, A., & Nollet, F. (2006). The reproducibility and validity of the Canadian Occupational Performance Measure in parents of children with disabilities. *Clinical Rehabilitation*, *20*(11), 980-988. doi: 10.1177/0269215506070703

Vidal, A., de Azevedo Fernandes, J. M. G., da Rosa Gutierres, I. C., da Silva, F. C., Silva, R., & Gutierres Filho, P. J. B. (2021). Effects of weekly hippotherapy frequency on gross motor function and functional performance of children with cerebral palsy: a randomized controlled trial. *Motricidade*, *17*(1), 79-86. doi: 10.6063/motricidade.23847

Vos-Vromans, D. C. W. M., Ketelaar, M., & Gorter, J. W. (2005). Responsiveness of evaluative measures for children with cerebral palsy: the Gross Motor Function Measure and the

Pediatric Evaluation of Disability Inventory. *Disability and Rehabilitation*, *27*(20), 1245-1252. doi: 10.1080/09638280500076178

Watson, M. J. (2002). Refining the ten-metre walking test for use with neurologically impaired people. *Physiotherapy, 88*(7), 386-397.

Weinberger, M., Oddone, E. Z., Henderson, W. G., Smith, D. M., Huey, J., Giobbie-Hurder, A., & Feussner, J. R. (2001). Multisite randomized controlled trials in health services research: scientific challenges and operational issues. *Medical Care*, 627-634. doi: 10.1097/00005650-200106000-00010

Welniarz, Q., Dusart, I., & Roze, E. (2017). The corticospinal tract: Evolution, development, and human disorders. *Developmental Neurobiology*, *77*(7), 810-829. doi: 1010.1002/dneu.22455

Wessel, M. J., Zimerman, M., & Hummel, F. C. (2015). Non-invasive brain stimulation: an interventional tool for enhancing behavioral training after stroke. *Frontiers in Human Neuroscience, 9,* 265. doi: 10.3389/fnhum.2015.00265

Whyte, J., & Hart, T. (2003). It's more than a black box; it's a Russian doll: defining rehabilitation treatments. *American Journal of Physical Medicine & Rehabilitation*, *82*(8), 639-652. doi: 10.1097/01.phm.0000078200.61840.2d

Wiethoff, S., Rothwell, J. C., & Hamada, M. (2014). Variability in response to transcranial direct current stimulation of the motor cortex. *Brain Stimulation*, *7*(3), 468-475. doi: 10.1016/j.brs.2014.02.003

Winstein, C., Lewthwaite, R., Blanton, S. R., Wolf, L. B., & Wishart, L. (2014). Infusing motor learning research into neurorehabilitation practice: a historical perspective with case exemplar from the accelerated skill acquisition program. *Journal of Neurologic Physical Therapy*, *38*(3), 190. doi: 10.1097/npt.0000000000000046

Wong, R. K. Y., McEwan, J., Finlayson, D., Chung, S., Wan, L., Salbach, N. M., . . . Wright, F. V. (2014). Reliability and validity of the acquired brain injury challenge assessment (ABI-CA) in children. *Brain Injury*, *28*(13-14), 1734-1743. doi: 10.3109/02699052.2014.947620

Woods, A. J., Antal, A., Liebetanz, D., Paulus, W., Bikson, M., Reato, D., . . . Nitsche, M. A. (2016). A technical guide to tDCS, and related non-invasive brain stimulation tools. *Clinical Neurophysiology*, *127*(2), 1031-1048. doi: 10.1016/j.clinph.2015.11.012

World Health Organization. (2001). International Classification of Functioning, Disability and Health (ICF). Retrieved from http://apps.who.int/iris/bitstream/handle/10665/42407/9241545429.pdf;jsessionid=BDBF8A3ACCFCE1397EDDBEA51C3A1FC7?sequence=1

Wright, F. V., Hung, R., & Ryan, J. L. (2018). *Evaluation of robotic gait training in early stage rehabilitation of children post-ABI* [conference session]. 42nd Annual Williamsburg Brain Injury Rehabilitation Conference, Williamsburg, United States.

Wright, F. V., Rosenbaum, P. L., Goldsmith, C. H., Law, M., & Fehlings, D. L. (2008). How do changes in body functions and structures, activity, and participation relate in children with cerebral palsy? *Developmental Medicine & Child Neurology*, *50*(4), 283-289. doi: 10.1111/j.1469-8749.2008.02037.x

Wright, F. V., Ryan, J., & Brewer, K. (2010). Reliability of the Community Balance and Mobility Scale (CB&M) in high-functioning school-aged children and adolescents who have an acquired brain injury. *Brain Injury, 24*(13-14), 1585-1594. doi: 10.3109/02699052.2010.523045

Wrightson, J. G., Twomey, R., Yeung, S. T. Y., & Millet, G. Y. (2020). No effect of tDCS of the primary motor cortex on isometric exercise performance or perceived fatigue. *The European Journal of Neuroscience*, *52*(2), 2905-2914. doi: 10.1111/ejn.14651

Wulf, G., Shea, C. H., & Whitacre, C. A. (1998). Physical-guidance benefits in learning a complex motor skill. *Journal of Motor Behavior*, *30*(4), 367-380. doi: 10.1080/00222899809601351

Xiao, S., Wang, B., Zhang, X., Zhou, J., & Fu, W. (2020). Systematic review of the impact of transcranial direct current stimulation on the neuromechanical management of foot and ankle physical performance in healthy adults. *Frontiers in Bioengineering and Biotechnology*, 1271. doi: 10.3389/fbioe.2020.587680

Yeo, S. S., Chang, P.-H., & Jang, S. H. (2013). The cortical activation differences between proximal and distal joint movements of the upper extremities: a functional NIRS study. *NeuroRehabilitation*, *32*(4), 861-866. doi: 10.3233/nre-130910

Zaaimi, B., Dean, L. R., & Baker, S. N. (2018). Different contributions of primary motor cortex, reticular formation, and spinal cord to fractionated muscle activation. *Journal of Neurophysiology*, *119*(1), 235-250. doi: 10.1152/jn.00672.2017

Zanca, J. M., Turkstra, L. S., Chen, C., Packel, A., Ferraro, M., Hart, T., . . . Dijkers, M. P. (2019). Advancing rehabilitation practice through improved specification of interventions. *Archives of Physical Medicine and Rehabilitation*, *100*(1), 164-171. doi: 10.1016/j.apmr.2018.09.110

Zaninotto, A. L., El-Hagrassy, M. M., Green, J. R., Babo, M., Paglioni, V. M., Benute, G. G., & Paiva, W. S. (2019). Transcranial direct current stimulation (tDCS) effects on traumatic brain injury (TBI) recovery: A systematic review. *Dementia & Neuropsychologia*, *13*(2), 172-179. doi: 10.1590/1980-57642018dn13-020005

Zeiler, S. R., & Krakauer, J. W. (2013). The interaction between training and plasticity in the post-stroke brain. *Current Opinion in Neurology, 26*(6), 609. doi: 10.1097/WCO.0000000000000025

Zewdie, E., Ciechanski, P., Kuo, H., Giuffre, A., Kahl, C., King, R., . . . Swansburg, R. (2020). Safety and tolerability of transcranial magnetic and direct current stimulation in children: Prospective single center evidence from 3.5 million stimulations. *Brain Stimulation*, *13*(3), 565-575. doi: 10.1016/j.brs.2019.12.025

Zhou, J., Lo, O.-Y., Lipsitz, L. A., Zhang, J., Fang, J., & Manor, B. (2018). Transcranial direct current stimulation enhances foot sole somatosensation when standing in older adults. *Experimental Brain Research*, *236*(3), 795-802. doi: 10.1007/s00221-018-5178-6

Ziviani, J. (2015). Occupational performance: a case for self-determination. *Australian Occupational Therapy Journal*, 62(6), 393-400. doi: 10.1111/1440-1630.12250

Ziviani, J., Ottenbacher, K. J., Shephard, K., Foreman, S., Astbury, W., & Ireland, P. (2002). Concurrent validity of the functional independence measure for children (WeeFIM (™)) and the pediatric evaluation of disabilities inventory in children with developmental disabilities and acquired brain injuries. *Physical & Occupational Therapy in Pediatrics*, 21(2-3), 91-101. doi: 10.1080/J006v21n02_08

Zwicker, J. G., & Harris, S. R. (2009). A reflection on motor learning theory in pediatric occupational therapy practice. *Canadian Journal of Occupational Therapy*, *76*(1), 29-37. doi: 10.1177/000841740907600108

Appendix A. MEDLINE search strategy for the systematic review

1. Transcranial Direct Current Stimulation/

2. ("TDCS " or " tDCS " or "anodal stimulation transcranial direct current stimulation* " or "anodal stimulation tdcs" or "cathodal stimulation transcranial direct current stimulation* " or "cathodal stimulation tdcs" or "transcranial electrical stimulation*" or "repetitive transcranial electrical stimulation*" or "transcranial direct current stimulation*" or "'cathodal tDCS" or "anodal tDCS").kf,tw.

3. or/1-2

4. exp Evoked Potentials, Motor/

5. electrodiagnosis/ or electromyography/

6. ("motor cortical excitability" or "MEP*" or "motor evoked potential*" or "cortical excitability" or "electrodiagnosis" or "electromyography").kf,tw.

7. Cortical Excitability/

8. (corticospinal adj2 excitability).kf,tw.

9. or/4-8

10. Animals/ not (Animals/ and Humans/)

11. 3 and 9

12. limit 11 to yr="2014 -Current"

13. 12 not 10

14. remove duplicates from 13

Appendix B

tDCS Pre-Session Status Assessment Form

*Research staff: Complete this form with a parent and/or child at the beginning of each tDCS session. When completing the form before the first treatment session, replace "**Since your last brain stimulation session**" with "**Since your admission to the Holland Bloorview**". For YES responses, follow directions in the "If YES, then" column. Go on then to complete p. 2. DO NOT proceed with the tDCS session for FACES scale ratings of 4. Instead notify the child's nurse and the primary investigators.*

QUESTION: Since your last brain stimulation session on [day]:

	NO	YES	If YES, then…	Details
1. Have you had any new physical or health concerns? (i.e., something that started to become a problem during this time or an old problem that got worse.)			*Record new concerns, time/date of onset, frequency, duration. Indicate if the symptoms of an old problem are getting worse.*	
2. Have there been activities that you didn't do as often or didn't do at all because you did not feel well?			*Record dates and missed activities. Indicate which symptoms caused the child to miss the activity.*	
3. Have you had any seizures?			***DO NOT** continue with tDCS session. Notify primary investigators. Record time, date, frequency.*	
4. Have you fainted?				
5. Has the skin on your head been red or irritated?			*Record location on head. If it is under the electrode sites, do not proceed with the session if the skin is broken. Notify physician. If skin is not broken, can proceed with session, but notify the nurse/physician after.*	

*When completing <u>Part A</u> before the first treatment session, replace **"Since your last brain stimulation session"** with "**Since your admission to the Holland Bloorview.**" For <u>Part B</u> of the remaining questions, ask the participant to rate their current symptoms using the FACES rating scale.*

				
Not at all **0**	**A little bit** **1**	**A bit more** **2**	**Even more** **3**	**A Whole Lot** **4**

	"Since your last brain stimulation session…"	NO	YES	If YES, then…	Details		FACES Rating	
6	**a) Have you felt more tired than usual?**			*Record time/date of extra fatigue onset and any activities they feel were related*		**6**	**b) How tired are you <u>right now</u>?**	
7	**a) Have you had headaches?**			*Record dates/times, frequency, duration*		**7**	**b) How much is your head aching <u>right now</u>?**	
8	**a) Have you had an upset stomach or thrown up?**			*Record which symptoms along with dates/times, frequency, duration*		**8**	**b) How upset is your stomach <u>right now</u>?**	
9	**a) Have you felt dizzy?**			*Record dates/times, frequency, duration, and activities leading up to symptoms.*		**9**	**b) How dizzy do you feel <u>right now</u>?**	

Appendix C

tDCS Session Tolerance

Instructions to the participant: "Tell me how the brain stimulation felt today. Did it/you feel ____ (on your head)? How ____ did it feel? Does it still feel _____ now?"

Instructions to staff: Place a checkmark in the rating the child provides. **If the symptom is still present at the end of the tDCS session, put an asterisk in the box beside the checkmark.**

	 Not at all 0	 A little bit 1	 A bit more 2	 Even more 3	 A Whole Lot 4
Itchy					
Tingly					
Hot					
Weird taste in mouth					
Tired					
Upset Stomach					
Headache					
Dizzy					
Other: _____					

How long did the feelings last? *Place a tick in the appropriate box.*

Symptom identified	Brief (few minutes)	About half of session	Most or all of session

Additional comments related to tolerance (continue on p. 2 as needed):

_____

_____

_____

If the child is still experiencing a symptom in a gray box at an intensity of 4 at the end of the session:

a) notify the child's nurse before leaving the unit,

b) notify the study principal investigators, and

*c) complete an **Adverse Events (AE) Form**.*

*For skin irritation beyond transient redness, syncope, or seizures that occur during a tDCS session, provide details the "additional comments section", and complete the **AE Form** with the study principal investigators.*

Appendix D

PARTICIPANT ID _____

PHYSIOTHERAPY TREATMENT LOG*

1. Record tasks completed in session in the order they occur
2. Include relevant details regarding variations, progressions, etc… (a new variation/progression can be listed in separate task box or indicated in 'details')
3. Indicate focus of the task (*1* for primary focus, *2* for secondary foci)
4. Use a checkmark to indicate if you provided task education or recommended practice outside PT
5. Use "other focus" box to capture 'motor learning' focus not indicated in other columns OR to describe a 'non-motor learning' focus (e.g. PROM)

DATE (*dd/mm/yy*)	**TASK**				**Stability/ Balance**	**Coordination**	**Strength**	**Motor Skills**	**Fitness/Endurance**	**Education**	**Practice Outside PT**	**Other Focus** (specify in box)
	Order	**NAME**	**DETAILS** *(include variation, equipment, or progression to differentiate btwn similar tasks)*	**DURATION** *(min)*								

*Adapted from Hilderley et al.'s (2016) Lokomat® and physiotherapy session logs

Appendix E

tDCS Eligibility Tracking Sheet

Check off all criteria that exclude child from being eligible for the tDCS study. The status of items in white boxes may be subject to change throughout admission. Consult with treating PT and/or physician to determine if/when re-evaluation is appropriate.

*** *When age excludes child, no further medical information will be screened beyond diagnosis and sex (unless they will be turning 5 years old during the admission, and then birthday (dd/mmm) will be noted in "date to re-evaluate" column).*

Child Number	**Diagnosis**	Date (*dd/mm/yy*)		**Sex**	**Age** (years)	Pre-existing seizures	Sz med uncontrolled	Bone flap out	Brain tumour	Scalp incisions/wounds	Head staples/stitches	Other Neuro Dx	Medical Stability	Behaviour	Communication	No active PT	Low Tolerance- PT	WB Restrictions	Act. Restrictions	Availability	>15 min non-ML	PT goals non-ABI	LOS <4 weeks	**Eligible?** (Y/N)	Date to re-evaluate *(enter child initials, so they can be identified on census)*
		Admission	Screening																						