Non-linear Centre of Pressure Analysis during Quiet Stance: Application to Mild Traumatic Brain Injury

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A thesis submitted to the

Faculty of Graduate and Postdoctoral Studies

in partial fulfillment of the requirements for the PhD degree in Human Kinetics

Human Kinetics
Faculty of Health Sciences
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List of Abbreviations

a/p	anteroposterior
β	beta
COP	centre of pressure
COM	centre of mass
DDE	delay differential equation
DT	dual-task
EC	standing with eyes closed
EO	standing with eyes open
fBm	fractional Brownian motion
fGn	fractional Gaussian noise
m/l	mediolateral
mTBI	mild traumatic brain injury
ODE	ordinary differential equation
PD	proportional + derivative
PID	proportional + integral + derivative
PSD	power spectral density
SD	standard deviation
SIN	single leg stance
TAN	tandem stance

Abstract

A quiet stance framework and a control system perspective were used to explore healthy balance and balance after mild traumatic brain injury. Linear and non-linear centre of pressure analyses were applied.

The foundation was laid by reviewing literature to understand how balance is achieved, how it is represented as a control system, what factors are known to affect balance, and the cornerstone—how to choose appropriate measures to quantify balance. To understand how mild traumatic brain injury affects the brain, a scoping review of the evolution of symptoms and effects was used to form a conceptual description. Findings described phases of functional effects that resulted from neurometabolic cascade; consequently, balance and dual-task functional effects were determined to stem from widespread not focal changes in the brain.

Subsequent studies were tailored to address gaps in knowledge. Linear and non-linear centre of pressure measures were first investigated in healthy young adults to determine what supplemental information could be provided by non-linear measures describing local stability and scaling. It was found that linear and non-linear measures were complementary in assessing balance system input-output, control, and integration. Furthermore, normative non-linear data were established for single leg and tandem stance.

Subsequently, these measures were investigated in young adults and adolescents with recent mild traumatic brain injury based on the hypothesis that altered mechanisms affecting balance would be reflected by changes in these measures. In young adults, increased complexity of short-term scaling indicated subtle changes to balance control after injury. In adolescents, linear and non-linear measures also demonstrated changes to output, control, and temporal relations of balance. Altered balance was also demonstrated while concurrently performing a Stroop task. On the whole, changes to multiple aspects of balance supported the concept of widespread effects resulting from mild traumatic brain injury.

Balance control in quiet stance was further explored using three-dimensional state space reconstruction of centre of pressure. Visual representations demonstrated that dynamic structure within centre of pressure reflected control characteristics. These control characteristics were still present after mild traumatic brain injury.

Résumé

Des méthodes linéaires et non-linéaires ont été appliquées à l'analyse du centre de pression pour enquêter l'équilibre chez des individus sain et chez des individus ayant subi une commotion cérébrale.

Une revue a été entreprise—de l'acheminement de l'équilibre, son traitement dans le cerveau, et sa représentation par des modèles de contrôle et les mesures quantitatives. De plus, un examen des travaux au sujet des effets de commotion cérébrale a mené à une description conceptuel d les conséquences de cascade neurométabolique et des effets fonctionnels et comment ils sont liés l'un à l'autre. Il apparaît que les effets qui se présentent en maintenant l'équilibre et pendant des tâches simultanées après une commotion cérébrale proviennent des changements qui s'étendent partout dans le cerveau.

Chez les jeunes adultes en bonne santé, les mesures linéaires et non-linéaires ont fourni de façon complémentaire de l'information sur les caractéristiques d'entrées/sorties, du contrôle, et des relations temporelles de l'équilibre. En plus, bien que ce qui se trouve actuellement dans la littérature inclut ni des données non-linéaires pour se tenir debout sur une jambe, ni des données non-linéaires pour se tenir debout en position 'tandem', ces données normatives ont été établies.

Chez les jeunes adultes qui ont récemment subi une commotion cérébrale, on s'est attendu à trouver que les mécanismes de l'équilibre modifiés seraient représentés par des changements au niveau des mesures. On a trouvé une réduction des relations aléatoires entre les points proches (à court terme)—ce qui indique des changements aux aspects temporels du contrôle. Les mesures linéaires et non-linéaires ont également démontré des changements dans l'équilibre chez les adolescents après une commotion cérébrale qui ont autant été démontrés en effectuant des tâches simultanées. Ces résultats soutiennent que des effets généralisés proviennent d'une commotion cérébrale.

Enfin, une reconstruction dans le domaine des états a été entreprise pour explorer la structure dynamique des variables d'état. Selon les représentations visuelles de la reconstruction, des caractéristiques de contrôle ont été identifiées. Ces caractéristiques étaient encore présentes après une commotion cérébrale.

Preface

Acknowledgements
I would like to thank my family for all their encouragement and support. Special thanks go to my supervisor Dr. Heidi Sveistrup for providing support, direction, and a great learning environment. I would like to thank Dr. André Longtin for his time and effort in reviewing my work and providing learning opportunities. I would also like to thank Coralie Rochefort for her assistance in data collection in addition to her collaboration. I'd like to recognize the contribution of Chrissy McPhee, Coach Réal Paiement & the University of Ottawa Men's Hockey team, and Coach Jamie Barresi & the University of Ottawa Men's Football team with gratitude. I'd also like to gratefully acknowledge the financial support of the University of Ottawa, the Ontario Graduate Scholarship program and the Queen Elizabeth II Graduate Scholarship in Science and Technology program.

Funding
Queen Elizabeth II Graduate Scholarship in Science and Technology, 2014-2015

Ontario Graduate Scholarship, 2012-2014

University of Ottawa Excellence Scholarship, 2012-2015

University of Ottawa Admission Scholarship, 2011-2012

Ethics approvals
Ethics approval was obtained from the University of Ottawa Ethics Board (*Linear and Non-linear Centre of Pressure Measures in Quiet Stance, Changes to Centre of Pressure in Quiet Stance After Mild Traumatic Brain Injury in Young Adult Football Players, Centre of Pressure During Quiet Stance and Dual-task 1 Month After Mild Traumatic Brain Injury: Adolescents, & A Preliminary Investigation of Visual Centre of Pressure State Space Representation During Quiet Stance*) and the Children's Hospital of Eastern Ontario Ethics Board (*Centre of Pressure During Quiet Stance and Dual-task 1 Month After Mild Traumatic Brain Injury: Adolescents*). Ethics certificates can be found in Appendix B.

Co-author contributions

Scoping Review: A 45-Day Timeline of Mild Traumatic Brain Injury Effects

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Marshall: Manuscript review

Sveistrup: Manuscript review

Linear and Non-linear Centre of Pressure Measures in Quiet Stance

Walters-Stewart: Study design, data collection, data analysis (& analysis materials), writing

Longtin: Manuscript review

Sveistrup: Study design, manuscript review

Changes to Centre of Pressure in Quiet Stance After Mild Traumatic Brain Injury in Young Adult Football Players

Walters-Stewart: Study design, data collection (& collection materials), data analysis (& analysis materials), writing

Longtin: Manuscript review

Sveistrup: Study design, manuscript review

Centre of Pressure During Quiet Stance and Dual-task 1 Month After Mild Traumatic Brain Injury: Adolescents

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A Preliminary Investigation of Visual Centre of Pressure State Space Representations in Quiet Stance: Healthy and mTBI

Walters-Stewart: Study design, data collection (& collection materials), data analysis (& analysis materials), writing

Longtin: Manuscript review

Sveistrup: Manuscript review

1. Main Introduction

1.1 Overview

Quiet stance can be described as simple yet complex, fundamental yet learned, static but not motionless. Because of these dualities, quiet stance is able to provide a framework for understanding how the brain and body coordinate to control the function of balance. This dissertation uses a quiet stance framework to explore balance from a control system perspective and to contribute to an understanding of healthy balance and how balance can be affected by mild traumatic brain injury (mTBI).

This dissertation is comprised of seven chapters: an introduction, five manuscripts (three submitted and two to be submitted for publication), and a concluding summary. Chapter 1 introduces the fundamental concepts and progresses from a general review of the physiological and functional balance control system, controlling variables of balance, and balance models to a review of the use of centre of pressure (COP) in investigating balance and the careful consideration of methodology that was undertaken at the outset. Thus, the first chapter establishes the basis for interpreting mTBI-related changes to balance. Chapter 2 presents a scoping review of recently published literature examining mild traumatic brain injury and its effect on the brain and related functions in the weeks after. The scoping review illustrates that mTBI recovery can be described in phases of neurometabolic change, altered activity and connectivity in the brain, and functional effects. Balance and dual-task effects coincide with functional dysfunction and compensatory mechanisms, but stem from the widespread changes that affect the brain. Chapter 3 presents the results of a study exploring healthy quiet stance in young adults using linear and non-linear methods of centre of pressure analysis. It demonstrates that linear and non-linear measures reveal different aspects of output and control in balance and provides an original contribution by establishing normative values for non-linear measures across numerous conditions. Chapters 4 and 5 utilize this understanding of linear and non-linear COP to contribute significant knowledge about the changes that occur to balance after mild traumatic brain injury in young adults and adolescents. Chapter 6 further contributes original and significant knowledge about the nature of non-linearities in balance control by examining visual representations of COP state space. COP state space is explored in healthy individuals and in individuals with mTBI. Finally, the main findings and implications of all studies are summarized in Chapter 7. Potential future applications of the knowledge gained from this body of work are also discussed.

1.2 Review of literature

1.2.1 Fundamental concepts

What are the main components of the balance system?

Balance is dependent on external factors, inputs (visual, vestibular, somatosensory), and outputs (motor) that are functionally and physiologically organized and integrated by the central nervous system. These are outlined below.

External factors

Human bipedal stance is unstable. Standing requires balance; however, in human beings, balance is not innate it must be learned. Gravity is a significant external environmental factor that shapes development of balance. The essence of maintaining upright posture is to counteract the pull of gravity (Fourre et al., 2009; Mergner & Rosemeier, 1998). Functional links between input systems are developed from experiencing inertia and establishing a base of support (Mergner & Rosemeier, 1998).

Inputs

Input systems of the body—the visual, vestibular, and somatosensory systems—situate the body by relating it to the external environment. Physiological development of these systems is also influenced by exposure to the external environment:

The visual system allows perception of spatial orientation with a subjective visual vertical (Daddaoua, Dicke, & Thier, 2008) and allows perception of position, motion, contrast, and colour (Tootell et al., 1995, 1997). It is comprised of physiology that transduces light into electrical and chemical signals. In each eye, the signal travels from the retina to the optic nerve where the nerve decussates at the optic chiasm. Most pathways continue to the lateral geniculate nucleus and finally to the visual processing areas of the cerebral cortex including the dorsal motion processing pathways on the lateral border of the occipital and medial/medial superior temporal lobes.

The vestibular system, in addition to providing information that stabilizes components of the visual system, has its own contribution to balance by allowing perception of gravity and motion. Vestibular structures are located within the head—one on either side. Each structure is comprised of calcium carbonate otoliths in the ampulla, three semi-circular canals arranged orthogonally, and the saccule and utricle. Mechanosensory cilia and cells line the fluid-filled components of the vestibular structure (Kelly & Chen, 2007; Rida & Chen, 2009). These physiological components of the vestibular system are able to sense gravitational, linear, and angular acceleration.

The somatosensory system is comprised of transducing cells: baroreceptors, mechanoreceptors, and nociceptors. These receptors within the joints, muscles, tendons, and skin allow for the perception (or proprioception) of the position and motion of one's body. Muscle spindles, Golgi tendon organs, pacinian corpuscles, ruffini endings, and free nerve endings provide information about changes in muscle length, muscle tension, vibration, joint range extremes, and pain, respectively. Processing of these stimuli occur at all levels—reflex, brainstem, subcortical, and cortical (Batson, 2009). Proprioception, an important function of the somatosensory system, allows the detection of torque about the ankle from gravity (Cnyrim, Mergner, & Maurer, 2009).

Output

The physiology of the body's output of movement (also known as the motor response) begins in the primary motor cortex, a somatotopic organization of neurons located at the precentral gyrus of the frontal lobe (Krebs, Weinberg, & Akesson, 2012). Upper motor neurons descend from the cortex through the midbrain and brainstem, decussating at the level of the medulla. These tracts (corticospinal, rubrospinal, tectospinal, vestibulospinal, and reticulospinal) synapse with lower motor neurons in the brainstem and spinal cord to innervate and control skeletal muscle. Extrapyramidal tracts in the brainstem and basal ganglia also contribute to the control of movement. Postural control, in particular, is influenced by the corticospinal, reticulospinal, and vestibulospinal tracts as well as the vestibular nuclei, basal ganglia, and subcortical nuclei. Lower limb skeletal muscle control in balance is a combination of the control of flexor tone and extensor tone to counter gravity in addition to voluntary movements and reflex activity (Krebs, Weinberg, & Akesson, 2012).

Physiological complexity and functional redundancy allow for the availability of multiple output strategies in maintaining balance. When standing, ankle control is a primary motor response strategy whereby muscles around the ankle are activated to counteract the torque produced by the weight of the body when it is no longer vertical. In hip control, another primary motor response strategy, the muscles of the hip joints are active and motion occurs, for the most part, about the hip joints (Horak & Nashner, 1986). These strategies are robust and have been found to be in use alone or in combination in quiet stance, during motion, and after external perturbations (Horak &

Nashner, 1986; Winter, 1995). Concurrent activation of the two strategies creates a gamut of possible muscle activation patterns (Torres-Oviedo & Ting, 2007). A stiffening strategy, one where motion about joints is reduced, has also been observed when individuals were afraid of falling (Carpenter, Adkin, Brawley, & Frank, 2006). In general, expectation, previous experience, habituation, muscle fatigue, central fatigue, and fear have been found to influence muscle synergy selection for postural control (Kennedy, Guevel, & Sveistrup, 2012, 2014; Torres-Oviedo & Ting, 2007). During simple quiet stance, however, predominant use of the ankle control strategy is a reasonable assumption and will be further discussed with respect to modelling quiet stance.

How is balance represented as a control system?

The organization and integration of sensory inputs, external factors, and motor response by the central nervous system to achieve balance can be modelled as a physiological control system. Control systems are characterized by a collection of components working together to achieve a desired response (Khoo, 1999). The most basic functions of the balance control system can be described as follows: Staying upright requires the integration of the sensory systems (Bugnariu & Fung, 2007) and the coordination of multiple muscles in space and time (Torres-Oviedo & Ting, 2007). Muscle strength must counteract torque in a sufficient amount of time to remain upright (Pijnappels, Bobbert, & van Dieën, 2005).

When an ankle control strategy is assumed, the body can be modelled as a rigid body with motion occurring about a point—an inverted pendulum. Motion of the inverted pendulum, balance control system output, can be represented by centre of mass (COM).

Centre of mass and controlling variables

Inverted pendulum control models have been used to investigate controlling variables in balance. Good candidates for the controlling variable(s)—system variable(s) that are monitored and adjusted to achieve the desired output—are centre of mass velocity, centre of mass acceleration, angular momentum, and torque. On one hand, angular momentum has been demonstrated to be a predictor of balance in gait (Allum & Carpenter, 2005; Bennett, Russell, Sheth, & Abel, 2010; Bruijn, Meijer, van Dieën, Kingma, & Lamoth, 2008; Herr & Popovic, 2008) and when tripping (Pijnappels, Bobbert, & van Dieën, 2004). On the other hand, torque has been successfully used in inverted pendulum models to investigate sensory integration (Maurer & Peterka, 2005; Mergner, Schweigart, Maurer, & Blümle, 2005). Velocity and acceleration are related to angular momentum, L, and torque, τ, respectively, by the cross-product of the distance of rotation and the mass product of velocity, $p=mv$ (where p is linear momentum) and the cross-product of the distance of rotation and the mass product of acceleration, $F=ma$ (where F is force).

$$\tau = r \times F \tag{1.1}$$

$$L = r \times p \tag{1.2}$$

Therefore, the distinction may not be crucial and any or all of these variables and other related variables of the COM appear suitable for modelling the output of the balance control system.

Centre of pressure and its relation to centre of mass

It follows that if certain COM variables are able to model the output of the system, corresponding COP variables are also likely to be suitable. COP is a coordinate that represents the weighted average of forces acting between the feet and the ground (Winter, Prince, Frank, Powell, & Zabjek, 1996). It represents the neuromuscular response of control of COM in balance (Milton, Cabrera, Ohira, Tajima, & Tonosaki, 2009; Winter et al., 1996); therefore, COP variables are similarly suitable as output measures of the balance control system. While, in general, COP reflects the larger trends of COM (van den Heuvel, Balasubramaniam, Daffertshofer, Longtin, & Beek, 2009), lower leg muscle contractions cause additional temporal variability in COP (Loram, Maganaris, & Lakie, 2005; Milton, Townsend, King, & Ohira, 2009; Sozzi, Honeine, Do, & Schieppati, 2013).

Inverted pendulum models

The inverted pendulum is a classic dynamics problem in which a rigid body in an upright position is unstable (Landry, Campbell, Morris, & Aguilar, 2005; Sieber & Krauskopf, 2004). Control of the human body in balance can be modelled as an inverted pendulum with motion described by the following ordinary differential equation,

$$x''(t) + \beta x'(t) - \alpha x(t) = F_{control}(t) \tag{1.3}$$

where $x(t)$ represents position, $x'(t)$ and $x''(t)$ are the first and second derivatives, respectively, and α and β are constants. The equation can be modified with delay terms, stochastic terms, or terms describing intermittent control to represent non-linearities. For any given equation, the parameters of the equation, the type of control and state (always on or conditionally on) of the controller, and the time delay affect the stability of the solution. Furthermore, while stability for an equation may be possible for a given set of conditions, it may not be plausible in human balance.

Ordinary differential equations are only useful in modelling systems where the equations of motion are known and instantaneous feedback can be assumed. While this can be the case in robotics, instantaneous control feedback is unlikely, if not impossible, in human postural control. Table 1.1 presents the types of control and corresponding types of stability given the constraints of the governing equation of motion that have been described by papers which have investigated balance models.

Table 1.1 Types of inverted pendulum control and stability in previous literature

Study	Type of Control	Solution/stability
	no control	unstable
Asai et al., 2009	linear PD	asymptotic stability possible
Asai et al., 2009	PD w/delay	asymptotic stability with additional conditions ∞ dimensional state space
Asai et al., 2009	intermittent PD w/ delay	dynamic stability: ON, unstable spiral; OFF, saddle equilibrium
Asai et al., 2009	intermittent PD w/ delay &dead zone	2 periodic attractors
Bottaro et al., 2008	intermittent	bounded stability (weaker than asymptotic)
Collins & De Luca, 1993	stochastic	coupled, bounded random walk (intermittent threshold based activation)
Milton, Cabrera, et al., 2009	2^{nd} order PID	asymptotic stability possible near upright
Milton, Cabrera, et al., 2009	2^{nd} order PID w/ delay	delay greater than critical delay, asymptotic stability possible
Ohira & Milton, 1995	stochastic w/delay	bounded by random walk

PD: proportional + derivative
PID: proportional+integral+derivative

Delay differential equations have been used to represent time delay effects in balance control (Guillouzic, L'Heureux, & Longtin, 1999) and to investigate the role of delays in the output of the system (Boulet, Balasubramaniam, Daffertshofer, & Longtin, 2010; van den Heuvel et al., 2009; Milton, Cabrera, et al., 2009; Peng, Havlin, Stanley, & Goldberger, 1995). Delays greater than the critical delay facilitate stability, but control remains suboptimal (Milton, Cabrera, et al., 2009). Only asymptotic stability is possible with linear control and even with delayed control, and in these cases, any extraneous sway is deemed as being "noise-driven" (Bottaro, Yasutake, & Nomura, 2008). Equations with stochastic terms allow representations of noise to provide driving perturbations to the system (Asai et al., 2009) and describe bounds of the system output (Ohira & Milton, 1995).

Intermittent control permits other types of stability and, in addition, extraneous sway arises not from noise but from a control mechanism (Bottaro et al., 2008). Equations describing intermittent control can be characterized by a switch function in phase space (Asai et al., 2009; Bottaro et al., 2008). Dynamic stability can be achieved by combining the stable part of a saddle and the unstable spiral regions (Asai et al., 2009) to limit motion to a particular area (bounded stability) (Bottaro et al., 2008).

Models must be evaluated on their ability to produce or explain aspects of behaviour or control in human postural movement. Milton et al. (2009) concluded from their observations that the balanced state is more complex than a fixed-point attractor. Other studies suggest that postural sway could be bounded by random walks (Collins & De Luca, 1993; Ohira & Milton, 1995). Many models rely on noise (stochastic terms) to drive the system and produce outputs with characteristics similar to postural sway; however, it has been suggested that complex (chaotic) systems appear stochastic when restricted to a dimension too small for the full dynamics (Rosenstein, Collins, & De Luca, 1993). Intermittent control model results produce outputs similar to empirical human postural sway (Asai et al., 2009; Bottaro et al., 2008). Most recently, Insperger, Milton, and Stepan (2015) have explored (using semidiscretization) a hybrid model that can transition between continuous and discrete control. These types of control and corresponding solutions should be considered when investigating COP state space.

1.2.2 Previous literature examining COP in quiet stance

What can alter balance?

COP has demonstrated changes to postural control in quiet stance with stance position, age, fatigue, pathology, and attention—each of which is reviewed below.

Stance condition or position

In healthy young adults, differences between standing with eyes open and eyes closed can also be present (Takala, Korhonen, & Viikari-Juntura, 1997). Other conditions (such as single leg, or tandem stance) may also be used to challenge balance. In healthy young adults, COP sway typically increases with single leg (Bisson et al., 2010; Takala et al., 1997) or tandem stance (Dault, Frank, & Allard, 2001).

Age

Balance control is different in children, adults, and elderly adults. Children demonstrate changes in balance control that occur as a result of progressive development while older adults demonstrate changes to balance control that occur as a result of diminishing function in contributing systems (loss of vision, loss of proprioception, reduced muscle strength) (Woollacott & Shumway-Cook, 1990). In children between the ages of 2 to 14, COP measures have shown posture in quiet stance to be more stable as age increases (Riach & Hayes, 1987). Riach's (1987) study also found that removing visual input had little effect on COP sway, and thus, the postural stability of children.[1] Similarly, somatosensory input and proprioception were found to be important for maintaining balance during quiet stance in children aged 6 to 15 when compared to other age groups up to 90 years old; removing visual input had less effect on the COP sway velocity of children, while altering somatosensory (using foam) and proprioception (using vibration) input adversely affected their postural stability resulting in increased sway velocity (Hytönen, Pyykkö, Aalto, & Starck, 1993). Hytönen et al. (1993) attributed these differences to undeveloped postural control and muscle synergies. Postural control was most stable in adults aged 30 to 60 (Hytönen et al., 1993; Thyssen, Brynskov, Jansen, & Munster-Swendsen, 1982). After the age of 60, body sway during quiet stance increases (Abrahamová & Hlavačka, 2008; Hytönen et al., 1993). Adults aged 76 to 90 were much more affected by the removal of visual input than children (Hytönen et al., 1993). Balance control in adults aged 76 to 90 was also more reliant on somatosensory information showing greater COP sway velocity than younger adults, but less than children (Hytönen et al., 1993). These studies have shown that, in both children and older adults, changes to COP measures demonstrate reduced sensory redundancy and absence of system integration in balance control, albeit for different reasons in each population group (Hytönen et al., 1993; Woollacott & Shumway-Cook, 1990).

Fatigue

Muscle fatigue alters both motor output and sensory input in quiet stance. In multiple studies, changes to COP after muscles were fatigued resulted in decreased postural stability in healthy young adults (Bisson, Chopra, Azzi, Morgan, & Bilodeau, 2010; Gribble & Hertel, 2004). When ankle plantar flexors were fatigued, COP sway measures (displacement and velocity) increased in multiple stance positions with eyes open or eyes closed (Bisson et al., 2010). Fatigue in other

[1] There is a difference between removing visual input and conflicting visual input. While quiet stance requires maintaining the status quo, conflicting visual input requires that the status quo be maintained despite false information. Some early papers reporting a dependence of postural stability on vision in young children, in fact, used a conflicting visual environment (Brandt, Wentzel, & Dichgans, 1976; Lee & Aronson, 1974). Therefore, this dependence actually reflected an inability to integrate conflicting sensory inputs. Further studies, albeit using quiet stance on a moving platform, demonstrated children relied on somatosensory input (Forssberg & Nashner, 1982) and did not deal well with sensory conflicts (Foster, Sveistrup, & Woollacott, 1996; Shumway-Cook & Woollacott, 1985).

lower limb muscles such as those of the knee and hip joints also result in increased COP velocity (Gribble & Hertel, 2004). Ankle muscle fatigue has been shown to increase COP displacement in a manner akin to applying vibration to impair proprioception (Vuillerme, 2002). Because balance was not further impaired when applying vibration to fatigued muscles, Vuillerme et al. (2002) suggested that when ankle muscles are fatigued, the central nervous system relies less on proprioception. (In contrast to removing visual input in addition to fatigue, which resulted in further increased COP measures (COP sway amplitude, velocity, and 95% ellipse area) than fatigue alone (Bisson et al., 2010)). These studies demonstrated that muscle fatigue alters balance control through multiple mechanisms. Though fatigue of lower limb muscles not involved in ankle proprioception increases COP velocity, fatigued ankle muscles increase COP displacement similar to when proprioception is impaired. Furthermore, increases to COP sway and velocity in quiet stance as a result of ankle muscle fatigue also occur when visual input is altered and with different stance positions. Therefore, changes to COP measures as a result of fatigue may not solely be as a result of altered muscle response and altered sensory input, but also as a result of altered integration of sensory and motor components.

Pathologies

Different pathologies can alter COP in quiet stance. Multiple stance conditions can be used to reflect more specific changes. Pathologies that affect the brain and nervous system such as multiple sclerosis, Parkinson's disease, cerebrovascular injury, and cerebellar injury each have the potential to alter balance control, yet each has a distinct mechanism.

A cerebrovascular injury (stroke) causes injury to regions of the brain by depriving them of blood flow, and is therefore, typically a focal injury—affecting a specific region rather than the whole brain (Pendlebury, Blamire, Lee, Styles & Matthews, 1999). The signs and symptoms of stroke depend on the region of injury; impaired balance control can be a consequence of stroke. Studies have demonstrated that individuals who have suffered from stroke had greater mediolateral COP amplitude and velocity in quiet stance demonstrating more postural sway and more instability than healthy individuals of a similar age (De Haart, Geurts, Huidekoper, Fasotti, & van Limbeek, 2004; Mizrahi, Solzi, Ring, & Nisell, 1989). These studies reported contradictory results with respect to the effect of removing visual input (eyes closed) in individuals post-stroke with one reporting a destabilization effect (De Haart et al., 2004) and the other reporting no effect (Mizrahi et al., 1989). De Haart et al. (2004) also showed that there was a reduction in visual dependence up to 12 weeks after the patients were first able to stand, whereas Mizrahi et al.'s (1989) assessment ranged from 5 to 42 weeks after stroke perhaps accounting for the differing results. De Haart et al. (2004) attributed the reduction in visual dependence to improvements in somatosensory integration and proprioception of the affected leg.

Multiple sclerosis is a neurological disease in which inflammation damages axons and results in delays in conduction pathways. Balance control can be impaired by this damage to the central nervous system (Huisinga, Yentes, Filipi, & Stergiou, 2012). In individuals with multiple sclerosis, changes to balance control have been demonstrated by altered COP in quiet stance with and without visual input. Abnormal anteroposterior COP displacement (three standard deviations greater than that of healthy individuals) was found in individuals with varying severity of multiple sclerosis (Daley & Swank, 1981). The difference between COP displacement with and without visual input was similar to that of controls indicating that visual dependence did not appear to be altered by multiple sclerosis.

In Parkinson's disease, neuronal death in the substantia nigra of the midbrain causes motor symptoms including tremor, rigidity, and bradykinesia (Samii, Nutt, & Ransom, 2004). Studies that have investigated Parkinson's disease and its effect on balance have found mixed results with respect to COP sway (for example, reduced COP sway (Horak, Nutt, & Nashner, 1992), or increased sway (Nardone & Schieppati, 2006; Stylianou, McVey, Lyons, Pahwa, & Luchies, 2011)). Nardone & Schieppati (2006) also found a dependence of balance control on visual input that may be explained by deficits in proprioception input and integration caused by changes to foot sensitivity in individuals with Parkinson's disease.

Cerebellar damage can also affect balance control depending on the location of the damage. When compared to healthy controls, individuals with vestibulocerebellar damage demonstrated greater COP sway and marked postural instability including dependence on visual input (Diener, Dichgans, Bacher, & Gompf, 1984; Mauritz, Dichgans, & Hufschmidt, 1979). On the other hand, sway in individuals with neocerebellar & hemispherical cerebellar damage was similar to that of the healthy controls. Individuals with anterior lobe damage in the cerebellum demonstrated greater anteroposterior COP sway than healthy; however, dependence on visual input was not affected (Diener et al., 1984; Mauritz et al., 1979).

In general, pathologies affecting parts of the brain with crucial contributions to physiological balance systems typically results in increased COP sway. Altered visual stabilization (differences between quiet stance with eyes open and eyes closed) can be an important indicator of the type of pathology or affected system.

Attention

Dual-task methodologies are based on the assumption that there is a limited central processing capacity of the brain, that any task requires a portion of the processing capacity, and that if processing capacity is exceeded when performing multiple tasks, performance of tasks can be affected (Lajoie, Teasdale, Bard, & Fleury, 1993). Balance control, therefore, requires processing capacity (attention). When performed concurrently with another task, either performance in balance or performance of the other task may be affected. All of the following studies mentioned here consisted of young healthy adults. In one study, reaction times when performing a verbal auditory task while standing were greater than reaction times when sitting (reaction times were also greater when walking than when standing or sitting) (Lajoie et al., 1993). In another study, working memory tasks (verbal, visuospatial, and central executive tasks) increased the frequency and decreased the amplitude of sway when standing while showing no change in performance of the working memory tasks (Dault et al., 2001). Balance steadiness has been found to be disrupted by spatial memory tasks, but not by non-spatial memory tasks implying that spatial processing and balance control share neural resources (Kerr, Condon, & McDonald, 1985) and that overall processing capacity may not be the only factor in resource sharing in the brain.

1.2.3 Methodology review

While COP has often been studied in balance, data collection methodology is not standardized. In a review of COP reliability in quiet stance, Ruhe and colleagues (2010) found that because of the perceived simplicity of this type of data collection, there is no standard procedure used in study design. Ruhe et al.'s (2010) review of studies (which included only those that had reported enough information about participant demographics and experimental setup to meet study criteria) yielded the following conclusions:

- a minimum of 90 seconds of data collection is required for most COP parameters,
- quiet stance with eyes closed shows slightly higher reliability than with eyes open,
- no conclusion could be reached with regards to foot placement, and

- a sampling frequency of 100Hz with a cut-off frequency of 10 Hz is recommended, when possible.

No single measure appeared significantly more reliable than others, though mean velocity of COP showed generally reliable results. Variability, estimated by the standard deviation of the time series, and curve length are two measures that were identified as often used and potentially reliable to characterize COP behaviour in quiet stance (Ruhe et al., 2010).

Position and velocity measures

COP range, amplitude, and displacement measures quantify position whereas mean path length, mean speed, and velocity measures quantify movement. Riley, Benda, Gill-Body, & Krebs (1995) hypothesized that postural stability requires control of both position and momentum of the body; therefore, phase plane plots (which are two-dimensional, typically position vs. velocity) show an ideal amount of information. COP phase plots have been shown to be practical (requiring only a force platform) and are a suitable alternative to obtaining COM phase plots (which may not be feasible since it requires a motion capture system). Yet, Riley and colleagues also recognized that the true state space of centre of mass and centre of pressure may be more than two-dimensional.

Non-linear measures

Non-linear analysis has been used to identify subtle trends in physiological data such as electrocardiogram (ECG) signals (Meyer & Stiedl, 2003), electroencephalogram (EEG) data (Cao & Slobounov, 2011), balance (De Beaumont et al., 2011; Gao, Hu, Buckley, White, & Hass, 2011; Parker, Osternig, van Donkelaar, & Chou, 2008) and gait (Dingwell & Cusumano, 2000; England & Granata, 2007). The reasoning behind these avenues of investigation is that the systems that control these aspects of physiology may be governed by complex non-linear rules.

In balance, non-linearities arise in the postural control system because of the elastic and damping properties of muscle and because of delays and thresholds in the nervous control system (Blaszczyk & Klonowski, 2001). While linear measures are suitable for capturing the general performance of postural sway, non-linear measures should be better able to represent non-linearities in postural sway.

Local stability and scaling behaviour have been investigated with respect to balance in healthy individuals (Borg & Laxåback, 2010; Donker, Roerdink, Greven, & Beek, 2007), healthy indiduals with lower limb fatigue (Mello, Oliveira, & Nadal, 2010), and in individuals with pathologies such as stroke (Roerdink et al., 2006) and multiple sclerosis (Huisinga et al., 2012).

Local stability

Conclusions on postural stability are often drawn by assuming that an increase in variability of the COP represents a decrease in stability. Variability as a measure of stability is not always a valid assumption (Roerdink et al., 2006). As a stability measure, variability doesn't take into account the temporal characteristics of COP (Dingwell & Cusumano, 2000). The Lyapunov exponent quantifies the divergence of neighbouring trajectories and can be used to estimate the local stability of a COP timeseries. Since this divergence is exponential in chaotic timeseries, the largest Lyapunov exponent will overtake the changes along other principal axes and ultimately represent the change of the attractor. Rosenstein et al.'s (1993) algorithm allows for the determination of trajectory divergence and if it is exponential, an estimate for largest exponential divergence can be obtained. Essentially, this calculation allows one to determine whether or not a timeseries has chaotic properties. Furthermore, the method shown by Rosenstein et al. (1993) has proven to be robust when considering the following potential influences on non-linear estimates: embedding dimension, data set size, reconstruction delay, and noise level. Despite the robust nature of the method, particular attention should be paid to embedding dimension and reconstruction delay in order to obtain the best and most appropriate estimate of the largest Lyapunov exponent.

The largest Lyapunov exponent has been used to estimate local stability in gait (Dingwell & Cusumano, 2000; England & Granata, 2007) and in quiet stance (Donker et al., 2007; Huisinga et al., 2012, Roerdink et al., 2006). Factors in quiet stance that resulted in an increase in Lyapunov exponent (i.e., a decrease in stability) were eyes closed condition compared to eyes open in young healthy (Donker et al., 2007), healthy elderly, and elderly stroke, and dual-task compared to single task in healthy elderly and elderly stroke (Roerdink et al., 2006). Rehabilitation was able to improve stability in older adults with stroke (Roerdink et al., 2006). On the other hand, in individuals with multiple sclerosis, the largest Lyapunov exponent was decreased compared to healthy individuals, and even more so when vision was removed (Huisinga et al., 2012). Huisinga et al. (2012) attributed these decreases to an inability to reorganize sensory input because of damaged pathways—decreased divergence was linked to less availability of options within the system. Huisinga et al. (2012) suggest that these results correspond well with the model of optimal movement variability hypothesis because there is an increased dependence on repeatable movement patterns in maintaining balance which could indicate an inability to adapt should the need arise. In gait, greater local stability was shown to occur at slower walking speeds (Dingwell & Cusumano, 2000; England & Granata, 2007).

Scaling parameter

The differences in system behaviour over different time scales are of particular interest in physiological timeseries. A scaling parameter (also known as a Hurst parameter or self-similarity parameter) and usually requiring a precise mathematical definition to define the variable that is used—is used to estimate the scaling properties of a timeseries. Because multiple numerical methods exist for estimating scaling and given the sensitivity of different methods to different factors when estimating the scaling parameter, it is useful to (1) choose method(s) suited to data length and type and (2) use several methods in conjunction (Rea, Oxley, Reale, & Brown, 2009). The reliability of scaling parameters in quiet stance has been shown to increase with trial duration (Lin, Seol, Nussbaum, & Madigan, 2008). However, this finding can be deceiving since increased trial duration only assures that longer time scales will be better represented in the estimate.

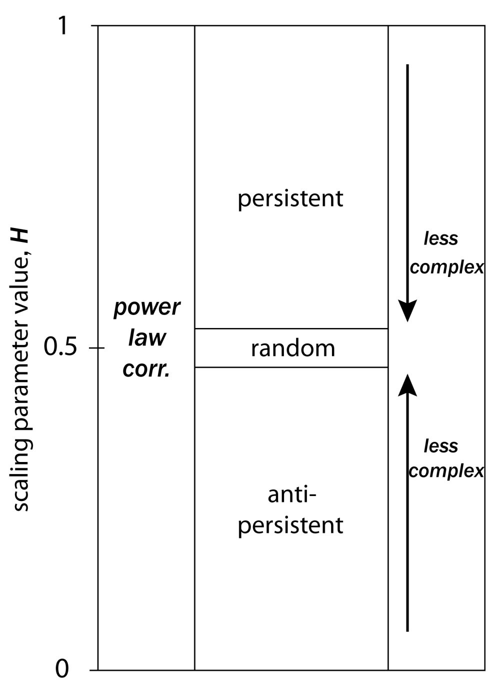

Figure 1.2 Scaling estimate values and corresponding scaling properties.
A scaling parameter of 0.5 for a timeseries demonstrates random correlations. Values closer to 0.5 represent more random correlations (as well as less complexity) in the timeseries than values farther from 0.5.

The estimated scaling parameter can be compared to known values of scaling properties such as random walk or white noise (0.5), persistent power law correlation (0.5 to 1.0), or anti-persistent power law correlation (0 to 0.5) (Peng et al., 1995) (Figure 1.2). A persistent value indicates that within a given time window, the timeseries follows the same trend (i.e., continue to increase if increasing or continue to decrease if decreasing). On the other hand, an anti-persistent value indicates the timeseries tends to reverse itself (i.e., decreases are followed by increases and vice versa). Scaling behaviour has implications for how stability is achieved over different time frames; as an example, over short windows of time, a COP timeseries could diverge (persistence), but over longer windows tend to reverse any changes (anti-persistence). In addition, any transitions between different time scales are of interest. In theory, a timeseries could have the same scaling property over all time windows (no transitions) or could have different scaling properties for different time windows (transitions would occur between each change in scaling properties). One possible interpretation of a transition from persistent to anti-persistent or vice versa is that a different mechanism is reflected in each region of the time series. In other words, scaling properties can be used a descriptor of a possible mechanism.

As a measure of balance during quiet stance, the scaling parameter has been used in the comparison of young adults before and after lower limb fatigue (Mello et al., 2010), elderly and stroke individuals (Roerdink et al., 2006), of visual conditions (Donker et al., 2007; Roerdink et al., 2006), and of single and dual-tasks (Donker et al., 2007). Despite this previous use, it is difficult to compare scaling values across studies because of different estimation methods, ranges of time scale (not simply trial duration), and definitions of the scaling variable reference scale.

Nevertheless, investigations of COP scaling properties have shown that a scaling transition between short-term and long-term scaling exists at a time scale of one second (Collins & De Luca, 1993). In healthy young adults, when lower limb muscles were fatigued, long-term scaling became less complex (Mello et al, 2010). It has also been shown that stroke does not lead to a breakdown in long-term (>1s) scaling of COP as has been shown to occur in some physiological variables in other pathologies (for example, heartbeat interval in individuals with cardiac disease (Stanley, Goldberger, & Havlin, 1999)), though a decrease in scaling[2] (in the anteroposterior

[2] In a subsequent paper, Donker et al. (2007) report an error was made in the linear transformation rule used to calculate the scaling parameter values. The retraction does not alter the statistical results presented by the paper, but it does not provide enough information to determine whether or not scaling properties (persistence or anti-persistence) were correctly determined.

COP direction) for the stroke group was demonstrated in comparison to the healthy elderly (Roerdink et al., 2006). Decreases in the scaling parameter have also been demonstrated between conditions (standing with eyes closed in comparison to standing with eyes open) and tasks (dual-task word reversal in comparison to single task) in healthy young adults (Donker et al., 2007). Again, statistical changes are the focus of the paper, and not enough attention is paid to the meaning of the scaling parameter, nor is enough information given to determine which scaling property is exhibited or how it changes. The investigation did conclude that while the scaling property (persistence or anti-persistence) did not change with pathology, task difficulty, or attention constraints, the scaling parameter value does change with pathology, task difficulty, and attention constraints.

State space

State space analysis is one method by which both linear and non-linear methods can be used in the investigation of physiological time series of movements (Commandeur & Koopman, 2007; Kraus et al., 2009). In a state space model, inputs and outputs are related by state variables in the time domain. Whereas phase space typically relates time derivatives of a variable, state space relates time-delayed instances of the variable. State space variables can be characterized in multiple dimensions by an attractor. State space and phase space are necessarily related and the terms are used interchangeably.

In literature, there is support for state space analysis of balance data to determine some of the fundamental dynamic characteristics that govern balance. In repetitive dynamic movements, typical data will show the structure of an attractor (Gates & Dingwell, 2009). Studies have also demonstrated that the neural representations of movements are likely stored as a system attractor in a connectivity matrix (Lukashin, Amirikian, Mozhaev, Wilcox, & Georgopoulos, 1996). Finally, animal studies have demonstrated that “muscle space” is a reasonable coordinate for the coding of motor neurons (Townsend, Paninski, & Lemon, 2006). From this literature, we can conclude that it may be possible to see the contribution of neural and muscle controllers of balance within the state space of COP signals.

Embedded delay state space reconstruction of COP

Reconstruction of the state space of a system can be accomplished using embedded delay methods. In the embedded delay reconstruction method, a timeseries is reinterpreted with respect to a time delay, τ, and an embedding dimension, m. The foundation of this method originates from dynamic theorems presented by Takens (1980). The selection of embedding dimension is made using the false nearest neighbour method described by Kennel, Brown, & Abarbanel, (1992). The minimum embedding dimension, *m*, is the smallest number of dimensions necessary to adequately describe the attractor, a representation of the dynamic system, with independent (orthogonal) components. Subsequently, principle component analysis can be applied to extract the best projection of each attractor (Huffaker, 2010; Williams, 1997). While this introduces some linear dependence (Daffertshofer, Lamoth, Meijer, & Beek, 2004; Williams, 1997), it also reduces redundancy and the effects of noise (Huffaker, 2010; Williams, 1997). Each point becomes a weighted version of the sampled point in the timeseries where the majority of variance, and thus, a high signal-to-noise ratio is present (Williams, 1997). Trajectories of the state variables around the system attractor are then represented by points around the principal axes. Distribution around these principal component axes provides information about the characteristics and behaviour of the dynamic system.

1.3 Application

Several important points can be summarized from this review of literature:

- What the balance control system represents—the interpretation of sensory input to allow motor output that will counteract gravity
- How the balance control system is modelled—as an inverted pendulum with motion governed by a control system
- Why COP variables are suitable to investigate balance control—COP reflects neuromuscular control and can be chosen to represent important system variables
- COP analysis of quiet stance can be used to investigate pathologies that affect the brain and nervous system
- Some important methodological considerations—(1) COP measures are reliable provided certain guidelines concerning data collection are followed (in particular, a minimum length of data collection of ninety seconds) and (2) non-linear measures such as local stability and scaling may provide additional information about balance control

The literature review also identified gaps in knowledge with respect to non-linearity in healthy balance control, confirmed the potential for extending its use for investigation of mild traumatic brain injury, and provided a framework for developing the following research questions—

- When considering mTBI as a pathology, what are the physiological and functional changes that arise as a result of the injury? How quickly do these changes resolve after injury? How has balance been used to investigate mTBI?
- What are typical non-linear COP results with respect to young healthy individuals in quiet stance? Is additional information provided by non-linear measures?
- What is the effect of mild traumatic brain injury on quiet stance? How is the pathology of mTBI related to changes in COP?
- Can the balance control system be represented in state space? Can changes in the state space attractor be used to examine the effect of mild traumatic brain injury on balance?

The studies that follow were designed to address these research questions with each study building upon the knowledge gained from the previous studies.

Novelty & original contribution

Studies aimed to contribute novel and original understanding by (1) providing an original synthesis of previous mTBI research by considering each individual work as a puzzle piece in a bigger picture, (2) providing normative linear and non-linear COP results for multiple conditions during healthy quiet stance, (3) contributing significant and original information about the changes that occur to balance in young adults and adolescents as a result of mTBI, and (4) presenting original and significant findings on the nature of non-linearities in balance control. Additional contributions include facilitating the use of an inexpensive, portable method for the collection of COP data (Appendix A). As a whole, these studies contribute to a better understanding of healthy balance as well as the effect of mTBI on balance.

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2. Scoping Review: A 45-Day Timeline of Mild Traumatic Brain Injury Effects

(submitted to the Journal of Head Trauma Rehabilitation)

Scoping Review: A 45-Day Timeline of Mild Traumatic Brain Injury Effects

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2.1 Abstract

This scoping review examined experimental studies published between 2002 and 2015 on the effects of concussion also known as mild traumatic brain injury. The purpose of the review was to facilitate the development of a conceptual description of the brain's reaction to mild traumatic brain injury based on symptom and effect evolution. Articles were included if they reported on the effects of mTBI within the first 45 days post-injury using qualitative or quantitative measures. Findings from 63 articles included physical symptoms as well as changes to brain activity, connectivity, neurometabolism, balance, or other functions. The findings reported by activity and connectivity studies and neurometabolic studies support the concept of phases of neurometabolic cascade after injury. Symptom, balance, motor, signalling, cognitive, neuropsychological, and dual-task findings supported the concept of functional phases concurrent with the neurometabolic phases. At the same time, it is not yet possible to assign a concrete timeline to these phases; however, the pattern of recovery appeared similar to other brain injuries such as stroke. On the whole, findings suggest mild traumatic brain injury is a diffuse rather than focal injury resulting in widespread and varying functional effects.

Keywords: concussion, mTBI, head injury, post-concussion recovery

2.2 Introduction

A mild traumatic brain injury (mTBI) is the result of an external force causing acceleration or deceleration of the head (Hoshizaki & Brien, 2004). Although an mTBI may result in neuropathological changes, the acute clinical symptoms largely reflect a functional disturbance rather than a structural injury and, as such, abnormalities are generally not evident on standard structural neuroimaging studies (Broglio, Moore, & Hillman, 2011; Giza & Hovda, 2001; McCrory et al., 2009). Nevertheless, individuals who sustain mTBIs may suffer negative lingering effects on academic and job performance. The National Center for Injury Prevention and Control estimates the economic impact of mTBIs to be almost $17 billion annually (Broglio et al., 2011).

It is a common injury, in both sports (Echemendia & Cantu, 2003)—in the United States, the incidence in adolescents and young adults has been found to be approximately 2.3 to 2.5 mTBIs per 10 000 athletic exposures (Gessel, Collins, Comstock, Dick, & Fields, 2007; Marar, McIlvain, Fields, & Comstock, 2012))—and in military service (Marion, Curley, Schwab, & Hicks, 2011). It is estimated that, annually, 42 million people worldwide suffer an mTBI (Gardner & Yaffe, 2015). Yet much uncertainty remains regarding the underlying mechanisms that result in mTBI symptoms. Acute post-injury signs and symptoms such as loss of consciousness, amnesia, headache, dizziness, fatigue, and nausea (Difiori & Giza, 2010; Prigatano & Gale, 2011; Shaw, 2002), metabolic consequences (Signoretti, Vagnozzi, Tavazzi, & Lazzarino, 2010; Slobounov, Sebastianelli, & Simon, 2002; Vagnozzi et al, 2008), impairment of cognitive functions including working memory (Pardini et al., 2010), and force regulation (Slobounov et al., 2002; Slobounov, Sebastianelli, & Moss, 2005), disruption of autonomic function (La Fountaine, Gossett, De Meersman, & Bauman, 2011; Leddy, Kozlowski, Fung, Pendergast, & Willer, 2007; Len & Neary, 2011), balance deficits (Catena, van Donkelaar, & Chou, 2009; Catena, van Donkelaar, Halterman, & Chou, 2009; Guskiewicz, 2011), and visual difficulties (Maruta, Suh, Niogi, Mukherjee, & Ghajar, 2010; Patel, Ciuffreda, Tannen, & Kapoor, 2011) are well documented.

Global effects of mTBI—such as metabolic changes, neural activity, and white matter connectivity—can be related to specific physiological processes in the brain while functional task-specific effects—balance, neurocognitive, motor, autonomic, verbal, and dual-task impairments—can be related to conceptual processing pathways which are general areas of the brain thought to be responsible for related functions. Previous research has proposed that phases exist in metabolic (Difiori & Giza, 2010; Leddy et al., 2007) and cognitive post-concussion recovery (Ellemberg, Henry, Macciocchi, Guskiewicz, & Broglio, 2009). This paper extends this work and examines literature published between 2002 and 2015 in order to develop a description of symptomology and recovery over a 45-day post-injury period. A preliminary version was presented at the Canadian Military and Health Veteran Research Forum (Walters-Stewart, Marshall, & Sveistrup, 2011).

2.3 Methodology

This scoping study was conducted according to the methodological framework outlined by Levac, Colquhoun, & O'Brien (2010). The benefit of a scoping study over other types of reviews, particularly when considering research in the field of mild traumatic brain injuries, is that an overview of findings can be conceptually summarized. Levac and colleagues' framework, a refinement of the Arksey & O'Malley (2005) methodology, can be defined in five stages:

Stage one: Identifying the research question.

What is the temporal evolution of recovery from an mTBI in adults? There is a clear knowledge gap regarding the course of recovery following diagnosis. Signs and symptoms of mTBI have been investigated as diagnostic criteria (Cantu et al., 2006; Michael McCrea et al., 2005; McCrory et al., 2009; Randolph et al., 2009), but have been reviewed in a limited fashion as markers of injury recovery. Thus, the research question driving this scoping study aims to clarify the evolution of the signs and symptoms of mTBI and their relation to the physiological and functional evolution of the injury.

Stage two: Identifying the relevant studies.

The following literature search methods were employed. An initial search in the *PubMed* database were entered using the following search phrase:

- concuss* OR mTBI OR ("mild traumatic brain") NOT (chronic OR post* OR management OR review OR child*)

with the following limits imposed:

i. Publication dates: 10 years
ii. Age: Adults 19+

iii. Subject: Human
iv. Field: Title
v. Language: English

These search parameters returned 462 articles published between May 2002 and May 2012. The titles and abstracts of these papers were reviewed in order to eliminate studies that did not report experimental findings. At the end of this stage, 207 articles remained.

Stage three: Study selection

An initial selection of articles was completed by reviewing each abstract a second time, in order to determine if the inclusion criteria listed below were met. In cases where the abstract did not provide the necessary information, the methods section of the article was also reviewed.

i. A sample population of individuals who had sustained an mTBI, and a basis for determining return to health such as a comparison with baseline data or a healthy control sample.
ii. An explicit statement of the interval between injury and the assessment dates or window of assessment. In papers where a range of testing days is reported, a suitably narrow window is required. Though somewhat subjective, this determination was made by considering whether the range, sometimes represented by a standard deviation, was shorter than the interval from the time of injury.
iii. One or more assessments completed between 0 and 45 days post-mTBI.
iv. No intervention in the study to treat the mTBI.

The initial 2002-2012 process identified 31 articles. When cross-referencing these articles, an additional 6 articles were identified. A subsequent update to include papers published between May 2012 and February 2014 yielded 18 additional articles. A final update, to include papers published between March 2014 and June 2015 yielded an additional 8 articles for inclusion. A total of 63 studies are presented in this scoping review.

Stage four: Charting the data

Duration (of the signs and symptoms after the time of injury (TOI)) was chosen as the scoping study's independent variable. Outcome, the dependent variable, was charted to display each study's post-injury assessments and the findings of each assessment. It should be noted that some studies report several findings. Each row contains a summary of the finding and a description of the method. Findings were charted as follows (also described in the legend of each figure):

i. The finding of an assessment is represented by a circle on the specific post-injury day.

ii. A testing window is represented by a circle with two delimiting vertical lines to the left and right.

iii. If the study did not report assessment days, but instead reported a mean or median duration, a square is used to represent the duration.

iv. In a few cases, where only a general period is reported, a horizontal bar marking that period is used.

v. Additional assessments past 45 days are denoted by a circle enclosing a plus sign at the end of the row.

Stage five: Categorization

This review separated the effects of mTBI into (1) global effects that include clinical symptom measures (Figure 2.1), measures of neural activity or estimates of neural connectivity (Figure 2.2), neurometabolic changes (Figure 2.3), and (2) functional effects that include changes to balance, motor, and signalling (Figure 2.4), neuropsychological measures (Figure 2.5), and dual-task (Figure 2.6).

2.4 Results

Global effects of mTBI

Physical symptoms

Physical symptoms occurring immediately after a mild traumatic brain injury include but are not limited to headache, nausea, dizziness, difficulty sleeping, and emotional problems (McCrea, Iverson, et al., 2009b). Clinical diagnostic tools such as the Concussion Symptom Inventory (CSI), Immediate Post-Concussion Assessment and Cognitive Test Total Symptom Scale (ImPACT TSS), and the Rivermead Post Concussion Symptoms Questionnaire (RPCSQ) use Likert scales to document symptoms experienced by the patient.

Many physical symptom assessment scales used in concussion research are subjective, often self-reported or self-rating Likert scales. Studies that were reviewed used self-reported symptoms (Figure 2.1; PS1, PS2, PS15), the ImPACT TSS (PS4-PS8), the RPCSQ (PS9-PS12), the CSI (PS16, PS17), the Beck Depression Scale (PS18, PS19), the Pittsburgh Sleep Quality Index

(PS20), and the Epworth Sleepiness Scale (PS21). Studies that assessed individuals on the day of injury reported symptoms at the time of injury (PS16, PS17). Studies that provided results in the form of means or medians were more likely to demonstrate longer duration of symptoms (PS2, PS5, PS6, PS7, PS9, PS10, PS11, PS15), whereas studies which report testing days (PS1, PS3, PS4, PS8, PS12, PS13, PS14, PS16, PS17, PS18) may show an early resolution (because symptoms that last past one assessment but resolve before the next would be represented as being resolved at the first assessment). Symptom durations ranged from being present just after the time of injury (PS17) to a couple of weeks (PS4, PS15), and in at least one study (PS3) symptoms were present one month after injury. In addition, studies that compared male and female population samples demonstrated that symptoms in women (PS7, PS10) appeared to last longer than in men (PS6, PS9). Studies that reported symptoms related to depression, anxiety, and sleep quality demonstrated lengthy duration (PS18, PS19, PS20) though day-time sleepiness was not found to be an issue (PS21).

Activity and connectivity

Functional connections between neurons can be examined via physical structure—for example, by investigating white matter tracts—or by functional estimates of metabolic and electrical activity (Figure 2.2). The studies included in this section can be divided into three main types: functional magnetic resonance imaging (fMRI) (AC1-AC4), diffusion tension imaging (DTI) (AC5-AC17), and electroencephalography (EEG) (AC18-AC25).

FMRI studies examine levels of neural activation based on oxygen uptake (blood oxygen level dependence) within the brain during functional tasks. A period of increased activation that lasts (around) one week after injury was reported in some regions (AC1-AC3). Decreased attention-related modulation (ARM) and impairments in regulating the default mode network (DMN) (described as failure to deactivate certain areas under high load) were reported around the second week after injury (AC4). Taken in concert, these results demonstrate that increased neural activation can occur in the first two weeks after injury.

Diffusion tensor imaging studies are used to determine the diffusion characteristics of brain tissue; however, the meaning of results must be inferred, and as a result, different studies that measure the same variable may come to different conclusions. Two variables commonly used in DTI studies are fractional anisotropy (FA) and mean diffusivity (MD). Studies investigating fractional anisotropy in various brain regions (AC6, AC7, AC8, AC10, AC11, AC13) showed decreases (AC6, AC7, AC11, AC13), increases (AC8), or both (AC10). Decreased fractional anisotropy within white matter was interpreted to signify that the integrity of the white matter tracts was impaired since the water within the cell fibres was no longer confined to move predominantly in the longitudinal direction. In short, a finding of reduced fractional anisotropy is indicative of diffuse axonal injury within the region of interest (Huisman et al., 2004). Reduced fibre integrity was reported at one day (AC7), two days (AC11), one week (AC6, AC13), and two weeks post-injury (AC10). At two weeks, fractional anisotropy findings that could indicate potential cytotoxic edema were also present (AC8). At one month, abnormal fractional anisotropy in white matter tracts were still present in one study (AC11), while normal in another (AC7). It can be concluded that fractional anisotropy abnormalities are certainly present early after injury, and may persist until one month after injury. Mean diffusivity appeared to be more limited in showing diffusion abnormalities than fractional anisotropy. Early mean diffusivity assessment (AC12, AC14) showed agreement with fractional anisotropy assessment (AC11), but by two weeks and one month after injury, mean diffusivity failed to show abnormalities where fractional anisotropy did (AC9 vs. AC8, AC12 vs. AC11). Abnormal fractional anisotropy soon after injury (three days) was correlated to functional impairment (AC5). Free water corrected DTI also demonstrated decreased extracellular space (AC17) supporting findings of swelling and cell damage from other DTI studies (AC8, AC14). Susceptibility weighted imaging (AC15) and magnetization transfer ratio (AC16) did not show any damage.

Quantitative EEG data have shown that the type of connections between different areas within the brain change post-concussion. Cao and colleagues demonstrated a departure from typical organization of the brain's networks (AC19), a departure from "small-world" network configuration with a decrease in long-distance connectivity, and a corresponding increase in short-distance connectivity (AC18). Results also demonstrated that at one week following injury, organizational changes were present including: (1) asymmetry between the hemispheres (AC21), (2) decreased coherence between the hemispheres (AC22), (3) abnormalities in beta wave activity (AC23), and for even longer duration (4) changes in the reallocation of brain resources (AC24), and (5) reduction of information quality within brain connections (AC25).

Neurometabolic

To better understand the neurometabolic changes that occur in the brain, this section digresses into a review of animal studies. Giza & Hovda (2001) present a comprehensive review of the "neurometabolic cascade" that occurs after mTBI where, in general, ionic concentration abnormalities are corrected early while glucose and energy metabolism deficits remain a concern. More specifically, Giza & Hovda (2001) show with animal studies that an increase in extracellular potassium, calcium, glutamate, lactate, and neurotransmitter accumulation occurs resulting from neuronal depolarization, which when left unbalanced can lead to cell damage or death. To restore normal balance, energy is expended (cerebral metabolic rate of glucose increases immediately after injury) and can be over-expended (increases in the metabolic rate of glucose utilisation are reversed and the rate drops below normal for several days). Meanwhile, cerebral blood flow is reduced further impairing the ability of the brain to deal with increased energy demands (Giza & Hovda, 2001). Giza & Hovda (2001) also explain that interpreting animal studies in the context of human time frames can be difficult. While in rats, impaired glucose metabolism is only present from seven to ten days, in human subjects, impaired glucose metabolism occurs between two and four weeks after injury (NM1). Identifying markers of this underlying neurometabolic cascade (namely neuronal death and impaired energy metabolism) remains the goal of neurometabolic studies involving human subjects, but with methods that are appropriately less invasive.

Neurometabolic markers have been investigated using magnetic resonance spectroscopy and blood serum analysis (Figure 2.3). In one study, markers of excitatory neurotransmitters (glucose/creatine, NM2), osmolytes and astrolytes (myoinositol/creatine, NM2), and neuronal loss (n-acetyl aspartate/creatine, NM2) did not show any differences from baseline measurements at any of the times taken after injury. In another study, results two days after injury for many of the same measures also did not show abnormalities (NM3). Other studies reported changes to n-acetyl aspartate/creatine ratios (NM4, NM5, NM6, NM7), choline/creatine ratios (NM8), and n-acetyl aspartate/choline ratios (NM9, NM10). N-acetyl aspartate is a neuron-specific marker indicative of mitochondrial phosphorylating capacity, and therefore, of the brain's energy state (Vagnozzi et al., 2008) and neuronal loss (Gasparovic et al., 2009). Creatine is a marker of cellular energy while choline is a marker of cell membrane turnover (Vagnozzi et al., 2013). In general, a depressed capacity for energy metabolism has been shown to be present from at least three days after the injury (NM4, NM5, NM9, NM10). A temporary increase in n-acetyl aspartate/creatine ratio has also been demonstrated (NM6). Along with the finding that the choline/creatine ratio had also increased (NM8), Vagnozzi and colleagues (2013) concluded that n-acetyl aspartate had, in fact, decreased, but at the same time, a decrease in the amount of creatine caused an overall increase in the n-acetyl aspartate/creatine ratio. It was suggested that this may also have been an effect of the general metabolic depression that occurs after injury (Vagnozzi et al., 2013).

Further support of metabolic depression was found in studies examining neurometabolic markers in blood serum. α-amino-3-hydroxy-5-methyl-4-isoazolepropionic acid receptor (AMPAR) peptide is a type of glutamate receptor that suggests the occurrence of neurotoxicity cascade (NM11). This marker was present between one and two weeks after injury. In another study, a compromised ability to use energy was demonstrated by decreases in branched chain amino acids (valine, isoleucine, leucine) in the first 24 hours after injury (NM12). These branched chain amino acids are involved in the synthesis of glutamate. In addition, neuronal trauma has been demonstrated by an increase in ubiquitin C-terminal hydrolase (UCH-L1), a protein found in neurons, and in elevated S100β protein levels found only hours after injury (NM13, NM14). Neuron-specific enolase protein was not found to be a significant neuromarker in the hours after injury (NM15).

Functional effects of mTBI

The timing, extent, and duration of the effects of mTBI on brain function depend, in part, on the task. Changes in balance, motor functions, autonomic signalling (Figure 2.4), neuropsychological measures (Figure 2.5), and dual-tasks (Figure 2.6), including motor-cognitive and visual-motor, have been reported.

Balance

Balance impairment is a common effect of brain injury. Three clinical balance outcome measures, the Balance Error Scoring System (Guskiewicz, 2011) (BESS), the Sensory Organization Test (SOT) (Guskiewicz, 2011; Peterson et al., 2003) and the Composite Balance Score have shown similar timing of recovery post-mTBI recovery (Peterson et al., 2003). The BESS (B1, B2) is a quick and basic test of static balance on two different surfaces (Guskiewicz, 2011). The SOT alters sensory information (visual and somatosensory) available to the subject standing on the tilting force platform (Guskiewicz, 2011). Studies that have used SOT have found a similar period of impairment to the BESS of not more than three days (B3). The composite balance score (B4), derived from the SOT appeared to recover within ten days. Some alterations to COP in simple quiet stance have also been found (B9).

However, more challenging dynamic balance tests demonstrate that individuals are unable to maintain balance in certain situations up to 30 days post-injury (B5, B6, B7) and need to employ a more cautious balance strategy (B8). It appears that though simple measures of balance resolve quickly, some deficits continue under more challenging situations at least one month after injury.

Motor potentials

Motor potentials of the upper body (MP1, MP2, MP3, MP4) and posture-related motor potentials (MP5) demonstrate impairments through to day ten. An important characteristic of this category is the transience demonstrated by altered motor potentials.

Signalling

Specific signalling deficits are suggested by the impaired regulation of saccadic components for vision tasks (SG1, SG2) and the impaired regulation of autonomic sympathovagal components (SG3, SG4, SG5, SG6). These effects are short in duration and they require very specific conditions to elicit the impaired response. It has been demonstrated that QT variability index differs in concussed individuals when measured at rest. These effects resolve sometime between two and seven days after injury (SG4). In a separate study from the same research group, it was also demonstrated that changes in heart rate complexity measured during an isometric handgrip test were apparent immediately post-injury, but were resolved by 14 days (SG3). In contrast, heart rate variability did not appear to change following injury (SG3). These effects of mild traumatic brain injury on heart rate complexity and QT interval variability are evidence of dysfunction of cardiac autonomic modulation (La Fountaine et al., 2011, 2009). The autonomic nervous system also contributes to the control of vasoconstriction and vasodilation in the brain. Cerebrovascular reactivity has also been found to be altered by mTBI. Changes in cerebral artery blood velocity (vMCA) and end-tidal carbon dioxide ($PETCO_2$) showed cerebrovascular reactivity in participants with mTBI did not recover as completely after repeated hyperventilation and breath holding intervals (SG5, SG6). The duration of this effect was around four to five days.

Neuropsychological

Neuropsychological tests have been used to determine post-injury impairments in reaction time and processing speed; however, reported findings are conflicting and show transient effects. Some consistent findings were slowed reaction time (NP1, NP2, NP3, NP4, NP5, NP13, NP14, NP15, NP16) and reduced math (NP1, NP2) and information processing performance (NP6, NP7, NP10, NP11, NP20). Reported slowed reaction time showed a short post-mTBI duration, from the time of injury to approximately five days, with the exception of one study which showed the presence of slowed reaction time at four weeks after injury (NP13). Some reported deficits in processing performance were resolved early (NP7); however, other studies had an unknown resolution (NP6) or showed deficits for a longer duration—approximately 12 days (NP11) and one month (NP20). Impaired working and visual memory were demonstrated by several studies (NP8, NP9, NP11, NP14, NP15, NP16, NP19), but normal visual memory was demonstrated as well (NP10, NP13, NP20). A correlation between high AMPAR (the neurotoxicity marker) and poor visual memory was found between one and two weeks after injury (NP19). In addition, a pattern of trading-off between visual memory and visual motor seemed to emerge in three ImPACT study results (NP13, NP14, NP15), while other ImPACT results highlighted the transient effect of impairments (NP16, NP17, NP18). Verbal memory was sometimes part of this trade-off (NP13, NP15). Verbal memory and other verbal neuropsychological test results demonstrated limited appearance and duration (NP15, NP17, NP22, NP24, NP25), or no appearance at all (NP13, NP20, NP21, NP22) of impairments. An exception was the linguistic task with auditory distraction in which deficits were present both at five days and one month after injury (NP23).

Dual-task

Dual-tasks involving motor tasks (such as postural tasks) also displayed transient recovery where impairment appeared to be resolved, but then reappeared at a subsequent testing date. Catena and colleagues (2011) noticed that while deficits in balance control such as a cautious gait and slowed reaction time were observed (DT2), one task would show impairment at the cost of the other with neither function consistently prioritized. Multiple studies showed an effect on the functional performance of one task (DT4, DT5, DT6) or both tasks (DT1, DT3, DT7, DT8, DT9). Impairment of dynamic tasks has further been demonstrated in visual tracking and motion perception experiments with previously injured individuals (Maruta et al., 2010; Patel et al., 2011). This effect is highlighted in a study which demonstrated that there was an increased cost in individuals with mTBI when performing two cognitive tasks that was not present when either task was performed alone (DT10).

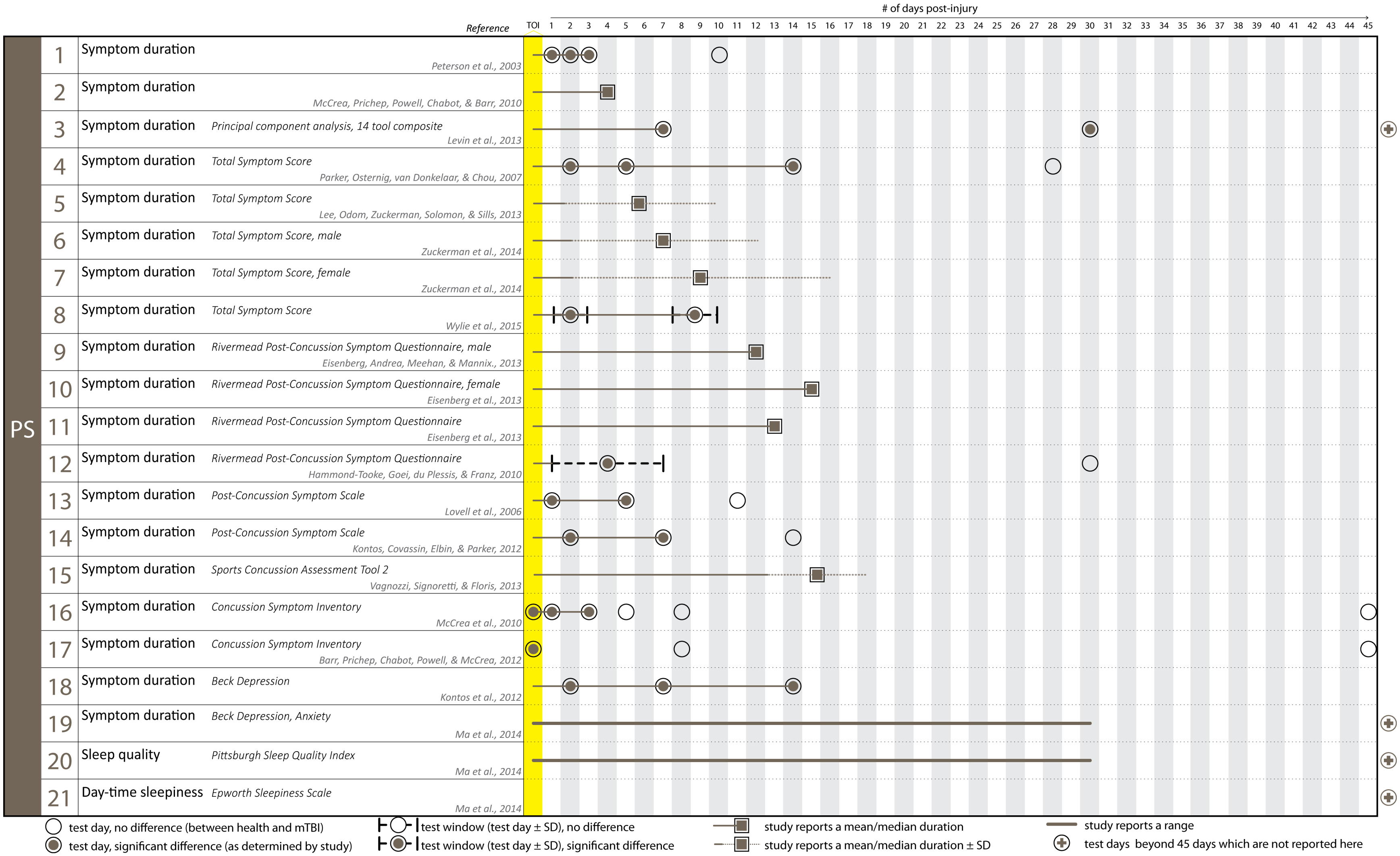

Figure 2.1 Physical Symptoms, PS.
Each row corresponds to results from an mTBI study and includes a short description of the finding. For example, PS12 refers to a study in which individuals were tested (using the RPCSQ) during the first week after injury as well as on day 30. Individuals with mTBI were found to show symptoms during the first testing window, but not on day 30.

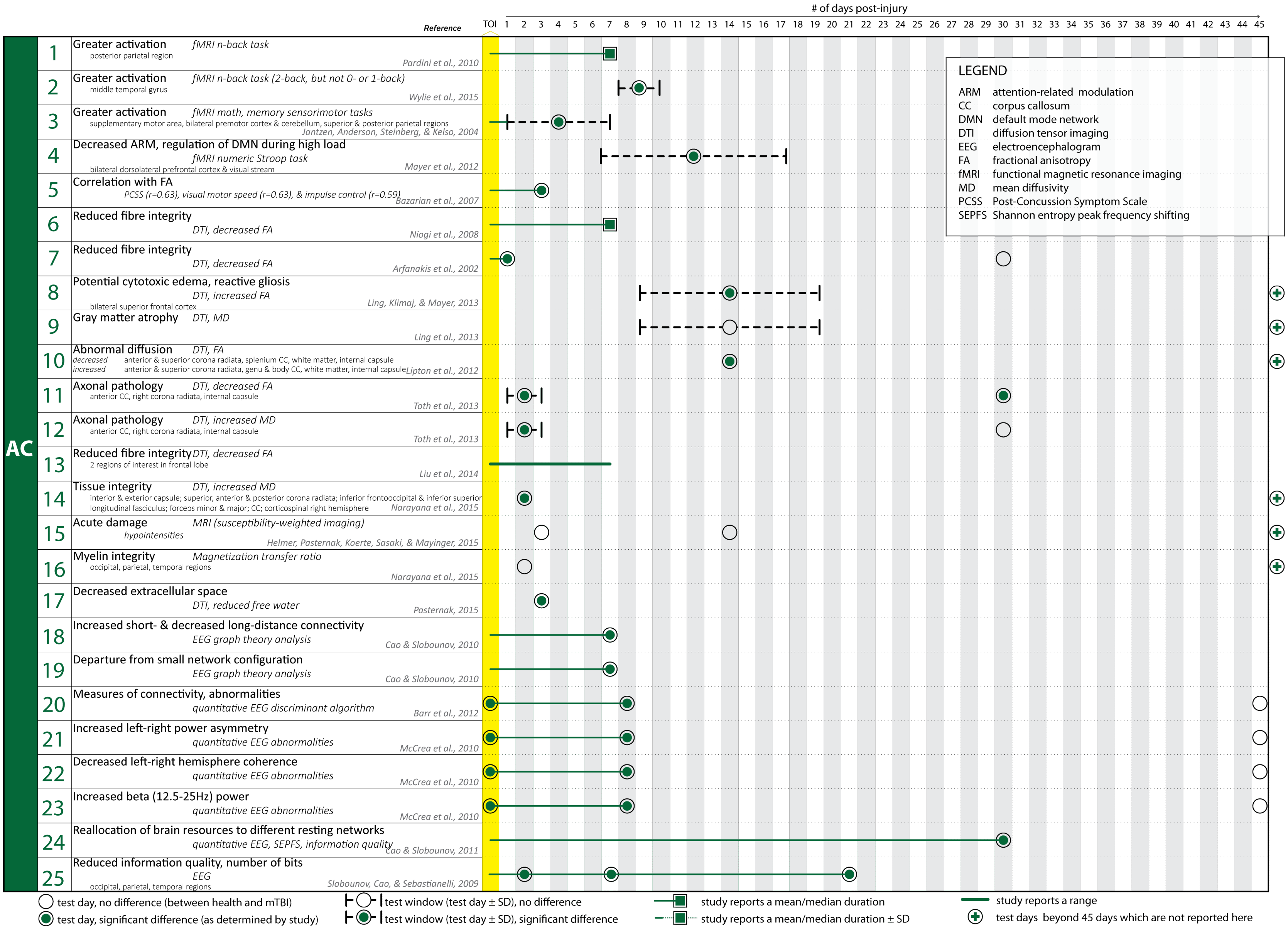

Figure 2.2 Activity and Connectivity, AC.
DTI, fMRI, and EEG findings are shown here. The type of task (fMRI) or measure (DTI, EEG) and region of interest are noted.

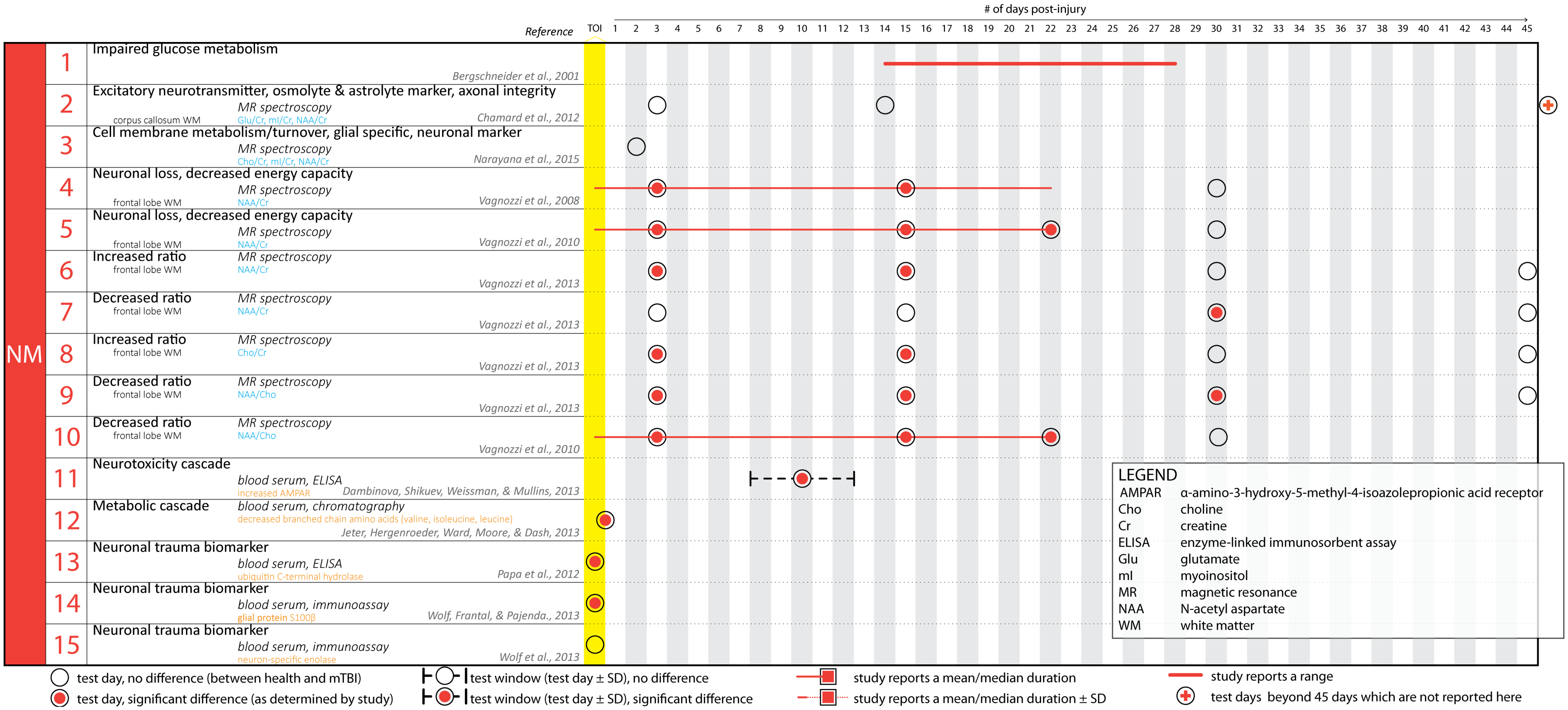

Figure 2.3 Neurometabolic markers, NM.
Metabolic experimental studies are often invasive, and consequently, limited to animal studies; however, less invasive MR spectroscopy and blood serum biomarker studies are suitable for humans. These types of study findings are included here.

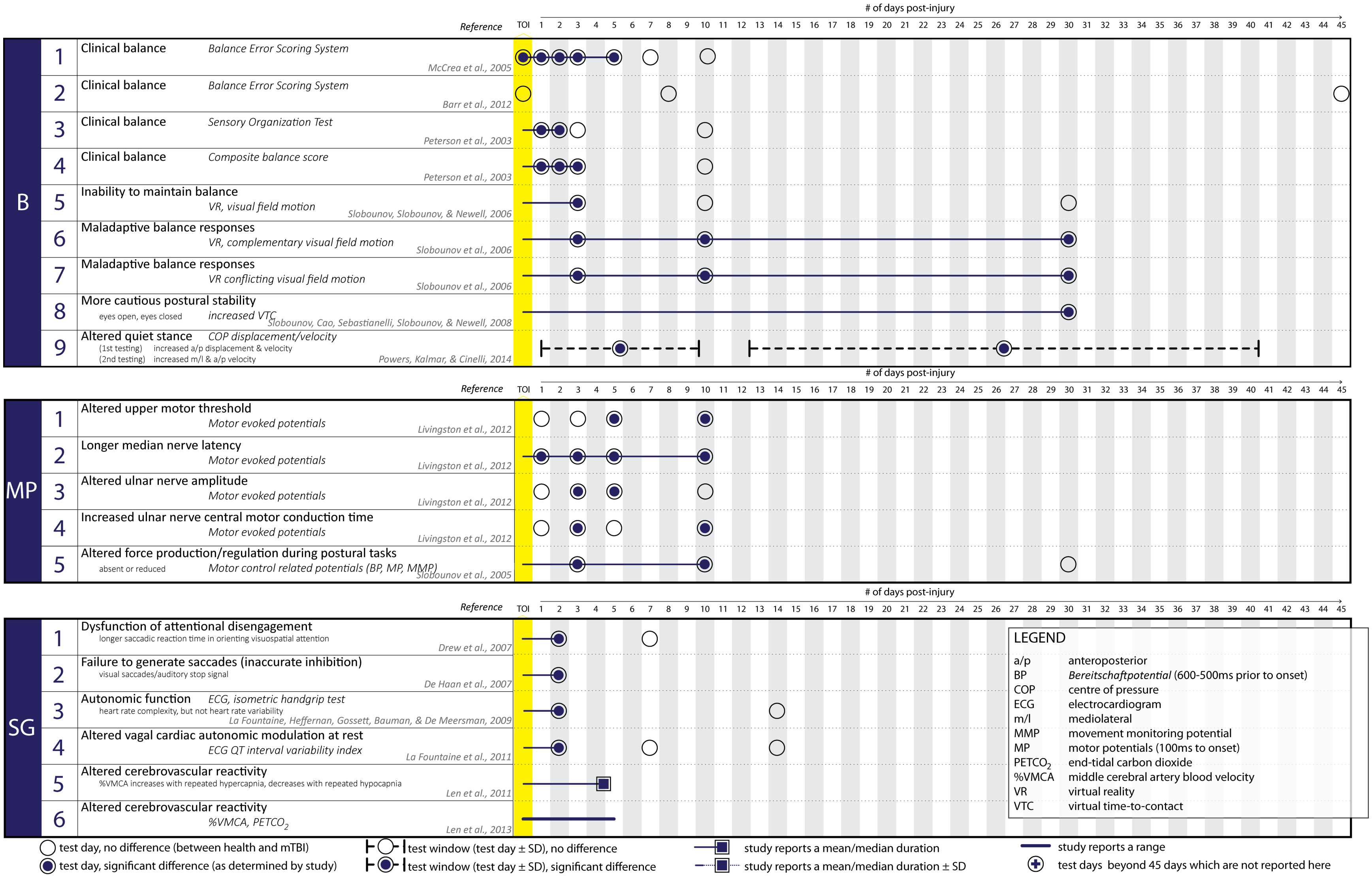

Figure 2.4 Balance, B, Motor potential, MP, and Signalling, SG.
It can be seen that the same test can yield results of different duration. For example, B1 & B2 show different results of the Balance Error Scoring System.

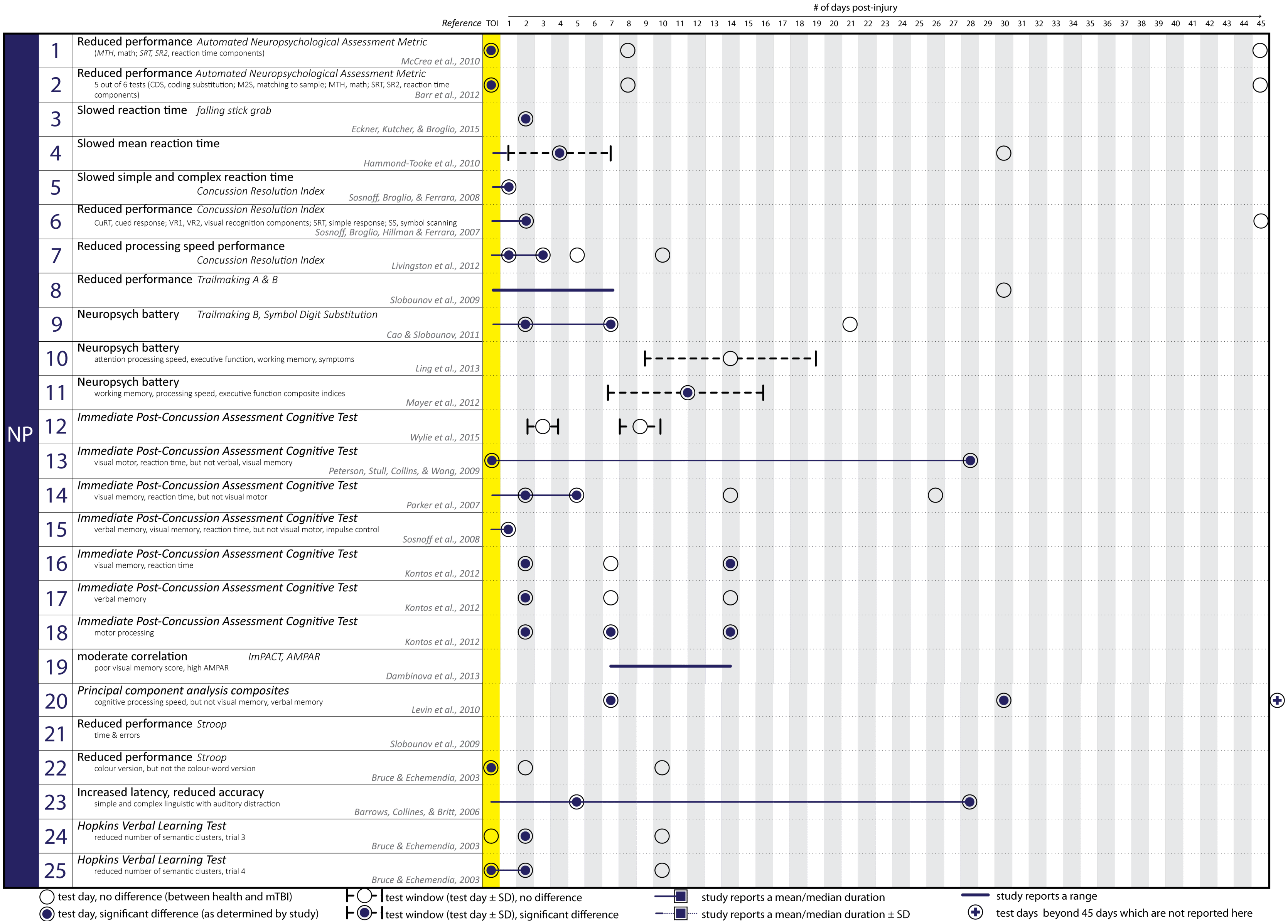

Figure 2.5 Neuropsychological, NP, and related tests.
A significant breadth of results are included. Most salient is the presence of gaps in the apparent duration of an impairment making estimates of duration a difficult task.

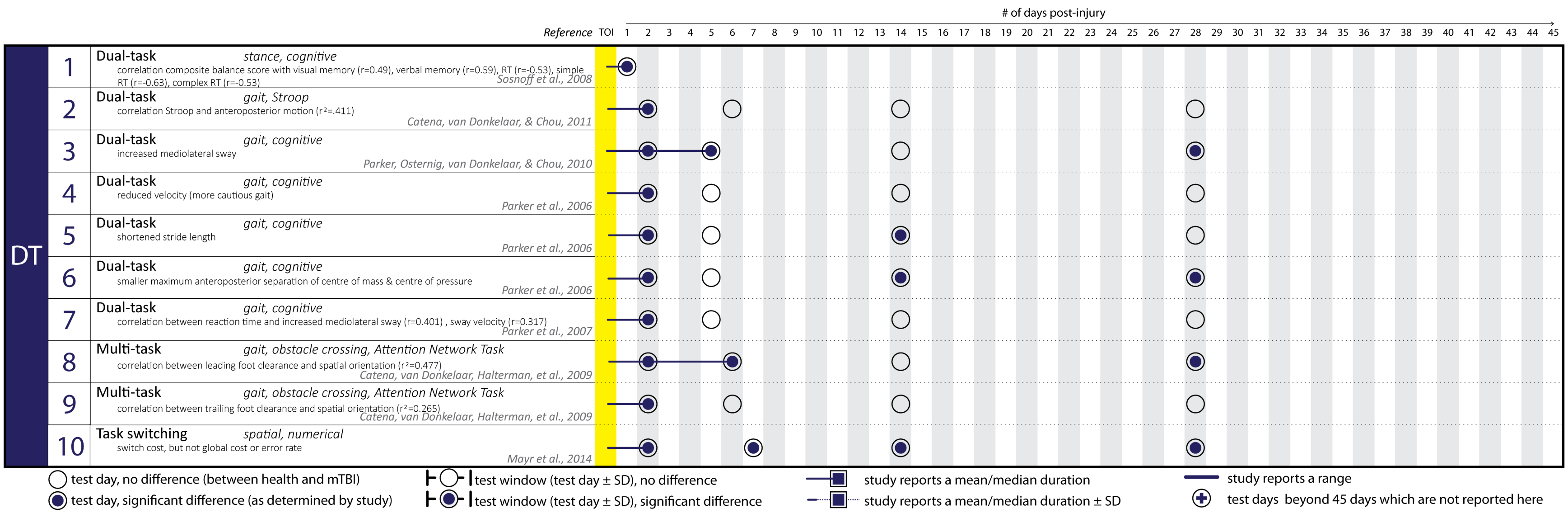

Figure 2.6 Dual-task, DT.
Dual-tasks, in particular, display transient recovery and trade-offs in effects.

2.5 Discussion

Both diffusion tensor imaging and electroencephalography studies demonstrated changes to connectivity that can begin right after injury and last until at least one month after injury. Functional magnetic resonance imaging studies demonstrated that under certain conditions (such as a specific task or a high load) changes in brain activity also appear to be present in at least the first two weeks after injury. Neurometabolic changes were demonstrated by studies using magnetic resonance spectroscopy and blood serum markers. These studies demonstrated that neurometabolic cascade begins almost immediately after injury, and can last up to three to four weeks. Decreased energy capacity and depressed metabolism appear to be significant features of the cascade. Activity & connectivity and neurometabolic changes shared a similar time frame, however, some brain activity studies also show functional performance may not be evident until high load or a specific task. This was supported by studies that showed functional tasks demonstrate transient effects, trade-offs, fast recovery of important functions (such as autonomic functions), and greatest effects with dual-task or high-demand some with duration on par with global effects.

Phases of mTBI recovery

Literature has previously described the effects of mTBI in terms of clinical phases or phases of recovery. In one paper, overt symptoms were thought to occur within an acute clinical phase, lingering symptoms persisted in a sub-acute phase occurring from six days to one month post-injury, and symptoms that persisted beyond one month after the injury were described as chronic (McCrea et al., 2009b). Recovery of the brain's metabolic functions have been described in terms of metabolic phases: a period of elevated metabolism, followed by a period of metabolic depression, and finally a period of metabolic recovery (Difiori & Giza, 2010). Similarly, recovery of the brain's cognitive functions have been described in terms of functional phases: the brain uses compensatory mechanisms to restore function, followed by plastic changes, and then neuronal recovery (Ellemberg et al., 2009). To fully understand mild traumatic brain injury, these concepts must be linked. This scoping review allows this by considering a conceptual description of recovery (Figure 2.7) where functional and global effects are described in interdependent phases.

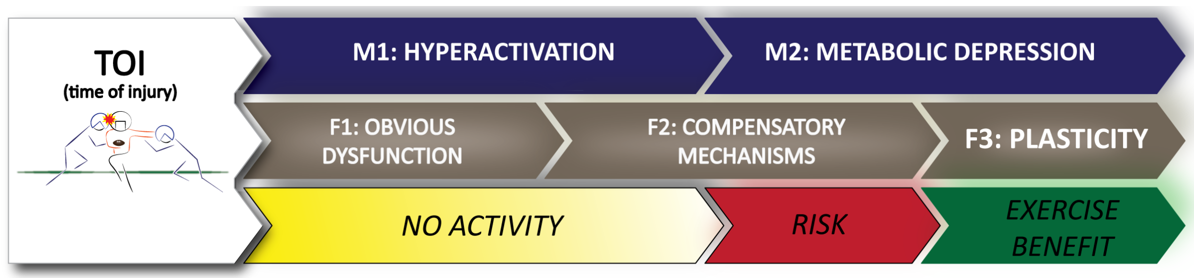

Figure 2.7 Description of mTBI recovery.
The most lacking component of this description is a uniform time scale. Certain phases are related and occur along a similar timeframe while the relationship between other phases is unknown. This figure illustrates one possible relationship between metabolic and functional phases where the start and end of blocked components are meant to suggest a temporal relationship. For example, the period of risk is thought to coincide with the onset of metabolic depression hence these two blocks are shown aligned.

Time of injury

At the time of injury, tissue deformation occurs due to shear and normal stresses and strain in the brain tissue (Arfanakis et al., 2002; Huisman et al., 2004; Niogi et al., 2008; Zhang et al., 2010). The deformation of brain tissue implies a corresponding deformation of cells within the injured tissue. Consequently, the membranes of these cells are subject to stretching and compression. While cell membranes are normally impermeable to ions (Nicholls, Martin, Wallace, & Fuchs, 2001; Shulman & Rothman, 2004), deformation of the cell and cell membranes can cause changes to membrane permeability (Giza & Hovda, 2001).

M1: Hyperactivation

The immediately resulting state is hyperactivation. Because the brain is a metabolically costly tissue with limited reserves; a balance between substrate availability and substrate use must be maintained (McCrea, 2008). Deformation of the brain tissue causes widespread depolarization indicated by an increase in extracellular potassium ions in animal studies (Giza & Hovda, 2001). Widespread depolarization, i.e., widespread activation releases more glutamate into the extracellular space, requires more energy to pump ions against their gradients in neurons and convert glutamate to glutamine in glial cells. Excess calcium in the extracellular space (Giza & Hovda, 2001) can be as a result of cell damage or death (Verkhratsky, Orkand, & Kettenmann, 1998). Other causes may be the coupled sodium-calcium co-transport in an attempt to restore sodium for action potential generation or to maintain pH (Nicholls et al., 2001). Inadequate glutamate clearance and excess potassium and calcium ions may signal the glial cells to make vascular alterations (Porter & McCarthy, 1997). Once released, calcium ion gradients favour re-entry and calcium overload further triggers cell death releasing even more substrates allowing perpetuation of the cycle of hyperactivation, ion imbalance, and cell damage (Verkhratsky et al., 1998). Glial cells struggle to clear the extracellular space of glutamate, as excess glutamate also causes damage to neurons (Shulman & Rothman, 2004). Biomarkers of compromised energy utilisation (NM12) and of neuronal trauma (NM13, NM14) shown to be present within the first 24 hours after injury as well as neurotoxicity markers in the second week (NM11) provide support in addition to the ion imbalances reported by animal studies for the initiation of metabolic cascade. In addition, increased activation was shown to be present in the first seven days (AC1, AC2, AC3) and in the second week (AC4) by fMRI studies. DTI studies also provide support for early axonal trauma (AC7, AC11, AC12, AC13, AC14).

F1: Functional dysfunction

In the brain, astrocytes separate and group functionally-related neurons into compartments and limit the spread of signalling by removing excess transmitters from each compartment space preventing diffusion to other areas (Nicholls et al., 2001). Therefore, during the hyperactivation phase, all the neurons in an affected compartment are presumed to be functionally compromised. Signs and symptoms likely arise when a functional compartment has been impaired. Normal neuronal signalling is disrupted by the widespread activation when excess neurons are depolarized as a result of injury, the brain may be misinformed. The initial symptoms of concussion—headache, nausea, dizziness, coordination and balance problems, sensitivity to noise and light, and memory problems (Lovell et al., 2007; Marion et al., 2011; McCrory et al., 2009; Randolph et al., 2009)—their intensity, and their duration are likely affected by the extent of the disruption.

Early functional impairments can also be attributed to hyperactivation and the initial consequences of neurometabolic cascade. This is supported by correlations between higher activation and symptoms (Pardini et al., 2010), correlations between axonal injury and symptoms (AC5), and correlations between biomarkers of neurotoxicity and poor visual memory (NP19). Another possible example is very short-term disruption to the autonomic functions of individuals (SG3-SG6). These studies determined that the sympathetic and parasympathetic systems may be suppressed in the initial period following a concussion. Areas of the brain charged with these functions and other similarly early and brief impairments are likely related to hyperactivation.

M2: Metabolic depression

Reduced substrate availability from reduced blood flow, decreased excitability from increased extracellular calcium (Nicholls et al., 2001), and continuous glial cell action eventually reduce the hyperactive state. A subsequent state of widespread metabolic depression preserves brain resources. Ultimately, as a result of the concussive injury, the balance between energy supply and demand in the brain is compromised (Giza & Hovda, 2001; Leddy et al., 2007; McCrea, 2008). Metabolic depression within the brain is a reflection of the brain attempting to conserve its resources. Since the energy used in neuronal signalling comprises the majority of the total brain's energy requirements, by limiting signalling, energy costs of the brain are significantly reduced (Shulman & Rothman, 2004). Metabolic disruptions continue to be present including impaired glucose metabolism (NM1) and decreased energy capacity (NM4, NM5, NM6). During M1, n-acetyl aspartate/creatine shows little change—only three percent between the first testing interval (NM4) (Vagnozzi et al., 2008); however, during M2, considerable improvement occurs. While a decrease in n-acetyl aspartate represents neuronal injury, improvement of the n-acetyl aspartate ratios in M2 suggests that in this phase metabolic preparation is made for neuronal recovery. Metabolic depression also signifies a period of risk. The brain is at or very near its limit of reversible metabolic disruption (Giza & Hovda, 2001; Leddy et al., 2007) and therefore, is more vulnerable to the consequences of head acceleration and deceleration (McCrea et al., 2009a; Vagnozzi et al., 2008). An increased risk of a second concussion has been reported in some studies. The time windows reported—between seven to ten days post-concussion (McCrea et al., 2009a) and ten to thirteen days post-concussion (Vagnozzi et al., 2008)—suggest that this period of risk occurs in the early part of metabolic depression. Accurate determination of this period of risk is important because, rarely, the outcome of a second mTBI can be catastrophic causing immediate life-threatening effects (Cantu & Gean, 2010).

In the latter part of M2 phase, as crucial metabolic substrates normalize, other metabolic concerns can be addressed including the requirements of neuronal repair. Exercise helps the brain make the crucial transition from metabolic depression (and associated functional limitations) to the improvement and reconstruction of neuronal pathways. Neurotrophic factors such as brain-derived neurotrophic factors, CREB (cyclic adenosine monophosphate response binding protein), and synapsin I levels, crucial in neuronal repair and growth (Leddy et al., 2007) are improved by well-timed exercise (Leddy et al., 2010; Leddy et al., 2007).

F2: Compensatory mechanisms

Cortical metabolic depression also affects the way in which information is processed and represented by neurons and neural connections (Shulman et al., 1997). Interestingly, it is believed the underlying mechanism of migraine visual auras is a spreading cortical depression. As the suppression of neural activity spreads over the visual cortex, visual disturbances are experienced by the migraine sufferer. The retinotopic location of the visual disturbances has been shown to coincide with fMRI activation (Hadjikhani et al., 2001). Hadjikhani and colleagues (2001) demonstrated that local metabolic depression can produce a discernable effect on the functional performance of brain areas under the effects of cortical depression, even in the short-term. In mTBI, this may be analogously demonstrated in mTBI by transient occurrence of functional impairments (MP1, MP3, MP4, NP16, NP24, DT3, DT5, DT6, DT8). In addition, impaired measures during dual-task activities such as correlations between demand and performance that would not usually arise (DT7, DT8, DT9, DT10) suggest there may be a mechanism limiting the availability of brain resources.

Compensatory mechanisms appear to start as early as metabolic conditions allow and continue as long as is necessary. In addition, functional improvements in abilities may arise at different periods after the injury. Yet, functional improvements may not always represent physiological improvements within the brain. The hierarchical organization of the brain is such that most functions can be preserved by the use of functional building blocks from uncompromised areas. Post-concussion compensatory mechanisms are analogous to the recruitment phase that occurs post-stroke (Warraich & Kleim, 2010). In this post-injury phase, areas of the brain that would normally not contribute or contribute very little to a particular function, but that are capable of performing the same task without training, are called upon to help the injured region. Quantitative EEG studies have reported measures that suggest the reorganization of different networks occurs until at least 30 days post-injury (AC24, AC25). Unfortunately, in individuals who have suffered an mTBI, the occurrence of improvements in functional performance may falsely suggest recovery. This phase instead indicates that resources are being limited through efficiency while still preserving as many functions as possible.

F3: Plasticity

The capacity of the brain to alter its neural structure and connections is the actual mechanism by which recovery takes place (Chen, Epstein, & Stern, 2010); however, more support and consequently more research into plasticity of the brain following an mTBI is necessary. After a mild diffuse injury (as opposed to a focal or more severe injury), renewal and stabilization of the existing brain networks are the main necessary steps in resetting the brain (Chen et al., 2010).

However, plastic changes in the brain require a significant amount of specialized resources. Intracellular calcium has an important role in plasticity as well as long-term potentiation, long-term depression, and post-tetanic potentiation (Chen et al., 2010). Brain-derived neurotrophic factor influences the growth and complexity of axons and dendrites, but it is physiological activity which regulates neurotrophins and trophic substances such as brain-derived neurotrophic factor, glial cell-derived neurotrophic factor, and fibroblast growth factor are crucial to neuron survival (Nicholls et al., 2001). Exercise up-regulates trophic factors while the abrupt cessation of exercise causes a dearth of neurotrophic factors in the brain (Nicholls et al., 2001). Therefore, return-to-activity is linked to the plasticity phase—or rather, when these two instances are decoupled, post-concussive syndrome symptoms may arise from the inability of the brain to make the necessary plastic changes due to a lack of resources. Exercise up-regulates the neurotrophins which prime the environment and allows pathways to elongate (Kleim, Jones, & Schallert, 2003). A lack of exercise can mean insufficient neurotrophic factors which, in turn, lead to mechanisms that will impair plasticity. The excitatory-inhibitory balance which controls activity within the brain also controls the environment for plasticity (Nicholls et al., 2001). Increases in GABA (γ-aminobutyric acid) inhibition which earlier may have functioned as a protective mechanism against cell death (Johnston, 2009) must be suppressed as a mechanism of plasticity. The capacity for plasticity may also be affected by a decrease in NMDA (n-methyl d-aspartate)-receptor functioning (De Beaumont, Tremblay, Poirier, Lassonde, & Théoret, 2012). The exact relationship between mTBI and plasticity mechanisms may require further research and is beyond the scope of this paper.

A general limitation of this scoping review was that findings were included from a broad variety of studies despite potential differences across studies. While most studies used similar criteria for defining a concussion (Glasgow Coma Scale score 13-15, etc.), some studies included additional exclusion criteria, while others may have been based solely on one type of group (for example, an athletic population). Where similar studies showed different results, it must be considered that differences in type of injury or individual response to trauma could be a factor. However, not all mTBI studies were included; each study had to meet this scoping review's inclusion criteria. It can be argued that having contributions from multiple studies better illustrates the big picture. Finally, since a scoping review provides a conceptual rather than a quantitative overview, these limitations are not as important a factor in the validity of the conclusions that were drawn.

Other brain injuries such as stroke show similar patterns of recovery albeit on a longer recovery time frame (Fineman, Giza, Nahed, Lee, & Hovda, 2000). Because an mTBI is a diffuse injury, i.e., has a widespread effect on the brain, it is the metabolic disruption which drives the recovery timeframe. Functional recovery phases are dependent on the metabolic environment. Yet, the brain's adaptability may indicate recovery at times when a return to activity could be detrimental. A close look at functional assessments to find suitable measures able to distinguish between compensation and plastic improvement is an important next step. Differentiation between phases and the clinical features of each phase is crucial in understanding the mechanisms of mTBI recovery and in determining the best and safest time for a return to activity following an mTBI.

Acknowledgements/Funding
The first author was supported by scholarships provided by the Government of Ontario (QEIIGSST, OGS) and by the University of Ottawa.

Conflicts of Interest Statement
There are no conflicts of interest to disclose.

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3. Linear and Non-linear Centre of Pressure Measures in Quiet Stance

(submitted to the Journal of Biomechanics)

Linear and Non-linear Centre of Pressure Measures in Quiet Stance

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3.1 Abstract

We investigated balance parameters in healthy young adults (n=32; 25 male, 7 female) during quiet stance using both linear and non-linear COP measures. The goal was to better understand what additional information could be provided by non-linear measures. Participants stood with eyes open, eyes closed, on a single leg, and in tandem stance. Normative data were established for both linear and non-linear measures—non-linear single leg and tandem stance normative data add to what is currently found in literature. Removal of visual input resulted in changes to anteroposterior output and control—demonstrated by increased position- and velocity-based measures as well as by the largest Lyapunov exponent. More difficult stance positions also demonstrated greater output and increased control requirements. Scaling parameter estimates provided additional information. Short-term scaling was less complex (closer to white noise) in the most biomechanically stable direction for each stance suggesting that less active control was required in this direction. While long-term scaling was similar across conditions, less complex anteroposterior than mediolateral scaling suggested differences in how control was integrated in each direction. Therefore, both linear and non-linear measures provided complementary tools for assessing balance system input and output as well as control and integration characteristics.

Keywords: Centre of pressure, quiet stance, balance control, scaling, self-similarity, largest Lyapunov exponent

3.2 Introduction

In balance, sensory input and motor output systems coordinate to maintain an upright posture. To better understand how balance is maintained, it can be studied as a control system. When a deviation from vertical is sensed, a force must be generated by the muscles to counteract the torque caused by gravity in a short enough time for the body to remain upright (Pijnappels, Bobbert, & van Dieën, 2005).

The centre of pressure (COP) defines the position of the weighted average of forces acting between the feet and the ground (Winter, Prince, Frank, Powell, & Zabjek, 1996) and represents the balance control output. Net COP combines the output of the left and right feet, and their respective outputs are the result of the combined action of muscle groups (evertors, invertors, plantarflexors, and dorsiflexors) (Winter, 1995). Though COP movement reflects trends in centre of mass (COM) movement (van den Heuvel, Balasubramaniam, Daffertshofer, Longtin, & Beek, 2009), the temporal variations in COP result from temporal variations in lower leg muscle contractions (Loram, Maganaris, & Lakie, 2005; Milton, Cabrera, Ohira, Tajima, & Tonosaki, 2009; Sozzi, Honeine, Do, & Schieppati, 2013). Therefore, neuromuscular control of COM is also represented in COP movement (Milton et al., 2009; Winter et al., 1996).

Understanding balance in healthy individuals is particularly important for understanding how balance can be affected by injury or disease. In quiet stance, the COP can be used to evaluate balance. Variations in visual condition—standing with eyes open versus standing with eyes closed—can elucidate whether vision is a stabilizing factor. And variations in stance position—standing on one leg or in tandem stance versus standing comfortably—can be employed to challenge motor integration and output.

Choosing an appropriate measure can also provide insight into the nature of balance control. Linear measures such as position- or velocity-based measures reflect the spatial characteristics of COP. While variability is a position measure, path length (normalized by time) and mean speed are movement or velocity-based (Kitabayashi, Demura, & Noda, 2002). Position measures better reflect output, whereas velocity-based measures are excellent candidates for reflecting control (Delignières, Torre, & Bernard, 2011; Jeka et al., 2004; Masani, Popovic, Nakazawa, Kouzaki, & Nozaki, 2003).

On the other hand, non-linear measures, such as scaling parameters and the largest Lyapunov exponent, provide additional information about underlying contributions to COP output by taking into account the higher dimension and temporal structure in the COP timeseries. In balance, conclusions on postural stability have often been drawn by assuming that an increase in COP variability represents a decrease in postural stability; yet, as a measure of stability, variability does not take into account the temporal characteristics of COP (Dingwell & Cusumano, 2000). The largest Lyapunov exponent can be used to estimate the local stability of a COP timeseries and is mathematically well defined (Rosenstein, Collins, & De Luca, 1993; Taqqu, Teverovsky, & Willinger, 1995). The largest Lyapunov exponent estimates local stability of a timeseries by quantifying the divergence of neighbouring state space trajectories. In state space, the relationship between inputs and outputs of a system are governed by equations that link state variables. The largest Lyapunov exponent has been used to estimate local stability in gait (Dingwell & Cusumano, 2000; England & Granata, 2007) and in quiet stance (Donker, Roerdink, Greven, & Beek, 2007; Roerdink et al., 2006). In gait, greater local stability was shown to occur at slower walking speeds (Dingwell & Cusumano, 2000; England & Granata, 2007). In quiet stance, removing visual input resulted in an increase in the largest Lyapunov exponent (i.e., a decrease in local stability) in healthy young adults (Donker et al., 2007), healthy elderly adults, and elderly adults who had suffered a stroke (Roerdink et al., 2006). Challenging attention capacity also caused a decrease in local COP stability in healthy elderly adults and elderly adults with stroke (Roerdink et al., 2006). This was investigated by comparing a dual-task (cognitive arithmetic task and quiet stance) to quiet stance alone. On the other hand, standard rehabilitation (over the course of 12 weeks) was able to increase local stability in elderly adults with stroke (Roerdink et al., 2006).

The scaling parameter quantifies self-similar correlations at different time scales within a timeseries (Hurst, 1955). The value of the scaling parameter, H, of a COP timeseries can be compared to known values which define scaling properties such as random walk (H=0.5), persistent power law correlation ($0.5<H<1.0$), or anti-persistent power law correlation ($0<H<0.5$) (Peng, Havlin, Stanley, & Goldberger, 1995). In this paper, we describe values that are closer to H=0.5, i.e., random walk, as being less complex while values that are farther away are more complex. A value in the persistent range indicates that within a given time window, the timeseries follows its previous trend (i.e., the timeseries continues to increase if previously increasing, or continues to decrease if previously decreasing). A value in the anti-persistent range indicates the trend of the timeseries tends to reverse itself (i.e., decreases followed by increases and vice versa) (Peng et al., 1995). Timeseries may exhibit the same scaling property over all time windows or could have different scaling properties for different time windows. One possible interpretation of the presence of multiple scaling regions is that multiple mechanisms contribute to shaping the timeseries.

Despite the previous use of scaling parameters in evaluating COP, it is difficult to compare values across studies because they can use different estimation methods, ranges of time scale (not simply trial duration), and definition of the scaling measure reference scale. For this reason, it is impossible to make a gross characterization of the scaling properties of quiet stance in healthy young adults based on previous literature. In general, however, investigations of COP scaling properties in quiet stance have shown: (1) differences between short-term and long-term scaling, that is, COP timeseries are persistent in the short-term and anti-persistent in the long-term (Chiari, Cappello, Lenzi, & Della Croce, 2000; Collins & De Luca, 1994; Schmid, Conforto, Camomilla, Cappozzo, & D'Alessio, 2002); (2) anti-persistent very long-term correlations (time windows ranging between 10 seconds and 10 minutes, timeseries up to one half hour in length) (Duarte & Zatsiorsky, 2001); (3) conflicting results with respect to removing visual input with studies reporting no difference (Chiari et al., 2000) or decreases in the scaling parameter when standing with eyes closed (Donker et al., 2007); and (4) decreases in the scaling parameter in dual-task (word reversal task during quiet stance) compared to quiet stance alone in healthy young adults (Donker et al., 2007).

In this paper, we report linear and non-linear measures of COP from four conditions in healthy young adults. The aim of this study was to clarify how non-linear measures describe COP in quiet stance by addressing conflicting results and knowledge gaps. By situating the study population with respect to other populations of healthy individuals using common linear measures, we hope to gain a better understanding of how these non-linear methods characterize balance in quiet stance. We hypothesized that both linear and non-linear COP measures would show differences between conditions related to visual input and stance difficulty.

3.3 Methods

Data collection

Healthy young adults (n=32 (25 male, 7 female) between the ages of 18 and 30) were asked to stand quietly without shoes on a solid surface for two minutes ($T\approx120$s) under four different conditions: feet together in a comfortable stance with eyes open (EO), feet together in a comfortable stance with eyes closed (EC), single leg with eyes open (SIN), and tandem stance with eyes open (TAN). Ground reaction forces and moments were recorded (D-flow 3.12, Motek Medical, The Netherlands) using two Bertec force platforms (f=60Hz). Net COP was computed in the mediolateral and anteroposterior directions. When eyes were open, a static visual target and a countdown clock were projected on a screen at eye level two metres in front of the participant.

Data analysis

COP timeseries—mediolateral, x_i, and anteroposterior, y_i, where i=1, 2,…, N and $N=Tf$

Table 3.1 COP measures

Measure	Symbol	Equation/Method	Description
Path length (normalized)	l	$\frac{1}{T}\sum_{i=1}^{N}\sqrt{(x_{i+1}-x_i)^2+(y_{i+1}-y_i)^2}$	The timeseries is normalized by the total time, T, to account for minor differences in length (number of samples); it can also be considered an estimate of average speed.
Mean speed	$(\bar{u}_x, \bar{u}_y)$	$u=\left(\frac{\lvert x_{i+1}-x_i\rvert}{t_s}, \frac{\lvert y_{i+1}-y_i\rvert}{t_s}\right)$	Mean speed (the mean instantaneous speed of the timeseries), unlike velocity, disregards direction when the absolute value (or square root of the squared velocity) is taken to avoid having the negative and positive values cancel. Unlike path length, it is calculated at each time step. Note: $t_s = 1/f$.
Variability	(σ_x, σ_y)	$\left(\sqrt{\frac{1}{N-1}\sum_{i=1}^{N}(x_i-\bar{x})^2}, \sqrt{\frac{1}{N-1}\sum_{i=1}^{N}(y_i-\bar{y})^2}\right)$	Variability of the COP timeseries is represented by the standard deviation.
Largest Lyapunov exponent (local stability)	(λ_x, λ_y)	Rosenstein's algorithm (Rosenstein, Collins, & De Luca, 1993)	The largest Lyapunov exponent estimates the local stability of the timeseries by quantifying the exponential divergence of initially close trajectories (the largest overtakes all others and is representative of the evolution of the state space volume). The algorithm uses the embedding dimension determined by false nearest neighbours (Kennel, Brown, & Abarbanel, 1992) and the mean period of the timeseries.
Scaling	(H_x, H_y) for each region	Multiple methods were averaged to yield an estimate: Aggregated variance, Absolute values, Rescaled range (R/S), Residuals (Rea, Oxley, Reale, & Brown, 2009; Taqqu et al., 1995)	The scaling parameter quantifies self-similar correlations within the timeseries at different time scales. Each method uses the original, differenced, or summed series depending on classification of the series as fractional Gaussian noise or fractional Brownian motion.

(N≈7200)—were used to calculate measures as described in Table 3.1. A second-order, low-pass Butterworth filter with a cut-off frequency of 10Hz (as suggested by Ruhe and colleagues (2010)) was applied to each timeseries before calculating linear measures (path length, mean speed, variability). Non-linear measures were calculated using unfiltered data. Data analysis was carried out in MATLAB (MATLAB 2013a, Mathworks Inc., Natick, Massachusetts) with additional material from MATLAB Central (Chu Chen, 2008; Mirwais, 2012a, 2012b).

An overview of the general steps used in calculating the scaling parameter is shown in Figure 3.1. From a suitably altered timeseries, we generate a power spectrum (see below).

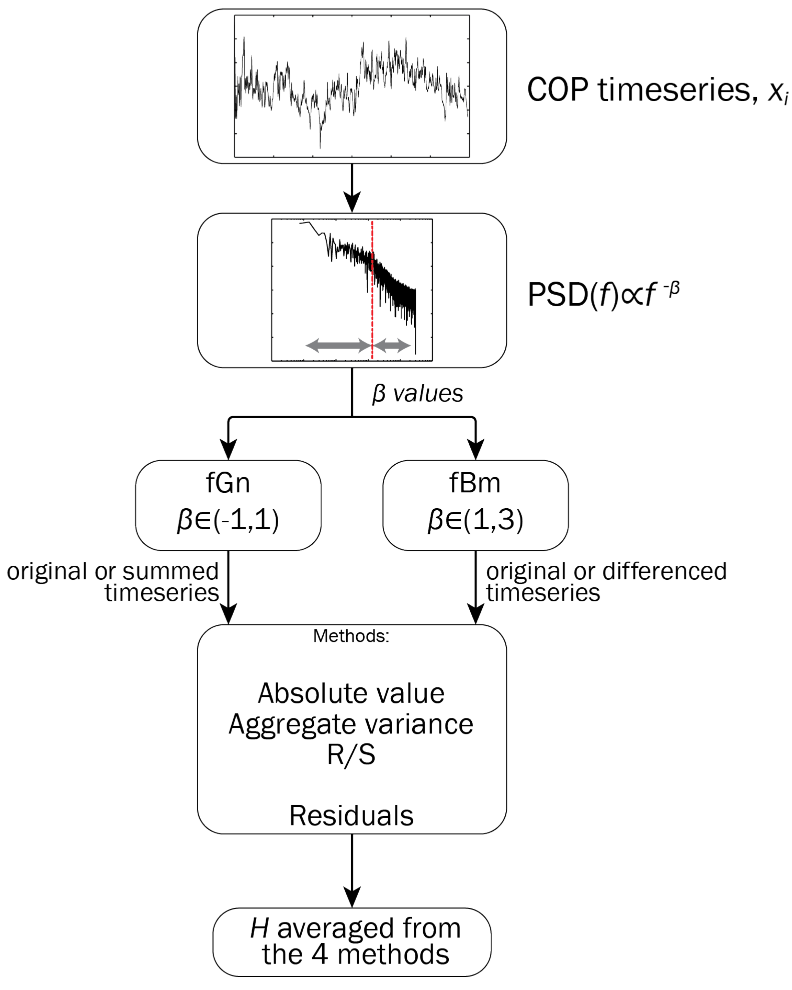


Figure 3.1 Data workflow for estimating scaling parameter.
The number of scaling regions and the type of timeseries (fGn or fBm) can be determined from the linear regions in the power spectrum plot. For fGn-type timeseries, the original timeseries was used for the absolute value, aggregate variance, and R/S methods. For the residuals method, the fGn-type timeseries was converted to fBm-type by summing the timeseries. For fBm-type timeseries, the original timeseries was used for the residuals method. For the absolute value, aggregate variance, and R/S methods, the fBm-type timeseries was converted to fGn-type by differencing the timeseries. The scaling parameter was averaged from the four methods.

The number of linear regions was determined by visual examination of the log-log plot of power spectrum (PSD plot). Each power spectrum had two regions. Beta (β) values were computed by determining the slope of each region in the PSD plot using the relation: $PSD(f) \propto f^{-\beta}$ (Serinaldi, 2010). In Figure 3.2, a sample timeseries and its corresponding PSD plot with calculated β values are shown.

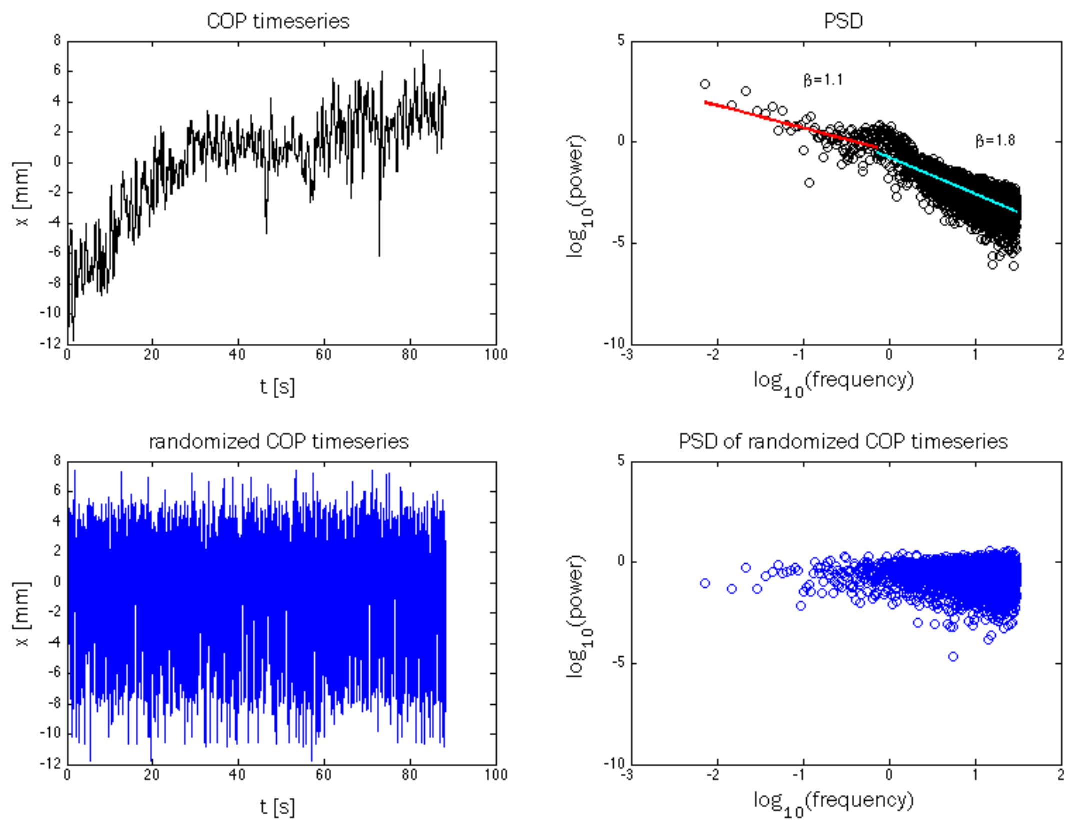


Figure 3.2 Data workflow for estimating scaling parameter.
The COP timeseries (upper left), x_i or y_i, was Fourier transformed using a periodogram spectral estimation method (which used a default rectangular window) to yield the PSD plot (upper right) (maximum frequency plotted is 60Hz/2=30Hz). Both regions in the power spectrum yielded β values that were between 1 and 3; therefore, both regions were classified as fractional Brownian motion. The lower left shows an example of the same timeseries which has been randomized. The lower right shows the power spectrum of the randomized plot as white noise (a flat slope).

From each region's β, the region was classified as fractional Gaussian noise (fGn, $-1<\beta<1$) or fractional Brownian motion (fBm, $1<\beta<3$). While the power spectral density was used to classify the regions, it was not used as an estimation method for the scaling parameter. The scaling parameter, H, was calculated by averaging estimates from four methods to avoid reliance on a single estimate method (Rea et al., 2009). These four methods were the absolute value, the aggregated variance, the rescaled range (R/S), and the residuals method (also known as detrended fluctuation analysis). Of the methods used, the absolute value, aggregated variance, and rescaled range (R/S) methods require fGn-type input, while the residuals method requires fBm-type input to preclude convergence of the result to a false value (Serinaldi, 2010; Rea, Oxley, Reale, & Brown, 2009; Taqqu et al., 1995). For the methods that require fGn-type timeseries, the raw timeseries was used directly as input if the spectral analysis revealed that it was of fGn-type; if, instead, the raw timeseries was of fBm-type, it was first converted to fGn-type by differencing it (i.e. replaced by the series of differences between successive values). Conversely, for the methods that require fBm-type timeseries, an fGn-type timeseries was first converted to an fBm-type timeseries by summing (integrating) the timeseries (i.e. replaced by the series of sums of successive values). Using each graphical estimation method, a scaling estimate for each region (analogous to each region found in the power spectrum—short-term or high frequency, H_1, and long-term or low frequency, H_2) was obtained from the slope of a line of best fit. These four estimates were averaged to yield a single scaling parameter value for each region. Randomized surrogate timeseries with the same linear properties as the original were also evaluated as a control for the methodology, to verify that randomized timeseries were properly identified as random by each method (Theiler, Eubank, Longtin, Galdrikian, & Farmer, 1992). Paired t-tests were used to compare between the calculated values and randomized surrogates.

For each measure, a single group mean was calculated. Statistical analyses were performed in SPSS (v23, IBM Corp., Armonk, NY). A one-way repeated measures ANOVA was used to compare between conditions for path length. For all other meaures, a two-way repeated measures ANOVA was used to compare condition and direction. Post-hoc Bonferroni-adjusted comparisons were also conducted.

3.4 Results

Values of means, standard deviations, and p-values can be found in Figures 3.3, 3.4 and Table 3.2. When ignoring direction, condition means differed significantly for all measures. Condition means for path length also differed significantly. When ignoring condition, direction means differed significantly for variability, the largest Lyapunov exponent, short- and long-term scaling, but mean speed direction did not differ significantly. There was a condition by direction interaction for all measures. Post-hoc comparisons are further discussed below.

COP timeseries showed two distinct scaling regions—short-term, H_1, and long-term, H_2. The majority (482 out of 512 regions; 94.1%) were classified as fractional Brownian motion. Short-term scaling was found to be persistent whereas long-term scaling was found to be anti-persistent. As expected, all surrogate timeseries demonstrated random correlations ($H \approx 0.5$). Surrogates were significantly different from calculated H values ($p < 0.05$) with the exception of short-term mediolateral eyes closed stance ($p = 0.051$).

Visual input

Removing visual input affected linear and non-linear COP measures. Path length (Figure 3.3A), anteroposterior mean speed (Figure 3.3B), anteroposterior variability (Figure 3.3C), and the anteroposterior largest Lyapunov exponent (Figure 3.3D) were significantly greater when standing with eyes closed (EC) than when standing with eyes open (EO). Short- and long-term anteroposterior scaling were more complex when standing with eyes closed than with eyes open.

Stance

When standing comfortably either with eyes open or with eyes closed, anteroposterior mean speed, variability, and largest Lyapunov exponent were significantly greater than the mediolateral. In contrast, greater mediolateral than anteroposterior mean speed and largest Lyapunov exponent were found in single leg and tandem stance.

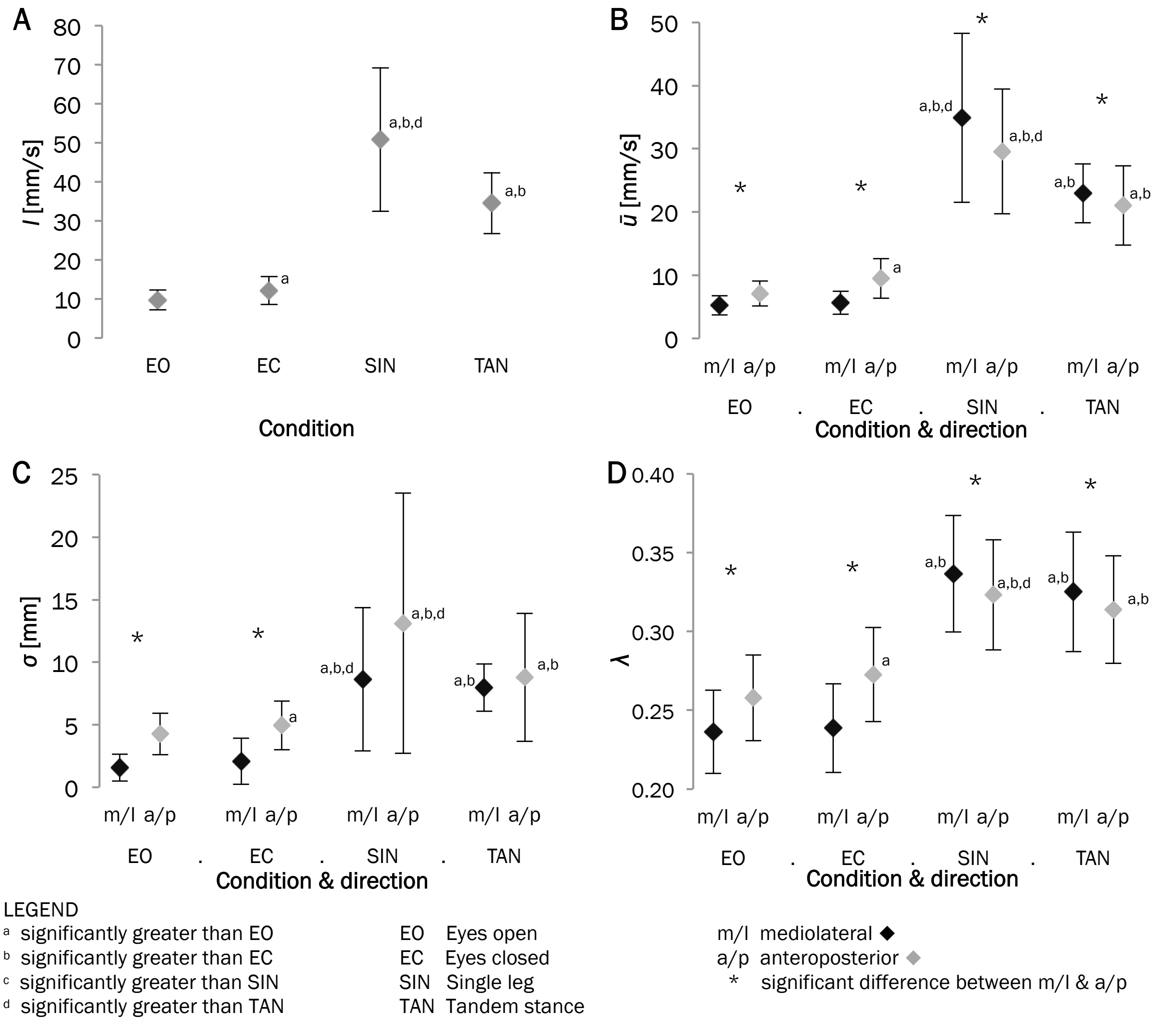


Figure 3.3 COP measures in young adults.
Normalized path length (l), mean speed ($\bar{u}$), variability (σ), and largest Lyapunov exponent (λ) mean ± one standard deviation. Significant differences between directions are marked with an asterisk. Significant differences between condition pairs are noted with the corresponding superscript. When standing with eyes closed versus standing with eyes open, path length, anteroposterior mean speed, anteroposterior variability and the anteroposterior largest Lyapunov exponent had greater values. Single leg showed greater values than two-legged stance (eyes open, eyes closed, and tandem stance). Tandem stance showed greater vales than comfortable stance (eyes open and eyes closed).

Path length, mean speed, and variability were significantly greater when standing on one leg (SIN) than when standing on two legs comfortably (EO, EC) or in tandem stance (TAN). Similarly, the anteroposterior largest Lyapunov exponent was greater when standing on one leg than in any of the two-legged stance conditions though the mediolateral was only greater when standing on one leg than the two comfortable stance conditions.

Path length, mean speed, variability, and the largest Lyapunov exponent were also greater when standing in tandem stance (TAN) than when standing comfortably (EO, EC).

Short-term

Short-term mediolateral scaling was least complex (closest to 0.5) when standing comfortably—significantly less complex when standing comfortably with eyes open than when standing on one leg or in tandem stance and significantly less complex when standing comfortably with eyes closed than in tandem stance. Short-term anteroposterior scaling was significantly less complex in tandem stance than when standing comfortably or when standing on one leg. Mediolateral scaling was significantly less complex than anteroposterior when standing comfortably with eyes open. Conversely, when standing on one leg and in tandem stance, anteroposterior scaling was significantly less complex than mediolateral.

Long-term

Long-term scaling was similar across conditions in each direction with the exception that anteroposterior scaling was significantly less complex when standing comfortably with eyes open than in any other condition. In every condition, anteroposterior scaling was significantly less complex than mediolateral scaling.

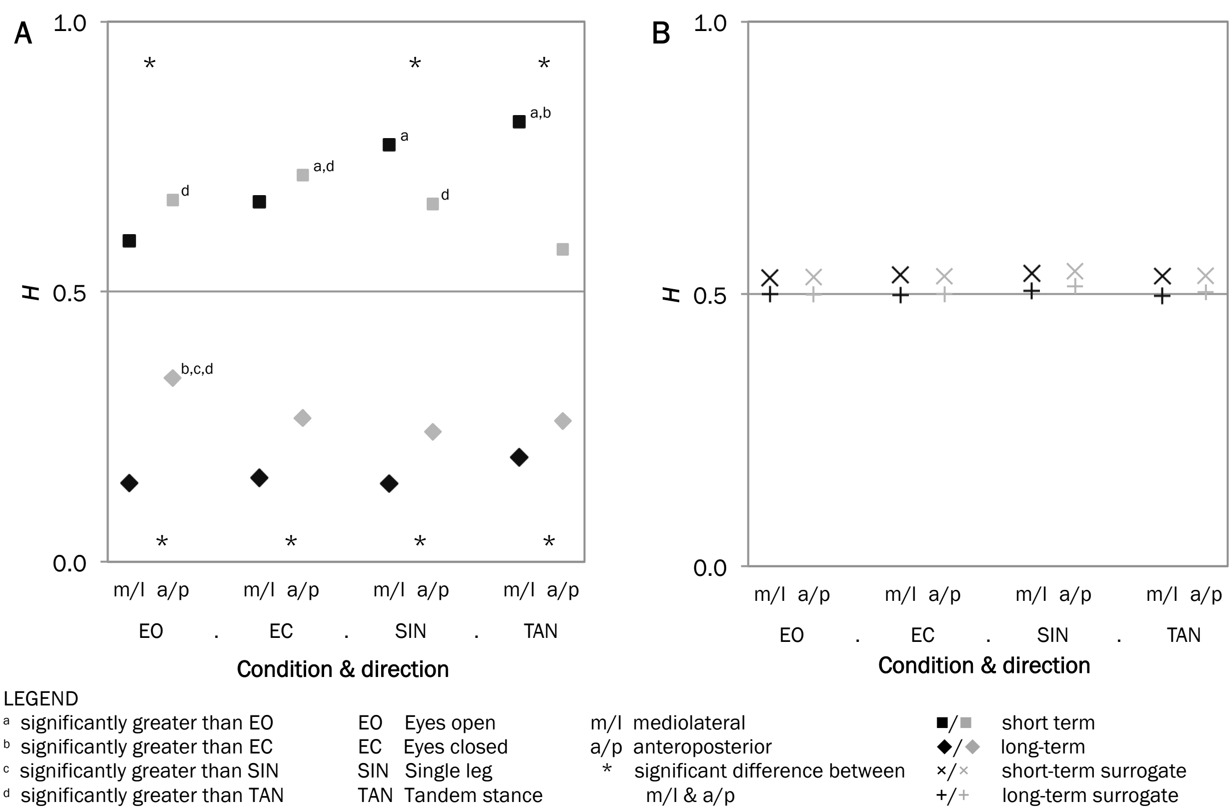


Figure 3.4 COP scaling and surrogates.
(A) Short-term and long-term scaling parameters. (B) Short- and long-term scaling parameters of surrogate randomized series. Standard deviation bars are excluded for clarity and can be found in Table 3.2. Short-term scaling parameters were persistent (greater than 0.5) while long-term scaling parameters were anti-persistent (less than 0.5).

Table 3.2 COP results for healthy young adults (mean±SD, *p*-values)

Measures		Conditions								ANOVA *p*-values		
		Eyes open		**Eyes closed**		**Single leg**		**Tandem**		**Condition**	**Direction**	**Condition* Direction**
l [mm/s]		9.78±2.59		12.21±3.57[a]		50.83±18.39[a,b,d]		34.60±7.81[a,b]		***$p<0.001$***	n/a	n/a
$\bar{u}$ [mm/s]	m/l	5.22±1.51	***$p<0.001$***	5.63±1.81	***$p<0.001$***	34.90±13.4[a,b,d]	***$p<0.001$***	22.98±4.68[a,b]	***$p=0.033$***	***$p<0.001$***	*$p=0.388$*	***$p<0.001$***
	a/p	7.09±1.96		9.50±3.14[a]		29.59±9.86[a,b,d]		21.06±6.30[a,b]				
σ [mm]	m/l	1.56±1.07	***$p<0.001$***	2.06±1.84	***$p<0.001$***	8.64±5.74[a,b,d]	*$p=0.681$*	7.96±1.88[a,b]	*$p=0.306$*	***$p<0.001$***	***$p=0.009$***	***$p=0.019$***
	a/p	4.27±1.66		4.95±1.96[a]		13.11±10.40[a,b,d]		8.80±5.13[a,b]				
λ	m/l	0.236±0.026	***$p<0.001$***	0.239±0.028	***$p<0.001$***	0.337±0.037[a,b]	***$p<0.001$***	0.325±0.038[a,b]	***$p=0.006$***	***$p<0.001$***	***$p<0.001$***	***$p<0.001$***
	a/p	0.258±0.027		0.273±0.030[a]		0.323±0.035[a,b,d]		0.314±0.034[a,b]				
H_1	m/l	0.594±0.177	***$p=0.010$***	0.666±0.184	*$p=0.142$*	0.772±0.161[a]	***$p=0.008$***	0.814±0.135[a,b]	***$p<0.001$***	***$p<0.001$***	***$p=0.006$***	***$p<0.001$***
	a/p	0.670±0.103[d]		0.716±0.073[a,d]		0.662±0.124[d]		0.578±0.067				
H_2	m/l	0.146±0.058	***$p<0.001$***	0.155±0.078	***$p<0.001$***	0.145±0.075	***$p<0.001$***	0.193±0.095	***$p=0.002$***	***$p=0.001$***	***$p<0.001$***	***$p<0.001$***
	a/p	0.340±0.075[b,c,d]		0.266±0.092		0.241±0.103		0.261±0.096				

Note: (1) Significant *p*-values (*$p<0.05$*) are in **bold**.

(2) *P*-values for post-hoc comparison between mediolateral and anteroposterior directions are shown adjacent to the means.

(3) *P*-values from the ANOVA are shown in the last 3 columns. *P*-values for post-hoc comparisons between conditions are not shown but qualitative results are noted (in the figures and in the table) with superscripts. Bonferroni adjustments were made when determining significance.

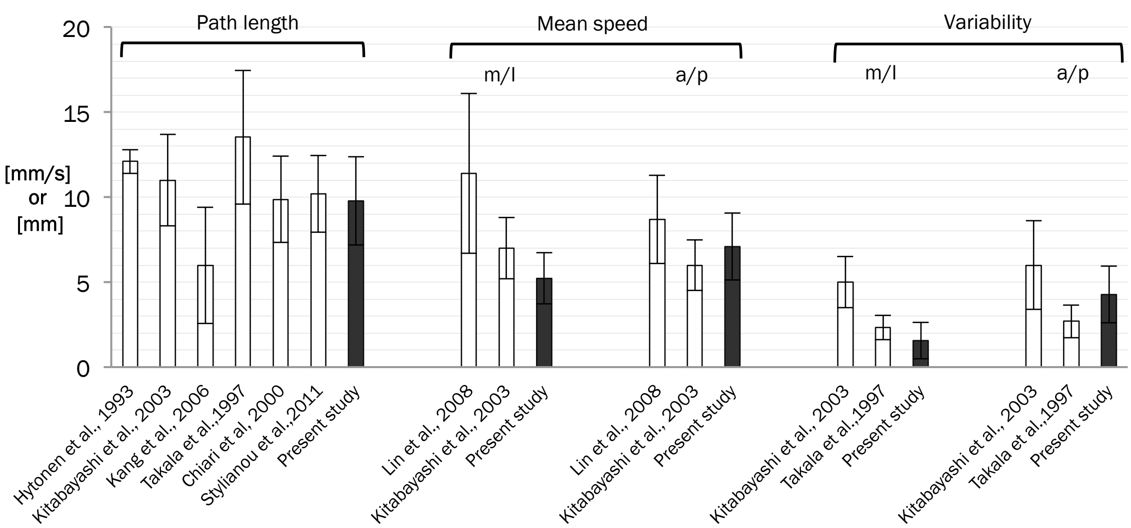
[a]significantly greater than eyes open
[b]significantly greater than eyes closed
[c]significantly greater than single leg
[d]significantly greater than tandem

3.5 Discussion

Linear measures

Position (variability) and velocity-based (path length and mean speed) linear COP measures demonstrated altered output and control when standing. Increased output and greater control requirements were evident (1) when visual input was removed, (2) when standing on a smaller base of support with reduced capacity for generating muscle force (standing on one leg versus standing on two legs), and (3) when the base of support was reduced in the mediolateral direction even though increased in the anteroposterior direction (tandem stance versus comfortable stance).

A comparison of previous studies reporting results for quiet stance with eyes open is shown in Figure 3.5.



Study		Age (range) or *mean±SD*
Chiari et al., 2000	n=12	(26,40)
Hytönen et al., 1993	n=45	(16,30)
Kang et al., 2006	n=20	40 (18,73)
Kitabayashi et al, 2003	n=220	19.8±1.8
Lin et al., 2008	n=16	20.3±1.4
Stylianou et al, 2011	n=10	23.9±2.5
Takala et al., 1997	n=265	40.6±7.7
Present study	n=32	(18,30)

Figure 3.5 Comparison of multiple studies reporting COP path length, mean speed, and variability in healthy adults during quiet stance with eyes open.

To be included, studies must have reported a clear description or equation and only those quantities that were calculated using the same equation were included (though measures may be called by a different name in their respective papers). The results of our present study are shown highlighted. Our study's results were found to be comparable with the results of previous studies.

Notwithstanding slight differences in quiet stance protocols (such as foot position and orientation), our values for linear measures were comparable to previous studies of quiet stance in healthy young adults (Chiari et al., 2000; Hytönen, Pyykkö, Aalto, & Starck, 1993; Kang & Dingwell, 2006; Kitabayashi et al., 2003; Lin, Seol, Nussbaum, & Madigan, 2008; Stylianou, McVey, Lyons, Pahwa, & Luchies, 2011; Takala, Korhonen, & Viikari-Juntura, 1997).

Studies have previously shown, with comparable measures, a destabilizing effect on quiet stance when there is a lack of visual input (Chiari et al., 2000). In our study, this effect was only seen in the anteroposterior direction. This suggests that vision plays a greater role in providing input to control anteroposterior movement than it does for mediolateral movement during quiet stance in healthy young adults.

When standing on a single leg compared to standing on two legs, not only is output altered by necessitating that torque be dealt with by only one leg, but control of output is also affected by how the single lower limb senses and integrates the work of the muscles. Consequently, position and velocity-based linear measures show markedly greater values. Previous studies have also found this to be the case, in comparable measures, when standing on one leg versus standing on two legs (Takala et al., 1997). Our findings showed that while, in tandem stance, the base of support is only reduced in the mediolateral direction, the effects (greater values of linear measures) were present in both the mediolateral and anteroposterior directions. Neuromuscular control in tandem stance is integrated for muscles in the mediolateral direction (invertors and evertors) and the anteroposterior direction (plantarflexors and dorsiflexors) around the ankle, in addition to contributions from the hip (Winter et al., 1996). In tandem stance, both the peroneus longus (an invertor) and the tibialis anterior (a dorsiflexor) are used in the control of balance (Sozzi et al., 2013). Greater path length, greater variability, and greater mean speed are a reflection of the increased challenge of integrating motor output and control in both directions during tandem stance when compared to standing comfortably.

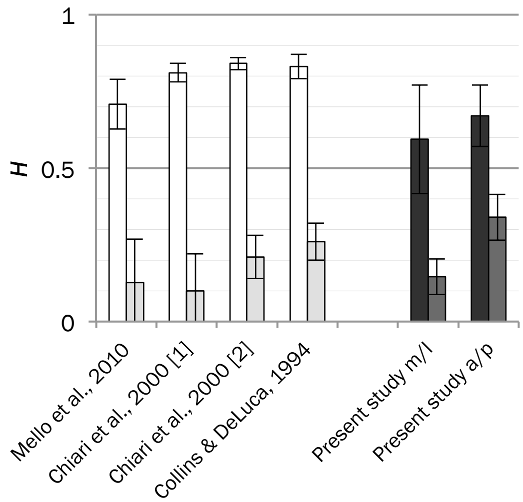
Differences in mediolateral and anteroposterior linear measures in quiet stance predominantly reflect position biomechanics. There is more demand for control in the direction with less biomechanical stability (a smaller base of support). When standing comfortably, greater anteroposterior mean speed than mediolateral was present, in contrast to tandem stance, where greater mediolateral mean speed than anteroposterior was present. When standing comfortably, this finding was similarly present—greater position variability demonstrated the effect of control on output. Single leg stance demonstrated a greater need for control (mean speed) in the mediolateral direction than in the anteroposterior, but not in the resulting output (variability). This suggests the mediolateral direction is less biomechanically stable than the anteroposterior and requires more regulation in single leg stance. This increased requirement is well met by the system and thus does not affect the output of the system.

Non-linear measures

The largest Lyapunov exponent demonstrated that removing visual input resulted in decreased local stability. Studies that have looked at both variability and the largest Lyapunov exponent to quantify quiet stance stability in healthy young adults have come to the same conclusion (Donker et al., 2007). We found agreement between variability and largest Lyapunov exponent results, but in addition, the largest Lyapunov exponent demonstrated that mediolateral local stability was reduced when compared to anteroposterior when standing on one leg or in tandem stance. These results supported conclusions that were drawn from mean speed and variability together, and thus, appeared to represent both output and control information.

In previous quiet stance studies of healthy young adults, there has been some inconsistency with respect to reported results for the largest Lyapunov exponent—considerably different values across studies—in the range of 1.6 to 1.9 (Donker et al., 2007), between 0.16 and 0.22 (Huisinga, Yentes, Filipi, & Stergiou, 2012), and 0.30±0.15 (Ladislao & Fioretti, 2007). Our findings are more consistent as they ranged from 0.24 to 0.27. It is unclear why one study found values that were larger by approximately a factor of five to ten despite similar methodology, but these inconsistencies emphasize the need for further investigation.

Similar to previous studies, our scaling results also showed that there are two regions, one with persistent behaviour in the short-term and the other with anti-persistent behaviour in the long-term (Chiari et al., 2000; Collins & De Luca, 1994; Mello, Oliveira, & Nadal, 2010). A comparison of previous scaling results when standing with eyes open is shown in Figure 3.6.



Study		Age (range) or *mean±SD*
Collins & DeLuca, 1994	n=10	22±2
Chiari et al., 2000	n=12	(26,40)
Mello et al., 2010	n=17	23.1±3.6
Present study	n=32	(18,30)

Figure 3.6 Comparison of multiple studies reporting scaling in healthy adults during quiet stance with eyes open. To be included, studies must have reported two scaling regions. Note: i) These studies report results using resultant COP, whereas our study reports mediolateral and anteroposterior separately. ii) Chiari et al. (2000) report two methods. Our study's results were comparable to the other studies.

We were able to extend this finding to multiple stance positions including single leg and tandem stance. Two regions of scaling suggest that at least two different time scales of control exist in balance regardless of stance position. While our study examined only healthy young individuals, we were able to see similarities across conditions (i.e., similar long-term scaling), which indicates robustness of this measure in healthy individuals.

"Irregularity and unpredictability" are important in healthy systems (Goldberger, Rigney, & West, 1990). Unpredictability, regardless of its dynamical origin, can be a desired trait—one that facilitates control—in physiological systems. Collins and De Luca (1994) describe, in terms of postural control, a system that is allowed "sloppiness" or to "drift" in the short-term. Therefore, deviations from random may reflect changes in control. If this is the case, our scaling results suggest that short-term differences in randomness may be control-related. Short-term scaling was least complex (closer to random walk) in the mediolateral direction when standing comfortably with eyes open and in the anteroposterior direction when standing in tandem stance. We hypothesize that control mechanisms may operate similarly along each position's stable direction, and in that stable direction, neural mechanisms may require less active or "ON" time. In the long-term, mediolateral scaling was always more complex than anteroposterior scaling, perhaps indicating that more control was "ON" in the mediolateral direction to deal with the asymmetries of muscle output in that direction. At the very least, it is clear that scaling parameters present additional and different information about quiet stance.

3.6 Conclusion

Quiet stance is a simple but nevertheless complex task that depends simultaneously on biomechanical stability and neural control. The use of both linear and non-linear measures in the evaluation of quiet stance continues to be an avenue that warrants further investigation in pathologies or injuries where balance may be affected. This study contributes to the field by providing non-linear data for additional quiet stance positions: single leg and tandem stance.

Acknowledgements

We would like to extend our thanks to the volunteers for participating in this study. We would also like to thank Coralie Rochefort for assisting in data collection.

Funding

The first author was supported by scholarships provided by the Government of Ontario (QEIIGSST, OGS) and by the University of Ottawa.

Conflicts of Interest Statement

There are no conflicts of interest to disclose.

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4. Changes to Centre of Pressure in Quiet Stance After Mild Traumatic Brain Injury in Young Adult Football Players

(submitted to Gait & Posture)

Changes to Centre of Pressure in Quiet Stance After Mild Traumatic Brain Injury in Young Adult Football Players

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4.1 Abstract

Centre of pressure (COP) timeseries analysis is well suited to the evaluation of balance control. Changes to COP variables can provide information about neuromuscular control and to controlling mechanisms of balance. Mild traumatic brain injury (mTBI) often results in functional impairments including balance impairments that are likely due to altered signalling within the brain. Altered mechanisms affecting balance after mTBI are likely to be reflected in changes to linear and non-linear COP measures. University football players (n=74) were tested prior to the start of the season as a baseline and were retested during the season if they sustained an mTBI (n=6, tested an average of 15.7±7.2 days after injury). Players who did not sustain an mTBI were also retested at the end of the season for comparison (n=17). Participants were asked to stand quietly with their eyes closed for 90 seconds on a portable force platform. Linear and non-linear measures were calculated for COP timeseries, however, the scaling parameter was the only measure to show meaningful significant differences in individuals with mTBI. COP path length, mean speed, variability, and the largest Lyapunov exponent did not. Specifically, short-term scaling became significantly more complex (farther from random walk) in individuals who had sustained mTBIs indicating that, while the overall ability to maintain balance did not appear to be altered, subtle changes to balance control were present after mTBI.

Keywords: Centre of pressure, quiet stance, balance control, scaling, self-similarity, largest Lyapunov exponent, mTBI, concussion

4.2 Introduction

Mild traumatic brain injuries (mTBIs) are the result of forces causing acceleration or deceleration of the head and brain; the injury results in functional impairments including balance impairments (Ontario Neurotrauma Foundation, 2013; McCrory et al., 2013). Both clinical measures of balance and non-clinical measures that quantify body motion during balance have been used to investigate the effect of mTBI. A scoping review of the effects resulting from mTBI showed clinical measures such as the Balance Error Scoring System and the Sensory Organization Test are able to show balance impairments from the time of injury up to five days after injury, while quantitative measures, dual-tasks, and virtual reality paradigms used to evaluate balance are able to show impairments up to 30 days after injury (Walters-Stewart, Marshall, & Sveistrup, 2016).

Centre of pressure (COP) is well suited to the evaluation of balance because it represents the neuromuscular control of the centre of mass in balance (Milton et al., 2009; Winter, Prince, Frank, Powell, & Zabjek, 1996). Typical COP variables such as position (and related measures such as range, variability, etc.) and velocity have been used to quantify postural sway and determine postural performance in health (Masani, Popovic, Nakazawa, Kouzaki, & Nozaki, 2003; Winter, 1995) and in individuals with mTBI (Powers, Kalmar, & Cinelli, 2014). These linear measures are of low order and reflect mostly the spatial characteristics of COP. On the other hand, non-linear measures can quantify the local stability (largest Lyapunov exponent) and the nature of temporal scaling (scaling parameter) in COP. The largest Lyapunov exponent quantifies the "divergence of initially close state space trajectories" (Rosenstein, Collins, & De Luca, 1993). The scaling parameter quantifies self-similar correlations at different time scales in the timeseries. The value of the scaling parameter (H) can be compared to known values of certain scaling properties such as random walk (H=0.5), persistent power law correlation (0.5<H<1.0), and anti-persistent power law correlation (0<H<0.5) (Peng, Havlin, Stanley, & Goldberger, 1995). We describe dynamics associated with H values that are closer to 0.5, i.e., closer to random walk, as being less complex, and those for values of H that are farther from 0.5 as more complex.

Extensive arguments have been made for the use of both linear and non-linear dynamic measures for a better understanding of underlying dynamics of movement (Stergiou & Decker, 2012).

Stergiou and Decker (2012) explain that while linear measures assume that a central value (the mean, for example) is correct and deviations from this value are errors, it is in fact the variations around the central value that represent control; therefore, non-linear measures offer tools for investigation of the temporal organization of variation in movement.

In a previous study, linear and non-linear measures were used to explore differences in balance control and output in various quiet stance positions in healthy young adults (Walters-Stewart, Longtin, & Sveistrup, 2016). The purpose of the present study was to determine if the same position- and velocity-based linear measures and non-linear COP measures can be used to identify changes to balance control in individuals who have sustained an mTBI. It was hypothesized that these COP measures would reflect altered balance after mTBI. Preliminary data were presented at the World Congress on Medical Physics and Biomedical Engineering 2015 (Walters-Stewart, Longtin, & Sveistrup, 2015).

4.3 Methods

Participants

Healthy elite athletes (University of Ottawa Men's Football Team) were invited to participate in this study and were tested at pre-season training camp (n=74, height 1.82±0.07m, weight 92.1±14.7kg). No participants reported any injuries at the time of testing. Individuals who suffered an mTBI during the course of the season were retested (n=6, height 1.84±0.09m, weight 99.0±11.9kg). These individuals were identified by the team athletic trainer and the diagnosis of mTBI was confirmed by the team physician. Testing occurred an average of 15.7±7.2 days after injury. After the end of the season (approximately 5 months after pre-season testing) players were invited for retesting (n=17, height 1.79±0.04m, weight 85.8±4.8kg). For data analysis, groups were divided as follows (an overview is provided in Table 4.1a): Baseline—pre-season values of the subset of participants who would later sustain mTBIs during the season (mTBI, n=6) and pre-season values of the subset of participants who were retested at the end of the season (Healthy, n=17)—and Post- —post-mTBI values of participants (mTBI, n=6) tested during the season after sustaining an mTBI (see Table 4.1b) and post-season values of participants (Healthy, n=17) tested at the end of the season who did not sustain an mTBI. At Baseline, Team (n=74) values are shown for reference in each figure.

Table 4.1a Testing groups

	Groups		
	mTBI (subset, n=6)	Healthy (subset, n=17)	Team (n=74)
Baseline	pre-season	pre-season	pre-season
Post-	post-mTBI	post-season	

Table 4.1b Testing group (mTBI)

Player	Days after injury	Returned to play at time of testing
mTBI 1	11	yes
mTBI 2	23	no
mTBI 3	5	no
mTBI 4	23	yes
mTBI 5	13	no
mTBI 6	19	yes

Data collection

Data were captured using the Nintendo Wii Balance Board. The use of the Wii Balance Board has been validated in previous studies (Clark et al., 2010; Huurnink, Fransz, Kingma, & van Dieën, 2013). A laptop computer with Bluetooth and an open-source programmable input emulator (GlovePIE v0.43, glovepie.org) was used to script a program for data acquisition (f=60Hz). Raw sensor data from the four load cells located at each corner of the platform were converted to net COP in MATLAB 2013a (Mathworks Inc., Natick, Massachusetts).

Each participant was asked to stand quietly with eyes closed for T=90 seconds which is the minimum recommended length for reliable results (Ruhe, Fejer, & Walker, 2010). The participant was asked to place each foot in the Balance Board's demarcated area for foot placement (located 135mm apart) to ensure that, in subsequent testing sessions, participants maintained similar foot positioning.

Data analysis

COP data analysis was carried out in MATLAB (2013a) with additional material from MATLAB Central (Chu Chen, 2008; Mirwais, 2012a, 2012b). COP timeseries—mediolateral, x_i, and anteroposterior, y_i, where i=1, 2,…, N and N=Tf—were used to calculate measures as presented in Table 4.2. A second-order, low-pass Butterworth filter with a cut-off frequency of 10Hz was applied to each timeseries before calculating linear measures (normalized path length, mean speed, and variability), except where noted. The largest Lyapunov exponent, λ, and scaling parameter, H, (Taqqu, Teverovsky, & Willinger, 1995) were calculated using unfiltered timeseries. Scaling parameter estimates—a short-term region, H_1, and a long-term region, H_2—were calculated as previously described (Chapter 3 (Methods); Walters-Stewart, Longtin, &

Sveistrup, 2015a). Surrogate scaling values (calculated on randomized versions of the COP timeseries) were also calculated as previously described—they were verified to be approximately equal to 0.5 and statistically different from calculated H values (p<0.05).

Table 4.2 COP measures

Measure	Symbol	Equation/Method	Description
Path length (normalized)	l	$\frac{1}{T}\sum_{i=1}^{N}\sqrt{(x_{i+1}-x_i)^2+(y_{i+1}-y_i)^2}$	The timeseries is normalized by the total time, T, to account for minor differences in length (number of samples); it can also be considered an estimate of average speed.
Mean speed	($\bar{u}_x$, $\bar{u}_y$)	$u=\left(\frac{\lvert x_{i+1}-x_i\rvert}{t_s},\frac{\lvert y_{i+1}-y_i\rvert}{t_s}\right)$	Mean speed (the mean instantaneous speed of the timeseries), unlike velocity, disregards direction when the absolute value (or square root of the squared velocity) is taken to avoid having the negative and positive values cancel. Unlike path length, it is calculated at each time step. Note: $t_s=1/f$.
Variability	(σ_x, σ_y)	$\left(\sqrt{\frac{1}{N-1}\sum_{i=1}^{N}(x_i-\bar{x})^2},\sqrt{\frac{1}{N-1}\sum_{i=1}^{N}(y_i-\bar{y})^2}\right)$	Variability of the COP timeseries is represented by the standard deviation.
Largest Lyapunov exponent (local stability)	(λ_x, λ_y)	Rosenstein's algorithm (Rosenstein, Collins, & De Luca, 1993)	The largest Lyapunov exponent estimates the local stability of the timeseries by quantifying the exponential divergence of initially close trajectories (the largest overtakes all others and is representative of the evolution of the state space volume). The algorithm uses the embedding dimension, lag determined by false nearest neighbours (Kennel, Brown, & Abarbanel, 1992) and the mean period of the timeseries.
Scaling	(H_x, H_y) for each region	Multiple methods were averaged to yield an estimate: Aggregated variance, Absolute values, Rescaled range (R/S) (Rea, Oxley, Reale, & Brown, 2009; Taqqu et al., 1995)	The scaling parameter quantifies self-similar correlations within the timeseries at different time scales. Each method uses the original, differenced, or summed series, as appropriate, depending on classification of the series as fractional Gaussian noise or fractional Brownian motion.

Statistical analyses were performed in MATLAB and SPSS. At Baseline, pre-season means of the mTBI subset and Healthy subset were compared using an independent t-test for each measure (significant when p>0.05). Paired t-tests were used to compare between Baseline and Post- within each group. Difference scores between Baseline and Post- for each group (mTBI and Healthy) were computed and also compared between groups using independent t-tests.[3] Because of the unequal sample sizes of the two groups, an independent t-test for unequal variances was used

[3] While an ANOVA would provide the same results, a time comparison might suggest the two time periods were equal. This method (change/gain/difference score analysis) yields equivalent statistical results to a 2x2 ANOVA with repeated measures since a paired t-test is simply a repeated measures ANOVA with only 2 levels. The independent t-test of the difference score yields the same results as the group*time interaction of the 2x2 ANOVA.

where necessary.

4.4 Results

Similar baseline for mTBI and healthy groups

Numerical COP results measures can also be found in the appendix (4.8). The pre-season linear and non-linear measures of the players who would later sustain an mTBI were similar to the other players with the exception of path length. No significant differences were found between healthy and mTBI pre-season mediolateral mean speed (Figures 4.1B, *p=0.147*, 95% CI [-0.38, 2.39]), anteroposterior mean speed (Figure 4.1C, *p=0.123*, 95% CI [-1.78, 11.51]), mediolateral variability (Figure 4.1D, *p=0.926*, 95% CI [-1.98, 1.81]), and anteroposterior variability (Figure 4.1E, *p=0.144*, 95% CI [-0.56, 3.63]).

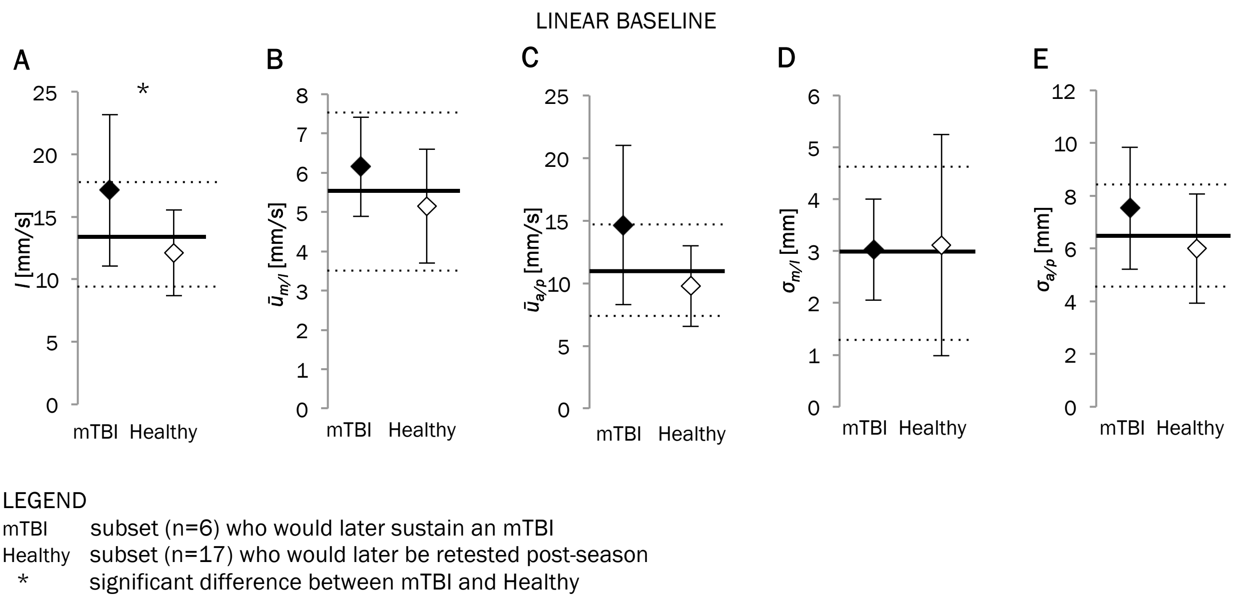

Figure 4.1 Comparison between pre-season linear COP measures (mean±SD).
Path length (l), mediolateral mean speed ($\bar{u}_{m/l}$), anteroposterior mean speed ($\bar{u}_{a/p}$), mediolateral variability ($\sigma_{m/l}$), and anteroposterior variability ($\sigma_{a/p}$). The team (n=74) mean and SD are shown with solid and broken lines, respectively. At the pre-season baseline only path length was significantly different between the mTBI (filled diamonds) and healthy (open diamonds) groups.

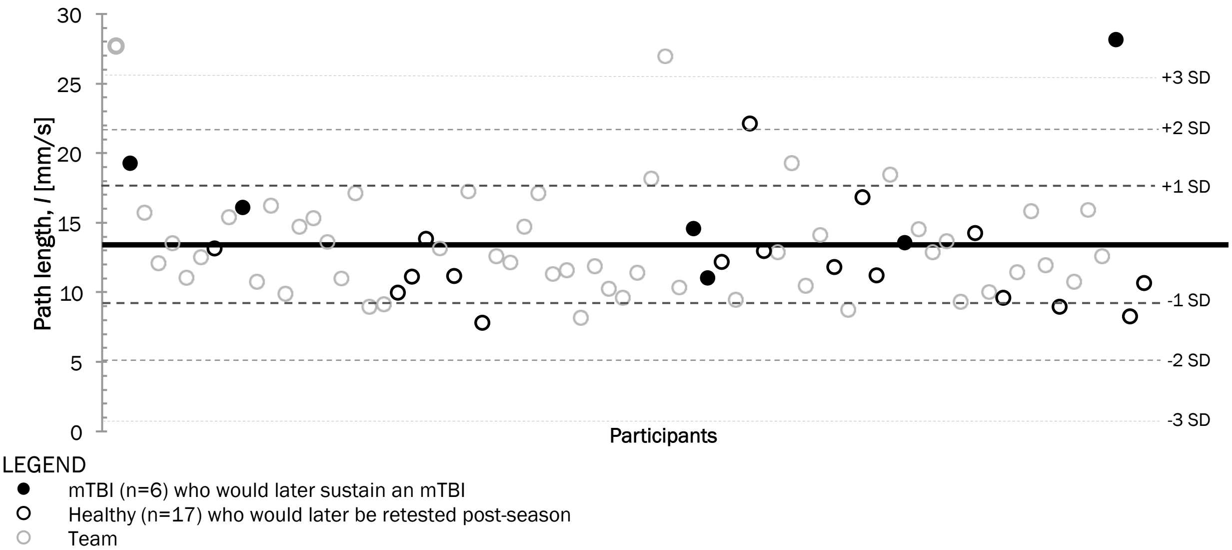

Figure 4.2 Pre-season path length for the team. Subsets are highlighted (mTBI and healthy).
Neither the mTBI nor the healthy subset displays a trend that stands out. The team mean is shown with a solid black line. Points are separated horizontally only for clarity.

The mTBI group's pre-season path length was significantly greater than that of the healthy group (Figure 4.1A, $p=0.021$, 95% CI [-1.78, 11.51]). Figure 4.2 shows how the path length of the players who sustained mTBIs compares to the path length of their teammates. No significant differences were found between healthy and mTBI pre-season mediolateral (Figure 4.3A, $p=0.063$, 95% CI [-0.001, 0.021]) or anteroposterior largest Lyapunov exponent (Figure 4.3B, $p=0.805$, 95% CI [-0.011, 0.014]). Nor were significant differences found between healthy and mTBI pre-season mediolateral (Figure 4.3C; H_1, $p=0.301$, 95% CI [-0.183, 0.059] & H_2, $p=0.450$, 95% CI [-0.039, 0.086]) or anteroposterior scaling (Figure 4.3D; H_1, $p=0.927$, 95% CI [-0.076, 0.083] & H_2, $p=0.496$, 95% CI [-0.106, 0.053]).

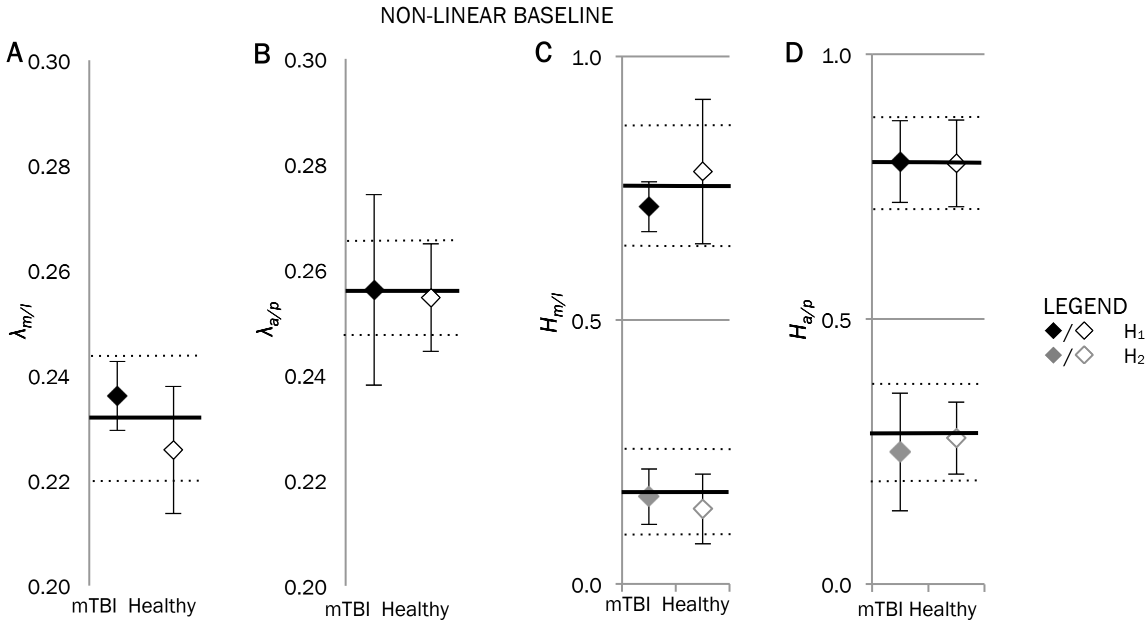

Figure 4.3 Comparison between pre-season non-linear COP measures (mean±SD).
Largest Lyapunov exponents (λ), short-term (H_1>0.5), and long-term (H_2<0.5) scaling parameters in the mediolateral (m/l) and anteroposterior direction (a/p). The team (n=74) mean and SD are shown with solid and broken lines, respectively. There are no significant differences between the mTBI (filled diamonds) and the healthy (open diamonds) group's largest Lyapunov, short-term, or long-term scaling measures.

mTBI vs. healthy

Linear measures

No significant differences were found between pre-season and post-mTBI for any linear measures. Non-significant decreases in path length (Figure 4.4A, *p=0.057*, 95% CI [-0.20, 8.81]), mediolateral mean speed (Figure 4.4B, *p=0.289*, 95% CI [-0.84, 2.29]), and anteroposterior mean speed (Figure 4.4C, *p=0.053*, 95% CI [-0.10, 8.67]) were present for the mTBI group. No change was apparent from pre-season to post-mTBI in mediolateral variability (Figure 4.4D, *p=0.988*, 95% CI [-1.61, 1.60]) or anteroposterior variability (Figure 4.4E, *p=0.973*, 95% CI [-5.11, 4.97]) in the mTBI group.

In the healthy group, no significant differences were found between pre-season and post-season path length (Figure 4.4A, *p=0.842*, 95% CI [-1.57, 1.90]), mean speed (Figure 4.4B, *p=0.328*, 95% CI [-0.43, 1.22] & 4.4C, *p=0.852*, 95% CI [-1.58, 1.32]), or variability (Figure 4.4D, *p=0.602*, 95% CI [-0.94, 1.56] & 4.4E, *p=0.547*, 95% CI [-0.77, 1.40]).

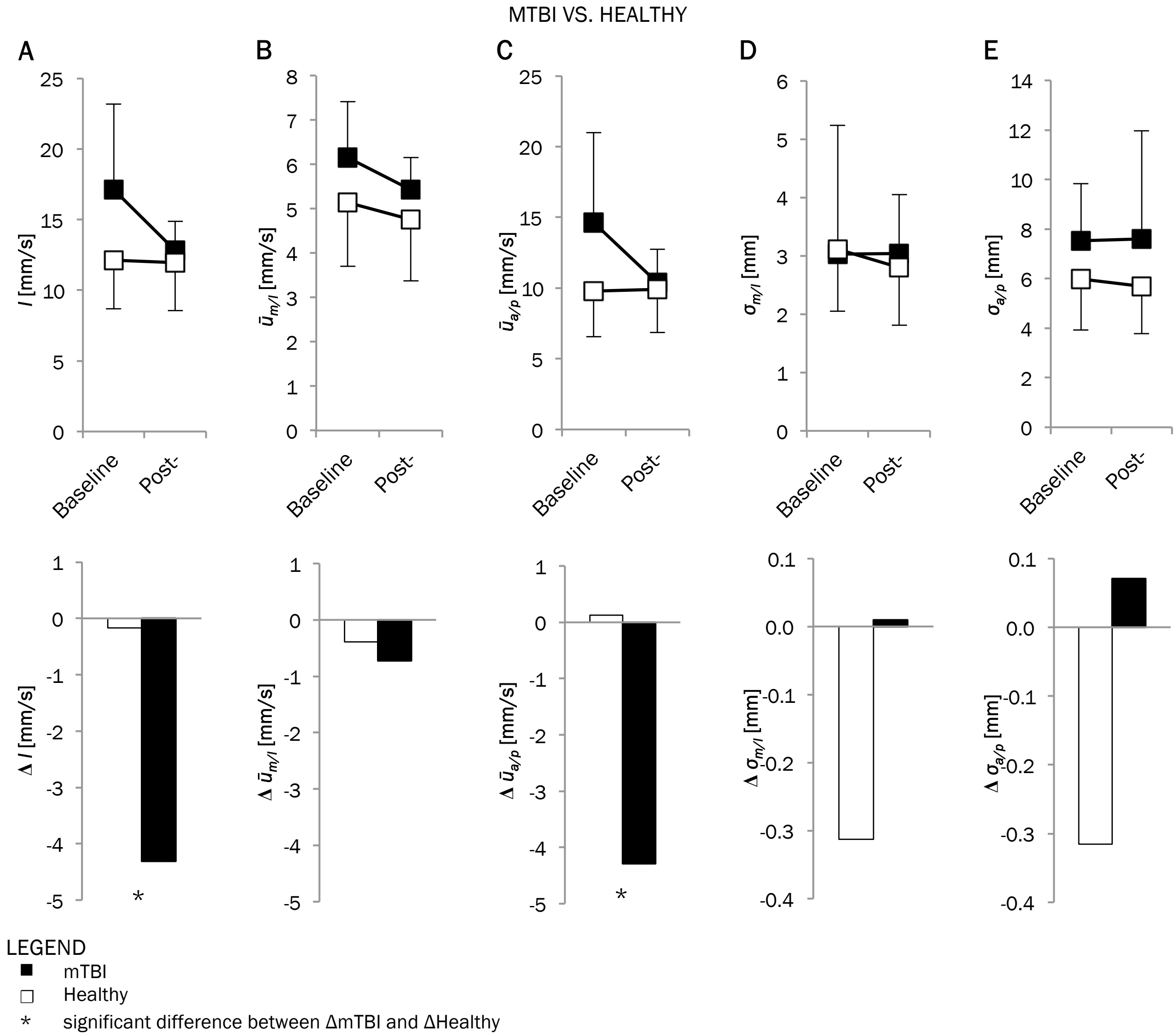

Figure 4.4 Comparisons between mTBI and healthy, baseline and post- (post-season/post-mTBI) linear COP measures (mean±SD).
Path length (l), mediolateral mean speed ($\bar{u}_{m/l}$), anteroposterior mean speed ($\bar{u}_{a/p}$), mediolateral variability ($\sigma_{m/l}$), and anteroposterior variability ($\sigma_{a/p}$). Differences (Δ) are presented in the bottom row. Note the scale varies. Though significant differences were found in the difference in trends between the mTBI and healthy group for path length and anteroposterior mean speed, neither the mTBI group nor the healthy group displayed any significant differences between their baseline and post-mTBI and baseline and post-season values, respectively.

Despite the lack of statistical significance above, the trend from pre-season to post-injury differed from the trend from pre- to post-season in some linear measures. Difference scores (also in Figure 4.4) of the mTBI group were significantly different from those of the healthy group for path length ($p=0.025$, 95% CI [-0.77, -0.57]) and anteroposterior mean speed ($p=0.008$, 95% CI [-7.57, -1.26]). Difference scores of the mTBI group were not significantly different from those of the healthy group in anteroposterior mean speed ($p=0.667$, 95% CI [-1.88, 1.23]), mediolateral variability (*p=0.765*, 95% CI [-1.89, -2.54]), and anteroposterior variability (*p=0.855*, 95% CI [-4.64, 5.41]).

Non-linear measures

Largest Lyapunov exponent

The largest Lyapunov exponents (Figure 4.5) of both groups demonstrated a similar change from baseline—increased mediolateral local stability and decreased anteroposterior local stability. The post-mTBI and post-season mediolateral largest Lyapunov exponents were significantly less than pre-season (*p=0.001*, 95% CI [0.010, 0.020] & (*p=0.023*, 95% CI [0.001, 0.015], for the mTBI and healthy groups, respectively). While the post-mTBI anteroposterior largest Lyapunov exponent was not significantly different from the pre-season (*p=0.158*, 95% CI [-0.029, 0.006]), the post-season was (*p=0.004*, 95% CI [0.020, 0.005]). Thus, difference scores of the mTBI group were not significantly different from those of the healthy group in either the mediolateral (*p=0.087*, 95% CI [-0.015, 0.001]) or anteroposterior directions (*p=0.896*, 95% CI [-0.016, 0.014]).

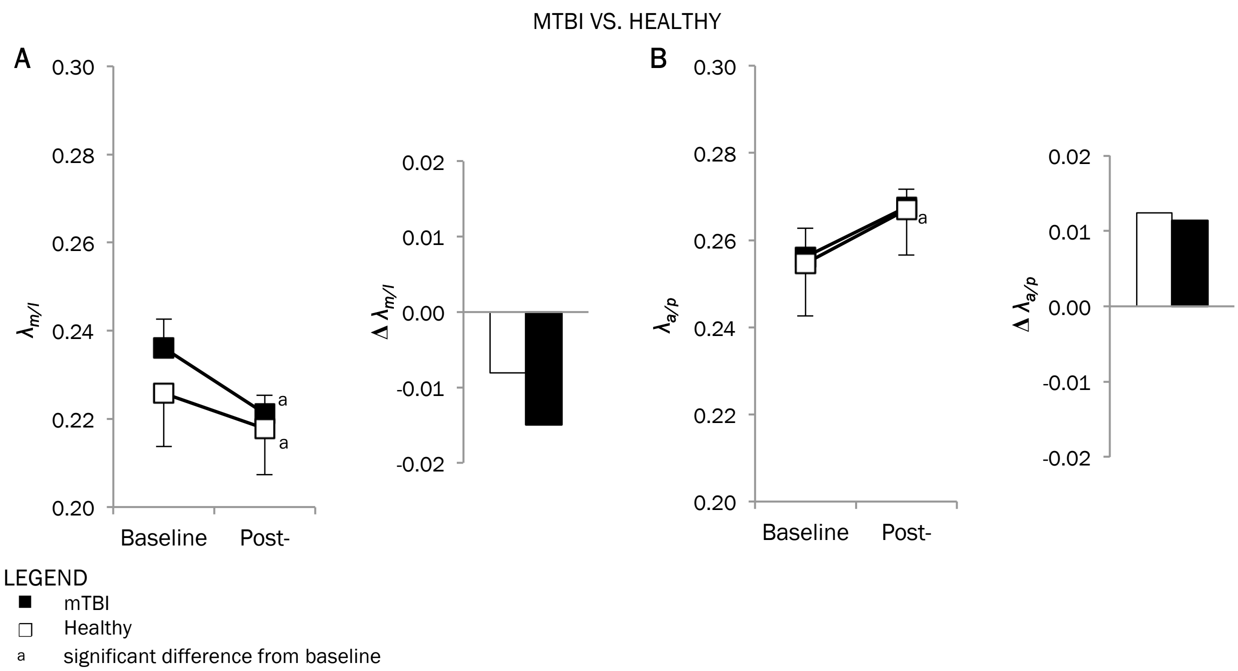

Figure 4.5 Comparisons between mTBI and healthy, baseline and post- (post-season/post-mTBI) largest Lyapunov exponent

$\lambda_{m/l}$ and $\lambda_{a/p}$—mediolateral and anteroposterior, respectively (mean±SD). Differences (Δ) between baseline and post- are also presented. Both the mTBI group and the healthy group demonstrated changes in their post-mTBI/post-season values of largest Lyapunov exponents from pre-season values in the mediolateral direction. The healthy group also demonstrated a significant change in the largest Lyapunov exponent from pre-season to post-season. No difference in trend was found between the two groups.

Scaling

COP timeseries demonstrated short-term persistence (H_1 was greater than 0.5) and long-term anti-persistence (H_2 was less than 0.5) as expected. The majority of regions were classified as fractional Brownian motion (Team (pre-season): 93.9%, post-mTBI: 87.5%, post-season: 94.1%).

Post-mTBI mediolateral short-term COP scaling was more complex than pre-season ($p=0.045$, 95% CI [0.006, 0.336]) while remaining consistent from pre-season to post-season ($p=0.400$, 95% CI [-0.147, 0.061]). Conversely, post-mTBI anteroposterior short-term scaling remained consistent with pre-season scaling ($p=0.196$, 95% CI [-0.021, 0.079]) while post-season anteroposterior short-term scaling was less complex than pre-season ($p=0.026$, 95% CI [-0.070, -0.005]) from baseline. Therefore, the difference scores indicated the trend from pre-season to post-mTBI differed significantly from the trend from pre- to post-season in the mediolateral

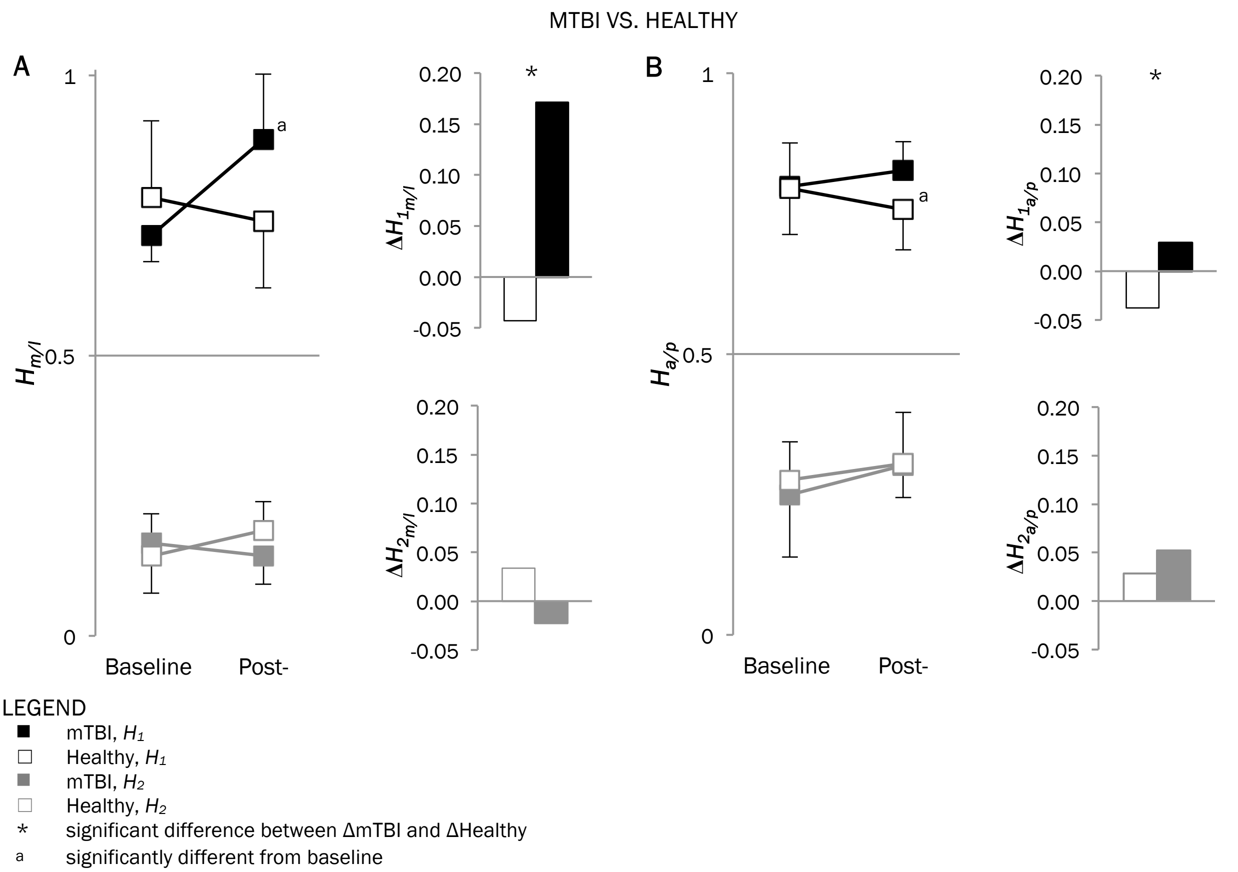

Figure 4.6 Comparisons between mTBI and healthy, baseline and post- (post-season/post-mTBI) scaling. Short-term (H_1>0.5) and long-term (H_2<0.5) scaling parameters in the mediolateral and anteroposterior direction (mean±SD). Differences (Δ) between baseline and post- are also presented. Short-term mediolateral scaling for the mTBI group was significantly different post-mTBI from pre-season. Anteroposterior short-term scaling was significantly different for the healthy group post-season from pre-season. This resulted in significantly different short-term scaling trends betwenn the mTBI and healthy groups. Significant differences are p<0.05.

(*p=0.030*, 95% CI [0.023, 0.405]) and anteroposterior directions (*p=0.029*, 95% CI [0.007, 0.125]) (also Figure 4.6).

No significant differences were found in long-term scaling (*p=0.426*, 95% CI [-0.090, 0.045] & *p=0.340*, 95% CI [-0.075, 0.180], mediolateral and anteroposterior, respectively) between pre-season and post-mTBI or between pre- and post-season (*p=0.059*, 95% CI [-0.001, 0.069] & *p=0.130*, 95% CI [-0.010, 0.068], mediolateral and anteroposterior, respectively). Therefore, the difference scores of the mTBI group did not differ significantly from the healthy group in either the mediolateral (*p=0.092*, 95% CI [-0.123, 0.010]) or the anteroposterior (*p=0.583*, 95% CI [-0.064, 0.111]) directions.

4.5 Discussion

In this study, both linear and non-linear measures showed players who would later be injured had similar balance characteristics to their teammates before the start of the season (as described by 10 of the 11 measures). Mean speed and variability were not altered from baseline by mild traumatic brain injury or by regular season activities, though some trends showed differences between players with and without mTBI. Local stability was altered, but similarly in both players with and without mTBI. Short-term scaling was altered by mild traumatic brain injury or by regular season activities, albeit differently—more complex in players with mTBI and less complex in players without. To our knowledge, the largest Lyapunov exponent and scaling parameter had not been previously used to investigate changes to COP in mTBI.

Our results for linear measures were comparable to previous results of healthy young adults (in quiet stance with eyes closed) (Chapter 3; Walters-Stewart, Longtin, & Sveistrup, 2015a). The pre-season mean path length for the mTBI group was greater than the healthy group's, but this was likely due to one player in the group who had a much greater path length than the others (see Figure 4.3). This effect was likely compounded by the small sample size. Two other players also had very large values for path length (one in the healthy group, one in the team); they affected the other group's mean values to a lesser extent. On the other hand, these three players may have had altered balance as a result of unreported injuries.

In a previous study that examined quiet stance COP in concussed university football players, increased anteroposterior displacement was found in the acute phase and increased anteroposterior velocity was found when players returned-to-play (Powers et al., 2014). Our study yielded different findings. In fact, players with mTBI demonstrated a decreased anteroposterior speed (magnitude of velocity). Several reasons for these seemingly contradictory findings may exist—(1) In our study, players who later sustained an mTBI demonstrated slightly greater (non significantly) anteroposterior COP velocity at baseline, yet post-mTBI values were on-par with the healthy group. This tendency was also seen in path length (which, as previously stated, can be considered an estimate of average speed) and mediolateral mean speed. (2) A wide range of values and considerable variation can exist in results for normal COP speed making it difficult to distinguish between healthy or impaired. (3) On the other hand, our study was limited by a smaller sample size for the mTBI group than Powers et al.'s (2014) study (in which they had nine injured individuals compared to our six). (4) Powers et al. (2014) tested players acutely (a mean of five days) and at return-to-play (a mean of 26 days). In our study, players were tested a mean of 16 days after injury and were at various stages (rest, practice only, returned to play). From a scoping review, we also know that mTBI can cause transient and different effects at different post-mTBI durations (Chapter 2; Walters-Stewart, Marshall, & Sveistrup, 2015). (5) Lastly, it is not known whether different mechanisms of injury cause different effects resulting in different changes to COP.

Powers et al. (2014) suggested that higher order measures are better able to discern differences between healthy and mTBI groups, which our results supported to some extent—some differences were demonstrated in velocity-based measures, none were demonstrated in position-based measures such as variability (velocity is one order higher than position). Non-linear measures also seem promising. Cavanaugh et al. (2006) previously used non-linear approximate entropy to determine that the COP of concussed athletes was more regular (decreased approximate entropy) when compared to their pre-season values. Like most non-linear studies, it was concluded that additional information was required to explain the results, but that the results themselves were interesting enough to merit further investigation (Cavanaugh et al., 2006).

Significant changes to local stability, a combination of both output and control (Chapter 3 (Discussion); Walters-Stewart, Longtin, & Sveistrup, 2015a), were demonstrated between pre- and post-season for healthy and pre-season and post-mTBI, but the trends were similar. This may indicate the largest Lyapunov exponent is not robust enough, is too sensitive for this particular application, or is not specific enough to isolate changes arising from mTBI from normal changes to local stability. Or, perhaps no changes to local stability arise from mTBI and the changes to local stability are the effect of regular season activities.

The scaling parameter demonstrated meaningful significant differences between health and mTBI where the Lyapunov exponent did not. Short-term scaling was less complex in players with mTBI and more complex in those without. Furthermore, opposite trends from baseline were evident in the respective groups. Complexity is a prominent and likely important feature of balance. We've previously investigated how changes to complexity affect control; more complexity may mean more active control is being employed in balance (Walters-Stewart, Longtin, & Sveistrup, 2015a). Others have suggested that healthy systems benefit from "chaotic temporal variations" as a way to allow flexibility and adaptation (Stergiou & Decker, 2012). Our findings also provide support for the idea that complexity is a feature of health and that a change in complexity may indicate a change to health.

While this study had a small sample size for the injured since the number was limited by the number of players who were injured during the course of the season, it was not uncommonly small when compared to similar studies (Powers et al., 2014). While the ability to demonstrate significant changes might have been limited by the small sample size, we were nevertheless, able to show significant findings. These findings suggest further investigation of the effect of mTBI on the scaling behaviour of COP is warranted.

4.6 Conclusion

While balance does not appear to be drastically altered after mTBI, in players who sustained mTBIs changes were indeed present. Though players with mTBI did not visibly demonstrate any difficulty remaining upright and linear COP measures did not show changes after mTBI that would suggest impairment or difficulty, the ability of linear measures to demonstrate significant changes might have been limited by the small sample size of the mTBI group. The scaling parameter was not similarly limited and showed that subtle changes to balance do occur. In particular, changes to scaling suggested that control mechanisms contributing to balance are affected by mTBI. Yet, whether these changes are indicative of impairment or of compensatory adaptation is an important issue for future discussion and further study.

Acknowledgements
We would like to extend our thanks to the volunteers for participating in this study.

Funding
The first author was supported by scholarships provided by the Government of Ontario (QEIIGSST, OGS) and by the University of Ottawa.

Conflicts of Interest Statement
There are no conflicts of interest to disclose.

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4.8 Appendix

Table 4.3 COP results for players with and without mTBI (mean±SD)

Measures		mTBI (n=6) Baseline	mTBI (n=6) post-mTBI	Healthy (n=17) Baseline	Healthy (n=17) End-of-season	Team (n=74) Baseline
l [mm/s]		17.12±6.06	12.81±2.08	12.12±3.45	11.95±3.39	13.41±4.18
$\bar{u}$ [mm/s]	m/l	6.15±1.26	5.43±0.73	5.15±1.45	4.76±1.38	5.54±2.01
	a/p	14.65±6.35	10.36±2.37	9.79±3.22	9.92±3.07	10.97±3.64
σ [mm]	m/l	3.03±0.98	3.04±1.23	3.11±2.13	2.80±1.25	2.99±1.65
	a/p	7.53±2.31	7.60±4.38	5.99±2.03	5.68±1.90	6.48±1.95
λ	m/l	0.236±0.007	0.221±0.004	0.226±0.012	0.218±0.010	0.232±0.013
	a/p	0.256±0.018	0.268±0.011	0.255±0.010	0.267±0.014	0.256±0.012
H_1	m/l	0.715±0.047	0.886±0.116	0.782±0.137	0.739±0.118	0.753±0.119
	a/p	0.798±0.077	0.827±0.051	0.795±0.082	0.757±0.072	0.797±0.075
H_2	m/l	0.165±0.053	0.143±0.051	0.142±0.066	0.188±0.051	0.167±0.082
	a/p	0.249±0.111	0.302±0.057	0.276±0.068	0.305±0.092	0.277±0.094

Note: Players in the mTBI and healthy groups are subsets of the players in the team group.

5. Centre of Pressure During Quiet Stance and Dual-task 1 Month After Mild Traumatic Brain Injury: Adolescents

(submitted to Experimental Brain Research)

Centre of Pressure During Quiet Stance and Dual-task 1 Month After Mild Traumatic Brain Injury: Adolescents

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5.1 Abstract

Mild traumatic brain injury is a common neurological condition affecting adolescents in North America. The purpose of this study was to investigate balance in adolescents with mTBI using linear and non-linear COP measures in quiet stance and in a dual-task. A control group of healthy adolescents (n=22) were tested once. Adolescents between 13 and 18 years of age who had been diagnosed with mTBI (n=25) were also tested once, approximately one month post-injury in four conditions: standing with eyes open, standing with eyes closed, standing on a single leg, and standing while performing a visual Stroop task. Compared to healthy adolescents, adolescents with mTBI demonstrated different output, control, and temporal aspects of balance. Notable differences in balance characteristics were also demonstrated when performing the dual-task. The recorded differences represent multiple aspects of balance at one month post-injury suggesting widespread effects as a result of mTBI.

Keywords: Centre of pressure, quiet stance, balance control, scaling, Hurst, self-similarity, largest Lyapunov exponent, mTBI, concussion, teens, adolescents, dual-task, Stroop

5.2 Introduction

Mild traumatic brain injuries (mTBIs) are one of the most common neurological conditions in Canada and the United States (Ontario Neurotrauma Foundation, 2013). In the United States, the incidence in adolescents and young adults has been found to be approximately 2.3 to 2.5 mTBIs per 10 000 athletic exposures (Gessel, Collins, Comstock, Dick, & Fields, 2007; Marar, McIlvain, Fields, & Comstock, 2012).

Previous studies have recorded centre of pressure (COP) measures during quiet stance, walking, and during dual-tasks in young adults and adolescents following mTBI. The objectives of these studies were to identify potential variables for use in characterizing impairments in individuals with mTBI and documenting recovery after mTBI (Dorman et al. 2015; Howell et al. 2013; Lee et al. 2013; Powers et al. 2014). The variables used to characterize COP inlude position and velocity-based measures and while these have identified impairments with mTBI, more subtle impairments to balance may be discernable using more complex analytical techniques. While position is likely an output measure, rather than a contributor to control mechanisms because of its low order, speed and velocity are related to momentum and are good candidates for characterizing postural control (Kitabayashi et al. 2002; Riley et al. 1995).

Non-linear measures can additionally account for dimensionality and temporal patterns within COP movement beyond the spatial information provided by position and velocity. Both the largest Lyapunov exponent and scaling parameter have previously been defined in literature (Rosenstein, Collins, & De Luca, 1993; Taqqu, Teverovsky, & Willinger, 1995). The largest Lyapunov exponent quantifies the divergence of nearby state space trajectories and reflects local stability of the timeseries (Rosenstein et al., 1993). The scaling parameter quantifies correlations in the timeseries at different time scales. Scaling parameter values (H) can be compared to known values of certain scaling properties such as random walk or white noise (H=0.5), persistent power law correlation (0.5<H<1.0), anti-persistent power law correlation (0<H<0.5) (Peng, Havlin, Stanley, & Goldberger, 1995). These non-linear measures have previously been used to investigate COP, albeit in young adults, in normal quiet stance (Chiari, Cappello, Lenzi, & Della Croce, 2000; Collins & De Luca, 1994), quiet stance after lower limb muscles have been fatigued (Mello, Oliveira, & Nadal, 2010), and quiet stance in pathologies such as multiple sclerosis (Huisinga, Yentes, Filipi, & Stergiou, 2012) and Parkinson's disease (Stylianou, McVey, Lyons, Pahwa, & Luchies, 2011). These measures have also previously been used in young adults with recent mild traumatic brain injury (Chapter 4; Walters-Stewart, Longtin, & Sveistrup, 2016b).

The aim of this study was to use linear and non-linear COP measures to investigate changes to balance in adolescents after mTBI during different quiet stance conditions.

5.3 Methods

Participants

The data were collected as part of a larger study (Rochefort et al., 2016; Zemek et al., 2013). Adolescents diagnosed at a tertiary children's hospital emergency room as having sustained an mTBI were invited to participate in the study (mTBI group). Healthy adolescents were also invited to participate in the study as controls (healthy group). Those individuals who had sustained an mTBI were tested approximately one month post-injury (32.4±3.4 days post-injury). Participant characteristics can be found in Table 5.1.

Table 5.1 Participant characteristics

	# of participants	Age (±SD) years
Healthy	n=22 (7 males, 15 females)	14.8±1.6
mTBI	n=25 (10 males, 15 females)	14.2±1.3

Data collection

A wireless mobile force platform (Nintendo Wii Balance Board video game controller) and a laptop computer with Bluetooth were used to measure COP. The use of the Wii Balance Board for COP measurement has been validated (Clark et al., 2010; Huurnink, Fransz, Kingma, & van Dieën, 2013). A free, open-source programmable input emulator (GlovePIE v0.43 glovepie.org) was used to script a program for Bluetooth data acquisition (at a frequency of 32Hz). Raw sensor data from four load cells (located at each corner of the platform) were converted to mediolateral and anteroposterior COP in MATLAB (MATLAB 2013a, The Mathworks, Inc., Natick, Massachusetts).

Participants were asked to stand quietly under four conditions: i) two minutes with eyes open (EO); ii) two minutes with eyes closed (EC); iii) two minutes in single leg stance with eyes open (SIN), and iv) while performing a visual Stroop colour-word task (DT) until the task was completed. For the Stroop colour-word task, a list of 100 words—red, yellow, green, blue—were presented in an incongruent ink colour (see Rochefort et al. (2016) for full details). Participants were asked to identify the colour of the text as quickly and as accurately as possible. For conditions EO, EC and DT, participants placed each foot in the demarcated area on the Wii Balance Board to maintain consistency in foot position across the study. When standing on one leg, participants positioned their foot in the centre of the platform.

Data analysis

Part A

COP data analysis was carried out in MATLAB (2013a) with additional material from MATLAB Central (Chu Chen, 2008; Mirwais, 2012a, 2012b). COP measures were calculated as described in Table 5.2 using mediolateral, x_i, and anteroposterior, y_i, timeseries where i=1, 2,…, N and $N=Tf$. For linear measures—path length, l, mean speed, $\bar{u}$, and variability, σ—a second-order, low-pass Butterworth filter with a cut-off frequency of 10Hz was applied. Non-linear

Table 5.2 COP measures

Measure	Symbol	Equation/Method	Description
Path length (normalized)	l	$\frac{1}{T}\sum_{i=1}^{N}\sqrt{(x_{i+1}-x_i)^2+(y_{i+1}-y_i)^2}$	The timeseries is normalized by the total time, T, to account for minor differences in length (number of samples); it can also be considered an estimate of average speed.
Mean speed	$(\bar{u}_x, \bar{u}_y)$	$u=\left(\frac{\lvert x_{i+1}-x_i\rvert}{t_s},\frac{\lvert y_{i+1}-y_i\rvert}{t_s}\right)$	Mean speed (the mean instantaneous speed of the timeseries), unlike velocity, disregards direction when the absolute value (or square root of the squared velocity) is taken to avoid having the negative and positive values cancel. Unlike path length, it is calculated at each time step. Note: $t_s=1/f$.
Variability	(σ_x, σ_y)	$\left(\sqrt{\frac{1}{N-1}\sum_{i=1}^{N}(x_i-\bar{x})^2},\sqrt{\frac{1}{N-1}\sum_{i=1}^{N}(y_i-\bar{y})^2}\right)$	Variability of the COP timeseries is represented by the standard deviation.
Largest Lyapunov exponent (local stability)	(λ_x, λ_y)	Rosenstein's algorithm (Rosenstein, Collins, & De Luca, 1993)	The largest Lyapunov exponent estimates the local stability of the timeseries by quantifying the exponential divergence of initially close trajectories (the largest overtakes all others and is representative of the evolution of the state space volume). The algorithm uses the embedding dimension, lag determined by false nearest neighbours (Kennel, Brown, & Abarbanel, 1992) and the mean period of the timeseries.
Scaling	(H_x, H_y) for each region	Multiple methods were averaged to yield an estimate: Aggregated variance, Absolute values, Rescaled range (R/S) (Rea, Oxley, Reale, & Brown, 2009; Taqqu et al., 1995)	The scaling parameter quantifies self-similar correlations within the timeseries at different time scales. Each method uses the original, differenced, or summed series, as appropriate, depending on classification of the series as fractional Gaussian noise or fractional Brownian motion.

measures—the largest Lyapunov exponent, λ, (Rosenstein et al., 1993) and scaling parameter, H, (Taqqu, Teverovsky, & Willinger, 1995)—were calculated using unfiltered timeseries. Scaling parameters estimates were calculated for the two scaling regions found to be present—a short-term region, H_1, and a long-term region, H_2—as previously described (Chapter 3; Walters-Stewart, Longtin, & Sveistrup, 2016a). Surrogate scaling values (calculated on randomized versions of the COP timeseries) were also calculated as previously described—they were verified to be approximately equal to 0.5 and statistically different from calculated H values ($p<0.05$).

Part B

The large standard deviations of the mTBI group's traditional measures when performing the dual-task led to an additional investigation (*Part B*) into the dissimilarities of the COP within the mTBI group. It was observed that there were two types of visually identifiable COP timeseries: typical and atypical (see Figure 1). Seven (29%) participants in the mTBI group exhibited visually discernable atypical COP only when performing the dual-task.

Statistical Analysis

Part A

Statistical analyses were performed in MATLAB and in SPSS (v23, IBM Corp., Armonk, NY). Repeated measures mixed model ANOVA was used to compare groups (healthy and mTBI) and conditions (EO, EC, SIN, and DT). Post-hoc pairwise comparisons were made using Bonferroni corrected values and deemed significant when $p<0.05$.

Part B

Statistical analyses were repeated to compare three groups—healthy, mTBI (typical), and mTBI (atypical). Note that, in this paper, the labels of typical and atypical mTBI are used to refer only to the visual appearance of COP. Post-hoc pairwise comparisons were made using Bonferroni corrected values and deemed significant when $p<0.05$.

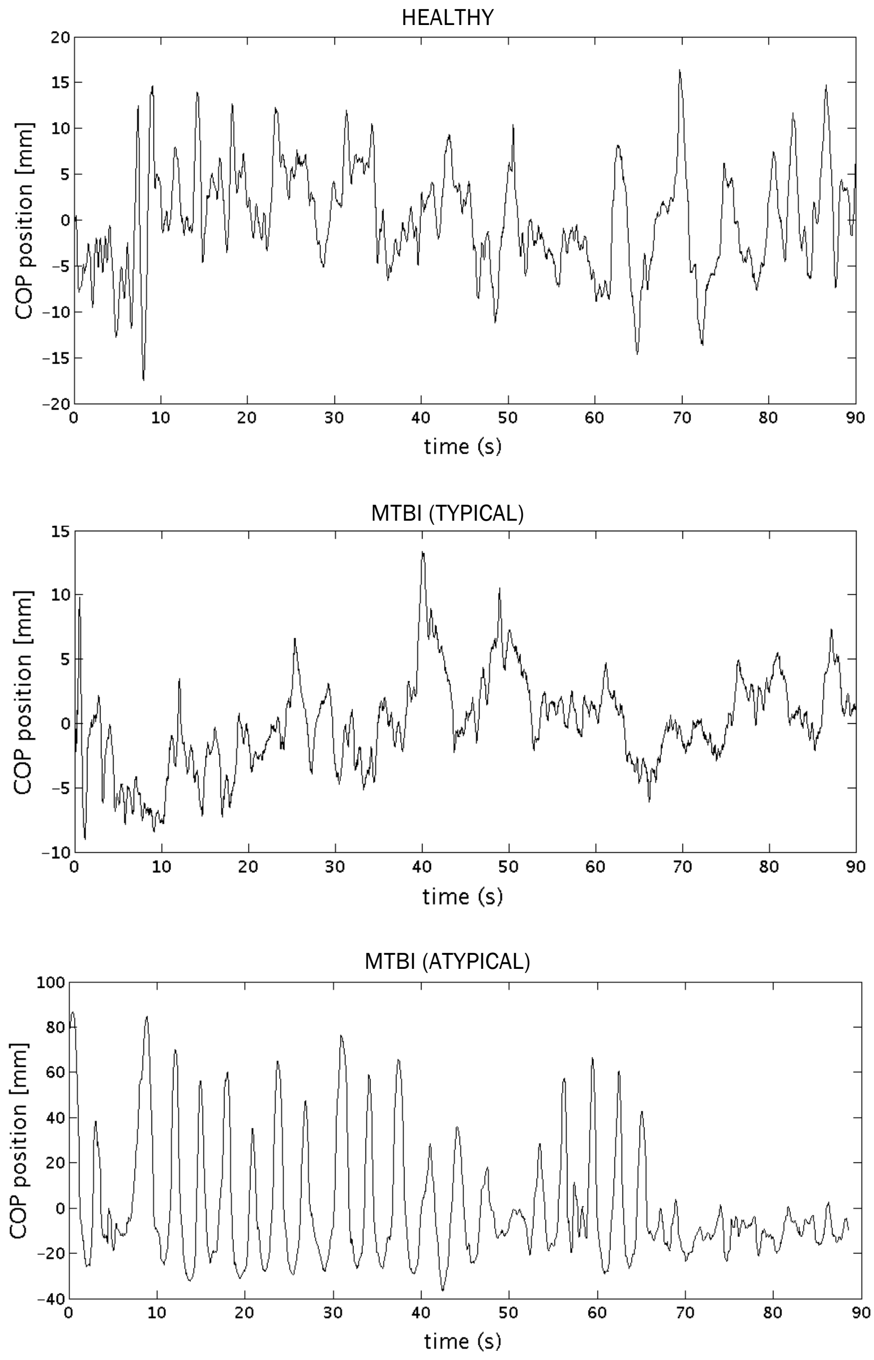

Figure 5.1 Examples of healthy, typical mTBI, and atypical mTBI COP timeseries.
In *Part B*, the mTBI group was divided by visual identification into two groups. The visual presentation of the typical mTBI is visually similar to healthy COP timeseries, but the atypical mTBI appears different. Note, in addition to the different pattern, the difference in scale.

5.4 Results

Two participants in the mTBI group and one participant in the healthy control group did not complete all four conditions. (One healthy participant and one participant with mTBI did not complete the dual-task and another participant with mTBI did not complete the single leg condition).

The majority of COP timeseries regions were classified as fractional Brownian motion (88.8% (309 out of 348) in healthy participants; 86.5% (339 out of 392) in participants with mTBI). The remaining regions were classified as fractional Gaussian noise. COP timeseries demonstrated short-term persistence, H_1>0.5, and long-term anti-persistence, H_2<0.5. As expected, scaling parameters of all randomized surrogate timeseries demonstrated random correlations and were statistically different from calculated H values (p<0.05).

Part A

When ignoring specific condition, linear COP measures—path length, mean speed, and variability—of the healthy group and the mTBI group differed significantly from one another. When ignoring specific condition, mediolateral local stability, anteroposterior short-term and mediolateral long-term scaling differed significantly between healthy adolescents and adolescent with mTBI. Anteroposterior local stability, mediolateral short-term, and anteroposterior long-term scaling did not. When ignoring specific group, all measures were affected by condition. Numerical results can be found in Table 5.3.

Healthy vs. mTBI

In adolescents with mTBI, path length (Figure 5.2A) and mediolateral mean speed (Figure 5.2B) were significantly greater than in healthy adolescents only when performing the dual-task (standing with eyes open while performing the Stroop task). In adolescents with mTBI, mediolateral variability (Figure 5.2D) was significantly greater than in healthy adolescents in all conditions, while anteroposterior variability (Figure 5.2E) was significantly greater only when standing with eyes closed. No other significant differences were found between the linear measures of the adolescents with mTBI and the healthy adolescents.

In adolescents with mTBI, mediolateral local stability was reduced when performing the dual-task when compared to healthy adolescents. No other significant differences in local stability were found between groups.

Mediolateral short-term (Figure 5.4A) and anteroposterior long-term (Figure 5.4B) scaling did not differ significantly between healthy and mTBI groups in any condition. When standing with eyes open and eyes closed, mediolateral long-term scaling was significantly less complex and anteroposterior short-term scaling was significantly more complex in adolescents with mTBI than in healthy adolescents.

One leg vs. two

In both healthy adolescents and adolescents with mTBI, when comparing between specific conditions, (1) linear measures were significantly greater when standing on one leg than when standing on two legs (with eyes open or closed) and in the case of path length and anteroposterior mean speed also when performing the dual-task, (2) mediolateral local stability was significantly reduced when standing on one leg than in any other condition and anteroposterior local stability was significantly reduced when standing on one leg than when standing with eyes open.

In the healthy group only, (1) mediolateral mean speed was significantly greater on one leg than when performing the dual-task and (2) less anteroposterior local stability was demonstrated when standing on one leg than when performing the dual-task; however, (3) anteroposterior short-term scaling was more complex when performing the dual-task than when standing on one leg.

Only in adolescents with mTBI, (1) mediolateral and anteroposterior long-term scaling were more complex when standing on one leg than when standing with eyes open and (2) anteroposterior short-term scaling was more complex when standing with eyes closed than when standing on one leg.

Eyes closed vs. eyes open

In both healthy adolescents and adolescents with mTBI, (1) anteroposterior mean speed was significantly greater and (2) mediolateral and anteroposterior local stability were significantly reduced when standing with eyes closed than when standing with eyes open. Only in adolescents with mTBI, (1) path length and mediolateral mean speed were significantly greater when standing with eyes closed than when standing with eyes open and (2) anteroposterior long-term scaling was more complex when standing with eyes closed than when standing with eyes open.

Dual-task

In both healthy adolescents and adolescents with mTBI, anteroposterior long-term scaling was more complex when performing the dual-task than when standing with eyes open. Only in adolescents with mTBI, (1) path length and mean speed were significantly greater, (2) mediolateral and anteroposterior local stability were reduced, (3) mediolateral long-term scaling was more complex when performing the dual-task than when standing with eyes open, and (4) mediolateral short-term scaling was more complex when performing the dual-task than when standing with eyes closed.

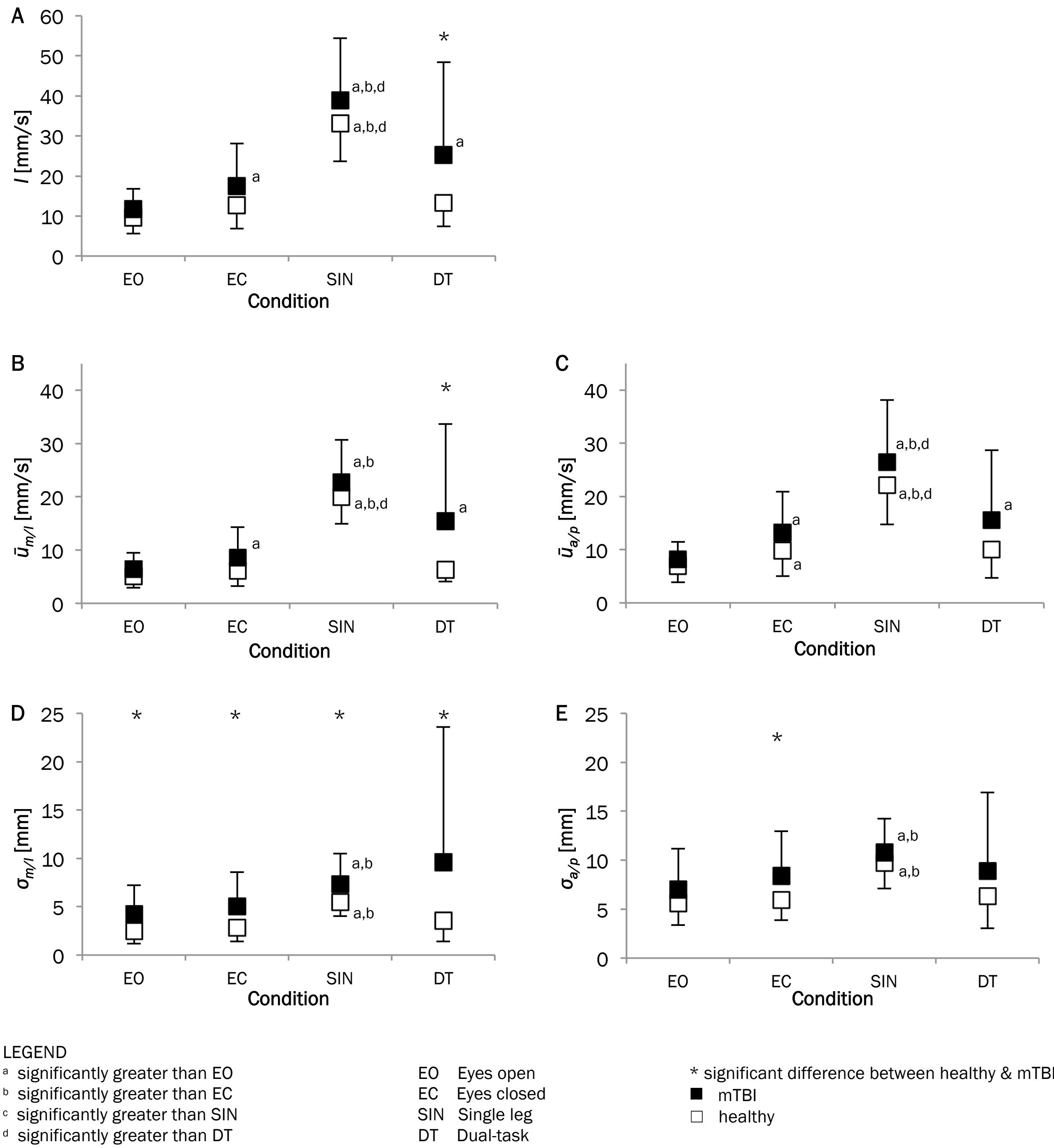

Figure 5.2 Comparison between healthy and mTBI linear COP measures.
Normalized path length, *l*, mediolateral and anteroposterior mean speed, $\bar{u}$, mediolateral and anteroposterior variability, σ, (mean±SD) of mTBI and healthy groups. The mTBI group is significantly greater than the healthy group in path length, mediolateral mean speed, and mediolateral variability for the dual-task condition; in all conditions for mediolateral variability; and in the eyes closed condition for anteroposterior variability. Significant differences are $p<0.05$.

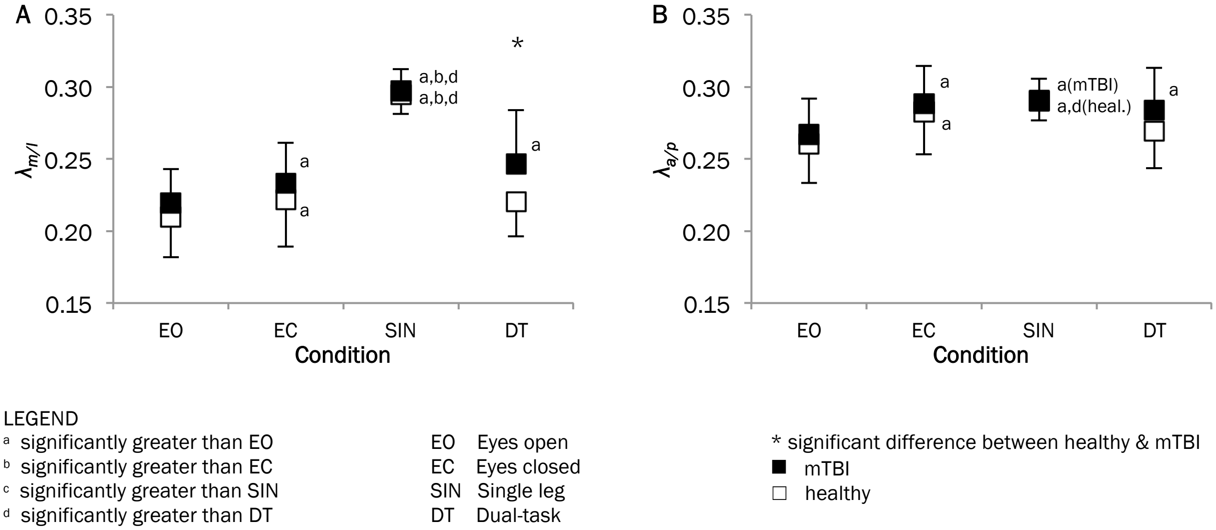

Figure 5.3 Comparison between healthy and mTBI largest Lyapunov exponent.
(A) mediolateral and (B) anteroposterior (mean±SD) of mTBI and healthy groups. In some cases, the healthy marker may be hidden by the mTBI marker. The mediolateral largest Lyapunov exponenet was significantly greater in the mTBI group than in the healthy group. In the mTBI group only, the dual-task condition was significantly greater than standing with eyes open for both mediolateral and anteroposterior largest Lyapunov exponents. In the healthy group only, single leg stance was significantly greater than the dual-task condition for the anteroposterior largest Lyapunov exponent. Significant differences are $p<0.05$.

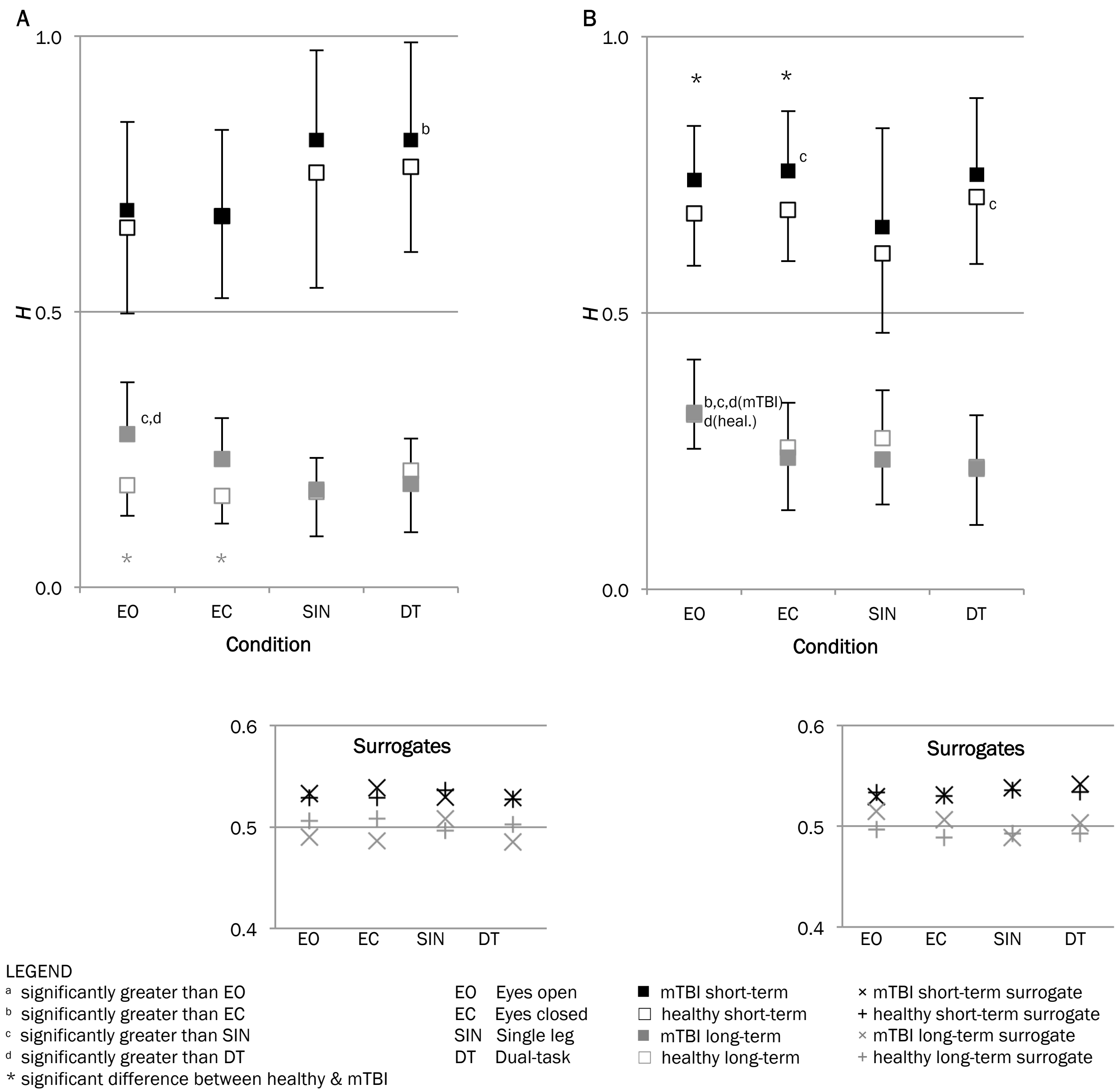

Figure 5.4 COP short-term and long-term scaling parameters (mean±SD).
MTBI and healthy in the (A) mediolateral and (B) anteroposterior direction. In some cases, the healthy marker may be hidden by the mTBI marker. Scaling parameters for surrogate timeseries are shown at the bottom. Scaling values for the short-term were greater than 0.5 and therefore persistent while long-term scaling values were less than 0.5 and therefore anti-persistent. Group differences between the mTBI group and the healthy group were found in anteroposterior short-term scaling values and mediolateral long-term scaling values for eyes open and eyes closed stance. Significant differences are $p<0.05$.

Table 5.3 COP results for adolescents *Part A:* Healthy vs. mTBI (mean±SD, *p*-values)

Measure		Eyes open (EO)		Eyes closed (EC)		Single leg (SIN)		Dual-task (DT)		p-values (α=0.05)		
		Healthy	mTBI	Healthy	mTBI	Healthy	mTBI	Healthy	mTBI	Group	Cond.	C*G
l [mm/s]		9.60±4.05	11.70±5.04	12.76±5.91	17.49±10.57[a]	33.18±9.51[a,b,d]	38.88±15.50[a,b,d]	**13.24±5.84**	**25.21±23.25**[a]	***p=0.016***	***p<0.001***	*p=0.119*
		p=0.125		*p=0.062*		*p=0.137*		***p=0.022***				
$\bar{u}$ [mm/s]	m/l	5.07±2.14	6.37±3.16	6.10±2.88	8.55±5.75[a]	19.92±4.98[a,b,d]	22.74±8.00[a,b]	**6.35±2.26**	**15.42±18.29**[a]	***p=0.012***	***p<0.001***	*p=0.080*
		p=0.110		*p=0.068*		*p=0.156*		***p=0.024***				
	a/p	6.98±3.11	8.23±3.29	9.78±4.75[a]	13.22±7.64[a]	22.11±7.39[a,b,d]	26.43±11.69[a,b,d]	10.07±5.41	15.54±13.13[a]	***p=0.035***	***p<0.001***	*p=0.348*
		p=0.190		*p=0.068*		*p=0.139*		*p=0.071*				
σ [mm]	m/l	**2.50±1.32**	**4.22±2.98**	**2.82±1.43**	**5.03±3.56**	**5.45±1.42**[a,b]	**7.32±3.15**[a,b]	**3.54±2.14**	**9.57±14.00**	***p=0.007***	***p=0.026***	*p=0.161*
		p=0.013		***p=0.008***		***p=0.013***		***p=0.048***				
	a/p	5.60±2.24	7.02±4.16	**5.94±2.08**	**8.39±4.56**	9.73±2.65[a,b]	10.82±3.43[a,b]	6.32±3.27	8.91±8.04	***p=0.049***	***p<0.001***	*p=0.491*
		p=0.146		***p=0.021***		*p=0.240*		*p=0.158*				
λ	m/l	0.210±0.028	0.219±0.024	0.222±0.032[a]	0.233±0.028[a]	0.295±0.013[a,b,d]	0.297±0.015[a,b,d]	**0.221±0.024**	**0.247±0.037**[a]	***p=0.033***	***p<0.001***	***p=0.028***
		p=0.217		*p=0.188*		*p=0.573*		***p=0.009***				
	a/p	0.260±0.027	0.267±0.025	0.282±0.029[a]	0.288±0.026[a]	0.290±0.013[a,d]	0.291±0.015[a]	0.269±0.026	0.284±0.029[a]	*p=0.202*	***p<0.001***	*p=0.156*
		p=0.382		*p=0.475*		*p=0.922*		*p=0.085*				
H_1	m/l	0.653±0.156	0.685±0.160	0.673±0.149	0.675±0.155	0.753±0.210	0.811±0.164	0.764±0.155	0.812±0.177[b]	*p=0.295*	***p<0.001***	*p=0.797*
		p=0.495		*p=0.972*		*p=0.298*		*p=0.340*				
	a/p	**0.680±0.095**	**0.740±0.099**	**0.687±0.093**	**0.758±0.107**[c]	0.608±0.144	0.655±0.180	0.710±0.122[c]	0.749±0.139	***p=0.029***	***p<0.001***	*p=0.900*
		p=0.039		***p=0.020***		*p=0.332*		*p=0.323*				
H_2	m/l	**0.185±0.055**	**0.278±0.094**[c,d]	**0.166±0.050**	**0.232±0.074**	0.173±0.062	0.164±0.085	0.155±0.058	0.177±0.088	***p=0.001***	***p=0.013***	***p<0.001***
		p<0.001		***p<0.001***		*p=0.834*		*p=0.287*				
	a/p	0.316±0.062[d]	0.319±0.097[b,c,d]	0.257±0.080	0.238±0.095	0.274±0.087	0.234±0.081	0.221±0.094	0.218±0.101	*p=0.316*	***p<0.001***	*p=0.462*
		p=0.909		*p=0.480*		*p=0.118*		*p=0.912*				

Applicable to between condition comparisons (Note: Bonferroni adjustment made when determining significance):

[a]significantly greater than EO
[b]significantly greater than EC
[c]significantly greater than SIN
[d]significantly greater than DT

Part B

Typical vs. atypical

There were no differences in linear measures (Figure 5.5) between the typical mTBI and healthy adolescent groups. The atypical mTBI group had significantly greater linear measures than healthy adolescents: mediolateral mean speed and mediolateral variability when standing with eyes open; path length, mediolateral mean speed, mediolateral and anteroposterior variability when standing with eyes closed; and in all linear measures when performing the dual-task. When performing the dual-task, adolescents in the atypical mTBI group additionally had significantly greater linear measures than those in the typical mTBI group.

When performing the dual-task, both the mediolateral and the anteroposterior largest Lyapunov exponents (Figure 5.6) of the atypical mTBI group were significantly greater than those of the typical mTBI and healthy groups.

Adolescents in the atypical mTBI group had significantly more complex short-term (anteroposterior and mediolateral) and long-term (anteroposterior only) scaling than both adolescents in the typical mTBI group and healthy adolescents when performing the dual-task (Figure 5.7). Mediolateral long-term scaling when standing with eyes open was significantly less complex in adolescents in the atypical mTBI group than in adolescents in the typical mTBI group which was, in turn, significantly less complex than in healthy adolescents. Mediolateral long-term scaling when standing with eyes closed was significantly less complex in both the typical and atypical adolescent groups than in the healthy adolescents.

One leg vs. two

In adolescents in the typical mTBI group, like in healthy adolescents, linear measures were significantly greater when standing on one leg than when standing on two legs in any condition including when performing the dual-task (with the exception of mediolateral variability). On the other hand, in adolescents in the atypical mTBI group, variability when standing with eyes open (mediolateral only) or closed was not significantly different from standing on one leg. Variability was significantly greater when performing the dual-task than standing on one leg.

In adolescents in the typical mTBI group, short-term mediolateral scaling was more complex when standing on one leg than standing with eyes open or closed and short-term anteroposterior scaling was less complex when standing on one leg than standing with eyes open or closed.

Long-term scaling was more complex when standing on one leg than when standing with eyes open only in adolescents in the atypical mTBI group.

Eyes closed vs. eyes open

In adolescents in the typical mTBI group, like in adolescents in the atypical mTBI group, path length was significantly greater when standing with eyes closed than when standing with eyes open. On the other hand, mediolateral mean speed in adolescents in the typical mTBI group was significantly greater when standing with eyes closed than when standing with eyes open similar to healthy adolescents.

Anteroposterior long-term scaling was more complex when standing with eyes closed than when standing with eyes open only in adolescents in the atypical mTBI group.

Dual-task

In adolescents in the atypical mTBI group, linear measures were significantly greater when performing the dual-task than when standing with eyes open or closed.

In adolescents in the atypical mTBI group, mediolateral short-term scaling was more complex when performing the dual-task than in any other condition, anteroposterior short-term scaling was more complex when performing the dual-task than when standing with eyes open, and anteroposterior long-term scaling was more complex when performing the dual-task than when standing with eyes closed. Long-term scaling was more complex when performing the dual-task than when standing with eyes open only in adolescents in the atypical mTBI group.

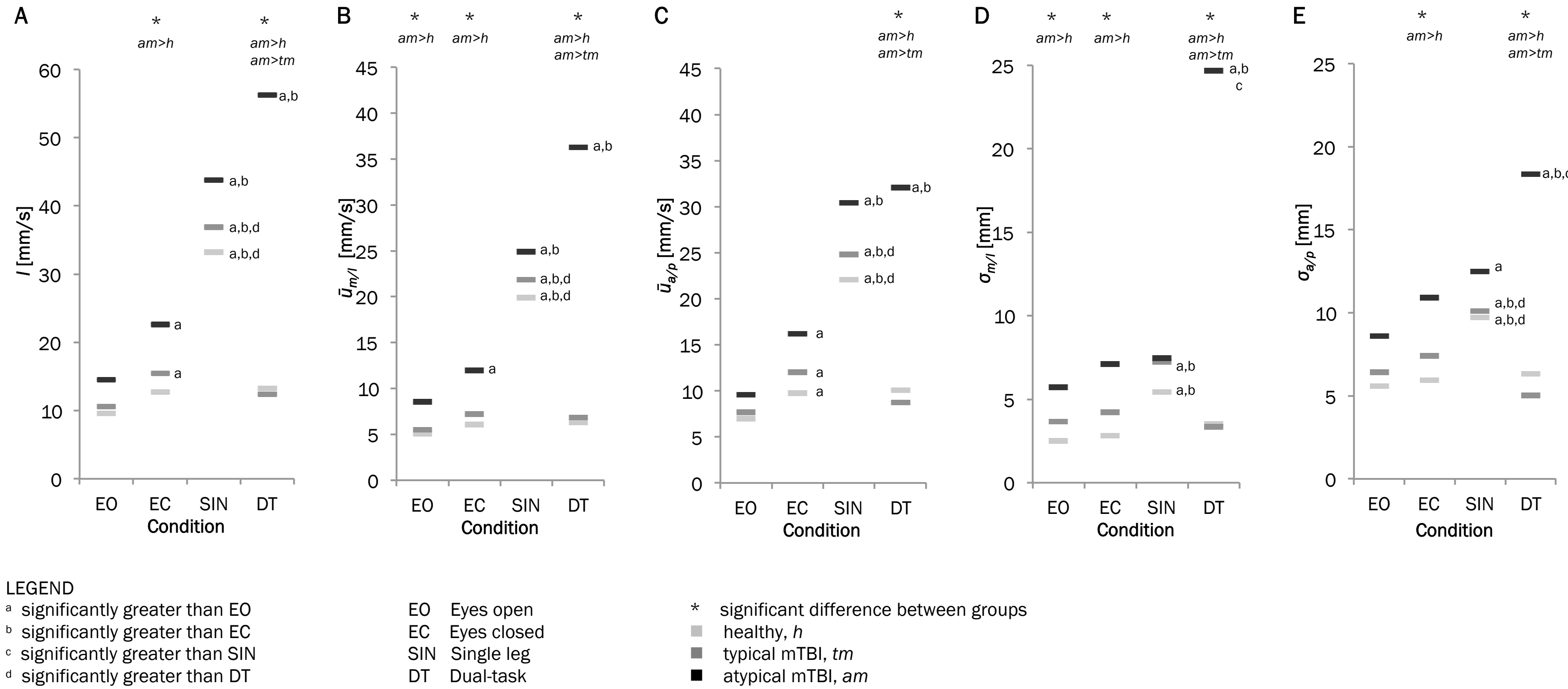

Figure 5.5 Comparison of healthy, typical mTBI, and atypical mTBI linear COP measures.
Normalized path length, l, mediolateral and anteroposterior mean speed, $\bar{u}$, mediolateral and anteroposterior variability, σ. Only means are shown for clarity. The dual-task condition highlights differences between the groups. For all measures shown, the atypical mTBI group's values were greater than both the typical mTBI and the healthy groups in the dual-task condition. The atypical mTBI group's dual-task condition was greater when compared to the eyes open and eyes closed condition for velocity-based measures (path length and mean speed) and when compared to all other conditions in the position-based measure (variability). Significant differences are $p<0.05$.

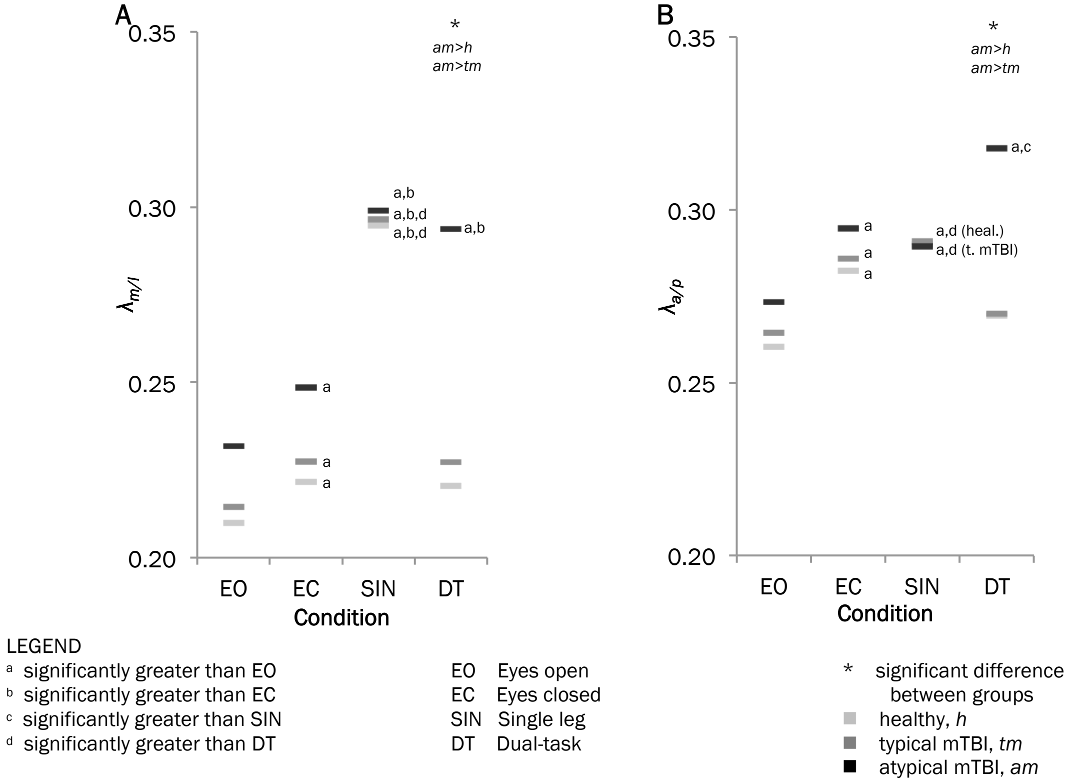

Figure 5.6 Comparison of healthy, typical mTBI, and atypical mTBI largest Lyapunov exponents.
(A) mediolateral and (B) anteroposterior. Only means are shown for clarity. The largest Lyapunov was greater in the dual-task condition for the atypical mTBI group than both the typical mTBI group and the healthy group in both the mediolateral and anteroposterior directions. Significant differences are p<0.05.

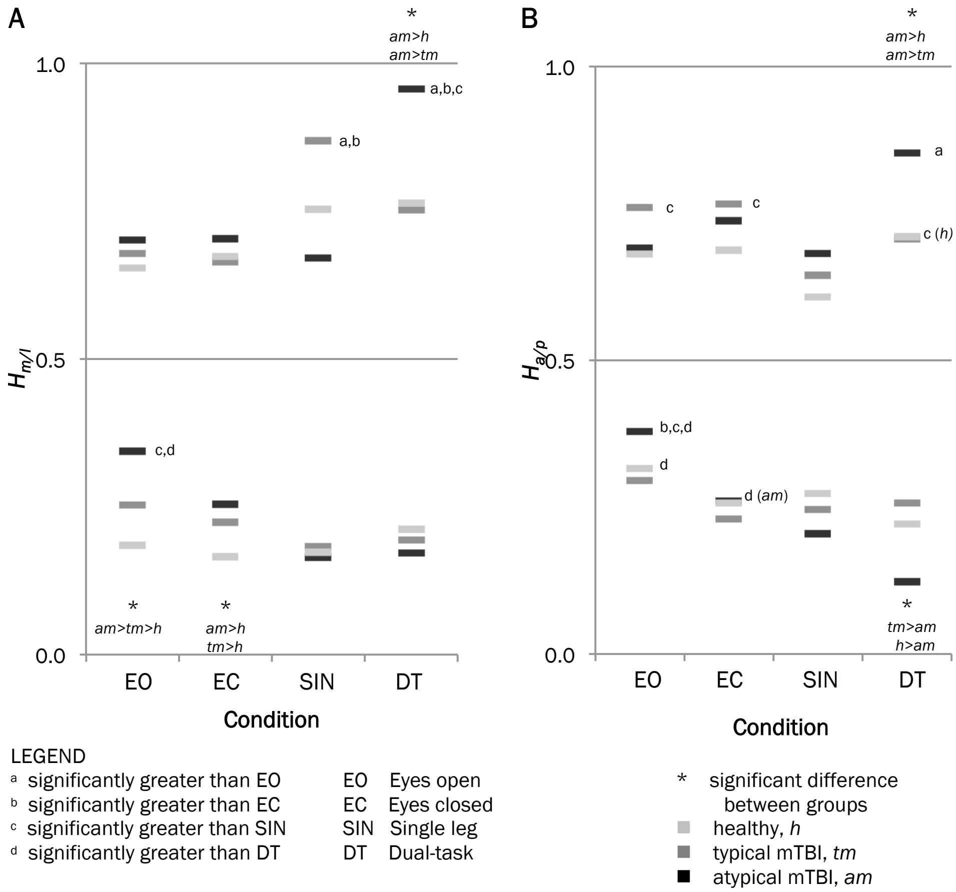

Figure 5.7 Comparison of healthy, typical mTBI, and atypical mTBI short-term (H_1>0.5) and long-term (H_2<0.5) scaling. (A) mediolateral and (B) anteroposterior. Only means are shown for clarity. In some cases, markers may be hidden by one another. The typical mTBI group showed long-term mediolateral scaling that was closer to random walk (H=0.5) than the healthy group in eyes closed and eyes open stance. In addition, the typical mTBI group's short-term scaling when standing on a single leg when compared to eyes open and eyes closed stance was farther from random walk mediolaterally and closer to random walk anteroposteriorly. For the atypical mTBI group, dual-task scaling was farther from random walk with the exception of long-term mediolateral scaling. In addition, dual-task short-term mediolateral scaling was farther from random walk than all other conditions and dual-task short-term anteroposterior scaling was farther from random walk than eyes open stance. Significant differences are p<0.05.

5.5 Discussion

Healthy adolescents show three general trends. One, healthy adolescents demonstrated less local stability (greater largest Lyapunov exponent), greater variability, and a need for more control (greater mean speed and path length) when base of support was reduced compared to conditions with a wider base even when attention resources were challenged (less local stability and a need for more control, although less short-term complexity (anteroposterior only) was also found). Two, healthy adolescents also demonstrated a need for more control (anteroposterior mean speed only) and less local stability when visual input was removed compared to when visual input was present. Three, though healthy participants demonstrated more long-term complexity (anteroposterior) when attention resources were challenged compared to when simply standing with eyes open, otherwise, no particular differences were demonstrated between the two conditions.

Adolescents with mTBI demonstrated greater variability, less local stability, more complexity, and a need for more control than healthy adolescents. But, how did the three trends across conditions differ in adolescents with mTBI? Some adolescents with mTBI (those with typical COP) demonstrated nearly identical trends to those of healthy adolescents. Adolescents in the typical mTBI group demonstrated more short-term complexity (mediolateral) when the base of support was reduced compared to conditions with a wider base (eyes open and eyes closed.) Adolescents in the atypical mTBI group demonstrated different trends—similar local stability and similar variability between standing on one leg and standing on two though more long-term complexity (eyes open)—and opposite trends—similar or greater local stability, less variability, and similar control when standing on one leg than when standing on two with attention being challenged, though less short-term complexity (mediolateral only). Similar to healthy adolescents, both mTBI groups demonstrated a need for more control and less local stability when visual input was removed; however, adolescents in the atypical mTBI group also demonstrated more long-term complexity. Adolescents in the typical mTBI group did not show more long-term complexity (anteroposterior) as the healthy adolescents did when attention was challenged compared to when simply standing, but similarly, no other particular differences were demonstrated between the two conditions. Adolescents in the atypical mTBI group did show more long-term and short-term complexity, and also demonstrated greater variability, a need for more control, and less local stability when attention was challenged compared to when simply standing.

Table 5.4 Overview of condition trends

	Groups		
	Healthy	mTBI (with typical COP)	mTBI (with atypical COP)
SIN vs. EO	-a need for more control	-a need for more control	-a need for more control
	-greater variability	-greater variability	-greater variability ***(a/p)***
	-less local stability	-less local stability	-***similar or*** less local stability
	- -	-more complexity ***(st, m/l)***	- more complexity ***(lt)***
EC	-a need for more control	-a need for more control	-a need for more control
	-greater variability	-greater variability	- -
	-less local stability (m/l)	-less local stability (m/l)	-***similar or*** less local stability
	- -	-more complexity (st, m/l)	- -
DT	-a need for more control	-a need for more control	-similar control
	- -	- -	-less variability (a/p)
	-less local stability	-less local stability	***-similar or*** less local stability
	-less complexity (st, a/p)	- -	-more complexity (st, m/l)
EC vs. EO	-a need for more control	-a need for more control	-a need for more control
	- -	- -	- -
	-less local stability	-less local stability	-less local stability
	- -	- -	-more complexity (lt, a/p)
DT vs. EO	- -	- -	-a need for more control
	- -	- -	-greater variability
	- -	- -	-less local stability
	-more complexity (lt, a/p)	- -	-more complexity ***(st &lt)***

In healthy adolescents, our results for path length were found to be comparable to Hytönen et al.'s (1993) results (called sway velocity) for young adults (aged 16 to 30). Our linear results were also comparable to young adults in other studies (Kitabayashi, Demura, & Noda, 2002; Walters-Stewart, Longtin, & Sveistrup, 2015b).

In a previous study that examined quiet stance, COP measures differed with age (Hytönen et al., 1993). In particular, children (aged 6 to 15) and young adults (aged 16 to 30) were notably different from one another. 59% of our healthy adolescent group and 76% of our mTBI group were aged 13 to 15, indicating that comparison of our results with results from young adults may not always be appropriate. Nevertheless, because of a dearth of mTBI and non-linear COP data, results from studies with young adults are used. While previous studies report a wide range for largest Lyapunov exponent results that make comparison difficult (Donker, Roerdink, Greven, & Beek, 2007; Huisinga et al., 2012), similar findings of scaling behaviour (short-term persistence, long-term anti-persistence) are found when reviewing other studies that report two-region quiet-stance scaling parameters (Chiari et al., 2000; Mello et al., 2010).

In our previous study which characterized healthy quiet stance in young adults (Walters-Stewart et al., 2016b) we also found that when standing on one leg, greater variability, a need for more control, and less local stability were evident when compared to standing with eyes open or closed. However, our previous study also indicated more short-term mediolateral complexity and more long-term anteroposterior complexity in healthy young adults when standing on one leg than when standing with eyes open. In healthy adolescents, this trend was present, but not significant. Like healthy young adults, healthy adolescents demonstrated a need for more control (anteroposterior) and less local stability (anteroposterior), when visual input was removed. In addition, adolescents showed trends of greater variability (anteroposterior) and more short-term complexity (anteroposterior) which, while not contradictory to the findings for healthy young adults, were not of a sufficient level to be significant. Indeed, the general trends of scaling parameters when comparing standing with eyes open, eyes closed, and single leg stance were similar in both studies.

In other studies that have examined COP in quiet stance (or dual-task) with mTBI, Powers et al. (2014) reported findings of increased anteroposterior displacement and velocity in young adults with mTBI and Dorman et al. (2015) also reported increased velocity in adolescents with mTBI. Our results support these findings with increased COP speed, albeit in the mediolateral direction in adolescents with mTBI.

To our knowledge, largest Lyapunov exponents and scaling parameters of COP have not previously been studied in adolescent mTBI populations or in adolescents when performing dual-tasks. Largest Lyapunov exponents of COP quiet stance have been studied in pathologies such as multiple sclerosis (Huisinga et al., 2012). Huisinga et al. (2012) found that in individuals with multiple sclerosis, the largest Lyapunov was less than in healthy controls and smaller when standing with eyes closed condition in comparison to eyes open. This "decreased divergence of sway" was attributed to less ability to reorganize the system with reduced information because of inflamed central nervous system pathways in multiple sclerosis (Huisinga et al., 2012). In contrast, our mTBI study demonstrated there was no change to largest Lyapunov exponent in simple quiet stance and, for all participants, the largest Lyapunov was greater when standing with eyes closed than when standing with eyes open suggesting that none of the same mechanisms are at play in mTBI that are present in multiple sclerosis. Quiet stance COP scaling parameters have been studied in fatigue (Mello et al., 2010). When the plantar flexor muscles were fatigued, scaling parameters indicated that a long-term mechanism was at play (an increased long-term scaling parameter (i.e., less complex)). In our study, the scaling parameter in adolescents with mTBI showed increased mediolateral long-term scaling as well as changes to short-term scaling. This may signify that in addition to mTBI-specific effects on short-term scaling, mechanisms common or similar to fatigue may be related to the changes in the long-term scaling demonstrated in adolescents with mTBI.

In addition, many measures differ only between healthy and mTBI groups during the dual-task (Stroop task and quiet stance), or are present only between dual-task and other conditions. During Stroop tasks, positron emission tomography scans have shown activation of extensive networks in the brain (Pardo, Pardo, Janer, & Raichle, 1990). While the Stroop task is associated with prefrontal function, it also requires inhibition of posterior areas of the brain (Bench et al., 1993). In addition, studies have shown that the parts of the prefrontal network activate only during dual-tasks or in poorly performing subjects which suggest supplementary process are provided “on-demand” (Goethals, Audenaert, Van De Wiele, & Dierckx, 2004). Because the Stroop task is associated with multiple areas in the brain, the effect on quiet stance while performing the Stroop task found in this study may demonstrate an aspect of widespread changes arising from mTBI.

5.6 Conclusion

The effects of mTBI on quiet stance are apparent in the output, control, and timing of balance. Changes to so many aspects of postural control suggest a wide effect rather than a single mechanism affecting balance in mTBI. Our findings of changes to quiet stance while performing the Stroop task also supports the premise that mTBI results in widespread whole brain disruptions of networks. These alterations to control should perhaps not be seen as impairments, but instead adaptations of the control that facilitates maintaining balance despite an altered state.

Acknowledgements

We would like to extend our thanks to the participants of this study and their parents as well as the staff at CHEO who aided in participant recruitment.

Funding

The first and second authors were supported by scholarships provided by the Government of Ontario (QEIIGSST, OGS) and by the University of Ottawa. This project was part of a larger study funded by a CIHR operating grant (MOP: #126197), a CIHR–ONF Mild Traumatic Brain Injury team grant (TM1: #127047), and a CIHR planning grant (MRP: #119829).

Conflicts of Interest Statement
There are no conflicts of interest to disclose.

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5.8 Appendix

Table 5.5a COP results for adolescents *Part B:* Typical vs. atypical COP (mean±SD)

Measure		Conditions											
		Eyes open			**Eyes closed**			**Single leg**			**Dual-task**		
		Healthy	mTBI (typ.)	mTBI (atyp.)	Healthy	mTBI (typ.)	mTBI (atyp.)	Healthy	mTBI (typ.)	mTBI (atyp.)	Healthy	mTBI (typ.)	mTBI (atyp.)
l [mm/s]		9.60±4.05	10.59±4.45	14.56±5.69	12.76±5.91	15.48±7.64	22.64±15.45	33.18±9.51	36.87±12.71	43.77±21.23	13.24±5.84	12.43±5.27	56.26±20.25
$\bar{u}$ [mm/s]	m/l	5.07±2.14	5.52±2.43	8.53±3.94	6.10±2.88	7.23±3.78	11.96±8.54	19.92±4.98	21.84±7.06	24.92±10.22	6.35±2.26	6.83±3.48	36.28±23.09
	a/p	6.98±3.11	7.70±3.20	9.60±3.34	9.78±4.75	12.05±6.00	16.23±10.79	22.11±7.39	24.79±9.06	30.42±16.70	10.07±5.41	8.74±3.30	32.04±13.52
σ [mm]	m/l	2.50±1.32	3.65±2.81	5.70±3.09	2.82±1.43	4.23±2.91	7.10±4.46	5.45±1.42	7.26±3.36	7.47±2.83	3.54±2.14	3.35±1.55	24.69±19.18
	a/p	5.60±2.24	6.41±3.42	8.60±5.67	5.94±3.71	7.40±3.71	10.92±5.81	9.73±2.65	10.12±3.19	12.50±3.66	6.32±3.27	5.02±2.52	18.35±9.15
λ	m/l	0.210±0.028	0.214±0.021	0.232±0.027	0.222±0.032	0.227±0.028	0.249±0.024	0.295±0.013	0.296±0.014	0.299±0.019	0.221±0.024	0.227±0.024	0.294±0.015
	a/p	0.260±0.027	0.265±0.026	0.273±0.024	0.282±0.029	0.286±0.028	0.295±0.024	0.290±0.013	0.291±0.015	0.289±0.016	0.269±0.026	0.270±0.021	0.318±0.014
H_1	m/l	0.653±0.156	0.678±0.158	0.701±0.177	0.673±0.149	0.664±0.155	0.703±0.164	0.753±0.210	0.869±0.101	0.671±0.208	0.764±0.155	0.752±0.179	0.956±0.020
	a/p	0.680±0.095	0.760±0.095	0.690±0.097	0.687±0.093	0.766±0.116	0.737±0.085	0.608±0.144	0.644±0.183	0.682±0.183	0.710±0.122	0.707±0.108	0.853±0.159
H_2	m/l	0.185±0.055	0.253±0.086	0.344±0.087	0.166±0.050	0.224±0.076	0.254±0.071	0.173±0.062	0.183±0.095	0.165±0.060	0.212±0.058	0.194±0.067	0.172±0.131
	a/p	0.316±0.062	0.295±0.091	0.379±0.089	0.257±0.080	0.230±0.093	0.260±0.106	0.274±0.087	0.246±0.083	0.205±0.073	0.221±0.094	0.257±0.085	0.122±0.071

Table 5.5b COP results *Part B:* Typical vs. atypical COP (*p*-values)

Measure			Conditions								*p*-values		
			Eyes open		**Eyes closed**		**Single leg**		**Dual-task**				
			mTBI (typ.)	mTBI (atyp.)	mTBI (typ.)	mTBI (atyp.)	mTBI (typ.)	mTBI (atyp.)	mTBI (typ.)	mTBI (atyp.)	Group	Cond.	C*G
l [mm/s]		Healthy	*p>0.999*	*p=0.051*	*p=0.965*	***p=0.039***	*p>0.999*	*p=0.176*	*p>0.999*	***p<0.001***	***p<0.001***	***p<0.001***	***p<0.001***
		mTBI (typ.)		*p=0.202*		*p=0.256*		*p=0.758*		***p<0.001***			
$\bar{u}$ [mm/s]	m/l	Healthy	*p>0.999*	***p=0.013***	*p>0.999*	***p=0.015***	*p=0.999*	*p=0.257*	*p>0.999*	***p<0.001***	***p<0.001***	***p<0.001***	***p<0.001***
		mTBI (typ.)		*p=0.059*		*p=0.094*		*p>0.999*		***p<0.001***			
	a/p	Healthy	*p>0.999*	*p=0.219*	*p=0.847*	*p=0.089*	*p>0.999*	*p=0.155*	*p>0.999*	***p<0.001***	***p<0.001***	***p<0.001***	***p<0.001***
		mTBI (typ.)		*p=0.601*		*p=0.531*		*p=0.653*		***p<0.001***			
σ [mm]	m/l	Healthy	*p=0.291*	***p=0.007***	*p=0.296*	***p=0.002***	*p=0.098*	*p=0.193*	*p>0.999*	***p<0.001***	***p<0.001***	***p<0.001***	***p<0.001***
		mTBI (typ.)		*p=0.205*		*p=0.063*		*p>0.999*		***p<0.001***			
	a/p	Healthy	*p>0.999*	*p=0.170*	*p=0.646*	***p=0.007***	*p>0.999*	*p=0.120*	*p>0.999*	***p<0.001***	***p<0.001***	***p<0.001***	***p<0.001***
		mTBI (typ.)		*p=0.526*		*p=0.094*		*p=0.248*		***p<0.001***			
λ	m/l	Healthy	*p>0.999*	*p=0.139*	*p>0.999*	*p=0.102*	*p>0.999*	*p>0.999*	*p=0.819*	***p<0.001***	***p=0.002***	***p<0.001***	***p<0.001***
		mTBI (typ.)		*p=0.508*		*p=0.377*		*p>0.999*		***p<0.001***			
	a/p	Healthy	*p>0.999*	*p=0.603*	*p>0.999*	*p=0.839*	*p>0.999*	*p>0.999*	*p>0.999*	***p<0.001***	*p=0.081*	***p<0.001***	***p<0.001***
		mTBI (typ.)		*p>0.999*		*p>0.999*		*p>0.999*		***p<0.001***			
H_1	m/l	Healthy	*p>0.999*	*p>0.999*	*p>0.999*	*p>0.999*	***p=0.016***	*p>0.999*	*p>0.999*	***p=0.017***	*p=0.512*	***p<0.001***	***p=0.003***
		mTBI (typ.)		*p>0.999*		*p>0.999*		*p=0.066*		***p=0.008***			
	a/p	Healthy	*p=0.074*	*p>0.999*	*p=0.093*	*p=0.754*	*p>0.999*	*p=0.580*	*p>0.999*	***p=0.033***	*p=0.065*	***p<0.001***	*p=0.075*
		mTBI (typ.)		*p=0.449*		*p>0.999*		*p>0.999*		***p=0.025***			
H_2	m/l	Healthy	***p=0.007***	***p<0.001***	***p=0.041***	***p=0.006***	*p>0.999*	*p>0.999*	*p>0.999*	*p=0.718*	***p=0.002***	***p<0.001***	***p<0.001***
		mTBI (typ.)		***p=0.010***		*p=0.615*		*p>0.999*		*p>0.999*			
	a/p	Healthy	*p>0.999*	*p=0.212*	*p=0.912*	*p>0.999*	*p=0.609*	*p=0.168*	*p=0.623*	***p=0.044***	*p=0.516*	***p<0.001***	***p=0.001***
		mTBI (typ.)		*p=0.089*		*p>0.999*		*p>0.999*		***p=0.005***			

Note: All the *p*-values in this table have been Bonferroni adjusted to maintain an $\alpha=0.05$.

6. A Preliminary Investigation of Visual Centre of Pressure State Space Representation In Quiet Stance: Healthy and mTBI

A Preliminary Investigation of Visual Centre of Pressure State Space Representation In Quiet Stance: Healthy and mTBI

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6.1 Abstract

Balance control can be modelled by an inverted pendulum which, though inherently unstable, can be maintained in an upright position by a time varying force. Balance control can be further explored using state space analysis. In this study, balance control system dynamics were characterized by reconstructing three-dimensional state space from one-dimensional centre of pressure (COP) of quiet stance with eyes closed in healthy young adults (n=32). In addition, university football players (n=6) were tested prior to the start of the season and were retested during the season if they sustained an mTBI. Dynamic structure was further clarified by transforming, using principal component analysis, the attractor to reveal the principal variance in the delay reconstructed timeseries. Two-dimensional projections of three-dimensional visual representation of the state space demonstrated that the structure within COP output was not random and was greater than two-dimensional. These characteristics were still evident even after mTBI.

Keywords: Centre of pressure, quiet stance, balance control, state space, phase space, attractor, delay reconstruction

6.2 Introduction

Balance can be modelled and studied as a control system. The inverted pendulum as a system model can be readily adapted to describe control of body movement during quiet stance. For example, an inverted pendulum can be characterized by the following second-order ordinary differential equation,

$$x''(t) + \beta x'(t) - \alpha x(t) = F_{control}(t) \tag{6.1}$$

where $x(t)$ represents the position of centre of mass (COM), $x'(t)$ and $x''(t)$ are the first and second derivative, respectively, representing the velocity and acceleration, and α and β are constants. The second-order ordinary differential equation representing the linearized motion of an inverted pendulum (Eq. 6.1) with no control (when $F_{control}(t) = 0$) has an unstable fixed point when the pendulum is completely upright. Unless the pendulum is placed motionless (velocity equal to zero) at that point (position equal to zero), the pendulum cannot remain upright. With control (when $F_{control}(t) \neq 0$, a time-varying force attempts to keep the inverted pendulum upright; therefore, trajectories are maintained at or near the fixed point), stability is possible. Solutions of the equation define the parameters for which the inverted pendulum can remain upright. The differential equation (6.1) can further be modified to represent delays, to add noise perturbations, or to describe intermittent control (Asai et al., 2009; Collins & De Luca, 1993; Milton, Cabrera, Ohira, Tajima, & Tonosaki, 2009) in order to account for non-linearities that may be present in balance control.

State space analysis can be used to investigate linear and non-linear characteristics of balance control. In a state space model, inputs and outputs of a system are related by state variables in the time domain (Commandeur & Koopman, 2007; Hsu, 2011). These state space variables can be characterized in multiple dimensions by an attractor. In turn, attractor characteristics convey information about the nature of the dynamic system. Reconstructed attractor representations using a single variable are known, based on studies with systems with known equations of motion (such as the chaotic Lorenz system), to contain the dynamic characteristics of these equations, which can be extracted when the attractor dimension when noise levels are small (Gates & Dingwell, 2009).

In balance, centre of pressure is a representation of neuromuscular control (Milton et al., 2009). Larger trends in COP reflect the movement of COM while much of the smaller fluctuations are the result of temporal variations in lower leg muscle contractions (Loram, Maganaris, & Lakie, 2005; Sozzi, Honeine, Do, & Schieppati, 2013). As such, COP can be chosen to represent system dynamics in a state space reconstruction.

Attractor representation of COP in standing balance has previously been investigated. Collins and De Luca (1994) investigated two-dimensional (2D) reconstructed COP plots, and found that the structure did not appear to differ from those based on surrogates (suitably randomized versions of the original data.) While Collins and De Luca (1994) were not able to discern any evidence of structure within their reconstruction, they demonstrated the unity line—a diagonal line that equated the abscissa variable and the ordinate variable in a one-to-one relationship. Snoussi et al. (2006) showed 2D reconstructions that appeared similar to Collins and De Luca's findings; they further introduced empirical decomposition of intrinsic mode functions, and obtained plots that demonstrated more discernible structure in COP time series. Snoussi et al. (2006) proposed that with their method, stochastic, chaotic, and deterministic elements of the timeseries could be separated. Zatsiorsky and Duarte (2000) also described decomposition of COP into components using two techniques (1) rambling and trembling and (2) gravity line decomposition. They explored the dynamics of COP involving the gravity line, which represents a vertical projection that passes through the COM, and control of the COP around the gravity line. In phase or state space, the gravity line, appears as a unity line (Zatsiorsky & Duarte, 2000). They determined that the gravity line and rambling (movement of the reference point) were closely related, and that trembling represented motion that occurs around rambling; however, in their study, the phase space was limited to 2D.

The purpose of our study was to qualitatively characterize system dynamics from reconstructed COP in three-dimensional (3D) state space. Because it has been suggested that more complex (such as chaotic) systems appear stochastic when restricted to a dimension that is smaller than that of the attractor (Rosenstein, Collins, & De Luca, 1993), it may be that 3D state space reconstruction can demonstrate characteristics of the system that have been, up until now, overlooked or inaccessible in 2D. In part A, it was hypothesized that the state space would demonstrate non-random and greater than 2D structure. In part B, it was also hypothesized that COP state space would demonstrate altered characteristics after mild traumatic brain injury.

6.3 Methods

Experimental data

Full details of the experiment and recording protocols can be found in Chapter 3 and Chapter 4 (Walters-Stewart, Longtin, & Sveistrup, 2016a; 2016b. In Part A, healthy young adults (n=32, 25 male, 7 female) stood quietly for two minutes ($T \approx 120$s), with eyes closed and with feet as close together as possible while still in a comfortable stance. In Part B, university football players (n=6 male) were tested prior to the start of the season and were retested during the season if they sustained an mTBI. Ground reaction forces and moments were recorded (frequency, f=60Hz). Net COP was computed in the mediolateral and anteroposterior directions, $x[i]$ and $y[i]$, respectively, where i=1, 2,…, N and $N=Tf$, were computed.

Delay reconstruction of COP

Analysis was carried out in MATLAB (MATLAB 2013a, Mathworks Inc., Natick, Massachusetts) with additional material from MATLAB Central (Mirwais, 2012). Each timeseries (here x is used to represent either x or y) was reconstructed as follows,

$$X = \{x[i], x[i-\tau], \dots, x[i-(m-1)\tau]\}, \qquad (6.2)$$

where τ represents the delay (or lag) and m represents the embedding dimension.

The ideal embedding dimension was determined using the false nearest neighbour method (Kennel, Brown, & Abarbanel, 1992). Hegger, Kantz and Schreiber (1999) recommend (in order to take advantage of noise averaging effects) choosing a shorter delay and a higher embedding dimension as well as experimentation to determine a suitable embedding dimension. In this paper, for noise reduction, the embedding dimension was chosen through trial and error to be m=14. Multiple methods exist to choose an effective lag length, i.e., one that contains neither too much nor too little redundancy (England & Granata, 2007), including trial and error (Williams, 1997). While redundancy is the major limitation of using a small τ value, a small value is acceptable when the sampling rate is not too high. A lag of τ=1 was used since no advantages were found using a higher value for time delay.

Principal component analysis (Daffertshofer, Lamoth, Meijer, & Beek, 2004; Hegger et al, 1999) or, similarly, singular system analysis (Hegger et al, 1999; Williams, 1997) can be applied to the reconstructed timeseries in order to extract the best projection of the attractor and mitigate redundancy. Principal components

$$p_k = \frac{1}{\lambda_k} X a_k, \tag{6.3}$$

where λ_k and a_k are the eigenvalues and eigenvectors, respectively, were determined, in order to represent the reconstructed space on axes that displayed the most variance of the data. While this method introduces some linear dependence, in addition to reducing redundancy, it can reduce the effects of noise and allow a high signal-to-noise ratio (Huffaker, 2010; Williams, 1997).

The COP state variables in the system attractor are then represented by trajectories around the principal axes (see Figure 6.1, lower right). The principal axes were normalized to the maximum value in the timeseries.

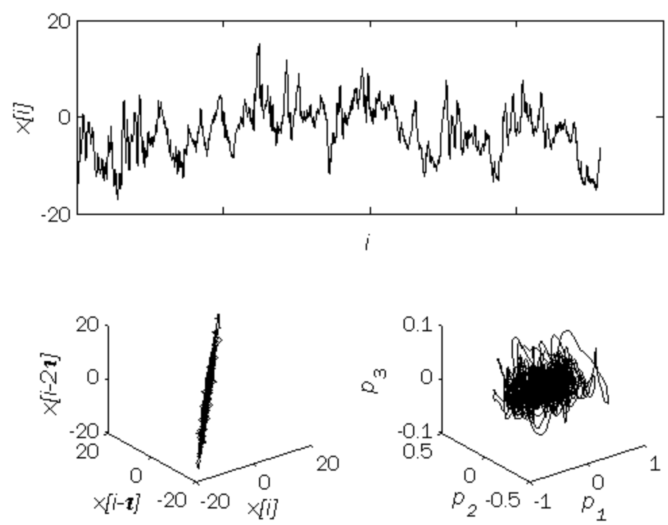


Figure 6.1 Reconstructed COP timeseries.
Original anteroposterior COP timeseries (upper) for a representative subject, delay reconstruction (*m*=3) (lower left), and a reconstruction using the first three principal components of the reconstruction as new “state variables” (lower right) for a representative (anteroposterior direction). To reduce noise, the series in the lower right was first embedded in *m*=14 dimension. Over 99% of the variance of the initial embedding is contained in the three components.

In Part A, surrogate series were then used for comparison to rule out identified structures being random: (1) the randomly shuffled original timeseries, and (2) a randomly generated series with normal distribution and the properties of the original timeseries (Theiler, Eubank, Longtin, Galdrikian, & Farmer, 1992). In Part B, the post-mTBI state space was compared to the pre-season state space.

6.4 Part A Results

Ideal embedding dimension

The ideal embedding dimension (Figure 6.2) for participants when standing with eyes closed is shown for the mediolateral and anteroposterior directions. For the majority of individuals, the ideal embedding dimension indicated by the false nearest neighbours method was m=5 in the mediolateral direction and m=4 in the anteroposterior direction.

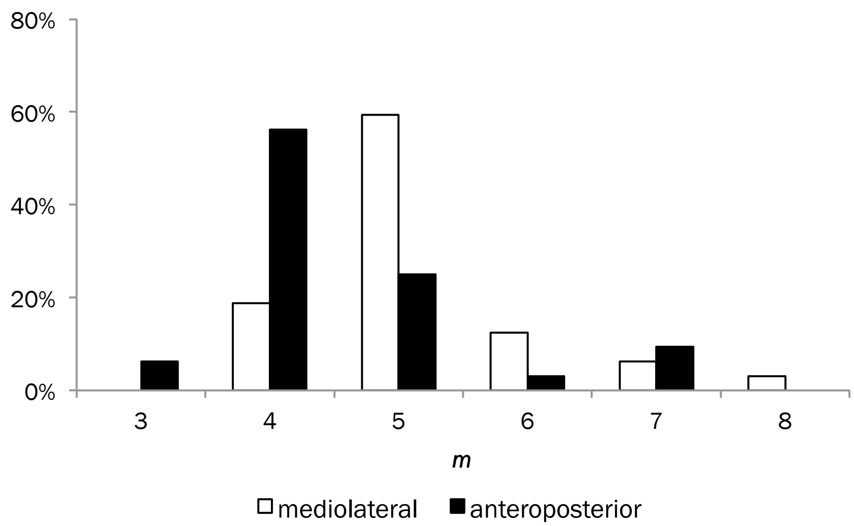


Figure 6.2 Ideal embedding dimension of COP for all participants.
The mode is m=5 for the mediolateral and m=4 for the anteroposterior direction.

COP state space reconstruction

The 3D state space reconstruction with and without noise reduction embedding can be displayed as three orthogonal projections (Figure 6.3). Trajectories are better displayed after noise reduction embedding. These reconstructions appeared similar among participants for both the mediolateral and anteroposterior timeseries.

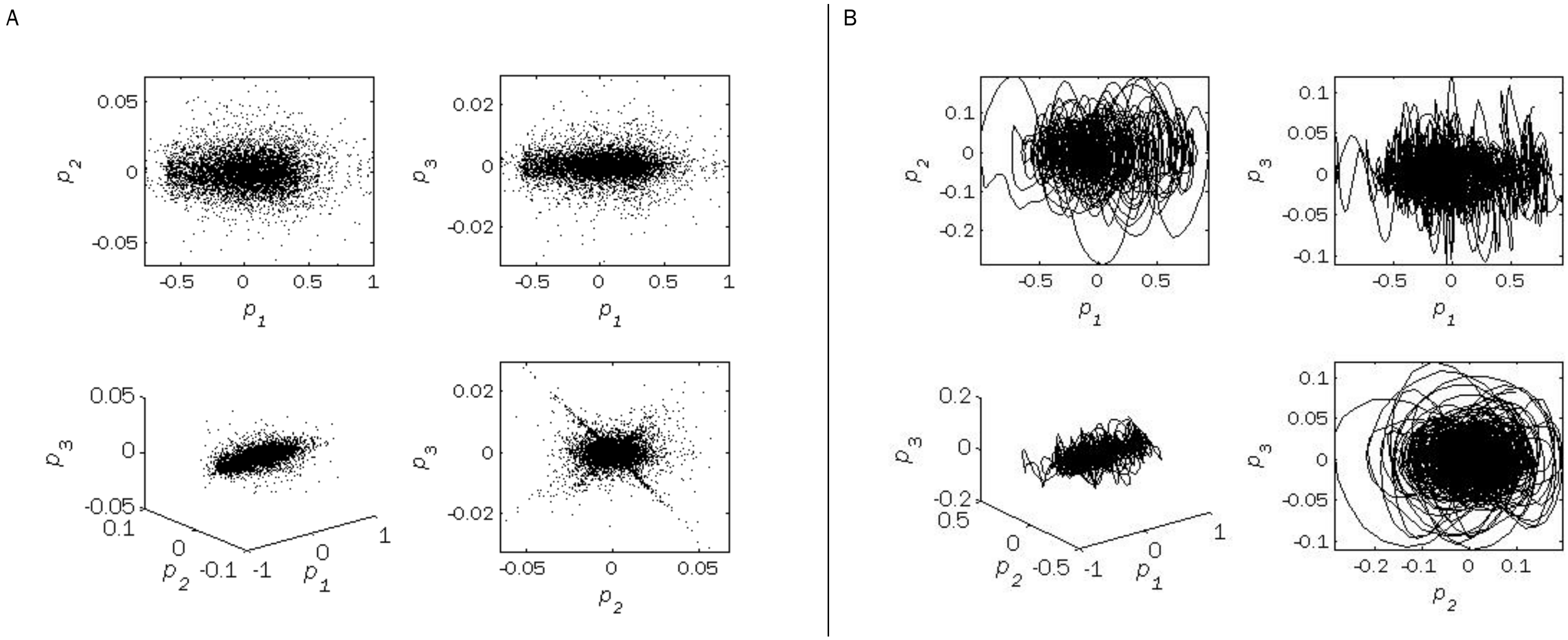


Figure 6.3 Orthogonal views of principal components.
(A) An example of a participant's reconstructed anteroposterior timeseries shown as points without noise reduction embedding in 3D (lower left) shown with three orthogonal projections: the first orthogonal view (upper left), the second orthogonal view (upper right), and the third orthogonal view (lower right). This four panel organization is used in subsequent figures throughout the chapter. (B) An example of a participant's reconstructed anteroposterior timeseries (3D(lower left) and three projections (upper left, upper right, & lower right) with noise reduction embedding.

Surrogates

It was important to determine whether findings were a reflection of the true underlying structure of the timeseries or simply an artifact of the numerical methods that were used. The reconstructed original COP timeseries demonstrated a structure that was distinct from surrogates. Figure 6.4 shows the lack of temporal structure in surrogate timeseries, and confirms the temporal structure found in the original timeseries is not random.

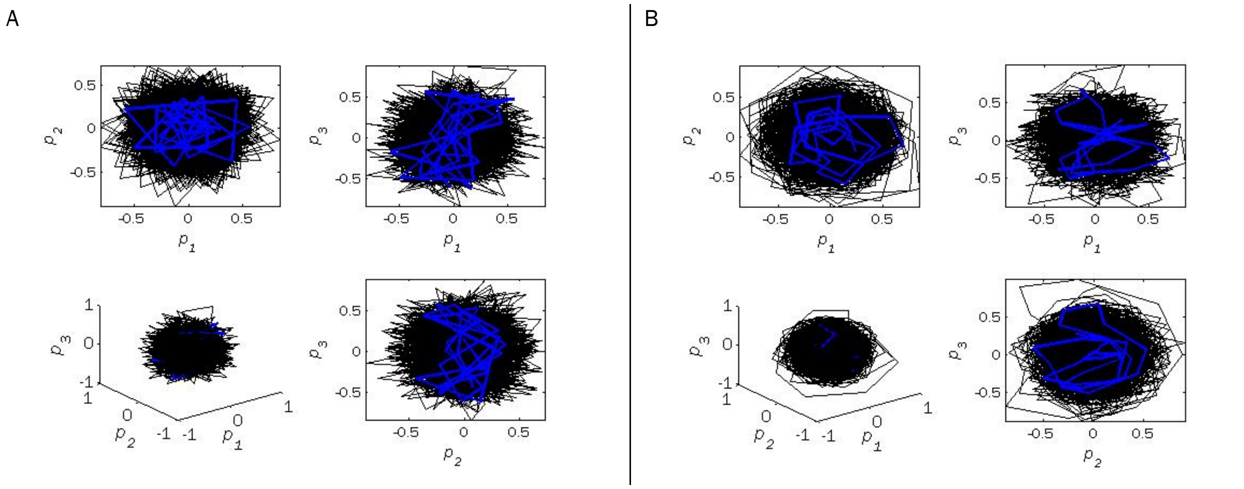


Figure 6.4 Surrogate timeseries.
Surrogates were generated by (A) randomizing the original COP timeseries and by (B) generating a random normal distribution.with the same mean and variance as the original COP timeseries. In each, the blue trajectory highlights a brief part of the timeseries to better show its random structure. The three-dimensional plot is shown in the lower left while the three projections are shown in the upper left, upper right and lower right of A and B, respectively. The random structure shown here can be compared to Figure 6.3B to see that theye are dissimilar in appearance.

Trajectories

The most variance in the original timeseries is represented by the data along the first principal component axis. The first principal component axis lies along the unity line that can be seen in the lower left panel of Figure 6.1. While the heavy concentration of trajectories makes it difficult to see, some structure can be discerned.

In the first orthogonal projection (Figure 6.5a or b, upper left panel), the trajectories appear to circle around multiple foci along the first axis. This shows that along the first principal component axis, p_1 moves along the axis in both directions; however, the movement along the axis demonstrates no apparent pattern. The most visible pattern can be seen in the movement around the first principal component axis as large departures from the axis. Shown in Figure 6.5a, the full pattern appears as a loop when viewed from the first orthogonal projection (upper left), but in the second orthogonal projection (upper right), has two sinusoidal components. In the

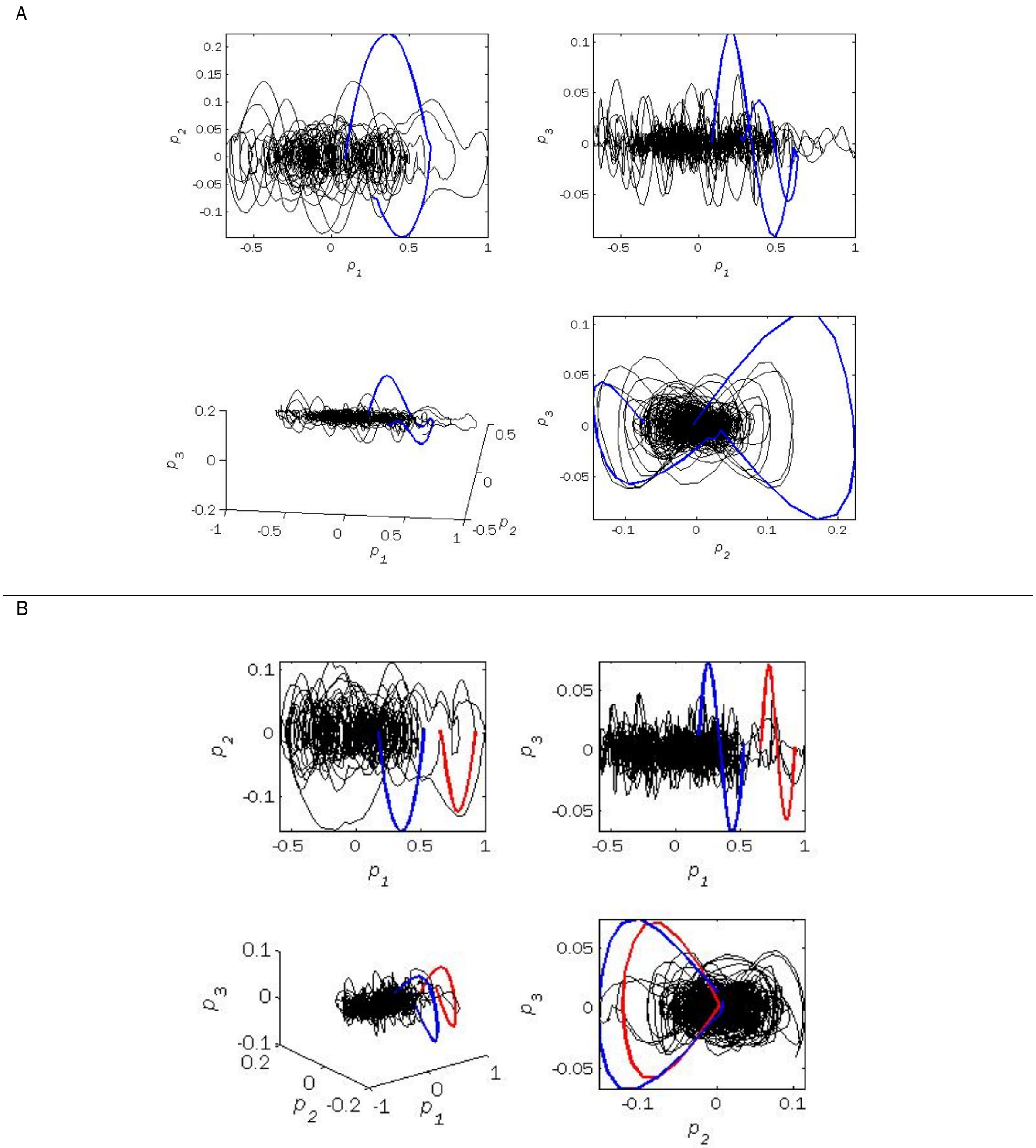


Figure 6.5 Common loop structures in the reconstructed timeseries.
(A)The full pattern (blue) is shown in orthogonal projections and in 3D while (B) separate instances of the half pattern are shown in red and in blue. The full pattern corresponds to the COP's movement anteriorly and then posteriorly. The half pattern corresponds to movemment in one direction only. The structure has a different appearance when viewed from different orthogonal projections. The appearance of the intersection of trajectories at the centre in the third orthogonal projection (lower right) is shown to be false in 3D (lower left).

third orthogonal projection (lower right), the pattern appears as double loop with points that seem to intersect near the origin but these points are, in fact, false neighbours. The full structure of this 3D pattern can be best viewed by rotating the plot (lower left). In Figure 6.5b, two instances of the half pattern are shown at different positions along the first principal component axis. This same pattern repeats itself at different locations along the first principal component axis and can also occur for smaller departures from the axis. It can be seen that despite being located at different positions along the axis, the trajectories behave similarly.

The pattern of movement around the first principal component axis—movement along the second and third principal component axes—requires 3D to see its complete structure and the information it carries. The 3D loop structure demonstrates how p_1, p_2, and p_3 are constrained with respect to one another. The pattern demonstrates that p_1 appears to be constrained to a particular vicinity when p_2 is limited by p_3. This can be seen in Figure 6.6a where positive p_2 and maximum p_3 change to maximum p_2 and zero p_3. In Figure 6.6b, p_2 starts to decrease as p_3 decreases to a minimum.

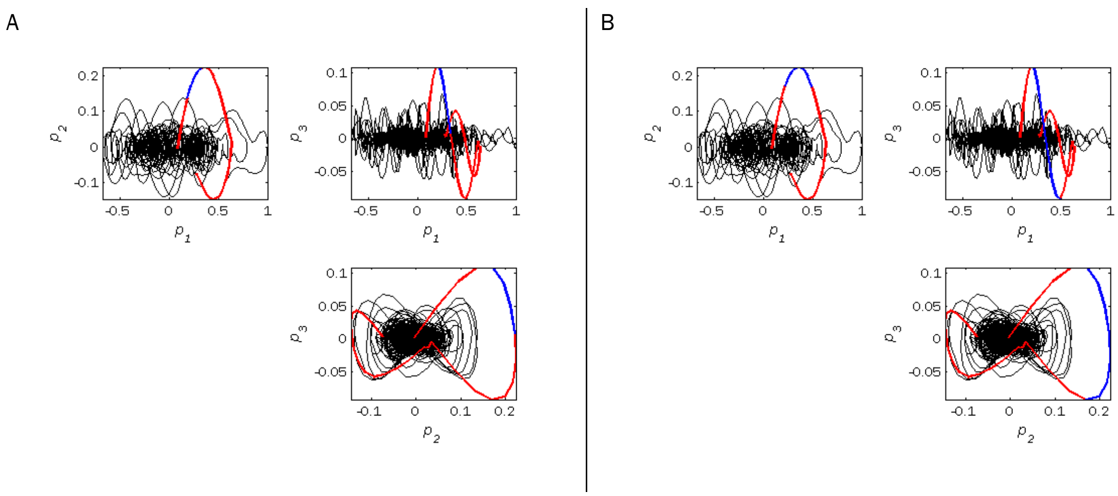


Figure 6.6 Pattern characteristics
This figure shows the characteristic shape from three projections (upper left, upper right, and lower right) of the same timeseries in A and B. Highlighted in blue to follow a portion of the trajectory, it can be seen that when p_2 is near its maximum, p_3 decreases from a local maximum (A) to zero and (B) to a local minimum.

For example, if the first and second orthogonal projections demonstrate the velocity (p_2) and acceleration (p_3), respectively, of the COP in state space with respect to the state space position (p_1, the first principal component axis), then large velocities are constrained through the action of the decreasing acceleration. The cusps (in the third orthogonal projections, where p_2 and p_3 start or return to near zero) demonstrate that at other times, the velocity and acceleration move in concert away from and towards zero which results in the characteristic shape (Figure 6.5a&b lower left panels). Since the pattern is seen at multiple positions along the first principal component axis, the local constraint of p_1 motion (within each instance of the pattern) does not depend the overall state space position, but depends on state space velocity and acceleration.

6.5 Part A Discussion

We aimed to discern underlying structure in COP, a timeseries in which discerning attractor structure is typically difficult. To this end, (1) embedded delay reconstruction and principal component analysis were used to reduce noise in the timeseries, and (2) 3D and 2D visual representations were used. Our findings show that COP structure in the state space reconstruction is not random. Our findings also demonstrate structures that are greater than 2D.

As previously mentioned in the introduction, Zatsiorsky and Duarte (2000) also explored two components of motion in the dynamics of COP. Their investigations using rambling-trembling decomposition and gravity line decomposition yielded similar results. They found that motion of the COP was comprised of motion of a reference point, which they termed rambling, and motion around the reference point, which they termed trembling. Our results can be interpreted through Zatsiorsky and Duarte's (2000) framework.

In our state space reconstruction of COP, it is useful to think of the first principal component axis in the reconstruction as being analogous to an axis of system reference points. Therefore, the reference point is not fixed since there is a lot of motion along the first principal component axis. The first principal component axis is also analogous to the gravity line. Each position on the first principal component axis coincides with a vertical projection of the COM. Therefore, when the trajectory of the reconstructed COP is on the first principal component axis, COP is coincident with the vertical projection of the COM. In particular, the third orthogonal view (for example Figure 6.5b, lower right) shows how COP trajectories move with respect to the vertical projection of the COM. The 3D view shows how this occurs at multiple positions of the moving reference point (for example Figure 6.5b, lower left). Thus, the characteristic pattern (Figure 6.5a,b) demonstrates how the COP moves with respect to COM vertical projections, which in turn provides information about how the COM is controlled.

The characteristic pattern qualitatively supports what has been demonstrated in intermittent activation balance control to achieve stability—velocity or phase plane activation rather than position-dependent activation. Bottaro, Yasutake, and Nomura (2008) presented an intermittent control model where phase plane activation is the result of large values in two diagonally opposite quadrants (one representing a progressive forward fall indicated by a large positive velocity, the other representing a progressive backward fall indicated by a large negative velocity) that activate control impulses to redirect the trajectory to the two quadrants represent an arrest of the fall (transition from forward to backward, and vice versa). In our work, large departures from the gravity line in state space, demonstrated by the characteristic pattern, suggest work is being done to arrest the fall in the manner described above. In Figure 6.6, we saw that when velocity is too large with respect to the vertical projection of the COM, the acceleration reduces and reverses the motion. In the characteristic pattern, demonstrated by the cusps, acceleration and, therefore, forces return to zero when not required to limit velocity. Asai et al. (2009) also explored phase plane activation and demonstrated that different types of dynamic stability could be achieved by intermittent state space-dependent activation.

6.6 Part B Results

Ideal embedding dimension

The ideal embedding dimension (Figure 6.7) for pre-season and post-mTBI football players are shown below in the mediolateral and anteroposterior directions. The ideal embedding dimension indicated by the false nearest neighbours method had a modal value of *m*=6 in both directions for the preseason COP and *m*=5 for both directions post-mTBI.

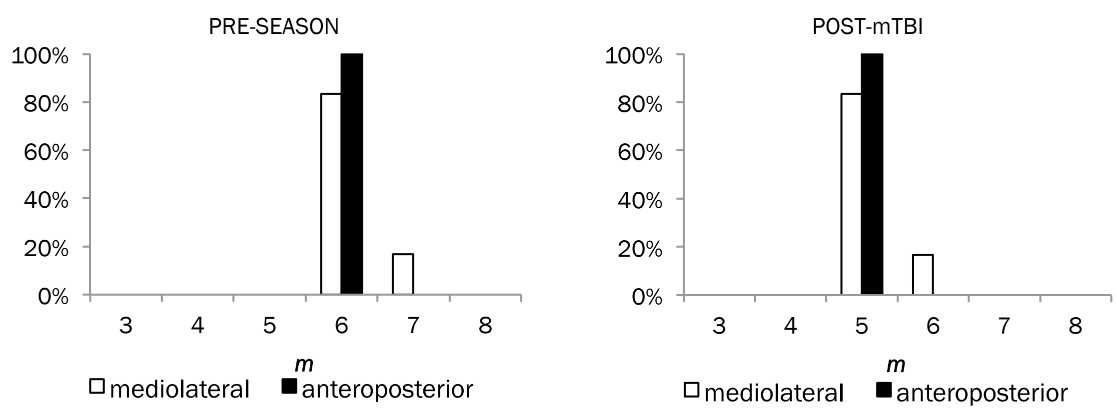


Figure 6.7 Pre-season and post-mTBI ideal embedding dimensions.
Above, the ideal embedding dimension show a modal value of m=6 before injury and a modal value of m=5 after injury.

Trajectories

Pre-season

Similar to the previous healthy results, the pre-season (healthy) COP reconstructions demonstrated movement along the first principal component axis and movement around the first principal component axis.

Large departures from the first principal component axis demonstrate the same patterns that were noted before in Figure 6.5. Below, in Figure 6.8 the characteristic semi-loop is seen in the first orthogonal projection, the sinusoid is seen in the second orthogonal projection, and the loop is seen in the third orthogonal projection. The rotated 3D view demonstrates that the two shapes that have been highlighted have similar characteristics in 3D.

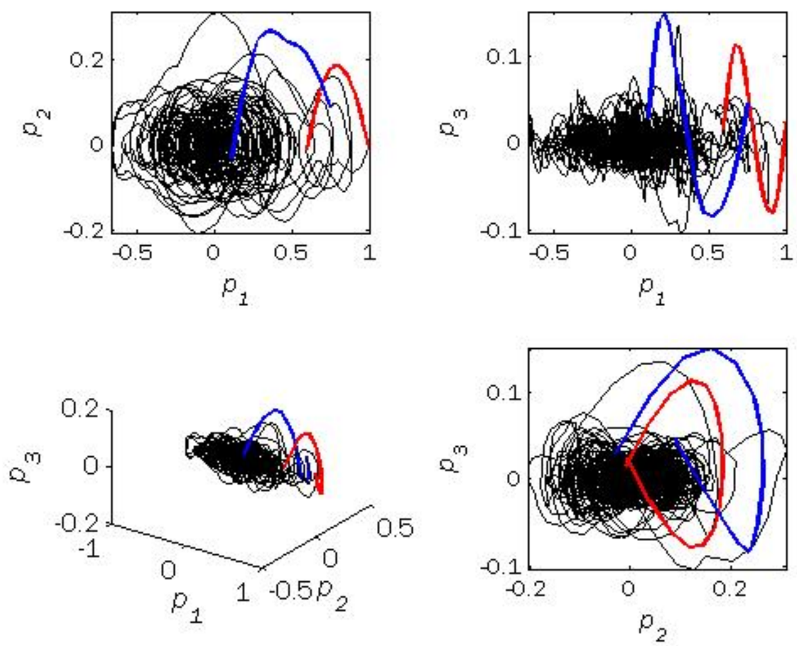
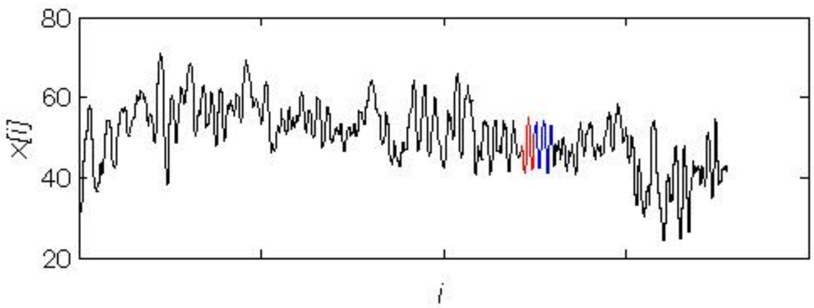


Figure 6.8 An example of a pre-season state space trajectory.
The characteristic structures (in red and blue) for large departures from the first principal component axis are shown in an example of a subject's anteroposterior pre-season COP state space. In three dimensions we see how these shapes have similar trajectories which may not be evident in projection views alone.

In Figure 6.9a, a portion of a COP timeseries is highlighted first in red then in blue. These correspond to the segments of the same colour shown in the state space below. In Figure 6.9b, in red, we note the characteristic loop, sinusoid, and loop with indentations that approach the first principal component axis. Subsequently, in blue, the loop appears the same while the shape in the second projection is no longer sinusoidal. The shape in the third projection eventually no longer has cusps (the indentations in the loop that approach the first principal component axis). The red shape appears to degenerate into the blue shape; despite looking similar in the regular COP timeseries (Figure 6.9a) and in the first orthogonal projection (Figure 6.9b upper left), there are subtle differences in the shapes with respect to the trajectories around the first principal component axis (Figure 6.9b lower right). If we again consider that the first and second orthogonal projections demonstrate the velocity (p_2) and acceleration (p_3), respectively, of the COP in state space with respect to the state space position (p_1, the first principal component axis), the degenerate shape shows acceleration continues to limit velocity but acceleration does not return to zero (when the cusp is not produced). Both these shapes and therefore both types of behaviour are found in the pre-season players COP state space though the degenerate pattern is typically not seen for large departures (large velocities).

A



B

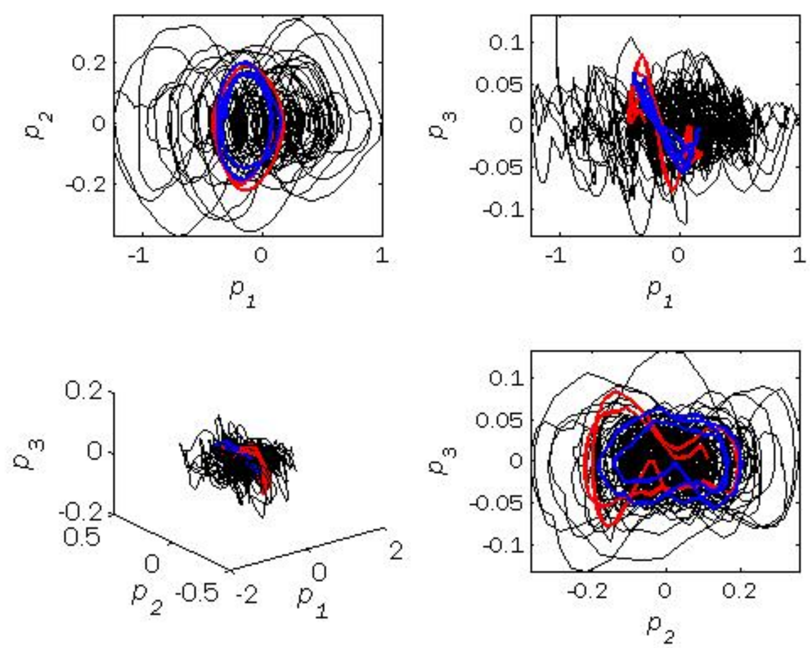


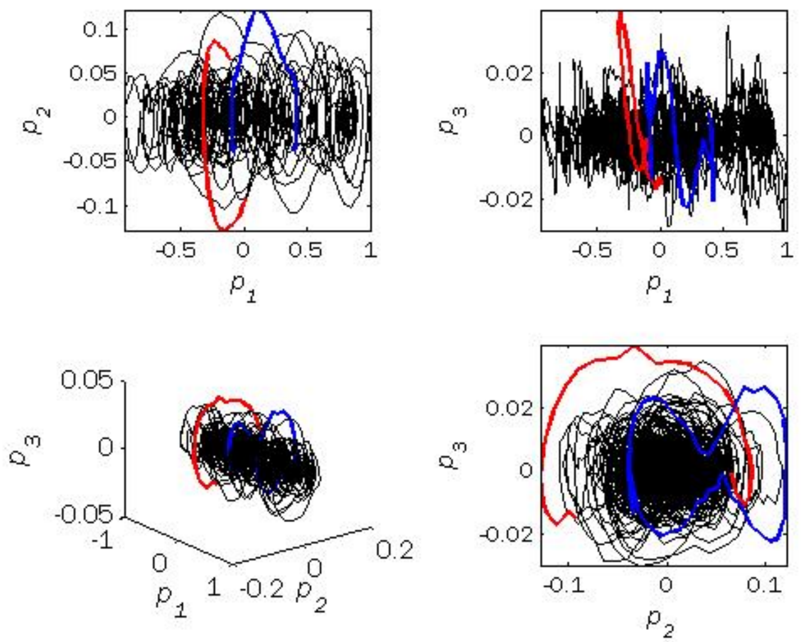
Figure 6.9 An example of a pre-season state space.
(A) A COP timeseries with a portion highlighted in red and blue. (B) The corresponding COP state space reconstruction. The characteristic shape is seen in red which changes to a different shape (blue) best shown in the second and third projections. Notice the in the original COP timeseries and in the first projection the blue and red trajectories seem the same as one another.

Post-mTBI

Post-mTBI COP reconstructions demonstrated movement along the first principal component similar to that of healthy or pre-season COP.

Some minor differences, however, were noted in the movement around the first principal component axis. Below we discuss some examples. In Figure 6.10a&b, we see that the degenerate shape appears for large departures from the principal component axis along with the characteristic shape that is typically seen. In Figure 6.10a, the characteristic pattern, in blue, though present is off-centred in the third orthogonal projection (lower right). The characteristic pattern is actually the half-version (half loop, one sinusoid, loop though with cusps). Yet, the cusps are present and out of place occurring at higher velocities rather than at or near zero. Also in Figure 6.10a, the degenerate shape, in red, appears as a portion of a loop in the first orthogonal projection, a check mark in the second orthogonal projection and a portion of a loop that stays well away from centre (near zero) in the third orthogonal projection. While in the first shape (blue), velocity is limited by acceleration in a typical manner (the characteristic cusps) but in an atypical portion of the loop (higher velocity not near zero), in the second shape (red) the trajectory of the check mark doesn't return to zero in the same manner as a sinusoid in the second orthogonal projection and in the third orthogonal projection, the trajectory of the loop stays well away from centre (away from zero velocity, zero acceleration). Figure 6.10b demonstrates a characteristic pattern (blue) that is off-centred and atypically shaped in the third orthogonal projection as well as a degenerate shape that lack a cusp at the top (also in the third orthogonal projection). These trajectories seen post-mTBI for large departures from the first principal component axis were not typically seen pre-season (when healthy) for large departures; they were only seen for smaller departures from the first principal component axis.

A



B

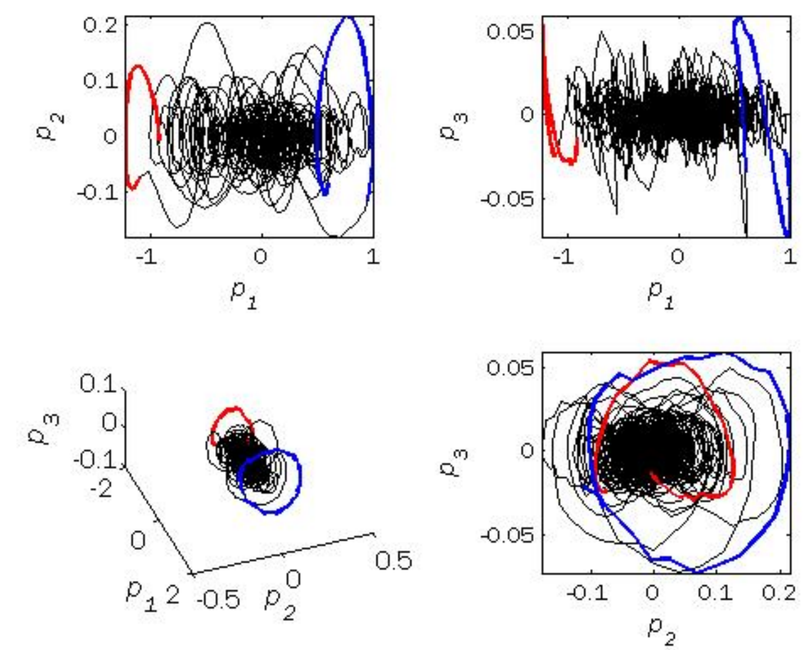


Figure 6.10 Examples of post-mTBI state space trajectories.
(A)The characteristic shape is still evident (blue) though with some differences as well the degenerate form (red) (B) The shapes that are seen blur the lines between characteristic and degenerate.

6.7 Part B Discussion

We aimed to discern whether or not the state space characteristics would be altered post-mTBI. The same state space characteristics were found in both pre-season and post-mTBI COP state space therefore we conclude that state space characteristics were not altered by mTBI although some interesting differences were noted.

In healthy young adults, in COP state space, large departure trajectories from the first principal component axis, and consequently the gravity line, demonstrate the characteristic that tends to return the trajectory to the gravity line. Smaller departures from the gravity line are likely to have much more varied shapes including the degenerate shape in which the trajectory does not return to the gravity line as often. Interestingly, this degenerate shape was sometimes evident for large departures in the state space of individuals who had sustained an mTBI. This demonstrates that large velocities were being limited by continuous non-zero acceleration as opposed to intermittent activation, however since both types of behaviour were present in pre-season and post-mTBI state space, it was not sufficient evidence to conclude that state space was altered by mTBI.

Zatsiorsky and Duarte's (2000) framework continues to be of use in interpreting the two-component movement of the COP. Movement along the first principal component axis and therefore the movement of the reference points appeared unaltered after sustaining mTBI. A limitation of the method of COP attractor reconstruction used in this study is that movement along the first principal component is composed of overlapping trajectories with multiple foci that create a picture that is not easily discernable. While 3D views of the trajectories offer a somewhat better view of the first principal component axis, the resulting picture is still not ideal. Furthermore, the cause of the motion along the axis is not represented and therefore leaves an open question as to what causes the continual movement of reference point.

On the other hand, the movement around the first principal component axis, that is, movement of COP around the reference point is well described by this method of COP attractor reconstruction and demonstrates that while there are many similarities to healthy and pre-season, some aspects of COP movement with respect to the vertical projection of COM are altered. These slight differences require further investigation to determine whether they are simply normal variations in control or a reflection of control altered by mTBI.

6.8 Conclusion

The visual representations of COP state space demonstrated potential control mechanisms in the form of attractor structure and were similar among healthy adults. The attractor structure in individuals who had sustained and mTBI had mostly similar characteristics to their healthy state space though there were some slight differences. In future research, the amount of time and relative frequency spent exhibiting the different attractor structures in each reconstructed timeseries can be explored as well as the muscle activation associated with each trajectory pattern. This may shed light conclusively on whether COP attractor structure is altered after mTBI.

Acknowledgements

We would like to extend our thanks to the volunteers for participating in this study. We would also like to thank Coralie Rochefort for assisting with data collection.

Funding

The first author was supported by scholarships provided by the Government of Ontario (QEIIGSST, OGS) and by the University of Ottawa.

Conflicts of Interest Statement

There are no conflicts of interest to disclose.

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7. Main Conclusion

7.1 Summary and discussion of significant findings

Chapter 1 introduced important concepts related to balance by reviewing system physiology, models of balance, methods of investigation and analysis, and their application to the investigation of sensory and motor integration and control in healthy and pathologically altered balance. Chapter 1 also (1) identified gaps in knowledge with respect to non-linearity in healthy balance control and (2) suggested potential avenues of investigation for mild traumatic brain injury. Sensory and motor systems develop and are integrated to allow the body to maintain balance in opposition to gravity. Physiological and functional integration of these systems permit multiple output strategies to accomplish this. Inverted pendulum models have been used to understand how the systems are integrated. In these balance control models, controlling variables such as velocity and acceleration of centre of mass or centre of pressure have been found to be plausible, reasonable, and relevant since within the body's sensory systems are components that are capable of transducing and integrating these types of variables. Balance studies that examined how factors such as age, fatigue, pathology, condition, and attention—in particular, how centre of pressure movement during quiet stance is altered by these factors—were reviewed. Reduced sensory redundancy and system integration in balance control were found in children and the elderly, but were the result of different changes. Fatigue appeared to alter muscle response, sensory input, and integration of these components. Furthermore, different pathologies demonstrated different effects. In focal injuries such as stroke and cerebellar injury, balance was most affected when an important contributing system was injured; however, even in the case of Parkinson's disease and multiple sclerosis, though a specific part of the balance control system may not have been affected, integration of systems was affected. Reviewed studies used visual condition, stance conditions, and attentional demands in quiet stance to demonstrate changes to visual dependence, system integration, and functional resource availability in balance. In the chapters that followed, visual condition, stance, and attention were likewise used as the basis for the investigation of mild traumatic brain injury. The final part of the first chapter laid the groundwork for advancing the investigation of control and integration in balance using local stability, scaling, and state space reconstruction methods. These were reviewed for the purpose of application to centre of pressure and to mild traumatic brain injury and applied in the experimental studies reported in the subsequent chapters.

Review of physiological and functional changes in mTBI

In chapter 2, the scoping review examined the functional effects of mild traumatic brain injury (including the effects not only on balance performance, but also on higher and related systems that could affect balance) in the weeks after injury. The review illustrated that mTBI recovery can be described in phases of neurometabolic change; altered brain activity and connectivity; as well as symptoms and functional impairments by consolidating findings in literature that support a description of likely events after mTBI. Initially, stretching and compression of neurons causes changes to membrane permeability, subsequent widespread depolarization results in an imbalance of substrates in and around neurons, which in turn causes cell damage that can affect a functional grouping of neurons as well as connectivity between groupings. Functional effects are strongly evident during these phases. The processes to normalize these changes take time; in the meantime, compensatory mechanisms may include functional limitations and trade-offs that preserve resources in the brain. Altered balance, in particular, was found up to 30 days after injury in several studies; however, findings that revealed altered balance for a longer duration after injury appeared to necessitate more complex and challenging protocols than those that reported symptoms or balance effects soon after the mTBI. This idea formed the basis for the use of non-linear measures and dual-task methodologies in the studies that followed.

Linear and non-linear COP in healthy quiet stance

Chapter 3 explored healthy quiet stance in young adults using linear and non-linear methods of analysis and established normative values for non-linear measures across numerous conditions, including single and tandem stance—on which non-linear data had not previously been published.

The complementary use of linear and non-linear measures was able to describe how balance in quiet stance was affected by lack of visual input and altered base of support in terms of control, output, and integration. Changes to output were identified by changes in position-based measures. Increased control requirements were identified by a relative increase in velocity-based measures because velocity-based measures reflect angular momentum and demonstrate how position is modified. In healthy young adults, when eyes were closed in order to remove visual input, increased control was needed to stand quietly. Removing visual input also demonstrated that anteroposterior system output was visually dependent. The increase in output represented a greater forward and backward displacement from centre—essentially leaning farther forward and backward—which necessitates greater torque and consequently greater motor and system output in the form of muscle strength. In this manner, more difficult stance positions also demonstrated greater motor output and increased control requirements, this time as a result of an altered based of support. When standing on one leg, the base of support was reduced both mediolaterally and anteroposteriorly. In tandem stance, the base of support was reduced mediolaterally. As a result of the reduced base of support, greater torque and hence greater strength were required. Furthermore, in tandem stance, integrated neuromuscular systems of the lower limb muscles manifested as greater mediolateral and anteroposterior output and greater mediolateral and anteroposterior control despite a reduction only in mediolateral base of support.

Decreased local stability also demonstrated changes to both output and control with absence of visual input and with more difficult stance positions. Decreases in local stability showed that nearby state space trajectories—two points initially representing similar position, velocity, acceleration, etc.—would show greater maximum divergence. Less local stability therefore represented a greater change in position, velocity, acceleration, and potentially higher order state variables—representing greater changes to output, control, control of control and so forth.

Scaling, on the other hand, appeared to indicate when active control was being employed. Changes to the amount of random correlations likely suggest a controlling mechanism being turned either on or off. Short-term scaling was less complex in the most biomechanically stable direction (the direction with the largest base of support) for each stance. Thus, less complexity may suggest less active control. While long-term scaling was similar across conditions, the presence of decreased mediolateral complexity relative to anteroposterior complexity in long-term scaling suggested there may be a difference in how active control was integrated.

Effect of mTBI on linear and non-linear COP

Chapter 4 and 5 utilized this understanding of healthy linear and non-linear COP to investigate the changes that occurred to balance in healthy young adults and healthy adolescents as a result of mild traumatic brain injury. The largest Lyapunov exponent and scaling parameter had not been previously used to investigate changes to COP in mTBI.

In the young adults, there were no indications that the individuals who sustained mild traumatic brain injuries, had been more susceptible as a result of pre-existing balance abnormalities. Prior to the start of their football season, balance in these individuals, as described by the linear and non-linear measures, was similar to their uninjured teammates as well as to other healthy young adults.

Linear measures did not show mTBI-related changes to balance output and control, nor did local stability demonstrate changes to higher-order control that were not a result of regular season activities. However, mTBI-related changes to balance did occur. More complex short-term scaling suggested that more active control mechanisms were required as a result of mild traumatic brain injury; however, the scaling changes were subtle—the short-term scaling mechanism nevertheless remained persistent. Because the effect was subtle and because it was present some time after injury, the increased complexity in temporal correlations that were reflected in scaling may have been the result of the compensatory reorganization and redistribution of functional resources that occur as discussed in chapter 2.

Healthy adolescents showed similar output and control characteristics to those of healthy young adults in quiet stance. The effect of attention resources on quiet stance was also investigate in adolescents. When attention resources were challenged by performing a simultaneous Stroop task, output and control characteristics were similar to those in simple quiet stance. Some adolescents with mTBI demonstrated nearly identical trends to those of healthy adolescents one month after having sustained an mTBI; however, approximately 30% of adolescents with mTBI, albeit of a small sample size, demonstrated altered balance characteristics. This suggests a different recovery profile.

When standing on one leg when compared to standing on both legs, in contrast with typical expectations as a result of the reduced base of support (greater output, greater control requirements, and less local stability), similar output and similar local stability were demonstrated. In these adolescents, when attention resources were challenged, greater output, greater control, and less local stability than even single leg stance were demonstrated. More complex short-term and long-term scaling were also markedly evident suggesting more active control. These changes to temporal correlations demonstrated a month after injury also support the concept of functional adaptations in the compensatory phase.

COP state space

Chapter 6 contributed significant understanding about the nature of balance control by employing three-dimensional visual state space representations. Previous literature had, up until now, only examined two-dimensional state or phase space and found it lacking a visually discernable structure. Here, dynamic structure was identified and further clarified by transforming the attractor. Dynamic stability was demonstrated by the system in the form of a characteristic pattern—supportive of intermittent control. In individuals with mTBI, this characteristic movement around the reference point was still present though other types of movement were also present.

7.2 Limitations

Like all undertakings, the studies presented in this dissertation have some minor limitations.

- The scoping review in chapter 2 was limited by sparse data for each specific type; therefore, drawing definite conclusions would not be appropriate. This limitation was addressed by making only general conclusions and not attempting to fit a precise timeframe across all study results.
- In chapter 3, the sample size for normative data was not as extensive as other studies where population sample sizes have been on the order of hundreds (rather than on the order of tens seen here). Yet, it is not unusual for studies that examine non-linear data to have smaller sample sizes. Because of the increased amount of analysis and processing, to keep studies feasible and within the scope of a PhD project, sample sizes were kept small.
- The study presented in chapter 4 had a small sample size for the injured, but not uncharacteristically so when compared to similar studies (since the number was limited by the number of players who were injured during the course of the study.) The ability of linear measures to demonstrate significant changes might have been limited by the small sample size of the mTBI group. In addition, since the exact circumstances and mechanisms of injury for each player were unknown, other factors which may determine whether or not balance is affected, how balance is affected, or the severity of the effect are unknown.
- As in chapter 4, in chapter 5, the exact circumstances and mechanisms of injury for each adolescent were unknown. Nor is it known, in general, how homogeneous effects are across individuals with mTBI. When differences emerged suggesting that balance in some individuals was affected to a different degree, this was explored.

- In the case of state space analysis, as in the case with most types of analysis and especially non-linear analysis, the major challenge was to avoid introducing artifacts from the analysis methods that were employed. To this end, surrogate comparisons were used.

Therefore, study limitations were addressed as described above, so that the conclusions drawn from these results of these studies can reasonably be considered valid.

7.3 Conclusion & future direction

State space reconstruction sheds light on the nature of balance control

State space reconstruction in chapter 6 suggests there are at least two components to balance control. While the concept of two or more reference spaces within balance control is not new, the ability to see structure within both spaces was novel. In previous literature, dual mechanisms of balance have been explored. Collins and De Luca (1993) suggested open- and closed-loop postural control by demonstrating a short-term persistent mechanism and a long-term anti-persistent mechanism. Short-term persistence and long-term anti-persistence in quiet stance have been reproduced in numerous studies (Chiari et al., 2000; Mello et al., 2010) and in the present studies as well (chapters 3, 4, & 5). Collins and De Luca (1993) concluded that in the short-term, balance moves away from an equilibrium point whereas in the long-term equilibrium is returned. Therefore, they postulated that control was a combination of deterministic and stochastic (random walk) mechanisms. Zatsiorsky and Duarte (2000) described the system dynamics—rambling and trembling—as migration of the system reference and movement around the system reference, respectively. Zatsiorsky and Duarte (2000) concluded the mechanism behind continuous migration of the reference was unknown, but possibly due to noise of the central nervous system or continuous exploration by the system to update somatosensory information. Movement around the reference was related to horizontal restoring forces. Bottaro et al. (2008) presented a model of balance control where tonic and phasic controllers, controlling the reference tilt and constraining movement to the neighbourhood of the reference respectively, are modelled to approximate experimental sway patterns. Their model allowed the dual components of balance control to be approached from the perspective of the mechanism underlying the movement to show how intermittent control can produce bounded stability. They conclude an intermittently closed loop that controls movement around the reference (phasic control) means that delays won't cause instability (similar to saccadic eye movement).

In my work, state space reconstruction demonstrated that there is a structure beyond noise in control components. In the reconstruction, movement of the reference is shown to have structure influenced in part by the biomechanics of quiet stance but also by a deterministic control that may be non-linear. Movement around the reference point demonstrates the type of quadrant control that can be described by Bottaro et al.'s (2008) intermittent control model, but also a fair amount of noise from when control is not activated. In my work, the combination of active control (fully persistent or anti-persistent movement) and inactive (random movement) is supported by quiet stance scaling that varies in complexity.

Output and control in quiet stance

Visual input and base of support had an effect on output and control in healthy adults. In healthy adolescents, the same was true. In both populations, visual dependence was limited to the anteroposterior direction. Attention resources were also studied in adolescents and were also found to affect output and control.

In age-related changes to balance and pathologically altered balance, visual dependence was able to demonstrate changes to sensory redundancy and sensory integration (Hytönen et al., 1993; Woollacott & Shumway-Cook, 1990). Changes to output can also be as a result of altered sensory integration. Attention resources are a reflection of processing resources within the brain (Lajoie, Teasdale, Bard, & Fleury, 1993). Changes to output and control were the foundation for determining changes to quiet stance as a result of changes to processing and sensory integration.

The effect of mTBI on balance is due to its effect on processing and integration

More active control (particularly visually dependent control) and attention-related changes to output and control suggest that mTBI affects balance by affecting sensory integration and processing of inputs and outputs. As a result of mild traumatic brain injury, during quiet stance, more active short-term control was employed (chapter 4). Some adolescents with mTBI demonstrated visually dependent scaling changes that indicated more active long-term control was necessary (chapter 5).

While quiet stance scaling had not previously been examined after mTBI, it had been examined in elderly individuals after stroke and in healthy young adults during fatigue. Elderly adults who suffered a stroke showed more complex and therefore more active control in balance than healthy elderly adults (Roerdink et al., 2006). On the other hand, muscle fatigue is a common physiological occurrence in healthy individuals. Ankle muscle fatigue resulted in less complexity and therefore less active long-term control of balance (Mello et al., 2010). Mello and colleagues (2010) attributed this to increased muscle stiffness and recruitment of more motor units to generate the same response as non-fatigued muscles.

In addition, while scaling had not previously been examined after mTBI, other measures of complexity such as approximate entropy have been used in the investigation of mTBI (Cavanaugh et al, 2006). Cavanaugh and colleagues (2006) found that COP was more regular after mTBI and put forth that reduced or distorted interactions among neurons increased the regularity of cortical oscillations that resulted in increased regularity (reduced randomness or increased active control) in COP. It can be speculated that the results of the present studies and Cavanaugh's study demonstrate that a widespread reallocation of resources as a result of the metabolic consequences of mTBI (as discussed in chapter 2) lead to more predictable (less random) control performance as a result of fewer resources being allocated. Though paradoxical, an increase in active control of balance as opposed to intermittent control of balance signals a decrease in processing resources in the brain perhaps as a result of less inhibitory activity. This proposed idea is in line with the example of fatigue seen above (Mello et al , 2010), where less active control was actually a result of increased motor resources.

Attention-related changes to output and control were likewise indicative of an effect on processing and integration activity in the brain (chapter 5). Mild traumatic brain injury has been known to affect force production and regulation in motor tasks (Slobounov et al., 2002), including the regulation of another function relying on intermittent control—saccadic eye movement (Drew et al., 2007). The effect of mTBI on shared attention resources has also been found in simultaneous walking and Stroop tasks (Catena et al., 2011; Howell et al., 2013). As in gait, in quiet stance, regulation in the form of active control, production in the form of output, and integration in the form of both output and control—which are already affected by mTBI—are also affected by the additional demand of the Stroop on widespread networks in the brain (Pardo, Pardo, Janer, & Raichle, 1990). These effects are a hallmark of the compensatory phase.

Future direction

Distinguishing compensation vs. plastic improvement for safe return-to-play

In chapter 2, the compensatory phase was related to an underlying cause—metabolic depression. Early metabolic depression also signified a period of risk where the brain, at its limit of reversible metabolic disruption (Giza & Hovda, 2001; Leddy et al., 2007), was more vulnerable to the consequences of a subsequent mTBI (McCrea et al., 2009a; Vagnozzi et al., 2008). The compensatory phase, on the other hand appeared to last considerably longer and transition in to a necessary phase of plasticity. Future studies using linear and non-linear measures as well as state space reconstruction on quiet stance and dual-task COP collected at multiple time points after injury may be able to clarify the timeframe of whether the alteration due to mTBI are early or late in the compensatory phase. This would further the ultimate goal of determining when it is safe to return-to-play (and when it is ideal to start exercise to further plastic development in the brain).

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Appendix A

A.1 Wii Balance Board calibration

Basic properties of the Wii Balance Board were verified. It was verified that the load cells output scaled linearly for the full range (18 kg, 36 kg, 45 kg, 68 kg, 90 kg, and 113 kg) of typical mass. The measured mass was determined to be 99.7% accurate. The calibration matrix for each Wii Balance Board was computed using standard methods.

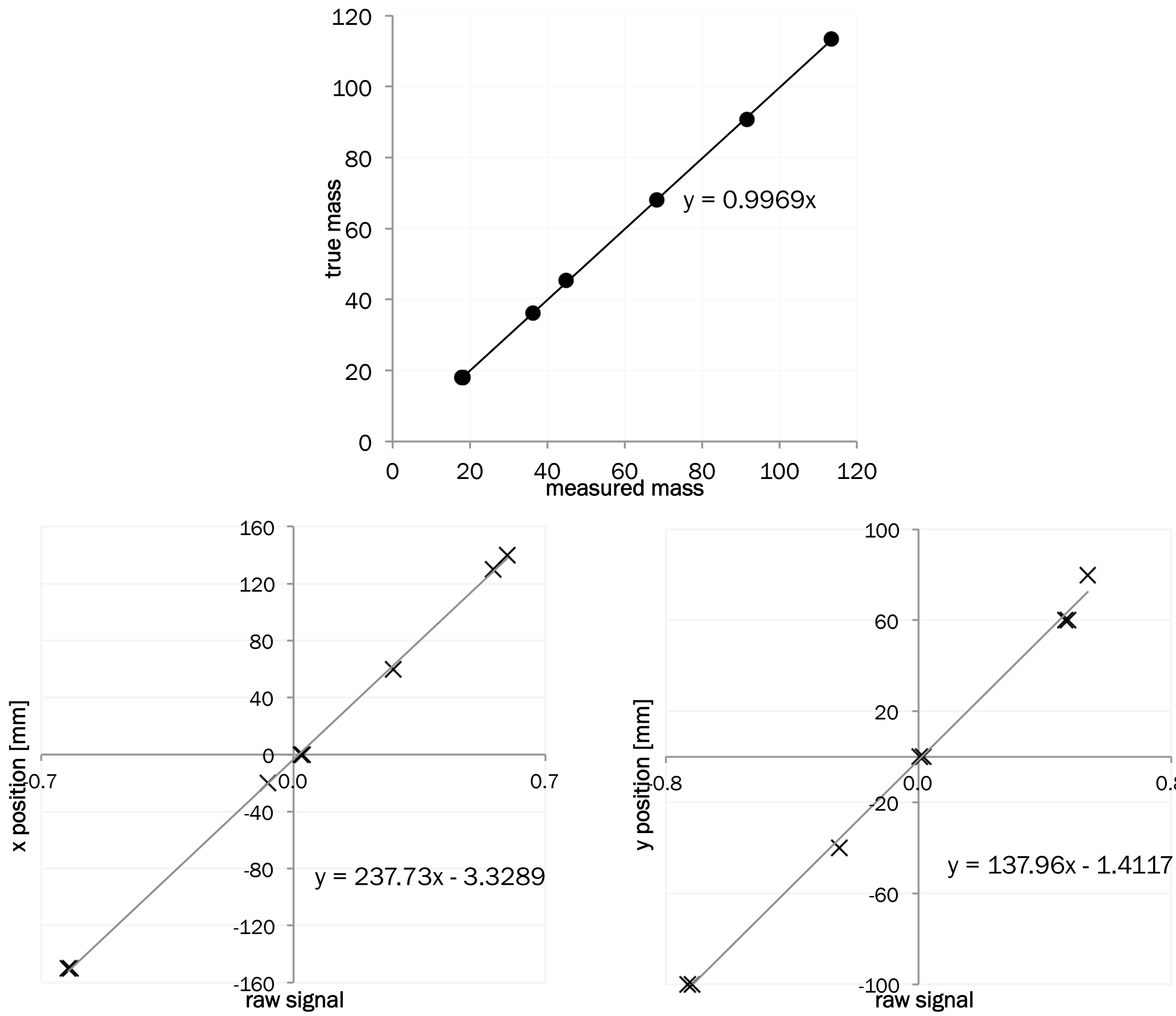

Figure A.1 Nintendo Wii Balance Board mass (top) and position (bottom) measurement properties.

A.2 Wii Balance Board validation

Centre of pressure is calculated using the forces and moments measured from a platform. The forces and moments are measured using multiple load cells that produce voltage according to the amount of applied strain in each of the three orthogonal directions. The Bertec (Model 4060-07) uses six strain gauge load transducers to measure six components—three forces and three moments—in the orthogonal directions. The Nintendo Wii Balance Board (US Patent 2009/0093305 A1) contains four load cells oriented only in the vertical direction and therefore does not account for forces that occur in the horizontal directions.

Previous studies have validated the use of the Wii Balance Board as a portable, wireless alternative to typically used force platforms such as the Bertec force platform in research and in clinical practice (Clark et al, 2010; Huurnink et al, 2013). Clark and colleagues compare 10-second duration (single leg stance) and 30-second duration (double leg stance) trials collected with each force platform separately. Huurnink and colleagues collected 10-second duration (single leg) trials of the Wii balance board and force platform simultaneously by placing the Wii Balance Board on top of the platform and making the appropriate correction to the surface height term of the COP equation. Therefore, this abridged study has the simple purpose of confirming that our lab's Balance Board provides similarly valid results.

Hardware and software

The Wii Balance Board measures approximately (maximum dimensions) 506 mm by 315 mm. The surface stands at a height of 54 mm. The Wii Balance Board contains a wireless module allowing for wireless communication through Bluetooth protocols. A PC laptop equipped with Bluetooth capability was used to receive the signal from the Wii Balance Board. Two Bertec force platforms each measuring 600 mm x 400 mm were mounted side-by-side in a stable base to form a surface 600 mm x 800 mm. The Wii Balance Board was placed with its x-y centre directly above the centre of the Bertec surface. GlovePIE, a programmable input emulator available online at no cost (www.glovepie.org), was used to acquire the raw signals from each of the load cells in the Wii Balance Board. The program allows the user to write a simple script to interface with third party controllers. The script instructs the Balance Board's power light to turn on when data is being collected, to display a counter (in seconds) while data is being collected, and to output the four raw signals in a text file. All commands used for the program were found in GlovePIE's online documentation.

The Bertec force plate calibration matrix is supplied by the manufacturer and is digitally stored on each force plate (Bertec Corporation Force Plate User Manual). MATLAB was used to process the Wii Balance Board signal using the computed calibration matrix. All data were collected at a frequency of 60 Hz. Ruhe and colleagues (2010) recommend collecting at a frequency of 100 Hz; however, the collection frequency of the Wii Balance Board is intrinsically limited to 60 Hz.

Comparison

Eight individuals were tested while standing quietly. Each trial yielded two timeseries, one for each force platform. In comparisons between the Bertec and the Wii Balance Board (Table A.1), the Bertec force platform was considered as the reference.

Table A.1 Difference between timeseries with Bertec as reference

	Difference mean [range]	
	Δx	Δy
mean [mm]	0.96 [.41, 2.2]	1.77 [0.8, 3.1]
maximum [mm]	7.81 [3.34, 10.8]	12.3 [6.47, 22.0]
error %	5.1 [3.1, 6.2]	4.6 [3.1, 6.7]

Measures that were calculated from the Bertec timeseries (column 1, Table A.2) and measures that were calculated using the Wii Balance Board timeseries (column 2) were not significantly different from one another though there was a trend for values calculated from the Wii Balance Board timeseries to be smaller. The mean difference between corresponding points in the Bertec timeseries and Wii Balance Board timeseries (Table A.1) was less than 1 mm in the mediolateral timeseries and less than 2 mm in the anteroposterior timeseries—approximately a 5% error. Spikes in the timeseries resulted in large maximum values; however, the maximum represents only a single point which is unlikely to affect measures which utilize all points in the timeseries. The Wii Balance Board is a suitable alternative to the Bertec force platform for the calculation of COP measures.

Table A.2 Difference between calculated measures

		Bertec	**Wii BB**	**Difference**	
				average	*p-value*
l [mm/s]		4.63	3.89	-0.74	*p=0.140*
$\bar{u}$ [mm/s]	x	1.79	1.42	-0.36	*p=0.082*
	y	3.91	3.34	-0.57	*p=0.165*
σ [mm]	x	2.81	2.30	-0.51	*p=0.132*
	y	5.96	5.29	-0.66	*p=0.273*

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Acknowledgements

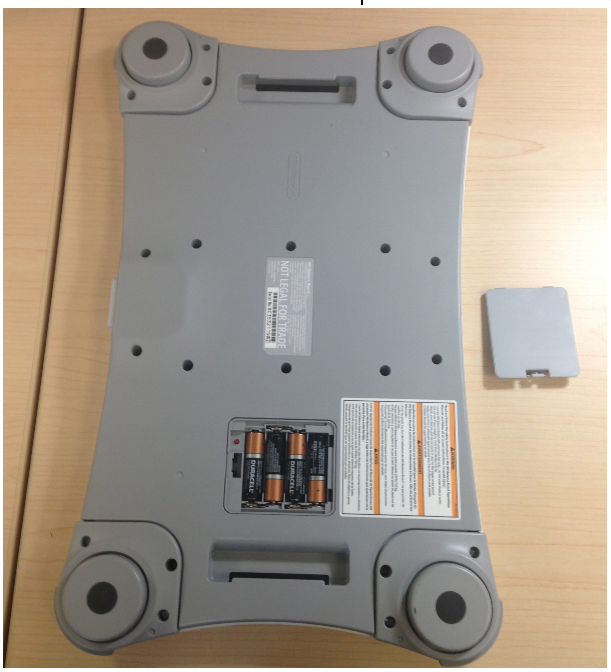
Data collection by Coralie Rochefort.

A.3 Wii Balance Board data collection protocol

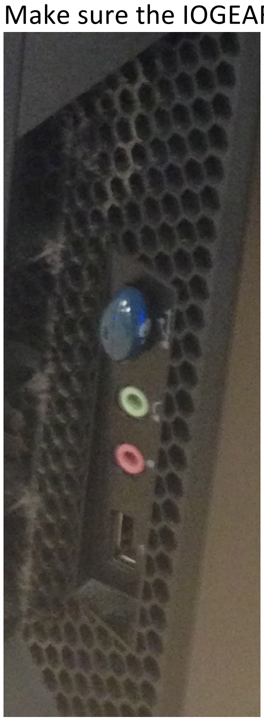
Part One

To setup up the Bluetooth connection

1. Place the Wii Balance Board upside down and remove the battery cover.



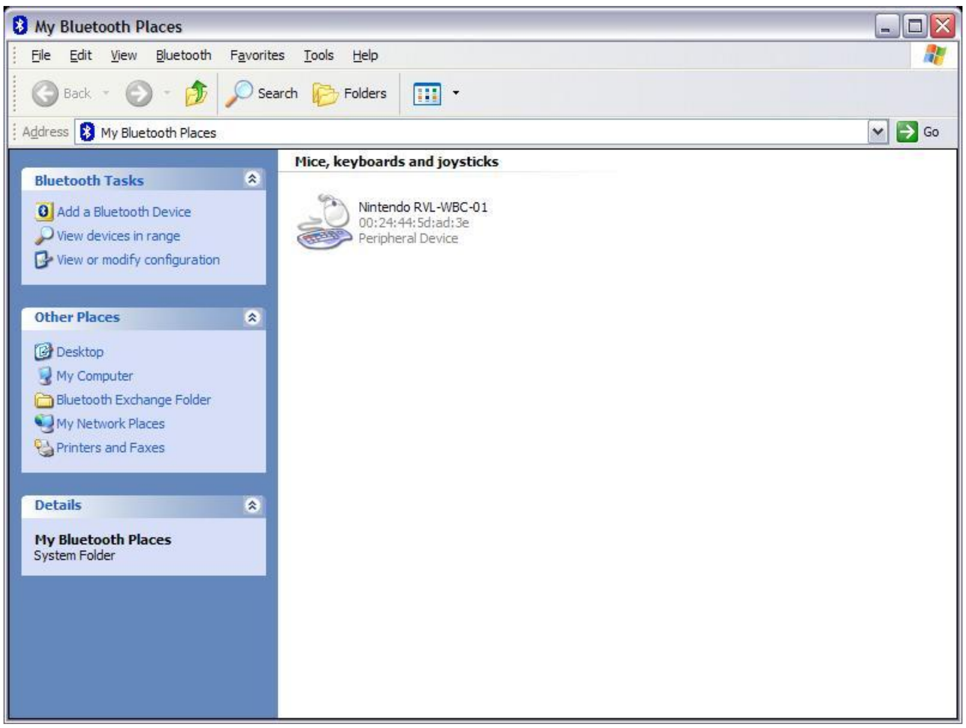
2. Make sure the IOGEAR Bluetooth adapter is in the USB port of the computer.



3. Start the computer and log on: (user) xxxxxxxx
(password) xxxxxxxx

4. Open **My Bluetooth Places**.

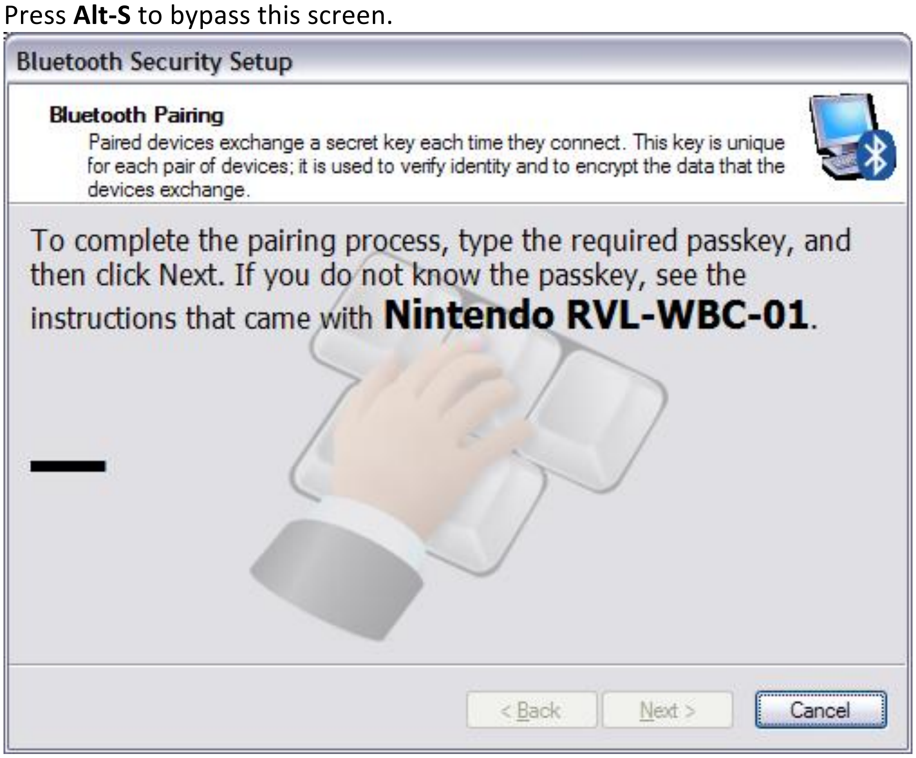
5. Click on **Add a Bluetooth Device** to open the Setup Wizard.
NOTE: The Wii Balance Board will be visible as Nintendo RVL-WBC-01*, but is not yet connected.*



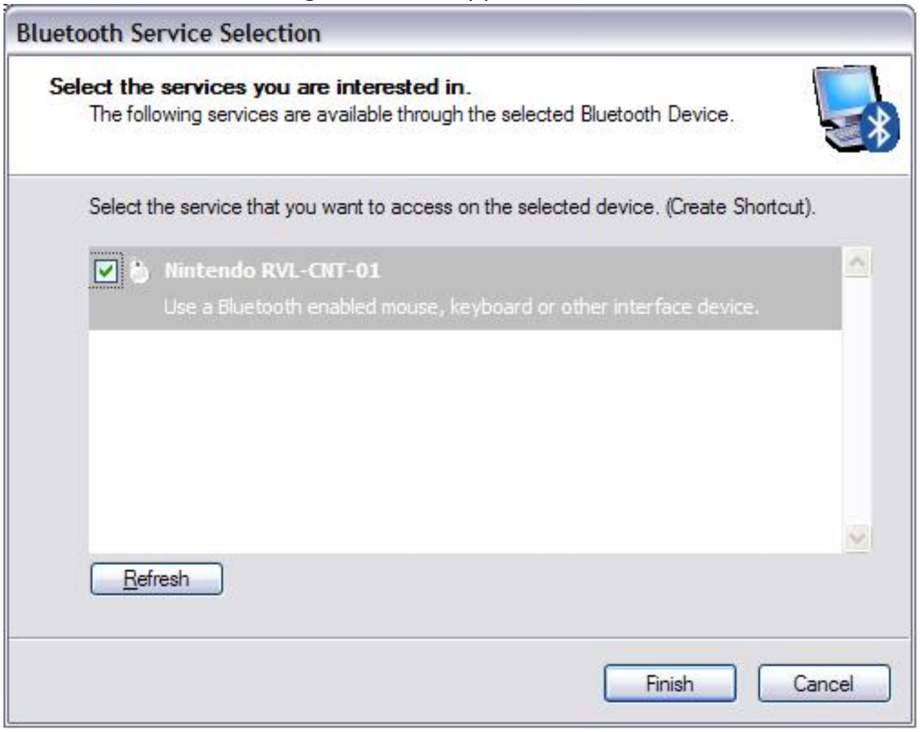
6. On the Wii Balance Board, press and hold (while completing steps 7 through 9) the red SYNC button inside the battery case of the Wii Balance Board. The blue power light on the Balance Board will flash.

7. Click on **Next**.

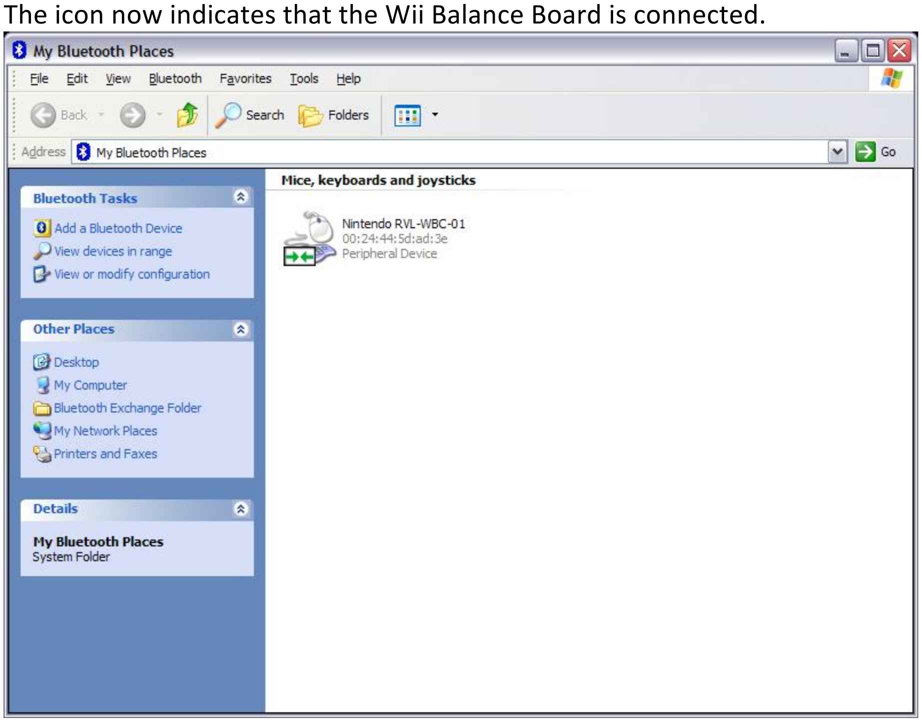
8. Press **Alt-S** to bypass this screen.



9. Click on the box to make green check appear. Then click **Finish**.



10. The icon now indicates that the Wii Balance Board is connected.

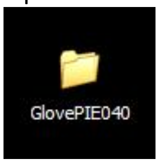


11. Replace the battery cover and place the Balance Board right-side up on the floor with the power light facing toward you.

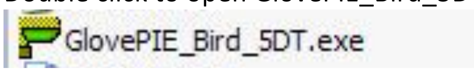
Part Two

To record data

1. Open the GlovePIE040 folder.



2. Double click to open GlovePIE_Bird_5DT.exe.

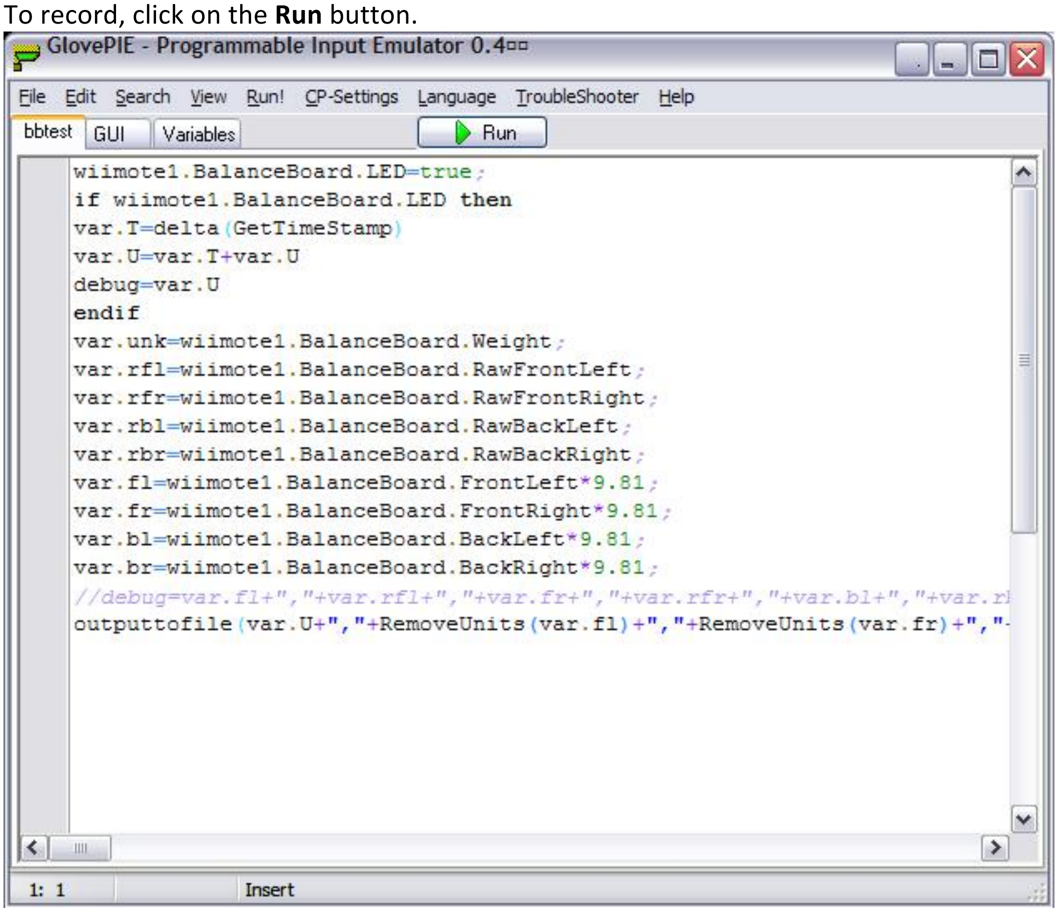


3. Go to

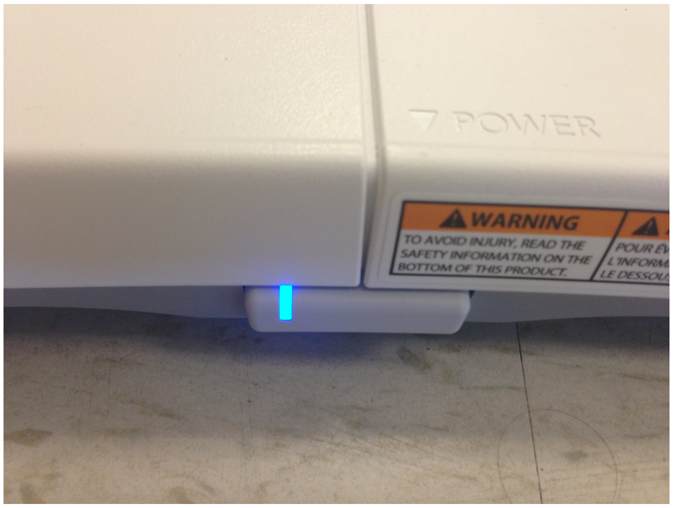
   File> Open> bbtest.PIE

   and double-click to open.

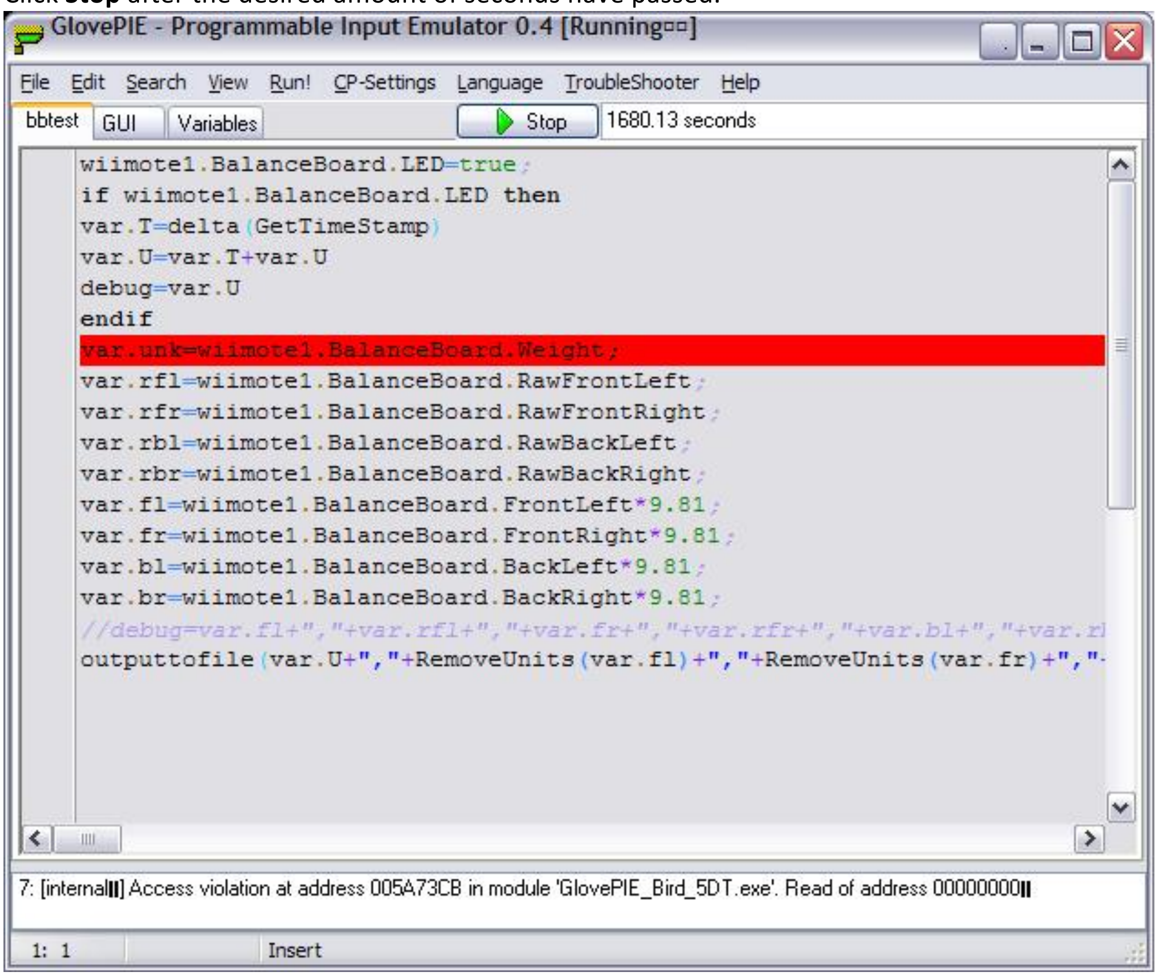
4. Have the subject stand on the Wii Balance Board in the designated foot areas with their toes facing towards you.
5. To record, click on the **Run** button.



6. While running, the program will appear as follows. The power light on the Balance Board will be a solid blue while the program is running.
NOTE: The time stamp will start at an arbitrary value.

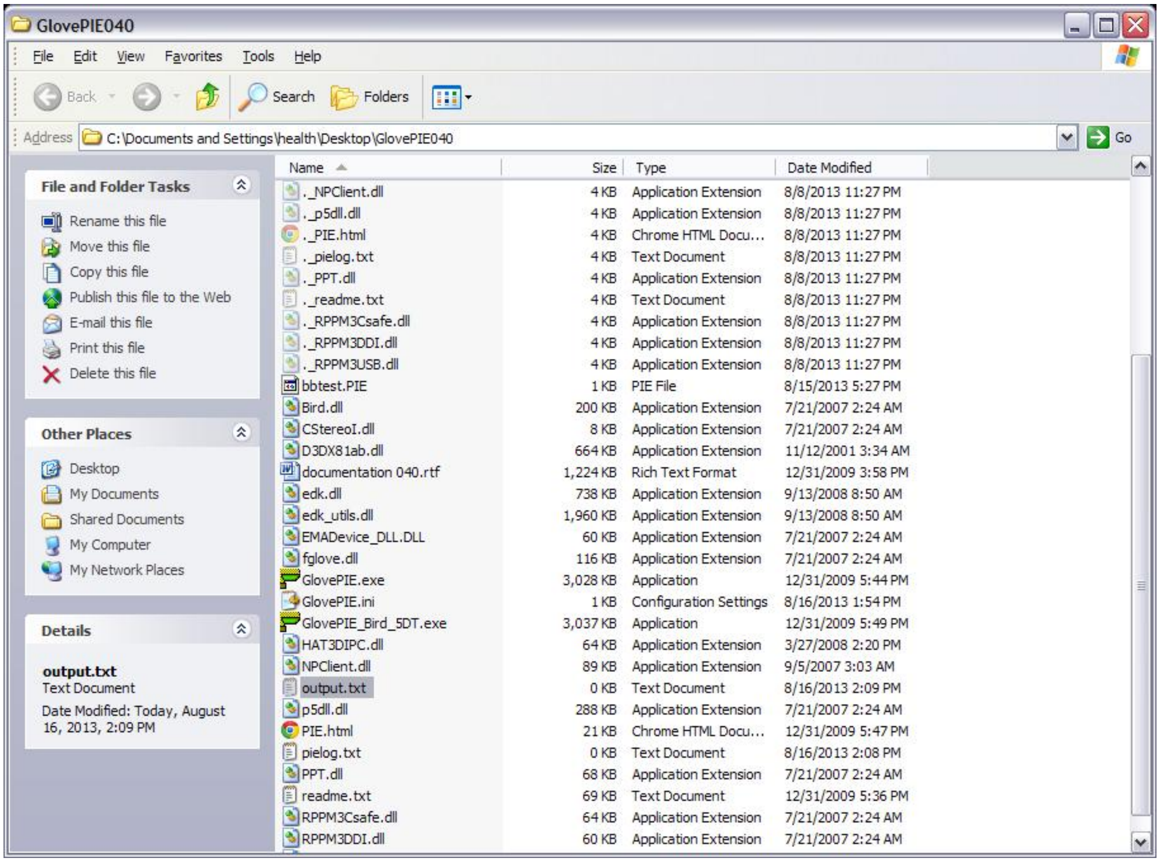


7. Click **Stop** after the desired amount of seconds have passed.



To save the data

8. In the GlovePIE040 folder, open the **output.txt** file and go to **File> Save As** and save it under a new name.
NOTE: This must be done because each time the GlovePIE program is opened the output.txt *file is overwritten.*



Appendix B

B.1 Ethics certificates

File Number: H03-12-02 **Date (mm/dd/yyyy):** 06/29/2012

Université d'Ottawa University of Ottawa

Bureau d'éthique et d'intégrité de la recherche Office of Research Ethics and Integrity

Ethics Approval Notice

Health Sciences and Science REB

Principal Investigator / Supervisor / Co-investigator(s) / Student(s)

First Name	Last Name	Affiliation	Role
Heidi	Sveistrup	Health Sciences / Occupational Therapy	Principal Investigator

File Number: H03-12-02

Type of Project: Professor

Title: Age-related Differences in Posture Control in a Dual-Task Paradigm

Approval Date (mm/dd/yyyy)	Expiry Date (mm/dd/yyyy)	Approval Type
06/29/2012	06/28/2013	Ia

(Ia: Approval, Ib: Approval for initial stage only)

Special Conditions / Comments:

Partial approval

Recruitment may begin at the Oxford Learning Centre (permission letter received).

Full approval will be granted once the written permission letters from the community centres where recruitment will take place are received.

This conditional approval is only valid for the English versions of the recruitment text and consent forms. Once the French versions are received, they will be added to the certificate.

550, rue Cumberland 550 Cumberland Street
Ottawa (Ontario) K1N 6N5 Canada Ottawa, Ontario K1N 6N5 Canada
(613) 562-5841 • Téléc./Fax (613) 562-5338
http://www.research.uottawa.ca/ethics/index.html
http://www.recherche.uottawa.ca/deontologie/index.html

File Number: H03-12-02 **Date (mm/dd/yyyy):** 11/15/2013

Université d'Ottawa
Bureau d'éthique et d'intégrité de la recherche

University of Ottawa
Office of Research Ethics and Integrity

Ethics Approval Notice

Health Sciences and Science REB

Principal Investigator / Supervisor / Co-investigator(s) / Student(s)

First Name	Last Name	Affiliation	Role
Heidi	Sveistrup	Health Sciences / Occupational Therapy	Principal Investigator
Andree	Begin	Health Sciences / Occupational Therapy	Research Assistant
Lyne	Boudreau	Health Sciences / Occupational Therapy	Research Assistant
Dominique	Legacy	Health Sciences / Occupational Therapy	Research Assistant
Coralie	Rochefort	Health Sciences / Others	Research Assistant
Coren	Walters-Stewart		Research Assistant

File Number: H03-12-02

Type of Project: Professor

Title: Age-related Differences in Posture Control in a Dual-Task Paradigm

Renewal Date (mm/dd/yyyy)	Expiry Date (mm/dd/yyyy)	Approval Type
06/29/2013	06/28/2014	Ia

(Ia: Approval, Ib: Approval for initial stage only)

Special Conditions / Comments:
N/A

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Ottawa (Ontario) K1N 6N5 Canada Ottawa, Ontario K1N 6N5 Canada
(613) 562-5387 • Téléc. /Fax (613) 562-5338
www.recherche.uottawa.ca/deontologie/ www.research.uottawa.ca/ethics/

File Number: H03-14-23 **Date (mm/dd/yyyy):** 04/28/2014

Université d'Ottawa
Bureau d'éthique et d'intégrité de la recherche

University of Ottawa
Office of Research Ethics and Integrity

Ethics Approval Notice

Health Sciences and Science REB

Principal Investigator / Supervisor / Co-investigator(s) / Student(s)

First Name	Last Name	Affiliation	Role
Roger	Zemek	Medicine / Medicine	Principal Investigator
Heidi	Sveistrup	Health Sciences / Occupational Therapy	Co-investigator
Coralie	Rochefort	Health Sciences / Human Kinetics	Co-investigator

File Number: H03-14-23

Type of Project: Professor

Title: Predicting Persistent Postconcussive Problems in Pediatrics: A Clinical Prediction Rule Derivation and Validation Study

Approval Date (mm/dd/yyyy)	Expiry Date (mm/dd/yyyy)	Approval Type
04/28/2014	04/27/2015	Ia

(Ia: Approval, Ib: Approval for initial stage only)

Special Conditions / Comments:
N/A

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Ottawa (Ontario) K1N 6N5 Canada

550 Cumberland Street, room 154
Ottawa, Ontario K1N 6N5 Canada

(613) 562-5387 • Téléc./Fax (613) 562-5338
www.recherche.uottawa.ca/deontologie/ www.research.uottawa.ca/ethics/

CHEO Research Ethics Board Approval - Minor Modification

Principal Investigator: Dr. Roger Zemek **REB Protocol No:** 13/94X **Romeo File No:** 20130258 **Project Title:** Predicting Persistent Postconcussive Problems in Pediatrics: A Clinical Prediction Rule Derivation and Validation Study **Primary Affiliation:** Clinical Research\Emergency **Protocol Status:** Active **Date Modifications Approved:** March 20, 2014 **Contingencies:** ***Not Applicable***

Documents Reviewed & Approved:

Document Name	Comments
Consent Form	Parental Consent form for sub-study associated with 5P study - Amendment #2
Consent Form	Parental Consent form for sub-study associated with 5P study (Control Group)- Amendment #2
Consent Form	Consent form for sub-study associated with 5P study - Amendment #2
Consent Form	Consent form for sub-study associated with 5P study (Control Group)- Amendment #2
Assent Form	Assent form for sub-study associated with 5P (Control Group) - Amendmer #2
Assent Form	Assent form for sub-study associated with 5P study - Amendment #2
Other Document	Script for Research Assistants
Other Document	Protocol Summary
Protocol	Protocol Sub-study

This is to notify you that the Children's Hospital of Eastern Ontario Research Ethics Board has granted approval for the modifications to the above named research study. The minor modification was reviewed and approved by the Chair, and would be ratified by the full Board at its subsequent meeting.

In fulfilling its mandate, the CHEO REB is guided by: Tri-Council Policy Statement (TCPS); ICH Good Clinical Practice Practices: Consolidated Guideline; Applicable laws and regulations of Ontario and Canada (e.g., Health Canada Division 5 of the Food and Drug Regulations & the Food and Drugs Act - Medical Devices Regulations). **Approval is granted with the understanding that the investigator agrees to comply with the following requirements:**

1. The investigator must conduct the study in compliance with the protocol and any additional conditions set out by the Board.
2. The investigator must not implement any deviation from, or changes to, the protocol without the approval of the REB except where necessary to eliminate an immediate hazard to the research subject, or when the change involves only logistical or administrative aspects of the study (e.g., change of telephone number or research staff). As soon as possible, however, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted to the Board for review.
3. The investigator must, prior to use, submit to the Board changes to the study documentation, e.g., changes to the informed consent letters, recruitment materials.
4. For clinical drug or device trials, investigators must promptly report to the REB all adverse events that are both serious and unexpected (SAEs). For SAE reports on CHEO patients, the investigator must also comply with the hospital-wide Policy regarding, Procedures For Considering Medical Error In The Differential Diagnosis of Severe Adverse Events (SAE) Associated with the Drugs Administered in a Clinical Trial (see http://cheonet/data/1/rec_docs/3792_Medical%20Error%20Policy%20revised%20january%2020061.doc).
5. For all other research studies, investigators must promptly report to the REB all unexpected and untoward occurrences (including the loss or theft of study data and other such privacy breaches).
6. Investigators must promptly report to the REB any new information regarding the safety of research subjects (e.g., changes to the product monograph or investigator's brochure for drug trials). Where available, any reports produced by Data Safety Monitoring Board should be submitted to the REB.
7. Investigators must notify the REB of any study closures (temporary, premature or permanent), in writing along with an explanation of the rationale for such action.
8. Investigators must submit an annual renewal report to the REB 30 days prior to the expiration date stated on the final approval letter.

9.Investigators must submit a final report at the conclusion of the study.
10. Investigators must provide the Board with French version of the consent form, unless a waiver has been granted.

The investigator must conduct the study in compliance with the protocol and any additional conditions set out by the Board.