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Brain-Computer Interface Fatigue in Children: Mechanisms and Impact

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Brain-Computer Interface Fatigue in Children: Mechanisms and Impact

by

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A THESIS

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Abstract

Communicating with others, exploring the environment, and playing games are essential components of child development. However, kids with severe physical disabilities such as quadriplegic cerebral palsy (QCP), are often unable to exercise such autonomy. Brain-computer interface (BCI) technology offer children with QCP unique opportunities for communication, environmental exploration, learning, and play. BCI research is rapidly developing but has neglected pediatric populations. Like many cognitively demanding tasks, fatigue is a critical factor to consider for BCI performance and enjoyment. BCI fatigue has been studied in adult populations, but there are no pediatric studies to date. Our prospective, cross over study assessed the effects of two BCI paradigms and a control condition on self-reported fatigue and electroencephalogram (EEG) biomarkers of fatigue. Thirty-two typically developing children aged 7-16 years participated in three sessions: motor imagery-BCI, P300-BCI, and film viewing (control). Self-reported fatigue and resting-state EEG alpha band power significantly increased across all sessions ($p < 0.001$; $p = 0.047$ respectively). These two measures of fatigue were uncorrelated to one another. No differences in fatigue development between sessions was observed. This project provides a baseline understanding of pediatric BCI fatigue. Short periods (30-mintues) of BCI use can increase self-reported fatigue and an EEG biomarker of fatigue. Performance was stable across BCI sessions and not associated with our measures of fatigue. The clinical implications and impact of fatigue on useability and enjoyment are unclear. Our results support the variability of fatigue and the overall BCI experience in children that warrant future investigation.

Preface

In fulfillment of a manuscript-based thesis, Chapter 2 has been submitted as “Keough JRG, Irvine B, Kelly D, Wrightson J, Comaduran Marquez D, Kinney-Lang E, Kirton A. Fatigue in Children Using Motor Imagery and P300 Brian-Computer Interfaces. *Journal of NeuroEngineering and Rehabilitation*. 2023”

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Dedication

This thesis is dedicated to the kids and families in the BCI4Kids program, whose unique experiences with BCI inspired this project. To the bright kids who've been among the first to learn how to control these challenging systems, and to the families who've supported and believed in their children, grandchildren, or siblings every step of the way.

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exogenous visual BCI paradigm not discussed in this thesis [5]. Image available for reuse in thesis Copyright © 2019 IEEE.

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List of Symbols Abbreviations and Nomenclature

AIC	Akaike information criterion
ALS	Amyotrophic Lateral Sclerosis
BCI	Brain-computer interface
BG	Basal ganglia
BOLD	Blood Oxygenation Level Dependent
CNS	Central nervous system
CP	Cerebral palsy
CST	Corticospinal tract
ECoG	Electrocorticography
EEG	Electroencephalography
ERD	Event related desynchronization
ERP	Event related potential
ERS	Event related synchronization
fMRI	Functional magnetic resonance imaging
fNIRS	Functional near infrared spectroscopy
GMFCS	Gross motor function classification system
HICCUP	Healthy infants & children clinical research program
HIE	Hypoxic ischemic encephalopathy
Hz	Hertz
iPSD	Integrated power spectral density
LIS	Locked-in-syndrome

MEG	Magnetoencephalography
MI	Motor imagery
MRI	Magnetic resonance imaging
P300	Positive P300 response
QCP	Quadriplegic cerebral palsy
RS	Resting state
SMR	Sensory motor rhythm
SSVEP	Steady-state visually evoked potential
VAS	Visual analog scale
VASF	Visual analog scale for fatigue
V	Volts
α	Alpha
β	Beta
δ	Delta
γ	Gamma
θ	Theta
μ	Micro
Ω	Ohm

Epigraph

“Can you read my mind? You can’t figure out who I have a crush on can you?”

- 7 year-old BCI fatigue study participant

1 Chapter 1 – Background

Cerebral palsy (CP) is a complex syndrome characterized by non-progressive, permanent movement dysfunctions present from early in life [6]. CP is the most common diagnosis among children with physical disabilities [7]. In the most severe cases individuals with CP may have very minimal to almost no volitional motor control [8]. Due to advancements in medicine, the probability of survival for children with even the most severe disorders has increased [9]. While some children may have visible and severe physical disability, many are highly capable and thus trapped with limited options to interact with the environment. To meet the outlined United Nations Rights of a Child, and Rights of Persons with Disabilities [10, 11], it is our responsibility to create these critically important means of alternative access for individuals with severe CP to interact directly with their family, peers, and the environment in meaningful and fun ways. Brain-computer interfaces (BCI) offer opportunities to realize these important goals through a direct translation of intentional brain activity to control effector devices, but they remain understudied in children. Fatigue is an important modulator of adequate BCI control as well as an impact factor for enjoyment [12–14]. A better understanding of BCI fatigue in children will aid in the optimization of BCIs as an access technology to enhance life participation for children with severe disabilities.

1.1 Nervous System Development & Plasticity

The brain is a sophisticated organ that orchestrates complex voluntary and non-voluntary behaviours. The brain enables self-expression and sensation of the environment. To accomplish these functions many cells, networks, and larger functional brain regions work together. It is the proper development and maturation of these cells, networks and the brain and nervous system as a whole that gives us our human capacities. The nervous system can be divided in two main

subsystems: central and peripheral. The central nervous system (CNS), comprising the brain and spinal cord, originates from the neural tube. Spatial patterning of the neural tube, neuron proliferation, and neuron migration are critical for initial brain and spinal cord development in utero.

The perinatal period, from 22 weeks gestation to one month post birth, is a critical and complex window for brain development [15] where neuron circuits and synapses are established and refined [16]. During this time there is rapid neurogenesis, gliogenesis, synaptogenesis, arborization, and apoptosis to refine circuits [15, 17]. The proliferation and integration of glial cells is critical for proper CNS functioning. Genetic mechanisms are largely responsible for ensuring that proper neuronal connections are established and maintained. CNS development and maturation is later driven by activity dependent mechanisms [18, 19]. There is a unique vulnerability for developing brain networks. Incredible accuracy of connections is critical for proper functioning and injuries that disrupt this development can lead to life-long disfunction that cannot be overcome. The CNS must develop specific functional networks and integrate with the peripheral nervous system and other organs. The importance of central and peripheral integration is exemplified by the motor system.

The motor system comprises components within the central and peripheral nervous systems as well as skeletal musculature that work together to plan, coordinate, and execute voluntary movement [20]. The motor system is complex with many working parts. Critical areas involved in producing a desired motor output include the posterior parietal cortex, the primary somatosensory cortex, the supplemental motor area, the premotor cortices, the basal ganglia (BG), and the primary

motor cortex. The primary motor cortex is the major output for the corticospinal tract (CST) which carries information about intended movement down the spinal cord to lower motor neurons which synapse directly with the target muscle at the neuromuscular junction. The vestibulospinal tract, reticulospinal tract, and rubrospinal tract all descend from the brain stem and contribute to movement [20]. Sensory information is critical in the production of accurate movements [21]. The posterior parietal cortex plays a role as an integrator of sensory and motor systems, using spatial information to plan goal-directed movement appropriately [22]. The supplemental motor area is activated during mental rehearsal or motor imagery (MI) [23]. The dorsal and ventral premotor cortices have unique roles within movement planning and execution. The dorsal premotor cortex is important in motor planning [23] while the ventral premotor cortex is activated during grasping or grasping observation [24].

Cortical areas, the BG, and the cerebellum are critical for skilled movements [25]. The cerebellum is also critical in coordination and balance. Before the final signal for voluntary movement is carried from the primary motor cortex down to deeper brain regions and into the spinal cord via the CST, brain areas like the BG influence this signal [25]. Within the BG, the striatum, made up of the caudate and the putamen, receives cortical input. BG outputs project to the thalamus, superior colliculus, and pedunculopontine nucleus [26]. Upper motor neurons originating in the primary motor cortex synapse with lower motor neurons in the spinal cord, and lower motor neurons synapse directly with the muscle. Injury to critical brain regions, the spinal cord, peripheral nerves, or the muscle itself may lead to motor dysfunction at all stages of life.

The brain is highly plastic, particularly during infancy and childhood. Neuroplasticity allows us to adapt and learn new things [16]. At the cellular level, this means the brain can form new connections, reorganize networks, and modify synapses [27]. During brain development and into infancy and childhood there is an overproduction of neurons and synapses [28]. Many of these synapses are pruned in development based on activity in the brain. Activity dependent changes to synaptic machinery, synaptic strength and synaptic numbers continues into adulthood [29]. However, because adult brains do not have the same level of neurogenesis and synaptogenesis, this plasticity is much more limited.

There is also a unique vulnerability of the developing brain. For example, children are much more vulnerable to sensory deprivation as these systems are still undergoing activity dependent maturation. It has also been reported that newborn rats experienced more cell death in response to trauma or an hypoxic-ischemic brain injury than adult rats due primarily to prolonged apoptosis [30]. An increased plasticity and openness of the brain to establish new connections may also result in maladaptive recovery after injury [31, 32].

Despite this vulnerability, plasticity can be a powerful tool in learning and illness or injury recovery [28]. Select treatments for broad neurological illnesses, including CP, even utilize brain stimulation in an attempt to modify cortical excitability [28, 33]. Unfortunately, there are limits to the positive impact of plasticity and neuromodulation after injury, some children have damage and functional loses that will never recover with therapy [33]. Like for children with severe CP, rather than therapy, we must bypass the motor system to give the brain direct access to the world.

1.2 Early Brain Injury and Cerebral Palsy

Neurodevelopment is highly organized with redundancy mechanisms in place, but it does not always progress typically and early injury may interfere with proper development. There is a wide range of disability or dysfunctions that can result depending on the time of the injury, injury severity, insult location, and individual recovery progression [15]. The third trimester, starting week 27, is a critical period for CST formation and motor system maturity and thus this network is particularly vulnerable to perinatal injury [34]. Injury often causes disruption of activity which can lead to dysfunction in activity dependent maturation mechanisms and more severe dysfunction overall. Brain injury impacting motor areas can lead to permanent motor impairment and CP [35, 36]. Hemiparetic CP commonly results from unilateral damage caused by a stroke in the perinatal period where only one CST is effected [37], while a more diffuse injury like hypoxic-ischemic encephalopathy (HIE) or premature white matter injury can negatively affect the brain bilaterally and result in more severe conditions such as quadriplegic CP (QCP) [36, 38].

1.2.1 Cerebral Palsy Classification & Symptomology

CP is the result of one or multiple early brain insults or developmental malformations leading to largely irreversible damage or changes to brain development [39]. This makes CP a non-progressive life-long disorder. The worldwide prevalence of CP is 2-3 cases per 1000 live births [6, 39] with some data indicating a prevalence above 3 out of every 1000 live births for regions such as the United States [6]. In its most severe form, QCP, early injury can lead to a lack of control of all limbs, the head, the neck, the trunk and may even result in the individual being unable to speak [7, 8]. Mobility and communication challenges are common for children who have CP [7]. While CP is primarily considered a movement disorder, it may also be considered a

neurodevelopmental disorder. CP is variably defined due to its complex etiology and individual variability [40]. It “is never the same disorder twice” [41]. Shevell has even argued for classification of CP as a spectrum disorder to better account to the variability of presentations [41]. Because each case is truly unique, and even in typically developing children there is a highly variable developmental timeline, CP is often not reliably diagnosed until after two years of age [8, 39, 42]. Investigation and diagnosis take place when children are missing developmental milestones without other explanations [8]. Children born extremely premature or having suffered an insult such as HIE are also monitored and undergo early surveillance.

There are numerous ways to classify different presentations of CP. Topographical classifications defines the affected limbs (see Figure 1.1), the most severe being quadriplegia where all limbs and the trunk are affected [6]. In addition to topographic classifications, CP is also described by the specific motor deficit [39]. For example, spastic CP is characterized by weakness, hypertonia, hyperreflexia, and uncontrollable involuntary muscle contractions [39]. The gross motor function classification system (GMFCS) is a standard measure used to classify CP severity based on an individual’s motor capabilities. Those with QCP are often higher levels on the GMFCS (e.g., level V) having limited ability to control posture, head, arm, and leg movements (see Figure 1.2, 1.3) [6]. Children with CP also often present with numerous other disturbances of cerebral functioning [40, 43]. These may include vision, speech and communication, hearing, oromotor, general sensory, and cognitive changes as well as epilepsy [40]. It is critical to assess for these other changes to best support children with CP.

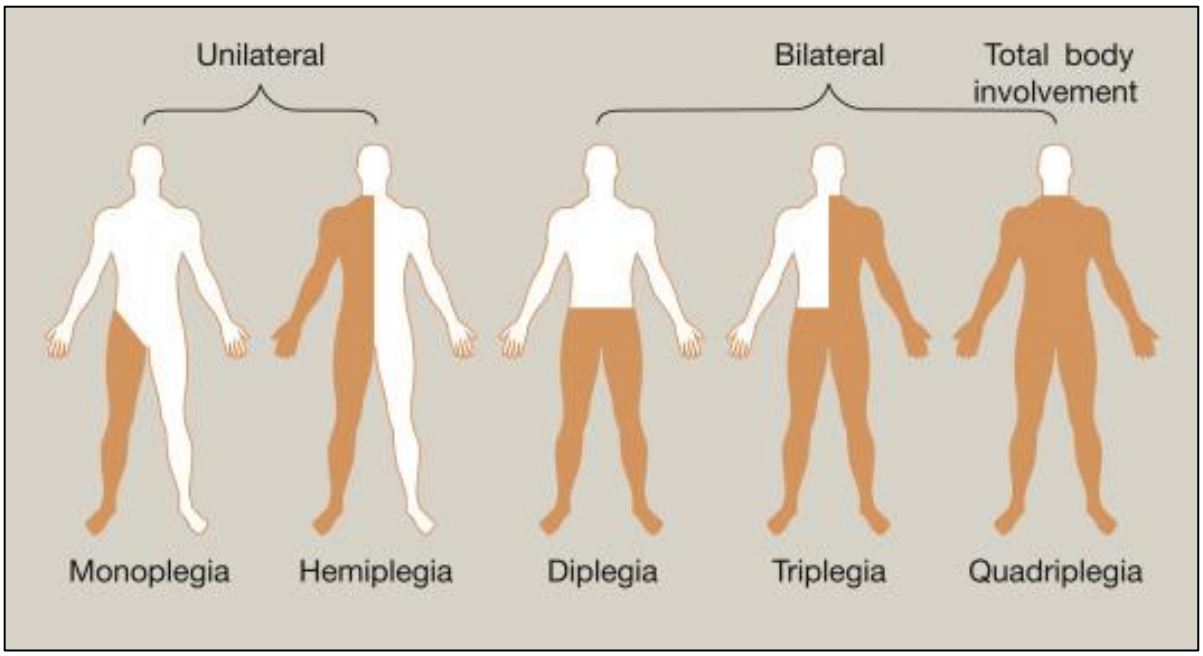

Figure 1.1. Topographic classification of cerebral palsy. *Shaded orange area represents the body parts impacted by the brain injury and subsequent motor impairment in each classification. Classifications are unique and determined by the injury location and severity. Figure from Peterson, 2016 [1], used with permission from Elsevier.*

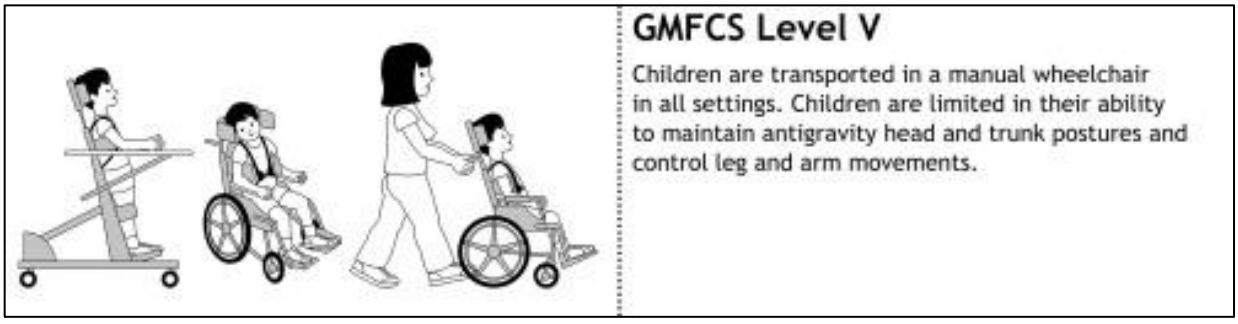

Figure 1.2 Gross Motor Function Classification System Level V Visual and Description. *Individuals at this level may benefit from assistive BCI. Figure from Peterson, 2016 [1], used with permission from Elsevier*

Figure 1.3. Children with Severe Quadriplegic CP. *On the left is John. John experienced a malformation of brain development due to genetic factors. On the right is Peyton. Peyton suffered from bilateral strokes during development. John and Peyton are bright young individuals with personalities that shine. Because of the way their brains developed, both John and Peyton have a GMFCS level V classification and have a diagnosis of QCP. This means they both require supports included stability aids for sitting and full-time wheelchair transport as seen in these images.*

Intellectual disability occurs in approximately 50% of children with CP and those with spastic quadriplegia are most affected [43]. However, the cognitive capabilities of children with severe motor impairments are often difficult to accurately assess due to communication barriers and biased assumptions of their cognitive capabilities based on their physical limitations [44]. Since assumptions are often made, it is hard to determine if the above statistic is an accurate description of the population. Cognitive impairments of children with QCP may also be overestimated due to

difficulty of performing standard tests [44]. This leaves a substantial percentage of children with severe CP at risk of unrecognized cognitive ability and individual capacity [44]. Cognitive impairments in children with CP may be compounded by the fact that cognitive abilities are heavily influenced by a child's environment and the opportunities they have to explore and actively participate in their lives [44].

Children meeting the following criteria, quadriplegia, no hand function, non-verbal, and preserved cortex and cognitive capacity, can be considered to have a form of 'trapped' or locked-in syndrome (LIS) [45]. This syndrome is typically described in adults who have suffered a brain stem stroke or have an advanced neurodegenerative disease like Amyotrophic Lateral Sclerosis (ALS) [45]. Nonetheless the same criteria can be met by some children with QCP, and similar interventions and access technology may be useful for them. A concept used to describe cases of LIS, and helpful in understanding the experiences of individuals with LIS is cognitive-motor dissociation. This concept emphasises how individuals with extreme motor dysfunction can have preserved higher cognitive functions. Sometimes this preserved cognitive function might only be assessed accurately by functional imaging techniques, not behaviourally [46].

1.2.2 Severe Quadriplegic Cerebral Palsy Etiology & Locked-In Syndrome

There are numerous potential causes of QCP. One of the most common is HIE [36, 47]. HIE occurs when there is a compromise of cerebral blood flow and delivery of oxygen to the brain. Acutely, HIE and the depletion of energy causes excitotoxicity leading to selective cell death. In severe injuries there are secondary and tertiary phases where cell death is more extensive. Within the tertiary phase along with cell death, the brain also tries to remodel [47]. Severe motor deficits, like

seen in QCP, can occur when this lack of blood flow damages essential components of the motor system, such as the posterior limb of the internal capsule and/or the BG [47]. This type of insult can severely damage the motor system while much of the cortex remains intact, thus sparing cognitive functioning. Some brain structures, including the BG, show selective vulnerability to hypoxic-ischemic insult [48, 49]. Figure 1.3 showed John and Peyton. Claire is another little girl with QCP (Figure 1.4A). When Claire was born she experienced acute HIE. Her MRI is shown in Figure 1.4B. The nature of Claire's HIE led to symmetrical damage of her posterior putamen and lateral thalamus, centres critical for movement generation. As is evident in her MRI, her cortex was left undamaged by her HIE injury, and she, like many others is highly cognitively capable. This makes her an ideal candidate for BCI use.

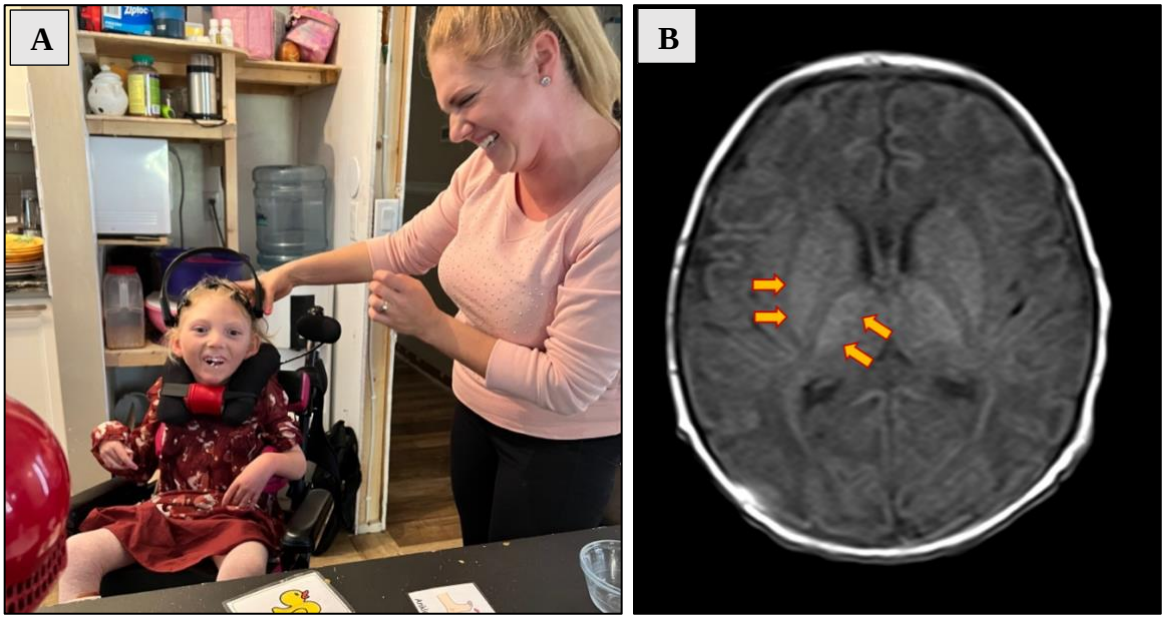

Figure 1.4. Hypoxic-ischemic encephalopathy case example. *A. On the left is Claire, a 7-year-old girl, smiling with a mouthful of whipped cream that she just whipped up with her BCI. B. Claire's axial T1 MRI at four days of age demonstrates symmetrical hyperintensity of the posterior*

putamen and lateral thalamus (arrows) consistent with acute total hypoxic-ischemic brain injury. Note that the rest of the brain including the cerebral cortex is uninjured.

Perinatal stoke can also lead to QCP [50], particularly if both hemispheres are impacted or a child suffers multiple strokes. Intraventricular hemorrhage and periventricular leukomalacia are common causes of QCP in children born prematurely [51]. The single most common risk factor for developing CP is extreme prematurity [15]. Within the preterm brain, cells of oligodendrocyte lineage as well as neurons in the subplace are selectively vulnerable to injury [48, 52]. Severe white mater injury can result in widespread degeneration of all cell types. Less severe white mater injury may also result in significant damage due to neuronal cell death that results from axonal injury and breakdown [52]. Intrauterine growth restriction is an additional important risk factor [51]. Other general causes include genetic disorders affecting brain development, and congenital infections [53, 54]. Many of these etiology's are related to similar pathogenesis mechanisms of ischemia and inflammation or infection. These mechanisms cause injury and cell damage via excitotoxicity and oxidative stress [52]. The location and extent of damage will impact the deficits observed but due to selective vulnerability some individuals will have cognitive-motor dissociation and largely intact cerebral cortices. Intact cortices are critical not only for preservation of cognition but also for access to brain waves via non-invasive electroencephalography (EEG) recording. Acquiring brain wave information is critical for BCI use.

1.2.3 Quadriplegic Cerebral Palsy Intervention & Care: Assistive Technology

There is no cure for CP and due to the complex nature of the condition, management is typically very challenging and multidisciplinary [43]. Magnetic Resonance Imaging (MRI) is often helpful

in defining the underlying cause of CP and may inform relative potential for therapy and assistive devices. EEG, vision, and hearing evaluations are often done to further inform the needs and best management strategies for individual children [43]. Common management approaches include physiotherapy and occupational therapy, medications to help with negative effects of spasticity, surgical therapies, and gastrostomy feeding [43]. Despite disability, 90% of those diagnosed with CP reach adulthood, though this rate is lower for those with the most severe disability [51]. Current management tools help to increase survival and can improve the lives of children with QCP, but there are currently very limited interventions to help significantly restore motor function in children with severe QCP. Motor functioning can significantly impact quality of life, participation, and developmental trajectories [55]. Child development typically involves communicating with others, exploring the environment, and playing games independently – all activities that typically require motor control. For children with severe neuromotor disabilities such as QCP, exercising such autonomy is often impossible and their participation in recreational, social, and self-improvement activities is lower than those with less significant impairment [55]. There are significant limitations in the ways children with LIS can interact with their environments, gain a sense of independence, and achieve their fundamental human rights [11, 56].

It is therefore critical that we create new ways for children with permanent and severe disability to better interact with the world throughout life. Eye-gaze systems and communication boards or books are currently used by children with QCP and their families, caregivers, and peers to increase autonomy. Eye-gaze systems allow individuals to communicate and make selections of letters, words, phrases, or pictures with their controlled eye movement. Communication boards allow individuals to make the same selections only via pointing with their finger or a pointer tool. These

technologies provide unique opportunity for expression and communication as well as play and learning. If they are the right fit for the child, they can greatly improve quality of life [57, 58]. Communication books can help with quicker communication and be quite extensive with their content as well as become personalized to the user over time. A large limitation of this access method is users must be able to reliably point to their selection on their own or with support. Eye gaze technology is a great alterative if an individual is unable to reliably use a communication book and has similar pros to the communication book. Limitations of eye gaze, similar to the communication book, include that the user needs reliable voluntary control of eye movements which is not always the case. Reliable yes/no signals are extremely helpful for communication but are extremely limited. How an individual communicates with their chosen access method or yes/no signals is something that family members, close peers, and aids are very familiarly with but may not be readily apparent to an outsider. For communication specifically, augmentative, and alternative communications devices don't meet the complex needs of some end-users [59]. BCIs are an additional access technology and may offer a means to overcome challenges associated with current assistive devices, further paving the way for children who are unable to move or speak to attain their fundamental human rights [2, 10, 56].

1.3 Brain-Computer Interfaces

Typically, the brain exerts control and enables us to interact with the outside world largely through direct control of muscles to produce movement. Voluntary movement is challenging or impossible when the ability to control muscles reliably and precisely is lost, as in the case of severe QCP. BCIs offer a unique potential solution for individuals unable to execute movement to be able to interact with the world in new ways. BCIs can bypass the motor system and musculature by sensing

the user's brain activity and directly transforming this activity to control specific effector outputs such as a wheelchair, computer, or videogame [60]. BCIs could also integrate as an important method of self-expression [44]. BCI systems work by acquiring brain signals, processing these signals, and extracting relevant features for classification. The classification is linked to a command and communicated to the device or application as the desired output [61]. The relevant features of brain activity depend on the method used for recording brain activity and the BCI paradigm used for control. The general process of translating brain signals to control a BCI is illustrated in Figure 1.5. Importantly, these are closed-loop systems and feedback is critical. BCI technology is particularly intriguing for individuals with LIS.

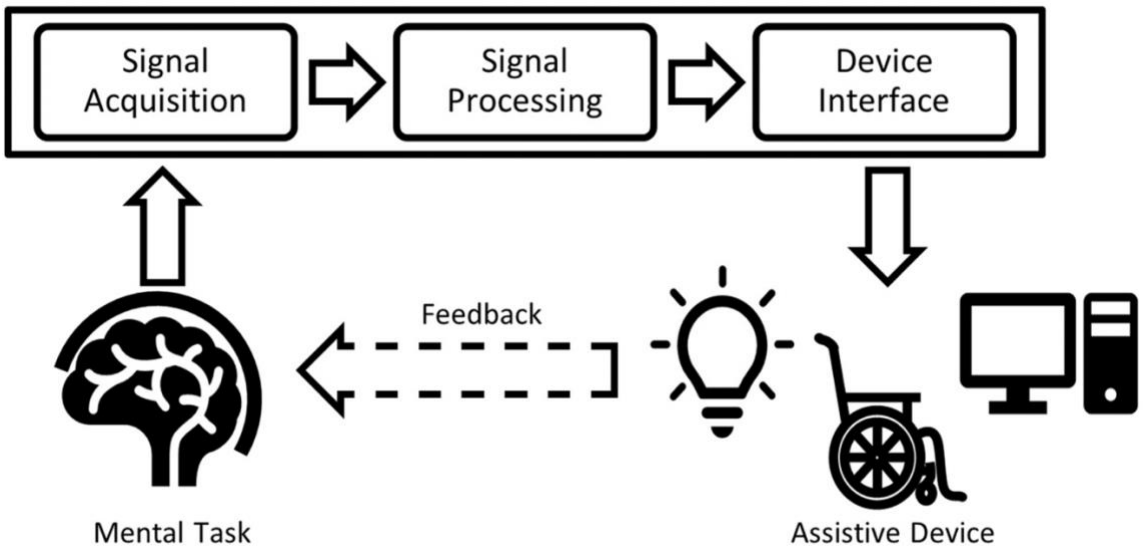

Figure 1.5. Brain-computer interface pipeline from brain signal acquisition to BCI control. *Various methods can be used to measure brain activity each with their own processing requirements. Many assistive devices can be used within a BCI system examples included here are environmental control, power wheelchair use, and computer use. Figure from Orlandi, 2021* [2], *under a creative commons attribution licence from frontiers*.

Neuroscience is continually uncovering fundamental information about brain functioning that has opened the door for BCIs. It is knowledge of functional brain topography and advancements in techniques to measure brain activity that has enabled scientists to begin designing functional BCI systems [62]. In developed brains, we have a strong and ever evolving understanding of the motor system, the somatosensory system, the visual and auditory networks, and even the brain regions and networks involved in complex cognition. This knowledge can be useful for working with individuals who've experienced early injury or developmental malformation, but it becomes much more complex with unpredictable brain circuits and functionality of remaining tissue. Still, our understanding of injured brains is also improving. Electrical and cerebrovascular recordings can measure brain activity through invasive and non-invasive methodologies [62, 63]. Electrical methods of detecting brain activity are shown in Figure 1.6. While invasive BCIs can acquire more detailed information about brain activity for very specific and targeted control of effector devices, non-invasive systems are often more desirable to avoid high complexity and dangerous surgical procedures.

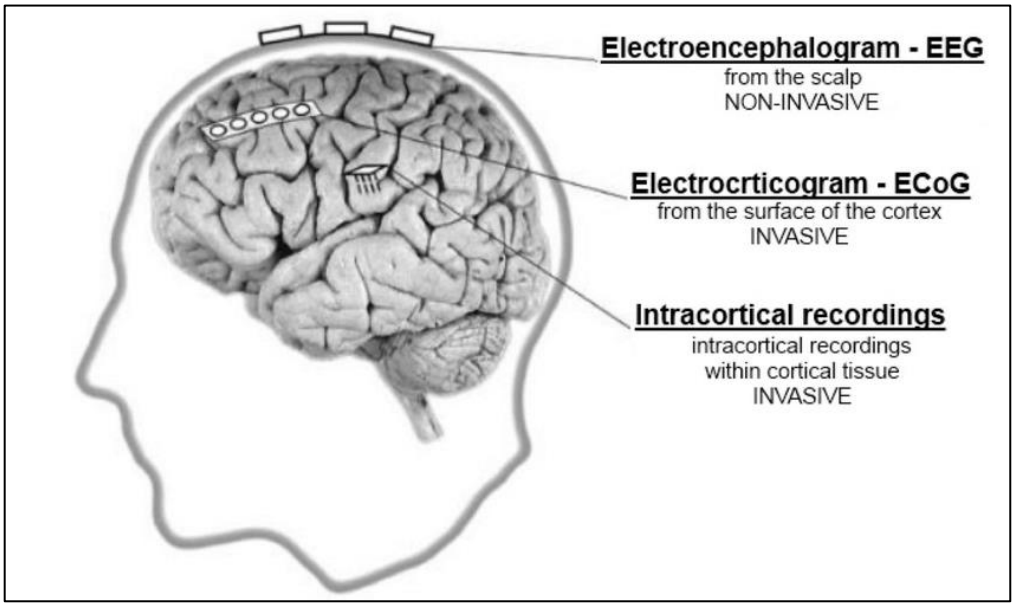

Figure 1.6. Methods of electrical brain recordings. *EEG is non-invasive and ECoG and Intercortical recordings are invasive. Intercortical recordings measure single unit activity. Figure from Kawala-Sterniuk, 2021 [3] available via licence: Creative Commons Attribution 4.0 International.*

1.3.1 Invasive & Non-Invasive Brain-Computer Interface Systems

Invasive BCIs require implanted electrodes that are either inserted into the grey matter (microelectrodes for single unit recording), or that sit directly on the surface of the brain (electrocorticography; See Figure 1.6). These implants provide increased spatial resolution and high temporal resolution. Non-invasive BCIs utilizing EEG still provide high temporal resolution however, they have poorer spatial resolution compared to the invasive methods due to the distance and tissues between the active neurons and the recording electrodes. EEG BCIs are discussed in further detail in section 1.3.2. In addition to electrical recordings, the brain signals requires for BCI use can be obtained through non-invasive functional magnetic resonance imaging (fMRI; [64], functional near-infrared spectroscopy (fNIRS;), and magnetoencephalography (MEG;). Multiple of these recording modalities can also be combined in hybrid BCI systems [65].

1.3.2 Electroencephalography Brain-Computer Interfaces

EEG is a measurement of electric fields, generated by brain activity, that are recorded non-invasively from the surface of the scalp [66]. This makes EEG a direct measure of neural activity in almost real time. The anatomical arrangement of pyramidal neurons in the cortex, perpendicular to the brain surface, allows for spatial and temporal summation of neuronal currents which travel towards the EEG electrodes and are large enough to be detected by the electrodes placed on the

scalp [67]. Electrons within the electrodes are pushed or pulled by the brain generated electric field. A corresponding current then moves through the EEG wire and a voltage can be detected by a computer. The process of the signal moving from the neurons towards the electrodes is visualized in Figure 1.7B. Volume conduction occurs only within the brain extracellular fluid. Capacitive conduction is the mechanism by which this signal travels through the meninges and the cranium where volume conduction is not possible [67]. It is currently believed that the EEG signal is mainly a product of thalamocortical and corticocortical neuronal communication [67]. EEG detects only highly synchronous neuronal activity from select populations of neurons thus EEG is not necessarily measuring the amount of total neural activity.

There are five frequency bands that are often used to analyze EEG data and draw inferences about an individual's mental state and brain function. Listed in order of ascending frequency, these are the delta (δ), theta (θ), alpha (α), beta (β), and gamma (γ) frequency bands [68]. Because this measurement system is recording from the scalp EEG it is not capable of measuring individual neuron firing or cell action potentials. Instead, it is a measure of post-synaptic potentials, both inhibitory and excitatory [67]. The excellent temporal resolution of EEG makes it possible to utilize this type of measure for BCIs. Unfortunately, due to its low spatial resolution, recording from a precise brain region or determining the origin of an EEG signal is not possible [67]. These qualities place both advantages and limitations on the application of EEG-based BCIs.

EEG oscillations are a result of both event related activity and non-event related ongoing activity [69]. Event-related potentials (ERPs) are post-synaptic potentials that occur very close in time in similarly oriented pyramidal cortical neurons. Summation allows these synchronous post-synaptic

potentials to reach electrodes on the scalp. As the name suggests, ERPs are a result of a specific event or stimuli either motor, sensory, or cognitive in nature. Importantly for EEG use in BCI applications, ERPs are time-locked to the event or stimuli and are transient [69].

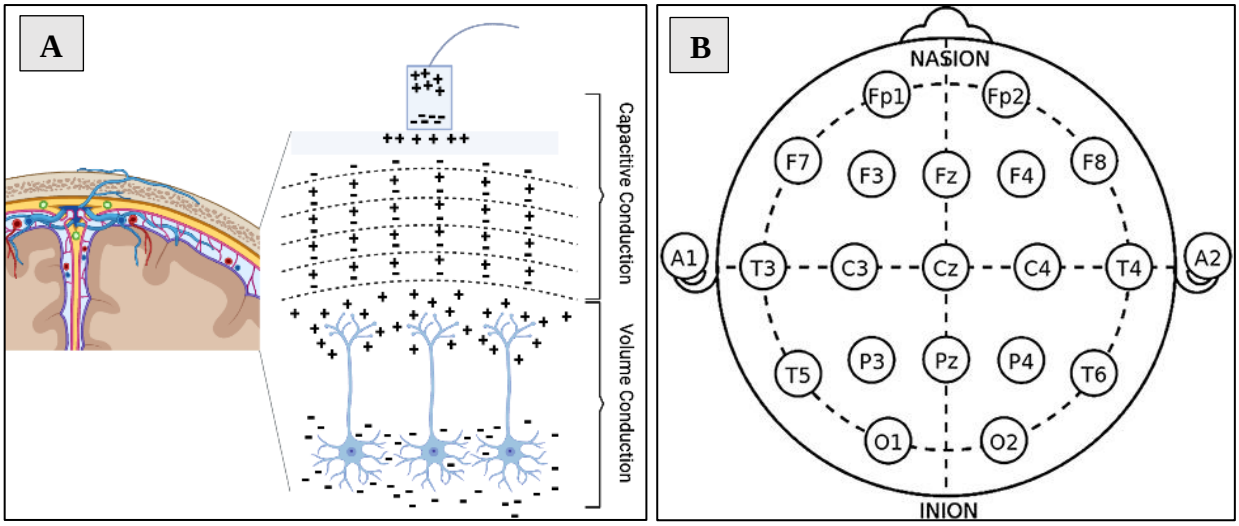

Figure 1.7. Electroencephalography signal input and recording locations. *A. Electric signal generation and travel from cortical neurons within the brain to EEG scalp electrodes. Image created with BioRender.com B. 10-20 EEG electrode set up [4]. Image is under a creative commons attribution licence from frontiers.*

A common set-up for EEG measurement is the 10-20 electrode placement system. Important landmarks in this set up include the nasion, inion, and left and right pre-auricular points (see Figure 1.7B). Cz lies at the overlapping midpoint between pre-auricular points horizontally and the nasion and inion vertically. From this point other electrodes are placed at 20% or 10% increments forwards and backwards and to the left and right of the head (ex. Fz is 20% forward from Cz along the midline and C3 is 20% to the left of Cz alone the line connecting pre-auricular points). Electrode placement is shown in Figure 1.7B. Gel is typically used between scalp and electrode to

provide another medium for conduction to easily occur while also increasing contact area for electron exchange thus improving the signal to noise ratio [67]. Recently there has also been advancements in producing dry electrode EEG hardware.

There are numerous different brain signals that can be extracted from the EEG and be useful in the operation of a BCI. Two common signals are the visual positive 300 response (P300) or visual evoked potential and MI. P300 BCIs rely on identification of the user's selection based off the evoked activity in the visual cortex that is time-locked to an external visual stimuli [70]. MI BCIs rely on event-related synchronization (ERS) and event related desynchronization (ERD) over the motor cortex and premotor areas to distinguish the users imagined movement of different body parts [71]. Other common BCI paradigms include steady-state visually evoked potentials (SSVEP), auditory evoked potentials, vibro-tactile evoked potential, and motion onset-visually evoked potential [72–74]. Hybrid paradigms may also be used [65, 75]. P300 and MI are discussed in further detail below.

P300 is an ERP, or a detectable change in brain activity, associated with and time-locked to a sensory event [70, 76]. This response is based off the odd ball paradigm [77]. Non-target stimuli are continuously presented and only occasionally the target stimulus is presented, thus providing an 'unexpected' stimulus which elicits the positive deflection in the EEG signal around 300ms after stimulus presentation [76]. Visual P300 responses will be utilized in this research. This involves flashes to elicit the detectable P300 response. While initially slow to integrate into BCI applications, P300-based BCIs are currently one of the most common paradigms with many different applications including P300-based speller systems [70].

Unlike P300, *MI* is an endogenous paradigm. The user intentionally generates the desired brain activity without the need to present external stimuli (ex. flashing for P300). MI can be separated into visual and kinesthetic MI. In visual MI the individual visualizes oneself performing a movement whereas in kinesthetic MI the person tries to remember and imagine the feeling of performing a movement [78]. The neurophysiological pattern picked up within the EEG signal is rhythmic activity from the somatosensory cortex produced by MI [71]. This signal is referred to as sensory motor rhythms (SMR) involving changes in α, β, and γ frequency bands [71, 79]. Over the motor area typical α frequency range is referred to as the mu rhythm. During MI ERD in mu and β and ERS in γ occurs over the sensorimotor area contralateral to MI while mu and β ERS occurs over the ipsilateral sensorimotor area [71, 80]. The fMRI blood-oxygen-level-dependent (BOLD) signal from contralateral motor areas positively correlates with mu and β ERD indicating an increase in neuron activity in the region. A BCI system that continually monitors brain activity can compare such ERS/ERD between a rest or baselines state and the motor imagery state (i.e. imaging opening and closing your left or right hand) to classify and drive the system.

1.3.3 Brain-Computer Interfaces as Rehabilitation Technology

BCI technology for hemiparetic deficit rehabilitation often utilizes MI. These devices are sometimes referred to as neurofeedback BCIs because they are used to help individuals regulate their brain rhythms with the ultimate goal of restoring impaired motor control [81]. The feedback in these systems can be delivered in many ways: visuals on a computer screen such as a moving mouse or movement of an avatar body part, body part movement visuals within a virtual reality display, or somatosensory feedback with robotic systems or even neuromuscular stimulation [81]. Since the aim of these systems is to help restore function, ERPs like the P300 response are not as

useful as SMR. While more randomized control trials with larger sample sizes are still needed, these systems show promise in improving limb function by clinically significant margins and are often superior to the currently available therapeutic alternatives [60, 81, 82]. Nierhaus and colleagues even present evidence of immediate brain plasticity following one hour of performing BCI tasks supporting therapeutic use [83]. When motor recovery is not feasible however, like in QCP, BCIs can be used as an assistive technology to help individuals perform a wide range of functions not otherwise possible due to deficits.

1.3.4 Brain-Computer Interfaces as Assistive Technology

BCI technology for replacing a lost function and enhancing independence has different priorities than rehabilitative BCIs. Some examples of assistive BCIs include enhancing communication, environmental control, and providing new opportunities for game play [84]. BCIs also have potential to be used for assessment of cognition in those unable to move or speak [44]. Further, BCIs may be used to support the development of cognition for those unable to interact with the world like we typically expect [44]. The application of BCIs to replace a lost function and enhance interactions with the world, rather than for motor rehabilitation purposes, will be the focus of this research.

A large percent of studies published on assistive BCIs use healthy participants with no motor impairments [75]. Working with healthy individuals is simpler and is often a first step to establish important principles, limitations, and new development opportunities. It is beneficial when looking at a new technology or a technology for an understudied group where fundamentals of use are unclear. A smaller number of investigations have also involved individuals with near LIS or

complete LIS. Borgheai and Colleagues had success using an fNIRS BCI with ALS patients including a patient with late-stage ALS [85]. Peters and Colleagues also used a BCI spelling application for communication with two late-stage ALS patients. While promising, performance with the system was extremely variable with mean accuracies of only 57% and 65% for the two study participants [86].

There have been efforts over the years to get BCI technology out of the lab and into home and clinical settings. Vaughan and Colleagues designed a BCI system with similar or increased accuracy and bandwidth to in lab systems, while ensuring the complexity of operation was appropriate for its users [87]. While still extremely limited, some individuals have been using BCIs consistently in their lives [88]. The home system explained and designed by Vaughan and Colleagues was also put to the test in the home of 27 individual with ALS. P300 spelling accuracy averaged across all participants and all use was 73%. Use of the system also had arguable improvements in quality of life [89]. For the purpose of the study individuals had the BCI at home for between 2 and 17 months. Following the study 88% of individuals chose to keep the system for continued at home use [89]. Implantable BCIs are even more rare. Limited scientific literature is available on the numbers, but recent news suggest that worldwide less than 40 people have BCI implants [90]. At home and in the community is where these technologies can make significant impacts, and development of easy to use at home systems should be a priority.

BCI research is progressing and often rightly prioritizes functionality for end users. These systems are already making an impact in adults. Despite still having a lot of room for improvement, BCI technology is overwhelmingly believed to have potential for improving quality of life [91]. 92%

of clinicians across Canada also think BCIs might have a utility in clinical practise [91], and importantly many adult end users believe in the potential of BCIs and support further research efforts [88]. BCI capacity and applications are advancing rapidly and there is widespread support for this technology, but pediatric populations have been almost entirely neglected from research [2, 13, 92].

1.3.5 BCI For Kids

In the last 50 years, there has been well over 5,000 BCI studies published [93]. Despite these numbers, Orlandi and colleages published a meta-analysis in 2021 reporting only 12 pediatric focused BCI studies with relevant outcome measures [2]. There are likely many reasons for this including the challenges of research on children and the added complexity of the injured developing brain where conditions exist from birth. In these individuals, there may be an absence of predictable cortical geography and networks that are present even in paralyzed adults [94, 95]. However, the fact that children with QCP now live for decades, rather than years, and have marked plasticity and capacity for learning [28], emphasizes the potential advantages of developing BCI applications early in life. Understanding the unique factors that dictate pediatric BCI performance are essential if the potentially life-changing effects of BCI are to be realized by children with disabilities. To accomplish this, rapidly developing BCI paradigms for the "hardwired" adult brain must be reconsidered for the unique, plastic, and developing brains of children.

The BCI paradigms used are an important consideration in children with QCP. For example, endogenous paradigms such as MI may be better for users with vison or auditory impairments and/or seizure disorders to avoid reliance on those sensory modalities and/or flashing BCI

applications. Even though MI might seem difficult for children who have never been able to perform voluntary movement, there are methods of accessing this approach with these children. For example, someone can move one of their limbs while they watch, and this can be a sensation they reimagine during BCI use.

Of the 12 studies identified by Orlandi and colleagues' meta-analysis, 8 were non-invasive BCI systems [2]. Vařeka used a data set of 250 healthy school aged children and achieved a P300 classification accuracy or 76-79%, comparable to adult literature [96]. Jochumsen and colleagues demonstrated that children with diplegic CP could produce ERS/ERD, the signals used in MI BCIs, with motor intent/execution [97]. Taherian and colleages, attempted to use BCI technology with individuals with spastic QCP. Within their eight participants, five were pediatric. Two of the five children had epilepsy, and active seizures sometimes made it difficult for them to complete full training sessions. Post seizure, the children were also quite fatigued which impacted concentration. Due to headset fit and comfortability as well as children not enjoying the BCI game application participation was discontinued for 2 other participants. Among other deficits in the BCI literature and in BCI design, the barriers Taherian and colleagues faced with these children highlight the importance of fatigue concerns for children with QCP and often other comorbidities [98]. Identifying and understanding unique pediatric issues will be essential for successful clinical translation.

Within the BCI4Kids lab, we have shown that both typically developing children [99] and those with cerebral palsy [100] can learn to control EEG-based BCI systems. There are currently numerous ongoing projects within our lab using BCI systems with typically developing children

and children with QCP. The national Canadian network is expanding rapidly [92]. Pediatric clinical BCI programs have been established at the Alberta Children's Hospital [101], Holland Bloorview Kids Rehabilitation Hospital in Toronto, and Glenrose Rehabilitation Hospital in Edmonton.

1.4 Fatigue and Fatigability

It is well established that fatigue impacts performance in many cognitive and physical tasks. It is often assumed that performance declines with fatigue, which may be true in some instances, but there is more nuanced complexity in the fatigue – performance interaction [102]. This complexity makes fatigue an important factor to study in the optimization of BCI systems. Despite the feeling of fatigue being universal and quite common, the concept of fatigue is complex and hard to define [102, 103]. Fatigue is studied in many broad research fields and has been defined in numerous different ways. The lack of common language for describing fatigue limits collaborations and knowledge generation and application more broadly, blurring our understanding of fatigue [103]. Fatigue is a sensation whereas fatigability is a measure of performance changes [104]. For the purpose of this research, fatigue will be defined as follows: "Fatigue is a sensation of tiredness, often accompanied by alterations in behaviour or performance, which can arise from sustained performance in a cognitively or physically demanding task" [102, 104, 105]. Additional probing questions can be used to separate an individual's experience of fatigue from sleepiness, boredom, and variations in mood.

There are many factors that will impact day to day non-pathological fatigue. These include but are not limited to sleep, exercise, nutrition, time since last meal, mood, stress, and hormone levels

[106, 107]. In the context of performance drops during a task, it is important to consider the effects of a fatigue, loss of interest, extremely high workload, and task achievability [102]. Concepts of attention, motivation, and fatigue are very intertwined. Fatigue impacts attention and motivation [108]. Changing attention and motivation may be caused by fatigue or may be unrelated to fatigue. Regardless, changing attention and motivation may also impact task performance [102]. Two opposing outcomes of mental fatigue are as follows: decreased effort often resulting in decreased performance or increased effort to compensate for fatigue thus maintaining performance [109]. These behaviours will reflect very different patterns of brain activity.

Measuring fatigue is challenging due to variability in definitions and poorly defined critical features. There are numerous self-assessment questionaries to evaluate perceived fatigue however, there are no standard measures used across disciplines and lab groups [110]. In a recent review of self-reported metrics, 24 options were highlighted [111]. In addition to perception tools, fatigue may also be measured from living patterns and sleep assessments [111]. Attempts have been made to assess fatigue with observable behavioural changes and physiological signals. A potential advantage of physiological signals may be the detection of change before any behaviour effects are noticeable, making them particularly valuable in early detection [112]. Examples of physiological signals include the electrocardiogram to assess heart rate or heart rate variability, electro-oculogram looking at eye movements, and EEG. EEG measures have also been combined with electromyography [112]. EEG measures are the most common measurement used for fatigue detection using physiological markers [112].

1.4.1 Electroencephalography Markers of Fatigue

EEG allows for the recording of synchronized brain activity with high temporal resolution. Changes in brain activity picked up by EEG likely reflect real time changes in cognitive processing and brain states. Of many biomarkers for fatigue being investigated, EEG is currently cited to be the most effective [113]. The EEG signal is complex offering many unique elements that may be useful, particularly measures of frequency, phase or coherence, entropy, spectral power, and signal amplitude [114, 115]. To further complicate this measure, EEG is often analysed both as an absolute measure and as a relative measure. As EEG is highly sensitive to different cognitive processes, analysing resting state (RS) data (eyes open and/or eyes closed) and task state data reveal different patterns [113].

On a superficial level, the different frequency bands within EEG are linked to various cognitive processes or behavioural states. δ waves (< 4Hz) are typically present during slow wave sleep, and thus are thought to be critical in memory consolidation. θ waves (4-7 Hz) are linked with focused attention especially during difficult tasks and are thought to be an indicator of workload. α waves (8-12 Hz) are thought to be important in regulating attention to external sensory stimuli. Unlike θ waves, α waves commonly desynchronize during focused attention. β waves (12-30 Hz) along the motor cortex are increased during planning of motor movements. Outside of the motor regions β waves might also reflect when the mind is busy or concentrating. Finally, γ waves (30-50 Hz) have a less familiar association with or impact on behaviour states but recent advances in signal processing are beginning to reveal their clinical significance [115].

1.4.1.1 Alpha Frequency Band

When looking specifically at mental fatigue, α waves are commonly studied and even cited as "the most sensitive indicator of brain fatigue" [109, 113]. During rest, activity in the α frequency range is the most prominent across the EEG spectrum [116]. The rhythmic α waves were first observed and documented in 1929 by Hans Berger [117]. Since then, many studies have tried to uncover the origin of the α wave and its role in various cognitive processes, both of which are still under heavy investigation. The dominant view of α origin being the thalamus, specifically the pulvinar nucleus and lateral geniculate nucleus, has recently been challenged by a study using intracortical electrodes to avoid localizing a source from an electrical signal with poor spatial resolution [118]. This research provides evidence supporting distinct α pacemakers in the thalamus and in the cortex [118]. Within the cortex it was previously demonstrated that rhythmic activity such as α waves are generated by pyramidal cells in layer V [119].

α is commonly analysed as activity between 8-12/13 Hz, however there is a lot of interindividual and intraindividual variability in the α wave [114, 120]. The α peak frequency has a genetic component, and is influenced by age and hormone activity, including progesterone and cortisol [121–123]. The α rhythm can also be divided into distinct lower α and upper α bands [116]. In a smaller percentage of individuals three distinct α components can be extracted [116]. The variability of this rhythm contributes to difficulty in determining the functional role of this dominant oscillation. As a marker of fatigue α is often analyzed in RS periods and Li and colleagues' findings support that using RS periods instead of task state is better when trying to understand and measure fatigue [113].

Consistent ERD/ERS in the α frequency band has been recorded in numerous studies on attention, perception and memory [120]. Individuals with higher α power perform better on BCI tasks and other attention tasks [124, 125]. Increasing the power of α is also a target for neurofeedback training approaches to increase attention and BCI performance [126, 127]. The reason α is often found to increase with fatigue is not clear. If α represents a state of cortical inactivity or decreased arousal [114] this may be one justification for its increase in fatigue. α decreases when mental effort is high [128]. When α is decreased we are thought to be more alert to our surroundings [128]. With this hypothesis, the opposite behaviour, a decrease in effort and alertness is in line with common understanding of fatigue. Past research alternatively suggests that the increase is related to greater mental effort needed to be vigilant when fatigued [129, 130]. The activity of α is topographically variable and changes in complex ways to different tasks making interpretation difficult.

1.4.1.2 Theta Frequency Band

In a systematic review and meta-analysis published in 2020, Tran and Colleagues found θ band power increase to be the best EEG band metric for detecting fatigue. They reported α to be the second best [109]. Li and Colleagues report increases in absolute θ power and relative θ power with fatigue that is in line with numerous other published works [113]. Studies correlating band power to BCI performance have also found higher θ correlates with worse BCI performance [125]. θ has long been believed to relate to arousal and attention or concentration and also characterizes the first sleep state [131, 132]. θ origin is thought to be from hippocampal-cortical networks [130, 132]. Hippocampal θ, which is related to EEG scalp θ, is important for working memory, memory

encoding, and memory retrieval [130, 133]. The θ band synchronizes as cognitive demands increase [132]. Despite not being a dominant rhythm in awake states, θ fluctuations are still extremely useful in understanding brain states. Unlike with α where the correlation with fatigue is somewhat counterintuitive to the correlation with BCI performance, results surrounding θ are more inline across theories. With θ being prominent in the first stage of sleep, it is not surprising that many reports show θ increasing with fatigue.

1.4.1.3 Important Electroencephalography Considerations for Children

There are several additional considerations when using pediatric EEG recordings as a fatigue biomarker and for a BCI system. Due to attentional differences, children often need shorter recording sessions. They are also more likely to have artifacts within recordings due to movement or speech. Classic EEG frequency bands evolve over development and are not typically fixed as we often assume in adults [134]. The spectrum shifts throughout development and might look quite different even between a 6 and a 10-year-old for example. What is believed to be the α band equivalent in childhood is from approximately 6-9Hz [135]. So while the classic EEG bands already have limitations when applied to adults [114, 116, 136], this is even more problematic in children. EEG power distribution also shifts in development. Generally lower frequencies dominate in childhood and decrease in power from adolescence to adulthood. Conversely, higher frequencies, namely the β band, are not as prominent in childhood but increase power and start to dominate in adulthood [137]. Total EEG power also decreases in adulthood [137, 138]. Given the above, applying our knowledge of adult spectral analyses to children must be done with caution.

1.5 Brain-Computer Interface Fatigue

An individual's mental state, which includes fatigue levels, attention level, and motivation influences the EEG signals and the ability of the BCI to classify a command [139]. Numerous adult studies have looked at BCI fatigue, and fatigue has been highlighted as a key BCI performance factor, consistent with many other cognitive tasks [12, 14, 59, 140]. Self-reported fatigue typically increases during BCI use in adults [5, 12, 14, 129, 140]. There are mixed results around the impact of fatigue on BCI performance, in keeping with the complexity of the fatigue-performance relationship [12, 14, 141, 142]. Fatigue is thought to be an important mediator in children, especially those who have had an early brain injury [2, 13, 98, 105]; yet there are no pediatric studies to date.

An ability to detect and predict fatigue changes could help optimize BCI performance, especially in non-verbal children for whom potential benefits are the greatest. Real-time detection may help increase BCI performance by informing caregivers of user fatigue and may contribute to adaptive BCI systems in the future. Previous studies found promising results using EEG data to monitor workload and mental fatigue during BCI use [5, 12, 140, 143, 144] . Seo and Colleagues found increases in α band power after both MI and P300 BCI tasks in healthy adults (see Figure 1.8). Many of the studies investigating fatigue monitoring are driving based, however, meta-analysis provides evidence that EEG measures are consistent with mental fatigue regardless of cognitive task [109]. Many useful EEG signals, such as the power of EEG bands discussed above, are strongly influenced by characteristics such as age [12]. It has been suggested that due to frequency shifts across development, there needs to be unique frequency bands with different associations to

cognition or behaviour for children [135]. This provides justification for investigating EEG correlates of BCI fatigue specifically in children.

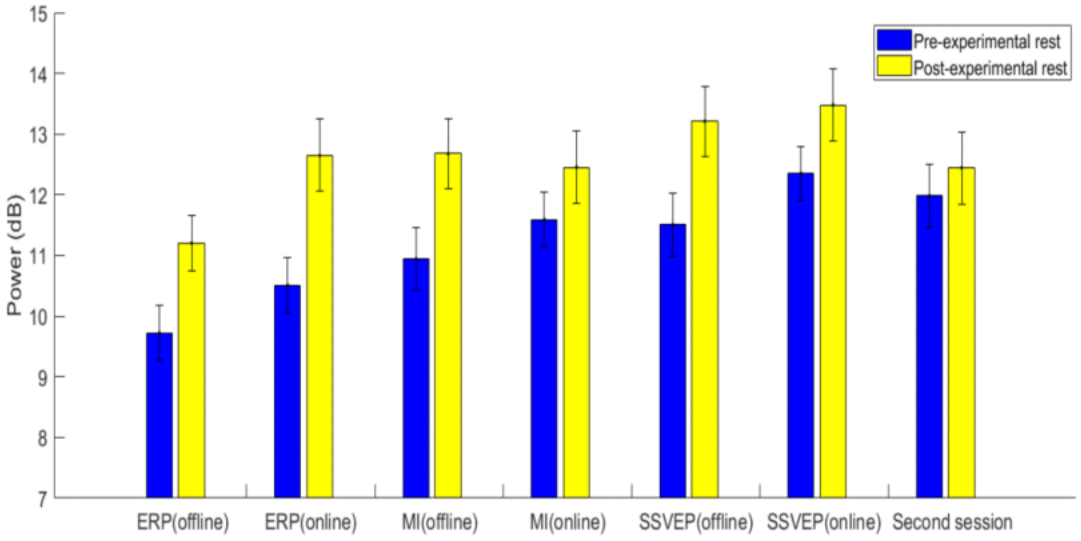

Figure 1.8. Alpha band power measured pre and post BCI tasks. *There were consistent increases in α band power between BCI paradigms. Statistical significance was reached in ERP tasks, MI (offline), and SSVEP tasks. Event Related Potential (ERP) session is a P300 BCI session. Error bars are standard error. Steady-State visually evoked potential (SSVEP) is an additional exogenous visual BCI paradigm not discussed in this thesis. Image from Seo, 2019 [5]. available for reuse in theses Copyright © 2019 IEEE.*

In addition to general cognitive or mental fatigue from the BCI task, it is possible that certain BCI systems might also cause fatigue through the activation of the central motor pathways and/or the visual system or other sensory systems [145, 146]. Research from Ioannucci and colleagues present data indicating how passive visual stimulation may be fatiguing [147]. Many adult studies investigating fatigue have very long periods of BCI use (up to 5 hours), however, even periods of

under 25 minutes have been shown to increase self-reported fatigue as well as result in EEG changes [140]. A MI BCI study conducted in adults had 5/11 participants quit part way through due to high fatigue across a 96 minute protocol, and 3 or these 5 quit at just 60 minutes [144]. No studies have looked at how long EEG biomarkers of fatigue continue after BCI use, but they do indicate that changes can be picked up in at least the minutes immediately following BCI use [5]. For long-term BCI use considering fatigue is critical. BCI fatigue in pediatrics has not yet been directly investigated. It is likely harder to measure, but it is an important concern for children and those with early brain injuries who may be more vulnerable to fatigue. We must understand BCI fatigue in children to optimize for it.

1.6 Rational, Aims, & Hypothesis

Our pediatric BCI program families have identified fatigue as an important, potentially modifiable, factor for successful BCI use and thus, it is an important aspect to explore. Fatigue along with many other important factors impact the feasibility of in-home or in-community use of BCIs with peers and families which is an important consideration for patient-centered research [72, 98, 148].

The general research objective guiding this project is to better understand the mechanisms and impacts of fatigue during BCI use in children. This knowledge can help us answer questions like: what are the effects of different BCI paradigms on fatigue and fatigability in children? How does fatigue impact BCI performance and enjoyment? Can EEG provide valuable data to quantify and monitor fatigue in children while operating BCIs? Do these EEG biomarkers correlate with subjective experiences of fatigue?

This project aims to,

(a) assess the effects of two BCI paradigms, MI and P300, and a video control on self-reported fatigue and fatigability in typically developing children and

(b) extract and analyse EEG correlates of fatigue, namely the α band power.

We hypothesize,

(a) self-reported fatigue changes will be greater with BCI paradigms compared to the video control and the MI-BCI paradigm will be more fatiguing compared to the evoked potential P300 BCI paradigm and

(b) there will be an increase in the power of the α band across each session, the degree of which will correlate with self-reported fatigue.

2 Chapter 2 – Manuscript

Title: Fatigue in Children Using Motor Imagery and P300 Brain-Computer Interfaces

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2.1 Abstract

Background: Brain-computer interface (BCI) technology offers children with quadriplegic cerebral palsy unique opportunities for communication, environmental exploration, learning, and game play. Research in adults demonstrates a negative impact of fatigue on BCI enjoyment, while effects on BCI performance are variable. To date, there have been no pediatric studies of BCI fatigue. The purpose of this study was to assess the effects of two different BCI paradigms, motor imagery and visual P300, on the development of self-reported fatigue and an electroencephalography (EEG) biomarker of fatigue in healthy children.

Methods: Thirty-seven typically-developing school-aged children were recruited to a prospective, crossover study. Participants attended three sessions: (A) motor imagery-BCI, (B) visual P300-BCI, and (C) video viewing (control). The motor imagery task involved an imagined left- or right-hand squeeze. The P300 task involved attending to one square on a 3x3 grid during a random

single flash sequence. Each paradigm had respective calibration periods and a similar visual counting game. Primary outcomes were self-reported fatigue and the power of the EEG alpha band both collected during resting-state periods pre- and post-task. Self-reported fatigue was measured using a 10-point visual analog scale. EEG alpha band power was calculated as the integrated power spectral density from 8-12 Hz of the EEG spectrum.

Results: Thirty-two children completed the protocol (age range 7-16, 63% female). Self-reported fatigue and EEG alpha band power increased across all sessions ($F_{(1,155)} = 33.9$, $p<0.001$; $F = 4.0_{(1,149)}$, $p = 0.047$ respectively). No differences in fatigue development were observed between session types. There was no correlation between self-reported fatigue and EEG alpha band power change. BCI performance varied between participants and paradigms as expected but was not associated with self-reported fatigue or EEG alpha band power.

Conclusion: Short periods (30-mintues) of BCI use can increase self-reported fatigue and EEG alpha band power to a similar degree in children performing motor imagery and P300 BCI paradigms. Performance was not associated with our measures of fatigue; the impact of fatigue on useability and enjoyment is unclear. Our results reflect the variability of fatigue and the BCI experience more broadly in children and warrant further investigation.

Key words: Brain-computer interface, Pediatrics, Fatigue, Electroencephalography, Cerebral palsy, P300, Motor imagery

2.2 Introduction

Cerebral Palsy (CP) is a group of heterogeneous movement disorders and the leading form of lifelong disability. In Canada alone it is projected that there will be nearly 100,000 individuals living with CP by 2031 [149]. In its most severe form, quadriplegic CP, individuals lack muscular control in all limbs, the head, neck and trunk [7, 8]. Many children with quadriplegic CP are cognitively capable but have no ability to move or speak, a condition known as "locked-in syndrome" [45]. Intellectual disability is thought to occur in approximately 50% of children with CP, with higher rates for those with spastic quadriplegic CP [43]. However, many individuals with this severe movement disorder are highly aware and capable. It is important to consider that cognitive impairments are likely overestimated, and deficits may be compounded by decreased opportunities for meaningful environmental interaction [44]. There is a critical need to develop alternative means of connection, communication, and play for children with quadriplegic CP, and brain-computer interface (BCI) technology has the potential to meet this need [92, 101].

A BCI translates a user's brain activity to directly control an effector device such as a game, wheelchair, or computer [60]. BCI research is dominated by studies in adult populations [2], but recently it has been demonstrated that children, both typically developing and those with CP, can learn to control BCI systems [96, 97, 99, 100]. Factors by which the young brains of children can achieve optimal BCI performance are unstudied but must be identified to improve such potentially life-changing interventions. In adults, operating a BCI has been associated with increased self-reported fatigue [12, 140], and fatigue may negatively impact BCI signal feature detection and operator performance [129]. Fatigue is also an important functional consideration for children with CP [98, 105]. Increased fatigue levels following BCI use have been anecdotally observed in our

clinical BCI program working with children on a regular basis but the effects of fatigue on BCI performance remain undefined in children.

The feeling of fatigue is common and universal, yet hard to define. For this research, fatigue will be defined as "a sensation of tiredness, often accompanied by alterations in behaviour or performance, which can arise from sustained performance in a cognitively or physically demanding task" [102, 104, 105]. In addition to self-reported metrics and performance changes, adult BCI studies have identified electroencephalography (EEG) biomarkers of fatigue [5, 143] most notably increases in alpha band power [113, 150].

BCIs can increase the ability of children with quadriplegic CP and locked-in-syndrome to actively participate in daily life. Research is needed to optimize such alternative access technologies specifically for children. An exploration of fatigue is not only useful for user-centered design of pediatric BCI systems but may contribute to the generation of early fatigue detection tools, mitigation strategies, and adaptive BCIs in the future. The goal of this study was to assess the effects of two commonly used BCI paradigms, motor imagery (MI) and visual P300, on self-reported fatigue and a resting state (RS) EEG correlate of fatigue in typically developing children. We hypothesized that fatigue would be greater in the MI-BCI compared to the P300-BCI and that there would be an increase in EEG alpha band power as self-reported fatigue increased.

2.3 Materials and Methods

Participants

Children were recruited from the community via HICCUP, the Health Infants and Children Clinical Research Program [151]. Inclusion criteria were age 6 – 17 years, absence of any neurological or neurodevelopmental conditions or medications, and informed consent/assent. The study protocol was approved by the Conjoint Health Research Ethics Board, at the University of Calgary (ID: REB22-0044).

A priori power analysis was performed using the power.mmrm function in the longpower R package [152] with an estimated one-tailed standardized effect size of 0.7, alpha = 0.05, beta = 0.8. An N of 33 participants was required to detect this effect.

Protocol

Participants attended three sessions on separate days at the Alberta Children's Hospital BCI4kids laboratory: two BCI sessions (one MI task and one P300 task), and an additional film viewing session (control condition). The session order was balanced using a Latin square design. The length of time between sessions was at least 24 hours. The protocol was identical in all three sessions before and after the unique session task. A protocol schematic is outlined in Figure 2.1.

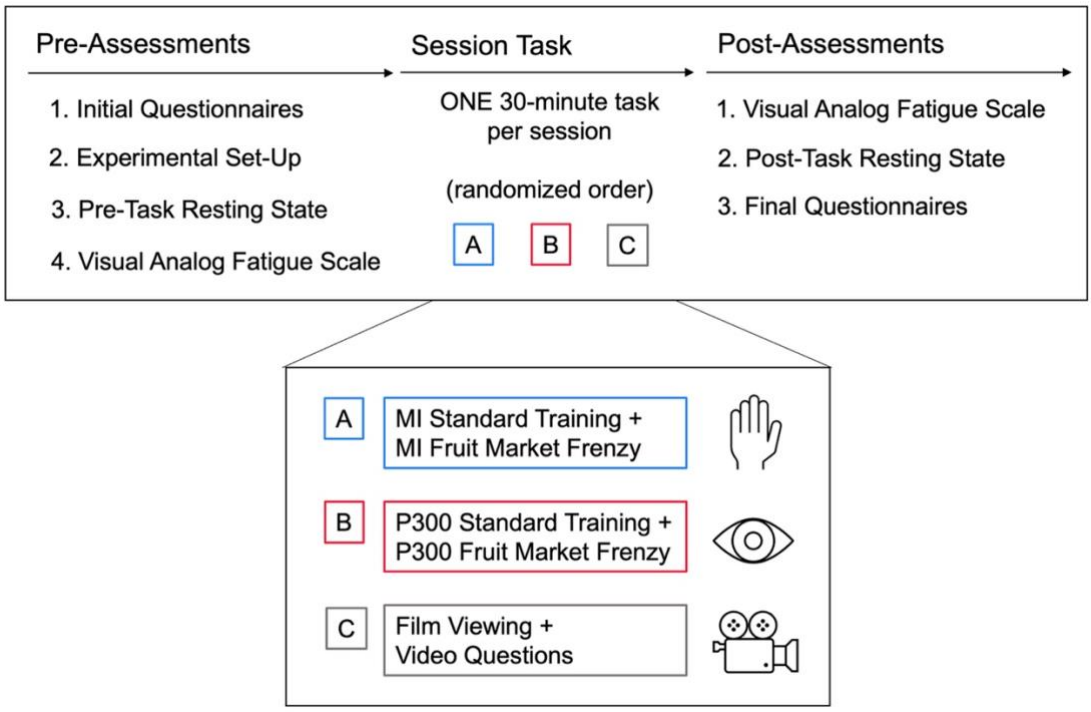

Figure 2.1. Protocol Schematic for All Three Sessions. *Session tasks were balanced using a Latin square design. Sessions lasted 60 to 90 minutes. MI = motor imagery.*

Experimental Set-Up and BCI System

Participants were seated in a chair in front of a 27" LG27GL850 (LG Corporation, Seoul, South Korea) computer monitor for the duration of each session. The monitor has a refresh rate of up to 144 Hz, and a pixel response time of 1 ms. The DSI24-C (Wearable Sensing, San Diego, USA) system was used for EEG monitoring. The DSI24-C is a child size dry electrode EEG headset with 19 active EEG electrodes. Data from this headset was sampled at 300 Hz. The DSI24-C has electrodes with preconfigured positioning. Electrode static positions: Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, P4, T6, O1, O2. Fpz was the ground electrode, and the left ear clip (A1) was used as reference to substantially reduce the occurrence of electrical and motion artifacts [153]. The DSI streamer software was used to establish connection during set up. For optimal

connection, we aimed to have impedance between 0.1-5MΩ, RMS Noise <20µV, and baseline DC shift < +/- 5000µV. Lab streaming layer (LSL) [154] was used with a custom Unity (San Francisco, USA) application and python backend during the data collection.

Questionnaires

Before each session, participants responded to predefined questions regarding potential factors affecting performance including, mood, sleep quality and duration, exercise, and time since their last meal in the Preliminary BCI Assessment. They also completed the PedsQL™ Multidimensional Fatigue Scale (MFS; acute scale, version 3.0) [155]. During the first session, participants also completed the Edinburgh Handedness Inventory. Assessments and questionnaires at the end of each session were an adapted Pediatric Motivation Scale [156], the Child-Adapted NASA-Task Load Index (TLX) [157], and the BCI Tolerability Assessment. A visual analog scale for fatigue (VASF) was included in the Preliminary BCI assessment and in the BCI Tolerability Assessment. Additional fatigue assessments were done with the VASF immediately before the BCI or film task and immediately after (see timing in Figure 2.1) as well as in 5-minute intervals throughout the session task. In the film viewing sessions, to ensure participants were paying attention to the film, they were asked additional questions about the content of the film. They were informed at the start of the task that there would be questions.

Resting State (eyes-open)

RS was completed immediately before and after the session task (pre-task and post-task). This was a 2-minute EEG recording period where participants were instructed to relax their body and face, refrain from speaking and moving, clear their mind, and look at a target on the computer screen.

BCI Applications

MI Application Training: Participants trained the classifier for 5 minutes. The MI task was an imagined hand squeeze. During the standard training, participants were presented with two boxes side by side on a black screen (see Figure 2.2A). Boxes alternated between being the standard size or a larger size. The larger box was the "train target". They were asked to perform their imagined squeeze with the hand on the same side as the "train target" (i.e., if the right box was larger, they performed right hand motor imagery). After one trial on each hand, they were given feedback in the form of the boxes changing colour. The right box became brighter orange when right hand MI was detected while the left box became brighter blue when left MI was detected. Figure 2.2A – top left panel - depicts the MI training task. EEG was collected for 12 seconds with 2 second windows and there was a 6 second break between trials. MI alternated between left and right hand for the entire training period. There was a total of 18 training selections. This training design was modified from mindBEAGLE SMR training [158] based on in lab pilot testing.

For MI classification, each 2 second window during MI was filtered with a 5^{th} order Butterworth bandpass filter with corner frequencies of 5 and 30 Hz. A covariance matrix was calculated for each 2 second window. Tangent space mapping was used to get a feature vector from the covariance matrix [159]. A logistic regression classifier was trained using the tangent space feature vectors with the corresponding window labels. This classifier, retrained from scratch every two training selections, was used to provide feedback to the user.

P300 Application Training: Participants trained the classifier for 5 minutes. During the standard training, a 3x3 grid of grey boxes was displayed on the computer screen, as seen in Figure 2.2C –

bottom left panel. The participants were instructed to focus their attention on the box where a target cursor would appear. They were instructed to only focus on the target box as they all began to flash red in random order. Boxes would turn red for 100 ms followed by a 75 ms pause before the next flash. Participants were instructed to count how many times the box they were focused on flashed. After a random flashing sequence of 15 single flashes per box, there would be a 2 s pause, before the target would appear in a new box, and they were instructed to shift their attention and repeat the above instructions. There was a total of 9 training selections (all the grid boxes). This training design was modified from Guger and Colleagues [160].

Throughout the training period, for each flash a window in the EEG, including the 600 ms from immediately when the flash goes on, was saved. All windows were then filtered with a 5^{th} order Butterworth bandpass filter with corner frequencies of 0.1 and 15 Hz and then were ensemble averaged to yield one window per box per trial. The window corresponding to the trials target box was labeled target and the rest are labeled non-target. XDawn covariance matrices were calculated from each ensemble average windows. Tangent space mapping was used to get a feature vector from the covariance matrix. Shrinkage Linear Discriminant Analysis (sLDA) was used to classify between target and non-target. The combination of XDawn, Riemannian geometry, and sLDA was based on recommendations in [161]. This trained a binary classifier. To make a selection, the posterior probability that each box is the target was calculated. The box with the greatest posterior probability was selected.

Common MI/P300 Game - Fruit Market Frenzy: This application was designed in-house using Unity (San Francisco, USA). Participants watch a fruit stand animation with moles bobbing in and

out of holes in the ground. The moles were throwing around common fruit on the screen. During the MI version, children were asked to determine if there was more of a certain kind of fruit (ex. apples) being thrown from the left of the right of the screen. They would verbalize their answer and then try and enter it using the BCI, doing their imagined hand squeeze action to move a cursor in the center of the screen to the left or right (Figure 2.2B). Four classifier selections in one direction minus any selections in the opposite direction were required to make a selection. This continued until a selection was made. During the P300 version, the same animation was used and children were asked to count the number of a certain kind of fruit being thrown around. After verbalizing, they then entered their answers on a 3x3 grid of numbers 1 through 9 by attending to the number they were trying to select as the board went through a random flash sequence, 15 flashes/square, similar to the P300 training (Figure 2.2D). Windows corresponding to each possible selection were ensembled averaged and classified. The window with the highest posterior probability of being the target was selected.

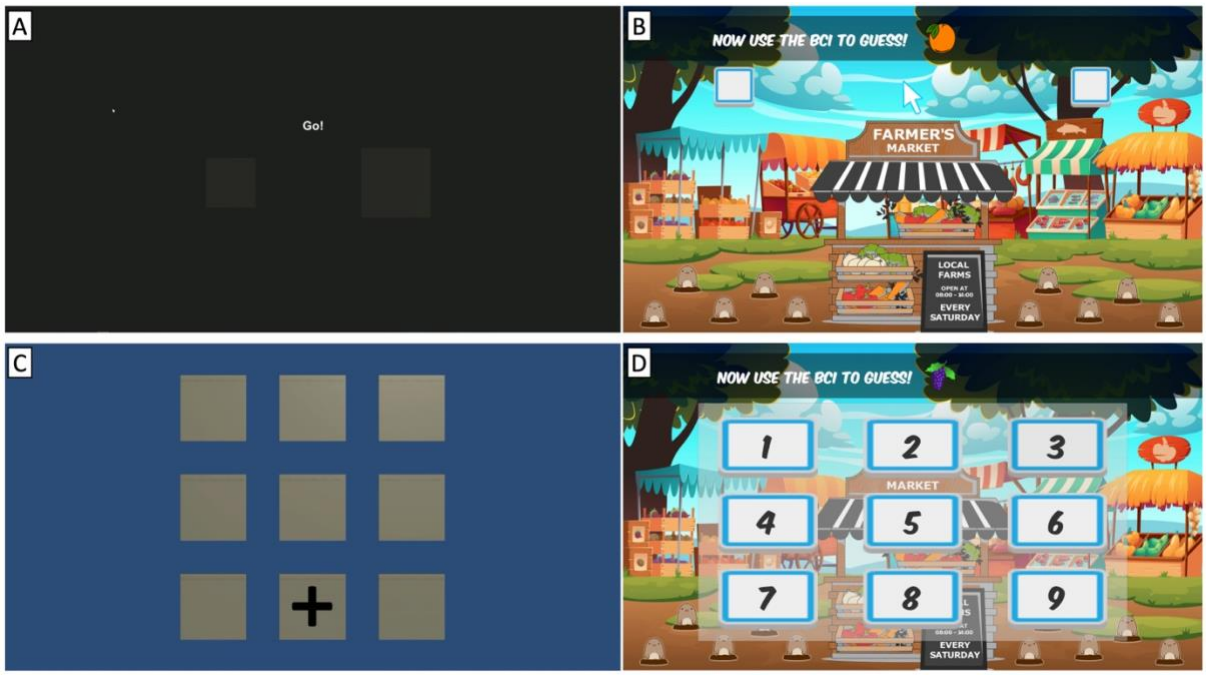

Figure 2.2. BCI Training and Fruit Marking Frenzy Game Applications. *A. Motor imagery training scene. B. Motor imagery game scene. C. P300 training scene. D. P300 game scene.*

Participants played these games for 25 minutes or until they requested to stop. Participants were free to terminate at any time for any reason. While the Fruit Market Frenzy Game involved counting, the "correct" answer for the BCI and the feedback that was given to participants was based on what they shared verbally to the individual collecting the data. This person entered the participants verbal answer with the mouse before participants went on to make their BCI selection.

Control Condition

Viewing a film (https://www.youtube.com/watch?v=Mik9iDj0seY): Participants watched 30 minutes of a YouTube film about nature and animals titled *The Most Amazing Master Builders in the Animal Kingdon* (linked above). Participants were free to terminate the video at any time for any reason.

Data Analysis

Primary outcomes included self-reported VASF and the RS alpha band power pre- and post-task. Channels with impedance greater than 5MΩ were removed. Electrodes were removed on a session-by-session basis with a total of 13 electrodes excluded from one session only during the 106 sessions). The integrated power spectral density (iPSD) was calculated using Welch's method with 10 s windows and 5 s overlap between windows [162]. iPSD was calculated for the entire 120 s RS window for frequency resolution < 0.01 Hz. The trapezoidal rule for integration was used to

get absolute power of the classic alpha band (8-12Hz). Alpha band power values greater than 99 $\mu V^2/Hz$ were excluded from analysis.

Composite scores for motivation, workload, and BCI tolerability questionaries were calculated for use in statistical models described below. Motivation was divided into two groups based on the range of participant scores. Scores ranged from 26-45. There was a higher (36-45) and a lower (26-35) motivation group that participants were categorized into. Workload was dived into four groups based on the range of the scale from 0-100. The performance questions was excluded. Low to high workload groups were split as follows: 0-24, 25-49, 50-74, 75-100. Tolerability scores were a composite of the pain question rated from 0-5. Participants were grouped into low to no discomfort (0-2) and higher discomfort (3-5). BCI metrics, accuracy, precision, recall, and the confusion matrix were recorded from the BCI training periods. Overall game performance was also calculated as number of trials correct/number of trials total in the Fruit Market Frenzy Game. Due to limited sample size, raw age values were divided into an upper and a lower half by date of birth.

Statistical Analysis

Statistical analyses were performed using R programming language (version 4.1.2) using the Jamovi software application (2.3.21.0), and the rm_corr library in python (3.8.13). Linear mixed modeling fit with restricted maximum likelihoods was used to assess differences in the two primary outcomes. The main models for both self-reported fatigue (ie. VASF) scores and alpha band power included session and time (pre/post) as factors and participants as the cluster variable. The random factor was participant intercepts. Age, sex, session length, time of the session, MFS

score, workload score, headset tolerability, and motivation score covariates/factors were included in the secondary models and model quality was compared using the Akaike information criterion (AIC) and examination of the fixed effects omnibus tests. Two additional models for VASF included (a) age and sex as factors, and (b) age and sex as factors and MFS score as a covariate. One additional model for alpha band power included motivation score and time of day as covariates.

In both primary outcome models, significant fixed effects omnibus tests underwent further post-hoc analysis with holm correction. Normality of the data was confirmed with visual inspection of Q-Q normality plots and density histograms. For the alpha iPSD model, outliers were also identified by visual inspection of residual histograms. To ensure outliers did not unduly influence statistical models, models were rerun with outliers removed. The threshold for rejecting the null hypothesis was $p < 0.05$. Error in measurement or absolute reliability was calculated for the main outcome measures, alpha band power and VASF score. The calculation methods can be found in Hopkins work [163]. Repeated measure correlations were performed to assess relationships between both primary outcomes as well as relationships between primary outcomes and secondary outcomes.

2.4 Results

Thirty-seven typically developing and healthy children participated in this study (median age 10, mean age 9.8, range 6-16, 58% female sex, 54% identify as women). Of the 37 participants recruited for this study, three individuals were subsequently realized to have a diagnosis of attention deficit hyperactivity disorder, and their data was excluded from analysis. One participant

chose to withdraw from the study part way through their first session and another individual did not fit our headset and thus could not participate. This left a final study population of 32 participants. Two of the final 32 had remote prior concussion. Three participants had a MFS score of less than 50 consistent across sessions.

Self-Reported Fatigue

There was a main effect of time on self-reported fatigue ($F_{(1,155)} = 33.9$, $p < 0.001$), but no main effect of session ($F_{(2,155)} = 2.5$, $p = 0.086$) or interaction effect of session and time ($F_{(2,155)} = 1.4$, $p = 0.250$) on self-reported fatigue. The estimated marginal mean VASF score across all sessions was 3.4 (95% CI 2.8-4.1) pre-task and 4.6 (95% CI 4.0-5.2) post task. The mean VASF pre- and post-task for each session is in Table 1 (Figure 2.3). The statistical model AIC value was 748.

An additional model with inclusion of age and sex (model 2) as factors demonstrated an interaction effect of age and time ($F_{(1,140)} = 4.5$, $p = 0.036$). The younger half of participants had a larger change in VASF from pre to post across all sessions. The addition of MFS score into the model with age and sex (model 3) found an effect of MFS scores ($F_{(1,129.2)} = 6.6$, $p = 0.012$). Those with MFS scores greater than one standard deviation from the mean had lower VASF values and those with scores one standard deviation lower than the mean had higher VASF values. Further information on secondary models is included in supplemental material Table 2.5 and Figure 2.7. There was no effect of time of day, session length, workload, motivation, headset tolerability, or BCI game performance on VASF.

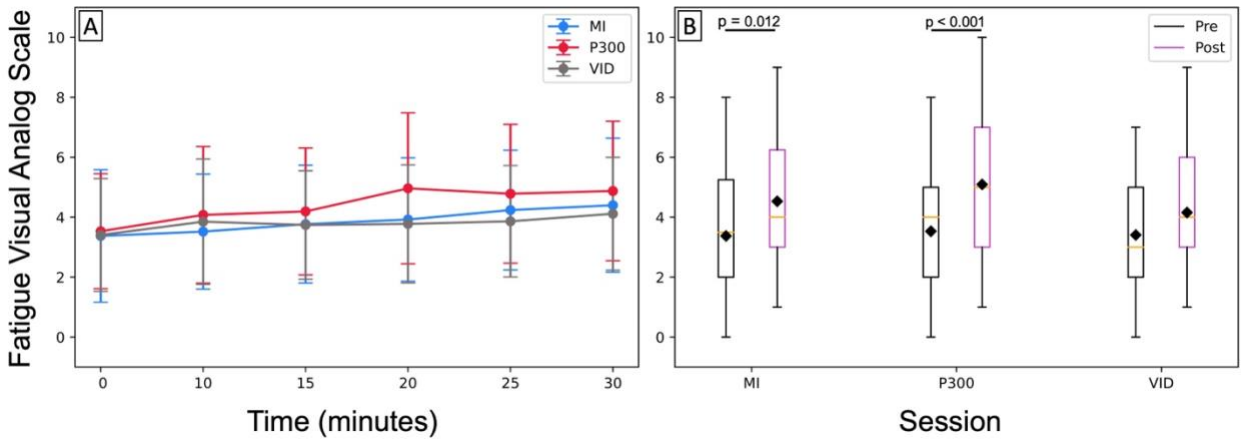

Figure 2.3. Self-Reported Fatigue. *a. Fatigue visual analog scale values reported across the session at time 0,10,15,20,25, and 30 minutes. b. Fatigue visual analog scale values pre-task and post-task for each session. Post-task was at time 30 for most participants, but for those who did not complete the full protocol post-task is not at time 30. Boxplot lines indicate quartiles. Orange lines indicate the median and black diamonds are sample mean. Bars are plus or minus 1.5x the interquartile range. MI: motor imagery; VID: video.*

Electroencephalography alpha band power

Before statistical analysis, EEG alpha band power values were excluded from 6/96 sessions. There was a main effect of time on alpha band power ($F_{(1,149)} = 4.0$, $p = 0.047$) but no effect of session ($F_{(2,149)} = 0.9$, $p = 0.418$) or interaction effect ($F_{(2,149)} = 0.7$, $p = 0.517$). When outliers were removed for a robustness check, results remained unchanged. The estimated marginal mean across all session was 27.9 $\mu V^2/Hz$ (95% CI = 23.0 – 32.9) during pre-task RS and 30.0 $\mu V^2/Hz$ (95% CI = 25.1 – 35.0) during post-task RS. The mean alpha band power pre- and post-task for each session is in Table 1 (Figure 2.4). The AIC value was 1363. Results from the secondary model with the addition of time of day and motivation rating is included in supplemental material Table 2.5. There

was no effect of age, sex, session length, workload, headset tolerability, or game performance on the alpha band power change.

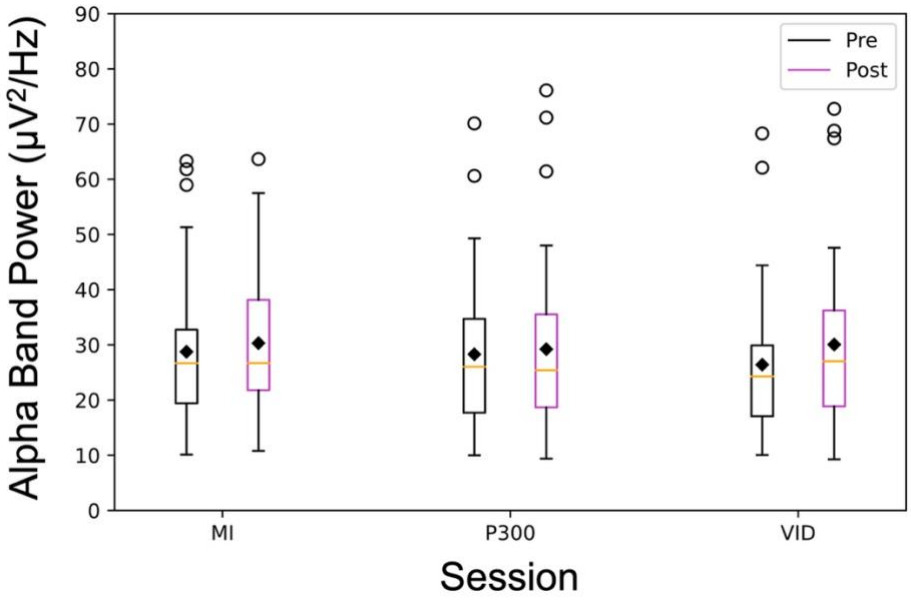

Figure 2.4. Alpha Band Power. *pre-task resting-state and post-task resting state alpha band power for each session. Boxplot lines indicate quartiles. Orange lines indicate the median and black diamonds are sample mean. Bars are plus or minus 1.5x the interquartile range. MI: motor imagery; VID: video.*

Table 2.1. Fatigue visual analog scale values and alpha band power pre- and post-task.

Session	Time	Self-Reported Fatigue (10 pt scale) (95% Confidence Interval)	Alpha Band Power ($\mu V^2/Hz$) (95% Confidence Interval)
MI	Pre	3.4 (2.6 – 4.1)	29.1 (23.9 – 34.4)
	Post	4.5 (3.8 – 5.3)	30.6 (25.3 – 36.0)
P300	Pre	3.5 (2.8 – 4. 3)	28.3 (23.0 – 33.6)
	Post	5.1 (4.3 – 5.8)	29.4 (24.0 – 34.7)
Video	Pre	3.4 (2.7 – 4.2)	26.3 (21.1 – 31.6)
	Post	4.2 (3.5 – 4.9)	30.1 (24.8 – 35.4)

Legend: *Values are estimated marginal means. MI: motor imagery.*

BCI Performance

BCI training scores are shown in Table 2.2 and 2.3 and BCI Fruit Market Frenzy performance is in Table 2.2 and Figure 2.5. For reference, during the Fruit Market Frenzy game, MI classification is binary with chance accuracy of 50%. P300 is a one in nine selection with a chance accuracy of 11%. Regardless of training scores, all participants played the Fruit Market Frenzy game. During MI training, only 3 individuals achieved a training accuracy above 70% (14 above 60%), but 7 individuals achieved greater than 70% during the MI Fruit Market Frenzy game following training (12 above 60%). All participants achieved training accuracy above 70% for P300 training. Eight individuals achieved this percentage in the P300 Fruit Market Frenzy game (16 above 60%). Comparisons for P300 training and game are more difficult because the training is a binary classification between 2 classes (chance=50%), and the game online accuracy is comparing

posterior probabilities of that classification for each of the 9 boxes (chance=11%). MI game performance ranged from 39% to 100%. P300 game performance ranged from 20% to 93%.

Table 2.2. BCI training and game performance scores

Performance Outcome	**Mean (%)**	**Range (%)**	**95% Confidence Interval**
Training accuracy			
MI	0.61	0.43	0.57-0.64
P300	0.94	0.15	0.93-0.95
Training precision			
MI	0.61	0.44	0.57-0.64
P300	0.91	0	0.80-1.01
Training recall			
MI	0.61	0.54	0.57-0.65
P300	0.48	1.00	0.36-0.59
Game performance			
MI	0.60	0.61	0.56-0.64
P300	0.55	0.84	0.48-0.61

Legend: *Training accuracy is the ratio of correct predictions over total predictions made by the model. Training precision is the ratio of true positives over all positive classifications (true and false positives). Training recall is the ratio of true positives over all actual positives (true positive and false negatives). Training scores computed by game performance was calculated by total trials correct/total trials. MI: motor imagery.*

Table 2.3. Confusion matrix for motor imagery and P300 training

Requested Selection

Participant Selection	Motor Imagery Mean			Motor Imagery Range	
		Target	Non-Target	Target	Non-Target
	Target	21	33	6-35	19-48
	Non-Target	33	21	24-48	3-36
	P300 Mean			P300 Range	
		Target	Non-Target	Target	Non-Target
	Target	5	0	0-9	0-3
	Non-Target	4	72	0-9	69-27

Legend: *Confusion matrix contains all classifications made in training. From left to right top to bottom of each quadrant they are true targets, false targets, false non-targets, and true non-targets.*

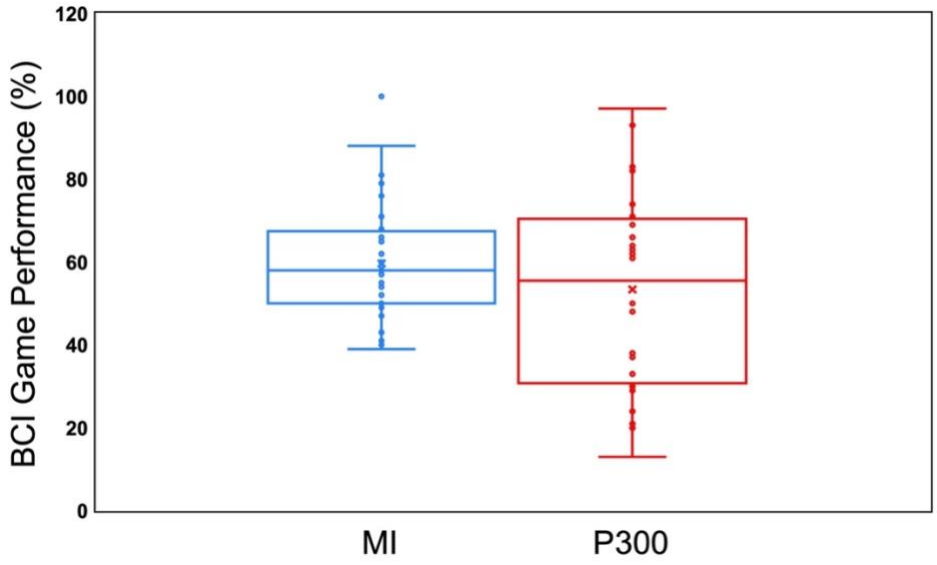

Figure 2.5. BCI Fruit Market Frenzy game performance. *Performance calculated by total trials correct/total trials for each session. Boxplot lines indicate quartiles, and all participant data is plotted. Bars are plus or minus 1.5x the interquartile range. BCI: Brain-computer interface; MI: motor imagery.*

Questionnaires: Mood, Workload, Motivation, and Tolerability

During 69% of the 96 sessions, participants came in with positive moods: 'excited', 'chill', 'pleasant', 'calm', 'happy', 'content', 'comfortable', 'lively', 'fulfilled'. In the other 31% of sessions, participants came in with more neutral or negative mood states: 'neutral', 'sleepy', 'tired', 'nervous', 'hurt', and 'bothered'. Ratings from the Pediatric Motivation Scale were similar across all sessions (Figure 2.6A; Table 2.4). Mental demand, temporal demand, effort, and frustration were all similar between both BCI sessions and tended to be higher compared to the control session (Figure 2.6B; Table 2.4). Physical demand was often higher in the MI BCI session compared to the P300 BCI session and the control (Figure 2.6B; Table 2.4). BCI tolerability ratings were similar between MI and P300 sessions (Figure 2.6C; Table 2.4). The majority of participants found the headset uncomfortable (72% during MI, 59% during P300, 53% during control). There was an increase in the number of individuals who reported discomfort across the three sessions, 56% during the first session, 59% during the second session, and 72% during the third session. 22% of participants did not report discomfort in any session. 25% of participants were unable to complete the whole protocol due to discomfort part way through the sessions.

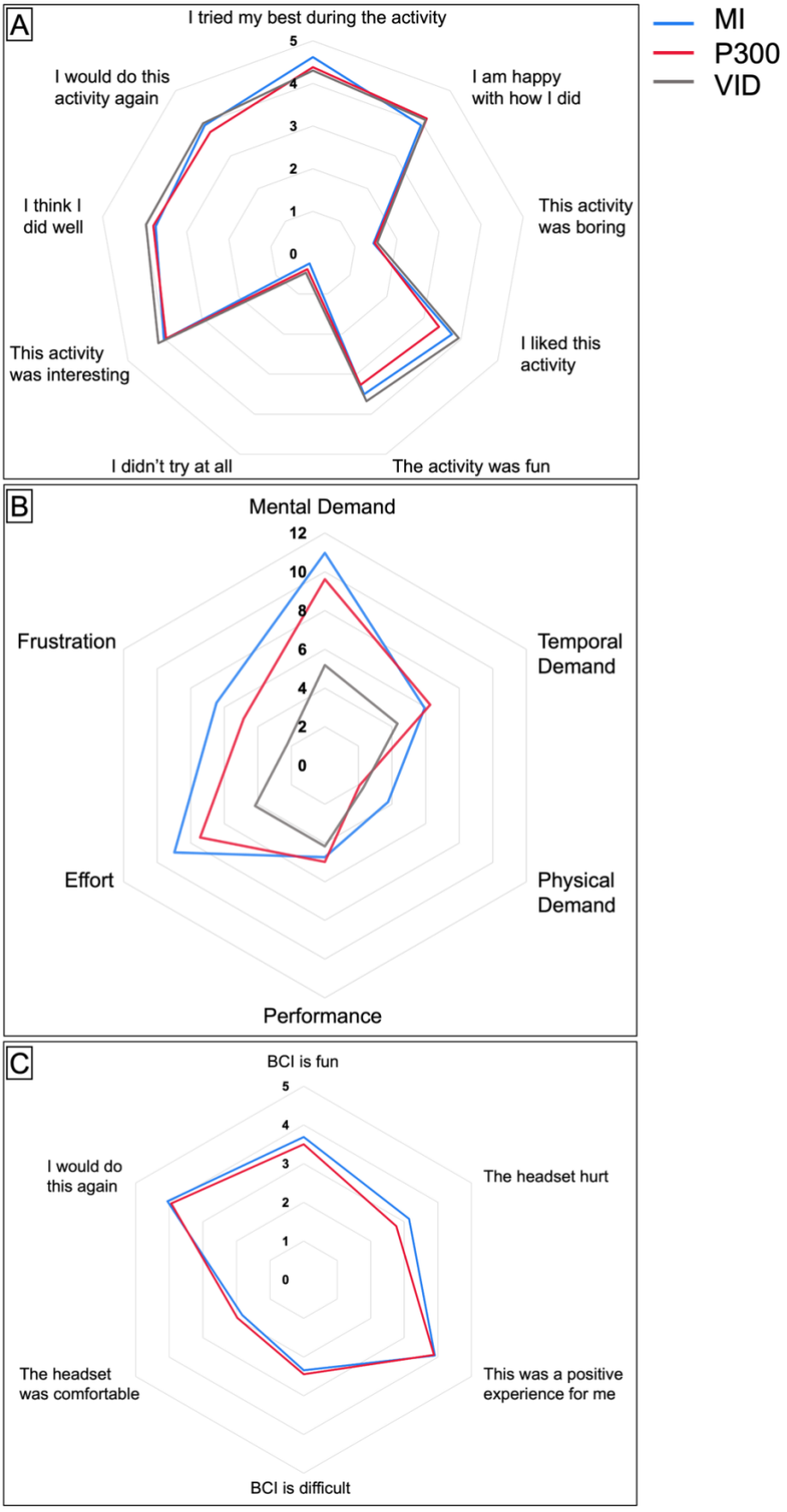
A
I tried my best during the activity
I am happy with how I did
This activity was boring
I liked this activity
The activity was fun
I didn't try at all
This activity was interesting
I think I did well
I would do this activity again
0
1
2
3
4
5
B
Mental Demand
Temporal Demand
Physical Demand
Performance
Effort
Frustration
0
2
4
6
8
10
12
C
BCI is fun
The headset hurt
This was a positive experience for me
BCI is difficult
The headset was comfortable
I would do this again
0
1
2
3
4
5
MI
P300
VID

Figure 2.6. Self-Reported Post-Task Questionnaire Metrics. A*. Pediatric Motivation Scale from not true at all (0 pts) to definitely true (5 pts) B. Child Adapted NASA Task-Load Index from low demand (0 pts) to high demand (20 pts). C. BCI Tolerability Scale from not true at all (0 pts) to definitely true (5 pts). BCI: Brain-computer interface; MI: motor imagery; VID: video.*

Table 2.4. Average questionnaire scores

Questionnaire	Mean	Median	Range	95% Confidence Interval
Motivation Scale (possible range = 0 – 50)				
MI	29.3	29.5	13	28.4 – 30.3
P300	28.4	29.0	20	27.4 – 29.4
Video	30.3	31.0	13	29.2 – 31.3
NASA – Task Load Index (possible range = 0 – 120)				
MI	41.4	43	71	36.4 – 46.4
P300	35.8	31	59	31.6 – 40.0
Video	22.2	20	57	18.6 – 25.8
BCI Tolerability Scale (possible range = 0 – 30)				
MI	19.2	20	11	18.4 – 19.9
P300	18.4	19	14	17.7 – 19.2

Legend: *MI: motor imagery*

Repeated measures correlation analysis revealed a negative correlation between change VASF and motivation ($r = -0.28$, $p = 0.022$). The VASF change was also positively correlated with the self-reported mental demand ($r = 0.28$, $p = 0.027$) but not temporal demand or physical demand.

Change in VASF was correlated with effort (r = 0.25, p = 0.044). Mental demand, temporal demand, and physical demand correlated with frustration (r = 0.45, $p < 0.001$; r = 0.28, p = 0.023; r = 0.35, p = 0.005 respectively). Motivation negatively correlated with frustration (r = -0.33, p = 0.01). Measured game performance was negatively correlated with self-reported performance evaluation (r = -0.47, p = 0.006). There was no correlation between change in self-reported fatigue and change in alpha band power (r = 0.04, p = 0.767).

2.5 Discussion

The aim of this research was to better understand the effect of different BCI paradigms on self-reported fatigue and EEG biomarkers in children. In all conditions, there was an increase in self-reported fatigue post-task compared to pre-task. The difference was small, roughly a 1.5 pt difference on a 10 pt scale. There was also a small increase in alpha band power in all conditions. Contrary to our hypothesis, it was not clear whether the increase in self-reported fatigue or RS EEG alpha band power related to BCI tasks was greater as compared to watching a video or if changes differed between P300 and MI tasks. There was also no correlation between the change in self-reported fatigue and alpha band power as described in adults. We demonstrated that short periods of both MI and P300 BCI operation increase self-reported fatigue in children, but our results do not support the use of EEG generic alpha band power as a sensitive biomarker for fatigue.

The increase in VASF during the P300 session was greater than the increase during the video session. There were also significant increases in VASF from pre- to post-task in the MI and P300 sessions but not the video session (Figure 2.3). It is possible that failure to clearly detect an effect

for our main research question is due to this study being underpowered for this modest effect size. Prior adult BCI studies looking at self-reported fatigue during BCI use have found increases of above 3 pts on a 10 pt scale [12, 144], and between 1-3 pt on a 20 pt scale [140]. The standard error of measurement of the VASF scale for our data was 1.1 pts. Calculated with this error, the minimum detectable change is predicted at 3.2 pts on the 10 pt scale, much larger than what we observed. Our hypothesis regarding self-reported fatigue for this study was built off unpublished work in our lab (Kelly et al. in progress). This work demonstrated variable fatigue with multiple BCI paradigms and MI-BCI was more fatiguing than P300-BCI with a roughly 1.5 pt VASF increase. In contrast we found that P300-BCI sessions had the greatest increase in VASF, P300-BCI was not associated with any increase in VASF in this unpublished work (Kelly et al. in progress).

This previous pediatric BCI study was a different experimental set up than the present study, and any number of differences may have impacted user experience and fatigue. P300 and MI tasks were completed on the same day in a randomized order and tasks were 8-20 minutes in length. The training, the task, and the BCI hardware/software were also not consistent between studies. In the prior study, the age of participants was slightly higher with a mean age of 11.3. The primary research question was about BCI control in children, with self-reported fatigue as a secondary outcome. Even though the task length was longer in the current study, results from self-reported fatigue indicate P300 was fatiguing even at 10 and 15 minutes. Similar numbers of participants had reported an increase by one or more points on the VASF in the P300-task and the MI-task by these time points (10 minutes: 8 participants in P300, 6 in MI; 15 minutes: 13 in P300, 12 in MI). Particularly in the P300 session, however, younger participants had a VASF increase of over two

points while older participants did not even have a one-point increase at this time. The slightly older participants in the prior study may have impacted the difference in P300 observed in these studies. The VASF score change observed across time in all sessions was greater for the younger children in this study. The older children and adolescents were better able to handle 30-mintues of a BCI task without significant fatigue and generally did not find the video session fatiguing (supplemental Figure 2.7). It is also likely that having the tasks in the same study session had a different impact on self-reported fatigue than having the tasks on separate days. Additional pediatric BCI fatigue studies considering these many variables are required.

Day-to-day chronic fatigue was assessed using the PedsQL^{TM}-MFS before each session in the present study. As expected, children with lower MFS scores (i.e., higher fatigue) reported higher VASF values pre- and post-task. The impact of more chronic and pathological fatigue will be an important consideration for understanding BCI fatigue in children with CP, who typically have higher chronic fatigue [105]. Further pediatric work is needed to draw conclusions on the impact of more significant fatigue at baseline and its impact on BCI performance and behavioural changes. We suggest that simple, validated measures like the PedsQL^{TM}-MFS, for which CP-specific versions are also available, be employed prospectively in BCI studies in such clinical populations to better characterize the role of fatigue in performance and other outcomes.

To our knowledge, this was the first trial to investigate EEG biomarkers of fatigue in children during BCI use. While adult studies show promise in tracking these biomarkers and associating them with self-reported fatigue, more work may be needed in children to refine these measures. During analysis some electrodes were excluded due to signal artifacts or noise. This was either

from sub-optimal connection at known specified electrode sites or from participants touching an electrode or moving the headset forehead strap. Identification of individualized alpha bands was unsuccessful with existing python algorithms for use with eyes-open RS. Pipelines were applied but resulted in non-physiological interparticipant and intraparticipant variability. Comparison of alpha band power results from the present work to past literature was also difficult due to variable units, use of undefined units, lack of values given, and use of both relative and absolute metrics. From our data, the standard error of measurement of this band power was 4.8 $\mu V^2/Hz$. Calculated with this error, the minimum detectable change is predicted at 13.3 $\mu V^2/Hz$. A change near this magnitude was not detected. Change in alpha band power magnitude in many prior adult studies is significantly larger and often correlates with self-reported fatigue [5, 12, 140]. Prior EEG studies have found that changes in EEG are not apparent until an individual is highly fatigued [164] and perhaps our interventions were not long or hard enough or lacked appropriate difficulty to reach such a threshold. Age-dependent developmental differences in EEG neurophysiology may also have affected our ability to detect fatigue-related changes.

Despite a broad acceptance of EEG band metrics as fatigue biomarkers, there is still inconsistency in the literature. Particularly in research looking at driver fatigue, several studies have found no change in alpha band power or even a decrease in alpha band power [165]. As an alternative metric, EEG entropy has been calculated as a biomarker for fatigue including during sustained attention cognitive tasks [166, 167] and high stress cognitive tasks [168]. In a driving simulator study, changes in sample entropy were more consistent during fatigued states than band metrics [169]. Peng and Colleagues also found that a multiscale entropy metric better distinguish fatigue states than the classic bands during a steady-state visually evoked potential BCI task [165]. Entropy may

therefore be a useful measure in children to help avoid difficult individual frequency band calculations or use of generalized bands which may be less accurate [134, 135, 137, 138]. Evaluation and comparison of pre- and post-task RS is complex as post-task RS brain activity can be modulated by other elements of the prior task outside of just fatigue [170]. A combination of band metrics, from the frequency domain, and entropy, from the time or the time-frequency domain [171], may be more useful for a deeper understanding of these complexities [170]. Such dual metric analysis should be investigated in children using BCIs.

Performance varied in both the P300 game and the MI game from 100% or nearly 100% to essentially no control at all considering chance accuracies for each paradigm (<11% in P300; <50% in MI). Interestingly, those who performed better tended to report feeling that they did worse than those who performed poorly although this was purely correlational. Performance did not decline across the BCI sessions. The larger their change in fatigue, the lower participants rated their session enjoyment. Correlational analysis also revealed that children who felt the tasks were more mentally, physically, and temporally demanding also reported being more frustrated. A link between frustration and workload was also noted in end users with motor impairments during BCI gaming [172]. This study had a small sample of four individuals, but interestingly, this association existed for those who had less severe motor impairment [172]. Due to potential EEG changes with frustration, it has been suggested that EEG signal, BCI classification, and performance may be impacted [173]. However, a previous study looking at the performance-frustration relationship did not report significant influences of frustration on performance [174]. Anecdotal reports from an additional study with Amyotrophic Lateral Sclerosis patients also noted that frustration did not seem to impact motivation [175], but we found a negative correlation between frustration and

motivation. Psychological factors such as frustration and motivation are clearly influenced by age and development and need to be considered carefully in pediatric populations.

Limitations

Our calculated but modest sample size is a potential limitation for this work. The present study was not adequately powered to draw conclusions about differences between sessions since changes in both primary outcomes were minimal. The broad age range (7-16), with inconsistent samples at each age, also presented additional challenges to age-based analysis that was overcome by splitting the sample into just an upper and a lower half by date of birth. Additional limitations include low headset tolerability that reduced the number of our participants completing the full study protocol. Time on task is accepted as a key predictor of fatigue for physical and cognitive tasks [176–179], and this inconsistency introduced more variability into the study. There is a relationship with fatigue and pain or discomfort and while self-reported pain and comfort ratings for the headset were controlled in the statistical models, discomfort is another potentially confounding variable.

Future studies should continue to evolve our understanding of BCI fatigue in children using larger samples, and/or smaller age ranges to overcome challenges of a highly variable population. Studies should also investigate longer durations of BCI use with a system that will be more broadly tolerated by children. It will be important to consider BCI experience and performance as not all children have good BCI control in one session with no prior training. An initial training session may be beneficial to ensure only those with adequate BCI control go forward and are involved with research questions surrounding fatigue. For those with lower BCI performance, future studies will also be needed to investigate predictors of performance as well as strategies to promote BCI

learning. Finally, and most importantly, studies on typically developing children should guide the development of similar studies in children with CP, the intended end users of this technology.

2.6 Conclusion

We found that 30 minutes of BCI task increased self-reported fatigue and the power of the EEG alpha band. There was no correlation between the change in self-reported fatigue and the change alpha band power. Differences in fatigue development across sessions were not clear with our sample. Large variations in children's experiences with BCI systems including tolerability, motivation, perceived workload, ability to control the applications, and feelings of fatigue were apparent in this study. Future studies are needed to look at longer time-on-task, additional EEG fatigue biomarkers in children, and importantly, to ask similar questions in clinical populations who may use BCI as an access technology.

2.7 Supplemental Material

Table 2.5. Secondary linear mixed models for self-reported fatigue and alpha band power

Model	AIC	Effect(s)
Fatigue Visual Analog Scale		
Additional Factors: Sex and Age	760	Session ($F_{(2,140)} = 3.4$, $p = 0.035$) Session-Age ($F_{(2,140)} = 3.2$, $p = 0.44$) Time-Age ($F_{(1,140)} = 4.5$, $p = 0.036$)
Additional Factors: Sex, Age, MFS	755	MFS ($F_{(1,129.2)} = 6.6$, $p = 0.012$)
Alpha Band Power		
Additional Factors: Motivation Covariates: Time of Day	1276	Session-Motivation ($F_{(2,132)} = 3.37$, $p = 0.037$)

Legend: *The primary model for both the fatigue visual analog scale and alpha band power included session and time as factors, participant as the cluster variable, and participant intercepts as the random factor. AIC; Akaike information criterion, MFS; PedsQL™ Multidimensional Fatigue Scale.*

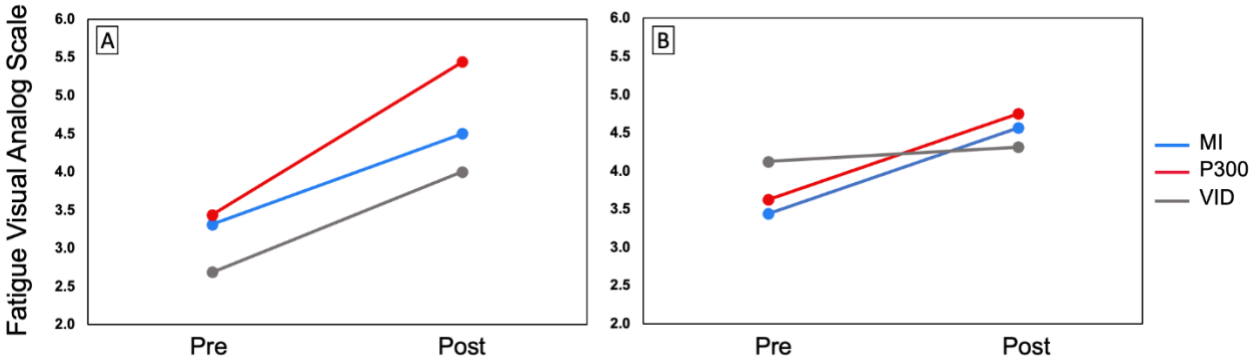

Figure 2.7. Visual Analog Scale Values for Self-Reported Fatigue Pre- and Post-Task. *A. the younger half of participants, and B. the older half of participants. MI: motor imagery; VID: video.*

2.8 Declarations

Abbreviations

BCI: Brain-computer interface; CP: Cerebral palsy; EEG: Electroencephalography; iPSD: Integrated power spectral density; MFS: multidimensional fatigue scale; MI: Motor imagery; RS: Resting-state; TLX: Task-load index; VASF Visual analog scale for fatigue

Ethics approval and consent to participate

Ethics approval for this study was granted by the University of Calgary Conjoint Health Research Ethics Board (CHREB). Ethics ID: REB22 – 0044.

Consent for publication

Not applicable

Availability of data and materials

The dataset supporting the conclusion of the article is available from the corresponding author on reasonable request.

Competing interests

Authors DK, EKL, and AK are co-founders of Possibility Neurotechnologies, a start-up company developing personalized BCI solutions for children with disabilities. None received any compensation for the work submitted, and the company played no role in the study design, execution, or interpretation of results. The authors declare no other competing interest.

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Authors' contributions

JK: conceptualization of research question and study protocol, participant recruitment and data collection, data analysis, figure development, and manuscript writing. BI: created the software for the BCI applications backend in python, wrote the electroencephalography analysis code, and assisted in writing the manuscript methods. DK: helped develop the study methods including protocol, pre- and post-task questionnaires, and P300 and MI BCI training applications. JW: assisted with conceptualization of research question and study protocol and provided guidance for the statistical analysis. DCM: assisted with generating the manuscript figures. EKL: conceptualization of research question, study design, and protocol. Designed the BCI applications for this study within Unity, project troubleshooting, provided guidance during participant data

collection, data analysis, and writing. AK: conceptualization of research question and study protocol, project troubleshooting, guided analysis, and writing. All authors read, edited, and approved the final manuscript.

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3 Chapter 3 – Conclusion & Discussion

We investigated the impact of two BCI paradigms on self-reported fatigue and an EEG biomarker of fatigue in typically developing children. To our knowledge, this was one of the first trials that analysed fatigue development during BCI use in children, one of few pediatric BCI studies more generally, and the only trial to have a control session comparison. Using linear mixed model analysis, we demonstrate an increase in self-reported fatigue and EEG α band power during both BCI sessions and the film viewing session. There was no correlation between self-reported fatigue change and EEG α band power change. While small effects cannot be excluded due to our study power, we did not find a significant difference in fatigue between MI and P300 sessions. Workload, motivation, and tolerability were similar between BCI sessions, and workload was higher in BCI sessions compared to control.

3.1 Summary of Main Findings

Self-reported fatigue increases were generally small and uncorrelated to α band power changes. There were significant increases in fatigue from pre- to post-task in the BCI sessions but no significant increases in fatigue from pre- to post-task in the control (see Figure 2.3). But, contrary to our hypothesis, this did not amount to an interaction between of time and session in our primary analysis model. Interestingly what we demonstrated is not what was previously observed by Kelly and colleagues (in progress) who found P300 to be less fatiguing than MI. In our correlational analysis, change in fatigue was correlated to mental, but not temporal or physical demand. Change in fatigue was also negatively correlated to session enjoyment (based on the motivation scale). EEG α band power also increased across each session, but changes were small and likely not of clinical significance, or useful in detecting this level of fatigue in children. Again, contrary to our

hypothesis this did not amount to a interaction effect of time and session in our primary analysis model. Additional band metrics and entropy analysis should be explored during BCI use in children.

BCI performance was variable as expected, but there was no change in performance across the BCI sessions and performance was not associated with measures of fatigue. This suggests that fatigue may not be a major determinant of performance in these paradigms during short 30-minutes sessions. Research with longer sessions or more difficult sessions is required to find the limits of BCI performance maintenance as an individual fatigues. It will be important to address these questions in larger groups of adequate to high performers as the number of participants that reached adequate BCI control in this study was limited impacting sample size. Ongoing projects outlined below in section 3.3 will also be valuable to shed light on any measurable changes in the P300 signal or the SMR signal that we observe across the 30-mintue BCI tasks. While we know EEG signal changes did not reach a point where they were having a negative impact on performance, the trajectory of any signal changes observed may provide additional insights on the ability of the classification algorithms to continue to classify brain activity accurately. Unlike the RS α band metric, these task-state metrics may have an association with self-reported fatigue. Addressing these questions will help to determine whether fatigue is an important factor in performance decline or whether other behavioural metrics might be better predictors of performance decline in children.

Our statistical analysis that included sex in the linear mixed models for primary outcomes did not reveal any key sex differences. For self-reported fatigue, inclusion of sex did improve the model,

but the same was not true for α band power. Performance also appeared comparable between males and females, with females performing slightly better in the game on average (58% vs 53%). The lowest performer was a male and highest performer was a female. Larger samples of children may be needed to further investigate any more subtle differences between males and females. There was an effect of age on self-reported fatigue but not α band power. Younger children found the sessions more fatiguing and drove the change in fatigue across the video session whereas older participants as a group were not fatigued by that session. Using smaller age ranges in future studies will be useful in understanding unique experiences of fatigue in younger children versus adolescents. As demonstrated here, the large variability in children's BCI experience may be made even more extreme by including such broad age ranges over a time period where there is substantial and rapid developmental change.

3.2 Limitations

Limitations of this study and consideration for future research include baseline variations in outcome metrics, children's tolerability of BCI equipment, and the length of sessions. Baseline VASF differences varied greatly ranging from 0pts to 8pts pre-task. This large range complicated analysis of fatigue changes. Fatigue fluctuated between individuals but also for the same individual on a daily, weekly, and more long-term scale. For a study with multiple sessions, holding sessions at consistent times of day when individuals are most likely to feel low to moderate fatigue at the beginning of a session, may help reduce this variability, but it is likely to still remain high. Baseline EEG α band power varied for individuals across sessions with up to 23.5 $\mu V^2/Hz$ difference, once again complicating analysis. Brain activity is a dynamic measure dependent on numerous personal

and environmental factors, that even with protocols in place to hold sessions at similar times of day it is unlikely to significantly reduce this variation. Instead to overcome these challenges, larger sample sizes may be need.

Children are expected to be less tolerable of long research sessions. Many adult studies have participants performing BCI tasks for periods of over an hour and up to five hours. It is hard to imagine being able to run a similar protocol in typically developing children or children with CP however, these upper limits remain undetermined. A barrier in this study to completing just a 30-minute task was the headset discomfort commonly experienced by participants. Future studies should ensure adequate system testing across all study ages and sexes prior to commencing research.

3.3 Ongoing & Future Projects

Extensions of the data obtained here are planned. For example, during data collection for this project, participants completed the Box & Blocks task at the beginning and the end of each session. This was video recorded from a camera set directly in front of the participant. With the use of video footage, we indented to dissect the question: does using a MI BCI fatigue the motor system or cause physical fatigue that is detectable in EEG recordings and physical movement observations during the Box & Blocks task? The number of blocks participants moved was recorded. Video recordings will be analysed using MediaPipe, an open-source software that can be used for motion tracking or pose estimation that has recently been validated for hand tracking in our lab against gold standard 3D motion capture. Unlike 3D motion capture, which requires markers, MediaPipe

is markerless. A 2023 summer student in our lab, Grace Attalla, will be working on analyzing the Box & Blocks videos using custom python scripts and MediaPipe to understand any physical movement changes and further uncover fatigue mechanisms. To complement this project, future work will also look at the EEG data recorded during the box and blocks task to assess any brain activity changes from pre- to post-task. For example, ERD/ERS magnitudes and /or localization during the task.

This research generated a large amount of pediatric BCI data including 5-mintues of P300 and MI standard training data followed by ~25 minutes of repetitive P300 or MI BCI game application. This data is going to be used in a transfer learning project lead by a Biomedical Engineering PhD student Brian Irvine. Transfer learning involves the use of training data from other participants or from past BCI sessions to help train a new system on any given day [180]. Transfer learning may be able to reduce BCI training or calibration time which can be quite time consuming and repetitive [180].

An additional future project will include quantifying changes within the EEG data throughout the training and game period as what was presented here is only from RS periods. The P300 amplitude, and the ERS/ERD will be quantified throughout the BCI protocols. During data collection additional electrocorticography bipolar electrodes were plugged into the headset and synchronized to the EEG markers. These sensors were placed around participants wrists to measure heart rate throughout the sessions. This electrical activity will be analysed alongside task EEG. Heart rate may provide additional insight into fatigue, as metrics such as heart rate variability have be previously associated with changes in attention and effort [132, 181]. These projects will help to

better understand the mechanism of fatigue across BCI paradigms and may provide valuable task-state EEG markers of fatigue in children. Finally, using LASSO regression, there will be a data driven exploration of the EEG, including other frequency bands and entropy, to determine the variables that may be best predictors or fatigue development in pediatrics.

There are several additional questions future research should address for consideration of how to optimize pediatric BCIs. EEG analysis studies should address the usefulness of this measure in children with QCP. How is baseline EEG activity different in children with QCP? Does the nature of the brain injury or malformation change the EEG patterns? What are the major similarities and differences in EEG from typically developing kids and those with CP? Are there sex differences? How can we use this information to monitor fatigue and mental state more broadly in children with QCP? Studies with larger sample sizes should utilize different experimental conditions (changing workload, game appeal, or task achievability) to better isolate the relationships between effort, enjoyment, performance and fatigue, and other critical elements in understanding fatigue and BCI optimization more broadly. The study conducted here should be modified and repeated in children with QCP. While many elements can remain the same, effort will have to go into adjusting for non-verbal communication.

3.4 Translational Significance

The aim of this study was to develop our understanding of BCI fatigue in children. Given the small changes in fatigue overall and between MI and P300 sessions comparatively, it is likely that for short BCI sessions, neither paradigm is inherently more fatiguing to a clinically relevant level. Both remain options for children that may struggle with fatigue and can be good options for at

home and in community use if tolerated and enjoyed by the user. Fatigue increase was also not shown to negatively impact performance, but it did correlate with decreased enjoyment which is important to consider for BCI adoption and continued use, particularly in children. Strategies for mitigating fatigue may help sustain motivation and ultimate utility. The changes in α band power we observed were small and did not correlate to the user's experience of fatigue. More research is needed, in RS and in task-state, before EEG biomarkers can be used to detect fatigue or design adaptive BCIs.

Data generated by this project can be used to answer further questions surrounding underlying fatigue mechanisms and the usefulness of EEG biomarkers of fatigue in children. Outside of this data set, future studies should utilize larger samples sizes or combined data sets to better understand BCI fatigue in children. If tolerated by children, sessions should be more extensive to consistently induce moderate to higher levels of fatigue. Finally, to compare to the baseline understanding of fatigue in children developed here, a similar study should be conducted to establish a baseline understanding of fatigue in children with CP. Inclusion of children with QCP, who likely stand to benefit the most from assistive BCIs in the future, should be prioritized.

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