THE EFFECTS OF CONCUSSION ON THE DETERMINANTS OF GAIT VELOCITY IN COMMUNITY-DWELLING MEN AND WOMEN

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Abstract

Concussions affect the complex act of walking. While factors like sex influence the effects of concussion, cognitive and motor challenges performed during gait evoke further deficits. The purpose of this thesis is to characterize factors that may affect gait velocity in people with concussion. Chapter 1 addresses the current literature on gait and concussion as they relate to sex, identifies gaps in the literature, and consolidates this information as a conceptual model. Chapters 2 and 3 focus on the studies that were conducted in this thesis. The findings of Chapter 2 highlight the different strategies that men and women use to achieve gait velocity, as well as sex-dependent differences in Step Length Variability. In Chapter 3, a lack of consistency is reported in the factors that predict concussion-induced alterations in gait over time. Finally, Chapter 4 discusses the overall findings of this thesis and presents an updated conceptual model.

Dedication

This work is dedicated to the Mahdi, one for whom education and advancements in science will be tools to establish truth and justice. And to those companions of the Mahdi who have lost their lives in pursuit of scientific advancement for the sake of this very truth.

Acknowledgements

I would like to begin by thanking God, to whom is all praise, for granting me the opportunity and capability to pursue to this degree. It is due to His mercy and blessings that I have managed to complete this thesis. I would then like to thank my supervisor, Dr. George Mochizuki for his invaluable advice and mentorship during the course of my Master of Science degree. His high level of experience and immense knowledge have truly contributed to my progress over the last two years. I would also like to offer my thanks to Dr. William Gage for his guidance and feedback during my degree. My sincere thanks to the research team at the Hull-Ellis Concussion and Research Clinic for their contributions and assistance in this research. Thank you to my lab mate Hajr Hameed, and all my colleagues in the Biomechanics lab at York University for their friendship and support. Finally, I am deeply grateful to my parents and my brother. I would not have been able to complete this thesis without their continuous encouragement and belief in me.

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Chapter 1: Introduction

The act of walking is often taken for granted. The daily use of the function of gait leads people to overlook its complexity. Yet, when injuries such as concussion severely affect people's ability to move around, it can be debilitating. The impact that concussion has on gait can be influenced by other factors like biological sex. Gait performed under cognitive or motor challenges may further be impaired in people with concussion. Impaired gait may also take time to recover. Therefore, research in this area is essential. Chapter 1 of this thesis present a literature review on gait and concussion, and their relationship to sex. A conceptual model is also presented to clarify the known knowledge in the literature and identify the gaps that this thesis aims to fill. Thereafter, Chapters 2 and 3 will focus on the studies that were conducted to achieve the purpose of this study. Lastly, Chapter 4 provides an overall discussion of the findings of this thesis and consolidates them in the form of an updated conceptual model.

Literature review

Gait is multifaceted function that comprises of many neural processes and features. The features of gait have been identified as markers of concussion injury and community ambulation. The pathophysiology of concussion is also well studied. Sex differences have been observed in both gait and concussion. This section aims to review the literature on gait and concussion as they relate to sex.

Gait

Gait refers to one's walking behaviour, which for many is an important part of everyday life. The ability to move around has many functional benefits that allow one to perform daily activities, play sports, and interact with the environment. Gait is a complex function that involves multiple brain areas

and neural mechanisms. A study looking at regional cerebral blood flow immediately after walking for 4 minutes found significant activity in the primary sensorimotor area, supplementary motor area, cerebellar vermis, visual cortex, and a part of the left medial temporal lobe (Fukuyama et al., 1997). This suggests neural activity in these brain areas during gait. An older study looking at locomotion in cats observed cortical cell activation during gait modification, suggesting the use of higher level control to fine-tune gait (Drew, 1988). These studies highlight the need for higher level control in gait. Research looking at dual gait tasks also points to the importance of attention capabilities during gait. A study analysing gait variables in young healthy adults found a decrease in stride velocity, and an increase in stride time and stride time variability when participants simultaneously counted backwards from 50 (Beauchet, Dubost, Herrmann, & Kressig, 2005). Similarly, increased stride length and stride time variability was observed in physically fit older adults who performed backwards counting and verbal fluency tasks during gait (van Iersel, Ribbers, Munneke, Borm, & Rikkert, 2007). Therefore, attention capabilities can influence gait in younger and older adults, even if they are physically fit. Executive function too is associated with gait. Holtzer and colleagues (2006) correlated cognitive battery test results of older adults with their gait velocity. Results showed that executive attention, memory, and verbal IQ were related to gait velocity in single task gait, and executive attention and memory were significant predictors of gait velocity in dual task gait as well (Holtzer, Verghese, Xue, & Lipton, 2006). An earlier study by Yogev and colleagues (2005) found similar results in gait variability in healthy older adults and Parkinson's disease patients. While they observed a weak correlation between executive function and gait variability in regular gait, this correlation strengthened in dual gait tasks, suggesting an increasing reliance on executive functioning in more challenging gait tasks (Yogev et al., 2005). From these studies, it is clear that gait is not a simple function and requires a series of neural processes to be in place for it to be effective.

Features of gait

Gait has many features, many of which can be used as indicators of the impact of disease or injury. Of the features of gait, those associated with gait velocity are particularly important because gait velocity has been identified as being efficient in predicting ambulation classification in neurological disorders such as stroke and Parkinson's disease (Elbers, van Wegen, Verhoef, & Kwakkel, 2013; Perry, Garrett, Gronley, & Mulroy, 1995). Research also shows that gait velocity is an overall indicator of health. A longitudinal study involving 3156 older adults, who were free from stroke, physical disability, and cognitive impairment showed that gait velocity was inversely associated with mortality risk and incident disability (Rosano, Newman, Katz, Hirsch, & Kuller, 2008). Similarly, a pooled analysis of 9 cohort studies from 1986 to 2000 showed that older adults with baseline data who were followed up from 6 to 21 years had an increased chance of survival with a 0.1m/s increment increase in gait velocity (Studenski, 2011). Given these established relationships between disability, mortality, and gait velocity, it is clear that gait velocity is an important indicator of overall health and community ambulation.

Gait velocity is defined to be a function of step length and cadence, where step length is the distance between the lateral malleoli of each foot when both feet are on the ground, and cadence is the number of steps taken per unit time. Both these variables differ amongst sexes (Callisaya, Blizzard, Schmidt, McGinley, & Srikanth, 2008; Frimenko, Goodyear, & Bruening, 2015; Oberg, Karsznia, & Oberg, 1993). Hence, step length and cadence are determinants of gait velocity. Men and women use different strategies to achieve gait velocity in non-pathological gait. Studies have shown that men tend to exhibit longer step lengths compared to women, while women tend to exhibit a higher cadence than men (Callisaya et al., 2008; Oberg et al., 1993). These results are in accordance with a meta-analysis that examines sex and aging in non-pathological gait (Frimenko et al., 2015). The results in this meta-analysis also showed that men walk at faster preferred speeds than women before data was normalized to body height (Frimenko et al., 2015). However, after data normalization, there appeared to be no differences

in preferred walking speed amongst men and women (Frimenko et al., 2015). These findings show that not only do men and women use different strategies for gait velocity, but the increase in cadence seen in women compensates for the shorter step length, while the larger step length observed in men compensates for the lower cadence.

Another important feature of gait is variability, or the fluctuations of gait measures between strides (Yu, Riskowski, Brower, & Sarkodie-Gyan, 2009). Gait variability has been identified as a predictor of fall risk in older adults as it is a marker of instability. A study analysing stride-to-stride variability in 75 older adults found that, variability in velocity, stride length, and double support was significantly associated with future falls, irrespective of the fear of falling (Maki, 1997). Similar results were observed for stride time where the likelihood of falling was increased five-fold when a moderate increase in variability was observed in older adults (Hausdorff, Rios, & Edelberg, 2001). Stride time variability was also associated with functional status and mental health (Hausdorff et al., 2001). In terms of step width, too much or too little variability has been associated with history of falls in individuals walking at a normal speed, where high variability has been attributed to instability (Brach, Berlin, VanSwearingen, Newman, & Studenski, 2005). Overall, as a marker of unsteady gait (Hausdorff, 2005; Heiderscheit, 2000) and fall risk (Hausdorff, 2005), high gait variability can be problematic. Although some studies do suggest that certain aspects of gait variability may be necessary for movement coordination and transition and do not necessarily always lead to instability (Beauchet, Allali, Berrut, & Dubost, 2007; Beauchet et al., 2009; Heiderscheit, 2000; van Emmerik & van Wegen, 2000). Nonetheless, gait variability is an important indicator of gait control and should be understood.

Of the various measures that contribute to gait variability, step length variability is of particular interest. Stride length variability is found to double the likelihood of future falls when increased by 3% (Maki, 1997). Additionally, step length variability has been related to metabolic cost of transport. Rock and colleagues (2018) assessed the effects of step-to-step variability on metabolic cost of transport in

healthy young adults. Results showed that step length variation may be positively correlated with metabolic cost of transport (Rock, Marmelat, Yentes, Siu, & Takahashi, 2018). Specifically, a 1% increase in step length variation would result in a 5.9% increase in metabolic cost of transport (Rock et al., 2018). These observations are in line with those of an earlier study that also found energy cost to be linearly dependent on step length and width variability in young adults (O'Connor, Xu, & Kuo, 2012). These results show that the impacts of step length variability are not limited to gait instability and fall risk in older adults, but extend to metabolic impacts in younger adults as well. Therefore, the effects of step length variability on adults in general are clear and are worth further investigation.

The body of literature focusing on the study of gait is extensive. It is clear from the research that gait is a multifaceted function, involves higher level control, and can be indicative of injury and behaviour. Gait velocity is an indicator of overall health and gait variability is a predictor of fall risk. Considering the effects that alterations in features of gait can have on overall quality of life, it is important for them to be well-studied and understood. Better understanding of changes in gait following concussion is especially important because it can be informative of the effect that the injury has.

Concussion

Research shows that determinants of gait velocity are influenced by concussion. A study examining gait recovery following concussion found that gait velocity and stride length were reduced in concussion patients during the first two days after injury during dual gait tasks (Parker, Osternig, Van Donkelaar, & Chou, 2006). Similarly, shorter stride lengths in both single and cognitive dual gait tasks have been observed in adolescents within 21 days of having a concussion (Berkner, Meehan, Master, & Howell, 2017). These same adolescents also displayed decreased gait velocity, cadence, and stride length in the dual gait task after symptom resolution (Berkner et al., 2017). Given that the impacts of concussion on

gait velocity and its determinants are observed in both the acute and chronic phases of injury, it would be of value to better understand the relationship between these variables.

Traumatic brain injuries (TBI) are a common form of injury among Canadians. There are 18,000 hospitalizations for TBI in Canada each year, and 2% of Canadians live with the effects of TBI (Brown et al., 2020). Concussion in particular is a mild TBI (mTBI) that results from biomechanical forces, possibly resulting in neuropathological changes and clinical symptoms (Ontario Neurotrauma Foundation, 2013) Symptoms of concussion include memory deficits, difficulty concentrating, sleep disturbances, drowsiness, light and noise sensitivity, and balance problems (Frommer et al., 2011). Lexically, the word 'concussion' comes from the Latin word *concussio*, which means 'to strike together' (Romeu-Mejia, Giza, & Goldman, 2019). However, functionally there is no one clear definition for concussion. According to the 2016 Berlin consensus, sport-related concussions are defined as a form of traumatic brain injury that result from biomechanical forces (McCrory et al., 2017). While a functional definition of concussion may not be clear, the physiological events that occur following a concussive blow, have been explained. Additionally, other variables have been studied in relation to concussion as well. This section discusses the ionic, metabolic, and axonal changes that result from concussions, as well as other correlates of concussion.

Ionic and metabolic changes

One of the immediate responses to a biomechanical brain injury is the release of neurotransmitters, and an influx and efflux of various ions across the cell membrane (Giza & Hovda, 2001). The shearing and stretching forces from the concussive blow causes mechanoporation – a disruption of cell membranes (MacFarlane & Glenn, 2015) – allowing for an efflux of intracellular potassium ions (Giza & Hovda, 2001, 2014; MacFarlane & Glenn, 2015), and an influx of sodium and calcium ions (Giza & Hovda, 2014). The potassium efflux is increased by the release of glutamate (Giza & Hovda, 2001). While glial

cells take up extra potassium under normal circumstances (Ballanyi, Grafe, & ten Bruggencate, 1987), they have been found to lose their potassium conductance following TBI (D'Ambrosio, Maris, Grady, Winn, & Janigro, 1999). This reduces the potassium uptake by glial cells, increasing the potassium concentration in the extracellular space. Additionally, the potassium in the extracellular space triggers a depolarization of the neuron, causing an even greater potassium efflux (Giza & Hovda, 2001). In this way, a self-regenerating wave is propagated (Ayata & Lauritzen, 2015). A wave of neural depression follows this hyperexcitability (Giza & Hovda, 2001). This self-propagating wave of depolarization followed by a wave of inhibition is termed 'spreading depression' (Costa et al., 2013), as initially proposed by Leao (1944). Spreading depressions have been suggested to be the underlying mechanism for migraine aura (Ayata, 2010; Hadjikhani et al., 2001; Russel & Olesen, 1996), a symptom commonly associated with concussion (Tad, 2018).

Another regulator of extracellular potassium is the sodium-potassium pump (Ayata & Lauritzen, 2015; Ballanyi et al., 1987). The sodium-potassium pump works actively requiring ATP as an energy source (Ayata & Lauritzen, 2015; Giza & Hovda, 2001, 2014). With the potassium efflux and sodium influx, the energy demand of the sodium-potassium pump increases (Ayata & Lauritzen, 2015; Giza & Hovda, 2001, 2014). To meet this demand, the body needs to increase its energy metabolism and enter a state of hyperglycolysis (Ayata & Lauritzen, 2015; Giza & Hovda, 2001, 2014). However, cerebral blood flow is reduced in individuals who sustain traumatic brain injuries as well, which in a state of hyperglycolysis, exacerbates the energy demand problem (Giza & Hovda, 2001, 2014).

Changes in aerobic metabolism and mitochondria

Anaerobic systems of metabolism are not the only ones to by impacted by concussions. One important organelle that sustains damage from concussions is the mitochondria. This is important because mitochondrial damage can lead to cell death (James & Murphy, 2002), and has been identified

as a possible trigger for neurodegenerative diseases (Guo, Sun, Chen, & Zhang, 2013). Mitochondrial damage resulting from concussion involves both morphological and biochemical changes.

A study by Lifshitz and colleagues (2003) observed that mitochondria from the parietotemporal cortex in rats had a smaller radius 1-day post-injury, while hippocampal mitochondria were enlarged only 3 hours after injury. Additionally, mitochondria from both these brain regions displayed inconsistent sizes and shapes (Lifshitz et al., 2003). Some mitochondria had a balloon-like appearance, damaged cristae, and a thinner outer membrane (Lifshitz et al., 2003). The authors of this study suggest that mitochondria in the injured brain are on a continuum where they are either healthy, damaged, or eliminated all-together (Lifshitz et al., 2003). The fraction of cortical mitochondria that are either damaged or eliminated due to injury increases during the first 24-hours post-injury (Lifshitz et al., 2003).

Similar results have been observed more recently in humans as well. Balan and colleagues (2013) studied morphology and ultrastructure of mitochondria in people with TBI. Mitochondria of all participants in this study consistently displayed morphological changes, conformational changes related to energy metabolism, mitochondria build-up in axons and dendrites, presence of granules and precipitates in the mitochondria, and mitochondrial swelling (Balan et al., 2013). This study also concluded that TBI severity is correlated with changes in the ultrastructure of the mitochondria, where the morphology of mitochondria in mTBI may not become permanently damaged as quickly as in more severe TBI (Balan et al., 2013). The results of these studies show that TBI, and by extension concussion, does lead to morphological changes in the mitochondria. These changes will inevitably affect the mitochondria's ability to effectively carry out its function.

While morphological mitochondrial damages have been recorded, the biochemical changes in mitochondria post-concussion are also well established. One biochemical pathway that is severely impacted by concussions is the process of oxidative phosphorylation. Of all the ionic changes that occur in the cell post-injury, calcium influx lasts the longest (Giza & Hovda, 2001, 2014). The glutamate-

mediated calcium influx results from the activation of N-methyl-D-aspartate (NMDA) receptors upon injury (Barkhoudarian, Hovda, & Giza, 2011; Lifshitz, Sullivan, Hovda, Wieloch, & McIntosh, 2004). While calcium influx may result from multiple sources, glutamate-mediated calcium influx is more toxic to other sources of calcium influx (such as voltage-gated calcium channel activation) (Tymianski, Charlton, Carlen, & Tator, 1993). In attempt to maintain calcium homeostasis, the high intracellular calcium levels are buffered by the mitochondria (Barkhoudarian et al., 2011; Lifshitz et al., 2004; Lyons et al., 2018). However the calcium accumulation in the mitochondria is toxic for the cell and can cause impaired aerobic function (Giza & Hovda, 2001, 2014; Lifshitz et al., 2004).

The mitochondrial calcium uptake induced by NMDA receptors results in permeability of the outer membrane of the mitochondria (Luetjens et al., 2000). Consequently, cytochrome c – a protein in the electron transport chain that transfers electrons from complex III to complex IV – is released (Luetjens et al., 2000). The loss of cytochrome c leaves complexes I and II in a reduced state where the electrons are unable to move along the transport chain. This disruption in the oxidative phosphorylation process prevents the production of more ATP, adding to the energy crisis that already exists. Moreover, the inhibition of complexes III and IV due to the loss of cytochrome c has been reported to result in increased superoxide levels, a type of reactive oxygen species (ROS) (Luetjens et al., 2000). Although oxidative phosphorylation normally leads to the production of ROS, it is well established that ROS levels increase significantly after traumatic brain injuries (Giza & Hovda, 2014; E. D. Hall, Kupina, & Althaus, 1999; Lifshitz et al., 2004; Opii et al., 2007; Sullivan, Geiger, Mattson, & Scheff, 2000). The added superoxide levels resulting from cytochrome c release add to the effects that impaired cell redox states have on mitochondria.

The loss of cytochrome c is not the only proposed mechanism for increased ROS levels. A review studying oxidative stress in ischemic brain injury suggests multiple mechanisms of ROS generation at complex III of the electron transport chain (Starkov, Chinopoulos, & Fiskum, 2004). Since the

mechanisms of calcium influx in ischemic brain injury are very similar to that of concussion, these ideas may be applied to concussion injury as well. Suggestions of ROS being generated at complex I of the electron transport chain have been made as well (Selivanov et al., 2011; Starkov et al., 2004). Nonetheless, possible mitochondrial damages that result from increased ROS levels include mutations of DNA and increased permeability of the mitochondrial membrane (Guo et al., 2013).

Therefore, the mitochondria can be severely impacted by concussions, both morphologically and biochemically. The effects that concussion has on mitochondria and aerobic metabolism adds to the increased energy demand that results from hyperglycolysis. The impacts on aerobic and anerobic metabolism together amplify the energy crisis that concussion patients experience.

Axonal damage

Axons are a key part of the nervous system, whose function and morphology is supported by neurofilaments (Siedler, Chuah, Kirkcaldie, Vickers, & King, 2014; Yuan, Rao, Veeranna, & Nixon, 2012). Morphologically, neurofilaments help maintain the neuron shape (Wagner et al., 2007), and are important for the radial growth of the axon (Hoffman et al., 1987). They determine the conduction velocity and diameter of the axon, also known as axon caliber (Hoffman et al., 1987; Hoffman, Griffin, & Price, 1984; Yum, Zhang, Mo, Li, & Scherer, 2009), which is regulated by the axonal transport of neurofilaments (Hoffman et al., 1984). Given the reliance of axonal structure on neurofilaments, damage to neurofilaments would cause axonal impairment as well.

Studies analysing the ultrastructure of neurofilaments have found that neurofilaments are impacted by brain trauma. A study by Pettus and Povlishock (1996) reported that cats who had sustained TBI had compacted neurofilament networks, and that these neurofilaments seemed to have lost their side arms. These changes were observed from 5 minutes to 6 hours post-injury (Pettus & Povlishock, 1996). Later

studies also observed neurofilament compaction in immature and adult rats following brain trauma (DiLeonardi, Huh, & Raghupathi, 2010; Okonkwo, Pettus, Moroi, & Povlishock, 1998; Stone, Singleton, & Povlishock, 2001).

The loss of neurofilament side arm extensions has been the suggested reason for neurofilament compaction as the distance between neurofilaments is thought to be maintained by these side arm extensions (Nixon, Paskevich, Sihag, & Thayer, 1994; Pettus & Povlishock, 1996). However, Okonkwo and colleagues (1998) found that neurofilament compaction was associated with a reduction in the sidearm height, rather than a total loss of the sidearm. Nonetheless, two main methods have been described for the changes in the neurofilament sidearm extensions. One method involves calpain-mediated dephosphorylation of the sidearm extensions (DiLeonardi et al., 2010; Okonkwo et al., 1998; Pettus & Povlishock, 1996; Siedler et al., 2014). Calpain is a calcium-dependent protease that is activated by the calcium influx which results from axonal permeability (Wu, Tomizawa, & Matsui, 2007). The activated calpain activates a phosphatase called calcineurin, which in turn dephosphorylates the neurofilament side-arm (Büki & Povlishock, 2006; Siedler et al., 2014). It is reported that this dephosphorylation reduces the sidearm angle, and consequently the electro-repulsion between neurofilaments (DiLeonardi et al., 2010; Okonkwo et al., 1998). This causes the distance between neurofilaments to decrease. The other mechanism proposed for neurofilament compaction involves direct calpain proteolysis of the neurofilament sidearm (G. F. Hall & Lee, 1995; Okonkwo et al., 1998; Siedler et al., 2014), which also decreases the distance between neurofilaments. While there is evidence to support both these mechanisms of neurofilament compaction, it is important to understand how this may impact the axon itself.

Neurofilament compaction has been correlated with axonal permeability as well as irregularities in the outer axonal structure resulting in the axon being separated from the myelin sheath (Pettus & Povlishock, 1996). A study analysing neurofilament compaction impacts on axons in rats over a period of

6 months, found that majority of compacted axons did recover over time (Gallyas, Pál, Farkas, & Dóczi, 2006). This study found that axons subjected to neurofilament compaction either recovered spontaneously, degenerated irreversibly, or degenerated reversibly (Gallyas et al., 2006). Most of those that degenerated reversibly initially underwent a degeneration process, but recovered their ultrastructure withing a few months (Gallyas et al., 2006). The results of these studies show that while axons may be impacted by the neurofilament compaction that results from brain trauma, it is possible for these axons to recover. Recovery times of the spontaneous and reversibly degenerating axons may be correlated with symptom resolution times post-concussion.

Axonal damage resulting from brain trauma is not limited to that caused by neurofilament compaction. Impaired axonal transport as well as axonal swelling have been reported post-injury as well (Creed, Dileonardi, Fox, Tessler, & Raghupathi, 2011; Marmarou, Walker, Davis, & Povlishock, 2005). It was previously believed that these forms of axonal damage were linked to cytoskeletal processes such as neurofilament compaction; however, more recent studies criticize this hypothesis and provide evidence to suggest that neurofilament compaction occurs independently of axonal swelling and impaired axonal transport (Marmarou et al., 2005; Stone et al., 2001). A review focussing on axonal pathology in traumatic brain injury also suggests axotomy as a consequence of brain trauma (Johnson, Stewart, & Smith, 2013). Axotomy can result from the axons becoming brittle with the rapid biomechanical load in TBI, although this is not commonly observed in brain trauma (Johnson et al., 2013). A possible mechanism that could explain these axonal changes post-injury, particularly in myelinated neurons, is Wallerian degeneration.

Traumatic axonal injury (TAI) in TBI is specifically a concern for white matter, composed entirely of myelinated neurons (Armstrong, Mierzwa, Marion, & Sullivan, 2016). TAI may cause the degeneration of the axon itself, leaving the myelin sheath to collapse and slowly degenerate after it (Armstrong et al., 2016). Although damage to the axon and myelin sheath can be reversible in mTBI patients (Armstrong et

al., 2016). Myelin plays an important role in the way TBI impacts white matter. In myelinated axons, the initial unmyelinated segments and the nodes of Ranvier are primary targets of degeneration and possible disconnection (Armstrong et al., 2016). Nerve fibres that are separated from their cell bodies may undergo Wallerian degeneration (Armstrong et al., 2016; Beirowski et al., 2005). Axonal degeneration is mediated by proteases that are activated by calcium influx (Stoll, Jander, & Myers, 2002). In response to axonal degeneration, Schwann cells reduce myelin protein synthesis and remove the myelin and axon debris (Stoll et al., 2002). The myelin debris is formed into bands of Bunger and later used for axon regeneration (Stoll et al., 2002). It is therefore clear that white matter tracts can be severely impacted by concussions, even if there is an opportunity for regeneration. White matter damage is of concern because of the effect it may have on cognitive function (Xiong et al., 2014).

As presented in the literature, axonal damage in TBI may presents itself in many forms. Damage to the axon may result from multiple types of changes. Given the critical role that axons play in conduction of electrical information (Waxman, Kocsis, & Stys, 1995), the damage sustained to the neural network is concerning.

Concussion and sex

Sex differences exist in the incidence of concussion in Ontario. Overall, the likelihood of being diagnosed by concussion is 58.8% in men, and 41.2% in women (Langer, Levy, & Bayley, 2020). However, in individuals older than 60 years, the number of diagnosed cases is higher in women than in men (Langer et al., 2020). Sex differences in concussion are not limited to the incidence and diagnosis rates. Research shows that the neurological symptoms of concussion differ amongst men and women as well. Frommer et al. (2011) analysed reported symptoms, symptom resolution time, and return to play time in athletes who had sustained a concussion from 100 high schools across the United States. Results showed that males reported to have more difficulty concentrating and remembering things following a

concussion than females did (Frommer et al., 2011). Females, on the other hand, reported more symptoms related to impairment in sleep, drowsiness, light and noise sensitivity, and balance problems. (Frommer et al., 2011). These results suggest that the types of symptoms that men and women experience post-injury are different. A meta-analysis comparing 21 studies that examined self-reported concussion symptoms in males and females confirms these results (Brown, Elsass, Miller, Reed, & Reneker, 2015). This study concluded that females were more likely to report the symptoms of headaches, difficulty concentrating, sleep/energy disturbances, hearing/vision problems, and emotional symptoms after a concussion (Brown et al., 2015). Males were also 45% more likely to report confusion after a concussion than females were (Brown et al., 2015). Moreover, females were more likely to report concussion symptoms than males (Brown et al., 2015), an observation that has been made by multiple other studies as well (Colvin et al., 2009; Covassin, Elbin, Harris, Parker, & Kontos, 2012; Covassin, Schatz, & Swanik, 2007). Hence, not only do men and women differ in the types of symptoms they report, but in the number of symptoms they experience as well.

A relationship between sex and concussion has also been established by observation of cognitive deficits in concussion patients. To assess the sex impacts on cognitive function in soccer athletes who sustained a concussion, the Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) was performed on 234 concussed soccer athletes (Colvin et al., 2009). ImPACT is a computer-based program used to assess concussion symptoms and neurocognitive functioning. Results showed that females with concussion displayed poorer reaction time scores than males (Colvin et al., 2009). Performance of ImPACT in a group of 79 athletes also revealed that women have lower visual memory scores, but higher verbal memory scores immediately post-injury (Covassin et al., 2007). Similarly, poorer visual memory task performance was observed in female high school and collegiate athletes with concussion as compared to males (Covassin et al., 2012). From these studies it is clear that sex impacts concussions differently in men and women. Such sex differences are not limited to the acute and post-acute phase of

injury. Sicard, Moore, & Ellemberg (2018) found that similar differences persist in the chronic phase of injury as well. The observed differences in cognitive deficits between concussed men and women is indicative of the impact that sex has on concussion.

The relationship between sex and concussion is further established by observation of motor deficits in individuals with concussion. A study conducted to assess the effects of mTBI on resting state networks revealed that male mTBI patients have more functional connectivity in motor, ventral stream, executive function, and cerebellum networks compared to female mTBI patients (Wang et al., 2018). Females on the other hand exhibit more functional connectivity in visual networks than men (Wang et al., 2018). Since concussion is a type of mTBI, and since these networks are associated with motor function, results of this study point to the sex differences in motor function post-concussion. Covassin et al. (2012) examined performance on the Balance Error Scoring System in male and female athletes and found that female collegiate athletes performed significantly worse than male collegiate athletes. These studies indicate that motor function deficits in women with concussion are more likely to be observed than in men with concussion. Therefore, concussion does not impact motor function in men and women the same way.

The different types of cognitive and motor deficits that men and women face post-injury highlights the influence that sex has on concussion. However, these studies also reflect the impact that concussion has on cognitive and motor function itself, making these variables important targets for further investigation.

From the literature it is evident that functions of concussion, cognition, and motor function are interrelated and that sex impacts each of these variables individually. However, the impact of sex on the relationship between cognitive and motor function and gait in individuals with concussion has not been fully explored.

Rationale and objective

Based on the literature it is established that men and women are differentially impacted by concussion. This is demonstrated by the differences in the cognitive and motor symptoms that men and women experience post-concussion. Given that cognitive and motor function are essential to gait, it is possible that features of gait, such as the determinants of gait velocity, are differently impacted in men and women. However, no previous studies have looked at how sex may impact this relationship between cognitive and motor function and the determinants of gait velocity. Additionally, since the side effects of concussion do not subside immediately, the effect of cognitive and motor function on the determinants of gait velocity may be long-lasting. It is not clear if this effect can be predicted by sex, or any other correlate of cognitive and motor function. Considering the emerging evidence surrounding the susceptibility of concussion symptoms in men and women and the long-term effects of the injury, this presents a considerable gap in the literature. Addressing this gap is important because it may have implications for how gait and concussion are viewed in relation to sex, and how concussion recovery is understood. Figure 1 presents a conceptual model that identifies the concepts included in this thesis.

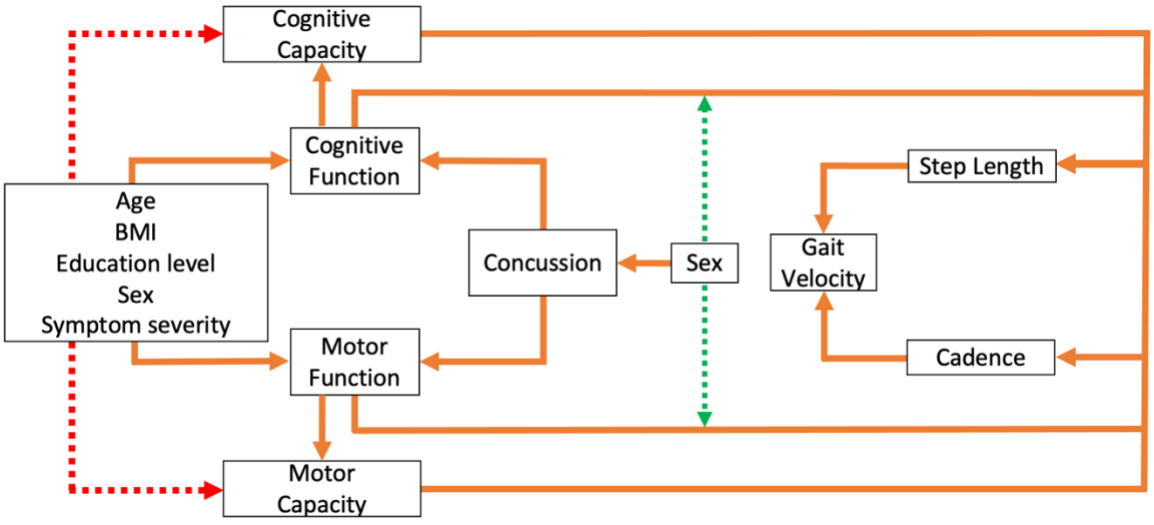

Figure 1 *- Conceptual model of the thesis depicting the relation between sex, concussion, cognitive and motor function, and the determinants of gait velocity. Orange arrows depict known relationships. Green arrows depict unknown relationships that will be examined in Study 1 of this thesis. Red arrows depict unknown relationships that will be examined in Study 2 of this thesis.*

A noteworthy point is that majority of concussion research has been conducted on athletes. Yet not everyone who sustains a concussion is necessarily and athlete. In fact, the annual concussion incidence rate for the community-dwelling population in Ontario is 1.2% (Langer et al., 2020). Despite this, concussions in the community-dwelling population are understudied. Considering the risk of injury that is associated with this population, the lack of observation in this population is a gap in the literature as well. Therefore, the **purpose of this thesis** is to characterize the effect of sex on the relationship between cognitive and motor function and the determinants of gait velocity and to identify factors that may predict gait impairment due to concussion in these domains, in community-dwelling adults with concussion.

This thesis will involve two studies. Study 1 will cross-sectionally examine the effects of sex on the relationship between cognitive and motor function and gait velocity determinants in community-dwelling people with concussions. Study 2 will aim to identify predictors of cognitive and motor capacity over a span of 4 months post-injury, in a subset of the same sample. The results of this study will not only add to the knowledge in this area, but will also inform clinical practices for community-dwelling patients who sustain a concussion.

Chapter 2: The effect of sex on the relationship between cognitive and motor function and the determinants of gait velocity

Abstract

Concussion impacts various aspects of gait, many of which have not been examined in the community-dwelling population. Gait velocity and its determinants in particular are impacted by concussion and differ in healthy men and women. The purpose of this study is to examine the effects of concussions on gait velocity determinants in community-dwelling men and women. Step Length, Cadence, Velocity, and Step Length Variability measures of community-dwelling male and female concussion patients were compared across four different conditions: Talking, Dual Task, Self-paced, and Maximum-paced. These tasks were chosen to probe the effect of sex on the relationship between cognitive and motor function and the determinants of gait velocity. Results showed a Sex x Condition interaction for Step Length in Motor Tasks, ($F(1,504) = 5.60$, $p < 0.05$), suggesting that women are more impacted by an added motor challenge during gait. During the Maximum-paced condition, men exhibited a higher Step Length than women (47 ± 0.6 vs 45 ± 0.4 % of body height), whereas women exhibit greater Cadence than men (138 ± 1.3 vs 130 ± 1.46 steps/min). Nonetheless, similar Velocities were observed among the sexes in this condition. The absence of this pattern when participants are subjected to a cognitive challenge suggests that cognitive challenges may be prioritized over maintaining gait patterns while walking. Step Length Variability was also observed to be higher in women than in men, irrespective of the condition. Observational comparisons to Healthy controls showed that concussion may impact Step Length Variability in women, and Step Length and Cadence in men in the Cognitive Tasks only. Overall, concussion seems to impact the cognitive and motor effects on gait velocity determinants differently in men and women. The results of this study are important in assisting clinicians in administering individualized treatment programs to concussion patients.

Introduction

Concussion is a form of traumatic brain injury that is induced by biomechanical forces and may cause neuropathological changes and clinical symptoms (Ontario Neurotrauma Foundation, 2013). Gait impairment is one of the many symptoms that result from concussion. Non-pathological gait requires a series of higher-level neural processes to be in place in order to be effective. This is evidenced by brain activity that has been observed in the primary sensorimotor area, supplementary motor area, cerebellar vermis, visual cortex, and a part of the left medial temporal lobe immediately after walking (Fukuyama et al., 1997). Attention capabilities can influence gait as well, as evidenced by the increased in stride variability observed in physically fit older adults during dual task gait (van Iersel et al., 2007). Lastly, executive function and memory have been found to be significant predictors of gait velocity during dual task gait (Holtzer et al., 2006).

Gait velocity is an important aspect of gait as it is an overall indicator of health and has been associated with incident disability (Rosano et al., 2008; Studenski, 2011). Gait velocity is defined as being a function of step length and cadence, where step length is the length of each step, and cadence is the number of steps taken per unit time. Men and women use different strategies to regulate gait velocity. Men tend to exhibit longer step lengths and women tend to exhibit a higher cadence in non-pathological gait (Callisaya et al., 2008; Oberg et al., 1993), despite the fact that overall gait velocity at preferred walking speeds has been reported to be similar amongst sexes (Frimenko et al., 2015). Consideration of the sex differences in gait velocity strategies is important as men and women experience the effects of concussions differently. Women tend to experience more neurological symptoms post-injury than men do (Brown et al., 2015; Frommer et al., 2011). Men and women also display different cognitive and motor impairments after concussion (Colvin et al., 2009; Covassin et al., 2012, 2007; Sicard et al., 2018).

Gait velocity and its determinants (step length and cadence) have previously been studied in relation to concussion. College-aged individuals have demonstrated reduced gait velocity and stride

lengths 2-days post-injury during dual gait tasks (Parker et al., 2006). Similarly, Adolescents have demonstrated reduced stride lengths 3 weeks after injury during single gait tasks, as well as after symptom resolution during dual gait tasks (Berkner et al., 2017). Together these studies indicate that concussions do impact gait. Despite this knowledge, it is unclear as to whether concussion impacts the determinants of gait velocity differently in men and women. Furthermore, the majority of what is known about concussions is based on adolescent, high school or university-aged athletes. Consequently, the sex-dependent impacts of gait on community-dwelling adults are not well understood. This is a problem because of the concussion risk associated with this population. The annual incidence rate of concussion in the community-dwelling population of Ontario is 1.2% (Langer et al., 2020). Therefore, it is important for concussion injury in this population to be studied.

Considering the lack of observation in the community-dwelling population and given the impacts of sex on cognitive and motor symptoms of concussion, the aim of this study is to identify the effect of sex on the relationship between motor and cognitive function and the determinants of gait velocity 1 week after injury. Since concussions seem to impact cognitive and motor function more in women than in men, it is hypothesized that men will exhibit a higher Step Length than women in both cognitive and motor gait tasks. For the same reason, men will also have less variable Step Length than women in both cognitive and motor gait tasks. Women will exhibit a greater Cadence than men in cognitive and motor gait tasks as this is observed in non-pathological gait as well. Lastly, since men are predicted to have a higher Step Length and women a higher Cadence, it is hypothesized that Velocity for men and women will be the same, as Step Length and Cadence are a function of Velocity.

If the results of this study support these hypotheses, then this study will provide evidence for the idea that concussion does differentially impact the cognitive and motor effects on gait velocity in men and women. Such evidence will have implications for the types of rehabilitation programs that clinicians use for concussion treatment that specifically align with the deficits experienced by men and women.

Methods

Participants

The data that was used for this study were collected at the Hull-Ellis Concussion and Research Clinic at the Toronto Rehabilitation Institute (University Centre) – University Health Network between the years 2016 and 2020. The Hull-Ellis Concussion and Research Clinic aims to provide care to concussion patients within one week of injury, while simultaneously conducting research on their progress and recovery. Patients are referred to the Hull-Ellis Concussion and Research Clinic from emergency departments of Toronto General Hospital, Toronto Western Hospital, Mount Sinai Hospital, Michael Garron Hospital, St. Joseph's Health Centre, and Sunnybrook Health Sciences Centre. For this study, all participants were referred from emergency departments of Toronto Western and Toronto General Hospitals. Data were collected at 1, 2, 4, 8, 12, and 16 weeks post-injury across a span of 3 years (2016-2019). A group of neurotypical controls, free of neurological and musculoskeletal injury was also recruited for participation in the study through word of mouth in the Toronto Rehabilitation Institute and University of Toronto communities. However, recruitment was terminated early due to COVID-19. This study was approved by the Research Ethics Boards at UHN (REB #15-9214) and York University (e2020-226).

Concussion group inclusion and exclusion criteria

The following is the clinical inclusion criteria for this study: no positive neuroimaging findings or focal neurological findings (if imaging was deemed necessary), Glasgow Coma Scale score of 13-15 on presentation to the emergency department, between the ages of 18-85, BMI < 30, concussion diagnosis by an emergency department physician, participant was willing to attend first appointment within 7 days of injury, and participant knew enough English to complete all tests in this study (Grade 6 reading level or higher).

The following exclusion criteria was applied to the Concussion group data prior to analysis: admission to in-patient care, symptomatic from a previous concussion that occurred within the last 3 months, third party insurance claim eligible (i.e., injury occurring due to a motor vehicle accident or workplace injury), community physician referrals, injury occurring more than 7 days prior to the first physician assessment at the Hull-Ellis Concussion and Research Clinic, previous musculoskeletal injury characterised by previous joint replacement surgery, previous other orthopaedic surgery, previous other lower limb condition/injury (causing muscular or joint pain or limited range of movement), or previous back pain or injury and has some missing data necessary for analysis.

Data collection

All gait data used in this research was collected using a 4.6-meter-long pressure-sensitive gait mat (GaitRite, CIR Systems, Clifton, NJ). Participants were asked to walk across the mat in 4 different conditions. For each condition, subjects walked across the mat until 16-18 footfalls were recorded. In the Self-paced condition individuals were instructed to walk across the mat at a self-selected pace. In the Maximum-paced condition subjects were to walk across the mat as quickly as possible. The Self-paced and Maximum-paced conditions together were termed the 'Motor Tasks'. The Self-paced condition served as the control task to the Maximum-paced condition. The third condition was the Talking condition where subjects were instructed to walk across the mat at a self-selected pace while counting upwards by ones, starting at a 3-digit number. Lastly, the Dual Task condition involved individuals walking across the mat at a self-selected pace while counting backwards by sevens, starting at a 3-digit number. The Backwards 7's dual task paradigm (Hayman, 1942) has been used in previous studies and has found to cause significant effects on gait speed (Li, Verghese, & Holtzer, 2014). The Talking and Dual Task conditions were be termed the 'Cognitive Tasks'. In this case, the Talking task served as the control task to the Dual Task condition. The Motor and Cognitive Tasks were used to probe

the effects of concussion on gait velocity determinants. As these tasks challenge the central nervous system in different ways, they were used to identify how the determinants of gait velocity would be impacted when individuals are subjected to motor and cognitive challenges.

Measures of interest included Step Length (cm), Step Length Variability (measured as coefficient of variation (CV; standard deviation/mean) in %), Velocity (cm/s), and Cadence (steps/min) as determined by the GaitRite software (GaitRite, CIR Systems, Clifton, NJ). Step Length and Velocity measures were normalized to body height (cm) before analysis so that Step Length was measured as a percent of body height. This was done to control for general anthropometric differences between men and women.

In addition to the gait data collected, demographic information such as age, sex, height, years of education, and prior health conditions was collected for Concussion and Healthy groups. Weight, concussion history, previous mental health conditions, time to first appointment post-injury, and previous migraines/headaches was collected for the Concussion group as well. In addition, the Post-concussion Symptom Scale of the Sports Concussion Assessment Tool Edition 3 (SCAT3) (Guskiewicz et al., 2013) was administered to the participants of the Concussion group at each visit. Weight data was not collected for the Healthy control group. Thus, for the analysis, it was assumed that individuals of this group had a BMI of less than 30.

Statistical Analysis

All statistical analyses were performed on RStudio (RStudio Team, 2020). Descriptive statistics were derived for both Concussion and Healthy control groups using the stat.desc() function in the pastecs package (Grosjean & Ibanez, 2018). Descriptive data was used to characterize the study cohorts. Analysis for this study was performed on data that was collected within 1 week of concussion injury (i.e., first visit to the clinic).

To test the hypothesis that men and women with concussion differ in Step Length, Step Length Variability, and Cadence, but not in Velocity, a 2-way ANOVA was performed on the Concussion group. Sex (male, female) was the between-subject factor, and Condition (Talking vs Dual Task – cognition; Maximum-paced vs Self-paced – motor) were within-subject factors. Analyses were performed separately on Cognitive and Motor Tasks. Hence, 1 2x2 ANOVA was performed for each task type and measure of interest, resulting in a total of 8 2x2 ANOVAs. Data was fit to an analysis of variance model using the aov() function. ANOVA results were computed using the Anova() function in the car package (Fox & Weisberg, 2019), where the significance value was set as $p = 0.05$. Any posthoc tests were performed separately after the ANOVA using the PostHocTest() function in the DescTools package (Signorell et al., 2020), where the Bonferroni correction was applied. The significance value for the Bonferroni correction was initially set to $p = 0.05$.

Prior to performing the ANOVAs, the assumptions for ANOVA were verified. To ensure normal distribution of the residuals, Shapiro-Wilk Normality tests were performed on residuals of each group in the data using the shapiro.test() function in the stats package (R Core Team, 2020). The significance value was set to $p = 0.05$. Histograms were also generated to visually analyze the distribution of the residuals of the data. To ensure homogeneity of data, the ggplot2 package (Wickham, 2016) was used to generate residual versus fitted plots. The full RStudio script for the statistical analysis of this study is reported in Appendix A.

Results

Participant characteristics

In total, 254 participants met the criteria to be included in the study. The participant characteristics for Concussion and Healthy groups are summarised in Tables 1 and Table 2 respectively. Based on the results of a t-test, the symptom evaluation score (out of 132) on the SCAT3 for the female group was significantly higher as compared to the male group ($t=7.12$, $df= 888.15$, $p<0.01$) (Table 1). A previous study found that people with concussion have an average symptom evaluation score of 7.44, 8 days post-injury (Chin, Nelson, Barr, McCrory, & McCrea, 2016). Hence, it seems that the symptom severity levels of the male and female concussion groups in this study are considerably higher.

Table 1 *– Summary of participant characteristics for the Concussion group. Symptom severity scores were determined from the symptom severity subscale of the SCAT3.*

	All participants	**Males**	**Females**
Sample size	254	102	152
Age	32.4±0.37	32.1±0.55	32.5±0.49
Education level			
Less than high school diploma	4	2	2
High school diploma	29	12	17
Incomplete post-secondary studies	21	10	11
Trade certificate/diploma or College, CEGEP, or other non-university certificate/diploma	38	17	21
Bachelor's degree	114	39	75
Master's degree	39	18	21
PhD	9	4	5
BMI	23.3±0.09	24.3±0.25	22.7±0.12
Symptom severity	41.1±0.85	34.0±1.3	45.9.0±1.1

Table 2 *– Summary of participant characteristic for the Healthy control group.*

	All participants	Males	Females
Sample size	12	4	8
Age	27.50±0.73	24.75±0.74	28.88±0.94
Education level			
Less than high school diploma	0	0	0
High school diploma	1	1	0
Incomplete post-secondary studies	0	0	0
Trade certificate/diploma or College, CEGEP, or other non-university certificate/diploma	2	1	1
Bachelor's degree	3	1	2
Master's degree	6	1	5
PhD	0	0	0

Assumptions of ANOVA

Initial Shapiro-Wilk test results indicated that Step Length CV residuals were not normally distributed. For this reason, Step Length CV values were log transformed and the Shapiro-Wilk test was performed again. The results showed that Step Length was the only variable with a normal distribution ($p>0.05$). Despite this, histograms showed a normal distribution for all measures of interest. The non-normal distributions observed in the Shapiro-Wilk tests were attributed to the outliers observed at the right tails of the Step Length CV, Velocity, and Cadence histograms. It was hence concluded that the requirement for the residuals of the data being normally distributed was met. Residual versus fitted plots showed no particular pattern in the data suggesting that the data is homogeneous. All figures and tables associated with the assumptions of ANOVA are reported in Appendix B.

Analysis of Variance for Cognitive Tasks and Motor Tasks

Across all participants in the Concussion group, normalised Step Length ranged from 23% to 51%, Step Length CV ranged from 1.22% to 14.85%, normalised Velocity ranged from 0.21 cm/s to 0.98 cm/s, and Cadence ranged from 49 steps/min to 132.6 steps/min in the Cognitive Tasks. For Motor Tasks, normalised Step Length ranged from 24% to 59%, Step Length CV ranged from 1.02% to 17.25%, normalised Velocity ranged from 0.27 cm/s to 1.64 cm/s, and Cadence ranged from 67.1 steps/min to 200 steps/min. Values for each measure in each condition are depicted in Figure 2 for the Concussion group, and Figure 3 for the Healthy control group.

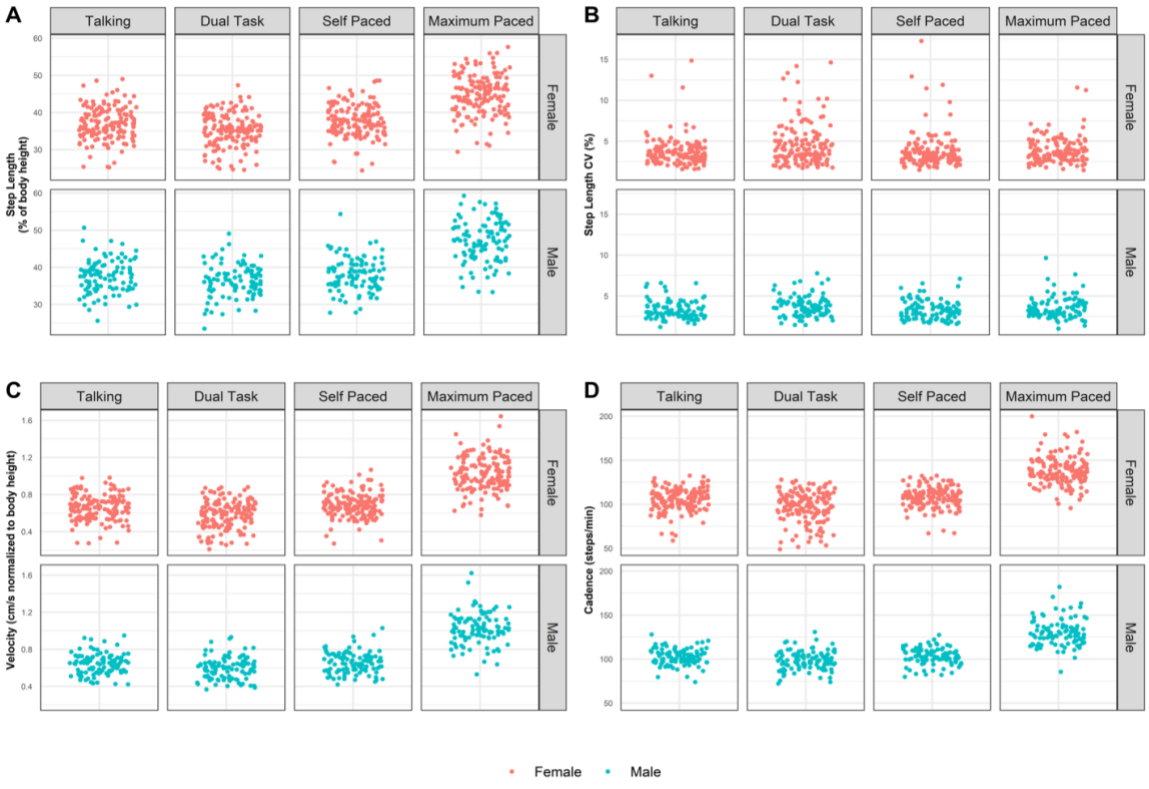

Figure 2 *- Data for each participant of the Concussion group for Talking, Dual Task, Self-paced and Maximum-paced conditions. A) Step Length (% of body height. B) Step Length CV (%). C) Velocity (actual velocity (cm/s)/body height (cm)). D) Cadence (steps/min).*

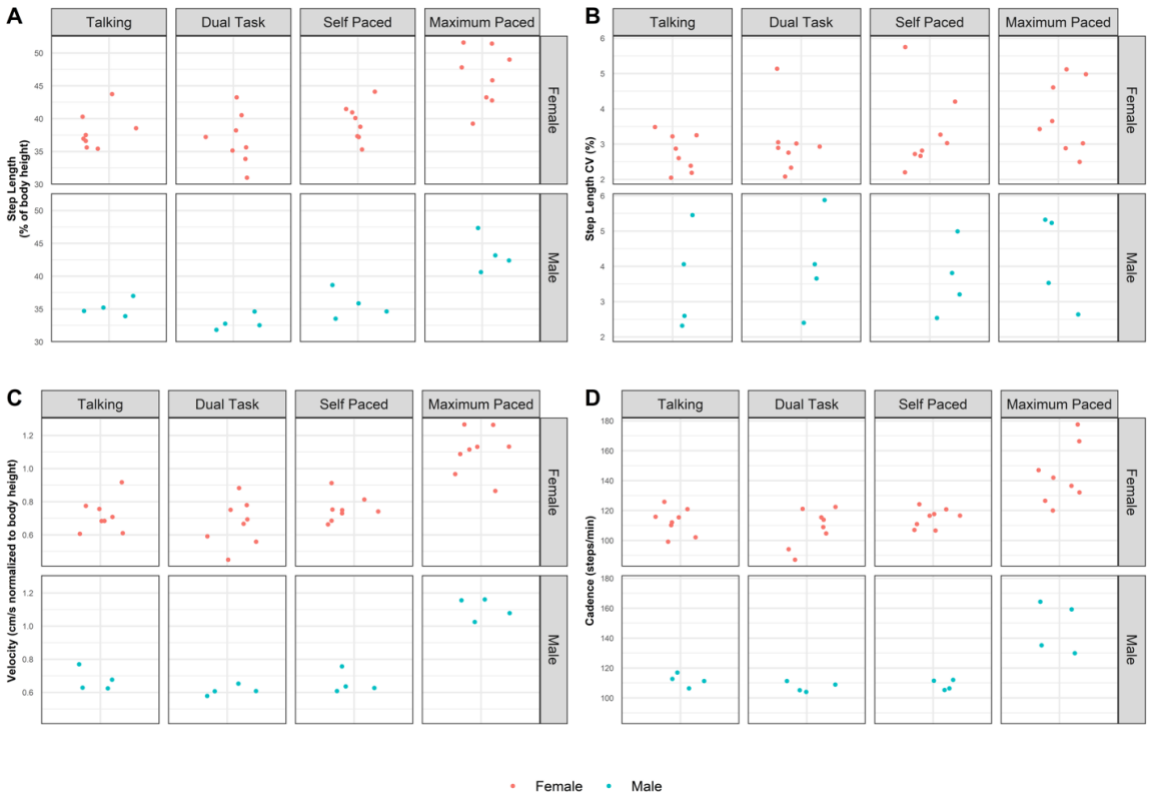

Figure 3 *- Data for each participant of the Healthy control group for Talking, Dual Task, Self-paced and Maximum-paced conditions. A) Step Length (% of body height. B) Step Length CV (%). C) Velocity (actual velocity (cm/s)/body height (cm)). D) Cadence (steps/min).*

For the Cognitive Tasks, analyses of variance showed a main effect of Condition for all 4 measures of interest: Step Length, ($F(1,504) = 15.19$, $p < 0.01$), Step Length CV, ($F(1,504) = 14.02$, $p < 0.01$), Velocity, ($F(1,504) = 26.49$, $p < 0.01$), and Cadence, ($F(1,504) = 23.89$, $p < 0.01$). In all cases performance was worse in the Dual Task compared to the Talking conditions (Figure 4). Additionally, a main effect of Sex was observed for Step Length, ($F(1,504) = 3.86$, $p < 0.05$) and Step Length CV, ($F(1,504) = 11.45$, $p < 0.01$), where women had lower, but more variable Step Length than men (Figure 4A-B). No Sex x Condition interactions were observed in any of the variables for the Cognitive Tasks.

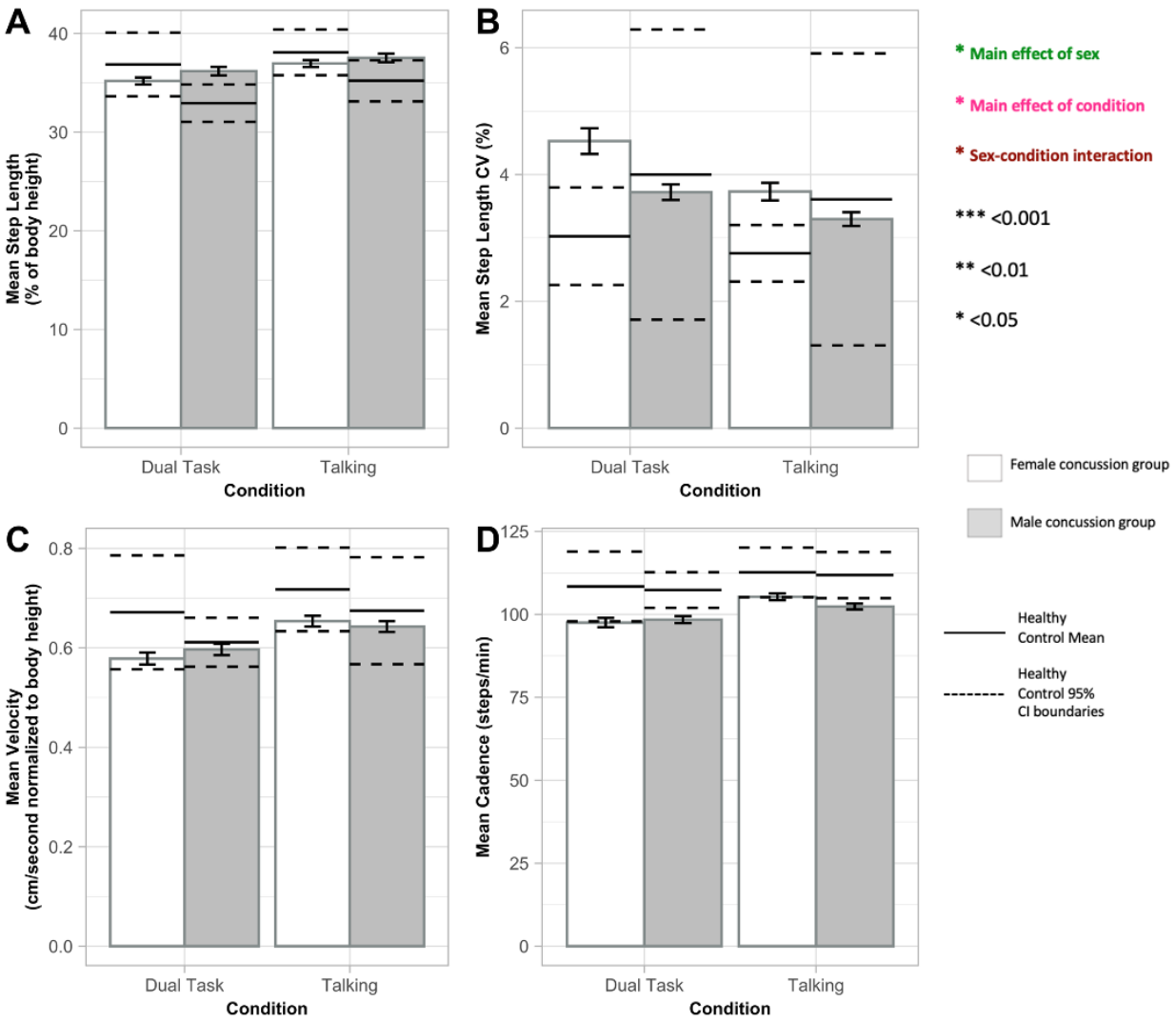

Figure 4 *- Comparison of means for male and female Concussion and Healthy control groups across Talking and Dual Task conditions. A) Step Length (% of body height). B) Step Length CV (%). C) Velocity (actual velocity (cm/s)/body height (cm)). D) Cadence (steps/min). Asterisks refer to significance levels for comparisons between the Concussion groups only.*

For Motor Tasks, analysis of variance for Step Length showed a main effect of Sex, ($F(1,504) = 8.58$, $p < 0.01$), and Condition, ($F(1,504) = 324.13$, $p < 0.01$), as well as a Sex x Condition interaction, ($F(1,504) = 5.60$, $p < 0.05$). Results for the Bonferroni multiple comparison's test showed that men and women had similar Step Lengths in the Self-paced condition (Figure 5). While the Step Length increased for both sexes in the Maximum-paced condition, men performed better than women in this condition (Figure 5). The results for the multiple comparison test are summarised in Table 3. No other Sex x Condition

interactions were observed in the analysis for Motor Tasks. A main effect of Sex was observed for Step Length CV ($F(1,504) = 7.60$, $p < 0.01$), and Cadence, ($F(1,504) = 26.08$, $p < 0.01$). A main effect of Condition was observed for Velocity, ($F(1,504) = 667.69$, $p < 0.01$) and Cadence, ($F(1,504) = 552.70$, $p < 0.01$). ANOVA tables for the analysis of both Cognitive and Motor Tasks are reported in Appendix C.

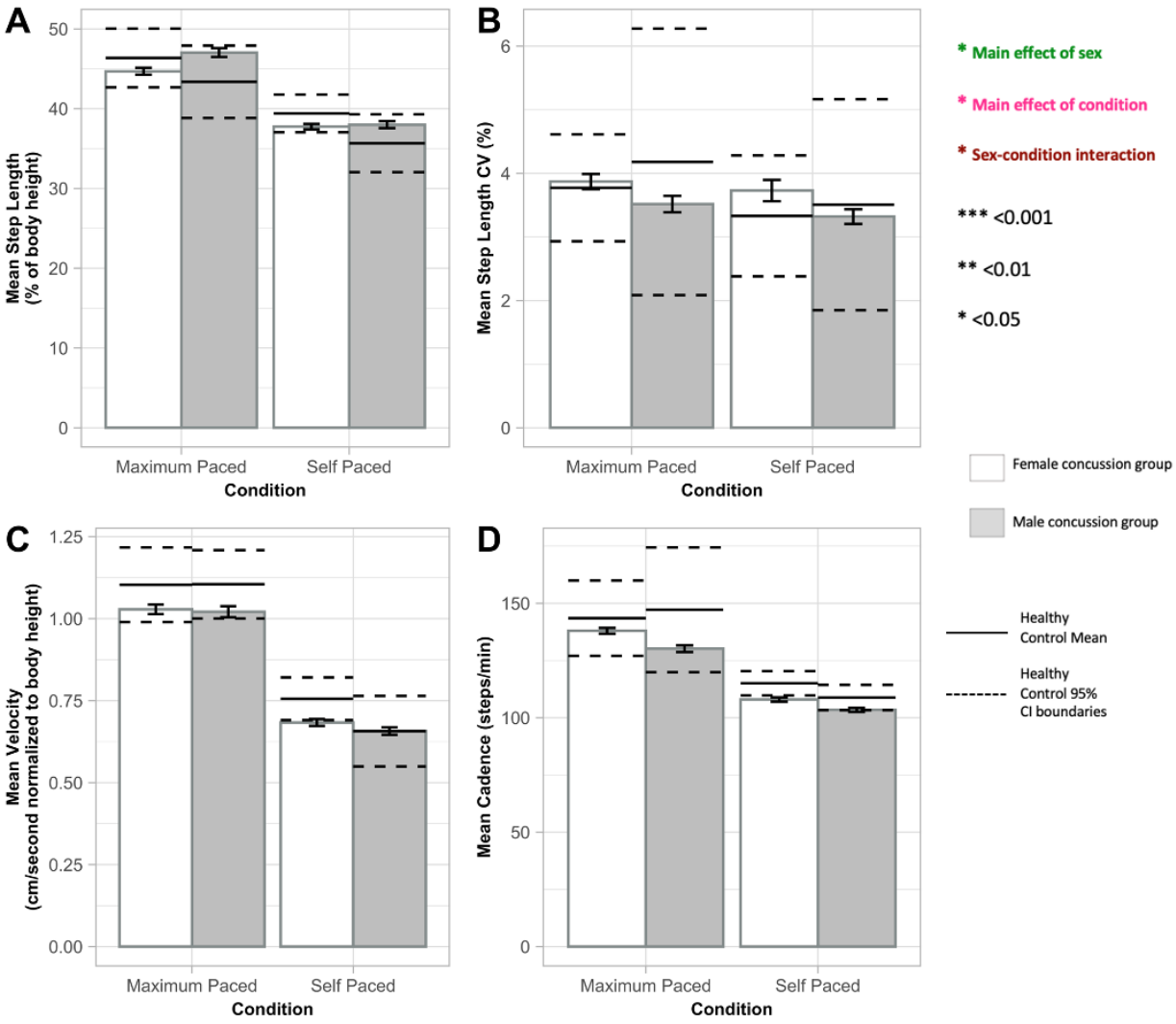

Figure 5 *- Comparison of means for male and female Concussion and Healthy control groups across Self-paced and Maximum-paced conditions. A. Step Length (% of body height). B. Step Length CV (%). C. Velocity (actual velocity (cm/s)/body height (cm)). D. Cadence (steps/ min). Asterisks refer to significance levels for comparisons between the Concussion groups only.*

Table 3 *- Bonferroni multiple comparison test for Step Length (% of body height) in the Motor Tasks.*

Group 1	Group 2	Difference	Lower Bound	Upper Bound	p-value	Significance Level
MP (male)	MP (female)	0.023510930	0.006882012	0.04013985	0.0012	**
SP (female)	MP (female)	-0.06941648	-0.08431908	-0.0545139	<0.001	***
SP (male)	MP (female)	-0.06692030	-0.08354922	-0.0502914	<0.001	***
SP (female)	MP (male)	-0.09292741	-0.10955633	-0.0762985	<0.001	***
SP (male)	MP (male)	-0.09043123	-0.10862337	-0.0722391	<0.001	***
SP (male)	SP (female)	0.002496181	-0.01413274	0.01912510	1.0000	

'***' p-value < 0.001, '**' p-value < 0.01, MP = Maximum-paced, SP = Self-paced

Observational comparisons with Healthy controls

For observational comparisons between the Concussion and Healthy control groups, instances where the standard error bars of the Concussion group fell above or below the confidence interval boundaries of the healthy control group were considered. Across all participants and conditions in the Healthy control group, normalised Step Length ranged from 31% to 52%, Step Length CV ranged from 2.05% to 5.88%, normalised Velocity ranged from 0.45 cm/s to 1.27 cm/s, and Cadence ranged from 87.1 steps/min to 177.5 steps/min. By observation, the female Concussion group exceeded the Healthy control confidence interval boundaries for Step Length CV in the Cognitive Tasks (Figure 2), implying increased Step Length Variability in the female Concussion group. The male Concussion group fell below the Healthy control confidence interval boundaries for Cadence, while exceeding them for Step Length in the Cognitive Tasks (Figure 2). While an increase in Step Length, Velocity, and Cadence would signify faster gait, the increase in Step Length and decrease in Cadence in the male Concussion group implies no change in overall Velocity. No noticeable observations were made in the Motor Tasks (Figure 3).

Discussion

Overall, this study shows that concussion differentially impacts gait behavior in men and women depending on whether a cognitive or motor challenge is applied. Additionally, this study is one of few to address gait behaviour post-concussion in the community-dwelling population. Focus on this population is of particular importance because this population is understudied, despite the risk of injury. Our results show that men and women used different strategies to achieve the same gait velocity when subjected to motor challenges. Women with concussion also displayed more variable Step Length than men. Moreover, concussion may impact women more than men as women with concussion seemed to have higher Step Length Variability than healthy women in the Cognitive Tasks, while Step Length Variability amongst the male groups seemed to be similar. Concussions may also lead men to increase the use of Step Length to achieve Velocity during Cognitive Tasks.

Sex x Condition interaction in Step Length for Motor Tasks

This study revealed a Sex x Condition interaction in the Step Length of Motor Tasks. While men and women had similar Step Lengths in the Self-paced conditions, men increased their Step Length to a greater extent than women when the motor challenge of walking as fast as possible was added. Given that women had a worse symptom severity score than men, a worse performance in the female group seems possible. With regards to step length, studies have shown that one of the determinants of step length is pelvic rotation. A study looking at pelvic rotation in relation to stride length in healthy people found that these variables were directly proportional to each other (Huang et al., 2010). These results were confirmed in a later study where internal and external pelvic rotation in healthy men were attributed to different parts of the gait cycle that contribute to step length (Nishimori & Ito, 2011). However, research has also shown that healthy women have a larger pelvic rotation than men (Bruening, Frimenko, Goodyear, Bowden, & Fullenkamp, 2015; Whitcome, Miller, & Burns, 2017). In

fact, women have displayed a higher pelvic rotation than men at higher walking speeds, which is suggested to have contributed to the increases in step length (Whitcome et al., 2017). These outcomes are contrary to the results of the present study. While the present study did not look at pelvic rotation in men and women, given that healthy women have been reported to have a larger pelvic rotation than healthy men, a greater Step Length would be anticipated in women when increasing gait velocity to maximum pace. However, in this study it seems that the impact of the motor challenge on Step Length was less in concussed men than women. A possible explanation for this could be that the concussion injury impacted pelvis rotation; however, this seems unlikely as the literature does not establish a connection between concussion and pelvic rotation. Research does, however, show a relationship between reduced step length and metabolic cost of walking (Gordon, Ferris, & Kuo, 2009). Given that metabolic cost of transport is also associated with step length variability, which in this study was found to be higher in the same group of women, the reduced Step Length observed in women with concussion is understandable. It is noteworthy that in attempt to control for possible effects of leg length, the Step Length data was adjusted for body height. Although leg length does not always correspond to body height, there is a lesser chance that the results may be due to anthropometric differences amongst sexes. Nonetheless, the reason for why the increase in walking speed had a different impact on men and women remains unexplained and warrants further research.

Sex differences in gait velocity strategies

When considering the Maximum-paced and Self-paced conditions independently, this study shows that despite men and women having similar Velocities, men have a higher Step Length and women have a higher Cadence in these conditions. Given that gait velocity is a function of step length and cadence, it is clear that men and women with concussion used different strategies to achieve the same Velocity. Previous studies have also shown that healthy men exhibit a higher step length and lower cadence than

healthy women (Booyens & Keatinge, 1957; Bruening et al., 2015; Oberg et al., 1993). The notion that women mainly use step frequency to increase their velocity is not novel either (Booyens & Keatinge, 1957). Hence, the use of different strategies to achieve gait velocity amongst men and women is not limited to concussion injury. However, this difference in gait velocity strategy was not observed in the Cognitive Tasks of this study. In the Cognitive Tasks, while men were observed to have a higher Step Length, Cadence and Velocity were similar in both conditions. It seems that the increase in Step Length in men was not sufficient for it to significantly increase Velocity in comparison to women during the Cognitive Tasks. Given the results of the Motor Tasks as well as previous accounts of sex differences in step length and cadence, a main effect of Sex in Cadence would have been expected as well. The fact that Cadence was similar amongst men and women suggests that the Cognitive Task may influence mechanisms used for cadence, thereby altering the typical patterns used to achieve gait velocity. A possible reason for this may be that the cognitive load results in participants prioritizing the Cognitive Task performance over the walking task. A trade-off between cognitive task performance and decrements in gait velocity determinants is not unexpected as it has been observed in healthy people as well (Kirkland, Wallack, Rancourt, & Ploughman, 2015). While Cadence in particular seems to have been influenced in this case, it is noteworthy that the Sex effect for Step Length was only just considered significant as the p-value was 0.049. Therefore, it seems that the Cognitive Task generally affected the strategies men and women use to achieve gait velocity, which reiterates the idea that the cognitive tasks were prioritized over the gait tasks. This points to the extent to which concussion injury impacts cognitive function and attention. It seems that the attention required for the Cognitive Tasks is sufficient enough for it to disrupt the commonly observed patterns of gait velocity determinants in people with concussion. The fact that concussion results in cognitive deficits only increases the attentional demand required during the Cognitive Tasks. Therefore, it can be concluded that motor challenges do not impact

the strategies that men and women with concussion use to achieve gait velocity; however, cognitive challenges have the effect of disrupting these patterns in people with concussion.

Sex differences in Step Length Variability

One of the major findings of this study is that women with concussion had more variable Step Length than men, irrespective of the added cognitive or motor challenge. Sex differences are expected given the difference in the symptom severity of men and women. Regarding step length variability, studies have shown that step length variability may be linearly correlated with increases in metabolic cost of transport (O'Connor et al., 2012; Rock et al., 2018). In a review looking at energetics of human walking metabolic cost of transport was attributed to muscular force production (McNeill Alexander, 2002). Hence, the increased Step Length Variability observed in women might suggest that women with concussion have a higher metabolic cost of transport, and as a result may have more deficits in muscle force production compared to men post-injury. Interestingly, increased metabolic cost of transport in women has also been observed in healthy people. A study revealed that normal-weight healthy women had a metabolic rate 20% larger than normal-weight healthy men (Browning, Baker, Herron, & Kram, 2006). Therefore, similar sex effects of step length variability may be seen in a healthy population.

Sex differences in variability have been observed in other gait parameters as well. A study found a 15% to 35% increase in variability measures of step length, stride velocity, step time, double support time, and stance time in elderly women compared to men during a dual gait task (Johansson, Nordström, & Nordström, 2016). Another study found stronger associations between age and step time variability in older women than in men (Callisaya, Blizzard, Schmidt, McGinley, & Srikanth, 2010). While these studies focus on the elderly population, there seems to be a possible relationship between sex and measures of gait variability, regardless of concussion injury. Based on the relationship between metabolic cost of transport, and sex differences observed in gait variability in healthy people, it may be concluded that the Sex effects observed in Step Length Variability may be independent of the

concussion injury itself. A study comparing gait in people with a history of concussion to people with no concussions found that people with no previous concussions had more variable step length than people with a history of concussions (Buckley et al., 2016). These results together with the results of Johansson et al. (2016) and Callisaya et al. (2010) reiterate the idea that Step Length Variability may not be related to the concussion injury. However, this conclusion is not in line with the results of the observational comparisons performed in this study. Comparisons between the Concussion and Healthy groups showed that healthy women had lower Step Length Variability than women with concussion in the Cognitive Tasks. These results suggest that these sex differences may in fact be a result of the injury. Since this observation was only made in the Cognitive Tasks, and not in the Motor Tasks, the observed sex difference may be related to the added cognitive challenge. Nonetheless, there seems to be a relationship between sex and concussion. Given previous accounts of sex differences in neurological, cognitive, and motor symptoms of concussion, such a relationship is plausible. It may be that the Sex effects may only be evoked when the nervous system is challenged in a particular way, as in the case of the Cognitive Tasks. Therefore, it is possible that certain aspects of the nervous system that relate to the Cognitive Tasks are differently impacted by concussion in men and women, and not others. Considering the evidence in the literature and the observations in this study, it seems that there may be inherent sex differences that contribute to the Sex effects observed post-concussion; however, the concussion injury itself seems to further exacerbate these differences as seen in the Cognitive Tasks of this study.

Comparison to Healthy controls

Observational comparisons of the Concussion group to the Healthy control group in the Cognitive Task revealed that concussion may result in increased Step Length Variability in women. However, this observation was not made in the male group. Therefore, it is possible that concussions may affect women more than men, which is in line with the fact that women had a higher symptom severity score

than men. A systemic review found that the differences in symptom reporting may be due to men's increased ability to withstand axonal damage, particularly in the corpus collosum (Solomito, Reuman, & Wang, 2019). This could be an explanation for why women might increase their Step Length Variability post-injury and men may not. Since women tend to rely more on interhemispheric connections than men, and since the corpus collosum has been identified as having the largest amount of shear and strain in concussion injury (Solomito et al., 2019), it stands to reason that extent of concussion impact in women would be greater. However, these results were not observed in the Motor Tasks, highlighting the added effect that the cognitive challenge may have had. While the task of walking itself may not illicit an increase in Step Length Variability (as observed in the Self-paced condition), the cognitive challenge during the walk did. Hence, cognitive tasks during gait may be useful in identifying concussion-induced alterations in gait in women only, rather than single-gait tasks.

Results of the observational comparison also revealed that men may reduce their Cadence and increase their Step Length post-injury during Cognitive Tasks. Given that Velocity was similar between the two groups, it seems that the increase in Step Length may be compensated by the decrease in Cadence. The injury may lead men to increase the use of step length strategy to achieve gait velocity when under a cognitive challenge. If, as in the case of the women, the cognitive challenge may lead to more deficits, then it could be that men choose to focus more on the step length strategy to mitigate the challenge. Since longer step length is generally associated with strategies that men use to achieve gait velocity, this may be a reason for the observations in the male group.

It is important to note that the sample sizes of the Concussion and Healthy control groups in this study were not comparable which may have contributed to the outcome. Future studies involving statistical analyses would need to be performed to verify the conclusions of this observational analysis.

Limitations and future studies

This study is not without its limitations. The sample size of the Healthy control group was considerably smaller than that of the Concussion group and comparisons were observational. Inclusion of a larger sample size of Healthy controls would have permitted statistical comparison of healthy individuals to people with concussion. Additionally, when analysing the Cognitive Tasks, task accuracy was not taken into consideration. Future studies are required to see if the number of errors in the cognitive task has an impacted on the cognitive effects on gait velocity determinants. Future studies are also necessary to more strongly establish the relationship between sex and step length during motor challenges in people with concussion and identify possible reasons for the observed results.

Conclusion

In conclusion, this study found that sex affects the relationship between cognitive and motor function and gait velocity determinants in people with concussion. Inherent sex differences may contribute to the increased step length variability observed in women but are likely amplified by the injury. Women also tend to take shorter step lengths when subjected to a motor challenge and employ different strategies to achieve gait velocity in the absence of a cognitive task. The results of this study are important in providing guidance to clinicians regarding specialized concussion rehabilitation approaches that can be applied. Currently there is a tendency for clinicians to apply a certain set protocols for concussion patients. For instance, clinicians may suggest taking physical and cognitive rest until the resolution of acute symptoms (Broglio, Collins, Williams, Mucha, & Kontos, 2015). According to the International Concussion in Sport Group, until acute symptom resolution, physical and cognitive rest are considered fundamental components of concussion management (McCrory et al., 2013). While such recommendations may be based in scientific research, they are also based on the premise that most, if not all, concussions are similar and have similar impacts. The present study focussed on specific factors

that may influence the nature and impact of a concussion, specifically with regards to the cognitive and motor effects that concussions have. Identification of sex differences in the impact of cognition and motor function in the gait of people with concussion allows aspects of concussions that relate to step length and cadence to be viewed from a more individualised perspective. This will allow clinicians to consider the sex of the patient in developing and suggesting treatment methods. Therefore, the results of this study allow for concussion rehabilitation programs to be reassessed for effectiveness and will aid clinicians in applying treatment methods that are more specific to individual deficits.

Chapter 3: Predictors of Cognitive and Motor capacity in Community-Dwelling Adults

Abstract

Community-dwelling adults with concussion experience deficits in cognitive and motor function. In the absence of baseline measures, post-concussion deficits and recovery over time can be assessed by measuring capacity – the difference in an outcome between a simple and difficult task. The purpose of this study is to identify the predictors of Cognitive and Motor capacity up to 4 months post-injury in individuals with concussion. Spatiotemporal gait measures of Step Length, Cadence, Velocity, and Step Length Variability of community-dwelling adults with concussion were used to assess capacity in cognitive and motor domains. Stepwise linear regressions were performed to determine whether the factors of Age, BMI, Education level, Sex, and Symptom severity were predictive of Cognitive and Motor capacity at various time points post-injury. Results showed that Age, BMI, Education level, Sex, and Symptom severity together were not predictive of Motor or Cognitive capacity at any of the selected time points. These factors did predict measures of Cognitive and Motor capacity individually, but the correlations were weak as adjusted R^2 values ranged from -0.013 to 0.199. Education level and Sex were the most common predictors of Cognitive and Motor capacity respectively. A secondary analysis of absolute gait measures (rather than capacity) showed that BMI was the most common predictor of normalized Step Length, irrespective of the condition or time point post-concussion. Symptom severity was rarely a predictor for any of the measures of interest, suggesting that self-reported symptoms may not be a reliable marker of concussion-induced gait impairment. Overall, the findings of this study highlight the uncertainty surrounding concussion recovery patterns.

Introduction

A common form of injury faced by many Canadians is concussion. Concussion is particularly common among Ontario residents. The annual incidence rate of concussions in Ontario is 1.2% in the community-dwelling population (Langer et al., 2020). Concussions involve a complex pathophysiological process that affects the brain and results from biomechanical forces (Ontario Neurotrauma Foundation, 2013).While there are many side effects to concussions, one of the impacts of concussion is gait impairment. Given the role that gait plays in allowing people to move around and interact with the environment, the effects that concussion has on gait can limit participation in activities of daily living. Gait velocity in particular is an important part of gait that is impacted by concussion. Studying gait velocity is important because of its association with overall health and incident disability (Rosano et al., 2008; Studenski, 2011). Previous concussion research has shown that lower gait velocity and shorter stride lengths in dual gait task are observed in youth participants within 2 days of injury (Parker et al., 2006). Adolescents also exhibit shorter stride lengths 3 weeks post-injury (Berkner et al., 2017). This same group of adolescents had impaired stride lengths while performing a dual gait task after symptom resolution as well (Berkner et al., 2017). Therefore, concussion does impact gait velocity and its determinants.

The cognitive and motor deficits that occur following concussion can be measured in multiple ways and are often used by clinicians to assess impairment due to concussion (Kontos & Collins, 2018). Results of such assessments are usually compared to normative or baseline values to identify the level of impairment and rate of recovery over time. However, normative or baseline values may not always be available for individuals with concussion, especially in the community-dwelling population. Another way to assess impairment due to concussion and injury recovery would be to observe one's ability to respond to an increase in task challenge. This way, the difference in performance of a simple and complex motor or cognitive task can explain concussion-induced impairment on an individual level. This difference in performance can be defined as capacity. If motor or cognitive capacity is analysed over a

period of time, then such variables can be important indicators of recovery. The benefit of this approach is that it removes the need for assessment results to be compared to that of healthy controls. Considering the variability that exists in concussion injury, this approach would be beneficial in helping clinicians better understand individual deficits of concussion patients. Previous accounts of capacity in the literature include medical decision-making capacity (MDC), which has been studied in terms of concussion. A study found that in people with traumatic brain injury, one's ability to make medical decisions, or consent capacity, was strongly related to severity of injury (Triebel et al., 2012). Impairment in consent capacity has been strongly associated with cognitive functions such as short-term verbal memory, and executive functioning and working memory has been associated with capacity improvement in people with TBI (Dreer, DeVivo, Novack, Krzywanski, & Marson, 2008). Therefore, the use of capacity to understand concussion is not novel and has been established in the literature.

If cognitive and motor capacity is to be used to identify concussion deficits, then the predictors of these variables must be understood. Identifying the predictors of cognitive and motor capacity would provide insight to the factors that contribute to the level of deficit at a given moment in time, or that influence recovery patterns. Possible predictors of cognitive and motor capacity can, among others, include: Age, BMI, Sex, Education level, and Symptom severity post-concussion. These are possible predictors because they are all somehow associated with cognitive and motor function. With regards to cognitive function, older individuals are found to have worse mobility performance when walking while simultaneously performing a cognitive task (Brustio, Magistro, Zecca, Rabaglietti, & Liubicich, 2017). BMI is negatively associated with cognitive function in athletes (Fedor & Gunstad, 2013). Education level has been found to affect cognitive performance (Guerra-Carrillo, Katovich, & Bunge, 2017). Women are reported to have better perceptual speed and accuracy, while men perform better on visual-spatial tests (Weiss, Kemmler, Deisenhammer, Fleischhacker, & Delazer, 2003). Lastly, difficulty remembering and concentrating are examples of self-reported cognitive symptoms of concussion on the SCAT3 (Ontario

Neurotrauma Foundation, 2013). With regards to motor function, increased mediolateral gait instability is observed in certain age groups (Terrier & Reynard, 2015). Lower gait velocity is observed in people with very high BMI (Lai, Leung, Li, & Zhang, 2008; Runhaar, Koes, Clockaerts, & Bierma-Zeinstra, 2011). Functional limitations are reported to be more common in poorly educated people (Hoogendijk, Groenou, Tilburg, & Deeg, 2008). Sex differences are observed in non-pathological gait (Frimenko et al., 2015), and balance problems and dizziness are examples of self-reported symptoms of concussion on the SCAT3 that may impact motor control (Ontario Neurotrauma Foundation, 2013). Therefore, Age, BMI, Education level, Sex, and Symptom severity are all generally associated with cognitive and motor function. For this reason, it is reasonable to consider that these factors may predict cognitive and motor capacity post-concussion as well. The purpose of this study is to identify the predictors of Cognitive and Motor capacity during 4 months of concussion recovery in community-dwelling adults. It is hypothesized the Age, BMI, Education level, Sex and Symptom severity together will predict both Cognitive and Motor capacity.

Methods

Participants

This is a retrospective study that looks at data collected at the Hull-Ellis Concussion and Research Clinic. The Hull-Ellis Concussion and Research Clinic at the Toronto Rehabilitation Institute provides care to concussion patients who are referred from emergency departments of Toronto General Hospital, Toronto Western Hospital, Mount Sinai Hospital, Michael Garron Hospital, St. Joseph's Health Centre and Sunnybrook Health Sciences Centre within one week of injury. Research is then conducted on these patients if they provide consent. Participants from this study were all referred from Toronto Western and Toronto General Hospital emergency departments. This study was approved by the Research Ethics Boards at UHN (REB #15-9214) and York University (e2020-226).

Inclusion and exclusion criteria

The clinical inclusion criteria were as follows: if imaging was deemed necessary, there were no positive neuroimaging findings or focal neurological findings, Glasgow Coma Scale score of 13-15 on presentation to the emergency department, between 18-85 years of age, BMI < 30, concussion diagnosis by an emergency department physician, participant agreed to attend first appointment within 7 days of injury, and enough English language proficiency to complete all tests in this study (Grade 6 reading level or higher).

Participants were excluded from the study if they met any of the following criteria: in-patient admission to hospital for the injury, symptomatic from a previous concussion that occurred within the last 3 months, eligible for third party insurance claims (i.e., injury occurring due to a motor vehicle accident or workplace injury), referral from a community physician, the first physician assessment at the Hull-Ellis Concussion and Research Clinic was more than 7 days post-injury, previous musculoskeletal injury characterised by previous joint replacement surgery, previous other orthopaedic surgery, previous other lower limb condition/injury (causing muscular or joint pain or limited range of movement), or previous back pain or injury and had data missing necessary for analysis.

Data collection

All gait data for this study was collected across a span of 3 years (2016-2019). Data for each participant was collected at 1, 2, 4, 8, 12, and 16 weeks post-injury. Data was collected using a pressure-sensitive gait mat (GaitRite, CIR Systems, Clifton, NJ) that was 4.6 meters long. Participants were instructed to walk across the mat in various conditions. For each condition, 16-18 footfalls were recorded as this was deemed as a sufficient amount of data for analysis. The first condition was the Self-paced condition where participants walked across the gait mat at a self-selected pace. This condition served as the control task to the Maximum-paced condition where participants walked across the mat

as quickly as they could. The Talking condition involved participants counting upwards by ones from a 3-digit number while walking across the gait mat. This condition served as the control task to the Dual Task condition, where participants counted backwards by sevens from a 3-digit-number (Hayman, 1942) while walking across the mat. The specific dual task selected for this study has been employed in previous studies and is known to significantly impact gait speed (Li et al., 2014). In both Talking and Dual Task conditions participants walked at a self-selected pace.

Measures of interest for all 4 conditions included Step Length (cm), Step Length CV (standard deviation/mean in %), Velocity (cm/s), and Cadence (steps/min). To account for possible anthropometric differences amongst participant groups, the variables of Step Length and Velocity were normalized to body height. Hence, Step Length was analyzed as a percent of body height.

All participants completed the Post-concussion Symptom Scale of the Sports Concussion Assessment Tool Edition 3 (SCAT3) (Guskiewicz et al., 2013) at each visit as well. Demographic information and relevant medical history, including sex, age, weight, height, highest level of education achieved, concussion history, previous health and mental health conditions, previous migraines and headaches, and time to first assessment post-concussion was also collected for each participant.

Primary Analysis

For this study, capacity was operationally defined as an improvement in behavior to match task's challenge. Cognitive and Motor capacity were calculated for each measure of interest. Cognitive capacity was calculated by subtracting the values for the Dual Task condition from those of the Talking condition.

$$Cognitive\ capacity = Talking - Dual\ Task$$

Motor capacity was calculated by subtracting the values for the Maximum-paced condition from those of the Self-paced condition.

$$Motor\ capacity = Self\text{-}paced - Maximum\text{-}paced$$

In this way, Cognitive and Motor capacity were defined as being the difference between the experimental and control tasks.

Statistical analyses were performed on RStudio (RStudio Team, 2020). The stat.desc() function in the pastecs package (Grosjean & Ibanez, 2018) was used to derive descriptive data. The analysis was performed on each of the time points at which data was collected. One walking trial was included in the analysis for each participant at each time point.

To probe the hypothesis that Age, BMI, Education level, Sex and Symptom severity predict Cognitive and Motor capacity, stepwise multiple linear regressions were performed. Symptom severity scores were derived from the symptom severity subscale of the SCAT3. Categorical data (such as Sex and Education level) was converted to nominal data. Data was grouped by week, and regressions were performed on Cognitive and Motor capacity values separately, at each of the 5 time points, for each of the 4 measures of interest. Stepwise regressions were performed using the ols_step_both_p() function in the olsrr package (Hebbali, 2020). The alpha to determine entrance ('pent' argument) and exit ('prem' argument) of a predictor in the model were both set to p = 0.05. The predicted model along with the adjusted R^2 values were recorded.

Prior to performing the stepwise regressions, the assumptions of a multiple linear regression were verified. Variance of inflation values were computed to check for multicollinearity of the predictors using the vif() function in the car package (Fox & Weisberg, 2019). Shapiro-Wilk Normality tests were performed on the residuals of the data using the shapiro.test() function in the stats package (R Core Team, 2020), where the significance value was set to p = 0.05. Histograms were generated for the residuals to verify and visualize the results of the Shapiro-Wilk test. Finally, residual verses fitted plots

were generated to ensure homogeneity of the data. All plots were generated using the ggplot2 package (Wickham, 2016). The full RStudio script for the primary statistical analysis of this study is reported in Appendix D.

Secondary Analysis

A secondary analysis was performed to see if the same factors that predicted Cognitive and Motor capacity would also predict the absolute values for each of the 4 conditions. For this analysis, the values for the control and experimental tasks were not subtracted from each other. Rather the raw values for each measure of interest predicted. Hence, these measures represented absolute values of the data. Analyses were performed for 4 measures of interest, in each of the 4 conditions, at each of the 5 different time points. To do this, stepwise linear regressions were performed. The stepwise regressions and their assumptions were computed the same way as in the primary analysis. Hence, the same RStudio functions and packages that were used in this analysis as in the previous analysis.

Results

Participant characteristics

In total, 48 participants met the inclusion criteria for the study. The participant characteristics for Concussion and Healthy control groups are summarised in Tables 1 and Table 2 respectively.

Table 4 *- Summary of participant characteristics.*

	All participants	Males	Females
Sample size	48	25	23
Age	33.9± 0.80	35.3 ±1.25	32.4±0.94
Education level			
Less than high school diploma	1	1	0
High school diploma	8	2	6
Incomplete post-secondary studies	2	1	1
Trade certificate/diploma or College, CEGEP, or other non-university certificate/diploma	7	5	2
Bachelor's degree	22	10	12
Master's degree	7	5	2
PhD	1	1	0
BMI	33.9±0.80	25.1±0.28	32.4±0.94
Symptom severity	41.2±1.66	37.9±2.21	44.7±2.46

Assumptions of multiple linear regressions

The variance of inflation value for each factor was between 1.12 and 1.27. This means that the collinearity among the predictors was very low and does not account for a major part of the variance observed in the results. For both the primary and secondary analysis, the Shapiro-Wilk tests for

normality showed that the residuals for at least half the groups were not normally distributed. After observing the histograms for each group, it was evident that for some of the groups the significant results observed in the Shapiro-Wilk test was due to outliers in the data, and not the overall distribution. Nonetheless, there were groups that were non-normally distributed. Given that linear regressions are robust again non-normal distributions of data (Knief & Forstmeier, 2021), this was not an issue in our analysis. Residual versus fitted plots for both primary and secondary values showed no particular pattern in the distribution of the data. Therefore, the data was considered to be homogeneous. All figures and tables associated with the assumptions of multiple linear regressions are reported in Appendix E.

Primary analysis

Values of Cognitive and Motor capacity for each participant at each time point are depicted in Figure 4, along with the mean value for each week. The models predicted by the stepwise linear regression for each variable for Cognitive and Motor capacity are summarised in Table 4. For every variable, each model had a maximum of 1 factor. The model for Velocity for Cognitive capacity at Week 16 has the lowest adjusted R^2 value (-0.01), and the model for Step Length for Motor capacity at Week 1 had the higher adjusted R^2 value (0.20). Hence, the predictive power for all models were weak. No particular patterns were observed for any given week, condition, or variable. The most common factor for Cognitive capacity, regardless of week or variable was Education level, and the least common was Symptom severity. Irrespective of week or variable, the least common factor for Motor capacity was Age, and the most common was Sex. Specifically, Sex was a predictor of Step Length and Cadence at 4 of the 5 time points. Symptom severity was not a common predictor for variables of Motor capacity either.

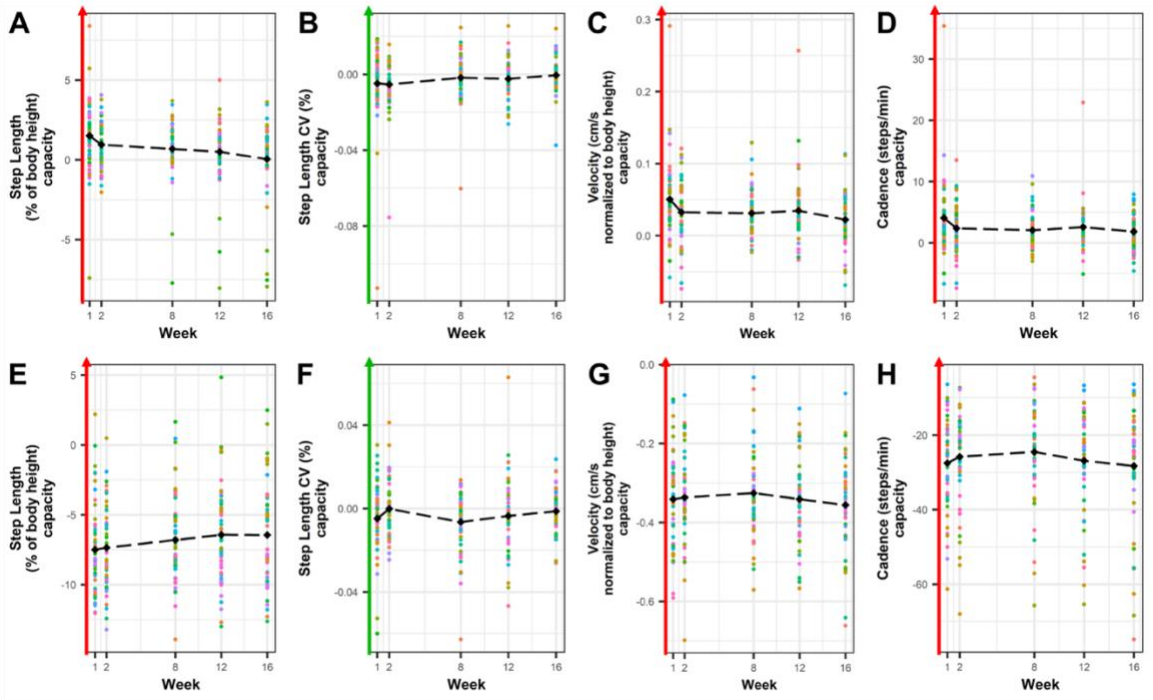

Figure 6 *- Cognitive (A-D) and motor (E-H) capacity values for each participant across 16 weeks post-injury. Black dots represent averages for each week. The black line represents the overall trajectory across the 4 months. Green arrows indicate improvement and red arrows indicate deficit at the magnitude of the capacity value increases.*

Table 5 *- Predicted models for Step Length (% of body height), Step Length CV (%), Velocity (actual velocity (cm/s)/body height (cm)), and Cadence (steps/min) for Cognitive and Motor capacity.*

		Week 1		Week 2		Week 8		Week 12		Week 16	
Condition	**Measure**	Model	Adj.R^2	Model	Adj.R^2	Model	Adj.R^2	Model	Adj.R^2	Model	Adj.R^2
Cognitive Capacity	Step Length	EL	0.04	A	0.03	S	0.01	S	0.03	EL	-0.01
	Step Length CV	SS	0.01	A	-0.01	EL	0.05	EL	0.05	B	0.07
	Velocity	S	0.05	EL	0.05	B	-0.00	S	0.01	EL	-0.01
	Cadence	S	0.01	EL	0.06	B	0.05	EL	0.02	EL	-0.01
Motor Capacity	Step Length	S	0.20	S	0.11	B	0.02	S	0.02	S	0.07
	Step Length CV	EL	0.04	EL	0.04	B	0.02	SS	-0.00	S	0.12
	Velocity	SS	0.03	B	0.04	S	0.07	B	0.08	B	0.09
	Cadence	SS	0.04	S	0.09	S	0.15	S	0.14	S	0.15

A = Age, B = BMI, EL = Education Level, S = Sex, SS = Symptom Severity

Secondary analysis

Absolute gait values for each condition and participant at each time point are depicted in Figure 5, along with the mean value for each week. The models predicted by the stepwise linear regression for the absolute variables of each condition are summarised in Table 5. For every variable, each model had either 1 or 2 factors. The lowest adjusted R^2 values was -0.011 (Step Length CV for the Dual Task condition at Week 1) and the highest R^2 value was 0.204 (Velocity for the Maximum-paced condition at Week 16). As in the primary analysis, the predictive power for all models were weak. Interestingly, BMI was a predictor for Step Length for all conditions, at every time point, except for Week 2. At Week 2, Sex was a predictor for Step Length. Irrespective of variable of condition, the most common predictor was BMI at weeks 1, 8, 12, and 16, and Sex at Week 2. BMI was also the most common predictor for each condition, regardless of week or variable. Moreover, Symptom severity was rarely a predictor for any of the models.

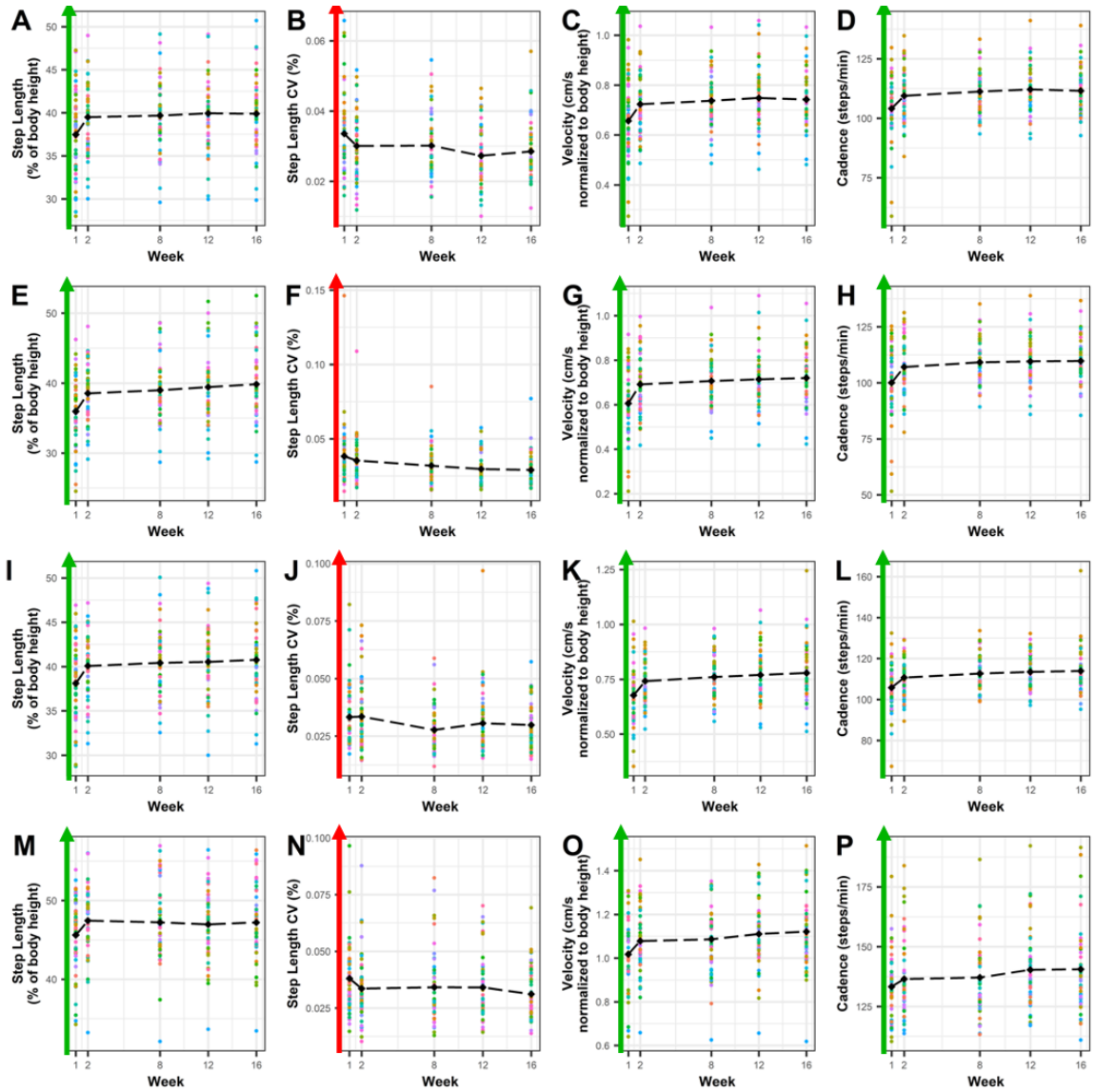

Figure 7 *- Step Length (% of body height), Step Length CV (%), Velocity (actual velocity (cm/s)/body height (cm)), and Cadence (steps/min) values for Talking (A-D), Dual Task (E-H), Self-paced (I-L), and Maximum-paced (M-P) conditions for each participant across 16 weeks post-injury. Black dots represent averages for each week. The black line represents the overall trajectory across the 4 months. Green arrows indicate improvement and red arrows indicate deficit as the magnitude of the value increases.*

Table 6 *- Predicted models for Step Length (% of body height), Step Length CV (%), Velocity (actual velocity (cm/s)/body height (cm)), and Cadence (steps/min) in each condition.*

		Week 1		Week 2		Week 8		Week 12		Week 16	
Condition	**Measure**	Model	Adj.R^2	Model	Adj.R^2	Model	Adj.R^2	Model	Adj.R^2	Model	Adj.R^2
Self-paced	Step Length	B	0.06	S	0.12	B	0.06	B	0.05	B	0.04
	Step Length CV	B	0.03	B	0.01	SS	0.03	B	0.00	A	0.13
	Velocity	B	0.03	S	0.14	B	0.05	B	0.06	S	0.08
	Cadence	A	0.04	S EL	0.05 0.12	S	0.01	S	0.02	S	0.08
Maximum-paced	Step Length	B	0.07	A	0.06	B	0.10	A B	0.11 0.19	B A	0.09 0.14
	Step Length CV	B	0.01	A	0.04	B	0.05	B	0.01	A	0.15
	Velocity	B	0.11	S	0.13	S EL	0.12 0.20	B	0.18	B A	0.14 0.20
	Cadence	B	0.04	S EL	0.14 0.20	S	0.18	S	0.18	S	0.17
Talking	Step Length	B	0.02	S	0.07	B	0.04	B	0.05	B	0.02
	Step Length CV	A	0.01	A	0.06	A	0.12	A	0.09	SS	0.04
	Velocity	B	0.04	S	0.09	EL	0.05	S	0.06	B	0.06
	Cadence	A	0.03	EL S	0.07 0.15	EL	0.05	S	0.05	S	0.07
Dual Task	Step Length	B	0.01	S	0.06	B	0.04	B	0.03	B	0.01
	Step Length CV	S	0.03	S	-0.01	E	0.04	E	0.02	A	0.09
	Velocity	B	0.03	EL S	0.05 0.11	B	0.06	B	0.04	B	0.05
	Cadence	B	0.02	E	0.12	B	0.04	E	0.04	S	0.07

A = Age, B = BMI, EL = Education Level, S = Sex, SS = Symptom Severity

Discussion

The aim of this study was to identify predictors of Cognitive and Motor capacity during the 4 months of concussion recovery in community-dwelling adults. The results showed that in the community-dwelling population, Age, BMI, Education level, Sex, and Symptom severity together do not predict Cognitive or Motor capacity in people with concussion. Rather, these factors were found to predict different Cognitive and Motor capacity measures individually, and weakly. Education level was identified as the most common predictor of Cognitive capacity measures, and Sex was the most common predictor of Motor capacity measures. While BMI and Step Length seem to be correlated, there seems to be a poor relationship between self-reported symptoms and measures of gait velocity post-concussion.

Predictors of Cognitive and Motor capacity

The present study found no clear pattern in the models that predicted each of the measures for both Cognitive and Motor capacity. Additionally, the factors seemed to be individually associated with the outcome measures. Both these findings have previously been observed in the literature. A systematic review looking at the predictors of clinical recovery of concussion concludes that the literature generally shows mixed results in terms of clinical recovery (Iverson et al., 2017). For instance, with regards to age, a study found that compared to college athletes, high school athletes has longer memory dysfunction post-injury (Field, Collins, Lovell, & Maroon, 2003). In contrast, a study looking at factors associated with delayed return to play after injury found no association between younger age and poor outcome post-injury (Asplund, Mckeag, & Olsen, 2004). Similarly, with regards to sex, females have been found to have longer concussion recovery times (Baker et al., 2016). Yet, a previous study analysing the same age group did not identify such a relationship (Moor et al., 2015). Therefore, the literature does present inconsistences in the predictors of clinical recovery of concussion.

The review by Iverson et al. (2017) also acknowledges that multiple studies see a decrease in significant univariate correlates of outcome measures related to concussion recovery when applying a multivariate model. Hence the findings of the present study correlate with those of previous studies, thereby confirming the idea that individual factors may not interact with each other in terms of predicting clinical recovery patterns, which are themselves variable.

Despite there not being a clear pattern in the results, Education level was observed to be the most commonly selected factor for measures of Cognitive capacity. This correlation between Education level and Cognitive capacity is not unexpected. A study looking at the effects of higher education on cognitive functioning and learning efficacy found a small, yet significant, effect of education level on cognitive performance (Guerra-Carrillo et al., 2017). Additionally, more years of full-time education is also associated with thicker mediofrontal, parietal, somatosensory and motor cortices in older adults (Cox et al., 2016). Frontal and parietal brain regions have also been associated with gait speed (Lee, Kim, & Shin, 2019). Given that decreases in brain volume have been observed in people with concussion (Spitz et al., 2013), it is possible that people with a higher Education level may have better Cognitive capacity in relation to gait velocity as these individuals have a larger brain volume in the first place. In this way, Education level may serve as a weak, yet protective, mechanism to gait deficits resulting from concussion. However, a study looking at the correlation between brain volume and dual task performance in people with cognitive impairment found that decreased brain volumes leads to more motor-prioritization during dual task gait (Longhurst et al., 2020). Based on this paper it would be unexpected for Education level to be predictive of Cognitive capacity during gait. Although, the study by Longhurst and colleagues (2020) focussed on people with mild cognitive impairment and dementia. However, the level of cognitive impairment in our participant group was unknown. Hence, the findings of Longhurst et al. (2020) may not be applicable to the present study. Therefore, it is more likely that

Education level was commonly predictive of Cognitive capacity because of its association with larger brain volume.

Just as Education level was the most common predictor for Cognitive capacity measures, Sex was the most common predictor for measures of Motor capacity. Specifically, Sex on its own predicted Step Length and Cadence at 4 of the 5 time points examined. These results are in line with the findings of Study 1 (Khimji et al, unpublished), where Sex differences were observed in the use of Step Length or Cadence to achieve Velocity in the Maximum-paced condition. The reduced presence of Sex as a predictor among Cognitive capacity values also aligns with the lack of a Sex effect observed in Step Length and Cadence in the Cognitive Tasks of Study 1. Therefore, not only do these results support the notion that men and women use different strategies to achieve gait velocity, but they also emphasize the point that the cognitive load may inhibit these patterns. The less this cognitive load impacts these patterns, the better one can effectively perform cognitive and gait tasks simultaneously as they have a higher Cognitive capacity. The idea of interference between gait and cognitive tasks is not new. Haggard and colleagues (2000) conducted a study on 10 healthy people and 50 patients in neurological treatment units where patients were asked to perform a series of cognitive tasks while walking. Results showed that interference between cognition and gait was present in people with brain injury as significant decrements in cognitive function and gait were observed (Haggard, Cockburn, Cock, Fordham, & Wade, 2000). However in Healthy controls the decrements were either small, or not observed at all (Haggard et al., 2000). A study looking at concussion in particular found similar results, where participants who performed a Stroop task while walking exhibited slower reaction times in the cognitive task and adapted a more conserved gait strategy (Catena, van Donkelaar, & Chou, 2011). Hence, cognitive-gait interference is a possible reason for the findings of the present study.

BMI as a predictor of Step Length

BMI was found to be a predictor of absolute Step Length at all time points except Week 2. The fact that Step Length was most commonly associated with BMI is expected as high BMI has been associated with stride length before. A study comparing gait velocity measure in obese and eutrophic women, as defined by BMI, found that obese women have lower step length, cadence, and velocity measures (da Silva-Hamu et al., 2013). Similar results have been observed in studies that look at men, or mixed groups of men and women (Lai et al., 2008; Spyropoulos, Pisciotta, Pavlou, Cairns, & Simon, 1991). Therefore, the finding of BMI being a predictor for Step Length at majority of the time points is understandable. However, that Sex was a predictor of Step Length in all conditions at 2 weeks post-injury, and not at any other time points is surprising. Results of Study 1 showed that men and women had different Step Length measures when walking at maximum pace 1-week post-injury. Sex differences in step length are observed in healthy people in self-paced gait as well (Frimenko et al., 2015). Based on these results one would expect Sex to be a predictor for Step Length in at least the Maximum-paced condition at Week 1 post-concussion. It seems that BMI and Sex together could not be predictors of Step Length or any other variables. This observation suggests that a Sex x BMI interaction may not exist with regards to gait velocity determinants post-concussion. However, since to our knowledge no studies have looked at Sex x BMI interactions in gait velocity determinants post-injury, future studies need to be performed to verify this conclusion.

Symptom severity and concussion-induced gait impairment

Symptom severity was rarely considered to be a predictor of any of the measures in this study. Symptom severity was calculated based on the SCAT3 symptom severity subscale, a scale that involves self-reporting of symptoms. The lack of correlation between self-reported symptoms and gait measures post-concussions points to the disconnect between subjective experiences of concussion injury and

objectively measured outcomes. Self-reporting of symptoms may not be a reliable source of identifying concussion-induced alterations in gait. A study comparing subjective and objectively measured balance disturbances in people with concussions derived a similar conclusion (Inness et al., 2019). It was suggested that relying exclusively on symptom reporting may result in inaccurate diagnoses of balance impairment (Inness et al., 2019). A later study looking at balance deficits in community-dwelling people with concussion also observed a poor relationship between clinical measures of balance and self-reported balance symptoms (Sweeny et al., 2021). Based on the results of the present study and previous research it can be concluded that using self-reported measures of symptom severity only may result in inaccurately defining level of impairment due to concussion. While this does not invalidate the subjective experiences that people with concussion face, it does have implications for clinical concussion management programs.

Limitations and future studies

There are limitations to this study. Cognitive capacity was defined by performance of the gait task; however, cognitive task accuracy was not considered. Future studies can include number of errors in the counting task in the model. Alternatively, cognitive task accuracy can be accounted for in the calculation of Cognitive capacity measures. Since Education level was associated with Cognitive capacity measures, it would also be beneficial to study the relationship between Education level and correlates of cognition, such as brain volume in people with concussion. This would help identify whether or not education level is protective against concussion injury. Future studies may also focus on identifying whether Sex x BMI interactions exist in relation to step length post-concussion. Such studies would better inform the observed results of this study.

Conclusion

This study does not support the hypothesis that Age, BMI, Education level, Sex, and Symptom severity together predict Cognitive and Motor capacity in people with concussion. If these factors predicted measures of Cognitive and Motor capacity individually, they did so weakly. No pattern was observed across the different time points or conditions, although Education level and Sex were most commonly predictive of Cognitive and Motor capacity respectively. While BMI was associated with absolute Step Length, self-reporting of symptoms did not seem to correlate with objective measures of gait velocity. The results of this study are beneficial in enhancing concussion management protocols that currently exist. The fact that no clear pattern was observed in terms of predictors of impairment over a span of 4 months post-injury shows that recovery trajectories for concussion in community-dwelling adults are variable and unpredictable. However, it is possible that more consistent patterns may be observed when examining other factors such as concussion history. Since concussions can have long-term effects, it is possible that a history of concussion may leave an individual more vulnerable to a more severe injury in the future. A good example of this is the case of 17-year-old rugby player who died as a result of second impact syndrome (Tator et al., 2019). While this case study involves repeated concussions within a short amount of time, if concussions can have a long-term effect, then it would be worth further investigating concussion history as a possible predictor of impairment due to concussion.

Overall, the lack of patterns observed in this study highlights that a single protocol may not be suitable for everyone. These results emphasize the need for individualized treatment plans that align with objective measures of concussion to be applied when treating concussion patients. While general guidelines for concussion recovery have been created by organisations such as the Ontario Neurotrauma Foundation (2013), it is important for clinicians to bear in mind the uncertainty that exists in recovery patterns of concussion, as evidenced in the present study.

Chapter 4: General Discussion and Conclusion

This thesis focusses on the factors that affect the determinants of gait velocity in community-dwelling people with concussion who are subjected to cognitive and motor challenges. In Study 1 the effects of sex on the relationship between cognitive and motor function and the determinants of gait velocity were examined. Sex was found to influence the determinants of gait velocity in the Motor Tasks, and Step Length Variability in both Cognitive and Motor Tasks. Study 2 showed that the predictors of Cognitive and Motor capacity are variable at different time points and for different measures of gait. Together the results of Study 1 and 2 inform our understanding of concussions in the community-dwelling population. Specifically, this thesis contributes to our knowledge of the relationship between sex and concussion, the ways in which cognitive and motor challenges influence the determinants of gait velocity, the use of determinants of gait velocity as a measure of gait dysfunction post-injury, and the predictors of concussion-related alterations in gait. This section will consolidate views on these concepts. In addition, an updated conceptual model will be proposed based on the findings of this research. The limitations of this thesis and suggestions for future steps will also be outlined.

Many studies have attempted to explain sex differences in concussion injury. Some studies have used imaging techniques to look at pathophysiological sex differences in concussion (Koerte et al., 2020). However, majority of studies characterise sex differences in concussion based on symptoms of injury. Symptoms are often identified by clinical tests based in self-reporting. Objective functional tests such as BESS and neurocognitive tests such as ImPACT have also been used for this purpose. Sex differences post-concussion have been further defined by gait analyses and measures of heart rate variability. While such studies struggle to directly relate their findings to the pathophysiology of concussion, they provide insight to the behavioural and neurological consequences of the injury.

The results of this thesis contribute to this aspect of the literature. It is important to characterise behaviour because impaired behaviour may have implications for performance in activities of daily living. This is especially important in the community-dwelling population where the goal of rehabilitation is to return to normal life, rather than return to play as is the case of athletes. If the behavioural consequences of concussion are understood, then clinicians can better target such consequences, thereby allowing patients to return to their normal lives sooner. Given that the literature on concussion and sex differences focusses mostly on sport-related concussion, the contributions of this thesis can be more easily generalised to a larger portion of the population that does not participate in high-level sport.

This thesis specifically focussed on gait measures of Step Length, Step Length Variability, Velocity and Cadence. Regarding Step Length Variability, given its association with metabolic cost of transport (Rock et al., 2018), and the sex differences observed in Study 1, it can be considered a measure of gait dysfunction. More varied step length implies less control and stability in gait, which suggests more impairment due to concussion. Given previous accounts of increased metabolic cost of transport in healthy men and women (Browning et al., 2006), and increased step length, step time, and stride velocity variability in women of the general population (Johansson et al., 2016), it may be seem that the observed sex differences in Step Length Variability in Study 1 were not due to the concussion itself. However, the results of the observational analysis suggest otherwise. Therefore, while inherent sex differences may have contributed to the observations in Study 1, the concussion seems to have amplified the sex differences in step length variability. This verifies the idea that step length variability is not only a measure of gait dysfunction, but may be a measure for concussion as well.

With regards to Step Length, Cadence, and Velocity, the patterns observed in men and women who walked at Maximum and Self-paced gait were similar to those observed in healthy people. Yet these patterns seemed to be disrupted when participants were subjected to a cognitive challenge. Therefore,

measures of Step Length, Cadence, and Velocity during cognitive dual task gait may not be effective measures of the impact of concussion. This is in part because it seems that the processes related to cognitive function and attention are more impacted by concussion than those related to motor function and control. If dual task gait involving a cognitive task were to be used to identify gait deficits in people with concussion, it would be challenging to discern whether the observed deficits are a result of the concussion or of the added cognitive challenge. Hence, cognitive dual gait tasks may not be the most effective way to identify sex specific differences post-concussion.

A theme observed across both studies was that Sex did not seem to relate to gait measures in the cognitive domain. Sex differences observed in the cognitive domain were also seen in the motor domain. With regards to the Motor Tasks, few studies have looked at sex differences in the patterns of gait velocity determinants at maximum versus self-paced gait. To my knowledge, this study is the first to compare maximum and self-paced gait to identify sex differences post-concussion. From the results we see that an added motor challenge results in lower Step Lengths in women than in men. This shows that comparing maximum and self-paced gait may be an effective way to assess the behavioural consequences of concussion in men and women.

Sex was not the only correlate to be examined in this thesis. While Age, BMI, Education level, Sex, and Symptom severity together were not predictive of Motor or Cognitive capacity, capacity seemed to be individually predicted by some of these factors. The fact the Symptom severity was rarely a predictor of Cognitive and Motor capacity, shows the self-reported symptoms may not be an effective marker of concussion severity. The variability observed in the models at various time points also highlights the variability that may exist in concussion recovery overall. It can be concluded that currently there may not be a single effective way to characterise concussion-induced impairment in gait. More research is required to identify other correlates that may be more reflective of concussion injury.

Revisiting the conceptual model

This thesis aimed to assess the factors that affect the determinants of gait velocity in people with concussion and was framed by the conceptual model presented in Chapter 1. In the original model, sex was predicted to influence the relationship between gait velocity determinants and cognitive and motor function. Age, BMI, Education level, Sex, and Symptom severity were together thought to predict Cognitive and Motor capacity. Based on the findings of Studies 1 and 2 a revised conceptual model is proposed (Figure 6). The details of the model reflect how Step Length Variability differed among sexes, outside the context of cognitive and motor function. Sex also influenced the motor, but not cognitive, contribution to the determinants of gait velocity. Age and Symptom severity were rarely found to influence Cognitive and Motor capacity, but relationships between Education level and Cognitive capacity, and Sex and Motor capacity were observed. A relationship between BMI and Step Length was also observed, irrespective of cognitive or motor function. Any observed relationships were independent as neither of these factors were found to influence Cognitive and Motor capacity together.

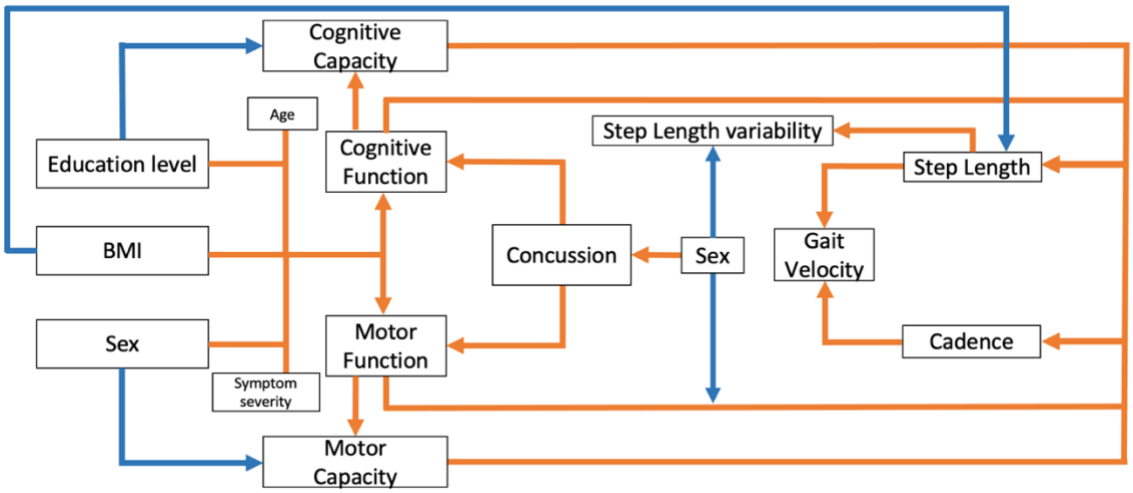

Figure 8 *- Alternative conceptual model based on the findings of this thesis. The orange arrows represent previously known relationships. The blue arrows represent relationships that were identified in this research.*

The revised conceptual model shows that biological sex does play a role in concussion. Impairment due to concussion and treatment cannot be considered the same way for men and women. Often times people with concussion are recommended to take a lot of rest and return to work or play once symptoms resolve (Ontario Neurotrauma Foundation, 2013). These return-to-activity guidelines are generally not specific to biological sex. For instance, a set of guidelines that was compiled by the Ontario Neurotrauma Foundation for professionals treating mTBI patients suggests that high school students who sustain a concussion should gradually start attending school within 2 weeks of injury, even if they are still symptomatic. This guideline is applied to both sexes. Although the results of this thesis are specific to community-dwelling adults, and not adolescents, the guidelines by the Ontario Neurotrauma Foundation do not specify sex-specific protocols either. Yet, by the results of this thesis the impacts of concussion differ amongst men and women, suggesting that recovery times may be different as well. Therefore, treatment guidelines must be adapted to be more sex-specific, not only in terms of their injury management protocols, but also with regards to recovery timelines.

Moreover, self-reported symptoms are used in clinical assessments of concussion. General practitioners may not assess objective measures of concussion before prescribing steps for recovery. While the subjective symptoms that patients experience post-injury is not to be ignored, it should not be a basis for determining the level of impairment due to concussion. Clinically, less reliance should be placed on self-reported symptoms, and more reliance should be placed on objective measures instead. This does not suggest that the subjective experiences of people with concussion should be undermined. While self-reported symptoms may not be an effective determinant of impairment due to concussion, steps should still be taken to manage them. Overall, the findings of this thesis suggest a need for greater focus on sex-specific treatment protocols, and objective measures of concussion in the clinical setting.

Limitations and future studies

While the conceptual model reflects what is known about concussion and the determinants of gait velocity, there is room for more research. The Covid-19 pandemic forced a stop to the data collection, thereby preventing sufficient Healthy control data to be collected to enable statistical comparisons with the Concussion group. This was one of the challenges of performing a retrospective analysis, where the data being used was collected prior to the exact analysis procedure being determined. The lack of statistical comparison made it challenging to determine whether the observations in the Concussion group in Study 1 were due to the injury itself, or other reasons such as inherent sex differences. Although conclusions about the effects of the injury were based in the literature, other studies were not necessarily conducted the same way. To verify the conclusions of the present research, it would be beneficial to repeat this study with a larger group of Healthy controls so that statistical comparisons between healthy and concussed people can be made, and more concrete conclusions about the effects of concussion can be determined. Although, the observational analysis did provide some insight on how the Concussion group compared to the Healthy control group and can serve as a preliminary analysis and starting point for future studies. While the comparison to the Healthy group was observational, all other analyses were statistical allowing for concrete conclusions to be made about the Concussion group.

Another limitation to this thesis is the fact that cognitive task accuracy was not considered. There is a possibility of a trade-off between task accuracy and gait performance, where better gait performance may have lead participants to make more errors in the counting task. Future studies should account for the number of errors in the cognitive task, either by including the number of errors as a covariate, or normalizing gait values to the number of errors. This way, the extent to which the cognitive task may interfere with the strategies used to achieve gait velocity will be clarified.

Lastly, future studies can focus on other factors that may impact concussion injury and recovery. The factors examined in this thesis were either rarely considered predictors, or were weak predictors of concussion-induced gait deficits. This does not suggest that other factors cannot be predictive of the injury. For instance, an individual with a history of concussion may be vulnerable to a more severe injury if they sustain another concussion. Socioeconomic status may impact concussion recovery too as individuals with a lower socioeconomic status may not have as much access to treatment. Since the participants in this study were recruited from an urban area, there is a likeliness that they may recover sooner than people living in a rural area where there are fewer hospitals and treatment centers. Therefore, future studies can focus on identifying the impact that these factors may have on concussion injury and recovery. It is also noteworthy that individuals who agree to participate in concussion research may not necessarily be individuals with a severe concussion injury, yet concussion recovery may be more pertinent to people with severe injury. Hence, when it comes to participant recruitment, studies should focus on targeting the group of people to whom the results would be most applicable. Conducting research that takes these elements into consideration will be beneficial in identifying factors of concussion injury which can then be used to create treatment protocols that are more standardized and applicable to the majority of the population.

Final conclusions

In conclusion, this thesis used the determinants of gait velocity in cognitive and motor tasks to characterise sex differences in concussion. This thesis also aimed to identify predictors of concussion-induced gait alterations at various time points. The results of this research add to the literature related to concussion in the community dwelling population. Specifically, evidence was provided to support the idea that sex does influence gait velocity and its determinants post-injury, particularly when participants are subjected to a motor challenge. Factors such as Age, BMI, Education level, Sex, and Symptom

severity are not predictive of Cognitive and Motor capacity together; however, BMI, Education level, and Sex may individually relate to Cognitive and Motor capacity. The lack of correlation between Symptom severity and measures of deficits due to concussion highlights the disconnect between subjected experiences of injury and objective measures of concussion. This thesis provides insight to the factors that affect concussion injury in the general population.

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Appendices

Appendix A: RStudio script for Study 1

```
#Change default setting 'helmert' contrast
(this allows ANOVA output to be calculated properly)
options(contrasts = c("contr.helmert", "contr.poly"))

#Call necessary packages
library(dplyr)
library(ggplot2)
library(ggpubr)
library(rstatix)
library(DescTools)
library(car)



### ASSUMPTIONS OF ANOVA COMPUTATIONS ###

#Shapiro test for residuals of the data

shapiro.resid<-rbind(
         (lm(StepLengthNorm~Sex*Condition,data=data)%>%resid%>%shapiro_test),
         (lm(slcv.log~Sex*Condition,data=data)%>%resid%>%shapiro_test),
         (lm(VelocityNorm~Sex*Condition,data=data)%>%resid%>%shapiro_test),
         (lm(Cadence~Sex*Condition,data=data)%>%resid%>%shapiro_test)
)


shapiro.resid<-as.data.frame(shapiro.resid)
shapiro.resid$variable<-NULL
shapiro.resid$Variable<- c("Step Length (% of body height)",
                           "Log Transformed Step Length CV (%)",
                           "Velocity (cm/s normalized to body height)",
                           "Cadence (steps/min)"
)


shapiro.resid<-shapiro.resid %>%
  rename(Statistic= statistic)
shapiro.resid<-shapiro.resid[,c("Variable", "Statistic","p.value")]
```

```r
#Histograms for residuals

#first fit the data to a linear model, extract the residuals, then plot the
residuals on a histogram


resid.nsl<-lm(StepLengthNorm~Sex*Condition, data=data)%>%
  resid %>%
  as.data.frame
resid.slcv<-lm(slcv.log~Sex*Condition, data=data)%>%
  resid %>%
  as.data.frame
resid.vn<-lm(VelocityNorm~Sex*Condition, data=data)%>%
  resid %>%
  as.data.frame
resid.c<-lm(Cadence~Sex*Condition, data=data)%>%
  resid %>%
  as.data.frame

histograms.resids<-ggarrange(
  (ggplot(data = resid.nsl, aes(x = .)) +
     geom_histogram(bins = 15, alpha = 0.75, color="black",
     fill="darkolivegreen3") +
     labs(x="Step Length (% of body height) Residuals",y = "Frequency")+
     theme_bw()+theme(text =element_text(size=7))),
  (ggplot(data = resid.slcv, aes(x = .)) +
     geom_histogram(bins = 15, alpha = 0.75, color="black",
     fill="darkolivegreen3") +
     labs(x="Log Transformed Step Length CV (%) Residuals",y = "Frequency")+
     theme_bw()+theme(text =element_text(size=7))),
  (ggplot(data = resid.vn, aes(x = .)) +
     geom_histogram(bins = 15, alpha = 0.75, color="black",
     fill="darkolivegreen3") +
     labs(x="Velocity (cm/s normalized to body height) Residuals",
     y = "Frequency")+
     theme_bw()+theme(text =element_text(size=7))),
  (ggplot(data = resid.c, aes(x = .)) +
     geom_histogram(bins = 15, alpha = 0.75, color="black",
     fill="darkolivegreen3") +
     labs(x="Cadence (steps/min) Residuals",y = "Frequency")+
     theme_bw()+theme(text =element_text(size=7))),
  ncol=2, nrow=2, labels = c("A","B","C","D"))
)
plot(histograms.resids)
```

```r
#Residuals vs. Fitted graphs
nsl.fit<-lm(StepLengthNorm~Sex*Condition, data=data)
slcv.fit<-lm(slcv.log~Sex*Condition, data=data)
vn.fit<-lm(VelocityNorm~Sex*Condition, data=data)
c.fit<-lm(Cadence~Sex*Condition, data=data)

fit.vs.res<-ggarrange(
  (ggplot(data = nsl.fit, aes(x = fitted(nsl.fit), y = resid(nsl.fit))) +
    geom_point(size = 0.5, colour = 'aquamarine4') +
    geom_hline(yintercept=0) +
    labs(x="Fitted values", y="Residuals")),
  (ggplot(data = slcv.fit, aes(x = fitted(slcv.fit), y = resid(slcv.fit))) +
    geom_point(size = 0.5, colour = 'aquamarine4') +
    geom_hline(yintercept=0) +
    labs(x="Fitted values", y="Residuals")),
  (ggplot(data = vn.fit, aes(x = fitted(vn.fit), y = resid(vn.fit))) +
    geom_point(size = 0.5, colour = 'aquamarine4') +
    geom_hline(yintercept=0) +
    labs(x="Fitted values", y="Residuals")),
  (ggplot(data = c.fit, aes(x = fitted(c.fit), y = resid(c.fit))) +
    geom_point(size = 0.5, colour = 'aquamarine4') +
    geom_hline(yintercept=0) +
    labs(x="Fitted values", y="Residuals")),
  labels=c('A','B','C','D')
)
plot(fit.vs.res)



### ANOVA COMPUTATIONS ###

#Divide data set into 'motor' and 'cognitive' subsets

cognitive<-filter(data, Condition=="Dual Task"| Condition =="Talking")
motor<-filter(data, Condition=="Self Paced"| Condition =="Maximum Paced")

#Convert independent variables to factors

cognitive$s<-cognitive$Sex
cognitive$c<-cognitive$Condition
motor$s<-motor$Sex
motor$c<-motor$Condition
```

```r
#Compute ANOVA using Anova() function in car package
#aov model is created within the function

anova.nsl.cog<-Anova(aov(StepLengthNorm~s*c, data = cognitive),
                     type=3)
anova.slcv.cog<-Anova(aov(slcv.log~s*c, data = cognitive),
                      type=3)
anova.vn.cog<-Anova(aov(VelocityNorm~s*c, data = cognitive),
                    type=3)
anova.c.cog<-Anova(aov(Cadence~s*c, data = cognitive),
                   type=3)
anova.nsl.mot<-Anova(aov(StepLengthNorm~s*c, data = motor),
                     type=3)
anova.slcv.mot<-Anova(aov(slcv.log~s*c, data = motor),
                      type=3)
anova.vn.mot<-Anova(aov(VelocityNorm~s*c, data = motor),
                    type=3)
anova.c.mot<-Anova(aov(Cadence~s*c, data = motor),
                   type=3)

#Post hoc analysis for cadence
posthoc.nsl.mot<-(PostHocTest(aov(StepLengthNorm~s*c,data=motor),
                              method="bonf", conf.level=0.95)
)
print(posthoc.nsl.mot)
```

Appendix B: Assumption tests for ANOVAs – Study 1

Table B1 *– Shapiro-Wilk test results for the residuals of the data*

Variable	Statistic	p-value
Step Length (% of body height)	0.9972692	0.0833366245847017
Log Transformed Step Length CV (%)	0.9823232	<0.001
Velocity (cm/s normalized to body height)	0.9921561	<0.001
Cadence (steps/min)	0.9794877	<0.001

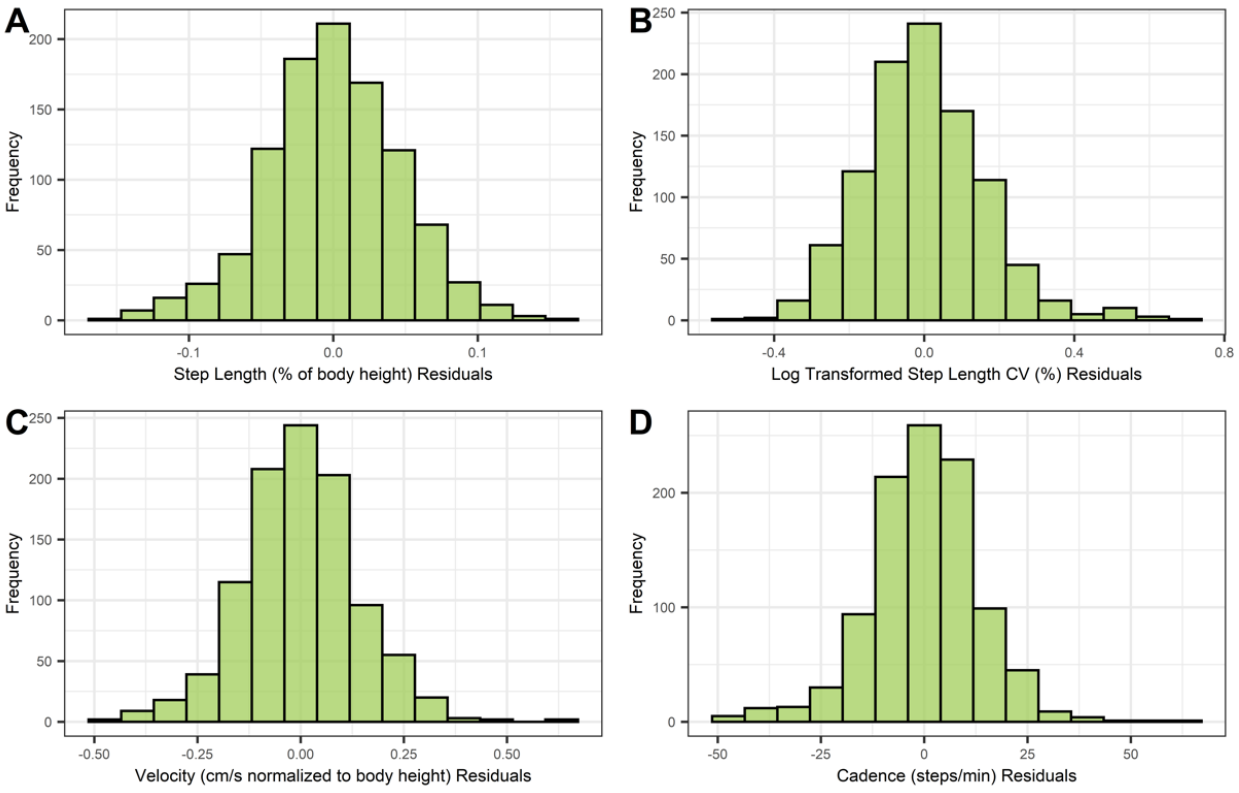

Figure B1 *- Histograms for the residuals of each measure of interest. A) Step Length (% of body height). B) Step Length CV (%). C) Velocity (actual velocity (cm/s)/body height (cm)). D) Cadence (steps/min).*

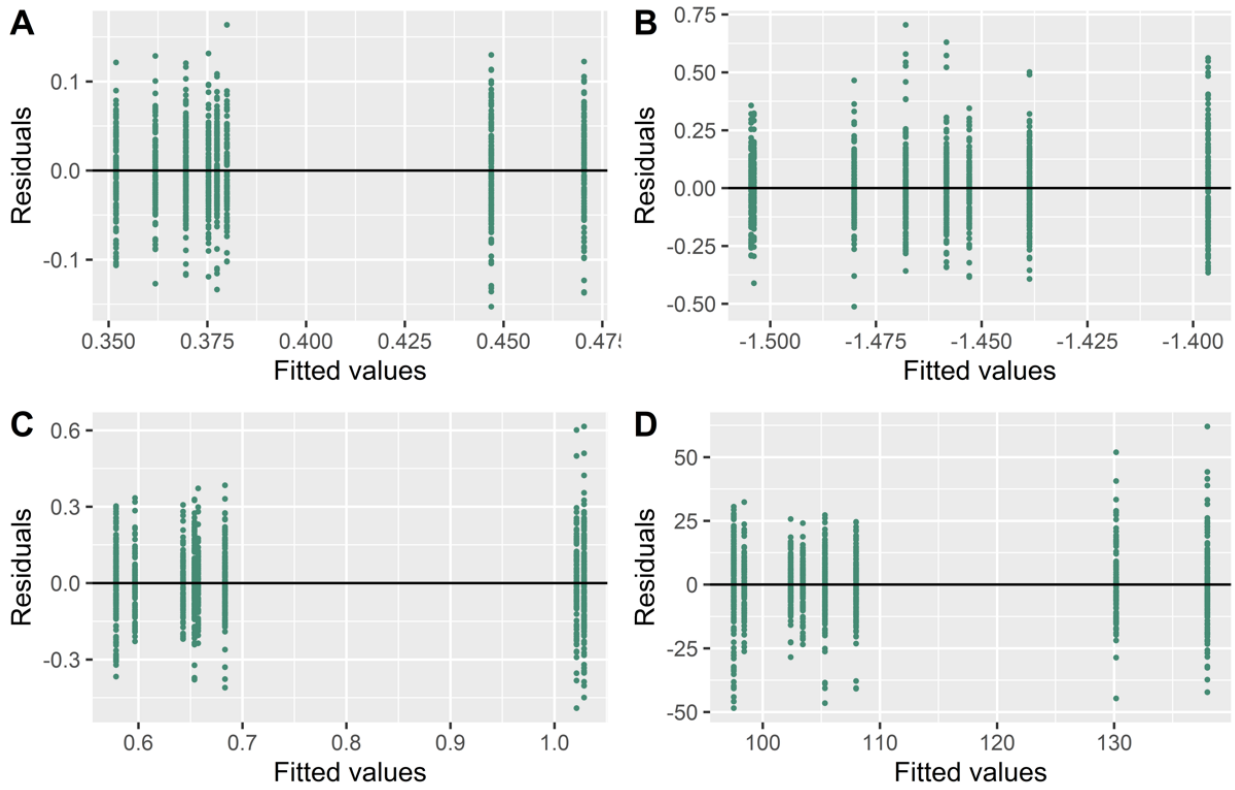

Figure B2 *– Residual verses fitted plots for each measure of interest. Each line represents each of the 8 groups on which the analysis was performed. A) Step Length (% of body height). B) Step Length CV (%). C) Velocity (actual velocity (cm/s)/body height (cm)). D) Cadence (steps/min).*

Appendix C: ANOVA tables for Study 1

Table C1 *– ANOVA table for Step Length (% of body height) – Cognitive Tasks*

	Sum of Squares	Degrees of Freedom	F-value	p-value	Significance Level
(Intercept)	64.927	1	33356.4282	<0.001	***
Sex	0.008	1	3.8605	0.0499835	*
Condition	0.030	1	15.1875	0.0001105	***
Sex x Condition	0.001	1	0.2845	0.5939860	
Residuals	0.981	504			

‘***’ p-value < 0.001, ‘*’ p-value < 0.05

Table C2 *– ANOVA table for Step Length CV (%) – Cognitive Tasks*

	Sum of Squares	Degrees of Freedom	F-value	p-value	Significance Level
(Intercept)	1030.76	1	37188.3339	<0.001	***
Sex	0.32	1	11.4519	0.0007699	***
Condition	0.39	1	14.0222	0.0002015	***
Sex x Condition	0.00	1	0.1321	0.7164063	
Residuals	13.97	504			

‘***’ p-value < 0.001

Table 03 *– ANOVA table for Velocity (cm/s normalized to body height) – Cognitive Tasks*

	Sum of Squares	Degrees of Freedom	F-value	p-value	Significance Level
(Intercept)	186.496	1	10951.6273	<0.001	***
Sex	0.002	1	0.0977	0.7547	
Condition	0.451	1	26.4938	<0.001	***
Sex x Condition	0.026	1	1.5227	0.2178	
Residuals	8.583	504			

'***' p-value < 0.001

Table C4 *– ANOVA table for Cadence (steps/min) – Cognitive Tasks*

	Sum of Squares	Degrees of Freedom	F-value	p-value	Significance Level
(Intercept)	4973019	1	28187.5387	<0.001	***
Sex	126	1	0.7134	0.3987	
Condition	4214	1	23.8854	<0.001	***
Sex x Condition	444	1	2.5180	0.1132	
Residuals	88919	504			

'***' p-value < 0.001

Table C5 *– ANOVA table for Step Length (% of body height) – Motor Tasks*

	Sum of Squares	Degrees of Freedom	F-value	p-value	Significance Level
(Intercept)	85.597	1	35578.5520	<0.001	***
Sex	0.021	1	8.5802	0.003552	**
Condition	0.780	1	324.1341	<0.001	***
Sex x Condition	0.013	1	5.6022	0.018315	*
Residuals	1.213	504			

‘***’ p-value < 0.001, ‘**’ p-value < 0.01, ‘*’ p-value < 0.05

Table C6 *– ANOVA table for Step Length CV (%) – Motor Tasks*

	Sum of Squares	Degrees of Freedom	F-value	p-value	Significance Level
(Intercept)	1059.25	1	43369.2161	<0.001	***
Sex	0.19	1	7.6017	0.006043	**
Condition	0.09	1	3.5979	0.058425	.
Sex x Condition	0.00	1	0.0303	0.861922	
Residuals	12.31	504			

‘***’ p-value < 0.001, ‘**’ p-value < 0.01, ‘.’ p-value < 0.1

Table 07 *– ANOVA table for Velocity (cm/s normalized to body height) – Motor Tasks*

	Sum of Squares	Degrees of Freedom	F-value	p-value	Significance Level
(Intercept)	350.85	1	15263.3045	<0.001	***
Sex	0.03	1	1.4609	0.2274	
Condition	15.35	1	667.6932	<0.001	***
Sex x Condition	0.01	1	0.4642	0.4960	
Residuals	11.59	504			

'***' p-value < 0.001

Table C8 *– ANOVA table for Cadence (steps/min) – Motor Tasks*

	Sum of Squares	Degrees of Freedom	F-value	p-value	Significance Level
(Intercept)	7017662	1	39482.1910	<0.001	***
Sex	4636	1	26.0846	<0.001	***
Condition	98238	1	552.7001	<0.001	***
Sex x Condition	322	1	1.8099	0.1791	
Residuals	89582	504			

'***' p-value < 0.001

Appendix D: RStudio script for Study 2

```
options(contrasts = c("contr.treatment")

#Call the necessary packages

library(dplyr)
library(ggplot2)
library(ggpubr)
library(rstatix)
library(DescTools)
library(car)
library(olsrr)


#Replace all 'M' in Sex column to 1 and all 'F' to 2

data$Sex[data$Sex == "M"] <- 1
data$Sex[data$Sex == "F"] <- 2



### ASSUMPTIONS OF LINEAR REGRESSION COMPUTATIONS ###

#Create linear models for each measure of interest (used for a few tests in t
he analysis)

nsl_cog_fit<-lm(nsl_cog~Age+BMI+Education.Level+Symptom.severity+Sex,
             data=data)
slcv_cog_fit<-lm(slcv_cog~Age+BMI+Education.Level+Symptom.severity+Sex,
             data=data)
vn_cog_fit<-lm(vn_cog~Age+BMI+Education.Level+Symptom.severity+Sex,data=data)
c_cog_fit<-lm(c_cog~Age+BMI+Education.Level+Symptom.severity+Sex,data=data)

nsl_mot_fit<-lm(nsl_mot~Age+BMI+Education.Level+Symptom.severity+Sex,
             data=data)
slcv_mot_fit<-lm(slcv_mot~Age+BMI+Education.Level+Symptom.severity+Sex,
              data=data)
vn_mot_fit<-lm(vn_mot~Age+BMI+Education.Level+Symptom.severity+Sex,data=data)
c_mot_fit<-lm(c_mot~Age+BMI+Education.Level+Symptom.severity+Sex,data=data)
```

```r
#Find the variance of inflation for each predictor in the model

vif(nsl_cog_fit)
#Since all the above fitted models have the same factors, and the same data
is used for each model, vif() can be applied to any of the fitted models



# Save residuals of each group (saves as a vector/'numeric')

nsl_cog_resid<-nsl_cog_fit%>%resid
slcv_cog_resid<-slcv_cog_fit%>%resid
vn_cog_resid<-vn_cog_fit%>%resid
c_cog_resid<-c_cog_fit%>%resid
nsl_mot_resid<-nsl_mot_fit%>%resid
slcv_mot_resid<-slcv_mot_fit%>%resid
vn_mot_resid<-vn_mot_fit%>%resid
c_mot_resid<-c_mot_fit%>%resid



# Perform shapiro tests on residuals

shapiro.resid<-rbind((nsl_cog_resid%>%shapiro_test),
                     (slcv_cog_resid%>%shapiro_test),
                     (vn_cog_resid%>%shapiro_test),
                     (c_cog_resid%>%shapiro_test),
                     (nsl_mot_resid%>%shapiro_test),
                     (slcv_mot_resid%>%shapiro_test),
                     (vn_mot_resid%>%shapiro_test),
                     (c_mot_resid%>%shapiro_test)
)

shapiro.resid<-shapiro.resid %>%
  rename(
    Variable = variable,
    Statistic= statistic)
shapiro.resid<-shapiro.resid[,c("Variable", "Statistic","p.value")]

shapiro.resid[1, 1] <- "nsl_cog"
shapiro.resid[2, 1] <- "slcv_cog"
shapiro.resid[3, 1] <- "vn_cog"
shapiro.resid[4, 1] <- "c_cog"
shapiro.resid[5, 1] <- "nsl_mot"
shapiro.resid[6, 1] <- "slcv_mot"
shapiro.resid[7, 1] <- "vn_mot"
shapiro.resid[8, 1] <- "c_mot"
```

```r
# Histograms for residual data

historgrams.resid.cog<-ggarrange(
  (ggplot(data = data, aes(x = nsl_cog_resid)) +
     geom_histogram(bins = 15, alpha = 0.75, color="black",
     fill="darkolivegreen3") +
     labs(x="Step Length (% of body height)",y = "Frequency")+
     theme_bw()+theme(text =element_text(size=8))),
  (ggplot(data = data, aes(x = slcv_cog_resid)) +
     geom_histogram(bins = 15, alpha = 0.75, color="black",
     fill="darkolivegreen3") +
     labs(x="Step Length CV (%)",y = "Frequency")+
     theme_bw()+theme(text =element_text(size=8))),
  (ggplot(data = data, aes(x = vn_cog_resid)) +
     geom_histogram(bins = 15, alpha = 0.75, color="black",
     fill="darkolivegreen3") +
     labs(x="Velocity (cm/s normalized to body height)",y = "Frequency")+
     theme_bw()+theme(text =element_text(size=8))),
  (ggplot(data = data, aes(x = c_cog_resid)) +
     geom_histogram(bins = 15, alpha = 0.75, color="black",
     fill="darkolivegreen3") +
     labs(x="Cadence (steps/min)",y = "Frequency")+
     theme_bw()+theme(text =element_text(size=8))),
  nrow=2, ncol=2, labels = c("A", "B", "C", "D")
)
plot(historgrams.resid.cog)

histograms.resid.mot<-ggarrange(
  (ggplot(data = data, aes(x = nsl_mot_resid)) +
     geom_histogram(bins = 15, alpha = 0.75, color="black",
     fill="darkolivegreen3") +
     labs(x="Step Length (% of body height)",y = "Frequency")+
     theme_bw()+theme(text =element_text(size=8))),
  (ggplot(data = data, aes(x = slcv_mot_resid)) +
     geom_histogram(bins = 15, alpha = 0.75, color="black",
     fill="darkolivegreen3") +
     labs(x="Step Length CV (%)",y = "Frequency")+
     theme_bw()+theme(text =element_text(size=8))),
  (ggplot(data = data, aes(x = vn_mot_resid)) +
     geom_histogram(bins = 15, alpha = 0.75, color="black",
     fill="darkolivegreen3") +
     labs(x="Velocity (cm/s normalized to body height)",y = "Frequency")+
     theme_bw()+theme(text =element_text(size=8))),
  (ggplot(data = data, aes(x = c_mot_resid)) +
     geom_histogram(bins = 15, alpha = 0.75, color="black",
     fill="darkolivegreen3") +
     labs(x="Cadence (steps/min)",y = "Frequency")+
     theme_bw()+theme(text =element_text(size=8))),
  nrow=2, ncol=2, labels = c("A", "B", "C", "D")
)
```

```
plot(histograms.resid.mot)



# Residuals vs fitted graphs

fit.vs.res.cog<-ggarrange(
  (ggplot(data = nsl_cog_fit, aes(x = fitted(nsl_cog_fit),
   y = resid(nsl_cog_fit))) +
     geom_point(size = 0.5, colour = 'aquamarine4') +
     geom_hline(yintercept=0) +
     labs(x="Fitted values", y="Residuals")),
  (ggplot(data = slcv_cog_fit, aes(x = fitted(slcv_cog_fit),
   y = resid(slcv_cog_fit))) +
     geom_point(size = 0.5, colour = 'aquamarine4') +
     geom_hline(yintercept=0) +
     labs(x="Fitted values", y="Residuals")),
  (ggplot(data = vn_cog_fit, aes(x = fitted(vn_cog_fit),
   y = resid(vn_cog_fit))) +
      geom_point(size = 0.5, colour = 'aquamarine4') +
      geom_hline(yintercept=0) +
      labs(x="Fitted values", y="Residuals")),
  (ggplot(data = c_cog_fit, aes(x = fitted(c_cog_fit),
   y = resid(c_cog_fit))) +
      geom_point(size = 0.5, colour = 'aquamarine4') +
      geom_hline(yintercept=0) +
      labs(x="Fitted values", y="Residuals")),
  labels=c('A','B','C','D')
)
plot(fit.vs.res.cog)

fit.vs.res.mot<-ggarrange(
  (ggplot(data = nsl_mot_fit, aes(x = fitted(nsl_mot_fit),
   y = resid(nsl_mot_fit))) +
     geom_point(size = 0.5, colour = 'aquamarine4') +
     geom_hline(yintercept=0) +
     labs(x="Fitted values", y="Residuals")),
  (ggplot(data = slcv_mot_fit, aes(x = fitted(slcv_mot_fit),
   y = resid(slcv_mot_fit))) +
     geom_point(size = 0.5, colour = 'aquamarine4') +
     geom_hline(yintercept=0) +
     labs(x="Fitted values", y="Residuals")),
  (ggplot(data = vn_mot_fit, aes(x = fitted(vn_mot_fit),
   y = resid(vn_mot_fit))) +
     geom_point(size = 0.5, colour = 'aquamarine4') +
     geom_hline(yintercept=0) +
     labs(x="Fitted values", y="Residuals")),
  (ggplot(data = c_mot_fit, aes(x = fitted(c_mot_fit),
   y = resid(c_mot_fit))) +
     geom_point(size = 0.5, colour = 'aquamarine4') +
```

```
    geom_hline(yintercept=0) +
    labs(x="Fitted values", y="Residuals")),
  labels=c('A','B','C','D')
)
plot(fit.vs.res.mot)



### STEPWISE LINEAR REGRESSION ###

step.nsl_cog<-ols_step_both_p(nsl_cog_fit,progress=TRUE, details=TRUE,
              pent=0.05, prem=0.05)
step.slcv_cog<-ols_step_both_p(slcv_cog_fit,progress=TRUE, details=TRUE,
               pent=0.05, prem=0.05)
step.vn_cog<-ols_step_both_p(vn_cog_fit,progress=TRUE, details=TRUE,
             pent=0.05, prem=0.05)
step.c_cog<-ols_step_both_p(c_cog_fit,progress=TRUE, details=TRUE,
            pent=0.05, prem=0.05)

step.nsl_mot<-ols_step_both_p(nsl_mot_fit,progress=TRUE, details=TRUE,
              pent=0.05, prem=0.05)
step.slcv_mot<-ols_step_both_p(slcv_mot_fit,progress=TRUE, details=TRUE,
               pent=0.05, prem=0.05)
step.vn_mot<-ols_step_both_p(vn_mot_fit,progress=TRUE, details=TRUE,
             pent=0.05, prem=0.05)
step.c_mot<-ols_step_both_p(c_mot_fit,progress=TRUE, details=TRUE,
            pent=0.05, prem=0.05)
```

Appendix E: Assumption tests for multiple linear regressions – Study 2

Table E1 *– Variation of Inflation values for all factors in Study 2*

Predictor	Variance of Inflation
Age	1.122456
BMI	1.266830
Education Level	1.232183
Sex	1.171868
Symptom Severity	1.252817

Table E2 *– Shapiro-Wilk test results for the residuals of cognitive and motor capacities at 1 week post-injury*

Condition	Variable	Statistic	p-value
Cognitive Capacity	Step Length (% of body height)	0.8951366	0.00043966116324595
	Step Length CV (%)	0.6931985	<0.001
	Velocity (cm/s normalized to body height)	0.8495050	<0.001
	Cadence (steps/min)	0.714093	<0.001
Motor Capacity	Step Length (% of body height)	0.9859767	0.829917450952801
	Step Length CV (%)	0.9296653	0.0066277181691082
	Velocity (cm/s normalized to body height)	0.9816082	0.646875691424362
	Cadence (steps/min)	0.9772889	0.471345857388326

Table E3 *– Shapiro-Wilk test results for the residuals of cognitive and motor capacities at 2 weeks post-injury*

Condition	Variable	Statistic	p-value
Cognitive Capacity	Step Length (% of body height)	0.98097832	0.619916414700507
	Step Length CV (%)	0.73592682	<0.001
	Velocity (cm/s normalized to body height)	0.96697857	0.192638130094797
	Cadence (steps/min)	0.97243467	0.31419467738239
Motor Capacity	Step Length (% of body height)	0.98547925	0.810485083532327
	Step Length CV (%)	0.94672702	0.0296651951614799
	Velocity (cm/s normalized to body height)	0.97058257	0.266858210452534
	Cadence (steps/min)	0.91810328	0.00255020904276082

Table E4 *– Shapiro-Wilk test results for the residuals of cognitive and motor capacities at 8 weeks post-injury*

Condition	Variable	Statistic	p-value
Cognitive Capacity	Step Length (% of body height)	0.79028758	<0.001
	Step Length CV (%)	0.86070444	<0.001
	Velocity (cm/s normalized to body height)	0.94629988	0.0285380518495251
	Cadence (steps/min)	0.95559663	0.0670287839657194
Motor Capacity	Step Length (% of body height)	0.95265304	0.0510403440919091
	Step Length CV (%)	0.92493509	0.00445738455596151
	Velocity (cm/s normalized to body height)	0.97439899	0.3719412540113
	Cadence (steps/min)	0.97094499	0.275597771131155

Table E5 *– Shapiro-Wilk test results for the residuals of cognitive and motor capacities at 12 weeks post-injury*

Condition	Variable	Statistic	p-value
Cognitive Capacity	Step Length (% of body height)	0.86043288	<0.001
	Step Length CV (%)	0.98152368	0.643245868983081
	Velocity (cm/s normalized to body height)	0.81797797	<0.001
	Cadence (steps/min)	0.75707479	<0.001
Motor Capacity	Step Length (% of body height)	0.95497469	0.0632707615820416
	Step Length CV (%)	0.95182637	0.0472942911292358
	Velocity (cm/s normalized to body height)	0.97387594	0.355786588333717
	Cadence (steps/min)	0.9514471	0.0456712389985253

Table E6 *– Shapiro-Wilk test results for the residuals of cognitive and motor capacities at 16 weeks post-injury*

Condition	Variable	Statistic	p-value
Cognitive Capacity	Step Length (% of body height)	0.79079592	<0.001
	Step Length CV (%)	0.94862387	0.03525628
	Velocity (cm/s normalized to body height)	0.9652759	0.164735349
	Cadence (steps/min)	0.98291471	0.703215795
Motor Capacity	Step Length (% of body height)	0.95708119	0.07694203
	Step Length CV (%)	0.98690252	0.864149958
	Velocity (cm/s normalized to body height)	0.97790835	0.49479171
	Cadence (steps/min)	0.92960018	0.006591257

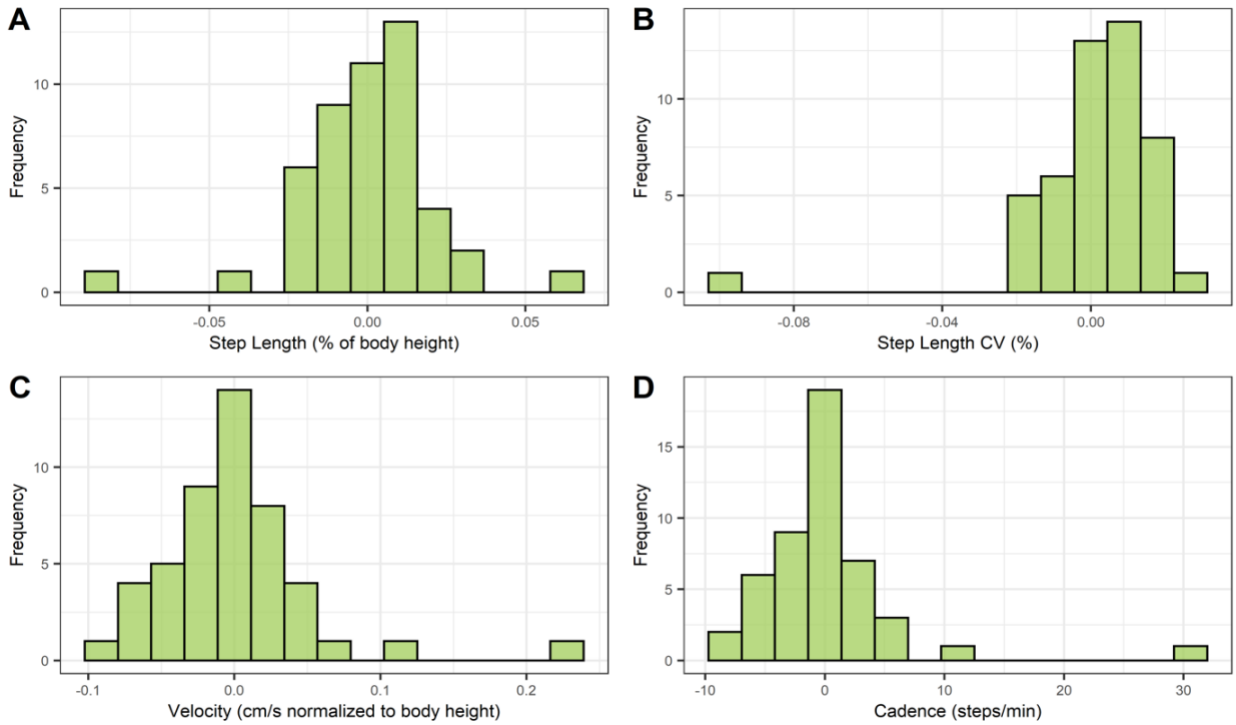

Figure E1 *– Histograms for the residuals of for cognitive capacities at 1 week post-injury. A) Step Length (% of body height). B) Step Length CV (%). C) Velocity (actual velocity (cm/s)/body height (cm)). D) Cadence (steps/min).*

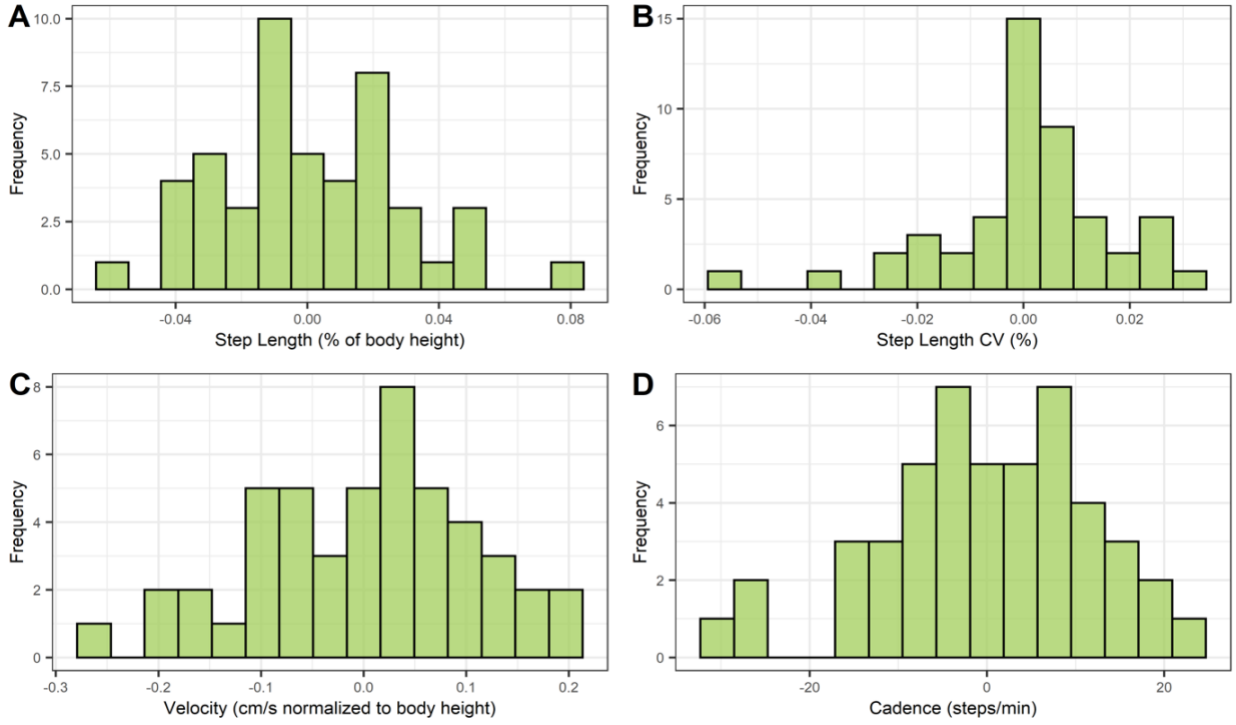

Figure E2 *- Histograms for the residuals of for motor capacities at 1 week post-injury. A) Step Length (% of body height). B) Step Length CV (%). C) Velocity (actual velocity (cm/s)/body height (cm)). D) Cadence (steps/min).*

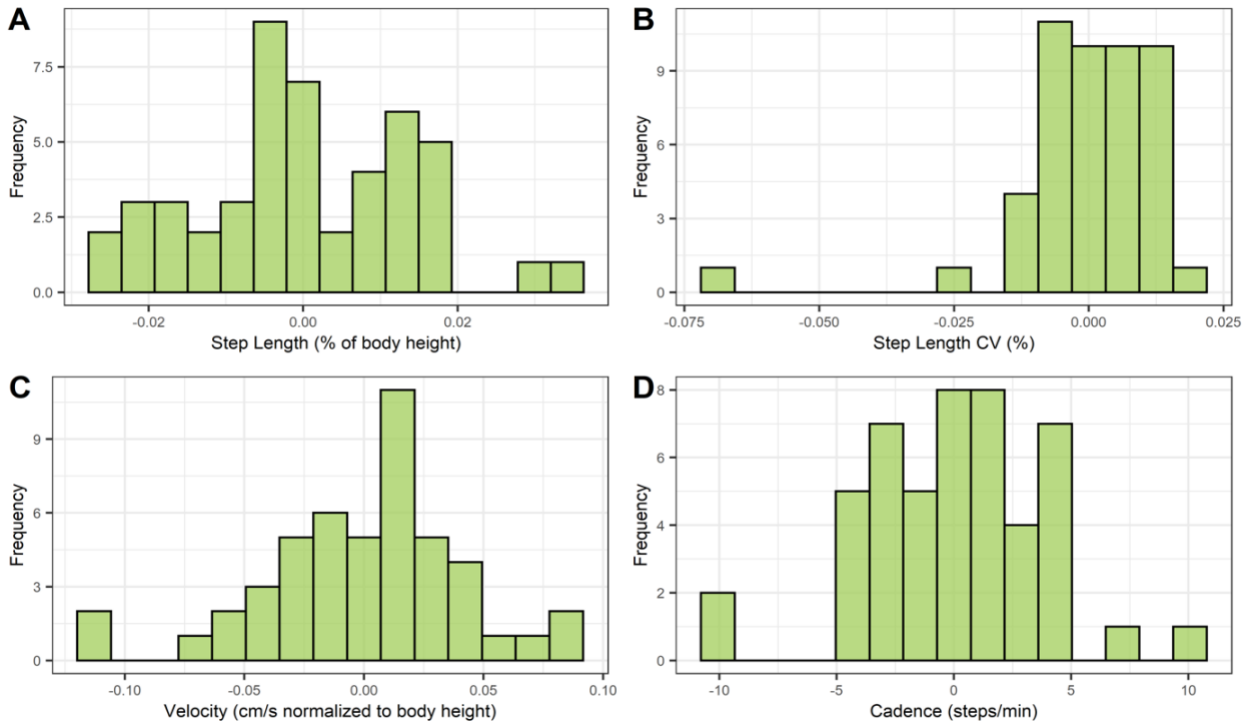

Figure E3 *– Histograms for the residuals of for cognitive capacities at 2 weeks post-injury. A) Step Length (% of body height). B) Step Length CV (%). C) Velocity (actual velocity (cm/s)/body height (cm)). D) Cadence (steps/min).*

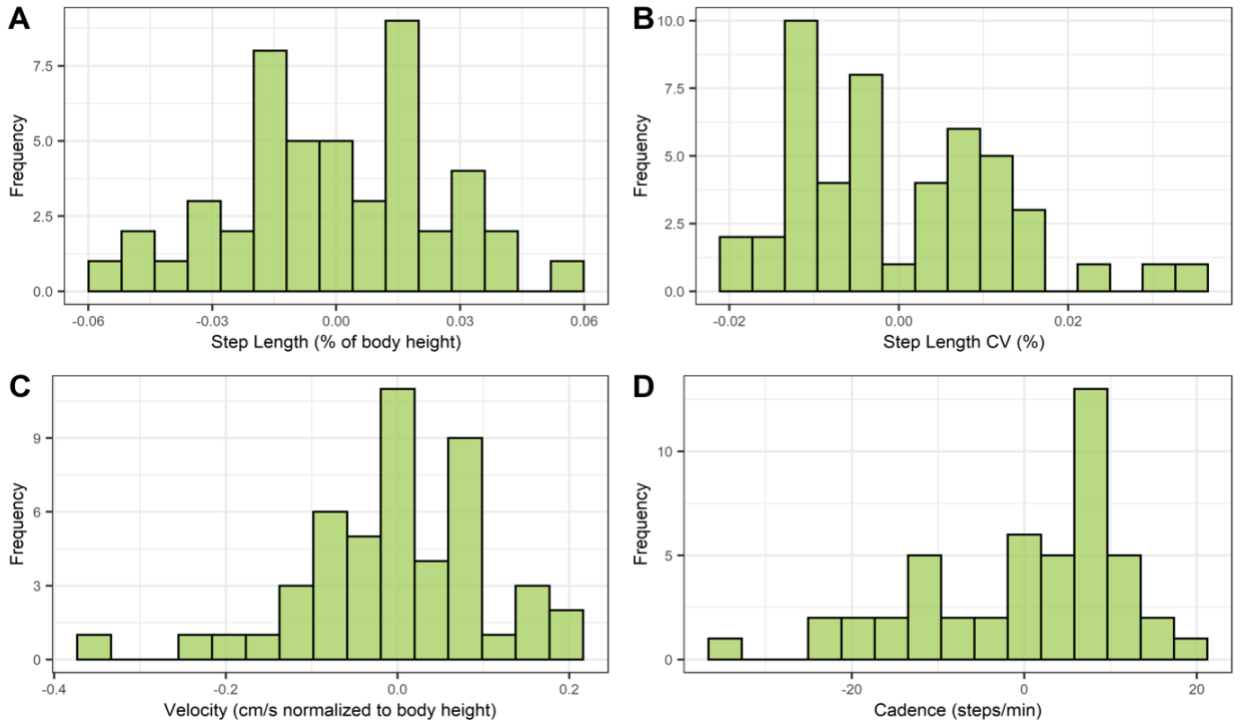

Figure E4 *- Histograms for the residuals for motor capacities at 2 weeks post-injury. A) Step Length (% of body height). B) Step Length CV (%). C) Velocity (actual velocity (cm/s)/body height (cm)). D) Cadence (steps/min).*

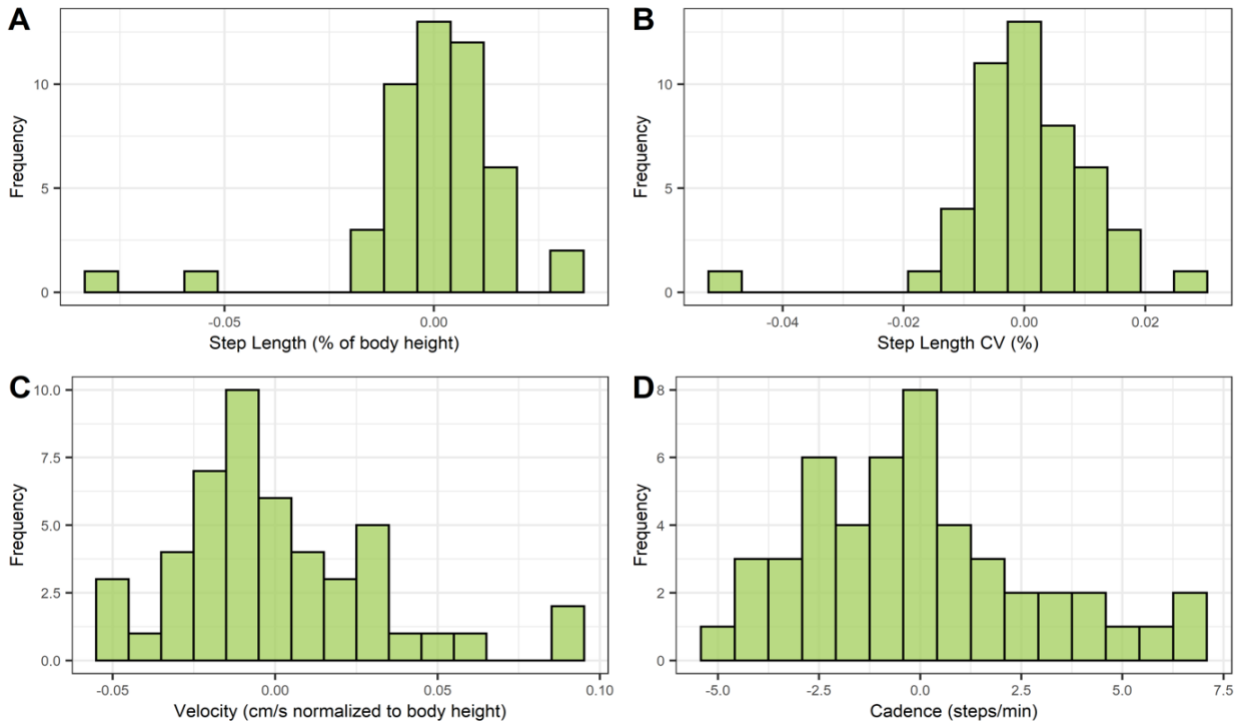

Figure E5 *– Histograms for the residuals for cognitive capacities at 8 weeks post-injury. A) Step Length (% of body height). B) Step Length CV (%). C) Velocity (actual velocity (cm/s)/body height (cm)). D) Cadence (steps/min).*

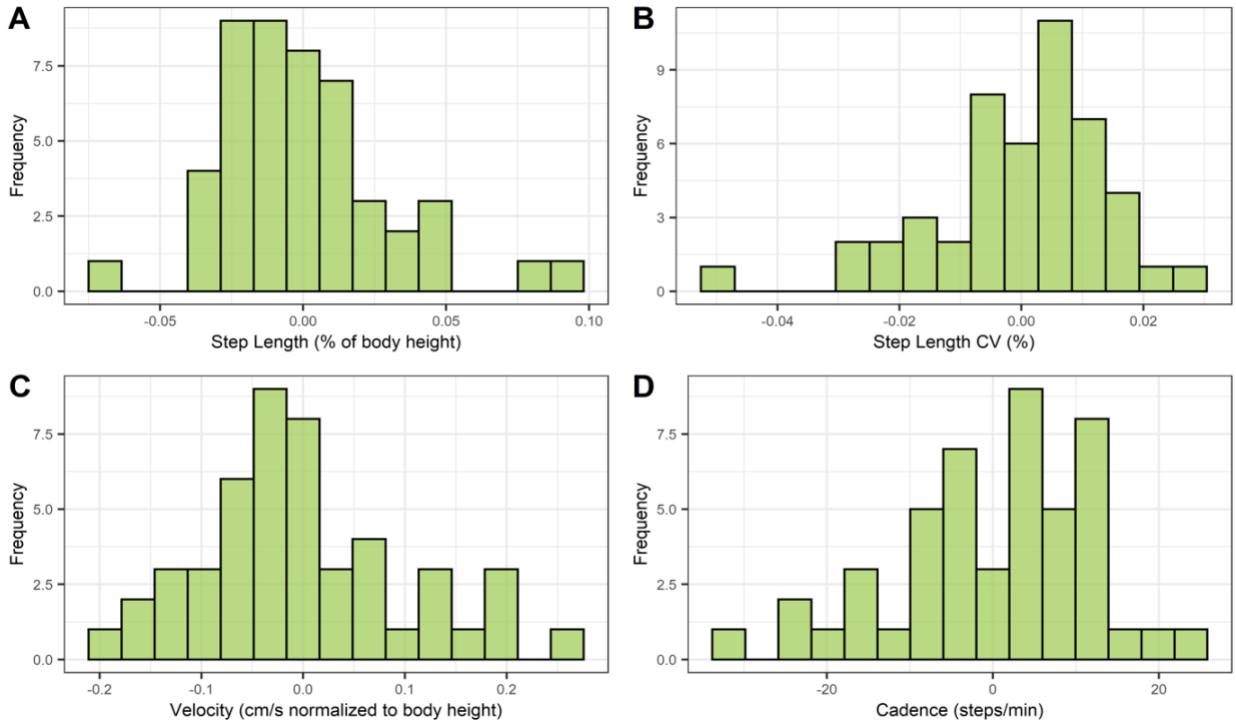

Figure E6 *- Histograms for the residuals for motor capacities at 8 weeks post-injury. A) Step Length (% of body height). B) Step Length CV (%). C) Velocity (actual velocity (cm/s)/body height (cm)). D) Cadence (steps/min).*

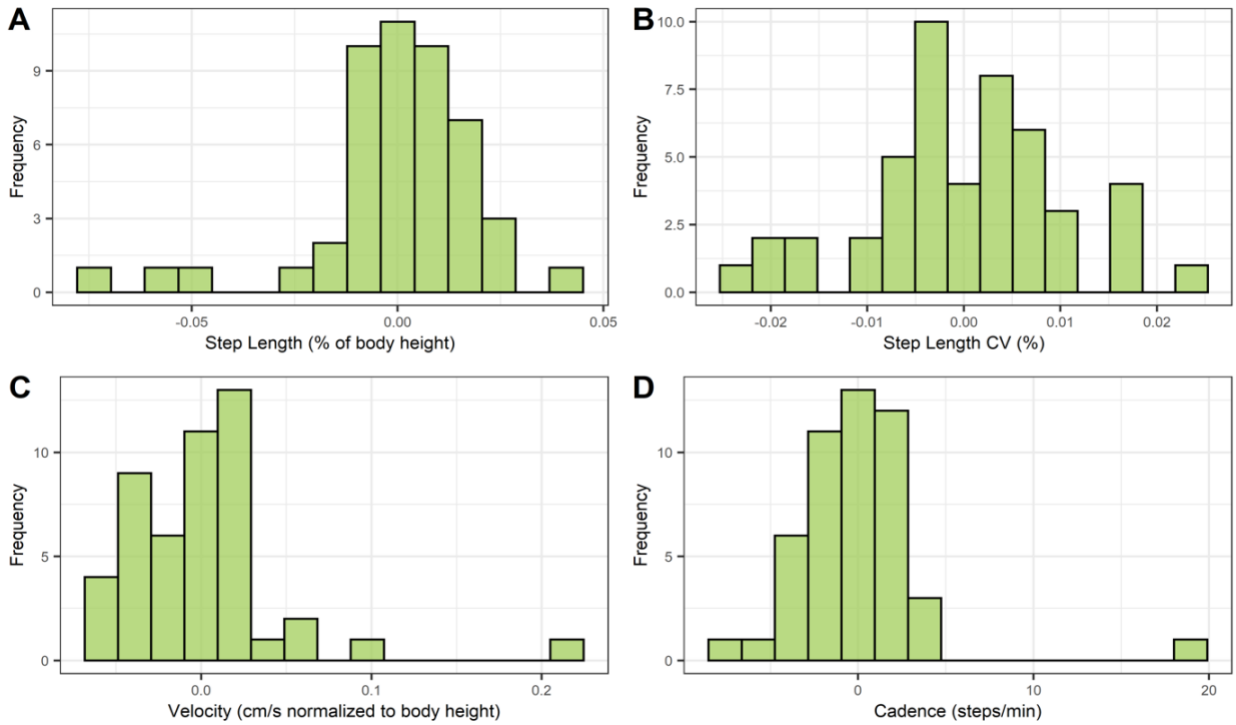

Figure E7 *– Histograms for the residuals for cognitive capacities at 12 weeks post-injury. A) Step Length (% of body height). B) Step Length CV (%). C) Velocity (actual velocity (cm/s)/body height (cm)). D) Cadence (steps/min).*

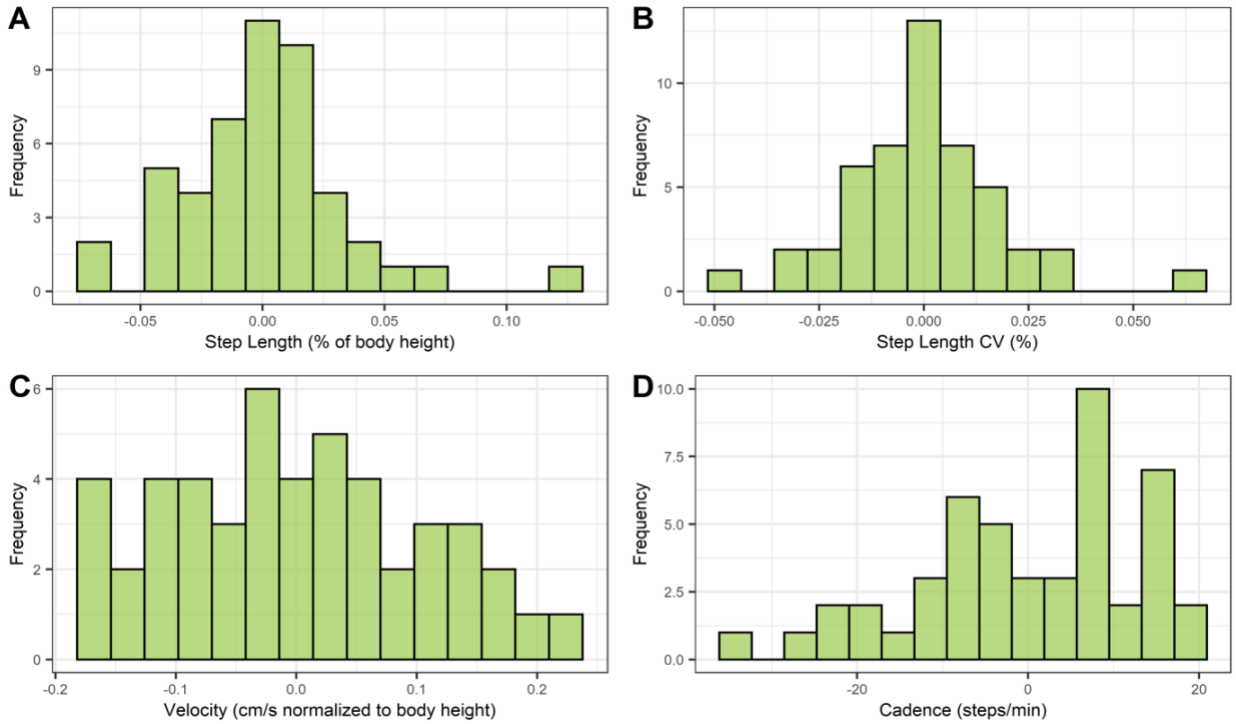

Figure E8 *- Histograms for the residuals for motor capacities at 12 weeks post-injury. A) Step Length (% of body height). B) Step Length CV (%). C) Velocity (actual velocity (cm/s)/body height (cm)). D) Cadence (steps/min).*

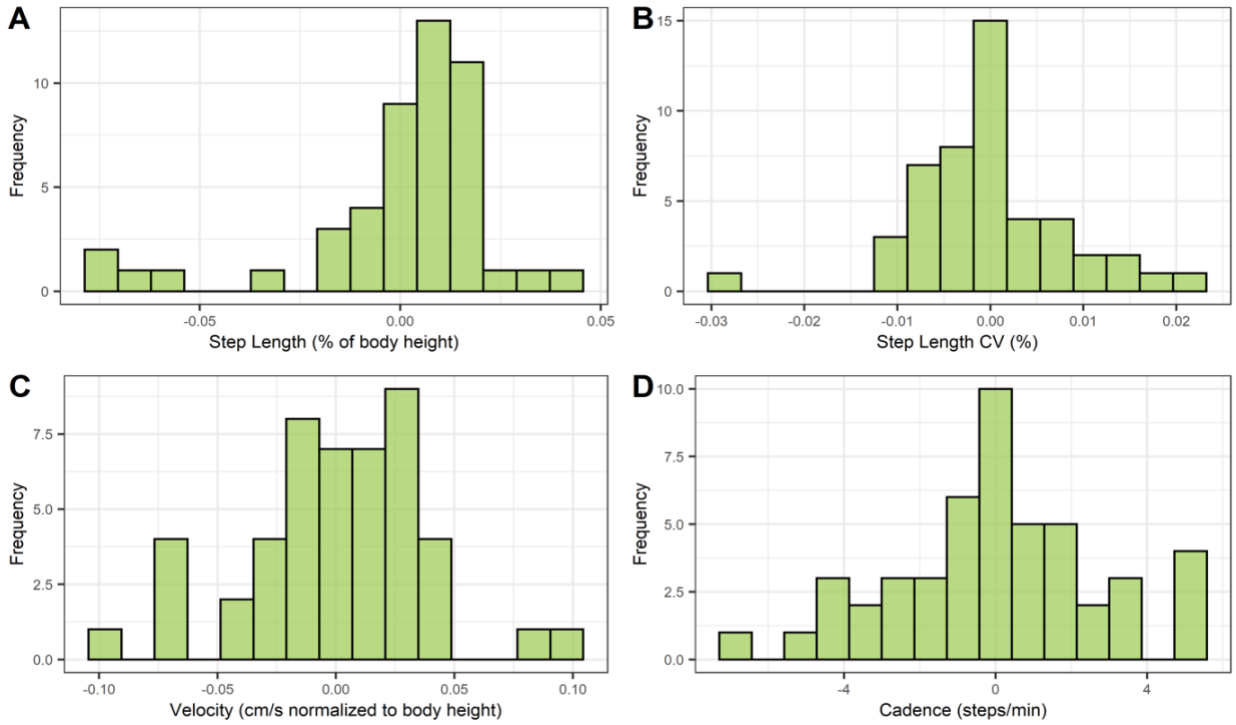

Figure E9 *– Histograms for the residuals for cognitive capacities at 16 weeks post-injury. A) Step Length (% of body height). B) Step Length CV (%). C) Velocity (actual velocity (cm/s)/body height (cm)). D) Cadence (steps/min).*

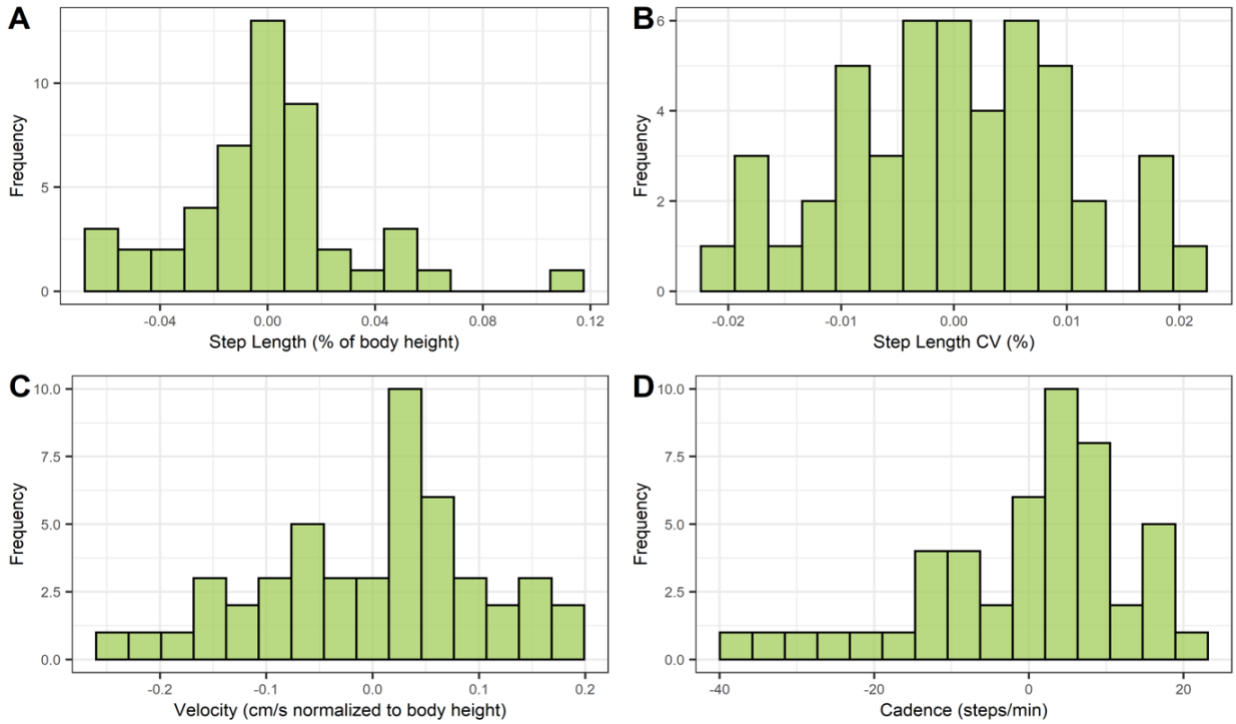

Figure E10 *- Histograms for the residuals for motor capacities at 16 weeks post-injury. A) Step Length (% of body height). B) Step Length CV (%). C) Velocity (actual velocity (cm/s)/body height (cm)). D) Cadence (steps/min).*

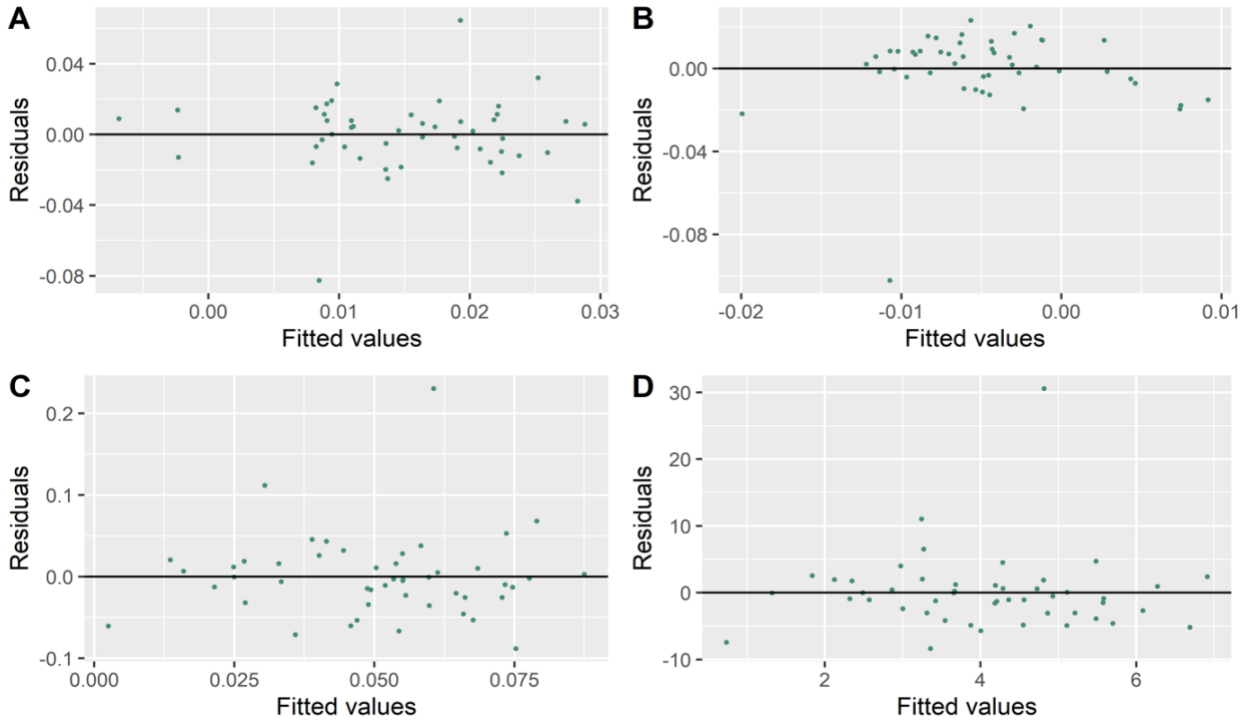

Figure E11 *– Residual verses fitted plots for cognitive capacities at 1 week post-injury. A) Step Length (% of body height). B) Step Length CV (%). C) Velocity (actual velocity (cm/s)/body height (cm)). D) Cadence (steps/min).*

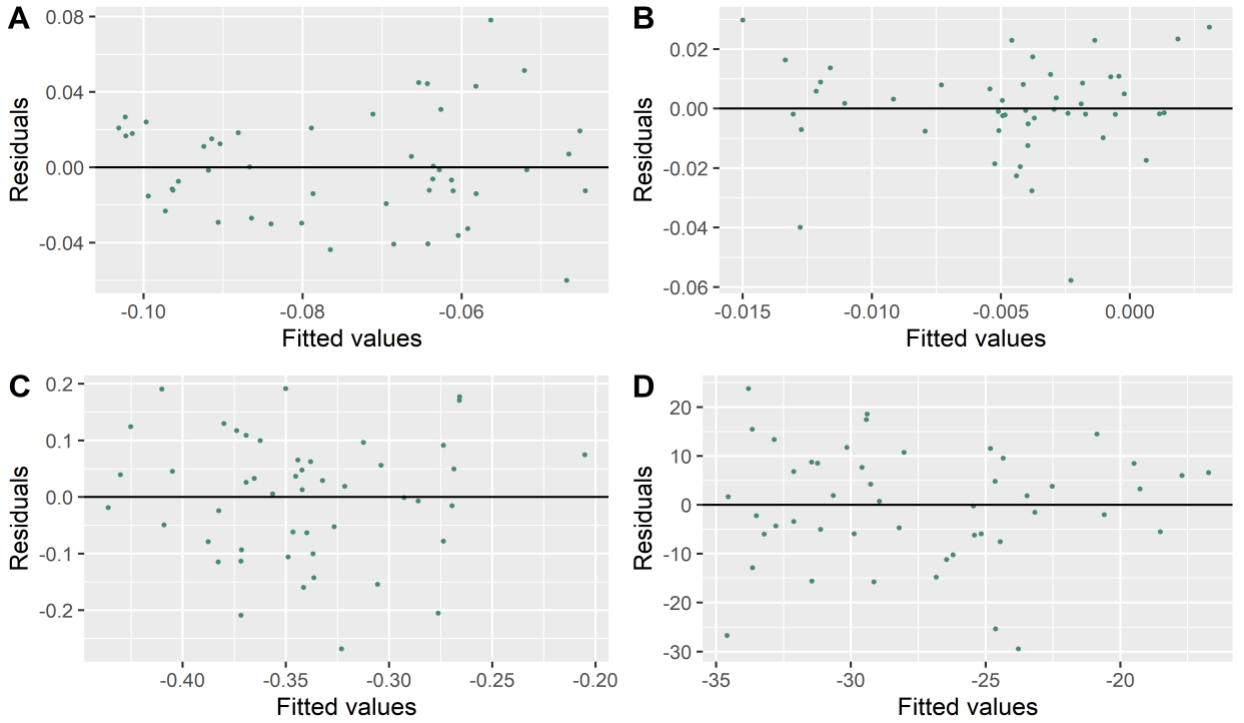

Figure E12 *– Residual verses fitted plots for motor capacities at 1 week post-injury. A) Step Length (% of body height). B) Step Length CV (%). C) Velocity (actual velocity (cm/s)/body height (cm)). D) Cadence (steps/min).*

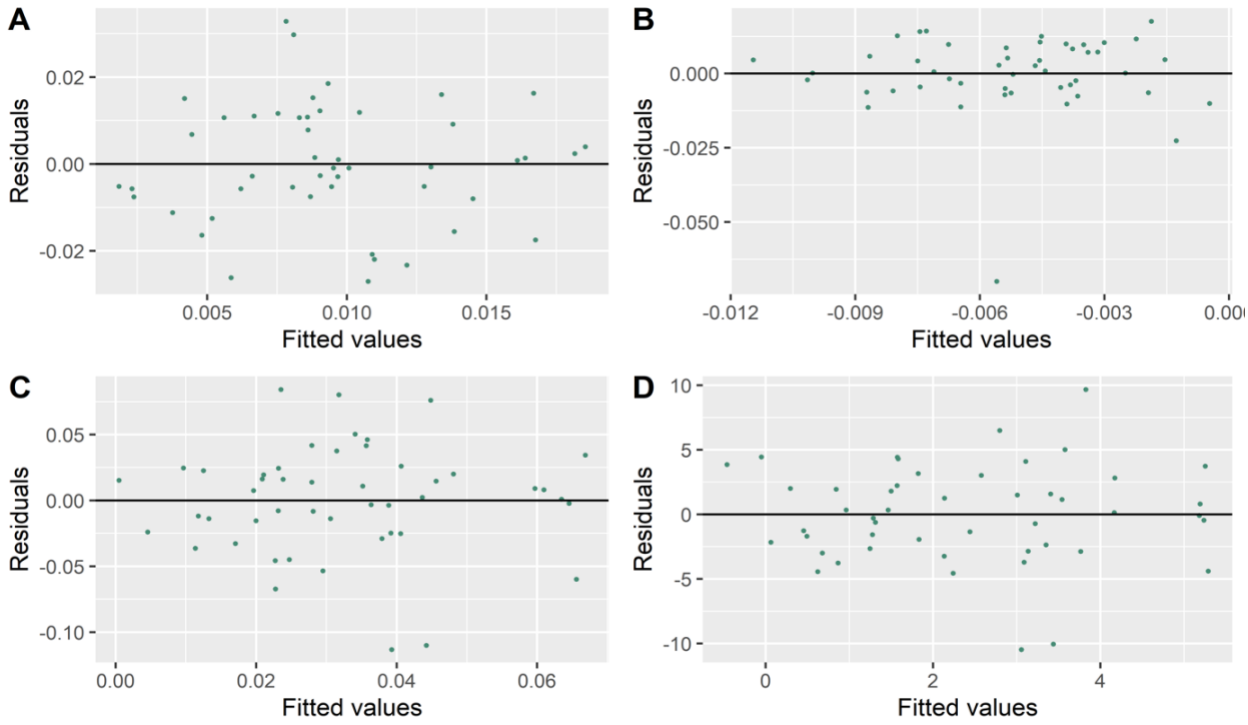

Figure E13 *– Residual verses fitted plots for cognitive capacities at 2 weeks post-injury. A) Step Length (% of body height). B) Step Length CV (%). C) Velocity (actual velocity (cm/s)/body height (cm)). D) Cadence (steps/min).*

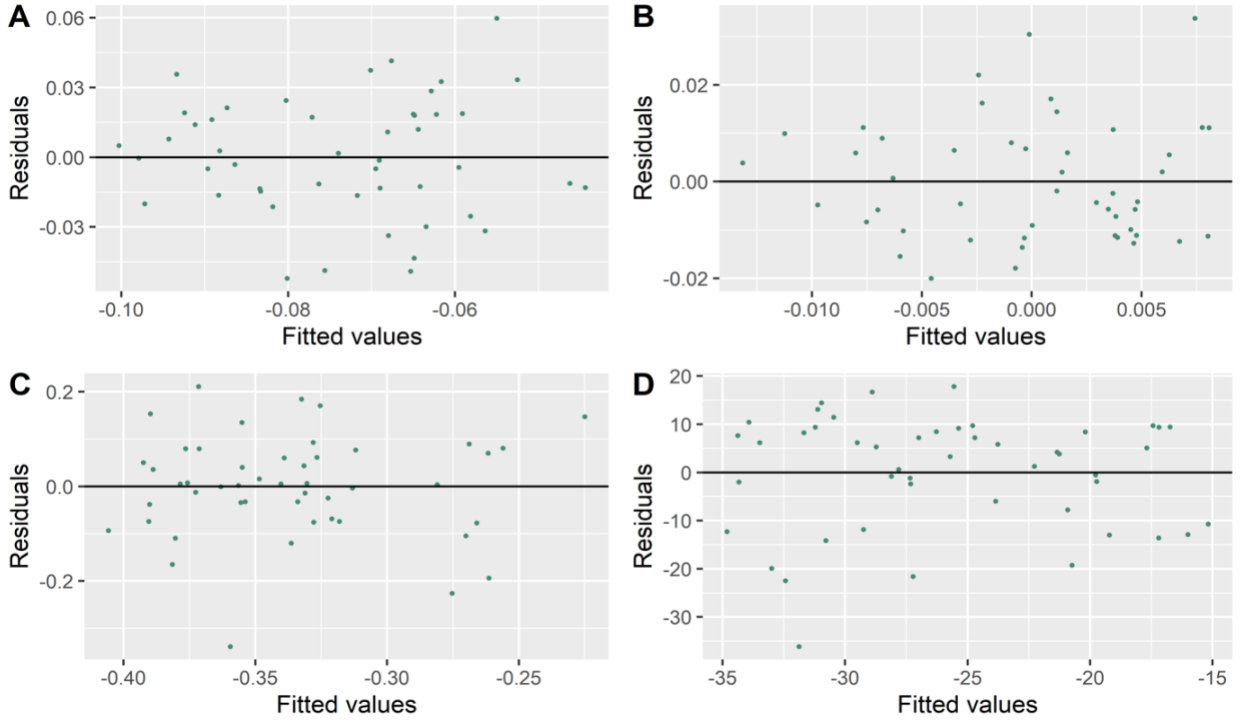

Figure E14 *– Residual verses fitted plots for motor capacities at 2 weeks post-injury. A) Step Length (% of body height). B) Step Length CV (%). C) Velocity (actual velocity (cm/s)/body height (cm)). D) Cadence (steps/min).*

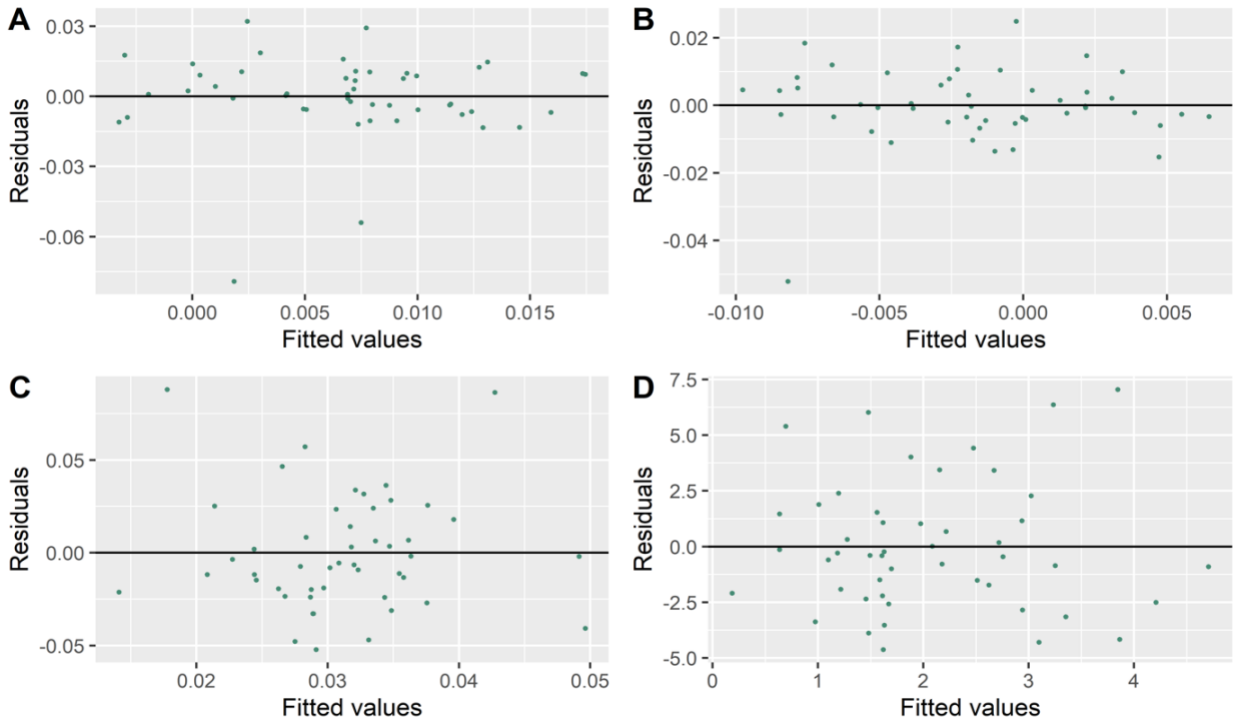

Figure E15 *– Residual verses fitted for cognitive capacities at 8 weeks post-injury. A) Step Length (% of body height). B) Step Length CV (%). C) Velocity (actual velocity (cm/s)/body height (cm)). D) Cadence (steps/min).*

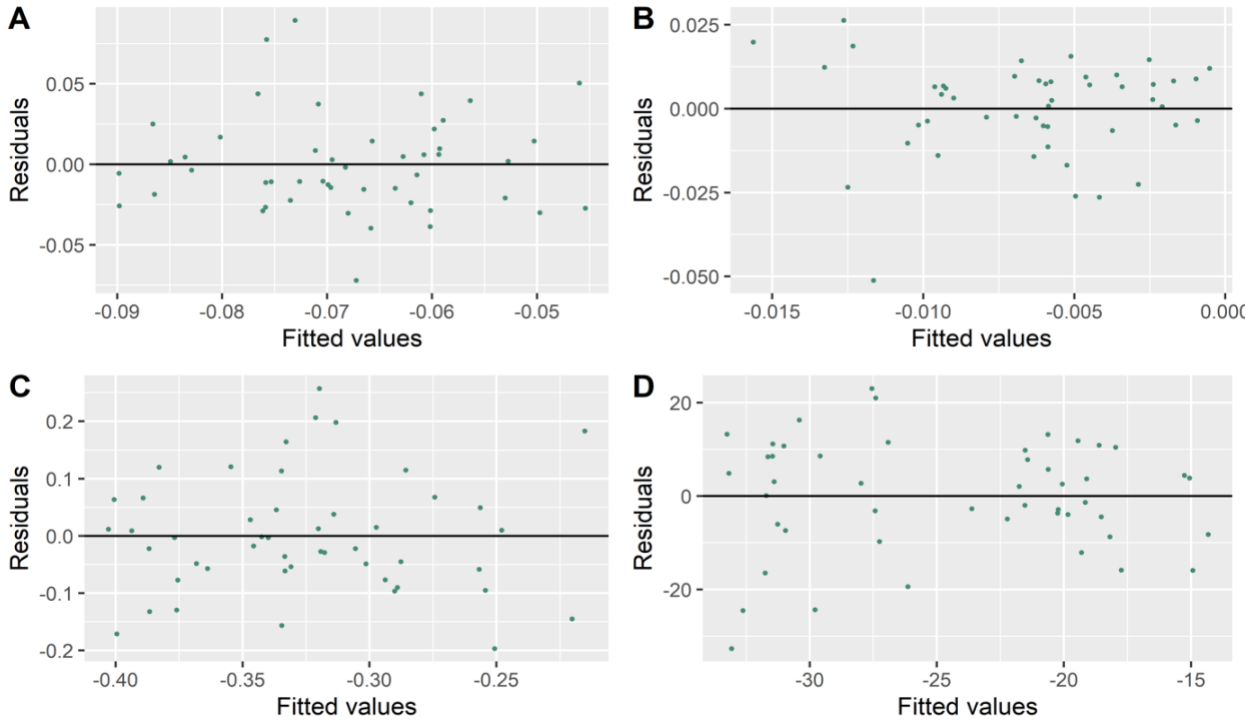

Figure E16 *– Residual verses fitted plots for motor capacities at 8 weeks post-injury. A) Step Length (% of body height). B) Step Length CV (%). C) Velocity (actual velocity (cm/s)/body height (cm)). D) Cadence (steps/min).*

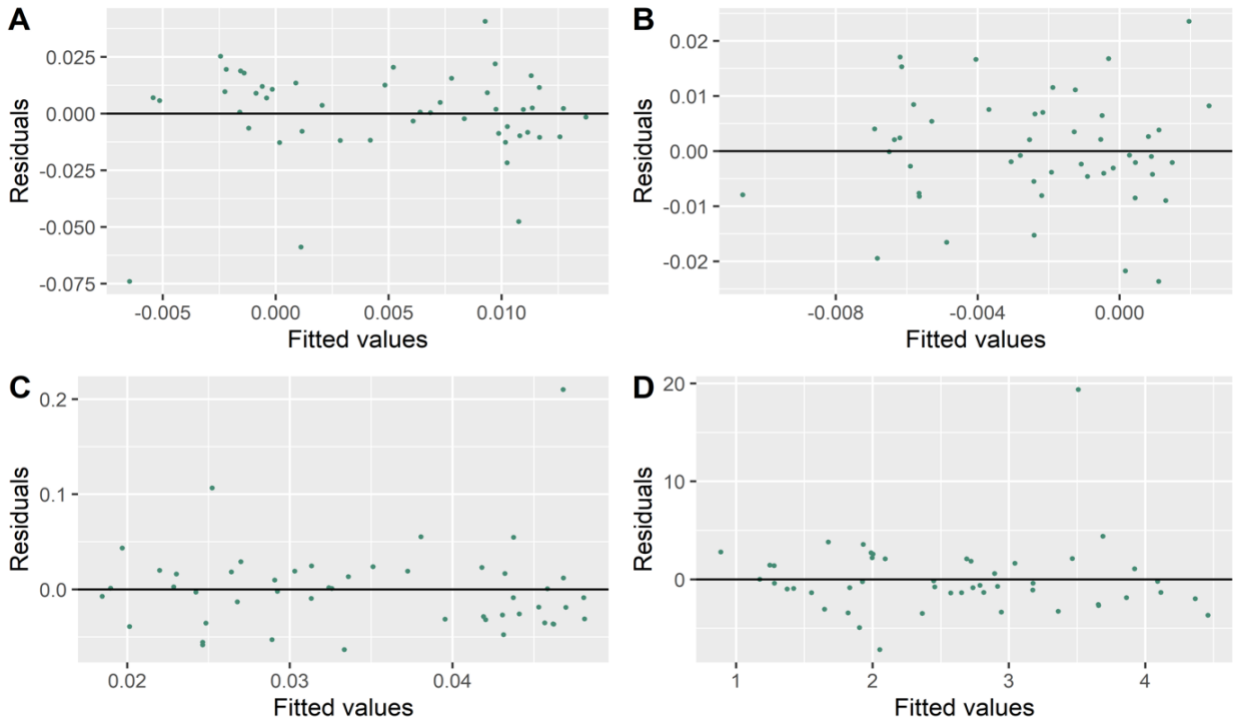

Figure E17 *– Residual verses fitted plots for cognitive capacities at 12 weeks post-injury. A) Step Length (% of body height). B) Step Length CV (%). C) Velocity (actual velocity (cm/s)/body height (cm)). D) Cadence (steps/min).*

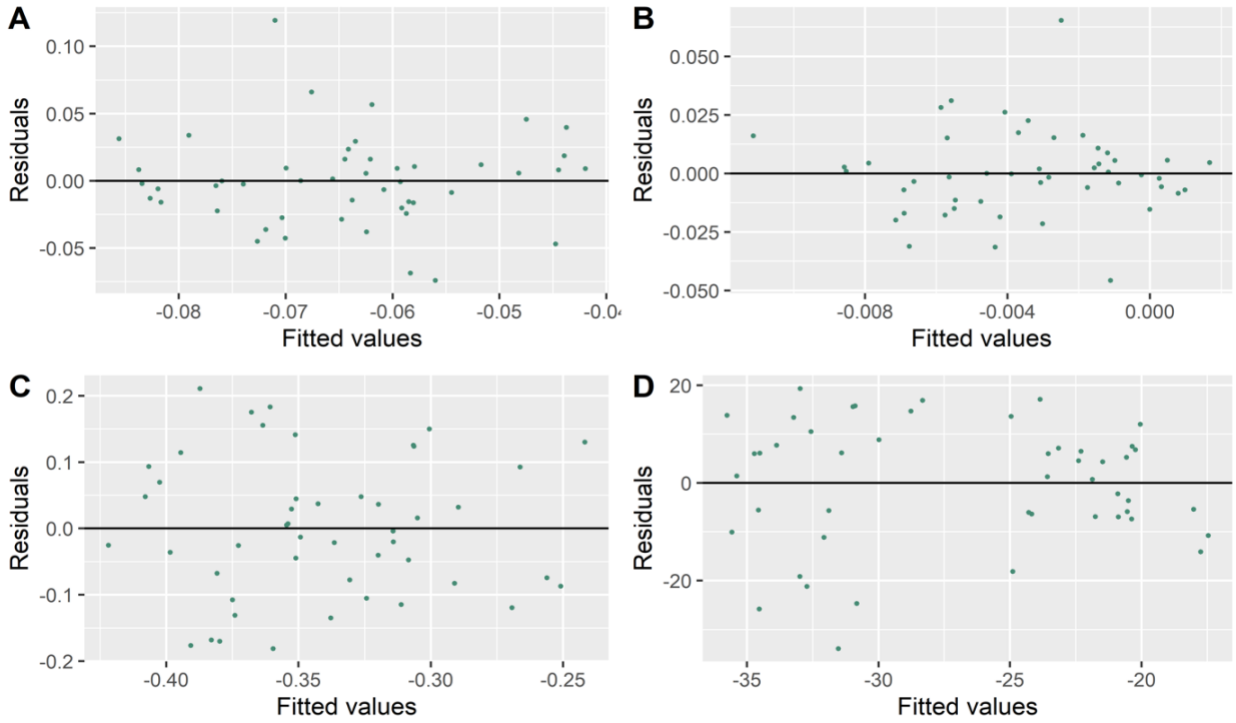

Figure E18 *– Residual verses fitted plots for motor capacities at 12 weeks post-injury. A) Step Length (% of body height). B) Step Length CV (%). C) Velocity (actual velocity (cm/s)/body height (cm)). D) Cadence (steps/min).*

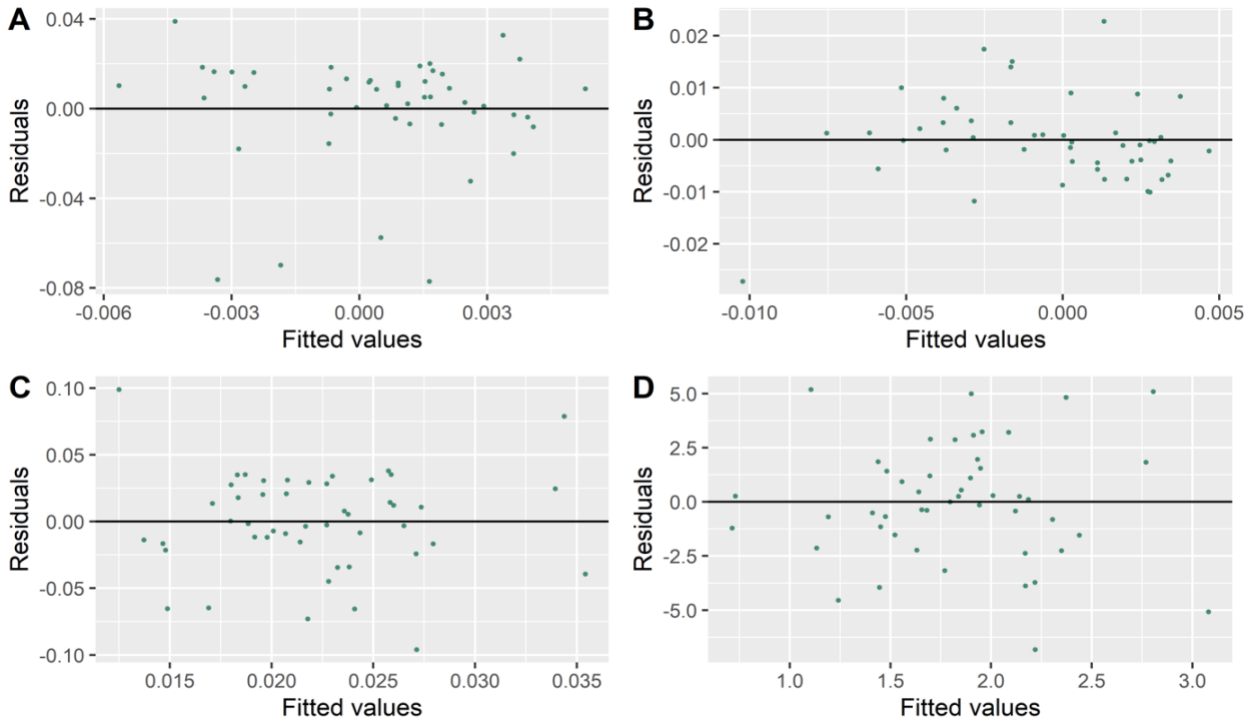

Figure E19 *– Residual verses fitted plots for cognitive capacities at 16 weeks post-injury. A) Step Length (% of body height). B) Step Length CV (%). C) Velocity (actual velocity (cm/s)/body height (cm)). D) Cadence (steps/min).*

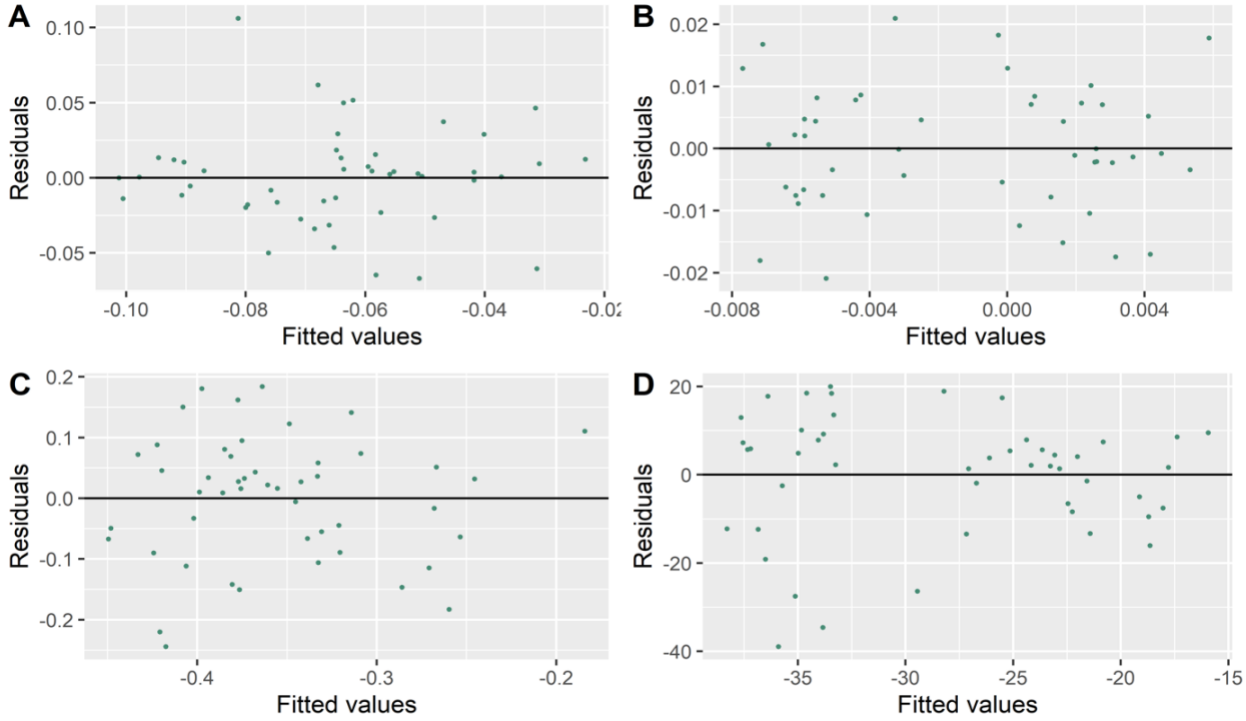

Figure E20 *– Residual verses fitted plot for motor capacities at 16 weeks post-injury. A) Step Length (% of body height). B) Step Length CV (%). C) Velocity (actual velocity (cm/s)/body height (cm)). D) Cadence (steps/min).*

Table E7 *– Shapiro-Wilk test results for the residuals of the raw data at 1 week post-injury*

Variable	Statistic	p-value
Step Length (% of body height)	0.99046992	0.233779629417035
Step Length CV (%)	0.81847798	<0.001
Velocity (cm/s normalized to body height)	0.96738986	0.000191852196635719
Cadence (steps/min)	0.97231913	0.000749809027087681

Table E8 *– Shapiro-Wilk test results for the residuals of the raw data at 2 weeks post-injury*

Variable	Statistic	p-value
Step Length (% of body height)	0.97429654	0.0013297392018417
Step Length CV (%)	0.89334687	<0.001
Velocity (cm/s normalized to body height)	0.93319131	<0.001
Cadence (steps/min)	0.93262872	<0.001

Table E9 *– Shapiro-Wilk test results for the residuals of the raw data at 8 weeks post-injury*

Variable	Statistic	p-value
Step Length (% of body height)	0.97156407	<0.001
Step Length CV (%)	0.90143054	<0.001
Velocity (cm/s normalized to body height)	0.92113108	<0.001
Cadence (steps/min)	0.91526972	<0.001

Table E10 *– Shapiro-Wilk test results for the residuals of the raw data at 12 weeks post-injury*

Variable	Statistic	p-value
Step Length (% of body height)	0.98312267	0.0207391065021636
Step Length CV (%)	0.8928525	<0.001
Velocity (cm/s normalized to body height)	0.93193872	<0.001
Cadence (steps/min)	0.92179697	<0.001

Table E11 *– Shapiro-Wilk test results for the residuals of the raw data at 16 weeks post-injury*

Variable	Statistic	p-value
Step Length (% of body height)	0.98086871	0.00999481016585391
Step Length CV (%)	0.94916814	<0.001
Velocity (cm/s normalized to body height)	0.92545541	<0.001
Cadence (steps/min)	0.88596542	<0.001

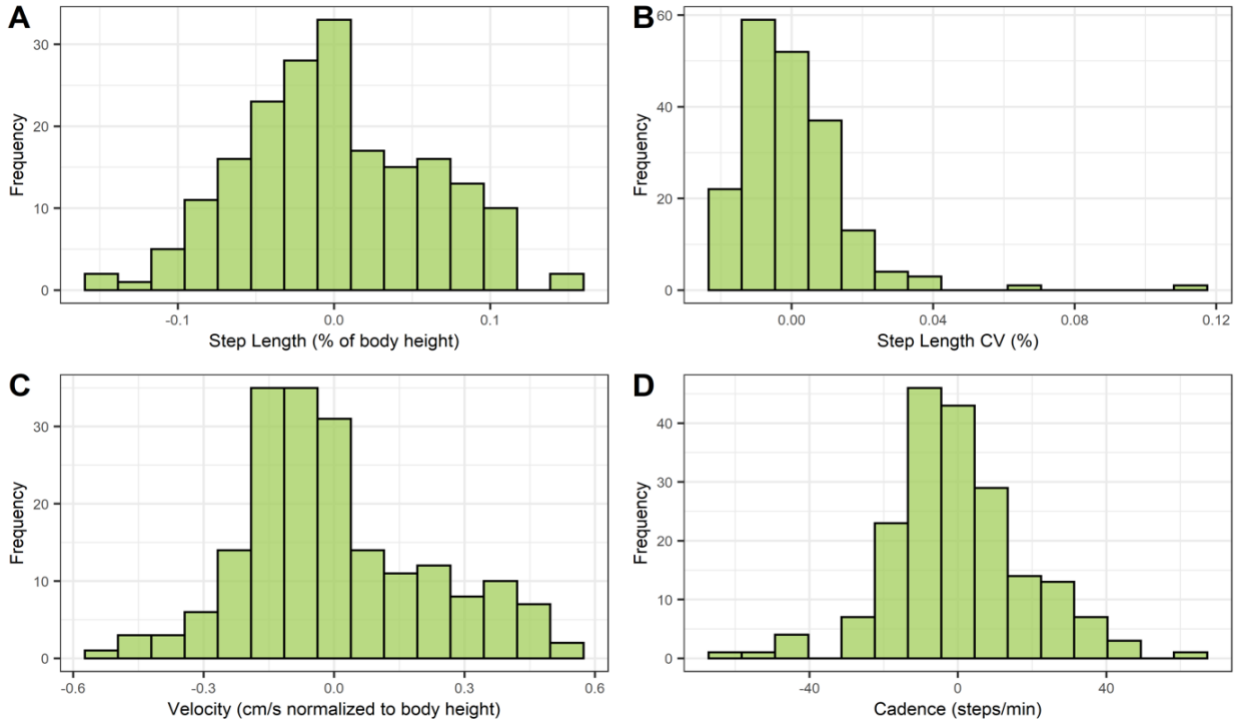

Figure E21 *– Histograms for each measure of interest for the raw data 1 week post-injury. A) Step Length (% of body height). B) Step Length CV (%). C) Velocity (actual velocity (cm/s)/body height (cm)). D) Cadence (steps/min).*

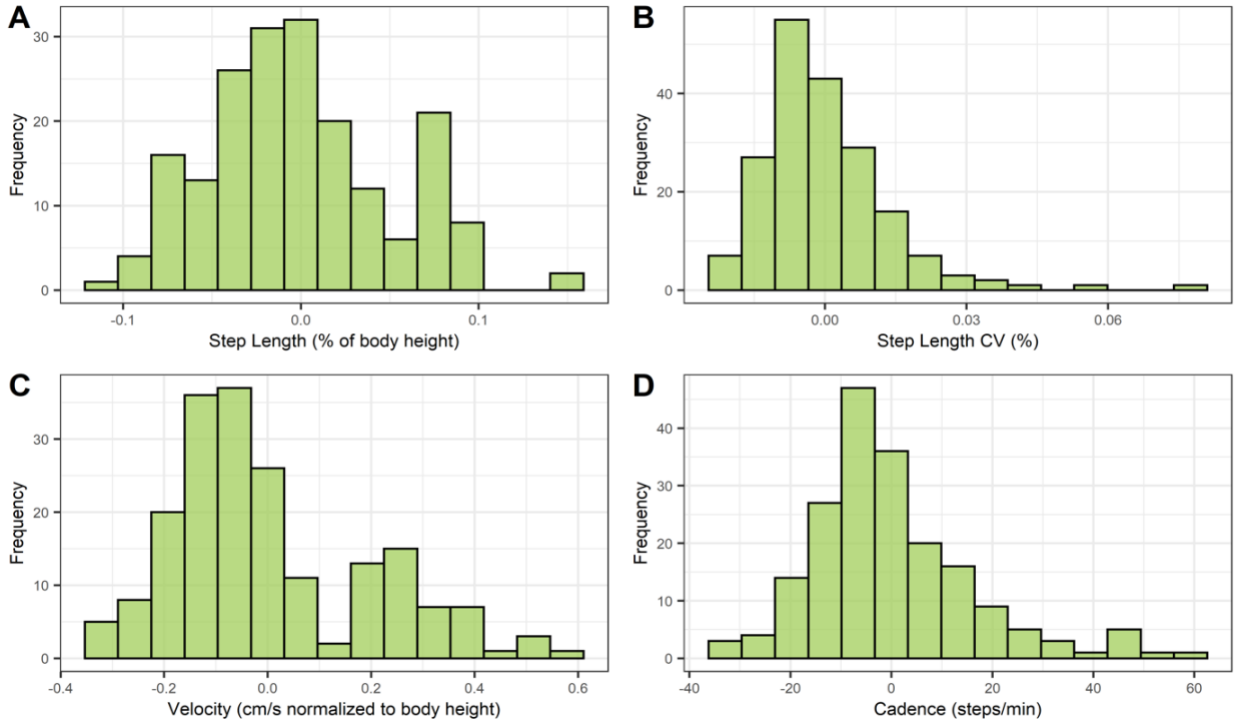

Figure E22 *– Histograms for each measure of interest for the raw data 2 weeks post-injury. A) Step Length (% of body height). B) Step Length CV (%). C) Velocity (actual velocity (cm/s)/body height (cm)). D) Cadence (steps/min).*

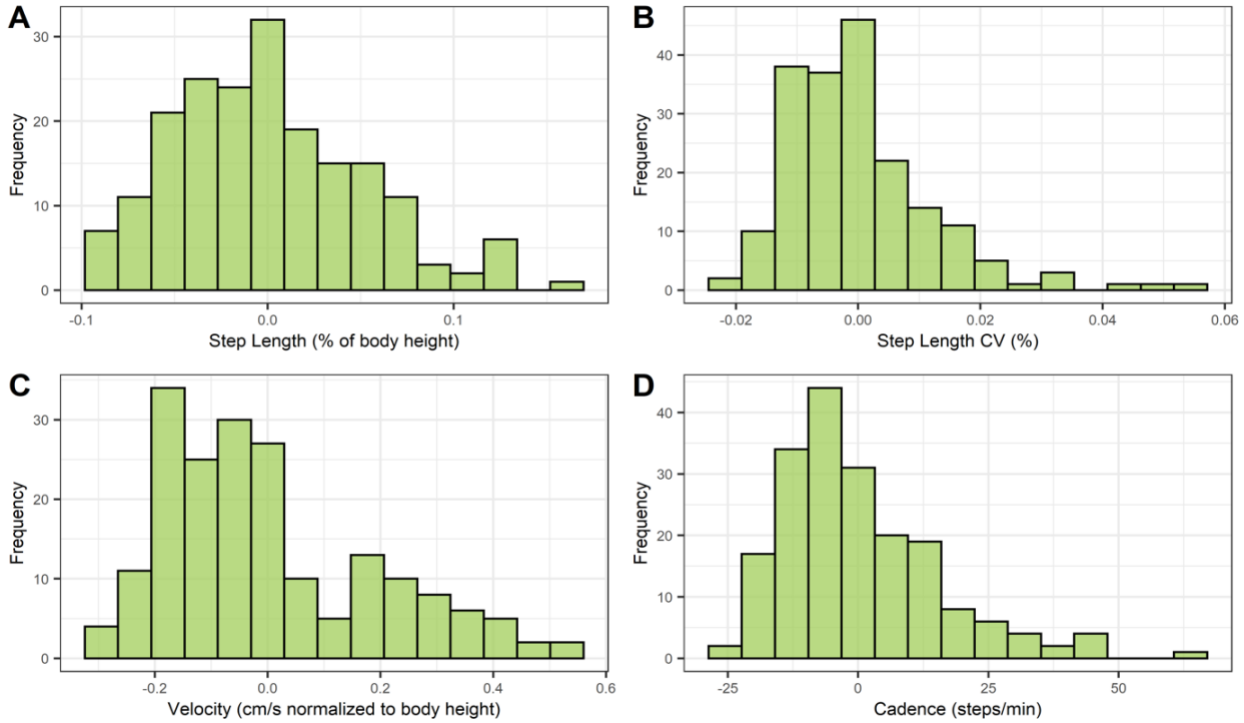

Figure E23 *– Histograms for each measure of interest for the raw data 8 weeks post-injury. A) Step Length (% of body height). B) Step Length CV (%). C) Velocity (actual velocity (cm/s)/body height (cm)). D) Cadence (steps/min).*

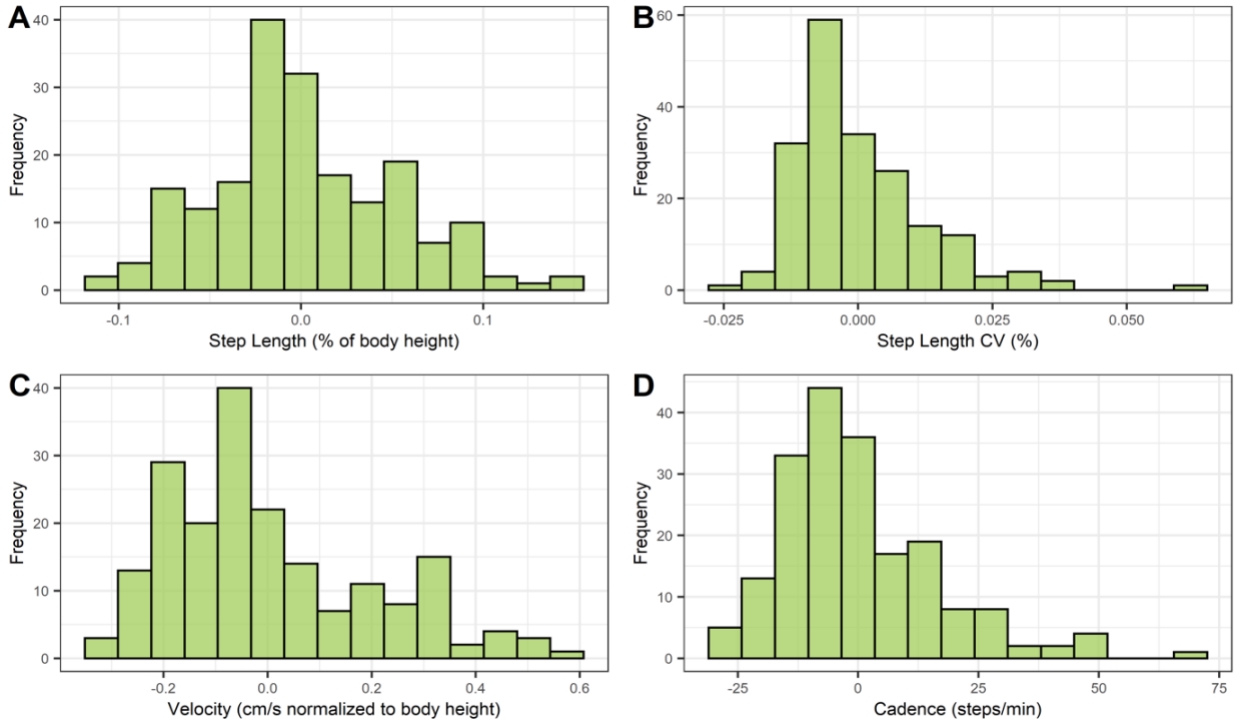

Figure E24 *– Histograms for each measure of interest for the raw data 12 weeks post-injury. A) Step Length (% of body height). B) Step Length CV (%). C) Velocity (actual velocity (cm/s)/body height (cm)). D) Cadence (steps/min).*

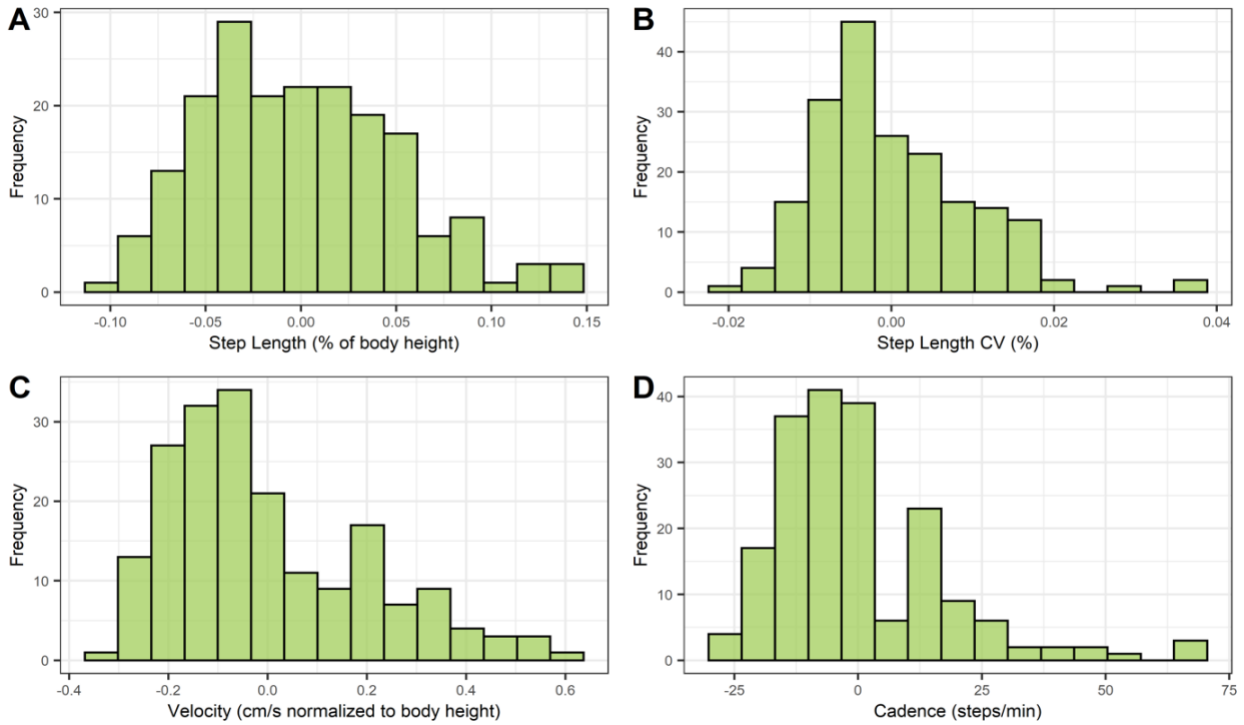

Figure E25 *– Histograms for each measure of interest for the raw data 16 weeks post-injury. A) Step Length (% of body height). B) Step Length CV (%). C) Velocity (actual velocity (cm/s)/body height (cm)). D) Cadence (steps/min).*

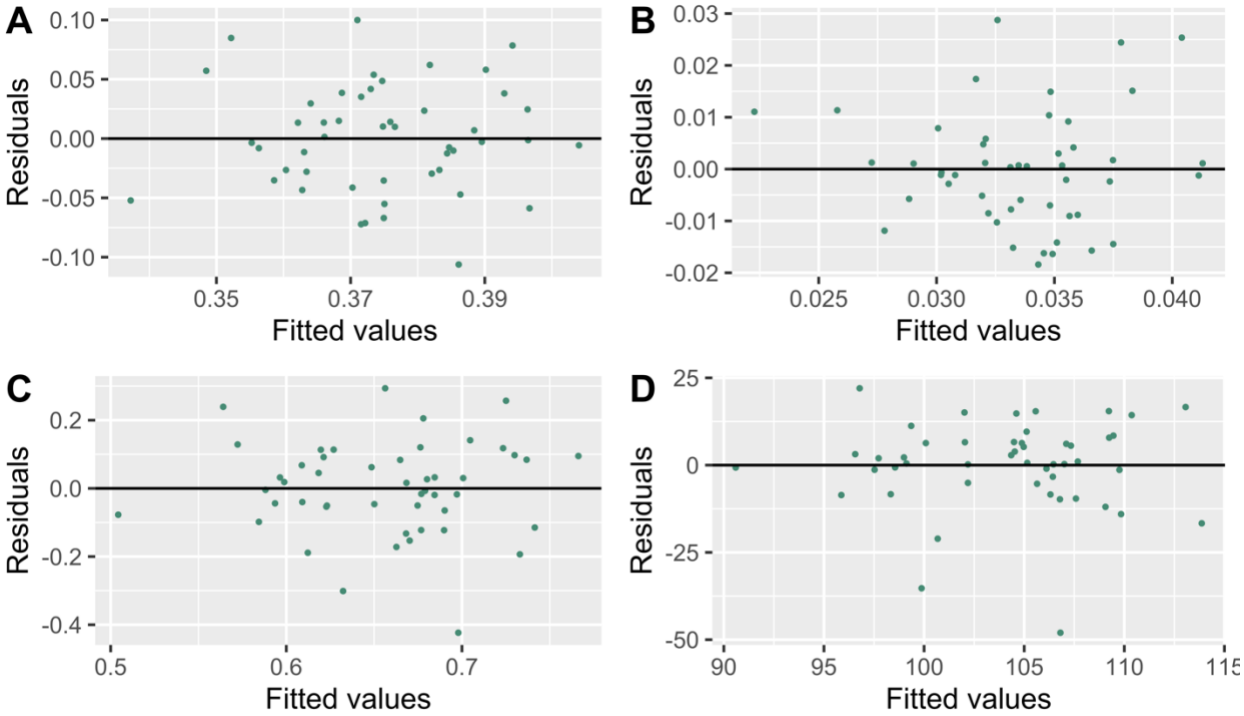

Figure E26 *– Residual verses fitted plots for the Talking condition at 1 week post-injury. A) Step Length (% of body height). B) Step Length CV (%). C) Velocity (actual velocity (cm/s)/body height (cm)). D) Cadence (steps/min).*

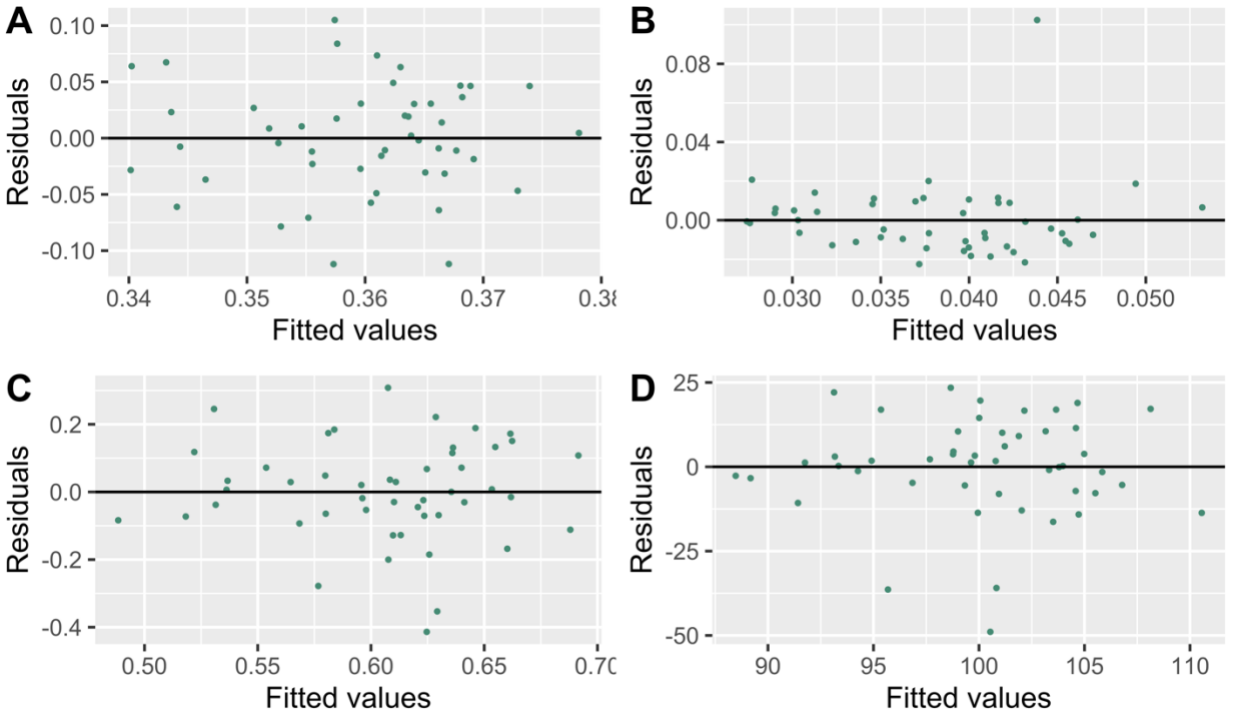

Figure E27 *– Residual verses fitted plots for the Dual Task condition at 1 week post-injury. A) Step Length (% of body height). B) Step Length CV (%). C) Velocity (actual velocity (cm/s)/body height (cm)). D) Cadence (steps/min).*

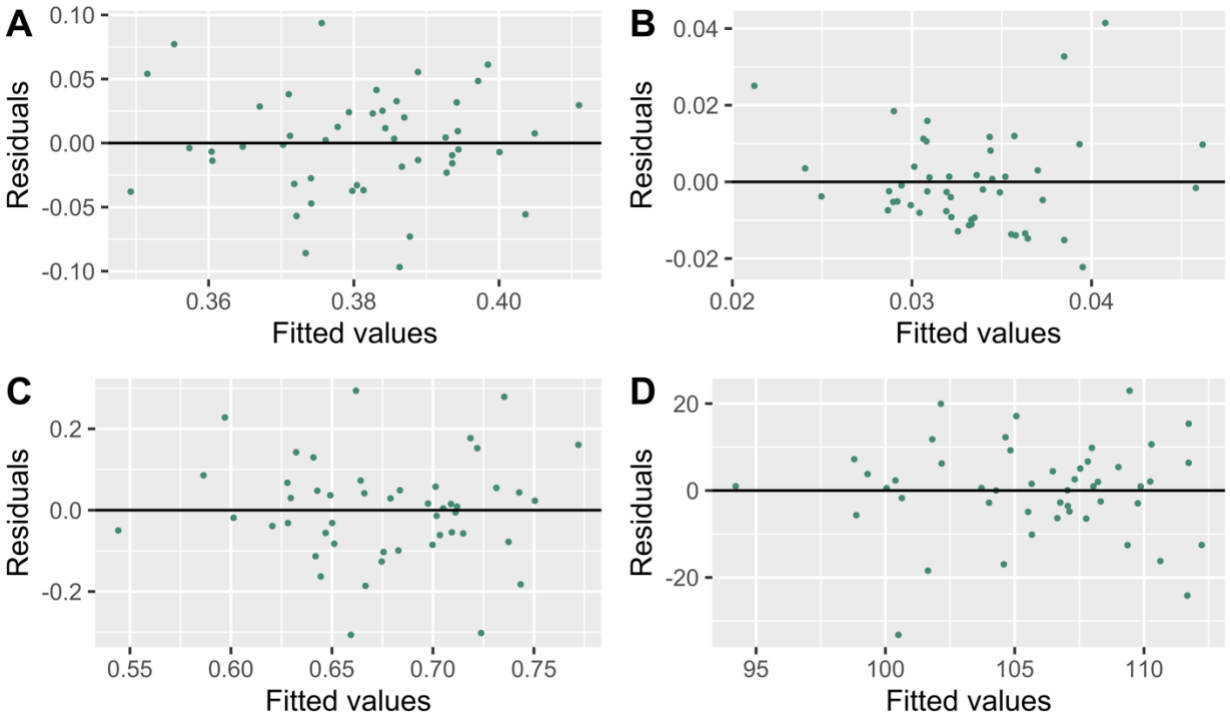

Figure E28 *– Residual verses fitted plots for the Self-paced condition at 1 week post-injury. A) Step Length (% of body height). B) Step Length CV (%). C) Velocity (actual velocity (cm/s)/body height (cm)). D) Cadence (steps/min).*

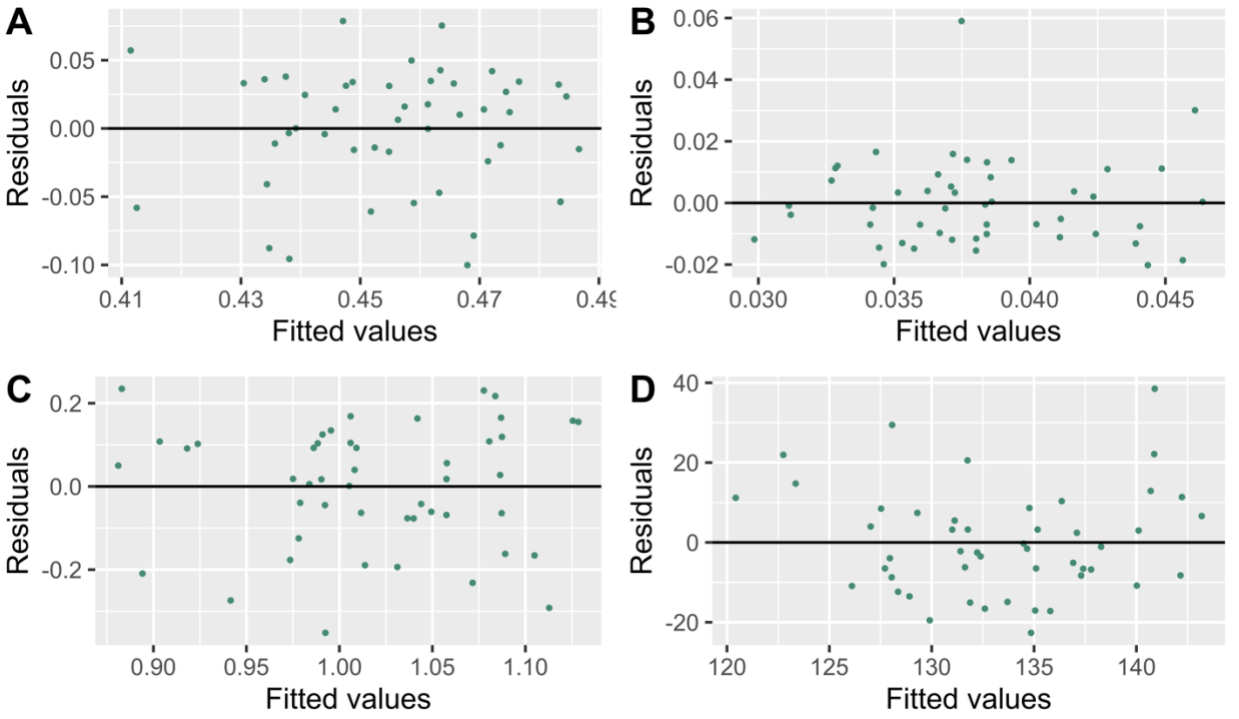

Figure E29 *– Residual verses fitted plots for the Maximum-paced condition at 1 week post-injury. A) Step Length (% of body height). B) Step Length CV (%). C) Velocity (actual velocity (cm/s)/body height (cm)). D) Cadence (steps/min).*

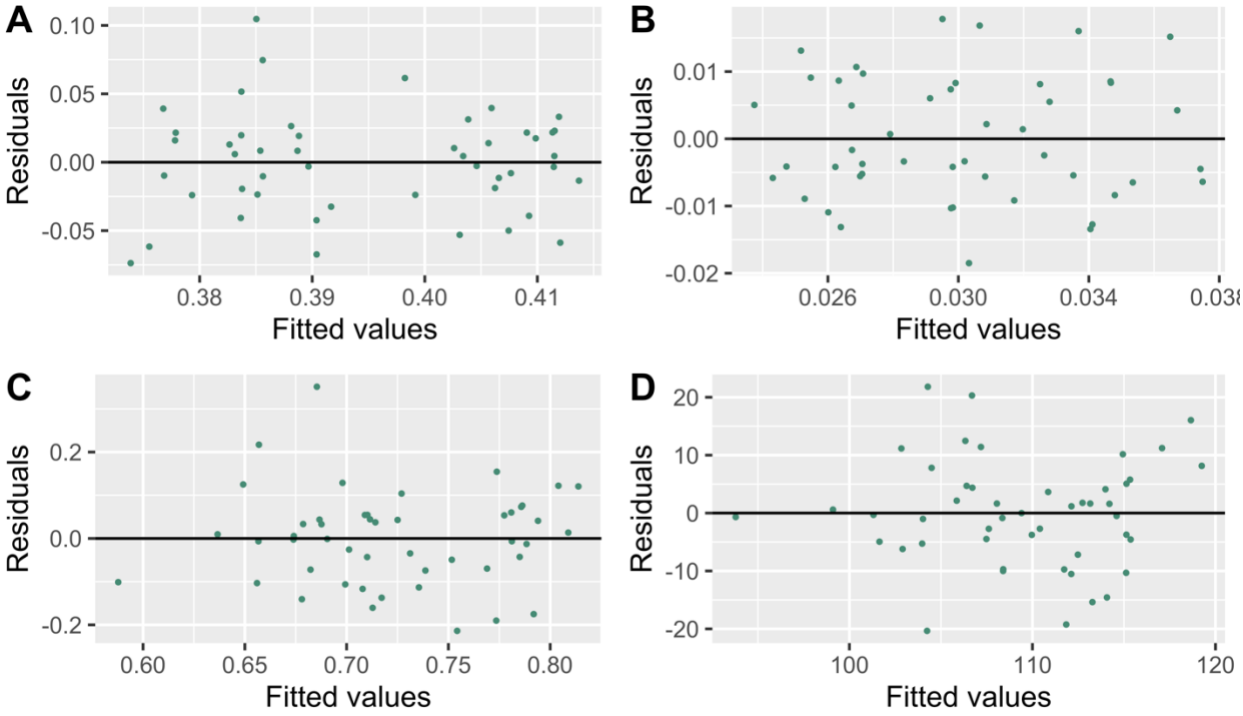

Figure E30 *– Residual verses fitted plots for the Talking condition at 2 weeks post-injury. A) Step Length (% of body height). B) Step Length CV (%). C) Velocity (actual velocity (cm/s)/body height (cm)). D) Cadence (steps/min).*

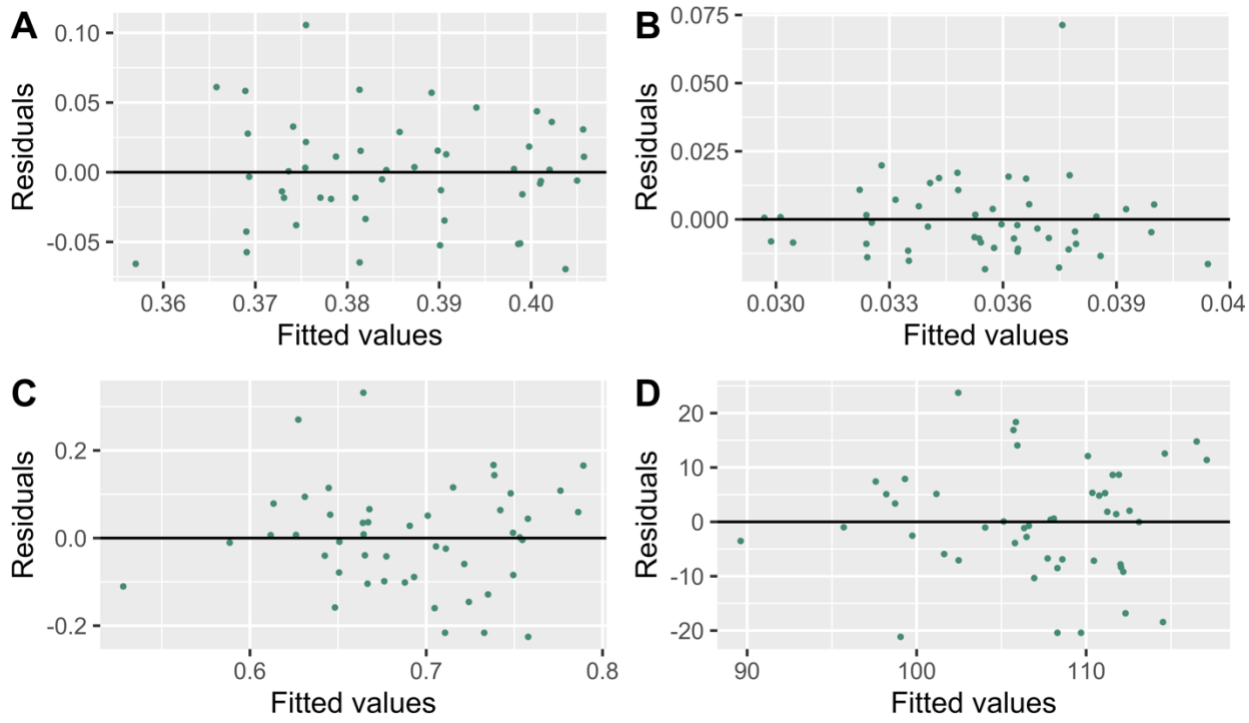

Figure E31 *– Residual verses fitted plots for the Dual Task condition at 2 weeks post-injury. A) Step Length (% of body height). B) Step Length CV (%). C) Velocity (actual velocity (cm/s)/body height (cm)). D) Cadence (steps/min).*

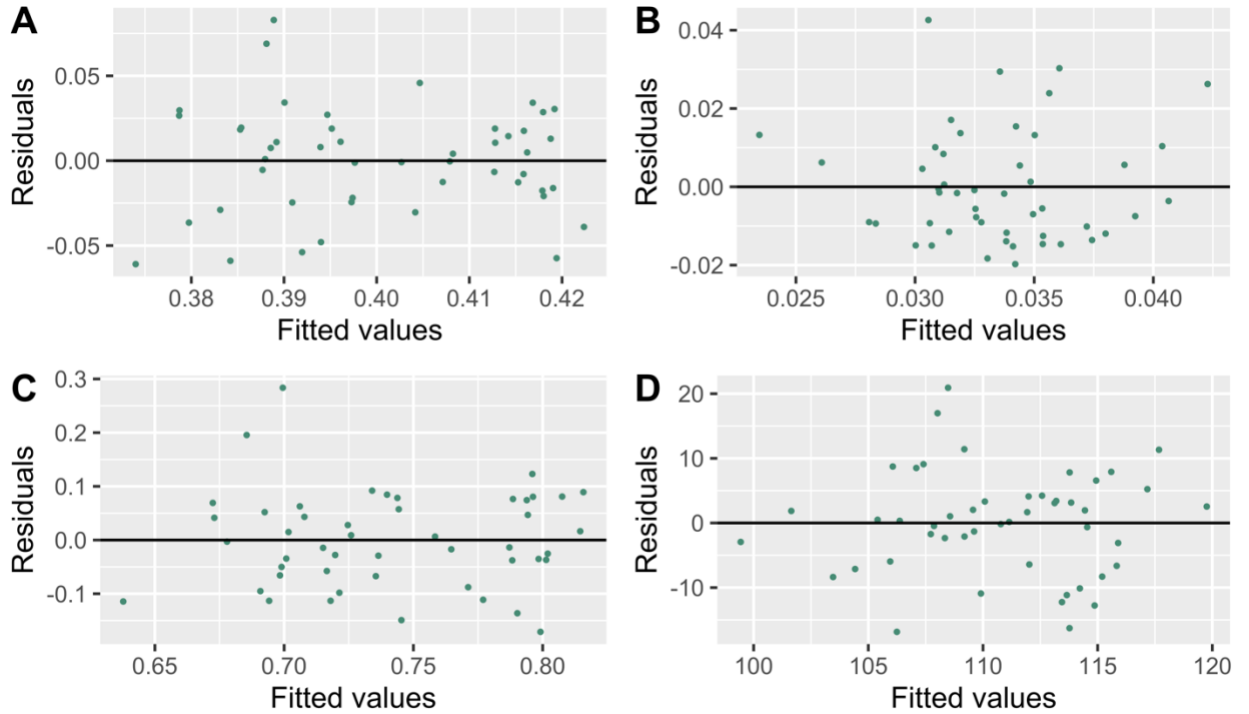

Figure E32 *– Residual verses fitted plots for the Self-paced condition at 2 weeks post-injury. A) Step Length (% of body height). B) Step Length CV (%). C) Velocity (actual velocity (cm/s)/body height (cm)). D) Cadence (steps/min).*

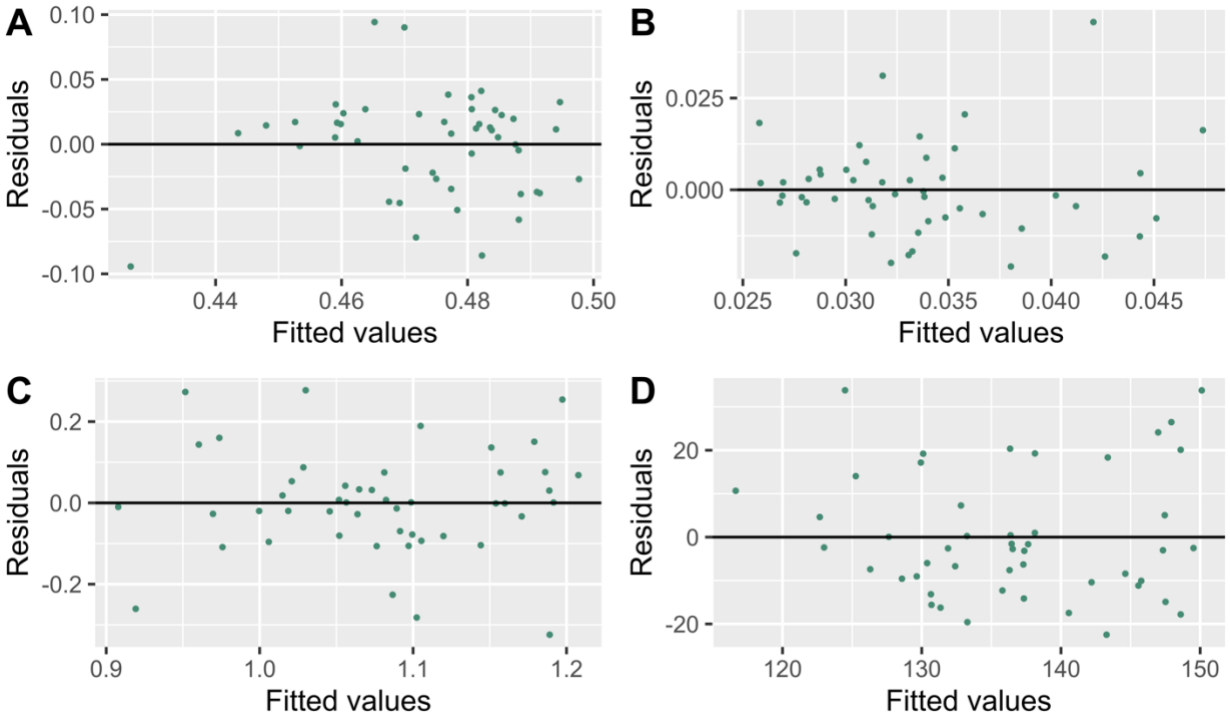

Figure E33 *– Residual verses fitted plots for the Maximum-paced condition at 2 weeks post-injury. A) Step Length (% of body height). B) Step Length CV (%). C) Velocity (actual velocity (cm/s)/body height (cm)). D) Cadence (steps/min).*

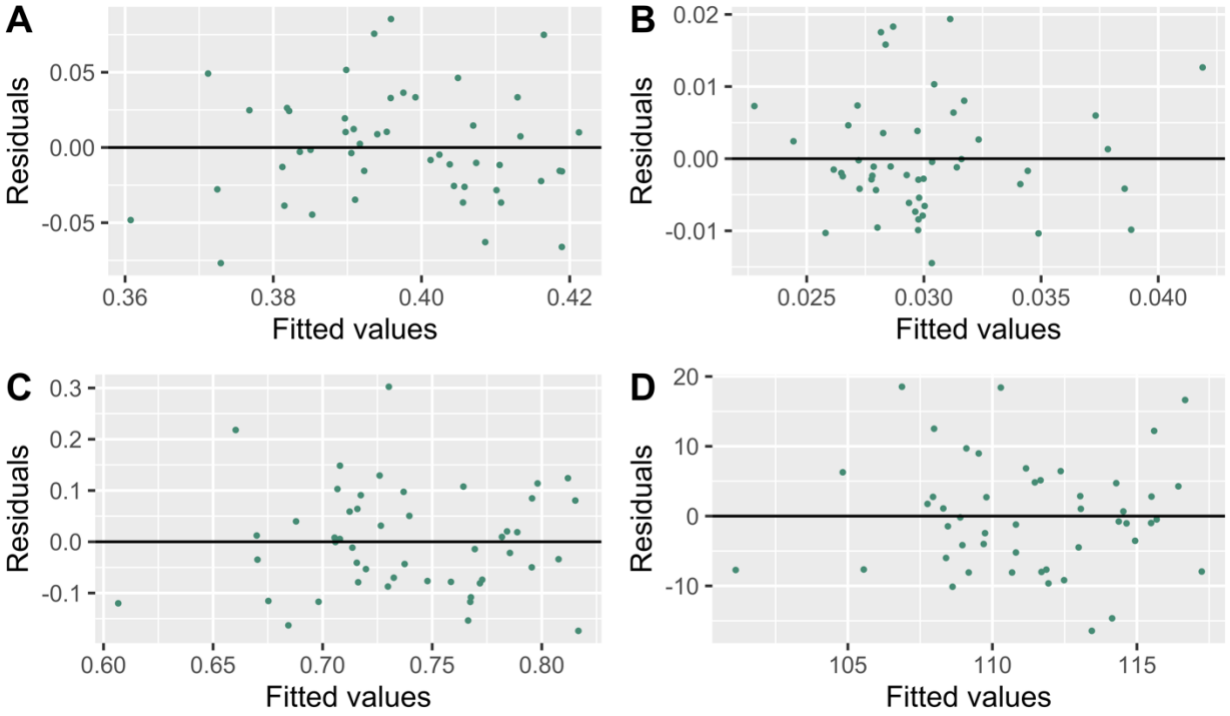

Figure E34 *– Residual verses fitted plots for the Talking condition at 8 weeks post-injury. A) Step Length (% of body height). B) Step Length CV (%). C) Velocity (actual velocity (cm/s)/body height (cm)). D) Cadence (steps/min).*

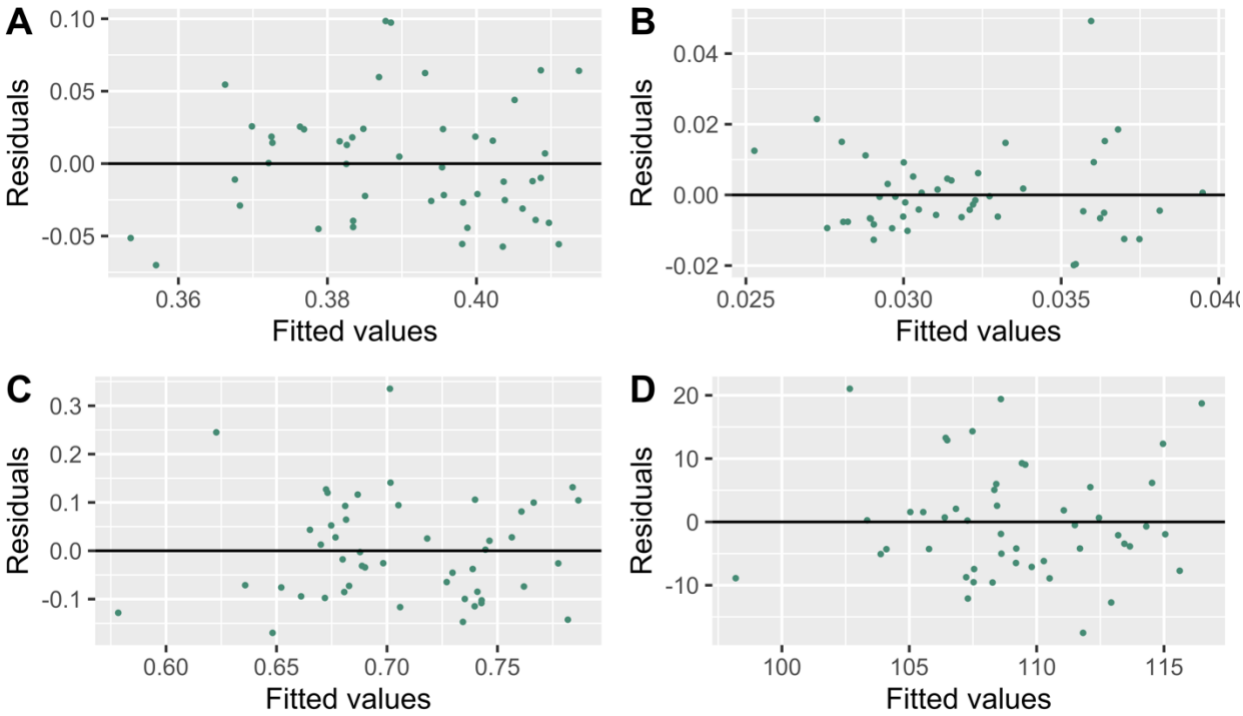

Figure E35 *– Residual verses fitted plots for the Dual Task condition at 8 weeks post-injury. A) Step Length (% of body height). B) Step Length CV (%). C) Velocity (actual velocity (cm/s)/body height (cm)). D) Cadence (steps/min).*

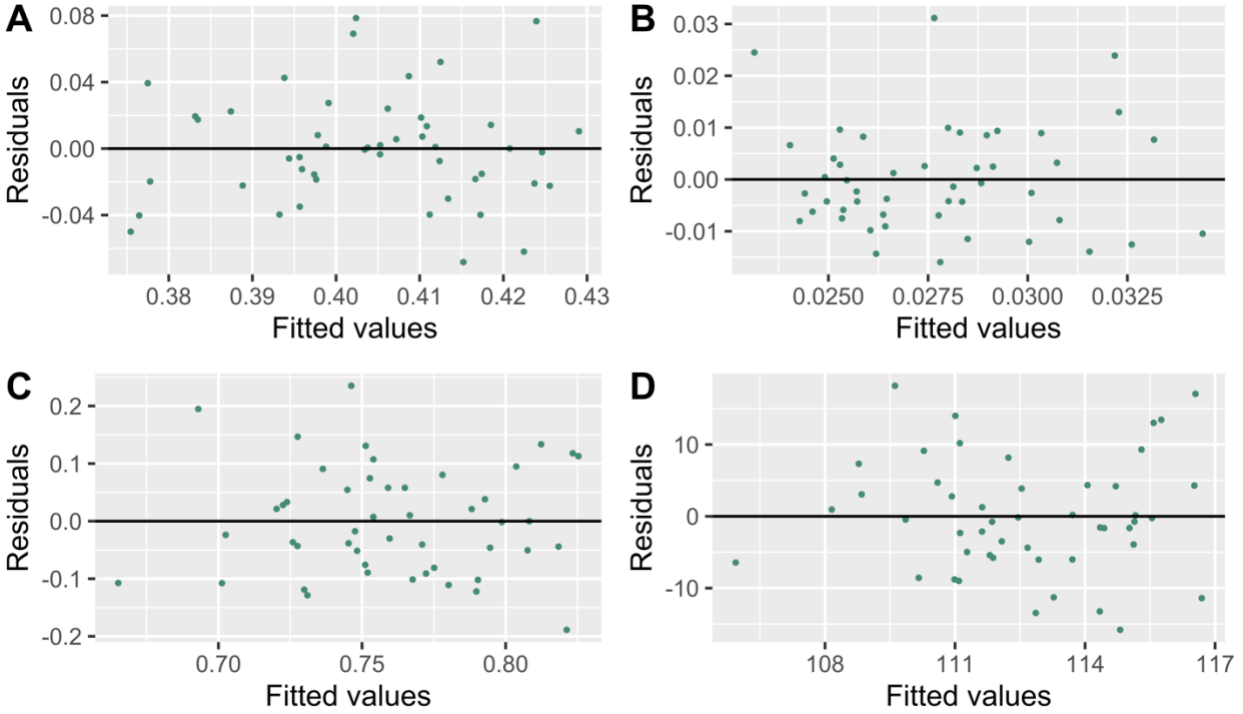

Figure E36 *– Residual verses fitted plots for the Self-paced condition at 8 weeks post-injury. A) Step Length (% of body height). B) Step Length CV (%). C) Velocity (actual velocity (cm/s)/body height (cm)). D) Cadence (steps/min).*

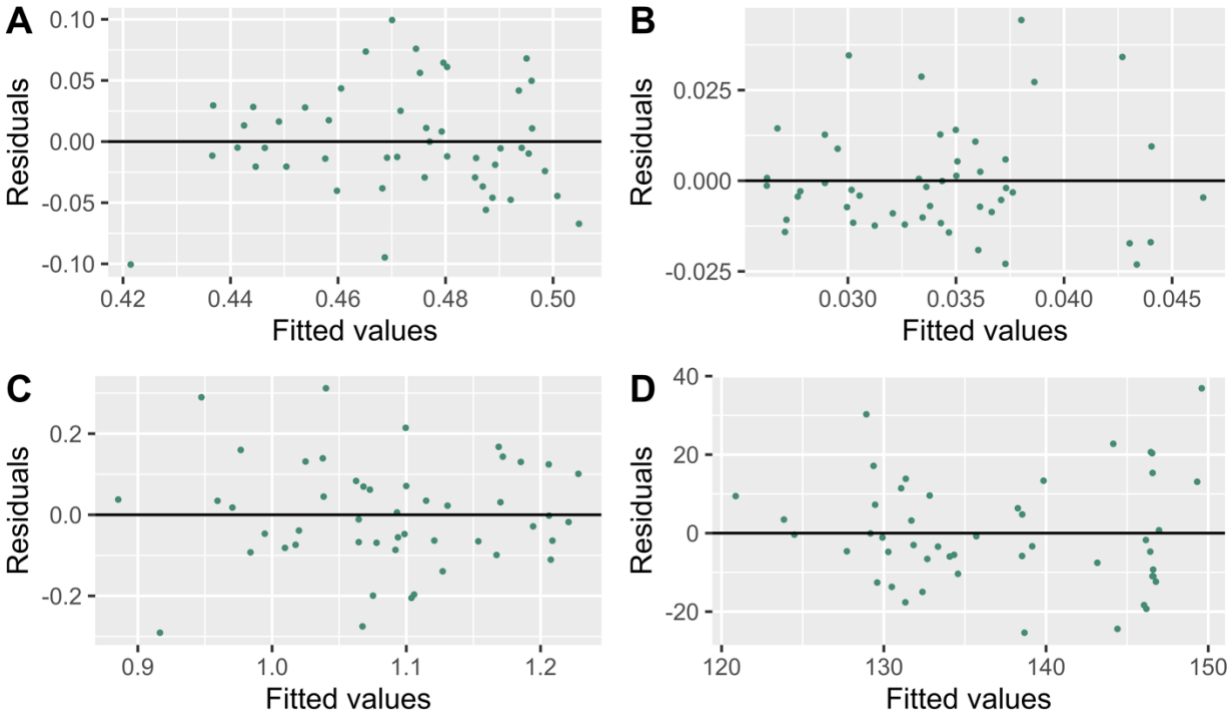

Figure E37 *– Residual verses fitted plots for the Maximum-paced condition at 8 weeks post-injury. A) Step Length (% of body height). B) Step Length CV (%). C) Velocity (actual velocity (cm/s)/body height (cm)). D) Cadence (steps/min).*

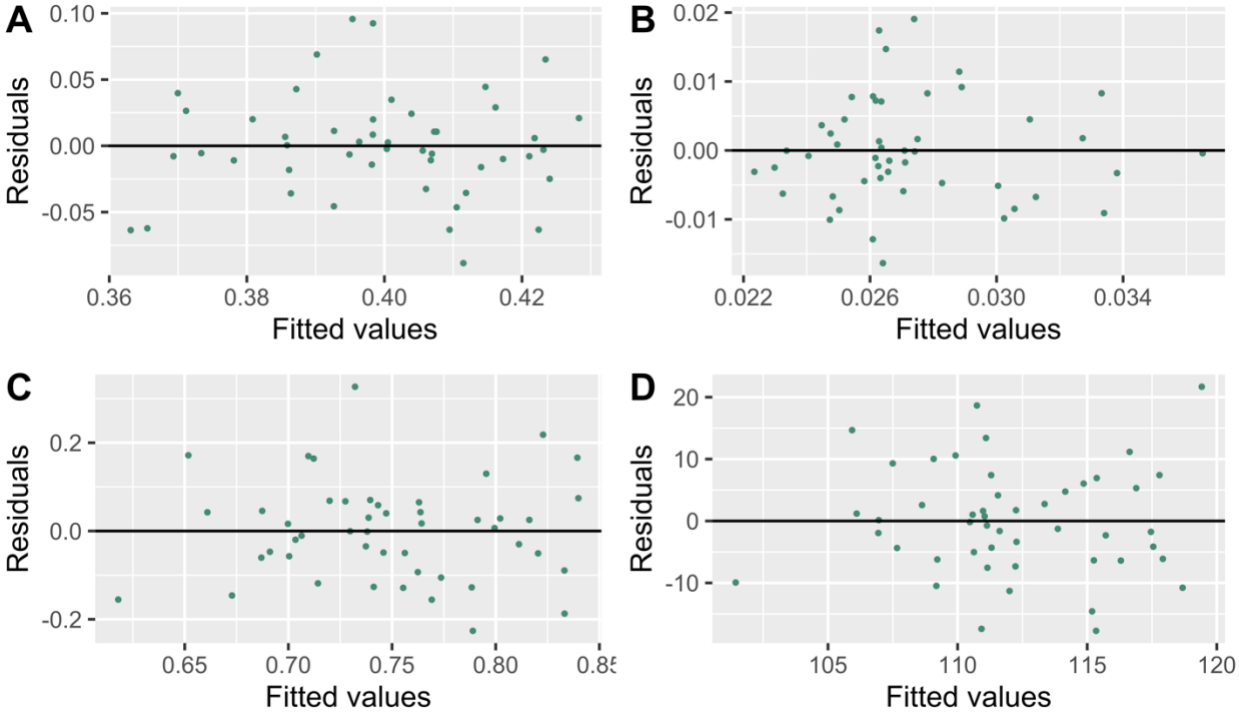

Figure E38 *– Residual verses fitted plots for the Talking condition at 12 weeks post-injury. A) Step Length (% of body height). B) Step Length CV (%). C) Velocity (actual velocity (cm/s)/body height (cm)). D) Cadence (steps/min).*

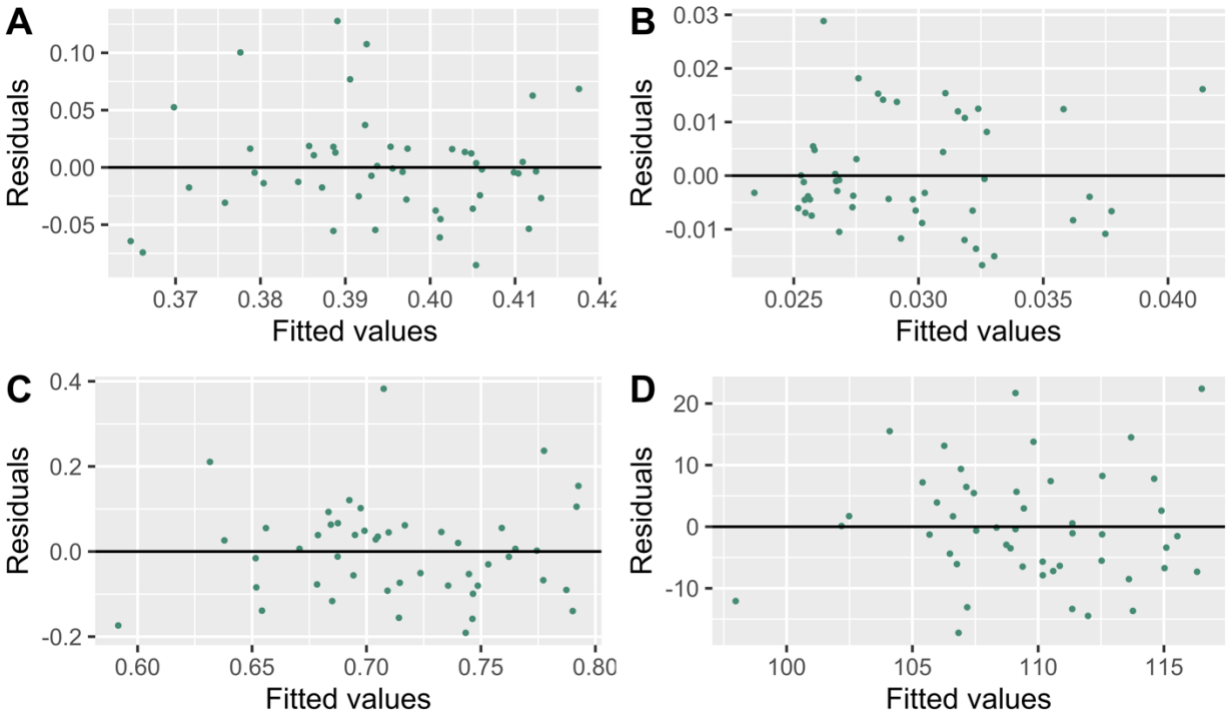

Figure E39 *– Residual verses fitted plots for the Dual Task condition at 12 weeks post-injury. A) Step Length (% of body height). B) Step Length CV (%). C) Velocity (actual velocity (cm/s)/body height (cm)). D) Cadence (steps/min).*

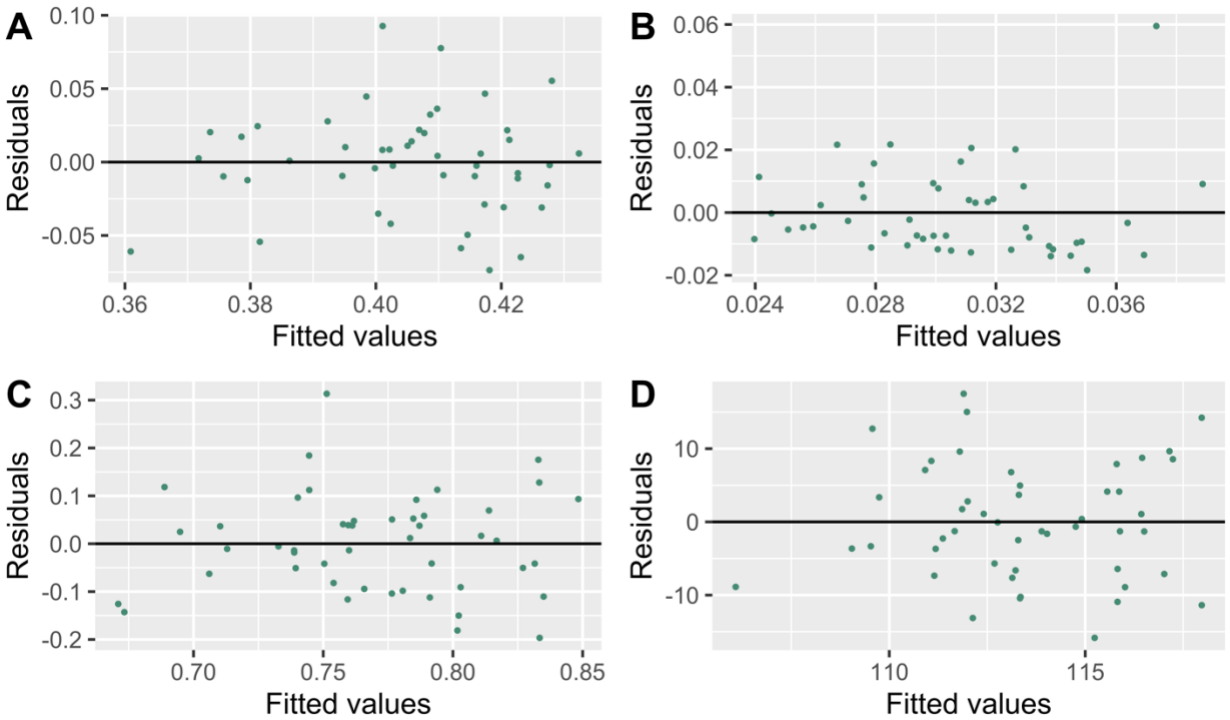

Figure E40 *– Residual verses fitted plots for the Self-paced condition at 12 weeks post-injury. A) Step Length (% of body height). B) Step Length CV (%). C) Velocity (actual velocity (cm/s)/body height (cm)). D) Cadence (steps/min).*

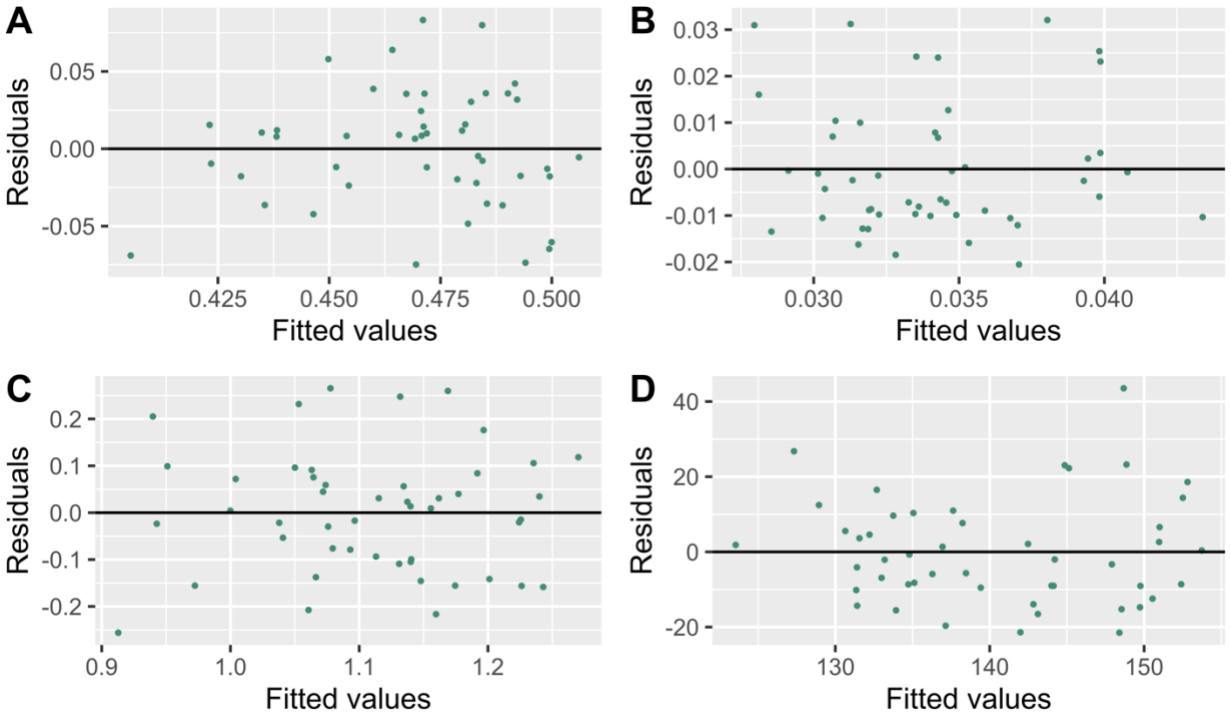

Figure E41 *– Residual verses fitted plots for the Maximum-paced condition at 12 weeks post-injury. A) Step Length (% of body height). B) Step Length CV (%). C) Velocity (actual velocity (cm/s)/body height (cm)). D) Cadence (steps/min).*

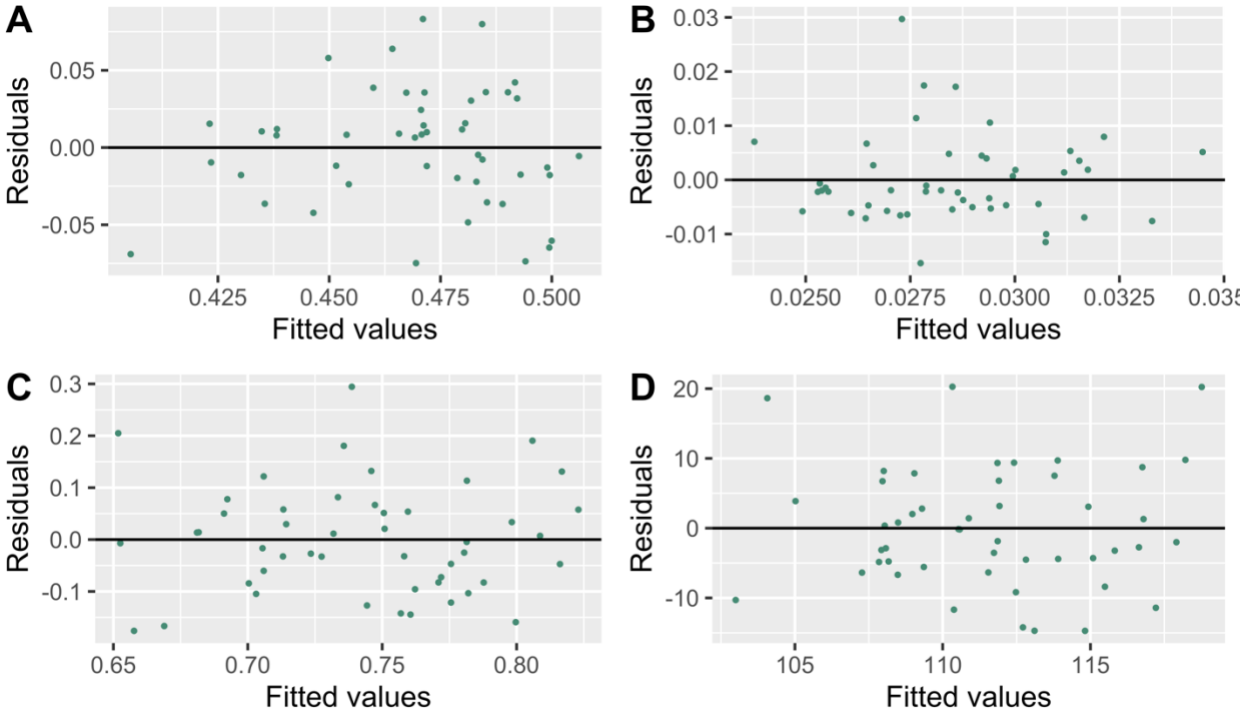

Figure E42 *– Residual verses fitted plots for the Talking condition at 16 weeks post-injury. A) Step Length (% of body height). B) Step Length CV (%). C) Velocity (actual velocity (cm/s)/body height (cm)). D) Cadence (steps/min).*

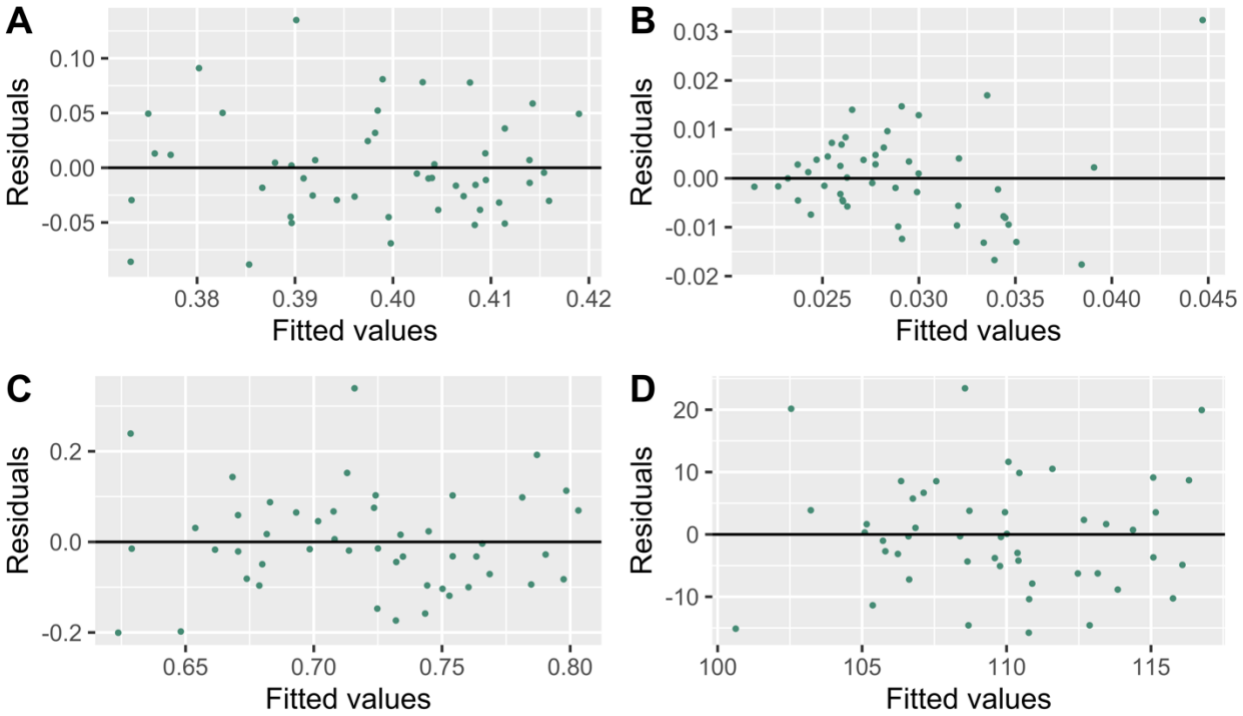

Figure E43 *– Residual verses fitted plots for the Dual Task condition at 16 weeks post-injury. A) Step Length (% of body height). B) Step Length CV (%). C) Velocity (actual velocity (cm/s)/body height (cm)). D) Cadence (steps/min).*

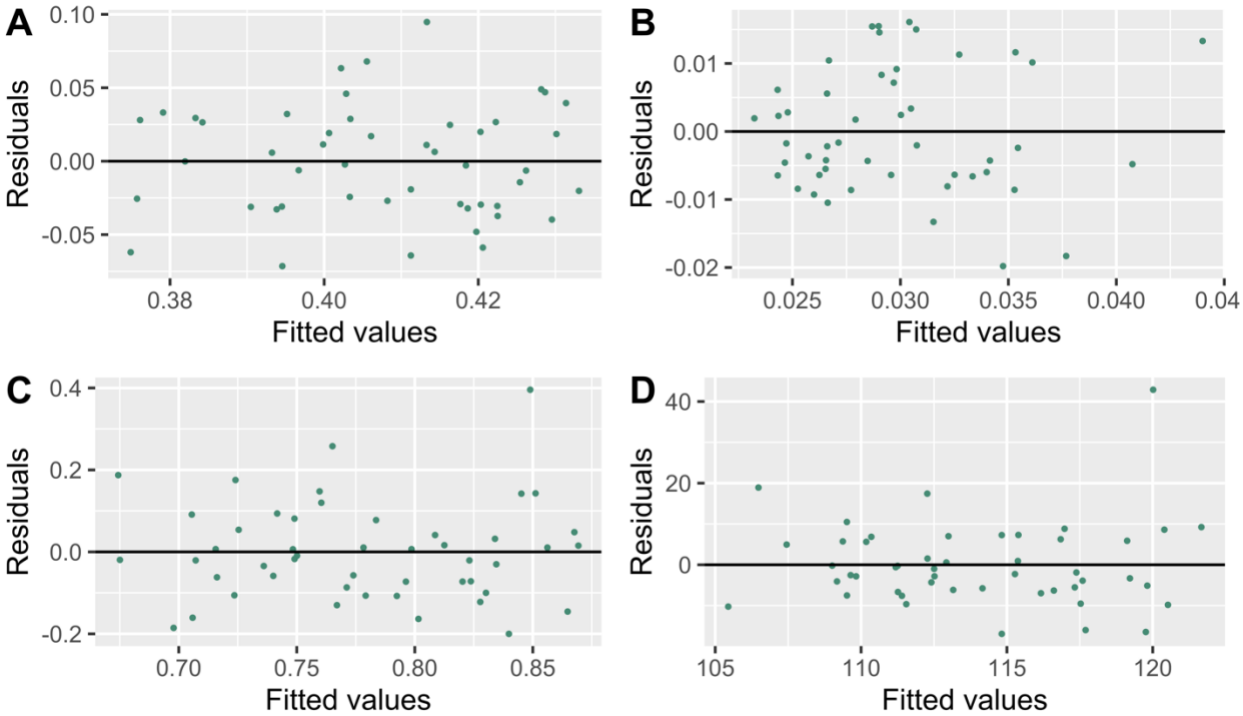

Figure E44 *– Residual verses fitted plots for the Self-paced condition at 16 weeks post-injury. A) Step Length (% of body height). B) Step Length CV (%). C) Velocity (actual velocity (cm/s)/body height (cm)). D) Cadence (steps/min).*

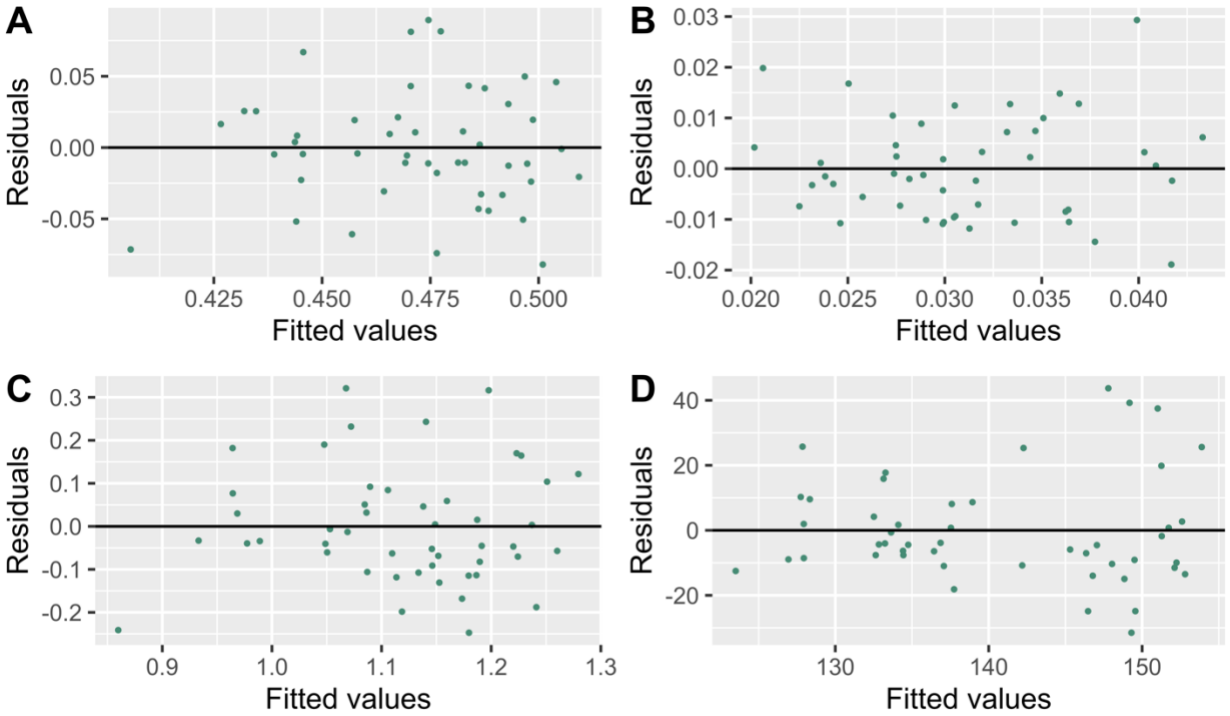

Figure E45 *– Residual verses fitted plots for the Maximum-paced condition at 16 weeks post-injury. A) Step Length (% of body height). B) Step Length CV (%). C) Velocity (actual velocity (cm/s)/body height (cm)). D) Cadence (steps/min).*