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THE EFFECTS OF PREVIOUS CONCUSSIONS ON THE PHYSIOLOGICAL
COMPLEXITY OF MOTOR OUTPUT DURING A CONTINUOUS
ISOMETRIC VISUAL-MOTOR TRACKING TASK

by

Adam C. Raikes

A dissertation submitted in partial fulfillment
of the requirements for the degree

of

DOCTOR OF PHILOSOPHY

in

Disability Disciplines

Approved:

Sydney Schaefer, Ph.D.
Major Professor

Thomas S. Higbee, Ph.D.
Committee Member

Breanna Studenka, Ph.D.
Committee Member

Eadric Bressel, Ph.D.
Committee Member

Idalis Villanueva, Ph.D.
Committee Member

Mark R. McLellan, Ph.D.
Vice President for Research and
Dean of the School of Graduate Studies

UTAH STATE UNIVERSITY
Logan, Utah

2017

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ABSTRACT

The Effects of Previous Concussions on the Physiological Complexity of Motor
Output During a Continuous Isometric Visual-Motor Tracking Task

by

Adam C. Raikes, Doctor of Philosophy

Utah State University, 2017

Major Professor: Sydney Schaefer, Ph.D.
Department: Kinesiology and Health Science

The majority of clinical impairments following a concussion resolve within 7-10 days. However, there is limited clarity as to long-term impact of this injury on neurocognitive function, motor control, and particularly integration of these domains. While repetitive head trauma is associated with numerous neurological disorders, the link is not well described. Visual-motor tracking tasks have been used to identify differences in visual processing, error detection, and fine motor control in aging and numerous pathologies. Examining the complexity of motor output from visual-motor tracking provides insight into multiple cognitive and motor function domains, and into fine motor control used for daily living, work, and sport. The purpose of this dissertation was, therefore, to: (1) use multiple regression to determine the extent to which concussion history and symptoms (loss of consciousness and amnesia) influence visual-motor task performance multiscale complexity, and (2) determine whether task performance complexity can distinguish, through logistic regression and prediction, between individuals with and without a history of concussion. In study 1, individuals with ($n = 35$) and without ($n = 15$) a history of concussion performed a visual-motor tracking task. Men

and women exhibited linear decreases in task performance complexity, as well as mid- and high-frequency task performance components, with increasing numbers of concussions. However, men and women exhibited differing patterns, as did those with and without a history of concussion-related loss of consciousness. Finally, trial-to-trial complexity variability increased with increasing numbers of concussions. Findings indicate (1) a cumulative reduction in the way in which previously concussed individuals process and integrate visual information to guide behavior and (2) gender is an important consideration in concussion-related visual-motor outcomes. In Study 2, individuals with ($n = 85$) and without ($n = 42$) a history of concussion performed a visual-motor tracking task. Linear and nonlinear measures of task performance were used to build gender-specific logistic classification models using 10-fold cross-validation. When ensuring 80% sensitivity, the best models were 75-80% accurate in predicting a history of concussion. Such discrimination has clinical value in identifying individuals who merit further evaluation and observation over time for conditions related to repetitive head traumas.

(169 pages)

PUBLIC ABSTRACT

The Effects of Previous Concussions on the Physiological Complexity of Motor
Output During a Continuous Isometric Visual-Motor Tracking Task

Adam C. Raikes

The long-term ramifications of single and multiple concussions are unclear, though they exist in the forefront of present social and scientific inquiry. While suicides linked to concussion histories by prominent current and former athletes sensationalize the issue, questions abound as to the safe and timely return to work, sport, and active military duty following a concussive event in addition to the link between concussion history and neurological disorders. As such, identifying lingering or persistent alterations in function following concussion is essential.

Nonlinear characteristics of visual-motor task performance, including the complexity of the performance, provide an avenue for quantifying visual processing, error detection, and visual-motor integration. In the context of concussion, we observed that complexity decreases as individuals sustain increasing numbers of concussions. Though clinically asymptomatic, these individuals presented with performance that differed from those with no history of concussion. This suggests that concussions may impart lasting changes in the ways in which individuals use visual information to guide behavior.

Furthermore, nonlinear measures of visual-motor task performance may provide a way to identify individuals who have previously sustained a concussion. In fact, 70-80% of the individuals predicted to have had a previous concussion based on their task performance did have such an history. Consequently, this task may provide clinically

relevant indications of individuals who may merit further observation and evaluation as our understanding of the relationship between concussions and long-term neurological dysfunction, as well as additional related risk factors, continues to evolve.

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Adam C. Raikes

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LIST OF ABBREVIATIONS

AE: Athlete-exposures; one athlete competing in one practice or competition

AIC: Akaike's Information Criterion

ALS: Amyotrophic Lateral Sclerosis

ApEn: approximate entropy

BESS: Balance Error Scoring System

CI: complexity index

CTE: Chronic Traumatic Encephalopathy

CV: Coefficient of Variation

DFA: detrended fluctuation analysis

EEG: electroencephalography

FFT: Fast Fourier Transform

fMRI: functional magnetic resonance imaging

Hz: Hertz

ImPACT: Immediate Post-Concussion Assessment and Cognitive Testing

LOC: loss of consciousness

MMSE: modified multiscale sample entropy

ms: milliseconds

MSE: multiscale entropy

MVC: maximum voluntary contraction

PFC: prefrontal cortex

ROC: Receiver operating characteristic

RMSE: root mean square error

SAC: Standardized Assessment of Concussion

SampEn: sample entropy

SRCs: Sport-related concussions

CHAPTER 1

INTRODUCTION

Background

The short- and long-term consequences and management of concussion have taken center stage in many scientific disciplines. Though sensationalized by popular media reports of death and long-term disability due to repetitive head traumas, definitive links between concussions and the development of Alzheimer's Disease, Parkinson's Disease, chronic traumatic encephalopathy, and depression among other neurological and cognitive impairments exist (H. Chen, Richard, Sandler, Umbach, & Kamel, 2007; Factor & Weiner, 1991; Harris, Shen, Marion, Tsui, & Teschke, 2013; Kerr, Marshall, Harding, & Guskiewicz, 2012; Lehman, Hein, Baron, & Gersic, 2012; McKee et al., 2009; Stern et al., 2011). Consequently, scientific inquiry into the pathophysiology as well as the short- and long-term effects of single and multiple concussions has increased dramatically in the last 30 years. A PubMed search for the term "brain concussion" yielded 2,252 citations total before 1990, while 433 studies have been published between January and May 2016 alone. While the acute neurocognitive and postural effects of concussion are well documented, less is known about the long-term effects in these domains as well as the acute and long-term effects in others commonly reported to be associated with concussion. For reference, "neurocognitive effects" include cognitive impairments in attention, memory, executive function, and reaction time (Giza et al., 2013; McCrory et al., 2013). Further, 'postural effects' generally are increases in postural sway and a reduced capacity to maintain balance (Giza et al., 2013; McCrory et al., 2013).

An estimated 1.6 to 3.8 million sport-related concussions (SRCs) occur each

year (Daneshvar, Nowinski, McKee, & Cantu, 2011; Langlois, Rutland-Brown, & Wald, 2006). Estimates of concussion risk indicate that the overall rate in collegiate sports from 2009-2010 to 2012-2013 was 4.47 per 10,000 athlete-exposures (AEs; one athlete competing in one practice or competition), a 130% increase from 2003-2004 and a 260% increase from 1988-1989 (Daneshvar et al., 2011; Zuckerman et al., 2015). Furthermore, concussion rates in high school athletes are estimated to be 2.5 per 10,000 AEs, representing approximately 9% of all injuries at this level (Gessel, Fields, Collins, Dick, & Comstock, 2007; Marar, McIlvain, Fields, & Comstock, 2012). However, these numbers may underestimate the actual number of concussions sustained by many individuals who either seek non-hospital care or do not report their injuries (Faul, Xu, Wald, & Coronado, 2010; Kerr, Register-Mihalik, Kroshus, Baugh, & Marshall, 2016; McCrea, Hammeke, Olsen, Leo, & Guskiewicz, 2004). In addition to SRCs, concussions are among the most common injuries in recent military endeavors, sustained by an estimated 15-25% deployed servicemen and servicewomen (Hoge et al., 2008; Terrio et al., 2009). Furthermore, the economic impact of concussions and mild traumatic brain injuries in the United States is approximately \$22 billion annually (Finkelstein, Corso, & Miller, 2006; National Center for Injury Prevention (US), 2003).

Concussion Definition and Pathophysiology

A concussion is a complex pathophysiological condition affecting the brain, which is the result of either direct (a blow to the head, face, or neck) or indirect (forces transmitted to the head from elsewhere on the body) biomechanical forces (McCrary et al., 2013). These forces result in a neurometabolic crisis in the brain (Giza & Hovda, 2001, 2014). However, concussions are rarely associated with structural abnormalities seen on conventional neuroimaging (Giza et al., 2013; McCrary et al., 2013). Thus, this

injury is generally considered to be functional in nature.

Acutely after injury, the consequences of this crisis include somatic symptoms (e.g., headache, dizziness, blurred vision, photosensitivity, phonosensitivity), neuropsychological and cognitive function impairment (e.g., working memory, reaction time, and executive function impairments), altered postural control (e.g., balance problems), behavioral changes (e.g., increased irritability, secondary attention deficit-hyperactive disorder), and sleep disturbance. From a clinical perspective, these symptoms and deficits resolve in the majority of cases within the first 7-10 days following injury (Guskiewicz, Ross, & Marshall, 2001; Iverson, Brooks, Collins, & Lovell, 2006; McCrea et al., 2003, 2005). Additionally, this neurometabolic crisis has been linked to an increased risk for subsequent concussion within the first 10 days of injury (Giza et al., 2013; Giza & Hovda, 2014; Guskiewicz et al., 2003; McCrea et al., 2009). Outside of this time frame, the risk of sustaining a concussion is higher for individuals with a previous concussion as compared to those with no history of concussion (Giza et al., 2013; Guskiewicz et al., 2003). Subsequent concussions often have protracted recovery times compared to the first concussion (Guskiewicz et al., 2003). Additionally, prior history of concussion, particularly multiple concussions, has been linked to the development of neurological conditions including depression (Kerr, Evenson, et al., 2014; Kerr et al., 2012), Alzheimer's disease (Guskiewicz et al., 2005; Lehman et al., 2012), Amyotrophic Lateral Sclerosis (ALS; H. Chen et al., 2007; Chiò, Benzi, Dossena, Mutani, & Mora, 2005), Parkinson's disease (Factor & Weiner, 1991; Goldman et al., 2006; Harris et al., 2013; Rugbjerg, Ritz, Korbo, Martinussen, & Olsen, 2008), and chronic traumatic encephalopathy (CTE; McKee et al., 2009, 2013; Omalu et al., 2005; Stern et al., 2011).

Given the prevalence of concussions, the associations between adolescent/early adulthood concussions and neurological and cognitive impairments in later adulthood,

and the high annual cost associated with concussions, there is a need for discovering cost-effective biomarkers that can be used to track an individual's recovery from a concussive event, and potentially identify those individuals at risk for developing negative long-term outcomes.

Structure of Dissertation

The general purpose of this dissertation is to describe a method for quantifying the integration of cognitive and motor functions following a concussion. The available literature supports the idea that this approach is appropriate for quantifying changes in function and may be useful in discriminating between individuals with and without a history of concussion. First, in Chapter 2, an overview of the literature regarding current practices and research for identifying and monitoring the effects of concussion on cognitive and motor function is presented. Second, a definition and explanation of physiological complexity, as well as the effects of aging and disease on complexity are provided. Third, the effects of concussion on physiological complexity are described. Fourth, a description of continuous isometric visual-motor force tracking is given along with an explanation of the advantages of this task over others in quantifying physiological complexity. Fifth, current gaps in the literature base regarding both the visual-motor force tracking task and the effects of concussion on complexity are identified. In Chapter 3, the results of a study identifying group differences in complexity during the visual-motor tracking task between healthy controls and previously concussed are detailed. In Chapter 4, the results of a study in which measures of complexity and gender were used to distinguish individuals with a history of concussion from those without such an history are presented. Finally, Chapter 5 includes a summary of the findings from these two studies as well as suggestions for future research.

CHAPTER 2

LITERATURE REVIEW

Identification and Monitoring of Concussive Effects: Current Practice and Research

Neurocognitive Deficits

Neurocognitive testing provides significant information guiding the clinical management of the acute concussion (Grindel, Lovell, & Collins, 2001) and has been described as a cornerstone of the clinical evaluation (Aubry et al., 2002). Acutely (within the first 5-7 days) concussed individuals exhibit deficits across multiple domains of function, including attention (Collie, Makdissi, Maruff, Bennell, & McCrory, 2006; Makdissi et al., 2001; McCrea et al., 2003; McCrea, Kelly, Kluge, Ackley, & Randolph, 1997), working and delayed memory (Barr & McCrea, 2001; Guskiewicz et al., 2001; Iverson et al., 2006; McCrea et al., 2003, 1997; Sim, Terryberry-Spohr, & Wilson, 2008), executive function (Gaines, Soper, & Berenji, 2016; Guskiewicz et al., 2001; Makdissi et al., 2001), and reaction speed (Bleiberg et al., 2004; Broglio, Macciocchi, & Ferrara, 2007; Iverson et al., 2006; Iverson, Lovell, & Collins, 2005; Maroon et al., 2000; Schatz, Pardini, Lovell, Collins, & Podell, 2006). The majority of these deficits generally resolve within 5-7 days following injury (Barr & McCrea, 2001; Bleiberg et al., 2004; Iverson et al., 2006; McCrea et al., 2003, 2005; T. M. Parker, Osternig, van Donkelaar, & Chou, 2007; Sim et al., 2008).

Numerous test batteries are available that can be used to identify neurocognitive deficits immediately following a concussion. These tests include the Standardized Assessment of Concussion (SAC; McCrea et al., 1998, 1997), Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT; Maroon et al., 2000),

Headminder Concussion Resolution Index (Erlanger et al., 2001), and Cogsport (Makdissi et al., 2001), all of which have all been developed specifically for concussion assessment. These are valid and reliable tests, sensitive to cognitive impairments within the first 14 days after a concussive event (Barr & McCrea, 2001; Broglio et al., 2007; Collie et al., 2003; Erlanger et al., 2001; Gardner, Shores, Batchelor, & Honan, 2012; Iverson et al., 2006; Lau, Collins, & Lovell, 2011; Louey et al., 2014; McCrea et al., 2003). In addition to the rapid resolution of the many symptoms within 5-7 days, individuals tested using *these metrics* are typically considered to be entirely asymptomatic by three months (Broglio & Puetz, 2008; Rohling et al., 2011).

However, there is evidence that individuals have longer-lasting cognitive impairments beyond the clinically accepted trajectory of recovery. Neuroimaging studies on asymptomatic persons in the post-acute and chronic stages of concussion recovery have shown persistent alterations in brain activation to working memory and executive function tasks as compared to healthy individuals, despite equivalent task performance (J.-K. Chen et al., 2004; J.-K. Chen, Johnston, Petrides, & Ptito, 2008a, 2008b; Gosselin et al., 2011; McAllister et al., 1999, 2001; Witt, Lovejoy, Pearlson, & Stevens, 2010). However, the nature of these alterations is unclear. In several studies, a focal increase in the activation of the prefrontal cortex (PFC), an area particularly involved in working memory and executive function, was observed in previously concussed individuals (Gosselin et al., 2011; McAllister et al., 1999, 2001). In other studies, a decrease in activation was observed in this region with a simultaneous increase in brain activity in temporal and parietal regions during working memory tasks (J.-K. Chen et al., 2004, 2008a, 2008b).

Additionally, individuals with a history of concussion demonstrate reductions in neuroelectric activity, quantified by electroencephalography (EEG), in response to

memory, attention, and executive function tasks (De Beaumont et al., 2009; De Beaumont, Brisson, Lassonde, & Jolicoeur, 2007; Segalowitz, Bernstein, & Lawson, 2001; Thériault, De Beaumont, Gosselin, Filipinni, & Lassonde, 2009). Furthermore, asymptomatic individuals with a history of concussion have decreased physiological arousal, as measured by electrodermal activity, to both error detection (O’Keeffe, Dockree, & Robertson, 2004) and decision-making tasks (van Noordt & Good, 2011) tasks as compared to healthy, never-concussed individuals.

In all of these cases, individuals with a history of concussion had equivalent performance on the cognitive tasks to healthy controls groups. Therefore, long-term changes in cognitive function subsequent to concussion are generally subtle and require a combination of cognitive tasks and neuroimaging or EEG studies to detect. However, both chronic traumatic encephalopathy and Alzheimer’s Disease, whose development and onset have been linked to prior history of concussion (Cantu, 2007; Guskiewicz et al., 2005; Lehman et al., 2012; McKee et al., 2009, 2013; Omalu et al., 2005), present with cognitive deficits and decline (Albert et al., 2011; McKee et al., 2009; Omalu et al., 2011; Stern et al., 2011; Terry et al., 1991). Therefore, these subtle differences in brain function may be important indicators of later decline.

From a clinical perspective, repeated neuroimaging to identify alterations in neurocognitive function, particularly in light of minimal differences in task performance, is impractical. A single neuroimaging session using functional magnetic resonance imaging (fMRI) can cost between \$800-\$1,200 (Centers for Medicare and Medicaid Services, 2016) and take at least 30 minutes, or longer depending on the task, at a time (Birn et al., 2013). There is, therefore, a need for clinically available and resource (time, money, personnel) appropriate methods for quantifying cognitive function and detecting subtle deficits in the long-term recovery from a concussion. This is particularly true given the

increased risk of subsequent concussions over the course of an athletic or military career once first concussed.

Motor Impairments

Motor impairments are among the most recognizable, yet under-investigated, long-term consequences of repetitive head trauma. First described in boxers by Martland (1928), the term “punch drunk” was used to describe patterns of “clumsiness in one foot,” ataxia, and transient confusion in boxers as a result of repetitive blows to the head. This was further described by (H. L. Parker, 1934) and given the term “traumatic encephalopathy.” In its persistent and chronic state, this condition has variously been termed “dementia pugilistica” and more commonly as chronic traumatic encephalopathy. Regardless of terminology, these conditions have been associated with repetitive head traumas sustained over time. While boxers served as the earliest examples of individuals with these impairments, more recent focus has shifted to all contact sports, particularly American football.

Acutely after a concussion, the most common motor impairments are related to maintaining balance. Clinically, balance impairments are commonly assessed using the Balance Error Scoring System (BESS; Riemann & Guskiewicz, 2000). Additionally, balance can be evaluated using instrumented methods including force plate assessment of sway velocity and displacement. On both clinical and instrumented tests of balance, concussed individuals consistently demonstrate increased instability, which generally improves to pre-injury levels within 3-10 days of injury (Furman et al., 2013; Guskiewicz, Perrin, & Gansneder, 1996; Guskiewicz et al., 2001; Hammeke et al., 2013; L. A. King et al., 2014; McCrea et al., 2003, 2005; McCrea, Guskiewicz, et al., 2013; Peterson, Ferrara, Mrazik, Piland, & Elliott, 2003; Register-Mihalik, Mihalik, & Guskiewicz, 2008;

Riemann & Guskiewicz, 2000). These measures have limited utility outside of the acute phase specifically because identified balance impairments tend to resolve quickly. There is further evidence that asymptomatic, previously concussed individuals have persistent alterations in sway patterns that are not detectable on clinical measures of balance (Buckley, Oldham, & Caccese, 2016; Cavanaugh et al., 2005, 2006; Sosnoff, Broglio, Shin, & Ferrara, 2011).

Additionally, acutely concussed individuals adopt conservative gait patterns, including slower gait speed (Buckley, Munkasy, Tapia-Lovler, & Wikstrom, 2013; Catena, van Donkelaar, & Chou, 2007a, 2007b; Howell, Osternig, & Chou, 2013), increased stride time (Catena et al., 2007b), decreased stride length (T. M. Parker, Osternig, Lee, van Donkelaar, & Chou, 2005; T. M. Parker, Osternig, van Donkelaar, & Chou, 2006), decreased midstance anterior-posterior sway velocity (Catena et al., 2007b; Catena, van Donkelaar, & Chou, 2009; T. M. Parker et al., 2006), and increased mediolateral midstance sway velocity (Catena et al., 2007a, 2007b) as compared to healthy individuals. Aspects of this altered gait pattern persist at least three months (Buckley et al., 2015; Catena et al., 2009; Howell et al., 2013) post-injury and as many as 3 years after injury (Basford et al., 2003; Chou, Kaufman, Walker-Rabatin, Brey, & Basford, 2004).

Furthermore, acutely concussed individuals exhibited decreased finger dexterity, measured as greater total movement time on the O'Connor Finger Dexterity test, as compared to healthy controls (Pearce et al., 2015). There is, however, limited clarity on the long-term effects of concussion on fine motor control. Individuals with a history of one or more concussions exhibit decreased finger dexterity (Pearce et al., 2014), greater movement times (Brown, Dalecki, Hughes, Macpherson, & Sergio, 2015; Dalecki, Albin, Macpherson, & Sergio, 2016), greater movement precision (children; decreased

error in a point-to-point finger sliding task) (Dalecki et al., 2016), decreased movement precision (adults; increased error in a point-to-point finger sliding task; Brown et al., 2015), and decreased ability to control isometric finger contractions over short durations (Slobounov, Sebastianelli, & Simon, 2002) relative to those with no such history. By contrast, athletes with a history of concussion have demonstrated equivalent performance on finger-to-target tasks compared with healthy athletes and healthy non-athletes (Locklin, Bunn, Roy, & Danckert, 2010). Additionally, children with a history of mild (defined as [1] loss of consciousness < 30 min; [2] amnesia lasting < 24 hours; [3] Glasgow Coma scale score 13-15 within 30 minutes of injury) traumatic brain injury demonstrated no difference in visuomotor control or dexterity on a gross- and fine-motor test battery (Bruininks-Oseretsky Test of Motor Proficiency) when compared with children with no history of brain injury (Dahl & Emanuelson, 2013).

Beyond the direct acute and chronic decreases in motor function following concussion, individuals with a history of concussion are predisposed to neurological conditions with motor impairments, including Parkinson's disease (Factor & Weiner, 1991; Goldman et al., 2006; Harris et al., 2013; Rugbjerg et al., 2008), amyotrophic lateral sclerosis (ALS; H. Chen et al., 2007; Chiò et al., 2005), and chronic traumatic encephalopathy (McKee et al., 2013; Omalu et al., 2005; Stern et al., 2011). These conditions generally present later in life with decreases in both cognitive and motor function.

Integration of Cognitive and Motor Processes

Sport, military, and daily activities require interacting with objects within an environment with both gross and fine motor skills. Many of these activities, such as holding a cup or shooting a basket, involve the combined action of sensory feedback

mechanisms for posture and error detection, cognitive processing, and motor output. Thus, it is necessary to consider both functional and ecologically-appropriate tasks that assess these systems. Despite observations of cognitive and motor symptoms in both the short- and long-term following a concussion, there has been limited effort address the integration of cognitive and motor skills. One method for evaluating the integration of sensory, cognitive, and motor functions is through quantifying physiological complexity (Lipsitz & Goldberger, 1992; Vaillancourt & Newell, 2002a).

Physiological Complexity

Physiological complexity can be defined in a number of ways. In this dissertation, there are two complementary definitions of complexity. First, complexity is the presence of a broad spectrum of frequencies within a signal (Lipsitz & Goldberger, 1992). Second, complexity is the coupling between components that work together to produce some physiological output (Vaillancourt & Newell, 2002a).

Complexity as A Broad Spectrum of Frequencies

Under this definition, complexity is identified through the presence of low- and high-frequency oscillations contained within a signal. For reference, these signals can be the measured output of any physiological system, including heart rate (R-R interval), blood pressure, postural sway, and continuous voluntary motor production among others. Generally speaking, healthy individuals exhibit greater complexity in these systems than individuals who are unhealthy or impaired in some way (Lipsitz & Goldberger, 1992; Vaillancourt & Newell, 2002a). For example, healthy individuals exhibit two dominant oscillatory patterns in heart rate variability (R-R interval) – a low-frequency (0.04-0.15 Hz) oscillation related to cardiovascular arrhythmia and a higher

frequency (0.2-0.4 Hz) oscillation stemming from the respiratory system (Hayano et al., 1990; Ryan, Goldberger, Pincus, Mietus, & Lipsitz, 1994).

With respect to motor system outputs, healthy individuals exhibit postural sway frequencies ranging from 0.05 Hz to 10 Hz. The majority of the spectral power occurs in frequencies lower than 1 Hz in both the anterior-posterior and medial-lateral directions (Aoki, Tokita, Kuze, Mizuta, & Ito, 2014; Lizama, Pijnappels, Reeves, Verschueren, & van Dieën, 2016; Loughlin & Redfern, 2001; Singh, Taylor, Madigan, & Nussbaum, 2012). These oscillations serve to maintain the center of pressure within the base of support. Additionally, individuals producing isometric finger force at a target level over time exhibit frequencies ranging from 0.05 Hz to 12 Hz, though the majority of the signal is observed at frequencies below 4 Hz (Baweja, Patel, Martinkewiz, Vu, & Christou, 2009; Hu & Newell, 2010; A. C. King & Newell, 2013, 2014, 2015; Slifkin, Vaillancourt, & Newell, 2000; Studenka & Newell, 2013). Therefore, both postural sway and isometric finger force exhibit complexity through the presence of multiple component frequencies that together produce the resultant sway pattern.

Complexity as Component Integration

The inclusion of multiple frequencies in a resultant signal can be viewed as the combined actions of the physiological components required to effect the task (Kello, Beltz, Holden, & Van Orden, 2007; Vaillancourt & Newell, 2002a). For example, in postural sway, maintaining the center of pressure within the base of support is the combined effect of proprioceptive, visual, and vestibular information to provide body position sense and motor neurons that make postural corrections based on that information (Kennedy & Inglis, 2002; Oie, Kiemel, & Jeka, 2002; Peterka, 2002; Roll, Kavounoudias, & Roll, 2002; Thompson, Bélanger, & Fung, 2011; Welgampola &

Colebatch, 2001). The resultant sway of the individual, which can be decomposed into component frequencies, is the combined behavioral outcome of all of these systems. Visual contributions to postural sway may exist across the spectrum of frequencies indicated above, while proprioceptive contributions appear in low-frequency (<1 Hz) and midrange (3-4 Hz) frequencies (Loughlin & Redfern, 2001; Singh et al., 2012). By contrast, maintaining the isometric force at a constant level is largely the interaction between visual information, feed-forward and feedback cognitive systems, and motor system integration. Therefore, in healthy individuals, complex signals are created through the combined action of multiple system components.

Complexity Is Not Variability

One essential distinction to make is that complexity and variability are not the same. Variability in a signal is a function of the amplitude of deflections and reflects an average characteristic of the signal, whereas complexity quantifies changes over the time course of the signal (Kaplan et al., 1991; Newell, Van Emmerik, Lee, & Sprague, 1993; Pincus, 1991; Vaillancourt & Newell, 2002a). For a sine wave with a single frequency, the complexity is relatively fixed (see QUANTIFYING COMPLEXITY). However, the variability in that sine wave is different depending on the amplitudes of the peaks (see Figure 2-1). Further, compared to a sine wave, a signal with multiple frequencies may be either more or less variable depending on the amplitudes contained within the signal, despite greater complexity (see Figure 2-1). In the example in Figure 2-1, the more complex signal has six component frequencies and has lower variability about its mean than the pure sine wave. Thus, though often used in conjunction with one another, complexity and variability are not the same (Kaplan et al., 1991; Newell et al., 1993).

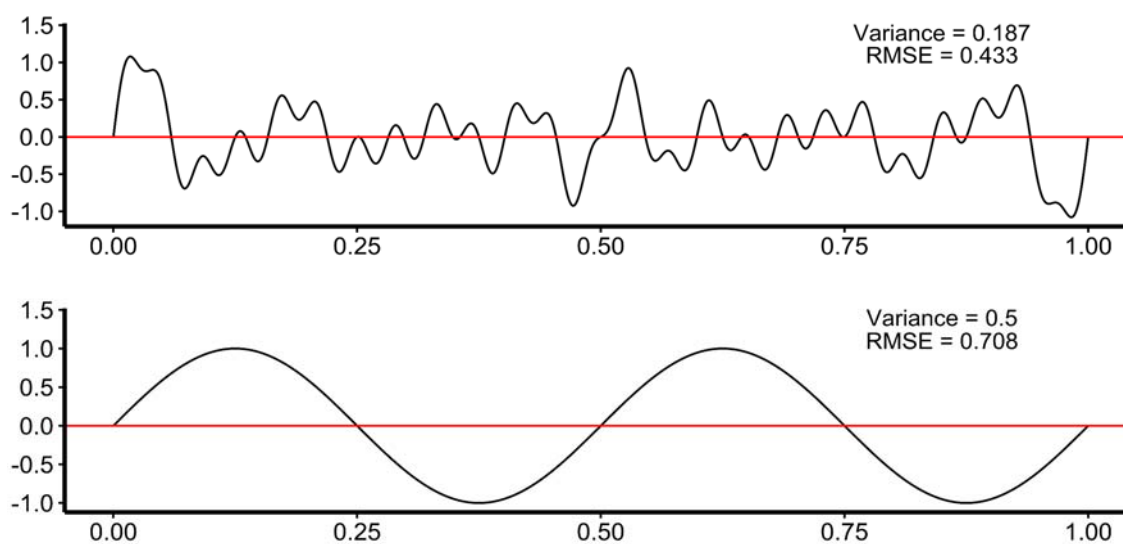


Figure 2-1. Example waveforms variance and target error.

Complexity as Error Reduction

A signal with greater complexity can exhibit reduced *target error*. In a system that fluctuates around a certain value, such as heart rate or isometric force produced at a target level, increased complexity reduces the variability relative to the target (Hu & Newell, 2010; Sosnoff & Newell, 2006a, 2008; Sosnoff, Vaillancourt, & Newell, 2004). Increasingly complex signals exhibit reduced root mean squared error (RMSE) relative to less complex signals (Hu & Newell, 2010; Mazich, Studenka, & Newell, 2015; Sosnoff & Newell, 2005b, 2006a, 2008; Sosnoff et al., 2004). For example, in Figure 2-1, the pure sine wave has an RMSE of 0.708, while the more complex signal composed of six frequencies has an RMSE of 0.433. Thus, complexity may serve to reduce error in systems where a relatively constant level of output is expected.

Loss of Complexity

In contrast to healthy individuals, loss of complexity can be the result of a number

of factors, particularly related to the integration of components. Here again, there are two primary ways in which loss of complexity can occur. The first is the loss of structural components. Given the previous examples, this may be the loss of sinus node cells affecting heart rate or dopaminergic cells from the basal ganglia in Parkinson's disease resulting in decreased tremor complexity (Hayano et al., 1990; Vaillancourt & Newell, 2002a; Vaillancourt, Slifkin, & Newell, 2001). Furthermore, this could reflect the loss of sensory input from the vestibular system, altering the complexity of postural sway and increasing reliance on the proprioceptive and visual systems to remain upright (Aoki et al., 2014).

Secondly, loss of complexity can occur through changes in the coupling between elements. This may be reflected in either a loss or reduction in connectivity between elements or an alteration in the time-scales at which certain connections operate (Lipsitz & Goldberger, 1992; Vaillancourt & Newell, 2002a). Manifestations of complexity loss are generally seen as increased regularity, reduced high-frequency contributions and increased low-frequency contributions to the outcome of interest (Lipsitz & Goldberger, 1992).

Across multiple systems, older individuals and those with defined pathologies exhibit reduced complexity. People with coronary artery disease are characterized by the low-frequency oscillation and a reduced presence (lower power – squared amplitude at a given frequency) of the higher frequency respiratory oscillation (Hayano et al., 1990). This decrease with the disease is enhanced with increasing numbers of affected vessels. Additionally, reduced power is observed in both heart rate frequency bands with increasing age (Ryan et al., 1994).

For healthy individuals holding a constant joint angle, resting is in the 8-12 Hz range (Deuschl, Raethjen, Lindemann, & Krack, 2001; Stiles & Randall, 1967). However,

in individuals with Parkinson's disease, this tremor shifts to the 4-7 Hz range, with a commensurate reduction in the higher frequencies' power (Findley, Gresty, & Halmagyi, 1981; Vaillancourt et al., 2001). Thus, the complexity of resting tremor for an individual with Parkinson's disease is lower than that for a healthy individual. Similarly, reductions in complexity have been observed for persons with Parkinson's disease in handwriting (Ünlü, Brause, & Krakow, 2006), isometric force production (Vaillancourt & Newell, 2000; Vaillancourt et al., 2001), and postural sway (Morrison, Kerr, Newell, & Silburn, 2008).

Furthermore, older individuals (generally 60-70 year-olds) exhibit lower complexity for postural sway and isometric force production as compared to younger individuals (Ko & Newell, 2016; Sosnoff & Newell, 2006a, 2008; Sosnoff et al., 2004). In both cases, there is a relative reduction in the higher frequencies typically observed for these tasks in healthy and younger individuals and a relative increase in the lower frequencies. Additionally, for isometric force production, this decrease in complexity appears to be partially explained by visual feedback (Hu & Newell, 2010; A. C. King & Newell, 2015; Mazich et al., 2015; Slifkin et al., 2000; Sosnoff & Newell, 2005b, 2006a). With either increased or decreased frequency of visual feedback, older individuals' force production tends to become more variable (greater error) and less complex as compared to younger individuals.

Cumulatively, with increasing age and/or pathology individuals exhibit reductions in complexity across multiple physiological systems. These reductions in complexity may reflect the loss of structural components within systems as well as the loss of, or alterations in the timing of, functional coupling between components. The behavioral result of this loss of complexity is a reduction in the capacity to minimize error.

Quantifying Complexity

There are numerous ways to quantify complexity. In light of the definitions previously provided, Fast Fourier Transforms (FFTs), which decompose a signal into individual frequencies and their respective power, are appropriate (Welch, 1967). However, many of the physiological systems display nonlinear properties that necessitate the use of other methods to fully explore complexity (Lipsitz & Goldberger, 1992; Vaillancourt & Newell, 2002a). Among the various methods of nonlinear assessment, the use of entropy is among the most common.

Broadly speaking, entropy measurements are an extension of information theory (Lipsitz & Goldberger, 1992; Pincus, 1991). Entropy reflects the degree to which future systems states are predictable based on the past and current states. These measurements provide a metric of regularity within a signal, where highly regular signals (such as a pure sine wave) are more predictable and have lower entropy as compared to a complex signal. The following sections explain the mathematical calculations of several forms of entropy, as well as discuss their relative merits and drawbacks.

Approximate Entropy

Approximate entropy (ApEn) is one of the earliest forms of entropy calculations applied to physiological systems. Originally devised for assessing heart rate variability (Pincus, 1991; Pincus & Goldberger, 1994; Pincus & Viscarello, 1992), ApEn has become a ubiquitous measure of physiological complexity (Cerutti et al., 2014; De Beaumont et al., 2011; Deutsch & Newell, 2004; Sosnoff et al., 2011; Studenka & Newell, 2013; Weippert, Behrens, Rieger, Stoll, & Kreuzfeld, 2013; Zhang et al., 2014). Approximate entropy is, in short, the logarithmic likelihood that matching patterns of points m points apart remain close at $m + 1$ points. The calculation of approximate

entropy is as follows (Pincus & Goldberger, 1994; Pincus & Viscarello, 1992):

1. Define m as a vector length and r as the tolerance, generally set between 0.1 and 0.2 standard deviations of the data.
2. Given N data points designated $u(1), u(2), \dots, u(N)$, form vectors defined as $x(i)$ through $x(N - m + 1)$, such that

$$x(i) = [u(i), \dots, u(i + m - 1)] \quad (2.1)$$

3. Define the distance

$$d[x(i), x(j)] \quad (2.2)$$

between vectors $x(i)$ and $x(j)$ as the maximum difference between their scalar components.

4. For $i \leq N - m + 1$ and the sequence $x(1), x(2), \dots, x(N - m + 1)$,

$$C_i^m(r) = \frac{\text{the number of } x(j) \text{ such that } d[x(i), x(j)] \leq r}{N - m + 1} \quad (2.3)$$

5. Define

$$\Phi^m(r) = \ln(C_i^m(r)) \quad (2.4)$$

6. Finally, define approximate entropy as

$$ApEn(m, r, N) = \Phi^m(r) - \Phi^{m+1}(r) \quad (2.5)$$

Lower values of approximate entropy indicate that there are higher numbers of $m + 1$ length vectors. Thus, within tolerance r , there are more repeating patterns within the signal. This high degree of repetition increases the predictability of the system and thus lowers the index of complexity.

However, approximate entropy has two major drawbacks. First, each template vector is counted as a match to itself (Richman & Moorman, 2000). Thus the calculation

of approximate entropy biases toward increased regularity, and thus less complexity. Second, ApEn is calculated on the raw signal. Template vectors are, therefore, temporally close. For a signal sampled at 100 Hz, each point in a template vector is separated by 10 milliseconds. This close temporal proximity limits the range of frequencies that can be identified by this process. Thus, the points used for template vectors are likely to be highly correlated with one another. Consequently, ApEn is biased toward quantifying regularity in high-frequency components and may leave out lower frequencies of interest. Furthermore, it is important to note that because ApEn may not capture the lower frequencies, it provides a measure of the *regularity* of data. To quantify the complexity requires metrics that address both low and high frequency components (Costa, Goldberger, & Peng, 2002a; Wu, Wu, Lee, & Lin, 2013). However, increases and decreases in regularity have been previously associated with increases and decreases in complexity, respectively (Vaillancourt & Newell, 2002b).

Sample Entropy

Sample entropy (SampEn) was developed to overcome the first drawback to approximate entropy (Lake, Richman, Griffin, & Moorman, 2002; Richman, Lake, & Moorman, 2004; Richman & Moorman, 2000). Here, the entropy of the signal is calculated as successive templates. Thus, there is no self-matching of vectors. The calculation is shown below (Richman & Moorman, 2000).

1. Define m as a vector length and r as the tolerance, generally set between 0.1 and 0.2 standard deviations of the data.
2. Define $N - m$ vectors of length m , such that $x_m(i)$ and $x_{m+1}(i)$ are defined for $1 \leq i < N - m$
3. Define:

$$B_i^m(r) = \frac{\text{the number of vectors } x_m(j) \text{ within } r \text{ of } x_m(i)}{N - m - 1}, 1 \leq j \leq N - m, j \neq i \quad (2.6)$$

4. Define:

$$B^m(r) = \frac{1}{N - m} \sum_{i=1}^{N-m} B_i^m(r) \quad (2.7)$$

5. Further, define:

$$A_i^m(r) = \frac{\text{the number of vectors } x_m(j) \text{ within } r \text{ of } x_m(i)}{N - m - 1}, 1 \leq j \leq N - m, j \neq i \quad (2.8)$$

6. And likewise define:

$$A^m(r) = \frac{1}{N - m} \sum_{i=1}^{N-m} A_i^m(r) \quad (2.9)$$

7. Finally, sample entropy is quantified as

$$\text{SampEn}(m, r, N) = -\ln[A^m(r)/B^m(r)] \quad (2.10)$$

Sample entropy has a similar interpretation to that of approximate entropy. Here, SampEn is the conditional probability that two vectors of length $m + 1$ are close together within tolerance r , given that they were close together at length m . Here again, the data points are temporally close and therefore SampEn quantifies the *regularity* of the higher frequency signal components (Costa et al., 2002a). Sample entropy was further extended to incorporate a time delay (δ) between the points in order to minimize the effect of the correlation between points (Govindan, Wilson, Eswaran, Lowery, & Preißl, 2007). This modification improved the ability to distinguish between healthy individuals and persons with congestive heart failure (Govindan et al., 2007). However, the

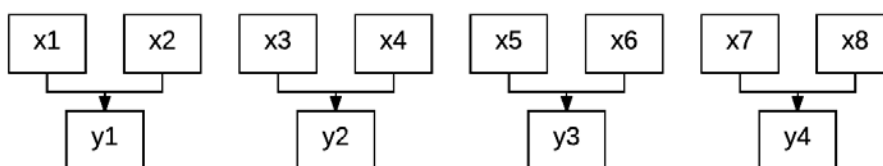
drawback remains that points in each vector are temporally close, may be highly correlated, and capture only high-frequency components.

Multiscale Entropy

To address the limitation in both approximate and sample entropy that points are temporally close and therefore entropy measures capture only high-frequency components, multiscale entropy (MSE) was developed (Costa et al., 2002a). MSE has two steps. First, the signal is course-grain averaged (averages computed in non-overlapping sections of the data) over windows of length τ , where $\tau = 1$ is the original signal. This scaling procedure has the effect of down-sampling the data by N/τ . This scaling is calculated at a scale factor of τ and for an original time series x (Figure 2-2) (Costa et al., 2002a; Wu et al., 2013):

$$y_j^\tau = \frac{1}{\tau} \sum_{i=(j-1)\tau+1}^{j\tau} x_i, 1 \leq j \leq \left\lfloor \frac{N}{\tau} \right\rfloor \quad (2.11)$$

Scale 2



Scale 3

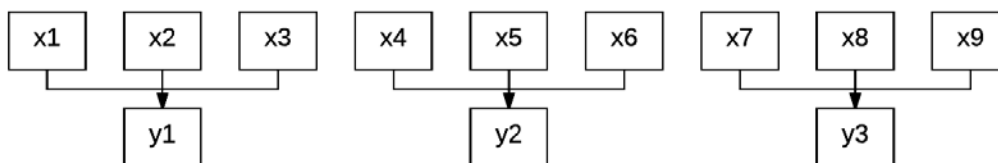


Figure 2-2. First two scaling factors under multiscale entropy (adapted from Costa et al. [2002]).

Sample entropy without the time delay is then calculated for each of the N/τ length signals. The lowest frequency upon which sample entropy is calculated at a given scaling factor is determined by

$$f_L = \frac{N_{\tau M}}{2 \times (m + 1) \times t} \quad (2.12)$$

where $N_{\tau M}$ is the number of data points remaining at scale factor τ ($N_{\tau M} = (f_s \times t)/\tau M$, f_s = the sampling rate), t is the duration of the signal, and m is the vector length is the sample entropy calculation (Gow, Peng, Wayne, & Ahn, 2015). Thus for a signal sampled at 100 Hz with $m = 2$, the lowest frequency at which sample entropy is calculated in the original signal, the signal upon which sample entropy would traditionally be computed, is 16.67 Hz. As previously identified, heart rate variability, postural sway, and isometric force all have frequencies less than 12 Hz and dominant frequencies below 5 Hz. Thus, sample entropy, without multiscale considerations, captures only high frequency information above what may be of interest.

MSE yields sample entropy values at each scaling factor, which correspond to successively lower frequencies in the signal. The overall complexity of the signal can be calculated as the sum of the sample entropy values for all scaling factors. This procedure has been used to quantify complexity in heart rate variability (Costa, Goldberger, & Peng, 2002b, 2005; Costa & Healey, 2003; Ferrario, Signorini, Magenes, & Cerutti, 2006; Huikuri, Perkiömäki, Maestri, & Pinna, 2009), gait (Costa, Peng, Goldberger, & Hausdorff, 2003; Kumar, Aziz, Saeed, Ahmed, & Hussain, 2013; Tao, Zhang, Chen, Wu, & Zhou, 2015), electrical activity in the brain via electroencephalogram (Catarino, Churches, Baron-Cohen, Andrade, & Ring, 2011; Mizuno et al., 2010; Park, Kim, Kim, Cichocki, & Kim, 2007; Takahashi et al., 2010), postural sway (Duarte & Sternad, 2008; Fournier, Amano, Radonovich, Bleser, & Hass,

2014; Kirchner, Schubert, Schmidtbleicher, & Haas, 2012; Yeh, Lo, Chang, & Hsu, 2014), and isometric force (Vaillancourt & Newell, 2002b; Vieluf, Temprado, Berton, Jirsa, & Sleimen-Malkoun, 2015).

However, MSE has several drawbacks. First, the repetitive scaling of the data and subsequent calculation of sample entropy is computationally intensive (Costa et al., 2002a). Thus, the time to compute MSE is dramatically greater than for approximate or sample entropy. Further, the number of data points required is substantive. The minimum number of points identified by Richman for calculating sample entropy is between 10^m , though 14^m to 23^m points provide reliable sample entropy calculations (Richman & Moorman, 2000).

For example, taking $N_{\tau M} = 100$ ($10^{m=2}$) points as the smallest number of necessary data points, 20 seconds of postural sway sampled at 100 Hz (2000 data points) can be used to calculate sample entropy as low as 0.83 Hz at scale factor $\tau = 20$. However, if $N_{\tau M} = 196$ ($14^{m=2}$) data points are used as the minimum number of points, then for 20 seconds of postural sway sampled at 100 Hz the maximum scale factor is $\tau = 10$ and the lowest frequency that can inform complexity is 1.67 Hz. This frequency is considerably greater than the frequencies (< 1 Hz) associated with variables of interest including, for example, proprioceptive contributions to postural sway (Aoki et al., 2014; Loughlin & Redfern, 2001; Singh et al., 2012). In order to quantify the complexity and include frequencies as low as 0.5 Hz, the sampling time required would be 65.33 seconds, rather than 20 seconds, based on Eq. 2.12.

Two approaches may be taken to overcome this. One is to increase the sampling rate. While this has the effect of increasing the number of data points available, the only aspect of the calculation that changes is the scaling factor used to reduce the original dataset down to the minimum (Gow et al., 2015). The denominator of Equation 11 does

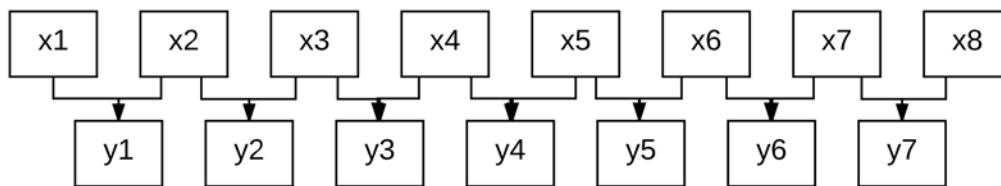
not change, and, therefore, the end result is the same lower frequencies. The second approach is to increase the sampling duration. Increasing from 20 seconds to 30 seconds in the original example ($N_{\tau M} = 100$), the maximal scaling factor is $\tau = 30$ and, the lowest frequency is 0.56 Hz. However, increasing the sampling duration may not be feasible due to constraints such as fatigue (Gow et al., 2015).

Modified Multiscale Entropy

Modified multiscale sample entropy (MMSE) deals with the shortcomings imposed from short ($N_{\tau M} < 100$) time series (Wu et al., 2013). This calculation has two principal differences from multiscale entropy. First, instead of course-grain averaging and down-sampling at a scale factor τ , a windowed moving average is computed at scale factor τ (Figure 2-3; Wu et al., 2013):

$$y_j^{(\tau)} = \frac{1}{\tau} \sum_{i=j}^{j+\tau-1} x_i, \quad 1 \leq j \leq N - \tau + 1 \tag{2.13}$$

Scale 2



Scale 3

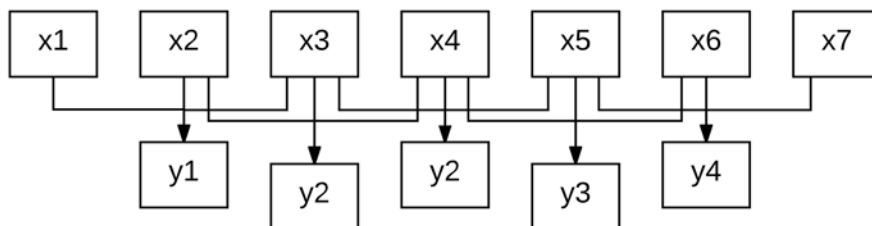


Figure 2-3. First two scaling factors for the moving average procedure in modified multiscale entropy (adapted from Wu et. al. [2013]).

The windowed moving average has the same effect of filtering high-frequency components out of the data. However, there is no subsequent down-sampling. Thus for a given series of points, the total number of points after averaging is $\tilde{N}(\tau) = N - \tau + 1$ rather than $\tilde{N}(\tau) = N/\tau$.

After applying the moving average for a given scale factor, sample entropy is then computed as the time-delayed modified sample entropy. Here the time delay is $\delta = \tau$. Like the down-sampling in MSE, the time-delayed sample entropy evaluates vectors of points which are more temporally remote from each other than in the original signal, thereby accessing lower frequencies in the signal. Thus, by applying the time delay, the spectral components described by Equation 2-11 are preserved, so that there is scale factor equivalence between MSE and MMSE (Wu et al., 2013). Previous investigations using MMSE and MSE have shown that MMSE can provide estimates of complexity for short time series ($N_{\tau M} \leq 100$) where MSE is undefined. Furthermore, MMSE provides more precise estimates of sample entropy (smaller standard deviations) at each scale value. This permits MMSE to capture lower frequency components in the complexity calculation of shorter time series than MSE does.

The major limitation in MMSE is that it is more computationally intensive than MSE (Wu et al., 2013). Therefore, MMSE is appropriate for short time series (where lowest target frequencies can only be obtained with $N_{\tau M} \leq 100$), whereas MSE is preferred for longer time series.

Physiological Complexity and Concussion

There has been limited application of nonlinear measures to concussion outcomes. Principally, entropy measures have been used to quantify changes in postural

sway following a concussion. There is evidence of subtle and persistent changes in postural sway regularity when analyzed using various forms of entropy in asymptomatic individuals with a history of concussion (Buckley et al., 2015; Cavanaugh et al., 2005, 2006; De Beaumont et al., 2011; Sosnoff et al., 2011). Specifically, previously concussed individuals demonstrate persistently more regular sway patterns than individuals with no history of concussion. In accordance with the definitions of complexity previously provided, these findings suggest that persons with a history of concussion have persistent alterations in the functional connections between proprioceptive, visual, vestibular, and postural effectors (Kennedy & Inglis, 2002; Oie et al., 2002; Peterka, 2002; Roll et al., 2002; Thompson et al., 2011). This is despite no clinical evidence of impairment.

Furthermore, in Studenka and Raikes (in press) asymptomatic individuals with a history of multiple concussions had greater regularity, as measured by sample entropy, than individuals with a single concussion during a seated continuous isometric visual-motor tracking task. Additionally, individuals with multiple concussions demonstrated greater regularity than people with no history of concussion. Interestingly, males in the sample exhibited few differences from each other in regularity across levels concussion history. Possible explanations for this outcome may include the presence of multiple sub-concussive impacts due to more “contact” sport participation and/or under-reporting of concussions (Gysland et al., 2012; Kerr et al., 2016; McCrea et al., 2004).

As opposed to postural tasks that integrate proprioception, vision, and vestibular function to maintain upright posture (Kennedy & Inglis, 2002; Oie et al., 2002; Peterka, 2002; Roll et al., 2002; Thompson et al., 2011), the visual-motor tracking task relies almost exclusively on visual information for error detection and correction (Cole & Sedgwick, 1992; Gandevia, Macefield, Burke, & McKenzie, 1990; Hu & Newell, 2011;

Teasdale et al., 1993; Tracy, 2007; Vaillancourt & Russell, 2002). Consequently, quantifying complexity in this task may provide valuable information about previously reported deficits in both visual information processing (Lachapelle, Bolduc-Teasdale, Ptito, & McKerral, 2008; Malojcic, Mubrin, Coric, Susnic, & Spilich, 2008) and error detection and correction processes following a concussion (De Beaumont, Beauchemin, Beaulieu, & Jolicoeur, 2013; Pontifex, O'Connor, Broglio, & Hillman, 2009).

Only one study to date has quantified complexity after concussion rather than solely regularity (Kelty-Stephen, Qureshi Ahmad, & Stirling, 2015). The authors used a circle tracing task and computed multiscale entropy (MSE). Complexity in this task provides information about the integration between proprioceptive and visual systems (Kelty-Stephen et al., 2015; Stirling et al., 2013). Concussed individuals exhibited decreased complexity in a circle tracing task within 1-11 days of injury, as compared to a pre-injury assessment. Additionally, concussed individuals' task complexity increased as time from injury increased. However, the authors do not indicate the time frame over which this increase occurred or whether performance returned to preinjury status (Kelty-Stephen et al., 2015).

Thus, across multiple studies, previously concussed individuals exhibit persistent decreases in the regularity of task-related motor outcomes. The findings of these studies suggest that, following concussion, there may be altered functional connectivity in task-relevant visual and error detection systems, thus reducing the ability to utilize this information to minimize error relative to a target (Buckley et al., 2016; Cavanaugh et al., 2005, 2006; De Beaumont et al., 2011; Kelty-Stephen et al., 2015; Sosnoff et al., 2011; Studenka & Raikes, in press). Additionally, it remains unclear what personal (sex, gender, age), activity (sport, concussion reporting norms, subconcussive impact risk), injury characteristics (concussion presentation, symptoms, duration, recurrence), and

time course (time from injury) characteristics may influence motor output complexity.

Continuous Isometric Force Tracking

Continuous isometric force tracking tasks, also referred to as visual-motor tracking, are a method for quantifying sensorimotor processing following a concussion. In these tasks, individuals attempt to maintain a constant force at a specified level or to produce an oscillating level of force at a shifting target level. These tasks have been used to examine various aspects of sensorimotor function in motor control, aging, Parkinson's disease (Deutsch & Newell, 2004; Hong, James, & Newell, 2008; Ko & Newell, 2016; Lafe, Pacheco, & Newell, 2016; Morrison & Newell, 2012; Newell, Mayer-Kress, & Liu, 2009; Newell, Vaillancourt, & Sosnoff, 2006; Sosnoff & Newell, 2005a, 2006a, 2006b, 2008; Sosnoff et al., 2004; Vaillancourt & Newell, 2000; Vaillancourt et al., 2001; Vaillancourt, Sosnoff, & Newell, 2004). Additionally, these tasks have pragmatic relevance given that fine motor tasks, such as manipulating objects for activities of daily living or work, require precision with respect to magnitude, direction, and timing of force. Collectively, such tasks require the integration of sensory information and the appropriate timing of motor output while accommodating time delays stemming from numerous sources, including neural depolarization, sensory information processing, and interactions at the neuromuscular junction.

Furthermore, specific regions of the frequency spectrum have been identified in this task to be associated with various task related processes. Low-frequency oscillations, 0-4 Hz, are associated with control related to sensory-motor processing and feedback (Miall, Weir, & Stein, 1985; Pew, 1974; Slifkin et al., 2000; Sosnoff & Newell, 2005a). These frequencies are also generally associated with cognitive processing, given that typical reaction times are approximately 200 milliseconds (ms). For reference,

a single cycle of a 4 Hz oscillation occurs over 250 milliseconds.

Midrange and high frequencies, those falling between 4 and 12 Hz, have been associated with feedforward and predictive control (Desmurget & Grafton, 2000; Pew, 1974; Sosnoff & Newell, 2005a; Sosnoff & Voudrie, 2009). Additionally, visual feedback processing occurs within this band, between 6-7 Hz (Slifkin et al., 2000). Higher frequency oscillations, those between 8 and 12 Hz, are associated with physiological aspects of tremor in healthy individuals (Deuschl et al., 2001; Stiles & Randall, 1967; Vaillancourt & Newell, 2000). Therefore, the visual-motor tracking task provides information about multiple processes that contribute to motor output.

Motor output in this task is highly dependent on multiple factors, including the frequency of visual feedback and the target force level. When visual feedback is withheld, there is an increase in error and variability of the signal as well as an increase in regularity (Miall et al., 1985; Slifkin et al., 2000; Sosnoff & Newell, 2005a, 2005b, 2006a). With increasing frequency of visual feedback, there is a subsequent decrease in error and variability as well as reduced regularity. Additionally, variability increases with force level. However, both regularity and complexity follow an inverted-U shaped distribution and complexity is maximized between 40% and 60% of participants' maximum voluntary contraction (MVC) force (Vieluf et al., 2015).

Prior studies have demonstrated that with increasing age, there is a reduction in the proportional contribution of higher frequency oscillations in the resultant motor output, when compared to younger individuals (Morrison & Newell, 2012; Newell et al., 2009, 2006; Sosnoff & Newell, 2006a; Sosnoff et al., 2004). Additionally, with increases in age, there is a concomitant increase in the regularity of the motor output and increase in the target error (deviation from the output target). Generally speaking, younger individuals have greater irregularity in their motor output in this task, which is often

viewed as a sign of greater complexity. However, few studies have quantified the complexity of this task using multiple-scale metrics.

This pattern of reduced high-frequency oscillations and greater regularity has additionally been observed for individuals with Parkinson's disease. Here, not only is there a reduction in the high-frequency oscillation associated with tremor, but the tremor frequency also shifts to the mid-range frequencies. Thus, the resultant motor output is composed of low- and mid-range frequency oscillations. Concomitant with this shift increased regularity and error.

With respect to concussions, the visual-motor tracking task has the added benefit of being heavily reliant on visual, not proprioceptive, feedback. By contrast, postural tasks integrate multiple sources of sensory feedback and therefore increases in error or deviation from a target may arise from alterations in functional couplings between many systems. The visual-motor task isolates effects on visual-motor processing beyond the clinical course of the injury as well as beyond the sensitivity of neurocognitive tasks that quantify visual-motor function and visual memory (Baker & Cinelli, 2014; Brown et al., 2015; Dalecki et al., 2016; Dean & Sterr, 2013; Gardner et al., 2012; Iverson et al., 2005; Locklin et al., 2010; Schatz & Maerlender, 2013; Schatz et al., 2006).

Studenka and Raikes (in press) used a constant continuous force tracking task with participants with and without a history of concussion, all of whom exhibited and reported no symptoms of concussion at the time of testing. Individuals with a history of multiple concussions exhibited increased error and decreased sample entropy, as compared to those with no history or history of one diagnosed concussion. Additionally, concussed individuals had decreased average power in the 8-12 Hz frequency band associated with physiological tremor. These findings indicate that previously multiply concussed individuals have a shift away from high-frequency oscillations resulting in an

increase in signal regularity. Thus, there are persistent changes in motor output in visual-motor tracking beyond the clinical course (generally 7-21 days) of the injury. However, no studies have looked at the multiscale complexity of this task with respect to a concussion. Given the observed alteration in the power spectrum of individuals with a history of multiple concussions, there is the need to examine the multiscale complexity of this task for people with any history of concussion.

Current Gaps in Knowledge

Visual-Motor Tracking

To date, there has been a limited effort to examine the multiscale complexity of performance on the visual-motor tracking task. Multiple studies demonstrate that aging individuals and people with certain pathologies exhibit critical shifts in the power spectrum of motor output and increased regularity in the fastest frequencies of motor output. Consequently, it is reasonable to examine the complexity across multiple time scales to determine whether this increase in regularity is confined to frequencies above the region of interest (0-12 Hz) or whether it affects lower frequencies as well.

Concussion and Visual-Motor Tracking

With respect to concussions, there remains much to be explored with visual-motor tracking. Studenka and Raikes (in press) demonstrated increased regularity in females with a history of concussion relative non-concussed females and males with prior history of concussion. For males, there were few differences in regularity, regardless of concussion history. In that sample, 73% of the males, including those reporting no prior concussions, previously or currently played football. Thus, the role of unreported concussions and sub-concussive impacts merits investigation. Individuals,

particularly in sports, may have numerous motivations for not disclosing the occurrence of a concussion (Kerr, Register-Mihalik, et al., 2014; Kerr et al., 2016), and estimates of nondisclosed concussion occurrence may range from 30-50% (Kerr et al., 2016; McCrea et al., 2004). Thus, thorough screening of individuals to more completely determine a history of concussion, including those suspected or undisclosed by the individual, is essential.

Additionally, gender may be an important consideration in this task. As stated, men and women with varying histories of concussion demonstrated differing patterns of regularity and performance on the seated visual-motor tracking task (Studenka & Raikes, in press). Additionally, gender-specific visual-motor differences in complexity and performance are evident in circle tracing (Stirling et al., 2013). Furthermore, men tend to have better visuospatial performance and worse motor processing speed than females both prior to (baseline) and following concussion (Broshek et al., 2005; Colvin et al., 2009; Covassin et al., 2006; Covassin & Elbin, 2011; Covassin, Elbin, Harris, Parker, & Kontos, 2012; Covassin, Schatz, & Swanik, 2007). However, to date, none of these studies has accounted for educational differences or differences in visual-spatial task exposure.

Finally, injury characteristics may play a role in recovery and merit examination as potential factors in subsequent visual-motor processing and motor output. Particularly, history of loss of consciousness has been associated with white matter damage after concussion (Wilde et al., 2016), decreased behavioral and altered neuroelectric outcomes in a visual oddball task (Parks et al., 2015), as well as increased postconcussive symptom duration (Barlow et al., 2010; Heyer et al., 2016; McCrea, Guskiewicz, et al., 2013; Taylor et al., 2010). Additionally, amnesia following a concussion has been indicated as a potential indicator of concussion symptom duration

(Barlow et al., 2010; Heyer et al., 2016; McCrea, Guskiewicz, et al., 2013; Yeates et al., 2009). These are in addition to gender, concussion history, age, and symptom severity at the time of injury.

Statement of Purpose

While the vast majority of clinical impairments due to one or more concussions resolve within the first 7-10 days, there is still limited clarity as to the long-term impact of this injury on neurocognitive function, motor control, and particularly the integration of these domains. Visual-motor tracking tasks have been used to identify differences in visual processing, error detection, and fine motor control in aging and numerous pathologies. Examining the complexity of the motor output in this task provides insight into multiple domains of cognitive and motor function, as well as insight into fine motor control used for activities of daily living, work, and sport, and therefore is appropriate for evaluating function following a concussion. Therefore, the purpose of this dissertation is, therefore, (1) to use multiple regression to determine the extent to which concussion history and concussion symptoms influence task performance multiscale complexity and (2) to determine whether task performance complexity can distinguish, through logistic regression and prediction, between individuals with and without a history of concussion.

CHAPTER 3

**THE IMPACT OF CONCUSSION HISTORY AND SYMPTOMS ON MULTISCALE
COMPLEXITY OF A VISUAL-MOTOR TRACKING TASK**

Abstract

Concussions, particularly in sport and military activity, are an issue of social and medical inquiry and concern. The prevalence of concussions, reported associations between repeated concussions and neurological and cognitive impairments in later adulthood necessitates methods of tracking recovery from a concussive event and identifying individuals at risk for developing negative long-term outcomes. Nonlinear dynamics, including measures of complexity and spectral power, may provide insight into functional connectivity within and between cognitive and motor processes following concussion. Individuals with ($n = 35$) and without ($n = 15$) a self-reported history of concussion completed 10 trials of a visual-motor tracking task. Individual multiple regressions were computed with gender, number of concussions, history of loss of consciousness, and history of post-concussion amnesia predicting average multiscale complexity, spectral power within three frequency bands (0-4Hz, 4-8Hz, and 8-12Hz), root mean squared error (RMSE), as well as intra-individual variation for these outcomes. We observed linear reductions in complexity, 4-8Hz average power, 8-12Hz average power, and increased RMSE and intra-individual variation in complexity with increasing numbers of concussions. Gender altered the slopes of these variables, as did the presence of loss of consciousness following concussion. These findings indicate a cumulative reduction in the way in which previously concussed individuals process and integrate visual information to guide behavior.

Introduction

Currently, an estimated 1.6 to 3.8 million sport-related concussions (SRCs) occur each year (Daneshvar et al., 2011; Langlois et al., 2006) and this likely underestimates the actual number due to underreporting of concussions (Faul et al., 2010; Kerr et al., 2016; McCrea et al., 2004). The economic impact of concussions and mild traumatic brain injuries in the United States is approximately \$22 billion annually (Finkelstein et al., 2006; National Center for Injury Prevention (US), 2003). Considerable research attention is, and has been, paid to the short- and long-term cognitive impacts of concussions (Barr & McCrea, 2001; Collie et al., 2006; Grindel et al., 2001; Guskiewicz et al., 2003, 2005, 2001; Iverson, 2006; McCrea et al., 2003, 2005; McCrea, Kelly, Randolph, Cisler, & Berger, 2002). Additionally, short-term postural instability has been documented following concussion (Covassin et al., 2012; Guskiewicz et al., 1996, 2001; McCrea et al., 2005).

However, despite links between concussion history and the onset of neurologic diseases such as Parkinson's disease and amyotrophic lateral sclerosis (H. Chen et al., 2007; Chiò et al., 2005; Factor & Weiner, 1991; Goldman et al., 2006; Harris et al., 2013; Rughjerg et al., 2008), there is only limited evidence of impaired motor function in measures of gait and fine motor control following concussion (Buckley et al., 2013; Catena et al., 2007a, 2007b; Dalecki et al., 2016; Pearce et al., 2014, 2015; Slobounov et al., 2002). The prevalence of concussions, the associations between adolescent/early adulthood concussions and neurological and cognitive impairments in later adulthood, and the high annual cost associated with concussions necessitates a search for cost-effective biomarkers that can be used to track an individual's recovery from a concussive event and identify those individuals at risk for developing negative long-term outcomes.

One such way of tracking and identification is the use of nonlinear complexity measures.

Physiological complexity is defined as the presence of a broad spectrum of low-to-high frequency oscillations within a physiological signal, such as heart rate (Lipsitz & Goldberger, 1992; Vaillancourt & Newell, 2002a). In healthy individuals, complex signals are created through functional connections between multiple system components (sensory, cognitive, motor) and are characterized by multiple frequencies in measured physiological output (Aoki et al., 2014; Hayano et al., 1990; Hu & Newell, 2010; Kello et al., 2007; Kennedy & Inglis, 2002; A. C. King & Newell, 2014, 2015; Lizama et al., 2016; Loughlin & Redfern, 2001; Oie et al., 2002; Peterka, 2002; Roll et al., 2002; Ryan et al., 1994; Singh et al., 2012). Such complexity can be observed for the measured signal (Pincus, 1991; Richman et al., 2004) as well as across multiple time scales, or oscillation frequencies (Costa et al., 2002a; Gao, Hu, Tung, & Blasch, 2011; Wu et al., 2013). Decreases in motor system output complexity have been observed in individuals with Parkinson's disease (Liao, Wang, & He, 2008; Ünlü et al., 2006; Vaillancourt & Newell, 2000; Vaillancourt et al., 2001), amyotrophic lateral sclerosis (Liao et al., 2008), tardive dyskinesia (Newell, Gao, & Sprague, 1995), normal aging (Newell et al., 2006; Vaillancourt et al., 2004) and following concussion (Buckley et al., 2016; Cavanaugh et al., 2005, 2006; Kelty-Stephen et al., 2015; Sosnoff et al., 2011).

As noted, complexity occurs over multiple time scales. When considering a single time scale, complexity is often indexed with *regularity*. Regularity is a reflection of the degree to which future systems states are predictable based on the past and current states (Lipsitz & Goldberger, 1992). These measurements, including approximate and sample entropy, provide a metric of regularity within a signal, where highly regular signals (such as a pure sine wave) are highly predictable and therefore have lower entropy as compared to a complex signal (Govindan et al., 2007; Pincus, 1991; Pincus &

Goldberger, 1994; Richman et al., 2004; Richman & Moorman, 2000). Thus, increased regularity is often associated with less complexity (Lipsitz & Goldberger, 1992; Pincus, 1991; Vaillancourt & Newell, 2002a).

Nonlinear regularity has been used to quantify changes in postural sway following concussions. Asymptomatic individuals with a history of concussion exhibit subtle and persistent increases in postural sway regularity when analyzed using approximate entropy (ApEn; Cavanaugh et al., 2005, 2006; De Beaumont et al., 2011; Sosnoff et al., 2011), as well as Shannon and Renyi entropies (Buckley et al., 2016). Given the definitions of complexity, these findings indicate that previously concussed individuals may have altered functional connections between sensory inputs (proprioceptive, visual, vestibular) and postural effectors to maintain upright posture (Kennedy & Inglis, 2002; Oie et al., 2002; Peterka, 2002; Roll et al., 2002; Thompson et al., 2011).

Studenka and Raikes (in press) observed that motor behavior of individuals with a history of multiple concussions had greater regularity, measured with sample entropy, than persons with a history of a single concussion or no concussion history during a seated visual-motor isometric force tracking task. This task relies on visual information for error detection and correction (Cole & Sedgwick, 1992; Gandevia et al., 1990; Hu & Newell, 2011; Teasdale et al., 1993; Tracy, 2007; Vaillancourt & Russell, 2002) with limited proprioceptive input and thus may provide valuable information about visual information processing and integration with error detection and correction processes.

Only one study to date has quantified complexity, observed over multiple time scales, after concussion rather than solely regularity (Kelty-Stephen et al., 2015). The authors used a circle tracing task, whose complexity provides information about the integration between proprioceptive and visual systems (Kelty-Stephen et al., 2015;

Stirling et al., 2013). Concussed individuals exhibited decreased complexity in a circle tracing task within 1-11 days of injury, as compared to a pre-injury assessment. In addition, concussed individuals' task complexity increased as time from injury further increased. However, the authors did not indicate the time frame over which this increase occurred or whether performance returned to preinjury status (Kelty-Stephen et al., 2015).

The purpose of this study is, therefore, to identify the impact of concussion history on the multiscale complexity of a continuous isometric finger contraction during a seated visual-motor tracking task. We hypothesized that individuals with a history of concussion would produce less complex multiscale force output as compared to individuals without a history of concussion. We additionally hypothesized that this effect would be greater for individuals with a history of unreported and undiagnosed concussions as compared to individuals in whom concussions were diagnosed. Furthermore, individuals with a history of concussion have been observed to have increased performance variability in visual-motor tasks (Maruta, Suh, Niogi, Mukherjee, & Ghajar, 2010; Robertson, Manly, Andrade, Baddeley, & Yiend, 1997; Stuss et al., 1989). Therefore, we further hypothesized that individuals with a history of concussion would have increased variability in trial-to-trial complexity. Given the extensive literature on complexity methodology, yet relative dearth in applying it to concussions as well as to fine motor control, these hypotheses test both logical and empirical extensions of previous work.

Methods

Participants

For this study, we recruited 50 participants through the Utah State University

Research Participation Portal (<https://usu.sona-systems.com>). Participants self-reported hand dominance and all were right-handed ($n = 49$) or ambidextrous ($n = 1$) (Appendix A). Descriptive characteristics of this sample can be found in Figure 3-1 and Table 3-1. These data collection procedures were approved by the Utah State University Institutional Review Board (Appendix B and C).

Individuals were screened for concussion history using a standardized form (Appendix A). Information regarding concussion history included self-reported numbers of diagnosed and suspected concussions as well as potential indicators of prolonged recovery including concussion-related loss of consciousness and post-concussive amnesia (Barlow et al., 2010; McCrea, Iverson, Echemendia, Makdissi, & Raftery, 2013; Parks et al., 2015; Taylor et al., 2010; Wilde et al., 2016; Yeates et al., 2009). Due to high rates of underreporting of concussions in athletics (Kerr et al., 2016; McCrea et al.,

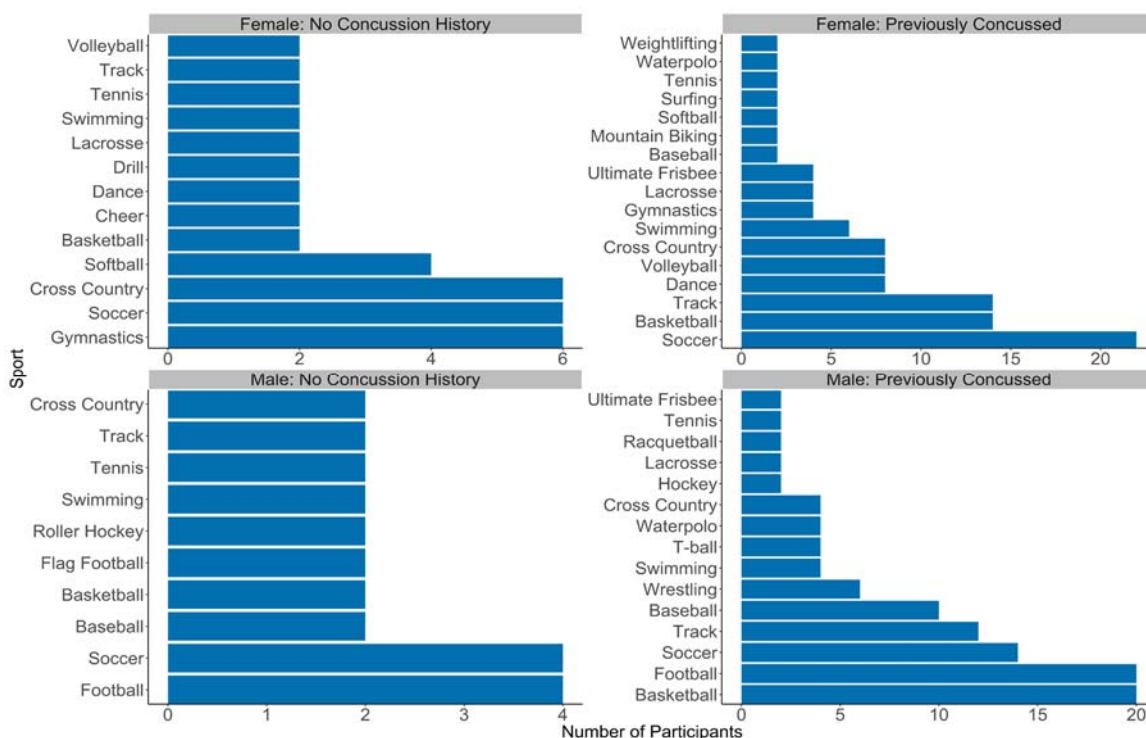


Figure 3-1. Study 1: Sport participation by gender and concussion history.

Table 3-1

Participant Demographic Information and Concussion History

Participant characteristics	Concussion history		Test	p value
	No history	History		
<i>n</i>	15	35		
Height (cm)	167.64 (7.57)	174.73 (9.04)	$t = -2.85$	0.008
Weight (kg)	67.31 (13.92)	71.89 (12.31)	$t = -1.1$	0.282
Age (years)	20.92 (2.21)	20.92 (1.98)	$t = -0.01$	0.995
Athletic exp. (years)	34.67 (14.93)	48.71 (22.14)	$t = -2.61$	0.013
Male/Female (<i>n</i>)	4/11	19/16	$\chi^2 = 0$	1
Right-handed (<i>n</i>)	15	34		
Race or Ethnicity (<i>n</i>)				
Caucasian/White	15	34		
Mexican		1		
Diagnosed concussions (<i>n</i>)		0 (25) 1 (7) 2 (1) 3 (2)		
Suspected concussions (<i>n</i>)		0 (3) 1 (18) 2 (7) 3 (4) 4 (3)		
Total concussions (<i>n</i>)		1 (18) 2 (7) 3 (5) 4 (2) 5 (2) 6 (1)		
History of LOC (<i>n</i>)		17		
History of RA (<i>n</i>)		5		
History of AA (<i>n</i>)		4		

Note. Values are mean \pm SD, unless noted otherwise. Athletic experience is cumulative experience across all sports played. LOC = loss of consciousness; RA = retrograde amnesia; AA = anterograde amnesia.

2004), these self-reports of suspected concussions help to more completely describe the participants' injury history than self-reported diagnosed concussion alone (Studenka & Raikes, in press). All participants reporting a history of concussion ($n = 35$) also self-reported no known persistent concussion symptoms. Further demographic data included

sport history and cumulative years of athletic experience.

Apparatus

Participants were seated at a table, facing a 22" (29 x 47 cm horizontal and vertical) LCD (Dell) monitor. An ATI Industrial Automation load cell (diameter 1.27 cm; Apex, NC) was affixed to a wooden block and secured with the load cell mounted just right of the center of the monitor and 35 cm from the bottom edge of the monitor. The output from the load cell was amplified through a National Instruments DAQ board (National Instruments, Austin, TX) with a resolution of 3.125 microNewtons. The participants pressed the load cell with the lateral aspect of the right index finger's distal interphalangeal joint. Abduction of the index finger registered force through the load cell. Data were sampled at 100 Hz, in keeping with recommendations that sampling rates be set to 5x the highest frequency of interest when calculating sample entropy (Gow et al., 2015). Physiological signals are generally observed between 0 and 20 Hz, making 20 Hz the upper limit of interest.

The task was administered in, and all data collected through, MATLAB (v. 2015a, The Mathworks Inc., Natick, MA, 2015). A white line displayed on the screen represented the force administered by the index finger. The delay between finger force application and output display is unavoidable but minimized and undetectable by the experimenters (~60 ms) (Studenka & Raikes, in press). A straight red line was displayed on the screen for the duration of each trial and served as the target waveform. The white line moved across the computer monitor from left to right, leaving a trace of its previous position (see Figure 3-2). For each trial, the line was centered in the middle of the screen at 40% of a participant's MVC. This value was chosen to maximize complexity (Vieluf et al., 2015). The entire screen ranged from 35–45% of a participant's MVC, which



Figure 3-2. Study 1: Visual-motor tracking task apparatus and display. The horizontal line is the target line. The white line is the participant's produced force.

provides sufficient visual gain for minimizing spurious error due to low resolution around the target line (Hu & Newell, 2011).

Procedures and Instructions

Three trials (5 s) of maximal finger force were performed. The maximal value of these three trials was recorded as that participant's maximal voluntary contraction (MVC). Each participant then performed 10 trials of tracking, which was enough trials to evaluate trial-to-trial consistency. Participants were instructed to minimize the difference between the white (participant produced) and red (target) lines. Each trial lasted 30 seconds.

Data Analysis

All data were processed using a custom-written Python (Python Software Foundation, <https://www.python.org/>) module (<https://github.com/araiques/physiologic-complexity>). Trial data were visually inspected for adherence to task instructions.

Individual trials were excluded for the following reasons.

1. Trials with fewer than 20% of the data points appearing on the screen
2. Trials with a loss of force applied to the load cell, indicating that the participant had removed the finger during the trial
3. Trials with visually abnormal patterns relative to the task, including rapid oscillations, delayed force application more than 4 seconds into a trial, or multiple oscillations approaching zero force.

Data were filtered with a 9th order forward-backward digital 20 Hz low-pass Butterworth filter. Prior to analyses, the first 4 s (1 s of the recorded trial following a 3 second “warm up”) and the last 1 s of force output were removed to account for changes that might occur as an individual acclimates to the task and changes that might occur as a person completes the task. Because sample entropy is influenced by non-stationarity in the data, all data were detrended using an adaptive fractal detrending method prior to complexity calculations (Gao, Hu, & Tung, 2011). Detrending was computed using a 2nd order polynomial fit over segment lengths of 129 data points to preserve data shape without overfitting (see Figure 3-3).

Amount of force variability. Root mean square error (RMSE) was calculated as a metric of overall task performance with the equation

$$RMSE = \sqrt{\frac{\sum (s - f_i)^2}{n - 1}} \quad (3.1)$$

where s is the target value (40% MVC), f_i is the i th force sample, and n is the number of data samples (Sosnoff & Newell, 2005a).

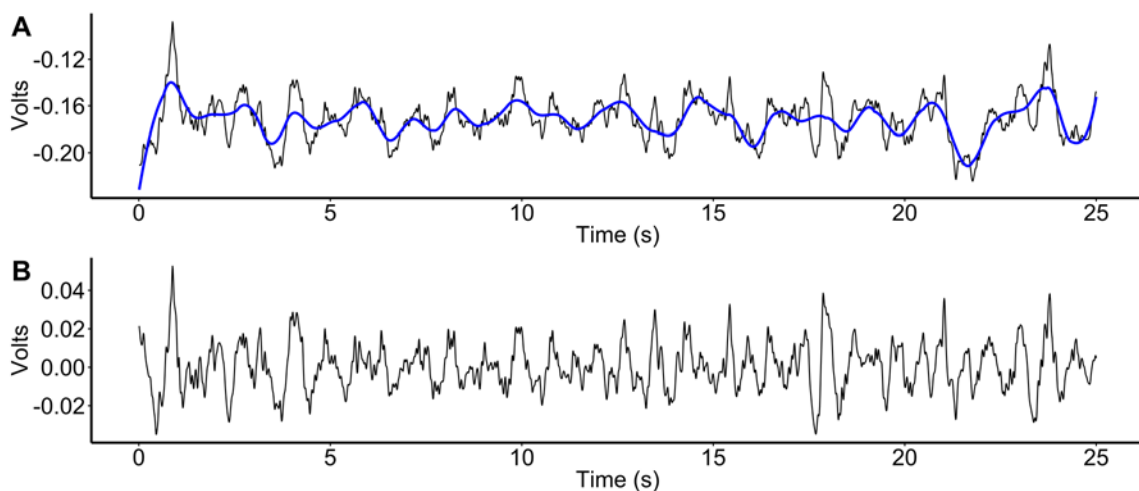


Figure 3-3. Study 1: Example of original signal and trend (A) and detrended signal (B). 1981; Stiles & Randall, 1967; Vaillancourt et al., 2001).

Structure of force variability. Frequency domain characteristics of the force output were calculated using custom-written software in Python. The Fourier transform of the force output yields the amplitude and phase of the time series in the frequency domain. The power in a given time series is equal to the square of the amplitude. Power within three different frequency bandwidths was examined. These bandwidths are associated with sensory-motor feedback and cognitive processing (0-4 Hz) (Miall et al., 1985; Pew, 1974; Slifkin et al., 2000; Sosnoff & Newell, 2005a), feedforward processing (4-12 Hz) (Desmurget & Grafton, 2000; Pew, 1974; Sosnoff & Newell, 2005a; Sosnoff & Voudrie, 2009), and physiological tremor (8-12 Hz; Deuschl et al., 2001; Findley et al.,

Force complexity was quantified with modified multiscale sample entropy (MMSE; Wu et al., 2013), an adaptation of multiscale entropy (Costa et al., 2002a) designed for short time series. In MMSE, sample entropy (Govindan et al., 2007) is calculated over multiple time scales of data to quantify the multiscale complexity of the signal.

Sample entropy quantifies the negative natural logarithm ratio of the likelihood

that a pattern (m samples long) and a longer pattern ($m + 1$) repeat throughout the time series. It is calculated as follows (Govindan et al., 2007; Wu et al., 2013):

1. Construct the i th template vector of length m as

$$x_i^m(\delta) = \{x_i x_{i+\delta} \dots x_{i+(m-1)\delta}\}, 1 \leq i \leq N - m\delta \quad (3.2)$$

where δ is a time delay between successive vector components.

2. Calculate the Euclidean distance d_{ij}^m for each pair of template vectors:

$$d_{ij}^m = \|x_i^m(\delta) - x_j^m(\delta)\|_{\infty}, 1 \leq i, j \leq N - m\delta, j > i + \delta \quad (3.3)$$

3. $n(m, \delta, r)$ is the total number of matched vector pairs of length m . A matched pair is defined as any pair such that $d_{ij}^m(\delta) \leq r$ where r is a pre-defined tolerance threshold. Increment $n(m, \delta, r)$ by one each time $d_{ij}^m(\delta) \leq r$ holds.
4. Repeat steps 1 through 3 for $m + 1$.
5. Sample entropy is thus:

$$SampEn(x, m, \delta, r) = -\ln \frac{n(m+1, \delta, r)}{n(m, \delta, r)} \quad (3.4)$$

In MMSE, sample entropy is calculated on the original time series. A scale-factored moving average of the time series of window length τ (see Figure 3) is computed as:

$$y_j^{(\tau)} = \frac{1}{\tau} \sum_{i=j}^{j+\tau-1} x_i, 1 \leq j \leq N - \tau + 1 \quad (3.5)$$

and sample entropy recalculated at each scale factor as:

$$MMSE(x, m, \tau, r) = SampEn(y^{\tau}, m, \delta = \tau, r) \quad (3.6)$$

We used scale factor values $\tau = 1$ to $\tau = 34$. This allows the calculation of complexity for frequencies from 16.7 Hz to 0.5 Hz (Gow et al., 2015). In previous work, individuals completing this task at 10% MVC exhibited frequencies from 0–12 Hz (Studenka & Raikes, in press). Consistent with previous work an $m = 2$, and $r = 0.15 *$

$SD_{time\ series}$ were used to calculate the sample entropy of the force output (Wu et al., 2013). Finally, the overall complexity (complexity index, CI) for the time series was the sum of the sample entropies for each scale factor (Figure 3-4). As with single-scale sample entropy, higher complexity index values indicate more complex force structures.

Intra-individual variability. To assess intra-individual variability for each outcome measure, the coefficient of variation for the trials was computed as

$$CV = \frac{\sigma_i}{\bar{x}_i}, \quad (3.7)$$

where σ_i is the standard deviation of the trial measurements for each outcome and \bar{x}_i is the mean outcome for participant i .

Statistical Analyses

All statistical calculations were performed in R v.3.3.2 (R Core Team, 2015), using the dplyr (Wickham & Francois, 2015), tidyr (Wickham, 2016), MASS (Venables &

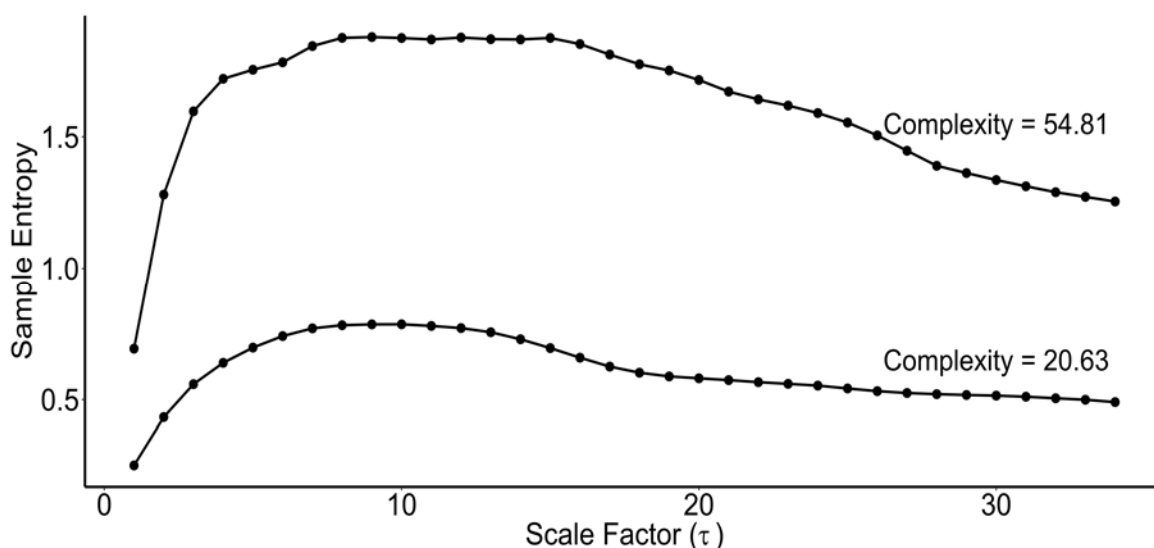


Figure 3-4. Study 1: Example complexity curves for two participants. At each scale factor, lower values indicate more regular signals. Complexity is the sum of the sample entropies at each scale factor. Lower values indicate less complex signals.

Ripley, 2002), *gvlma* (Pena & Slate, 2012, 2014), and *heplots* libraries (Fox, Friendly, & Monette, 2016).

To evaluate differences between concussed and unconcussed participants, individual multiple linear regressions for the average complexity index (CI) per participant, the mean RMSE, the mean average power in the frequency bands 0-4 Hertz, 4-8 Hertz, and 8-12 Hertz, as well as the coefficients of variation for all outcomes were fit. Prior to model fitting, continuous predictors were assessed for normality using quantile-quantile plots (Q-Q plots) and Shapiro-Wilk test. These variables were transformed as needed.

Initial models were fit with the number of diagnosed and suspected concussions, as well as self-reported histories of loss of consciousness (yes/no) and amnesia (yes/no) directly resulting from a concussion. Loss of consciousness and amnesia have both been shown to influence recovery trajectories following concussion (Barlow et al., 2010; Heyer et al., 2016; McCrea, Iverson, et al., 2013; Parks et al., 2015; Taylor et al., 2010; Wilde et al., 2016; Yeates et al., 2009). Initial models included both main and all two-way interaction effects. Residuals for the initial models were plotted and evaluated for approximate normality (Q-Q plot) and non-constant variance (plot of residuals vs. fitted values). Covariates included in the final model were determined using an automated step-down procedure that minimizes Akaike's Information Criterion (AIC). Final model fits were described using adjusted R^2 to evaluate overall model fit, as well as individual predictor coefficients and 95% confidence intervals as well as partial R^2 values (indicating variance explained by an individual variable, a measure of effect size). Partial R^2 was calculated as:

$$R^2 = \frac{SS_{effect}}{SS_{effect} + SS_{error}} \quad (3.9)$$

where values between 0.02 – 0.13 are generally interpreted as small effects, 0.13 – 0.26 as medium effects, and above 0.26 as large effects.

Results

A Priori Predictors

Complexity index. Two observations were dropped to meet assumptions of normality and homoscedasticity. Retained predictors and model fit statistics following the step-down AIC procedure are presented in Table 3-2. Partial R^2 values for retained predictors are shown in Table 3-3. This model was not significant, and none of the predictors exhibited any statistical significance.

The model for the complexity index coefficient of variation required log transformation [$y = \ln(CV_{CI})$] to meet the assumptions of normality and homoscedasticity. Retained predictors and model fit statistics following the step-down AIC procedure are presented in Table 3-2. Partial R^2 values for retained predictors are presented in Table 3-3. The model was significant. However, none of the retained predictors were statistically significant.

Root mean squared error. The model for the averaged RMSE required log transformation to meet the assumption of normality. After the step-down AIC procedure, no variables were retained, indicating that no concussion-related predictors provided information about a linear relationship between concussions and task-related error. The model for the RMSE coefficient of variation required log transformation to meet the assumption of normality. After the step-down AIC procedure, no variables were retained, indicating that there were no concussion-related variables that provided information about a linear relationship between concussion-related predictors and intra-individual RMSE variability.

Table 3-2

A Priori and Best Alternative Models for Complexity Multi-Trial Mean and Coefficient of Variation

Predictor	Mean		Coefficient of variation	
	A priori	Best alternative	A priori	Best alternative
Diagnosed conc.			0.724 (0.405, 1.294)	1.132 (0.743, 1.723)
Suspected conc.	0.504 (-0.658, 1.665)		1.065 (0.892, 1.271)	1.053 (0.852, 1.303)
Males		4.695*** (2.167, 7.223)		0.620 (0.346, 1.109)
Total conc.		-0.815* (-1.554, -0.077)		
LOC	1.215 (-3.035, 5.464)	2.343 (-1.042, 5.728)	1.058 (0.654, 1.712)	0.837 (0.210, 3.341)
Amnesia	-1.458 (-5.855, 2.938)	2.448 (-0.349, 5.245)	1.036 (0.440, 2.441)	0.880 (0.354, 2.190)
Males x diagnosed conc.				0.441 (0.168, 1.156)
Males x suspected conc.				0.961 (0.655, 1.409)
LOC x suspected conc.	-1.577 (-3.898, 0.744)			0.959 (0.478, 1.926)
Diagnosed x suspected conc.			1.202 (0.927, 1.558)	
LOC x amnesia	4.963 (-1.005, 10.930)		0.413 (0.133, 1.283)	
Males x amnesia x diagnosed conc.				6.249* (1.155, 33.809)
Males x LOC x suspected conc.				1.899 (0.766, 4.705)
Males x LOC		-3.432 (-7.866, 1.002)		0.795 (0.152, 4.168)

(table continues)

Predictor	Mean		Coefficient of variation	
	A priori	Best alternative	A priori	Best alternative
Males x amnesia				0.369 (0.098, 1.390)
Amnesia x diagnosed				0.615 (0.169, 2.234)
Observations	48	50	50	50
R^2	0.149	0.327	0.255	0.451
Adjusted R^2	0.048	0.250	0.151	0.253
Residual Std. Error	3.543 (<i>df</i> = 42)	3.462 (<i>df</i> = 44)	0.620 (<i>df</i> = 43)	0.581 (<i>df</i> = 36)
<i>F</i> Statistic	1.474 (<i>df</i> = 5; 42)	4.266** (<i>df</i> = 5; 44)	2.457* (<i>df</i> = 6; 43)	2.278* (<i>df</i> = 13; 36)

Note. Values are reported as b (95% CI). Coefficient of variation models required log transformation to meet model assumptions. Those coefficients and confidence intervals have been re-exponentiated and reflect ratios of increase or decrease between unit increases. Conc. = concussions; LOC = loss of consciousness.

* $p < 0.05$.

** $p < 0.01$.

*** $p < 0.001$.

0-4 Hertz average power. A single outlier was dropped to meet the assumptions of normality and homoscedasticity for 0-4 Hertz average power. Retained predictors and model fit statistics following the step-down AIC procedure are presented in Table 3-4. Partial R^2 values for retained predictors are shown in Table 3-5. This model was not significant. However, average power in this frequency band was higher for individuals with a history of loss of consciousness. The model for the 0-4 Hertz average power coefficient of variation met assumptions for both normality and homoscedasticity without transformation. Retained predictors and model fit statistics following the step-down AIC procedure are presented in Table 3-4. Partial R^2 values for retained predictors are

Table 3-3

Partial R² Values for Retained Predictors in Complexity Mean and Coefficient of Variation Models

Predictor	Mean		Coefficient of variation	
	A priori	Best alternative	A priori	Best alternative
Gender		0.219		0.157
LOC	0.000	0.003	0.010	0.004
Amnesia	0.016	0.066	0.082	0.080
Diagnosed conc.			0.001	0.026
Suspected conc.	0.001		0.049	0.066
Total conc.		0.101		
Gender x amnesia				0.004
Gender x LOC		0.052		0.065
Gender x diagnosed conc.				0.007
Gender x suspected conc.				0.007
LOC x amnesia	0.063		0.054	
LOC x suspected conc.	0.043			0.061
Amnesia x diagnosed conc.				0.053
Diagnosed conc. x suspected conc.			0.045	
Gender x amnesia x diagnosed conc.				0.119
Gender x LOC x suspected conc.				0.054

Note. Conc. = concussions; LOC = loss of consciousness, RA = retrograde amnesia.

Table 3-4

A Priori and Best Alternative Models for 0-4 Hertz Average Power Multi-Trial Mean and Coefficient of Variation

Predictor	Mean		Coefficient of Variation	
	A priori	Best alternative	A priori	Best alternative
Suspected Conc.	-0.070 (-0.486, 0.346)		-0.010 (-0.038, 0.017)	
LOC	2.043* (0.228, 3.858)		-0.033 (-0.130, 0.065)	
Males		0.476 (-0.503, 1.456)		
Diagnosed Conc.		0.241 (-0.616, 1.098)	-0.050* (-0.091, -0.009)	
Amnesia	0.969 (-0.810, 2.748)	-0.444 (-1.975, 1.086)		
LOC x Suspected Conc.	-0.681 (-1.616, 0.254)		0.048 (-0.009, 0.105)	
LOC x Amnesia	-2.151 (-4.605, 0.303)			
Males x Diagnosed Conc.		-1.781* (-3.516, -0.045)		
Amnesia x Diagnosed Conc.		1.846 (-0.040, 3.733)		
Total LOC				1.009 (0.875, 1.163)
Total RA				0.637** (0.473, 0.857)
Total LOC x Total RA				1.775* (1.088, 2.896)
Observations	49	50	50	50
R^2	0.133	0.109	0.171	0.182
Adjusted R^2	0.032	0.008	0.097	0.129
Residual Std. Error	1.449 (df = 43)	1.542 (df = 44)	0.094 (df = 45)	0.322 (df = 46)
F Statistic	1.320 (df = 5; 43)	1.077 (df = 5; 44)	2.320 (df = 4; 45)	3.412* (df = 3; 46)

Note. Values are reported as b (95% CI). The best alternative CV model required log-transformation. The coefficients and confidence intervals for this model have been re-exponentiated. Conc. = concussions; LOC = loss of consciousness; RA = retrograde amnesia.

- * $p < 0.05$.
 ** $p < 0.01$.
 *** $p < 0.001$.

Table 3-5

Partial R^2 Values for Retained Predictors in 0-4 Hertz Average Power Mean and Coefficient of Variation Models

Predictor	Mean		Coefficient of variation	
	A priori	Best alternative	A priori	Best alternative
Gender		0.000		
LOC	0.037		0.025	
Amnesia	0.002	0.008		
Diagnosed Conc.		0.003	0.121	
Suspected Conc.	0.028		0.000	
Total LOC				0.011
Total RA				0.085
Gender x Diagnosed Conc.		0.089		
Amnesia x Diagnosed Conc.		0.081		
LOC x Amnesia	0.068			
LOC x Suspected Conc.	0.048		0.060	
Total LOC x Total RA				0.108

Note: Conc. = Conc.; LOC = loss of consciousness, RA = retrograde amnesia.

presented in Table 3-5. This model was not significant. However, the coefficient for the number of diagnosed concussions was significant, reducing the coefficient of variation by 0.05 per diagnosed concussion.

4-8 Hertz average power. A single outlier was dropped to meet the assumptions of normality and homoscedasticity for 4-8 Hz average power. Retained predictors and model fit statistics following the step-down AIC procedure are presented in Table 3-6. Partial R^2 values for retained predictors are shown in Table 3-7. This model was marginally significant ($F_{5,43} = 2.396$, $p = 0.053$). 4-8 Hz average power decreased by 0.089 per diagnosed concussion. This relationship was mediated by a history of loss of consciousness, increasing average power in this frequency band by 0.14. Furthermore,

Table 3-6

A Priori and Best Alternative Models for 4-8 Hertz Average Power Multi-Trial Mean and Coefficient of Variation

Predictor	Mean		Coefficient of variation	
	A priori	Best alternative	A priori	Best alternative
Males		1.591* (1.105, 2.290)		-0.234** (-0.375, -0.092)
Diagnosed Conc.	-0.089* (-0.163, -0.014)	0.216* (0.066, 0.702)	-0.229 (-0.469, 0.011)	
Suspected Conc.	0.003 (-0.020, 0.026)		-0.002 (-0.053, 0.048)	
LOC	0.140** (0.053, 0.226)	0.926 (0.523, 1.640)	-0.292** (-0.496, -0.088)	
Diagnosed x Suspected Conc.	0.037* (0.004, 0.071)			
LOC x Suspected Conc.	-0.062* (-0.111, -0.012)		0.186** (0.074, 0.298)	
Amnesia		0.896 (0.525, 1.529)	-0.014 (-0.197, 0.170)	
Males x Diagnosed Conc.		2.684 (0.901, 7.996)		
Males x LOC		1.248 (0.607, 2.565)		
LOC x Diagnosed Conc.		5.180* (1.502, 17.865)	0.267* (0.025, 0.508)	
Amnesia x Diagnosed Conc.		1.717 (0.829, 3.556)	0.200 (-0.061, 0.461)	
Males x LOC x Diagnosed Conc.		0.206* (0.054, 0.789)		
Total Conc.				-0.011 (-0.063, 0.042)
Total LOC				-0.202* (-0.384, -0.020)
Total RA				-0.133 (-0.333, 0.068)
Males x Total Conc.				0.063 (-0.018, 0.145)

(table continues)

Predictor	Mean		Coefficient of variation	
	A priori	Best alternative	A priori	Best alternative
Males x Total LOC				0.152 (-0.014, 0.318)
Total Conc. x Total LOC				0.062* (0.012, 0.111)
Total LOC x Total RA				0.240 (-0.050, 0.529)
Observations	49	50	50	50
R^2	0.218	0.350	0.302	0.428
Adjusted R^2	0.127	0.204	0.186	0.316
Residual Std. Error	0.076 (<i>df</i> = 43)	0.479 (<i>df</i> = 40)	0.172 (<i>df</i> = 42)	0.157 (<i>df</i> = 41)
<i>F</i> Statistic	2.396 (<i>df</i> = 5; 43)	2.395* (<i>df</i> = 9; 40)	2.601* (<i>df</i> = 7; 42)	3.836** (<i>df</i> = 8; 41)

Note. Values are reported as b (95% CI). The best model for the trial averages required log-transformation. The coefficients and confidence intervals have been re-exponentiated. Conc. = concussions; LOC = loss of consciousness; RA = retrograde amnesia.

* $p < 0.05$.

** $p < 0.01$.

*** $p < 0.001$.

while the interaction between diagnosed and suspected concussions increased the average power, the interaction between suspected concussions and a history of loss of consciousness decreased the average power. The model for 4-8 Hz average power coefficient of variation met assumptions for both normality and homoscedasticity without transformation. Retained predictors and model fit statistics following the step-down AIC procedure are presented in Table 3-6. Partial R^2 values for retained predictors are shown in Table 3-7. This model was significant. A history of loss of consciousness and diagnosed concussions were associated with reduced trial-to-trial variability in 4-8 Hz average power, while the interactions between suspected concussions and loss of consciousness and between diagnosed concussions and loss of consciousness increase

Table 3-7

Partial R² Values for Retained Predictors in 4-8 Hertz Average Power Mean and Coefficient of Variation Models

Predictor	Mean		Coefficient of variation	
	A priori	Best alternative	A priori	Best alternative
Gender		0.217		0.061
LOC	0.089	0.024	0.000	
Amnesia		0.004	0.011	
Diagnosed Conc.	0.019	0.006	0.001	
Suspected Conc.	0.000		0.065	
Total Conc.				0.097
Total LOC				0.052
Total RA				0.001
Gender x LOC		0.002		
Gender x Diagnosed Conc.		0.001		
Gender x Total Conc.				0.056
Gender x Total LOC				0.077
LOC x Suspected Conc.	0.129		0.211	
Amnesia x Diagnosed Conc.		0.053	0.054	
Diagnosed x Suspected Conc.	0.104			
Total Conc. x Total LOC				0.132
Total LOC x Total RA				0.064
Gender x LOC x Diagnosed Conc.		0.124		

Note: Conc. = concussions; LOC = loss of consciousness, RA = retrograde amnesia.

trial-to-trial variability.

8-12 Hertz average power. The model for 8-12 Hz average power required log transformation to meet the assumption of normality. Retained predictors and model fit statistics following the step-down AIC procedure are presented in Table 3-8. Partial R^2 values for retained predictors are presented in Table 3-9. This model was significant ($F_{6,43} = 4.090$, $p = 0.002$). 8-12 Hz average power decreased approximately 78% per diagnosed concussion, and individuals with a history of loss of consciousness had 7.58 times greater average power than individuals without. The interaction between suspected concussions and a history of loss of consciousness further reduced this average power. Finally, the interaction between diagnosed and suspected concussions increased 8-12 Hz average power by 0.037.

The model for 8-12 Hz average power coefficient of variation met assumptions for both normality and homoscedasticity without transformation. Retained predictors and model fit statistics following the step-down AIC procedure are presented in Table 3-8. Partial R^2 values for retained predictors are shown in Table 3-9. This model was significant ($F_{3,46} = 3.532$, $p = 0.022$). A history of loss of consciousness was associated with reduced trial-to-trial variability in 8-12 Hz average power, while the interaction of suspected concussions and loss of consciousness increases trial-to-trial variability.

Alternative Models

After adjusting for the number of retained predictors, the variance explained by the models for both trial-averaged outcomes and the intra-individual variation was low. The 8-12 Hertz average power model explained the greatest amount of variance of any model, after adjusting for the number of retained predictors (adj. $R^2 = 0.2745$).

Table 3-8

A Priori and Best Alternative Models for 8-12 Hertz Average Power Multi-Trial Mean and Coefficient of Variation

Predictor	Mean		Coefficient of variation	
	A priori	Best	A priori	Best
Males		2.016* (1.085, 3.746)		-0.112 (-0.227, 0.004)
Diagnosed Conc.	0.320** (0.153, 0.669)	0.207** (0.083, 0.517)		
Suspected Conc.	1.021 (0.813, 1.282)	0.909 (0.719, 1.149)	-0.013 (-0.070, 0.045)	-0.006 (-0.062, 0.050)
LOC	7.580*** (3.056, 18.797)	7.825*** (2.606, 23.495)	-0.200 (-0.407, 0.006)	-0.153 (-0.359, 0.053)
Amnesia	0.587 (0.306, 1.127)			
Males x Suspected Conc.		1.306 (0.883, 1.932)		
Males x LOC		0.422 (0.165, 1.078)		
Diagnosed x Suspected Conc.	1.504* (1.079, 2.098)	1.463* (1.042, 2.056)		
LOC x Diagnosed Conc.		1.814 (0.944, 3.487)		
LOC x Suspected Conc.	0.412*** (0.249, 0.683)	0.432*** (0.269, 0.693)	0.178** (0.056, 0.300)	0.158* (0.038, 0.278)
Observations	50	50	50	50
R^2	0.363	0.540	0.187	0.251
Adjusted R^2	0.275	0.437	0.134	0.184
Residual Std. Error	0.757 (<i>df</i> = 43)	0.667 (<i>df</i> = 40)	0.201 (<i>df</i> = 46)	0.196 (<i>df</i> = 45)
F Statistic	4.090** (<i>df</i> = 6; 43)	5.219*** (<i>df</i> = 9; 40)	3.532* (<i>df</i> = 3; 46)	3.760* (<i>df</i> = 4; 45)

Note. Values are reported as b (95% CI). Mean models required log-transformation. Coefficients and confidence intervals have been re-exponentiated. Conc. = concussions; LOC = loss of consciousness; RA = retrograde amnesia.

* $p < 0.05$.

** $p < 0.01$.

*** $p < 0.001$.

Table 3-9

Partial R² Values for Retained Predictors in 8-12 Hertz Average Power Mean and Coefficient of Variation Models

Predictor	Mean		Coefficient of variation	
	A priori	Best alternative	A priori	Best alternative
Gender		0.248		0.078
LOC	0.154	0.105	0.009	0.025
Amnesia	0.059			
Diagnosed Conc.	0.085	0.203		
Suspected Conc.	0.004	0.010	0.024	0.031
Gender x LOC		0.080		
Gender x Suspected Conc.		0.045		
LOC x Diagnosed Conc.		0.078		
LOC x Suspected Conc.	0.225	0.244	0.158	0.135
Diagnosed x Suspected Conc.	0.125	0.114		

Note: Conc. = concussions; LOC = loss of consciousness, RA = retrograde amnesia.

Exploratory data analyses of the current data indicated between-gender differences on all outcomes. This was further supported by gender-specific findings in visual-motor tasks (Stirling et al., 2013; Studenka & Raikes, in press) as well as visuospatial and motor processing tasks (Broshek et al., 2005; Colvin et al., 2009; Covassin et al., 2006; Covassin & Elbin, 2011; Covassin et al., 2012, 2007). Therefore, new models were fitted with gender as a predictor. For each outcome of interest, three alternative models were fit.

1. The original model with the addition of gender as a main effect and all three-way interactions.
2. It is possible that the role of diagnosed and suspected concussions separately is less informative than the cumulative number of concussions. Therefore, a model with main effects of gender, total concussions (diagnosed + suspected), history of loss of consciousness, and history of amnesia along with all three-way interactions was fit.

3. Additionally, there may be differences related to the number of concussions with a loss of consciousness or amnesia that gets over-simplified by considering only history (yes/no). Consequently, a model with main effects of gender, total concussions (diagnosed + suspected), the number of occurrences of loss of consciousness, the number of occurrences of retrograde amnesia, and the number of occurrences of anterograde amnesia along with all three-way interactions was fit.

Models were fitted in the same way as the original models, including verification that the models met assumptions of normality and homoscedasticity as well as the step-down AIC procedure for variable selection. Results from these models are described in the same manner as the original models.

Complexity index. The alternative model that explained the greatest variance for the trial-averaged complexity index was model 2; however, all three models performed comparably. Model 2 was statistically significant and retained predictors and model fit statistics following the step-down AIC procedure are presented in Table 3-2. Partial R^2 values for retained predictors are presented in Table 3-3. This model met the assumptions of normality and homoscedasticity without transformation. Males in this sample had significantly greater complexity than females, and this difference had a moderate to large effect. Additionally, complexity decreased by 0.815 for each concussion, diagnosed or sustained, and this was statistically significant (Figure 3-5 A).

For the complexity index coefficient of variation, the alternative models required log-transformation to meet the assumptions of normality and homoscedasticity. Model 1 explained the greatest variance and was statistically significant. Retained predictors and model fit statistics for this model following the step-down AIC procedure are presented in Table 3-2. Partial R^2 values for retained predictors are shown in Table 3-3. The three-way interaction between gender, amnesia, and diagnosed concussions was significant and had a small to moderate effect on the model. Though the coefficient was not

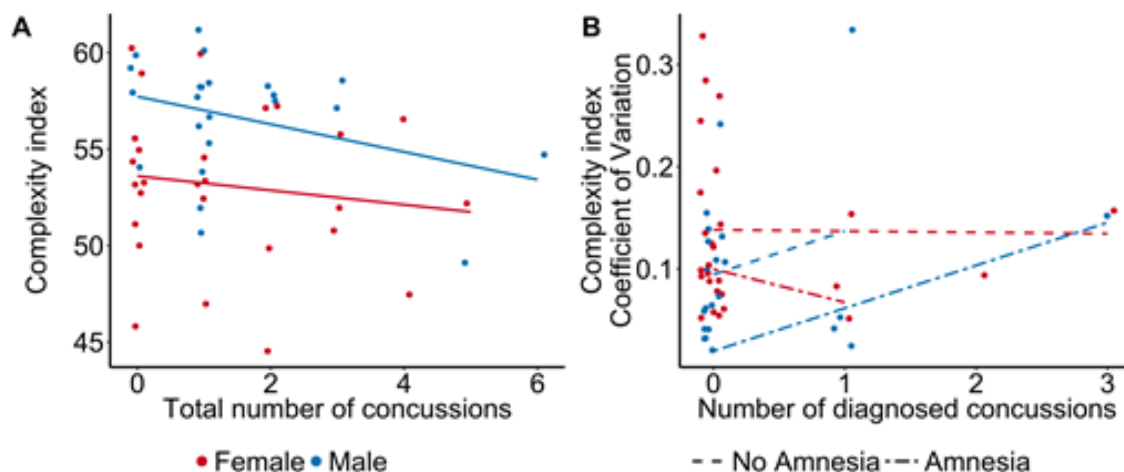


Figure 3-5. Study 1: Complexity mean (A) and coefficient of variation (B) models.

significant, gender also had a moderate effect. Males with no history of concussion had 38% lower complexity than females with no history. Males demonstrated increasing trial-to-trial variability with increasing numbers of concussion regardless of a history of amnesia. Additionally, males with a history of amnesia had lower trial-to-trial variability across diagnosed numbers of concussions. By contrast females with no history of amnesia demonstrated little change in trial-to-trial variability with increasing numbers of diagnosed concussions, and females with a history of amnesia demonstrated a decrease in trial-to-trial variability (Figure 3-5 B).

Root mean squared error. The alternative models for root mean squared error required log-transformation to meet assumptions of normality and homoscedasticity. None of the models were significant. Model 2 provided the greatest explanation of variance after adjusting for the number of predictors; however, the model was not significant, and the adjusted R^2 remains very low. Retained predictors and model fit statistics for model 2 are presented in Table 3-10. Partial R^2 values for retained predictors are shown in Table 3-11. Males with a history of loss of consciousness have

Table 3-10

A Priori and Best Alternative Models for RMSE Multi-Trial Mean and Coefficient of Variation

Predictor	Mean		Coefficient of variation	
	A priori	Best	A priori	Best
Males		1.177 (0.630, 2.199)		0.604** (0.432, 0.844)
Total Conc.		1.246 (0.978, 1.586)		
Diagnosed Conc.				0.050*** (0.010, 0.248)
Suspected Conc.				1.040 (0.915, 1.183)
LOC		1.342 (0.338, 5.333)	0.024 (-0.112, 0.159)	1.452 (0.806, 2.618)
Amnesia		1.632 (0.910, 2.927)	0.223 (-0.018, 0.463)	14.274*** (3.733, 54.580)
Males x Total Conc.		0.719 (0.513, 1.008)		
Males x Diagnosed Conc.				25.278*** (4.068, 157.075)
Males x LOC		0.396 (0.081, 1.936)		0.880 (0.421, 1.839)
LOC x Total Conc.		0.725 (0.437, 1.202)		
Males x LOC x Total Conc.		1.983* (1.033, 3.805)		
LOC x Amnesia			-0.286 (-0.606, 0.034)	
Males x Amnesia				0.299* (0.118, 0.761)
Diagnosed Conc. x Suspected Conc.				1.549** (1.172, 2.048)
LOC x Diagnosed Conc.				6.704* (1.590, 28.272)
Amnesia x Suspected Conc.				0.159*** (0.063, 0.404)
Males x LOC x Diagnosed Conc.				0.023*** (0.003, 0.196)

(table continues)

Predictor	Mean		Coefficient of variation	
	A priori	Best	A priori	Best
Observations	50	50	49	50
R^2	0.000	0.184	0.080	0.506
Adjusted R^2	0.000	0.025	0.019	0.346
Residual Std. Error	0.669 (<i>df</i> = 49)	0.661 (<i>df</i> = 41)	0.197 (<i>df</i> = 45)	0.434 (<i>df</i> = 37)
<i>F</i> Statistic		1.155 (<i>df</i> = 8; 41)	1.308 (<i>df</i> = 3; 45)	3.163** (<i>df</i> = 12; 37)

Note. Values are reported as *b* (95% CI). All models except the a priori CV model required log-transformation. Those coefficients and confidence intervals have been re-exponentiated. Conc. = concussions, LOC = loss of consciousness.

* $p < 0.05$.

** $p < 0.01$.

*** $p < 0.001$.

Table 3-11

Partial R^2 Values for Retained Predictors in RMSE Mean and Coefficient of Variation Models

Predictor	Mean		Coefficient of variation	
	A priori	Best alternative	A priori	Best alternative
Gender		0.012		0.316
LOC		0.017	0.005	0.003
Amnesia		0.065	0.013	0.005
Diagnosed Conc.				0.013
Suspected Conc.				0.035
Total Conc.		0.020		
Gender x LOC		0.020		0.028
Gender x Amnesia				0.157
LOC x Amnesia			0.067	
Gender x Diagnosed Conc.				0.010
Gender x Total Conc.		0.025		
Amnesia x Suspected Conc.				0.301
Diagnosed x Suspected Conc.				0.214
LOC x Total Conc.		0.004		
Gender x LOC x Diagnosed Conc.				0.257
Gender x LOC x Total Conc.		0.099		

Note: Conc. = concussions; LOC = loss of consciousness, RA = retrograde amnesia.

approximately twice the RMSE for each concussion sustained (diagnosed and suspected). This contrasts with males with no history (approximately 38.1% lower RMSE per concussion) and females with a history of loss of consciousness (approximately RMSE 37.5% lower per concussion; see Figure 3-6 A).

Alternative models for RMSE intra-individual variation required log-transformation to meet assumptions of normality and homoscedasticity. Model 1 provided the greatest explanation of variance, and the model was significant. Retained predictors and model fit

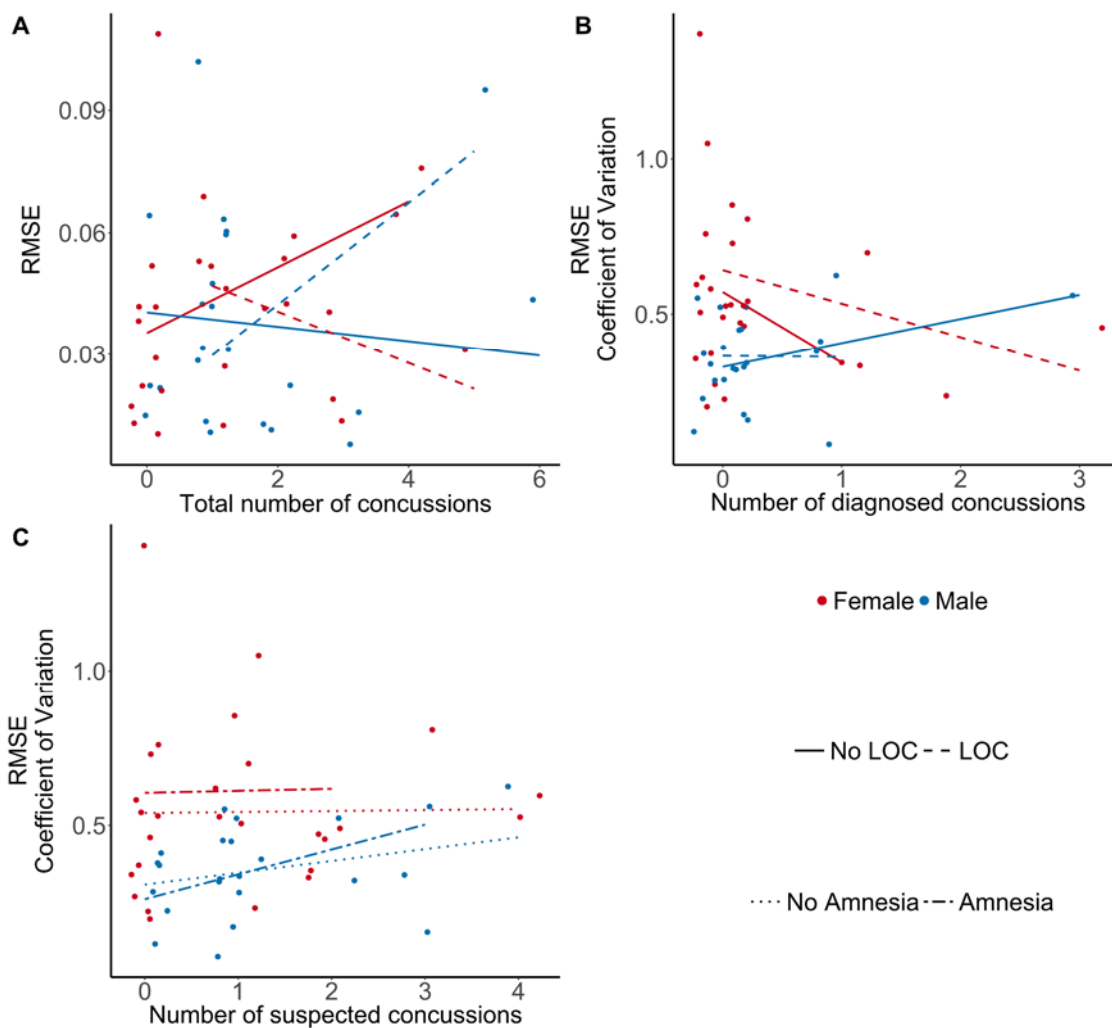


Figure 3-6. Study 1: Root mean squared error mean (A) and coefficient of variation (B, C) models.

statistics for this model after the step-down AIC procedure are presented in Table 3-10. gender, as well as the interactions between amnesia and suspected concussions, and between gender, loss of consciousness and diagnosed concussions, were observed.

Males and females in the sample showed differing responses with respect to diagnosed concussions and history of loss of consciousness, and this effect was large. Females with no history of loss of consciousness in this sample had lower RMSE intra-individual variability per diagnosed concussion than the males (Figure 3-6 B). Additionally, the intra-individual variability was approximately 6.7 times greater per diagnosed concussion with a history of loss of consciousness than without. Large effects of concussion for the women with a history of loss of concussions than without. By contrast, males without a history of loss consciousness showed an increase in intra-individual variability with increasing numbers of concussions while those with a history of loss of consciousness showed relatively no change (Figure 3-6 B).

Additionally, males had lower trial-to-trial variability than females in this sample across all numbers of suspected concussions regardless of amnesia history. However, men with a history of amnesia trended toward greater variability than women with increasing numbers of suspected concussions (Figure 3-5 C).

0-4 Hertz average power. Alternative models for the trial-averaged 0-4 Hertz average power did not require transformation to meet assumptions of normality or homoscedasticity. The retained predictors and model fit statistics for model 1 were presented in Table 3-4. None of the models were significant and none of the models greater variance than the *a priori* model.

Alternative models 1 and 2 for 0-4 Hertz average power intra-individual variation did not require transformation to meet assumptions. However, alternative model 3 required log transformation to meet assumptions, explained the greatest amount of

variance after adjusting for the number of covariates, and was significant. Retained predictors and model fit statistics after the step-down AIC procedure were presented in

Table 3-4. Effect sizes reported as partial R^2 values for retained predictors were presented in Table 3-5. For individuals with no history of loss of consciousness, trial-to-trial variability in 0-4 Hertz average power decreased by approximately 46.3% for each concussion (up to two) resulting in retrograde amnesia. By contrast, individuals who had also sustained a loss of consciousness (up to one) saw a 77% increase in variability (Figure 3-7).

4-8 Hertz average power. The alternative models of trial-average 4-8 Hertz average power required log transformation to meet the assumptions of normality and homoscedasticity. Model 1 explained the greatest variance in the observations, and the model was statistically significant. Retained predictors and model fit statistics alternative models after the step-down AIC procedure were presented in Table 3-6. Partial R^2 values for retained predictors were shown in Table 3-7. Gender had a moderate effect on the model, as did the interaction between gender, loss of consciousness and diagnosed concussions.

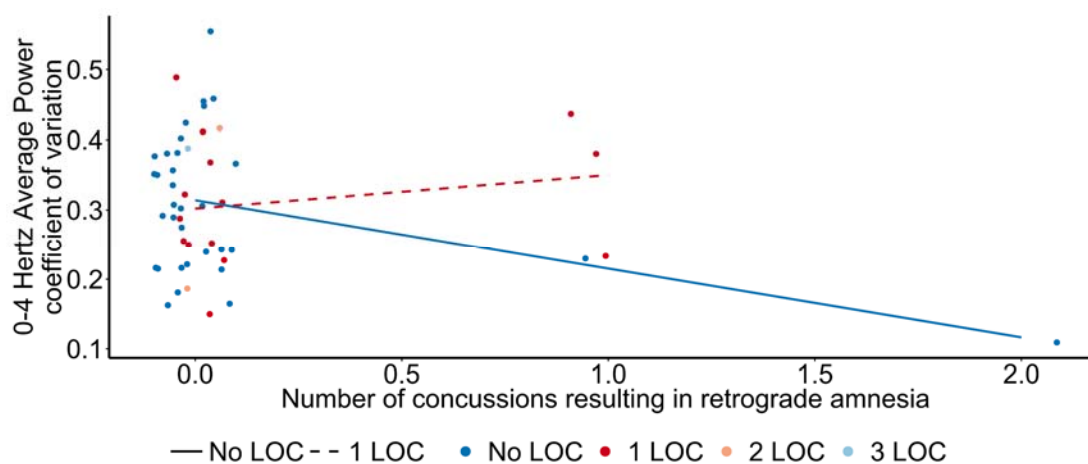


Figure 3-7. Study 1: 0-4 Hertz average power coefficient of variation model.

Males and females showed differing patterns of responses to both numbers of diagnosed concussions and history of loss of consciousness. Males with no history of concussion had greater 59% greater 4-8 Hertz average power than females. For each diagnosed concussion, 4-8 Hertz average power decreased approximately 78.4%. Additionally, males with a history of concussion exhibited a greater decrease in average power per diagnosed concussion than those without. By contrast, 4-8 Hertz average power in females with a history of loss of consciousness was approximately five times greater per diagnosed concussions than for those without showed a decrease (Figure 3-8 A).

The first alternative model for the coefficient of variation for 4-8 Hertz average power required log transformation to meet model assumptions. Model 3 explained the greatest amount of variance after adjusting for the number of retained predictors and was significant. Retained predictors and model fit statistics after the step-down AIC procedure were presented in Table 3-6. Partial R^2 values for retained predictors were presented in Table 3-7. Males with no history of loss of consciousness had lower trial-to-trial variability in 4-8 Hertz average power than similar females. Additionally, trial-to-trial

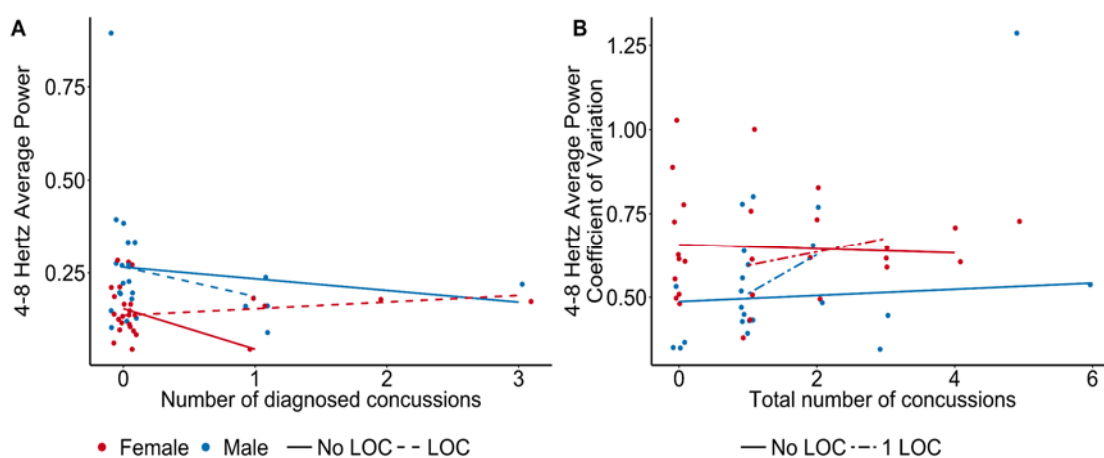


Figure 3-8. Study 1: 4-8 Hertz average power mean (A) and coefficient of variation (B) models.

variability significantly increased with increasing total numbers of sustained concussions and total numbers of occurrences of loss of consciousness (Figure 3-8 B).

8-12 Hertz average power. The trial-averaged 8-12 Hertz average power required log-transformation to meet the assumptions of normality and homoscedasticity. Model 1 explained the greatest amount of variance in the observations and the model was significant. Retained predictors and model fit statistics after the step-down AIC procedure were presented in Table 3-8. Partial R^2 values for retained predictors were shown in Table 3-9. Moderate effects were observed for gender, diagnosed concussions, and the interaction between history of loss of consciousness.

The average power in this frequency was approximately twice as high for males as for females with no history of concussion. Additionally, average power in this frequency band decreased approximately 79.3% per diagnosed concussion. For females with a history of loss of consciousness, average power was approximately 7.8 times greater than for those without and 57.8% lower for males with a history of loss of consciousness. For individuals with no history of diagnosed concussion, men and women with no history of loss of consciousness, men's average power in this frequency band increased slightly and women's decreases slightly over the range of suspected concussions. By contrast for those with a history of loss of consciousness, both males and females had a steep decrease in average power with increasing numbers of suspected concussions (Figure 3-9 A). Additionally, males and females with a history of one diagnosed concussion and a history of loss of consciousness, average power decreases with increasing numbers of suspected concussions. However, this decrease is much more pronounced for men than for women.

The models for the coefficient of variation for 8-12 Hertz average power did not require a transformation in order to meet assumptions of normality and

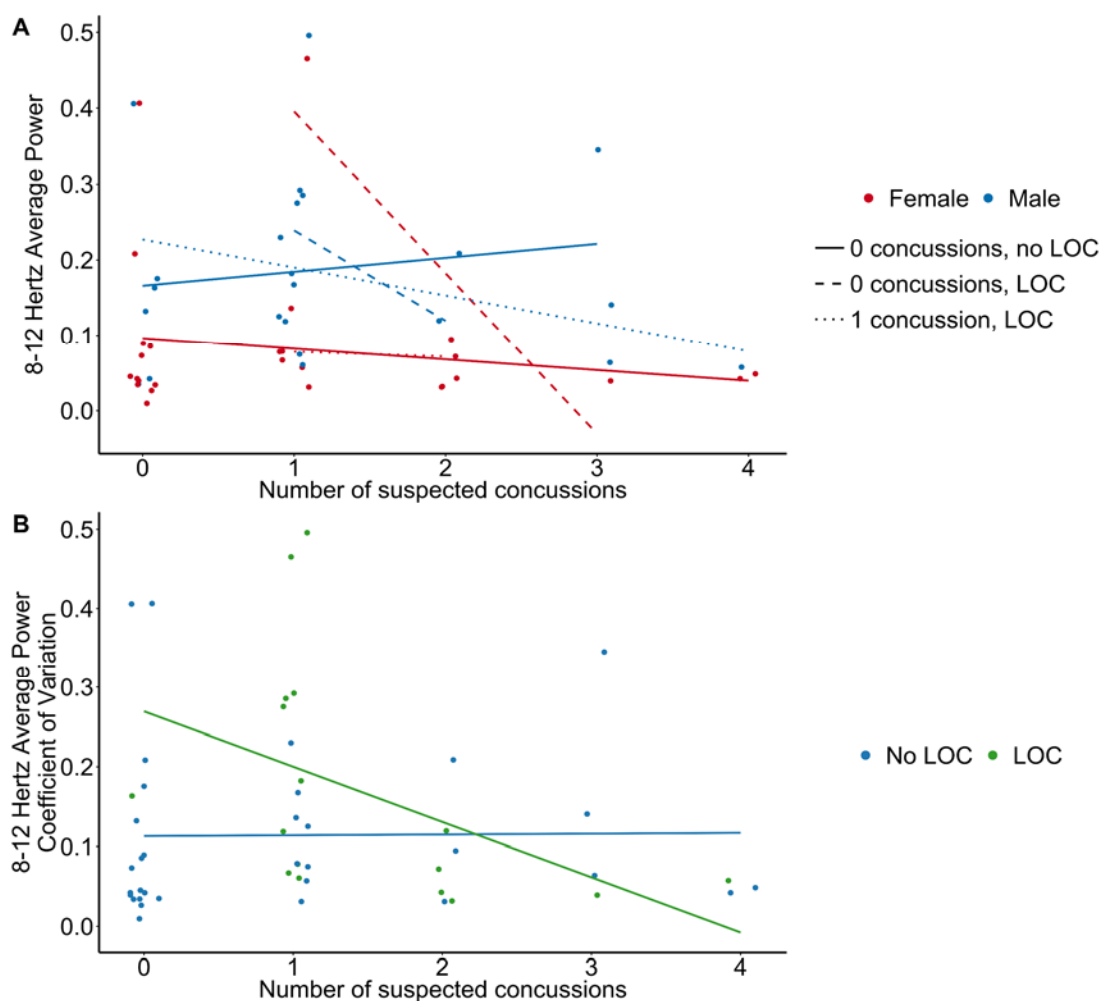


Figure 3-9. Study 1: 8-12 Hertz average power mean (A) and coefficient of variation (B) models.

homoscedasticity. Model 1 explained the greatest variance after controlling for the retained predictors and was significant. Retained predictors and model fit statistics following the step-down AIC procedure for all three alternative models were presented in Table 3-8. Partial R^2 values for retained predictors were shown in Table 3-9. For those with no history of loss of consciousness, intra-individual variability remains relatively consistent across the total number of suspected concussions. For those with a history of loss of consciousness, there was a decrease in intra-individual variability increasing numbers of concussions (Figure 3-9 B).

Discussion

The purpose of this study was to identify the impact of concussion history on the multiscale complexity of fine motor control as quantified by a continuous isometric contraction during a seated visual-motor tracking task. We hypothesized that individuals with a history of concussion would produce less complex multiscale force output as compared to individuals without a history of concussion. We additionally hypothesized a greater effect for individuals with a history of unreported and undiagnosed concussions as compared to individuals in whom concussions were diagnosed. We further hypothesized that individuals with a history of concussion would have increased trial-to-trial complexity variability (Maruta et al., 2010; Robertson et al., 1997; Stuss et al., 1989).

Average Outcomes

The *a priori* models for complexity, average power, and RMSE included only numbers of diagnosed and suspected concussions as well as histories of loss of consciousness and amnesia. These models for complexity, RMSE, and average power from 0-4 Hertz explained little variance and predictors were not significant. Alternative models including gender significantly increased the amount of explained variance, with the exception of 0-4 Hertz average power, and included predictors that significantly predicted the trial-averaged outcomes.

Our initial hypotheses regarding complexity were confirmed in the gender-stratified model. For both men and women, complexity was lower with increasing cumulative numbers of concussions. Males in this sample had greater overall complexity than females. These findings agree with previous single-scale sample entropy findings from this task (Studenka & Raikes, in press), suggesting that men generally produce

more complex waveforms in response to this particular task and that increasing numbers of concussions increase signal regularity.

Additionally, 4-8 Hertz average power decreased with increasing numbers of diagnosed concussions for women with no history of loss of consciousness and men regardless of the loss of consciousness history, while increasing for women with a history of loss of consciousness. Additionally, 8-12 Hertz average power decreased with increasing numbers of suspected concussions for women with any history of diagnosed concussions and loss of consciousness, as well as men with any history of loss of consciousness. By contrast, 8-12 Hertz average power increased with increasing numbers of suspected concussions in men without a history of diagnosed concussions and loss of consciousness. Taken together, both diagnosed and suspected concussions were generally related to reduced average power in these frequency bands, with the rate of reduction being moderated by a history of loss of consciousness.

The loss of average power in these frequency bands cumulatively results in lower signal complexity, as previously observed. Additionally, processes related to feedforward and predictive control (Desmurget & Grafton, 2000; Pew, 1974; Sosnoff & Newell, 2005a; Sosnoff & Voudrie, 2009), visual feedback processing and physiological aspects of tremor in healthy individuals (Deuschl et al., 2001; Stiles & Randall, 1967; Vaillancourt & Newell, 2000) generally correspond to frequencies in these frequency bands. Thus, loss of average power in these frequency bands for this task suggests alterations in processes ranging from sensory-motor processing to visual feedback processing and physiological tremor for individuals with increasing numbers of concussions.

Finally, men and women with no history of loss of consciousness exhibited different patterns task-related performance with increasing numbers of concussions. Women's error increased while the men's' error decreased and this is reasonable and

expected, given that their complexity was lower than the men's. This pattern reversed, however, for those who had experienced any loss of consciousness. Because loss of consciousness was not also significantly associated with reduced complexity, this finding is less easy to explain. However, the increase in 4-8 Hertz average power for women with a history of loss of consciousness and decrease in both 4-8 Hertz and 8-12 Hertz average power for men with a history of loss of consciousness may partially account for these differing patterns of RMSE responses.

These results echo previous findings related to nonlinear measurements from other motor performance tasks following concussions. Postural sway is more regular both immediately after a concussion (within the first 7-10 days of injury) (Buckley et al., 2016; Cavanaugh et al., 2005, 2006; Fino, Nussbaum, & Brolinson, 2016; Gao, Hu, Buckley, White, & Hass, 2011), as well as when asymptomatic (De Beaumont et al., 2011; Quatman-Yates et al., 2015; Sosnoff et al., 2011). It is important to note that these studies found differences between concussed individuals and their pre-injury assessments or healthy participants without considering gender. We observed a significant linear decrease in complexity with increasing numbers of concussions only when stratifying by gender, which supports previous concussion-related findings for this task (Studenka & Raikes, in press).

Additionally, these results agree with those from a circle-tracing task. Concussed individuals demonstrated lower complexity in this task at the time of injury with a progressive increase in complexity as time from injury increased (Kelty-Stephen et al., 2015). Though those authors did not stratify outcomes by gender, a significant gender effect has been noted, with healthy males producing more complex circles than healthy females in a previous study of that particular task (Stirling et al., 2013). Thus, gender is an important consideration for visual-motor tracking tasks when single- and multi-scale

metrics of complexity are of interest.

It is also important to note that, though the present findings of reduced complexity with increasing numbers of concussions echo those from other motor tasks, the reasons and mechanisms for this reduction are not well-documented and are not necessarily the same across tasks. From a task-performance perspective, maintaining upright posture requires the integration of proprioceptive, visual, and vestibular information (Oie et al., 2002; Thompson et al., 2011). By contrast, the visual-motor tracking task in the present study is a vision-dominant task with little input from proprioceptors (Hu & Newell, 2011). Therefore, the present findings contribute to a larger body of findings of decreased complexity across multiple motor tasks in individuals with a history of concussion but do not implicate a common mechanism.

With respect to postural sway, proposed mechanisms for increased regularity post-concussion include reductions in neurophysiological adaptation (Lipsitz & Goldberger, 1992; Quatman-Yates et al., 2015; Sosnoff et al., 2011), sensorimotor integration (Quatman-Yates et al., 2015), and lower extremity muscle stiffness (Fino et al., 2016), as well as more broad alterations in motor cortex activation (Fino et al., 2016). While these mechanisms may also contribute to decreased visual-motor tracking output complexity, individuals with a history of sports-related concussion may also have reduced functional connectivity in visual attention networks as well as the cerebellum (Churchill, Hutchison, Leung, Graham, & Schweizer, 2016). If this is the case, then decreases in visual-motor tracking complexity may provide behavioral evidence of these functional connectivity changes. Additionally, the loss of complexity in aging and disease hypothesis would support this interpretation, where decreases in complexity are the result of either the loss of, or a change in, the connectivity between structural units (Lipsitz & Goldberger, 1992; Vaillancourt & Newell, 2002a).

Additionally, the gender-specific findings are supported by neurocognitive findings of greater task performance for men than women in visuospatial tasks (Broshek et al., 2005; Colvin et al., 2009; Covassin et al., 2006; Covassin & Elbin, 2011; Covassin et al., 2012). While the relationship between task performance and gender was altered by the history of loss of consciousness, men exhibited greater task performance than women with no history of loss of consciousness with increasing numbers of concussions. These findings are in concert with the findings for the complexity of the force output and suggest that, like single-scale measures of regularity for this task (Studenka & Raikes, in press), gender is an important consideration when reporting multiple-trial average outcomes.

Coefficient of Variation

As with the trial-averaged outcomes, the inclusion of gender as a predictor improved the coefficients of variation models. Additionally, our initial hypothesis about increased trial-to-trial variability in complexity was partially confirmed with a gender-stratified model, rather than the *a priori* predictor model. The men's trial-to-trial complexity variability increased with the number of diagnosed concussions, whereas women showed a decrease. For the women, this effect was driven by a history of amnesia, whereas men demonstrated similar patterns of increase regardless of amnesia history.

We additionally observed differing patterns of trial-to-trial variability for the low-frequency band (0-4 Hertz). While this relationship was not driven by increasing numbers of concussions, increasing numbers of occurrences of concussion-related retrograde amnesia were associated with a reduction in 0-4 Hertz average power trial-to-trial variability. This relationship is additionally influenced by the total number of

occurrence of concussion-related loss of consciousness. For those with a history of loss of consciousness, variability increases with occurrences of retrograde amnesia, while those with no history see a decrease.

Furthermore, the total number of concussion-related loss of consciousness events was associated with increased 4-8 Hertz and decreased 8-12 Hertz trial-to-trial variability for both men and women with increasing numbers of total concussive events. These findings were in contrast to the overall findings for complexity, where increasing numbers of concussions were associated with decreased complexity and increased variability. In these frequency bands, increasing numbers of concussions and loss of consciousness are associated with both decreased average power and decreased variability.

The pattern of observations for trial-to-trial performance variability is more complex than for the trial-averages. Broadly, men's RMSE variability increased with diagnosed concussions, while the women's variability decreased. History of amnesia was associated with more rapid increases in variability for men and decreases in variability for women, while a history of loss of consciousness had an opposite effect. Furthermore, for those with suspected concussions, a history of amnesia was associated with increased trial-to-trial variability.

Trial-to-trial variability in measures of complexity and spectral properties have not been previously reported. The findings of the present study demonstrate that increasing numbers of concussion are related to altered consistency in these measures. Additionally, concussion-related loss of consciousness appears to moderate the relationship between complexity and the spectral components. The patterns observed here suggest that individuals with a history of concussion-related loss of consciousness have increasingly stable trial-to-trial high-frequency components and more variable low-

frequency components with increasing numbers of concussions. This in turn leads to more variable complexity and lower overall complexity. Additionally, these patterns have a gender-specific influence on task performance. For those without a history of loss of consciousness, women had more task-related error with lower variability as the number of concussions increased. This pattern was reversed in the men in this sample.

Previous studies have also reported increased performance variability on visual-motor tasks in the presence of concussion (Maruta et al., 2010; Robertson et al., 1997; Stuss et al., 1989). One possible explanation for this increase in performance variability is the observation of damaged white matter tracts in the anterior corona radiata and the genu of the corpus callosum (Maruta et al., 2010). These areas are centers of attention and spatial processing, along with the dorsolateral prefrontal cortex (DLPFC), and may be susceptible to damage with concussions (Jonides et al., 1993; Miller & Cohen, 2001). Given the potential disruption of visual attention networks with concussion, damage in these areas may explain increases in performance variability as well as decreases in task performance and motor complexity. Furthermore, post-concussion syndrome (persistent concussive symptoms lasting beyond the usual time course of recovery) may be related to damage in the connections to the right DLPFC (Stein & McAllister, 2009). Thus, visual-motor tracking performance may provide insight into DLPFC function and be useful as a metric of long-term concussion-related outcomes. However, gender-related differences in performance variability, such as those in the present study, have not been reported and merit further investigation.

The present findings contribute to a larger body of work indicating that concussion results in increased intra-individual variability across multiple domains of cognitive, motor, and behavioral function (Beaupré, De Guise, & McKerral, 2012; Hill, Rohling, Boettcher, & Meyers, 2013; Maruta et al., 2010; Parks et al., 2015; Raikes &

Schaefer, 2016; Robertson et al., 1997; Stuss et al., 1989; Stuss, Pogue, Buckle, & Bondar, 1994). Intra-individual variation is an indicator of overall neurological health and increases in such variability tend to reflect reductions in health (MacDonald, Nyberg, & Bäckman, 2006). The findings of the present study, in conjunction with these other findings, indicate that not only should multiple-trial averages be considered in the evaluation of long-term concussion recovery, but that intra-individual variability is an additionally important indicator of function.

The Role of Loss of Consciousness

The role of loss of consciousness in concussion is not well understood. Individuals with concussion-related loss of consciousness often have prolonged recovery times and trajectories (Heyer et al., 2016; Parks et al., 2015; Taylor et al., 2010; Yeates et al., 2009), though this is not always the case (Collins et al., 2003; Howell, O'Brien, Beasley, Mannix, & Meehan, 2016; Lovell, Iverson, Collins, McKeag, & Maroon, 1999; Mickevičiene et al., 2002, 2004; Sterr, Herron, Hayward, & Montaldi, 2006; Umile, Sandel, Alavi, Terry, & Plotkin, 2002). Neuroimaging findings related to traumatic brain injury, including concussion, have consistently revealed reduced brain stem white matter structure (Delano-Wood et al., 2015), ventral prefrontal areas (Sorg et al., 2014), as well as areas related to visual and prefrontal cortex integration (Wilde et al., 2016) for individuals with concussion-related loss of consciousness. Notably, the reduced brainstem white matter integrity occurred in the pontine tegmentum, whose fibers have projections to both ascending sensory and descending motor tracts (Delano-Wood et al., 2015). Additionally, the upper brainstem is involved in the integration of eye movement, which may be related to post-concussion syndrome (Heitger et al., 2009). Therefore, the relationship between loss of consciousness and the outcomes observed in the present

study may reflect such losses of white matter integrity in areas related to visual integration, attention, and motor control.

Limitations

There are several limitations in the present study. First, all participants provided only a self-reported history of concussion. It is possible that individuals who reported no history of concussion did indeed have a history. For those who reported diagnosed concussions, it is reasonable to assume that these individuals recalled receiving a diagnosis by a medical professional. Additionally, to better account for the high prevalence of underreporting of concussions (Gysland et al., 2012; Kerr et al., 2016; McCrea et al., 2004), individuals also self-reported their history of suspected concussions. This required participants to retrospectively self-diagnose themselves and therefore, individuals may have reported suspected concussions that were indeed not concussions. This applies, in particular, to those who only reported suspected concussions without any diagnosed concussions for reference ($n = 25$). However, conservative approaches to concussion management suggest that any time a concussion is *suspected*, individuals should be held out for evaluation and observation (Giza et al., 2013; McCrory et al., 2013). Therefore, if individuals are able to retrospectively self-identify times at which they likely should have been evaluated but were not, then these results approximate the effects of concussions under the most conservative management plans.

Secondly there is an unavoidable delay between force being applied to the load cell and being plotted on-screen (≤ 60 ms). However, the delay was consistent for all individuals, and therefore any influence that such visual lag had on task performance should also be consistent across individuals. Furthermore, short delays (< 100 ms) have

minimal on task performance and nonlinear metrics (Sosnoff & Newell, 2008). Additionally, participants task performance may have improved with practice and therefore may have influenced the findings. However, previous research related to this task has demonstrated minimal within-day learning effects for the structure of force output, though there may be an improvement in RMSE (Studenka, King, & Newell, 2014). Future research should identify the extent to which within-day and across-day learning occurs and alters task performance, temporal structure, and spectral characteristics of visual-motor tracking tasks following a concussion. Additionally, though gender differences were observed, these analyses do not take into account education level or prior visuo-spatial task exposure. Finally, other tracing patterns (e.g., sine wave, circles) may identify other patterns of impairment and merit further investigation.

In light of the fact that individuals with a history of concussions, and particularly females, generally exhibited lower complexity irrespective of target error, this information may be useful in informing the clinician of persistent, subclinical visual-motor impairments. Nonlinear characteristics of visual-motor tracking performance, in addition to common assessments of cognition and balance as well as intra-individual variability in these measures, may help to provide a complete view of the overall neurological recovery of the concussed individual. Doing so may lead to better identification of individuals at risk for poor long-term outcomes that are currently associated with repetitive head trauma (H. Chen et al., 2007; Chiò et al., 2005; Factor & Weiner, 1991; Goldman et al., 2006; Harris et al., 2013; Kerr, Evenson, et al., 2014; Kerr et al., 2012; McKee et al., 2009, 2013; Omalu et al., 2005; Rugbjerg et al., 2008; Stern et al., 2011)

Conclusion

Asymptomatic individuals with a history of concussion exhibit altered patterns of

visual-motor tracking performance, signal complexity, and high-frequency oscillations as compared to individuals with no such history. These metrics are linearly associated with increasing numbers of concussions and are influenced by both gender and a history of concussion-related loss of consciousness. These findings indicate a cumulative reduction in the way in which previously concussed individuals process and integrate visual information to guide behavior and this may be related to losses of white matter integrity in the brainstem, visual networks, and prefrontal areas.

CHAPTER 4
DISCRIMINATING PREVIOUSLY CONCUSSED INDIVIDUALS FROM HEALTHY
CONTROLS WITH MEASURES OF PHYSIOLOGICAL COMPLEXITY

Abstract

The occurrences of concussion, particularly in sport and military activity, are presently an issue of social and medical inquiry and concern. Given the associations between repeated concussions and later adulthood neurological and cognitive impairments, screening methods to identify individuals with a past history of concussion are of value. Nonlinear dynamics, including measures of complexity and spectral power, may provide insight into the functional connectivity in cognitive and motor processes following concussion, and thus may provide insight into the presence of past concussions. Individuals with ($n = 84$) and without ($n = 43$) a self-reported history of concussion completed 10 trials of a visual-motor tracking task. We fit individual 10-fold cross-validated logistic regressions using average multiscale complexity, root mean square error, detrended fluctuation α , and spectral power in three frequency bands (0-4Hz, 4-8Hz, and 8-12Hz) and gender (all models) to predict prior history of concussion. Outcomes included sensitivity (true positive rate), specificity (true negative rate), positive (probability of concussion history given a positive prediction) and negative predictive value (probability of no concussion history given a negative prediction). Positive predictive value, reflecting the capacity to predict a positive concussion history from a clinical perspective, was high ($\leq 70\%$) despite moderate sensitivity (49.41%-76.47%) and specificity (47.62%-71-47%) in the gender-stratified models. Such clinical prediction capacity is valuable in identifying individuals who merit further evaluation and observation over time for conditions related to repetitive head traumas.

Introduction

Physiological systems exhibit complex patterns under healthy conditions. Complexity is typically defined as functional connectivity between sensory, cognitive, and motor systems and manifested as multiple frequencies present in a produced signal (Lipsitz & Goldberger, 1992; Vaillancourt & Newell, 2002a). With respect to motor output, quantifying complexity provides information about both sensory-motor function and motor control (Hu & Newell, 2011; Newell et al., 2006; Sosnoff & Newell, 2005a; Vieluf et al., 2015). Complexity has been quantified through measures of regularity (approximate entropy, sample entropy; Govindan et al., 2007; Pincus & Goldberger, 1994; Pincus & Viscarello, 1992; Richman & Moorman, 2000; Slifkin et al., 2000), multiscale complexity (multiscale entropy; Costa et al., 2002a, 2003; Kelty-Stephen et al., 2015), Fourier transform-based spectral analyses (Slifkin et al., 2000; Sosnoff & Newell, 2008; Vaillancourt et al., 2001), and long-range correlations between points across multiple time scales (detrended fluctuation analysis; Peng, Hausdorff, Goldberger, & Walleczek, 2000; Peng, Havlin, Stanley, & Goldberger, 1995; Penzel, Kantelhardt, Grote, Peter, & Bunde, 2003; Vaillancourt & Newell, 2003).

Additionally, with both aging and disease, individuals exhibit a loss of complexity across multiple physiological systems including cardiac, respiratory, sleep, and motor (Hayano et al., 1990; Kelty-Stephen et al., 2015; Lee, Kim, Kim, Park, & Kim, 2002; Morrison & Newell, 2012; Newell et al., 2009; Peng et al., 2000; Penzel et al., 2003; Pincus & Goldberger, 1994; Sosnoff et al., 2011; Sosnoff & Newell, 2006b; Vaillancourt et al., 2001). This loss of complexity is generally reflected by a relative reduction in the contribution of high-frequency components, an increase in single-scale metrics of regularity, decreases in multiscale complexity, and deviations away from long-range

correlations into either random or uncorrelated structures (Costa et al., 2005, 2003; Lipsitz & Goldberger, 1992; Loughlin & Redfern, 2001; Morrison & Newell, 2012; Newell et al., 1995, 2009, 2006; Ofori, Samson, & Sosnoff, 2010; Peng et al., 2000; Pincus & Goldberger, 1994; Richman & Moorman, 2000; Singh et al., 2012; Sosnoff et al., 2011; Sosnoff & Newell, 2005a; Vaillancourt & Newell, 2002a, 2003).

There have been limited applications of these methods to outcomes following concussions. Concussions are defined as biomechanical events resulting from a blow to the head or body resulting in a disruption of normal brain function (McCroory et al., 2013). Concussions present as impairments in multiple domains of cognition (Barr & McCrea, 2001; Bleiberg et al., 2004; Collie et al., 2006; Gaines et al., 2016; Guskiewicz et al., 2001; Iverson et al., 2006; Makdissi et al., 2001; McCrea et al., 2003; Schatz et al., 2006) and motor control (Buckley et al., 2013; Catena et al., 2007b, 2009; Furman et al., 2013; Guskiewicz et al., 1996; Hammeke et al., 2013; Pearce et al., 2015; Riemann & Guskiewicz, 2000) among others. The majority of these impairments resolve within 5-7 days (Barr & McCrea, 2001; Bleiberg et al., 2004; Furman et al., 2013; Guskiewicz et al., 1996, 2001; Iverson et al., 2006; McCrea et al., 2003; Peterson et al., 2003; Register-Mihalik et al., 2008; Riemann & Guskiewicz, 2000; Sim et al., 2008). However, there is accumulating evidence of long-term impairments in cognitive and motor functions (Buckley et al., 2015, 2016, J.-K. Chen et al., 2004, 2008a, 2008b; De Beaumont et al., 2009; Gosselin et al., 2011; Howell et al., 2013; Pearce et al., 2014; Slobounov et al., 2002; Witt et al., 2010). Additionally, history of concussion is a predictor of the eventual development of later-in-life cognitive and motor disorders including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and chronic traumatic encephalopathy (Cantu, 2007; H. Chen et al., 2007; Chiò et al., 2005; Factor & Weiner, 1991; Goldman et al., 2006; Guskiewicz et al., 2005; Harris et al., 2013; McKee et al.,

2009, 2013; Rughjerg et al., 2008). At present, there are no ways to discriminate those individuals who are at risk for these conditions, and there are only limited ways for identifying people with residual impairments that do not present clinically. Additionally, there is evidence that a significant proportion of individuals may not report the occurrence of a concussion (Gysland et al., 2012; Kerr, Register-Mihalik, et al., 2014; Kerr et al., 2016; McCrea et al., 2004). Therefore, there is a need for objective methods that discriminate between persons with a history of concussion and those without. Quantifying complexity in motor output may provide such a metric for identification.

Nonlinear regularity has been used to quantify changes in postural sway following concussions. There is evidence of subtle and persistent increases in postural sway regularity during stationary stance when analyzed using approximate entropy (ApEn) (Cavanaugh et al., 2005, 2006; De Beaumont et al., 2011; Sosnoff et al., 2011), as well as Shannon and Renyi entropies (Buckley et al., 2016), in asymptomatic individuals with a history of concussion. Given the definitions of complexity, these findings indicate that previously concussed individuals have altered functional connections between sensory inputs (proprioceptive, visual, vestibular) and postural effectors to maintain upright posture (Kennedy & Inglis, 2002; Oie et al., 2002; Peterka, 2002; Roll et al., 2002; Thompson et al., 2011).

Studenka and Raikes (in press) observed greater regularity in individuals with a history of multiple concussions than individuals with a single concussion during a seated visual-motor tracking task. This task relies on visual information for error detection and correction (Cole & Sedgwick, 1992; Gandevia et al., 1990; Hu & Newell, 2011; Teasdale et al., 1993; Tracy, 2007; Vaillancourt & Russell, 2002) and thus may provide valuable information about visual information processing and integration with error detection and correction processes following concussion.

Only one study to date has quantified complexity, observed over multiple time scales, after concussion rather than solely regularity (Kelty-Stephen et al., 2015). The authors used a circle tracing task, whose complexity provides information about the integration between proprioceptive and visual systems (Kelty-Stephen et al., 2015; Stirling et al., 2013). Concussed individuals exhibited decreased complexity in a circle tracing task within 1-11 days of injury, as compared to a pre-injury assessment. Additionally, concussed individuals' task complexity increased as time from injury further increased. However, the authors do not indicate over what time frame this increase occurred or whether performance returned to preinjury status (Kelty-Stephen et al., 2015).

While group differences have been observed between individuals with and without a history of concussion, there have been few, if any, efforts to determine the extent to which these measures may be able to predictively distinguish individuals with a history of concussion from those without. Accurate discrimination would provide valuable clinical information regarding a person's health status, including past concussion history as well as recovery from a concussion. Additionally, given the relationship between prior concussion history and later-in-life conditions, such measures may help to discriminate at-risk individuals.

There are a limited number of reports focusing on distinguishing people with a history of concussion from those without. The majority of these studies report use of neurocognitive testing to distinguish persons with acute concussions from healthy individuals (Barr & McCrea, 2001; Broglio et al., 2007; Collins et al., 1999; Iverson et al., 2006; Louey et al., 2014; Lovell et al., 2003; Schatz et al., 2006; Van Kampen, Lovell, Pardini, Collins, & Fu, 2006). Additionally, several studies have utilized neurocognitive testing outcomes and symptoms to distinguish acutely concussed individuals at risk for

prolonged recovery times from those with shorter recovery times (Lau et al., 2011; Lau, Collins, & Lovell, 2012). One study utilized a neurocognitive screening tool to differentiate between individuals with traumatic brain injuries from nonbrain injured individuals (McKay, Wertheimer, Fichtenberg, & Casey, 2008). Though the participants in that study included individuals with concussions, the traumatic brain injury group had people with a range of severities and most had moderate-to-severe TBIs. Thus, few studies have undertaken to differentiate between asymptomatic persons with and without a history of concussion, particularly with a motor-based task.

The purpose of this study was to determine whether various measures of nonlinear regularity and complexity accurately discriminate between individuals with and without a history of concussion. We applied these measures to the output of a continuous isometric visual-motor tracking task. This task has been previously used to study changes in sensory-motor integration and motor control in aging individuals with various conditions, including concussions.

Methods

Participants

One hundred twenty-seven right-handed participants were recruited from club sports at Utah State University as well as through the Utah State University Research Participation Portal (<https://usu.sona-systems.com>). Descriptive characteristics of this sample can be found in Table 4-1 and Figure 4-1. These data collection procedures were approved by the Institutional Review Board (Appendix B and C).

Individuals were screened for concussion history using a standardized form (Appendix A). Information regarding concussion history included self-reported numbers of diagnosed and suspected injuries as well as potential indicators of prolonged recovery

Table 4-1

Study 2: Participant Demographic Information and Concussion History

	Concussion history		Test	p value
	No History	History		
<i>n</i>	42	85		
Height (in)	66.30 (3.26)	68.63 (3.68)	$t = -3.625$	< 0.001
Weight (kg)	146.29 (27.44)	157.90 (27.85)	$t = -2.229$	0.028
Age	20.55 (2.03)	20.58 (1.91)	$t = -0.010$	0.935
Athletic exp. (years)	35.95 (22.62)	47.27 (23.26)	$t = -2.629$	0.01
Male/Female	12/30	43/42	$\chi^2 = 4.689$	0.03
Right-handed	41	83		
Race or Ethnicity				
Caucasian or White	40	82		
Asian	1			
Mexican	3	3		
Spanish	1			
Argentinian	1			
Peruvian		1		
Multiple	1	1		

Note. Athletic experience is cumulative experience across all sports played. LOC = loss of consciousness; RA = retrograde amnesia; AA = anterograde amnesia.

including loss of consciousness and post-concussive amnesia (Barlow et al., 2010; McCrea, Iverson, et al., 2013; Parks et al., 2015; Taylor et al., 2010; Wilde et al., 2016; Yeates et al., 2009). Due to high rates of underreporting of concussions in athletics (Kerr et al., 2016; McCrea et al., 2004), these self-reports more completely describe the participants' injury history than self-reported diagnosed concussion alone (Studenka & Raikes, in press). All participants who reported a history of concussion also self-reported no known persistent concussion symptoms. Further demographic data collected sport history and cumulative years of athletic experience.

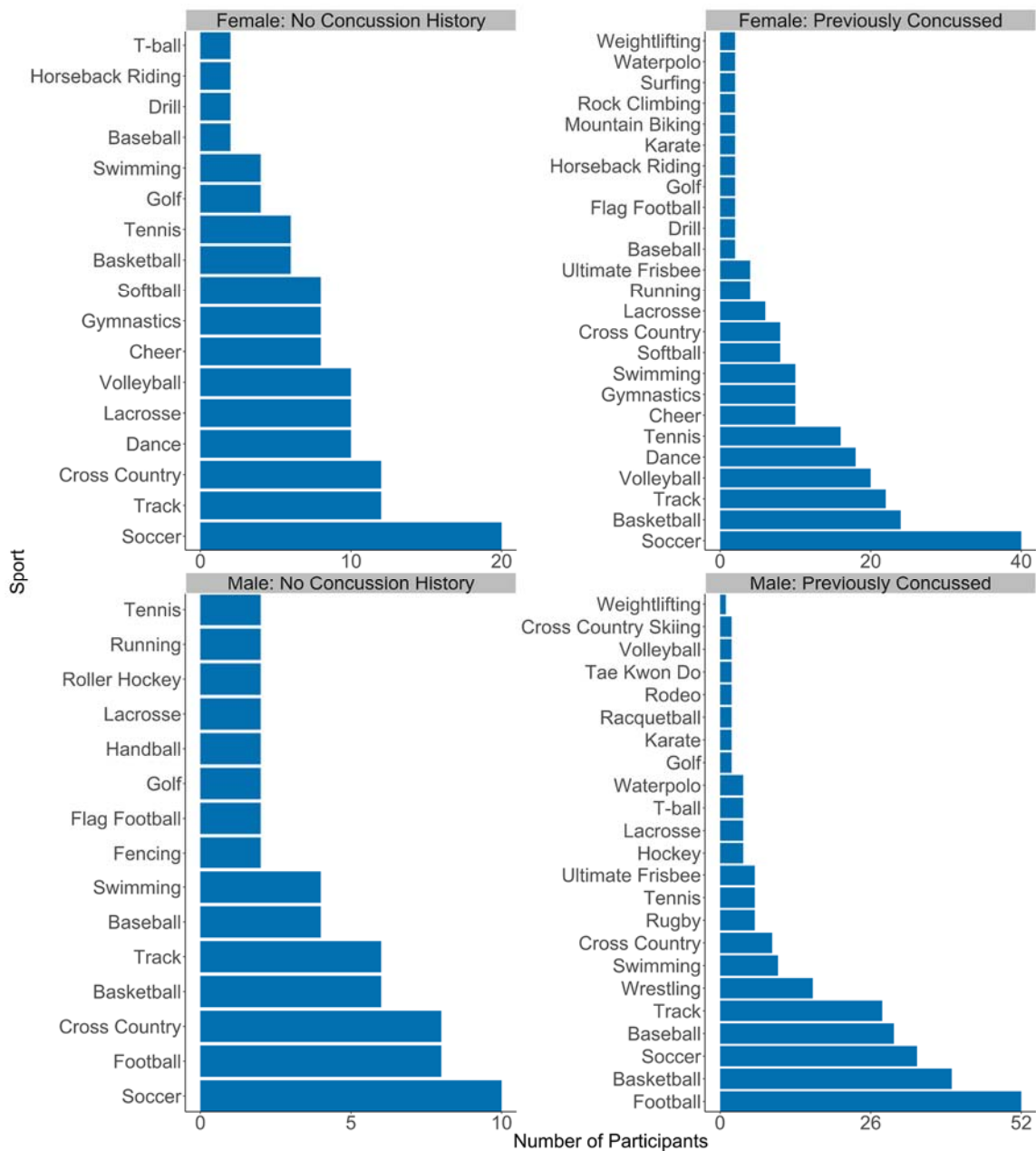


Figure 4-1: Study 2: Sport participation by gender and concussion history.

Apparatus

Participants were seated at a table, facing a 22" (29 x 47 cm horizontal and vertical) LCD (Dell) monitor. An ATI Industrial Automation load cell (diameter 1.27 cm; Apex, NC) was affixed to a wooden block, and secured with the load cell mounted just right of the center of the monitor and 35 cm from the bottom edge of the monitor (Figure 4-1). The output from the load cell was amplified through a National Instruments DAQ board (National Instruments, Austin, TX) with a resolution of 3.125 microNewtons. The participants rested their right hands on the right side of the load cell and pressed the load cell with the lateral aspect of the right distal interphalangeal joint. Abduction/adduction of the index finger registered force through the load cell. Data were sampled at 100 Hz, in keeping with recommendations that sampling rates be set to 5x the highest frequency of interest when calculating sample entropy (Gow et al., 2015). Physiological signals are generally observed between 0 and 20 Hz, making 20 Hz the upper limit of interest.

The task was administered in, and all data collected through, MATLAB (v. 2015a, The Mathworks Inc., Natick, MA, 2015). A white line was displayed on the screen representing the force administered by the index finger. The delay between finger force and output display is unavoidable but is minimized and undetectable by the experimenters (~60 ms; Studenka & Raikes, in press). A straight red line was displayed on the screen for the duration of each trial and served as the target waveform. The white line moved across the computer monitor from left to right, leaving a trace of its previous position (see Figure 4-2). For each trial, the target line was centered in the middle of the screen at 40% of a participant's MVC. This value maximizes complexity (Vieluf et al., 2015). The entire screen ranged from 35%–45% of a participant's MVC.



Figure 4-2. Study 2: Visual-motor tracking task apparatus and display. The horizontal line is the target line. The white line is the participant's produced force.

Procedures and Instructions

Participants performed three trials (5 s) applying maximal finger force. The maximal value of these three trials was recorded as that participant's maximal voluntary contraction (MVC). Each participant then performed 10 trials of tracking. Participants were instructed to minimize the difference between the white (participant produced) and red (target) lines. Each trial lasted 30 seconds.

Data Analysis

All data were processed using a custom-written Python (Python Software Foundation, <https://www.python.org/>) module (<https://github.com/araikes/physiologic-complexity>). Trial data were visually inspected for compliance with instructions and validity. Individual trials were excluded for the following reasons.

1. Trials with fewer than 20% of the data points appearing on the screen
2. Trials with a loss of force applied to the load cell, indicating that the participant had removed the finger during the trial
3. Trials with visually abnormal patterns relative to the task, including rapid oscillations, delayed force application more than 4 seconds into a trial, or multiple valleys approaching 0 force.

Data were filtered with a 9th order forward-backward 20 Hz low-pass digital Butterworth filter. Prior to analyses, the first 4 s (1 s of the recorded trial following a 3 second “warm up”) and the last 1 s of force output were removed to account for changes that might occur as an individual acclimates to the task and changes that might occur toward task completion. Because sample entropy is influenced by nonstationarity in the data, all data were detrended using an adaptive fractal detrending method prior to complexity calculations (Gao, Hu, & Tung, 2011). Detrending was computed using a 2nd order polynomial fit over segment lengths of 129 data points to preserve data trends without overfitting (see Figure 4-3).

Amount of force variability. Root mean square error (RMSE) was calculated as a metric of overall task performance as

$$RMSE = \sqrt{\frac{\sum (s - f_i)^2}{n - 1}}, \quad (4.1)$$

where s is the target value (40% MVC), f_i is the i th force sample, and l is the number of data samples (Sosnoff & Newell, 2005a).

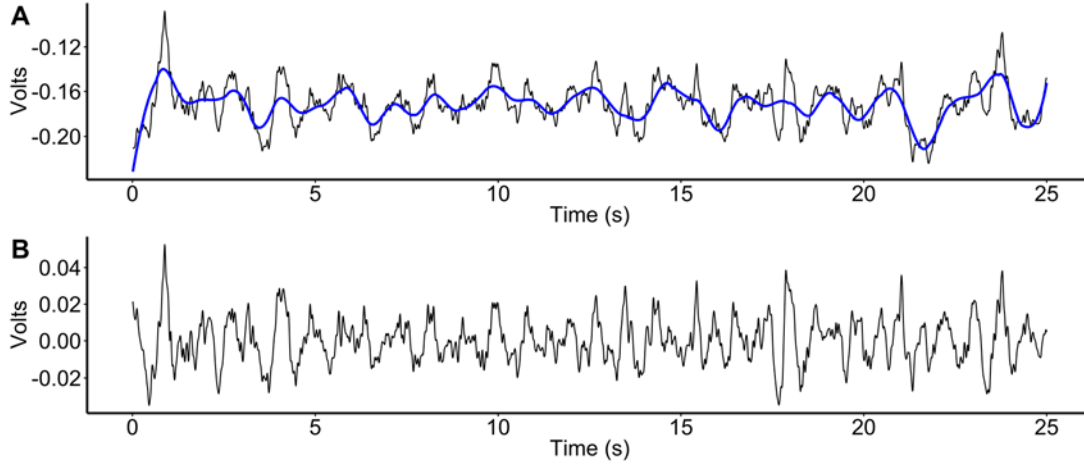


Figure 4-3. Study 2: Example of original signal and trend (A) and detrended signal (B).

The structure of force variability. The structure of force variability was examined using several time- and frequency-domain analytic methods. We used sample entropy, modified multiscale entropy, detrended fluctuation analysis, and frequency analysis.

Sample entropy. Sample entropy quantifies the negative natural logarithm ratio of the likelihood that a pattern (m samples long) and a longer pattern ($m + 1$) repeat throughout the time series. It is calculated as follows (Govindan et al., 2007; Wu et al., 2013):

1. Construct the i th template vector of length m as

$$x_i^m(\delta) = \{x_i \ x_{i+\delta} \ \dots \ x_{i+(m-1)\delta}\}, 1 \leq i \leq N - m\delta \quad (4.2)$$

where δ is a time delay between successive vector components.

2. Calculate the Euclidean distance d_{ij}^m for each pair of template vectors:

$$d_{ij}^m = \|x_i^m(\delta) - x_j^m(\delta)\|_\infty, 1 \leq i, j \leq N - m\delta, j > i + \delta \quad (4.3)$$

3. $n(m, \delta, r)$ is the total number of matched vector pairs of length m . A matched pair is defined as any pair such that $d_{ij}^m(\delta) \leq r$ where r is a pre-defined

tolerance threshold. Increment $n(m, \delta, r)$ by one each time $d_{ij}^m(\delta) \leq r$ holds.

4. Repeat steps 1 through 3 for $m + 1$.
5. Sample entropy is thus:

$$SampEn(x, m, \delta, r) = -\ln \frac{n(m+1, \delta, r)}{n(m, \delta, r)} \quad (4.4)$$

Sample entropy is a metric of regularity. It is applied to the original data and considers only a single time scale

Modified multiscale entropy. Force complexity was quantified with modified multiscale sample entropy (MMSE; Wu et al., 2013), an adaptation of multiscale entropy (Costa et al., 2002a) designed for short time series. In MMSE, sample entropy (Govindan et al., 2007) is calculated over multiple time scales of data to quantify the multiscale complexity of the signal.

In MMSE, sample entropy is calculated on the original time series. A scale-factored moving average of the time series of window length τ (see Figure 3) was then computed as:

$$y_j^{(\tau)} = \frac{1}{\tau} \sum_{i=j}^{j+\tau-1} x_i, \quad 1 \leq j \leq N - \tau + 1 \quad (4.5)$$

and sample entropy recalculated at each scale factor as:

$$MMSE(x, m, \tau, r) = SampEn(y^\tau, m, \delta = \tau, r) \quad (4.6)$$

Scale factor values ranged from $\tau = 1$ to $\tau = 34$. This allows complexity calculations for frequencies from 16.7 Hz to 0.5 Hz (Gow et al., 2015). In our previous work, individuals completing this task at 10% MVC exhibited frequencies from 0–12 Hz (Studenka & Raikes, in press). Consistent with previous work, an $m = 2$, and $r = 0.15 *$

$SD_{Time\ series}$ were used to calculate sample entropy (Wu et al., 2013). Finally, we computed the overall complexity (complexity index, CI) for the time series as the sum of

the sample entropies for each scale factor (Figure 4-4). As with single-scale sample entropy, higher complexity index values indicate more complex force structures.

Detrended fluctuation analysis. Detrended fluctuation analysis (DFA) quantifies long-range correlations across multiple timescales. In the presence of long-range correlations, data exhibit self-similarity, where smaller units of the whole data resemble increasingly larger units of data at various scaling factors. Additionally, DFA has been used to identify long-range correlations in non-stationarity data (those with a trend) as well as avoids detecting long-range correlations that exist due to non-stationarity.

To calculate DFA, the entire time series is first integrated as (Peng et al., 2000, 1995):

$$y(k) = \sum_{i=1}^k [B(i) - B_{ave}] \quad (4.7)$$

where $B(i)$ is the i th force sample, and B_{ave} is the average force. The integrated time series is then divided into bins of length n . A least squares line is fit within each bin,

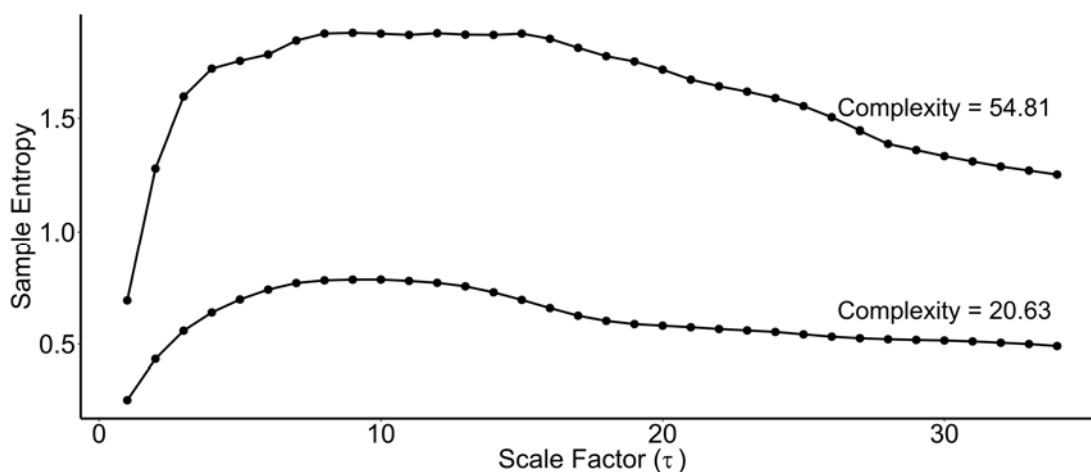


Figure 4-4. Study 2: Complexity curves for two different participants. At each scale factor, lower values indicate more regular signals. Complexity is the sum of the sample entropies at each scale factor. Lower values indicate less complex signals.

reflecting the trend in that bin. The integrated time series is detrended by subtracting the trend in each bin. The size of fluctuation for the detrended time series is calculated as:

$$F(n) = \sqrt{\frac{1}{N} \sum_{k=1}^N [y(k) - y_n(k)]^2}. \quad (4.8)$$

This process is repeated over multiple bin sizes, reflecting multiple time scales.

After computing $F(n)$ over all time scales, the slope of the line relating $\log(F(n))$ and $\log(n)$ is computed as α , the self-similarity parameter. Uncorrelated data (white noise) is reflected by $\alpha = 0.5$. $0.5 < \alpha \leq 1$ reflect persistent long-range correlations. Correlated data with $\alpha > 1$ is associated with brown noise, the integration of white noise in which correlations are the result of random walk processes. Consistent with previous work calculating DFA on continuous isometric force tracking, bin sizes of length $10 \leq n \leq 122$, corresponding lengths of data ranging from 100 ms to 1.2 seconds, were used (Vaillancourt & Newell, 2003).

Spectral analysis. Frequency domain characteristics of the force output were calculated using custom written software in MATLAB (2015). The Fourier transform of the force output yields the amplitude and phase of the time series in the frequency domain. The power in a given time series is equal to the square of the amplitude. Power within three different frequency bandwidths was examined. These bandwidths are associated with sensory-motor feedback and cognitive processing (0-4 Hz) (Miall et al., 1985; Pew, 1974; Slifkin et al., 2000; Sosnoff & Newell, 2005a), feedforward processing (4-12 Hz) (Desmurget & Grafton, 2000; Pew, 1974; Sosnoff & Newell, 2005a; Sosnoff & Voudrie, 2009), and physiological tremor (8-12 Hz) (Deuschl et al., 2001; Findley et al., 1981; Stiles & Randall, 1967; Vaillancourt et al., 2001).

Statistical Analyses

All statistical calculations were performed in R (v. 3.3.2; R Core Team, 2015), using the dplyr (Wickham & Francois, 2015), tidyr (Wickham, 2016), pROC (Robin et al., 2011), and caret packages (Wing et al., 2016). To examine the predictive capability of RMSE, SampEn, complexity, DFA α , and frequency domain characteristics to discriminate between individuals with and without a history of concussion, separate logistic regressions were fit and validated using a 10-fold cross-validation procedure. The dependent variable was previous concussion status (TBI or control), determined as any history of self-reported diagnosed or suspected concussion. The individual independent variables were the 10-trial averages of RMSE, SampEn, complexity, DFA α , and average power between 0-4 Hz, 4-8 Hz, and 8-12 Hz.

Logistic regressions were fitted using a 10-fold cross-validation method. In this approach, the dataset was divided 10 times into two groups. For each division, a logistic regression was fit on 90% of the participants (training group) and this model was used to predict the history of concussion of the remaining 10% (test group). This process was repeated until each individual served in the test group once. The predictions made onto the testing groups are the probability that a person sustained a concussion. Receiver operating characteristic (ROC) curves were used to determine cutoff values distinguishing positive from negative results for each variable (Hanley & McNeil, 1982). For this study, cutoff values maximized the sum of sensitivity and specificity (Table 4-2).

Sensitivity, in this case, is the proportion of predictions of correctly predicted TBI participants out of all TBI predictions. Specificity is the proportion of correctly predicted control participants out of all of the predicted controls. Positive predictive value is the proportions of individuals predicted to have had a concussion who in fact did. Negative predictive value is the proportion of individuals predicted not to have a concussion who

Table 4-2

Example Confusion Matrix

Actual	Predicted		Diagnostic metrics
	History	No History	
History	True positive (A)	False Negative (B)	$Sens = \frac{A}{A + B}$
No history	False Positive (C)	True Negative (D)	$Spec = \frac{D}{C + D}$
Clinical metrics	$PPV = \frac{A}{A + C}$	$NPV = \frac{D}{B + D}$	$Acc = \frac{A + D}{A + B + C + D}$

Note. Sens = Sensitivity; Spec = Specificity; PPV = Positive Predictive Value, a measure of precision; NPV = Negative Predictive Value, a measure of precision; Acc = Accuracy

really did not. Finally, overall accuracy is the proportion of correct predictions out of all predictions. Sensitivity and specificity provide metrics of diagnostic value, while positive and negative predictive value provide metrics of clinical value. Additionally, the area under the curve (AUC) for each ROC curve is reported as a measure of the overall discriminability and its associated p -value tests the degree to which this discrimination is greater than 50% ($H_0: AUC = 0.5$). Additionally, to evaluate the predictive capacity of multiple nonlinear metrics of complexity, an additive model was fitted with using both complexity and DFA α , as well as an additive model with all of the signal characteristics. The same model fitting and prediction methods were applied.

Results

A Priori Models

With respect to the discriminability of these models, none of the AUC's were statistically significant (Figure 4-5 and Table 4-3). Diagnostic and clinical utility measurements maximizing the sum of sensitivity and specificity for each of the models

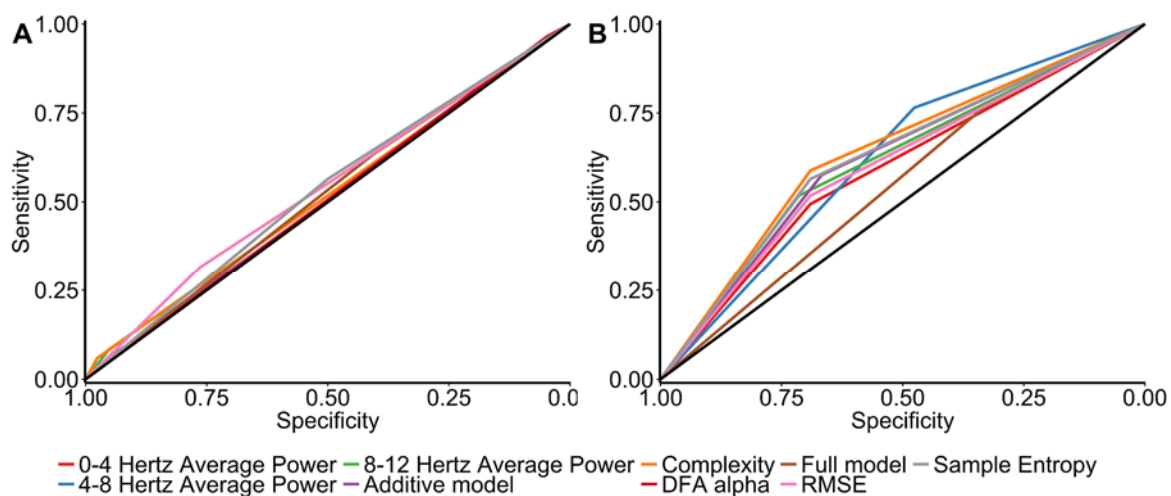


Figure 4-5. Study 2: Areas under the curve for a priori (A) and gender-stratified (B) models.

Table 4-3

Receiver Operator Characteristic Curve AUC and p Values

Predictor	A priori models		Gender models	
	AUC	<i>p</i> value	AUC	<i>p</i> value
DFA α	0.506	0.372	0.604	0.014
Complexity	0.518	0.194	0.639	0.002
Sample entropy	0.532	0.247	0.628	0.004
0-4 hertz average power	0.500	1.000	0.592	0.025
4-8 hertz average power	0.505	0.417	0.620	0.003
8-12 hertz average power	0.517	0.239	0.616	0.007
Root mean squared error	0.540	0.178	0.604	0.014
Additive model	0.506	0.400	0.622	0.005

Note. AUC = Area under the curve; DFA = detrended fluctuation analysis; The additive model included DFA α and complexity as predictors. The gender models included gender as a main effect as well as the interaction between gender and the predictor.

are presented in Table 4-4. Models for 0-4 Hertz average power and DFA α exhibited high sensitivity, indicating that individuals with a history of concussion were identified as such 100% and 96.4% of the time, respectively. However, this is at the cost of a high number of false positives. In these models, nearly all of the individuals in the sample are classified as having had a history of concussion. By contrast, models with high specificity (> 90%) had very low sensitivity, indicating that individuals without a history of concussion were accurately classified, but individuals with a history of concussion in these models are misclassified almost completely.

Alternative Models

Exploratory analyses of the present data indicated that the independent variables in each of the models differed in magnitude by gender. This is further supported by prior visual-motor tracking findings (Stirling et al., 2013; Studenka & Raikes, in press). Consequently, the *a priori* models were refit with the original predictors, an additional

Table 4-4

Sensitivity, Specificity, and Predictive Values for Linear and Nonlinear Metrics

Predictor	Sens. (%)	Spec. (%)	PPV (%)	NPV (%)	Acc. (%)
DFA α	96.47	4.76	67.21	40.00	66.14
Complexity	5.88	97.61	83.33	33.88	36.22
Sample entropy	56.47	50.00	69.57	36.21	54.33
0-4 hertz average power	100.00	0.00	66.93	-	66.93
4-8 hertz average power	8.24	92.86	70.00	33.33	36.22
8-12 hertz average power	8.24	95.24	77.78	33.90	37.01
RMSE	31.75	76.19	72.97	35.56	46.46
Additive model	5.88	95.24	71.43	33.33	35.43

Note. Sens. = sensitivity; Spec. = specificity; PPV = positive predictive value; NPV = negative predictive value; Acc. = accuracy; DFA = detrended fluctuation analysis; RMSE = root mean squared error; The additive model included DFA α and complexity as predictors.

main effect of gender, and the interaction between the predictor and gender. The AUC's for these models were all significant (Table 4-3 and Figure 4-5). These gender-stratified models exhibited a greater balance between sensitivity and specificity, avoiding an extremely high value for one and an extremely low value for the other (Table 4-5). All of these models had positive predictive values between 75-80%, indicating that 75-80% of the individuals for whom the metrics predicted a history of concussion did indeed have a history of concussion. However, these metrics correctly identified individuals with a history of concussion between 50-76% of the time and those without a history between 48-71% of the time.

Additionally, using cutoffs that ensure 80% sensitivity when using neurocognitive tests to predict both acute concussion and lengthy recovery times (> 14 days) have improved clinical diagnostics and identification of those requiring greater recovery

Table 4-5

Sensitivity, Specificity, and Predictive Values for Models Including Gender and Linear and Nonlinear Metrics

Predictor	Sens. (%)	Spec. (%)	PPV (%)	NPV (%)	Acc. (%)
DFA α	51.76	69.05	77.19	41.43	57.48
Complexity	58.82	69.05	79.37	45.31	62.20
Sample Entropy	56.47	69.05	78.69	43.94	60.63
0-4 Hertz Average Power	49.41	69.05	76.36	40.28	55.91
4-8 Hertz Average Power	76.47	47.62	74.71	50.00	66.93
8-12 Hertz Average Power	51.76	71.43	78.57	42.25	58.27
Root mean squared error	51.76	69.05	77.19	41.43	57.48
Additive model	57.65	66.67	77.78	43.75	60.63

Note. Sens. = sensitivity; Spec. = specificity; PPV = positive predictive value; NPV = negative predictive value; Acc. = accuracy; DFA = detrended fluctuation analysis; The additive model included DFA α and complexity as predictors.

opportunity (Collins et al., 1999; Iverson et al., 2006; Lau et al., 2011, 2012; Lovell et al., 2003; Schatz et al., 2006; Van Kampen et al., 2006). For comparison with this literature base, specificity, as well as positive and negative predictive value when holding sensitivity constant at 80%, are presented in Table 4-6. Overall, specificity of these models decreases as sensitivity increases. However, positive predictive value remains at approximately 70%.

Discussion

The purpose of this study was to determine whether various individual linear (RMSE) and nonlinear (complexity, DFA α , average power) metrics of the motor output from an isometric visual-motor tracking task could be used to discriminate individuals with a history of concussion from those without, based on a logistic regression classifier. The models based on individual metrics exhibited a limited capacity to discriminate between those with and without a history of concussion. In general, low-frequency (0-4

Table 4-6

Specificity and Predictive Values for Models Including Gender and Linear and Nonlinear Metrics at 80% Sensitivity

Predictor	Spec. (%)	PPV (%)	NPV (%)	Acc. (%)
DFA α	38.10	72.34	48.48	66.14
Complexity	33.33	70.83	45.16	64.57
Sample entropy	33.33	71.13	46.67	65.35
0-4 hertz average power	16.67	66.67	31.82	60.63
4-8 hertz average power	42.86	74.19	52.94	68.50
8-12 hertz average power	26.19	69.00	40.74	62.99
Root mean squared error	28.57	69.70	42.86	63.78
Additive model	35.71	71.58	46.88	65.35

Note. Sens. = sensitivity; Spec. = specificity; PPV = positive predictive value; NPV = negative predictive value; Acc. = accuracy; DFA = detrended fluctuation analysis; The additive model included DFA α and complexity as predictors.

Hertz) average power and long-range correlations in the data (DFA alpha) predicted nearly 100% of the individuals in the study, regardless of concussion history, as having had a history of concussion. Likewise, complexity and mid- (4-8 Hertz) and high-frequency (8-12 Hertz) average power classified more than 90% of the participants as having no history of concussion, misclassifying those with a history of concussion.

Previous studies with this task and measures of multiscale complexity on another visual-motor tracking task indicate that gender is an important consideration when using these metrics in the context of a concussion (Stirling et al., 2013; Studenka & Raikes, in press). When gender was included in the models in the present study, the discrimination capacity of each of the models was significant (Tables 4.3, 4.5). From a diagnostic perspective, the sensitivity and specificity of these models were lower than desirable. Approximately 56% of the individuals with a history of concussion were predicted to have such a history. The specificity of the models was higher, with approximately 67% of those with no history of concussion being classified as such. These metrics indicate that approximately 44% of the individuals with a history of concussion were classified as having never had a concussion and 33% of the individuals without a history were classified as having had a concussion. From a clinical perspective, however, the positive predictive values are encouraging. For individuals predicted to have had a concussion in the gender-stratified models, approximately 77% of those individuals had a history of concussion.

The ability to discriminate between individuals with and without a history of concussion is of clinical value when considering the potential long-term ramifications of concussions. Previous work has linked concussion history to conditions including ALS, Parkinson's disease, and chronic traumatic encephalopathy. Additionally, there is substantive evidence that, despite efforts to educate coaches and athletes on

concussions and concussion management, the nonreporting rate for concussive events remains high. Indeed, 45% of the participants in the present sample reporting suspecting at least one concussion without ever having received a diagnosis. This level of undiagnosed, but suspected, concussions agrees with previously reported levels of non-diagnosed concussions in athletics (Gysland et al., 2012; Kerr et al., 2015, 2016; McCrea et al., 2004). Consequently, metrics that can distinguish individuals who have previously sustained a concussion from those who have not, regardless of diagnosis, may provide methods for screening individuals at risk for those conditions associated with repetitive head traumas.

There are a limited number of reports focusing on distinguishing people with a history of concussion from those without. A number of studies using neurocognitive testing have been able to distinguish individuals with acute concussions from healthy individuals with reasonably high sensitivity and specificity (Barr & McCrea, 2001; Broglio et al., 2007; Collins et al., 1999; Iverson et al., 2006; Louey et al., 2014; Lovell et al., 2003; Schatz et al., 2006; Van Kampen et al., 2006). Additionally, several studies have reported the ability to distinguish concussed individuals at risk for prolonged recovery times from those with shorter recovery times (Lau et al., 2011, 2012). One study reported high sensitivity and specificity in distinguishing individuals with traumatic brain injuries from non-brain injured individuals (McKay et al., 2008). Though the participants in that study included people with concussions, the traumatic brain injury group's injuries ranged in severity and most had moderate-to-severe TBIs. Thus, the present study is one of few to provide diagnostic and clinical metrics for distinguishing between asymptomatic individuals with a history of concussion and those with no such history.

Importantly, when jointly maximizing the sensitivity and specificity, the findings reported here are similar in magnitude to those reported for neurocognitive tests, when

used to identify individuals at risk for a lengthier recovery (> 14 days) than for those whose recovery time is shorter (≤ 7 days) (Lau et al., 2011, 2012). When ensuring 80% sensitivity (80% of the individuals with a history of concussion are classified as such) to compare with the findings of these studies, the specificity and positive predictive values were greater on average than those reported for predicting prolonged recovery (Lau et al., 2012).

When ensuring higher sensitivities in the present study, the false positive rate increased. Thus, individuals with no history of concussion are more likely to be classified as having a history of concussion than not (low specificity). Though the specificity is lower than would be desired, the risks of false positives, in this case, are minimal. At present, there are no effective preventative measures available to reduce the incidence of conditions related to repetitive head traumas. Consequently, classification of an individual as having had a history of concussion at this point only indicates that a person *may be at risk* for such conditions and merits follow-up evaluation. This reflects the similarly conservative approach advocated in recent international consensus statements regarding sport-related concussion management, advocating that individuals be held out for evaluation and observation any time a concussion is suspected (Giza et al., 2013; McCrory et al., 2013). Thus, being classified as having had a history of concussion in the present study provides a conservative approach to long-term evaluation and observation. However, with high sensitivity and positive predictive values of 70%-75%, those individuals classified as having had a history of concussion generally do.

It is additionally important to note that the various measures of clinical and diagnostic utility are presented when the linear and nonlinear measures from this visual-motor tracking task are considered in isolation from each other and consider only one aspect of overall function. Furthermore, with the exception of the individual's gender,

these predictions did not take into account other personal characteristics, including age, or types and years of athletic experience (indicating concussion exposure risk). Studies distinguishing between individuals on concussion recovery time suggest that variables from multiple domains, including neurocognitive function and concussive symptoms, improve sensitivity, specificity, and positive predictive value (Lau et al., 2011). Thus, the inclusion of additional metrics, including neurocognitive function, in conjunction with the linear and nonlinear outcomes from the visual-motor tracking task may improve the discrimination between individuals with a history of concussion and those without, and therefore merit further investigation.

Limitations

There are several limitations in the present study. First, all participants provided only a self-reported history of concussion. It is possible that individuals who reported no history of concussion did indeed have a history. For those who reported diagnosed concussions, it is reasonable to assume that these individuals recalled receiving a diagnosis by a medical professional. Additionally, to better account for the high prevalence of underreporting of concussions (Gysland et al., 2012; Kerr et al., 2016; McCrea et al., 2004), individuals also self-reported their history of suspected concussions. This required participants to retrospectively self-diagnose themselves. Thus, individuals may have reported suspected concussions that were indeed not concussions or neglected to report a concussion because of a limited capacity to remember such occurrence and self-diagnose. This applies in particular to individuals reporting only suspected concussions without any diagnosed concussions for reference ($n = 58$). However, conservative approaches to concussion management suggest that any time a concussion is *suspected*, individuals should be held out for evaluation and

observation (Giza et al., 2013; McCrory et al., 2013). Therefore, if individuals are able to retrospectively self-identify times when they likely should have been evaluated but were not, then the sensitivity, specificity, and positive predictive values reported here reflect the more conservative views of concussion management.

Additionally, the generalizability of these findings is presently limited. Our participants were all college-aged individuals. Previous work has demonstrated that the linear and nonlinear metrics used in the prediction models here are affected by aging. Consequently, the current models may have limited utility with different age groups. Further research is needed to identify the generalizability of this predictive method outside of early adulthood.

Finally, the outcomes in the present study reflect only logistic regression and subsequent prediction. Other machine learning methods – such as random forests, support vector machines, and naïve Bayes methods – may provide better discrimination between groups but require substantively larger sample sizes. However, the findings from this study provide a proof-of-concept that linear and nonlinear characteristics of continuous isometric force production can be used to discriminate previously concussed individuals from those with no history of concussion.

Conclusion

Individuals with a history of concussion exhibit different patterns of linear and nonlinear metrics on a continuous isometric force tracking task. The findings here indicate that these metrics can be used, in conjunction with the individual's gender, to discriminate between people with and without a history of concussion. Approximately 75% of the individuals predicted to have a history of concussion did indeed have such a history. Such discrimination has clinical value in identifying individuals who merit further

evaluation and observation over time for conditions related to repetitive head traumas, including ALS, Parkinson's disease, and chronic traumatic encephalopathy. These findings merit further validation in larger samples, other age groups, with other large-sample appropriate machine learning methods, and in conjunction with measures of neurocognitive function known to be sensitive to the acute effects of a concussion.

CHAPTER 5

CONCLUSION AND RECOMMENDATIONS

Summary of Findings

The research in the two studies in this dissertation contributes to an increasing body of work demonstrating lasting reductions in motor output complexity subsequent to sustaining a concussion. First, individuals exhibited a decrease in complexity and an increase in target error in a continuous isometric force tracking task. This reduction exhibited a linear relationship with the number of sustained concussions, with individuals with greater numbers of concussions exhibiting lower complexity than those with fewer or none.

Physiological complexity requires the inclusion of a wide range of frequencies in a physiological signal (Lipsitz & Goldberger, 1992) and reflects the coupling of components that work together to produce physiological output (Vaillancourt & Newell, 2002a). Reduced complexity is a natural consequence of aging and is additionally linked to pathology across multiple physiological systems (Findley et al., 1981; Hayano et al., 1990; Ko & Newell, 2016; Mazich et al., 2015; Morrison et al., 2008; Ryan et al., 1994; Sosnoff & Newell, 2006b, 2008; Sosnoff et al., 2004; Ünlü et al., 2006; Vaillancourt & Newell, 2000; Vaillancourt et al., 2001). Such reductions are purportedly the result of either the loss of structural components (Aoki et al., 2014; Hayano et al., 1990; Vaillancourt et al., 2001) or changes in the connectivity of these components (Lipsitz & Goldberger, 1992; Vaillancourt & Newell, 2002a).

So to have reductions in complexity been reported following a concussion, both in postural sway and visual-motor tracking as well as both acutely following concussion and remotely. The findings in Chapter 3 extend these findings to self-reported

asymptomatic individuals with a history of concussion and a continuous isometric force production task with a target force at 40% of a person's MVC, where previously only 10% MVC had been used. There was a significant decrease in the average complexity and an increase in the trial-to-trial variability in complexity, which was associated with an increase in the number of concussions sustained. In light of the loss of complexity hypothesis previously described and the linear nature of the relationship between decreased complexity and increased numbers of concussions, these results suggest that there may be a cumulative effect of concussions on visual-motor pathways.

Whether this effect is related to the loss of structural components or to alterations in connectivity between components is not yet clear. There is evidence to suggest that individuals with a history of concussion have a reduction in the functional connectivity in visual attention networks (Churchill et al., 2016), which could certainly influence task performance in the present task. Furthermore, previous work has linked concussions to white matter reductions in areas related to attention, spatial processing, visual networks, dorsal and ventral prefrontal areas, as well as areas related to the integration of these centers. Consequently, reduced visual-motor tracking complexity may reflect some of these structural and functional alterations. If this is the case, then complexity in visual-motor tracking tasks could provide a metric for quantifying such alterations without the need for monetarily costly and time-consuming neuroimaging studies.

Importantly, the findings here reiterate previous findings that motor complexity in visual-motor tracking tasks has significant gender effects that must be considered. The men in Chapter 3 exhibited greater complexity than the women. However, both exhibited similar patterns of reduced complexity. Additionally, a history of concussion-related loss of consciousness was associated with altered rates of reduced complexity. Individuals with a history of loss of consciousness have reduced white matter structure in areas of

the brainstem and ventral prefrontal cortex on neuroimaging, lending further evidence for the viability of complexity on this task as a potential indicator of damage to, or altered function in, these regions.

Furthermore, signal characteristics for the visual-motor tracking task exhibited potential as metrics for discriminating between individuals with and without a history of concussion. Participants in Chapter 4 were correctly identified as having a history of concussion or not approximately 60% of the time when considering both gender and signal characteristics. When holding the sensitivity at 80% (identifying 80% of the individuals with a history of concussion correctly), this accuracy increased to 65-68% of the time. More importantly, however, 70-80% of the individuals predicted to have sustained a concussion based solely on gender and signal characteristics did indeed have a history of concussion. In light of the association between concussion history and the later development neurological and neuropsychological conditions (H. Chen et al., 2007; Factor & Weiner, 1991; Harris et al., 2013; Kerr, Evenson, et al., 2014; Lehman et al., 2012; McKee et al., 2009), this prediction rate provides a clinically-relevant metric for identifying individuals who may be at risk for these conditions and merit further evaluation.

Importantly, these predictions included a substantial number of individuals in whom one or more concussions were suspected but had never been diagnosed. Consistent with previous reports of concussion nonreporting rates (Gysland et al., 2012; Kerr et al., 2015, 2016; McCrea et al., 2004), 45% of the individuals in Chapter 4 reported sustaining a concussion or concussion-like event that had never been diagnosed by a medical professional. Thus, gender and outcomes related to this visual-motor tracking task may provide a pathway toward identifying individuals with previously undiagnosed concussions.

Taken together, the results from the present research affirm that persons with a history of concussion exhibit differences in the linear and nonlinear characteristics of motor output in response to a visual-motor tracking task. These differences appear to have a cumulative response to the number of previously sustained concussions and may reflect altered functional connectivity in visual-motor pathways. Furthermore, these differences are substantive enough that these measures may provide a screening method to identify individuals with a history of concussion, even those that went undiagnosed. Finally, given the evolving evidence linking repetitive head trauma to neurological and neuropsychological conditions, outcomes from this task may be useful in both quantifying persistent dysfunction following one or more concussions as well as identifying individuals for whom follow-up evaluation and long-term monitoring may be beneficial.

Future Research Considerations

There are numerous opportunities to expand upon the research presented here. While previous research has identified altered functional connectivity in visual networks as well as reduced white matter structure in relevant visual-motor areas, the connection between the outcomes observed here and such findings is, at present, speculative. Additional research is needed to link visual-motor tracking outcomes with neuroimaging findings.

Additionally, though the predictive utility of the measures from the visual-motor tracking task is promising, there are additional considerations that should be expanded upon in future research. These include the addition of other metrics, such as neurocognitive outcomes, to improve the specificity of the predictions as well as adding other age groups and larger samples to develop robust predictive models.

With concussion rates exceeding 3 million annually and the economic cost to manage such injuries topping \$22 million per year, the impetus to develop cost- and time-effective metrics for identifying not only acute but persistent changes in function following a concussion is high. The findings here provide yet another pathway toward understanding the long-term implications of single and multiple concussions. With additional refinement, larger samples, and in tandem with measures of function in other domains, nonlinear measures of visual-motor tracking performance may help to provide a complete view of how to identify concussion-related deficits as well as to identify those most at risk for the more severe consequences of repetitive head trauma.

Implications for Clinicians

The findings from Chapters 3 and 4 offer several clinical applications. First, the findings in Chapter 3 indicate that there is a cumulative effect of multiple concussions on visual-motor tracking task complexity. The lower complexity with multiple concussions suggests that there may be a change in the way in which visual information is utilized. Therefore, this may be an opportunity for the clinician to engage in rehabilitative exercises that selectively target visual-motor tracking processes to restore functionality that may be impaired (Gallaway, Scheiman, & Mitchell, 2017; Leddy, Baker, & Willer, 2016).

With respect to the predictive modeling in Chapter 4, there are discrepancies between self-reported and predicted histories. However, the predictive capability of the gender-specific models still offers clinically useful information. Though it may be more feasible to ask an individual about his or her concussion history, having a measure that can discriminate between those with and without a history allows the clinician some more objective corroboration of the individual's history. While this may not be particularly

necessary for individuals with a history of diagnosed concussions, it may be very important for those with suspected concussions. For those individuals, the clinician is, in effect, asking the individual to retrospectively self-diagnose an injury based upon the best recollection of symptoms and prior events. While this provides a starting point, it is valuable to be able to substantiate these self-reports.

Additionally, the effects of a concussion exist along a continuum (from mild to severe impairments) and the long-term trajectories of specific impairments may likewise exist along similar continuums (from quickly resolving to persistent; mild to severe). Thus, measures such as the nonlinear aspects of visual-motor tracking may provide insight into those for whom the effects of one or more concussion have fully recovered, leading to a negative predicted history despite sustaining a concussion, as opposed to those in whom there are residual deficits. Therefore, such discrimination may improve the identification of individuals whose concussion histories and clinical presentation merit follow-up evaluation to provide early identification of conditions associated with repetitive head trauma.

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APPENDICES

Appendix A

Participant Demographic and Concussion History Screening Form

PERSONAL INFORMATION

Biological Sex: **M F** Gender: **M F Other** Handedness: **R L** DOB: ___/___/___
 Height: ___ft ___in Weight: ___lbs Are you currently pregnant? **Y N**

Optional

Please indicate your identification with the following groups (mark all that apply):

Non-Hispanic: ___ Hispanic: ___ If Hispanic, nationality(-ies): _____

Caucasian or White: ___ Black or African American: ___ Asian: ___
 American Indian or Alaska Native: ___ Native Hawaiian or Other Pacific Islander: ___
 Unknown: ___

How many caffeinated beverages have you consumed in the past 12 hours? _____
 (One caffeinated beverage is one can of soda, 8oz of coffee, equivalent. Do not include energy drinks)

How many energy drinks have you consumed in the past 12 hours? _____

SPORT AND GAME PARTICIPATION HISTORY

Have you been involved in sports in the past? **Y N**

List sports played competitively:

Sport: _____	Age started: _____	Years played: _____
Sport: _____	Age started: _____	Years played: _____
Sport: _____	Age started: _____	Years played: _____
Sport: _____	Age started: _____	Years played: _____
Sport: _____	Age started: _____	Years played: _____

List sports played exclusively recreationally:

Sport: _____	Age started: _____	Years played: _____
Sport: _____	Age started: _____	Years played: _____
Sport: _____	Age started: _____	Years played: _____

List sports actively participating in, competitively or recreationally:

Sport: _____	Age started: _____	Years played: _____
Sport: _____	Age started: _____	Years played: _____
Sport: _____	Age started: _____	Years played: _____

How frequently do you currently participate in sports (circle one):

None	Not often (a few times per year)	A few times per month	A few times per week	Nearly every day
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Have you played more than 20 cumulative hours of sports, role-playing, MOBA, real-time strategy (RTS), or first-person shooter video games? **Y N**

MEDICAL HISTORY

Do you have a hearing loss that has been diagnosed? **Y N**

Do you have a balance disorder that has been diagnosed? **Y N**

Have you ever been diagnosed with or treated for a brain tumor? **Y N**

Have you ever been diagnosed with or treated for any of the following conditions?

Epilepsy: _____ Other seizure types: _____
 Migraines: _____ Cluster headaches: _____ Other headache condition: _____
 Peripheral neuropathy (non-diabetic): _____ Cystic fibrosis: _____
 Fibromyalgia: _____ Multiple sclerosis: _____

Have you ever been diagnosed with or treated for any of the following neurodegenerative disorders:

Alzheimer's Disease: _____ Parkinson's Disease: _____ Huntington's Disease: _____
 Amyotrophic Lateral Sclerosis: _____ Other: _____

Has a near relative (biological parent, grandparent, sibling) been diagnosed with or treated for any of the preceding neurodegenerative disorders (including write-in "other")?

Relationship: _____	Disorder: _____	Age at diagnosis: _____
Relationship: _____	Disorder: _____	Age at diagnosis: _____
Relationship: _____	Disorder: _____	Age at diagnosis: _____
Relationship: _____	Disorder: _____	Age at diagnosis: _____
Relationship: _____	Disorder: _____	Age at diagnosis: _____
Relationship: _____	Disorder: _____	Age at diagnosis: _____
Relationship: _____	Disorder: _____	Age at diagnosis: _____
Relationship: _____	Disorder: _____	Age at diagnosis: _____

Have you ever sustained a brain injury requiring surgical decompression or mechanical ventilation? **Y N**

Have you ever sustained a brain injury resulting in a coma? **Y N**

CONCUSSION HISTORY

Have you ever been diagnosed with a concussion? **Y N**

If yes, how many times: _____
 Age at first diagnosed concussion: _____
 Age at most recent diagnosed concussion: _____

Of the total number, how many times were you diagnosed by a medical professional:
 (Do not double count. If diagnosed by both a doctor and athletic trainer, only count the final diagnosis)

Physician (MD or DO): _____

<p>Athletic Trainer: _____ Physical Therapist: _____ Chiropractor: _____ Other: _____ # _____</p> <p>Of the total number, how many times did you receive an: MRI: _____ CT Scan: _____ PET Scan: _____ Other neuroimaging: _____</p>
<p>Have you ever suspected you had a concussion that was not specifically diagnosed? Y N (This may include getting 'dinged', getting your 'bell rung', 'needing to clear cobwebs', or any period of forgetfulness after a specific blow to the head or body. Do not include concussions for which you were diagnosed by a medical professional.)</p> <p>If yes, how many times: _____ Age at first suspected concussion: _____ Age at most recent suspected concussion: _____</p> <p>Of this total number, how many did you report to someone: _____ (This could be a coach, parent, athletic trainer, physician, teacher, school nurse, teammate, etc.)</p>
<p>Out of the total number of diagnosed and suspected concussions, have you ever lost consciousness (been unconscious, been knocked out, blacked out, passed out). Y N</p> <p>If yes, indicate the number of times and durations: (e.g. Number: 2 and Duration: 30sec would indicate losing consciousness on two occasions for 30 sec)</p> <p>Number: _____ Duration: _____ Number: _____ Duration: _____ Number: _____ Duration: _____ Number: _____ Duration: _____</p>
<p>Out of the total number of diagnosed and suspected concussions, have you ever experienced convulsions (seizures) after a concussive event? Y N (Do not include seizures related to epilepsy or other diagnosed seizure disorder)</p> <p>If yes, how many times: _____ Age at first occurrence of convulsions: _____ Age at most recent occurrence of convulsions: _____</p>
<p>Out of the total number of diagnosed and suspected concussions, have you ever experienced amnesia (a loss of memory related to a specific blow to the head or body)? Y N</p> <p>Amnesia includes:</p> <ul style="list-style-type: none"> • Retrograde amnesia – A loss of memory prior to injury. This may be a loss of memory for the injury event and may also include seconds, minutes, hours, or days prior to injury. For example, you may remember being evaluated on the sidelines for a concussion but not the injury itself or events (plays, pre-game/practice, meals) leading up to the injury

- Anterograde amnesia – A loss of memory subsequent to injury. This may include a loss of memory for the injury event and may also include seconds, minutes, hours, or days following the moment of injury. For example, you may remember the play not but remember getting hit or getting to the sidelines or being evaluated by medical personnel.

If yes above, how many times have you experienced:

Retrograde amnesia: _____

Duration (minutes lost): _____ Age: _____

Duration (minutes lost): _____ Age: _____

Duration (minutes lost): _____ Age: _____

Duration (minutes lost): _____ Age: _____

Duration (minutes lost): _____ Age: _____

Duration (minutes lost): _____ Age: _____

Duration (minutes lost): _____ Age: _____

Anterograde amnesia: _____

Duration (minutes lost): _____ Age: _____

Duration (minutes lost): _____ Age: _____

Duration (minutes lost): _____ Age: _____

Duration (minutes lost): _____ Age: _____

Duration (minutes lost): _____ Age: _____

Duration (minutes lost): _____ Age: _____

Duration (minutes lost): _____ Age: _____

Out of the total number of diagnosed and suspected concussions, how many times have your symptoms lasted for the following durations:

Symptoms may include (but are not limited to):

- Somatic: Headache, sensitivity to light or sound
- Cognitive: Feeling like in a fog, memory impairment, impaired reaction times
- Altered emotions, unusual irritability
- Sleep disturbance

One day or less: _____ 1-3 days: _____ 4-7 days: _____ 8-30 days: _____

1-3 months: _____ 3-6 months: _____ 6 months – 1 year: _____

More than 1 year: _____

Out of the total number of diagnosed and suspected concussions, how many times were symptoms recurring particularly with exertion? _____

Are you still experiencing any effects from your most recent concussion? **Y** **N**

If yes, please describe the effects:

Appendix B

Informed Consent for Individuals with No History of Concussion



Department of Health, Physical Education
and Recreation
7000 Old Main Hill
Logan UT 84322-7000
Telephone: (435) 797-0109



Page 1 of 2
USU IRB Approval: Sept. 20, 2013
Amend#5 Approved: 04/27/2016
Approval Terminates: 09/19/2016
Protocol #5303
IRB Password Protected per IRB Coordinator

INFORMED CONSENT

Isometric Force Tracking-Post-Test Control Subjects

Introduction/ Purpose Dr. Breanna Studenka, in the Department of Health, Physical Education and Recreation at Utah State University is conducting a research study to find out more about changes that occur in the frequency of produced movements due to different experimental and environmental manipulations. Additionally, we aim to determine if the frequencies present in force production change with age. Results from this study will help us to develop an understanding of how the central nervous system follows object moving in the environment. You have been asked to take part because you are between the ages of 18 and 85. There will be approximately 325 total participants in this research. One or two undergraduate students researcher will help Dr. Studenka conduct this research.

Procedures If you agree to be in this research study, you will be asked to complete an intake survey that's approximately 5-10 minutes long. Then you will complete a 15-60 minute testing session. You will sit in front of a computer screen with your right index finger pressed against a force transducer (a sensor that picks up the force that your finger produces). A target path (e.g., a sine wave) will appear as a red line and will move across the screen from the left to the right, and you will trace this target line by pressing harder and softer on the force transducer. The force you produce will appear on the screen as a white line. An eye tracker may be used to track your eye movements during this experiment. This eye tracker uses a video camera to track the dark part of your pupil as you look at things on the computer screen. In addition, you may be asked to complete an mBESS and a SCAT2 assessment (typically used to diagnose concussion). This is only so we can compare you to someone who has been concussed. Your data will not be shared with your coaches or administrators, and will not be used as a concussion diagnosis, it will only be reported in group data and will not have your name attached to it.

If you are receiving credit for participation, you will receive 1 experimental credit for participation through the SONA system. We will give you credit through the SONA sign up, and we will also document your credit in case of any discrepancy.

Risks The risks are no more than those of daily life. The task is not fatiguing. There is a small risk of loss of confidentiality but we will take steps to reduce this risk. You may get tired of sitting, or your finger may get fatigued. We will provide you opportunities to stand and or rest if needed.

Benefits There are no measurable benefits to you for participation in this study, however, this work may help advance knowledge in the fields of motor control related to vision and tracking. If you are interested we can share with you the results of this study.

Explanation & offer to answer questions Dr. Studenka and/or a student researcher has explained this research study to you and answered your questions. If you have other questions or research-related problems, you may contact Dr. Breanna Studenka at (435) 797- 0109 or by e-mail at breanna.studenka@usu.edu

Payment/Compensation You will not be compensated for your participation in this experiment. If you are participating in this research for class credit, you will receive 1 credit upon completion of your participation.



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INFORMED CONSENT

Isometric Force Tracking-Post-Test Control Subjects

Voluntary nature of participation and right to withdraw without consequence Participation in research is entirely voluntary. You may refuse to participate or withdraw at any time without consequence or loss of benefits.

Confidentiality Research records will be kept confidential, consistent with federal and state regulations. Only Dr. Studenka and her student researchers will have access to the data, which will be kept in a locked file cabinet or on a password protected computer in a locked room. To protect your privacy, personal, identifiable information will be removed from study documents and replaced with a study identifier. Identifying information will be stored separately from data. Digital data will be stored on a protected hard disk. Data are stored with reference to subject number, group name and trial number. There is no identifying information on the data storage media. We only report data that has been averaged or individual trials with no subject number or any other identifying information. The data are not destroyed. The number linking your subject sheet to the consent form will be removed and destroyed once the experimental session is completed.

IRB Approval Statement The Institutional Review Board for the protection of human participants at Utah State University has approved this research study. If you have any questions or concerns about your rights or a research-related injury and would like to contact someone other than the research team, you may contact the IRB Director at (435) 797-0567 or email irb@usu.edu to obtain information or to offer input.

Copy of consent You have been given two copies of this Informed Consent. Please sign both copies and keep one copy for your files.

Investigator Statement "I certify that the research study has been explained to the individual, by me or my research staff, and that the individual understands the nature and purpose, the possible risks and benefits associated with taking part in this research study. Any questions that have been raised have been answered."

Dr. Breanna Studenka, Principal Investigator
(765) 797-0109
breanna.studenka@usu.edu

Signature of Participant By signing below, I agree to participate.

Participant's signature

Date

Appendix C

Informed Consent for Individuals with A History of Concussion



Department of Health, Physical Education
and Recreation
7000 Old Main Hill
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INFORMED CONSENT

Isometric Force Tracking-Concussion

Introduction/ Purpose Dr. Breanna Studenka, in the Department of Health, Physical Education and Recreation at Utah State University is conducting a research study to find out more about changes that occur in the frequency of produced movements due to different experimental and environmental manipulations. Additionally, we aim to determine if the frequencies present in force production change with age. Results from this study will help us to develop an understanding of how the central nervous system follows object moving in the environment. You have been asked to take part because you are between the ages of 18 and 85 with a past history of concussion. There will be approximately 325 total participants in this research. One or two undergraduate students researcher will help Dr. Studenka conduct this research.

Procedures If you agree to be in this research study, you will be asked to complete an intake survey that will take approximately 5-10 minutes, and then a 15 minute testing session. You will sit in front of a computer screen with your right index finger pressed against a force transducer (a sensor that picks up the force that your finger produces). A target path (e.g., a sine wave) will appear as a red line and will move across the screen from the left to the right, and you will trace this target line by pressing harder and softer on the force transducer. The force you produce will appear on the screen as a white line. An eye tracker may be used to track your eye movements during this experiment. This eye tracker uses a video camera to track the dark part of your pupil as you look at things on the computer screen. We will ask for contact information following your first testing session and will follow up at 1 week, 1 month, 3 months, and 6 months following your first visit. If you agree, we will ask you to come back to the lab, or we will meet you at a convenient location and have you perform the 15-minute force testing protocol again. At this point we will re-gain your consent and explain the task again. It will be the same exact task as you had previously performed.

Risks The task is not typically fatiguing. There is a small risk of loss of confidentiality but we will take steps to reduce this risk. You may get tired of sitting, or your finger may get fatigued. We will provide you opportunities to stand and or rest if needed. In addition, due to your concussion, the computer task may be difficult to perform, and may cause nausea or disorientation. If this occurs, you should stop and we will not continue the protocol. At your permission, we will follow up with you in 1 week to see if you are feeling better and may begin the testing protocol at that point.

Benefits There are no measurable benefits to you for participation in this study, however, this work may help advance knowledge in the fields of motor control related to vision and tracking. If you are interested we can share with you the results of this study.

Explanation & offer to answer questions Dr. Studenka and/or a student researcher has explained this research study to you and answered your questions. If you have other questions or research-related problems, you may contact Dr. Breanna Studenka at (435) 797- 0109 or by e-mail at breanna.studenka@usu.edu

Payment/Compensation You will not be compensated for your participation in this experiment. If you are participating in this research for class credit, you will receive 1 credit upon completion of your participation.



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Logan UT 84322-7000
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Approval Terminates: 09/19/2016
Protocol #5303
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INFORMED CONSENT

Isometric Force Tracking-Concussion

Voluntary nature of participation and right to withdraw without consequence Participation in research is entirely voluntary. You may refuse to participate or withdraw at any time without consequence or loss of benefits.

Confidentiality Research records will be kept confidential, consistent with federal and state regulations. Only Dr. Studenka and her student researchers will have access to the data, which will be kept in a locked file cabinet or on a password protected computer in a locked room. To protect your privacy, personal, identifiable information will be removed from study documents and replaced with a study identifier. Identifying information will be stored separately from data. Digital data will be stored on a protected hard disk. Data are stored with reference to subject number, group name and trial number. There is no identifying information on the data storage media. We only report data that has been averaged or individual trials with no subject number or any other identifying information. The data are not destroyed. The number linking your subject sheet to the consent form will be removed once the experimental session is completed.

IRB Approval Statement The Institutional Review Board for the protection of human participants at Utah State University has approved this research study. If you have any questions or concerns about your rights or a research-related injury and would like to contact someone other than the research team, you may contact the IRB Director at (435) 797-0567 or email irb@usu.edu to obtain information or to offer input.

Copy of consent You have been given two copies of this Informed Consent. Please sign both copies and keep one copy for your files.

Investigator Statement "I certify that the research study has been explained to the individual, by me or my research staff, and that the individual understands the nature and purpose, the possible risks and benefits associated with taking part in this research study. Any questions that have been raised have been answered."

Dr. Breanna Studenka, Principal Investigator
(765) 797-0109
breanna.studenka@usu.edu

Signature of Participant By signing below, I agree to participate.



Department of Health, Physical Education
and Recreation
7000 Old Main Hill
Logan UT 84322-7000
Telephone: (435) 797-0109



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INFORMED CONSENT
Isometric Force Tracking-Concussion

Participant's signature

Date

CURRICULUM VITAE

ADAM RAIKES

1683 S 1150 W
 Logan, UT 84321
 Phone: 520-271-9538
 Email: adam.raikes@usu.edu

EDUCATION

- 2017 PhD, Disability Disciplines, Special Education and Rehabilitation Department, Utah State University, Logan, UT
 Program: Disability Disciplines
 Specialization: Pathokinesiology
 Dissertation: The effects of previous concussions on the physiological complexity of motor output during a continuous isometric visual-motor tracking task
- 2012 M.S., Health and Human Performance, Department of Health, Physical Education and Recreation, Utah State University, Logan, UT
 Specialization: Sports Medicine
 Thesis: Reliability and diagnostic accuracy of the yes/no scapular dyskinesis test when used by graduate assistant athletic trainers
- 2009 B.S., Athletic Training, Temple University, Philadelphia, PA

EMPLOYMENT

- 2011-Present Instructor, Department of Health, Physical Education and Recreation, Utah State University, Logan, UT
- 2009-2012 Graduate Assistant Athletic Trainer, Utah State University Sports Medicine, Logan, UT

RESEARCH SUPPORT

- 2014-2016 **Principal Investigator:** National Athletic Trainers' Association Research and Education Foundation Doctoral Grant #14DGP013
 Total award: \$2500
 Title: "Measurement of Sleep Quantity and Quality During Acute Concussion via Actigraphy"
- 2012-2016 Co-Principal Investigator; statistical consultant (Alisha Wackerle-Hollman, PI; Lillian Durán & Michael Rodriguez, Co-PIs): Goal 5, Institute of Education Sciences, National Center for Education Research (CDFA: 83.305A; Award #R305A120449)
 Total award: \$1,598,000
 Title: Research and development of Spanish individual growth and development indicators (S-IGDIs): Early literacy identification and progress monitoring in Spanish-English bilingual children.

RESEARCH EXPERIENCE

- 2015-2017 The effects of previous concussions on the physiological complexity of motor output during a continuous isometric visual-motor tracking task (PI: Studenka)
- 2014-2016 Measurement of sleep quantity and quality during acute concussion via actigraphy (Faculty Advisor: Schaefer)
- 2014-2015 Physiological correlates of self-efficacy during design-heuristic augmented learning of engineering skills (PI: Villanueva)
- 2014-2015 Development and evaluation of a novel self-efficacy scale for undergraduate engineering students (PI: Villanueva)
- 2012-2014 Electrodermal responses during the Standardized Assessment of Concussion (PI: Schaefer)
- 2011-2013 The effect of foot placement on latency in the Smart Equitest Motor Control Test (PI: Dolny)
- 2010-2012 M.S. Thesis: Reliability and diagnostic accuracy of the yes/no scapular dyskinesis test when used by graduate assistant athletic trainers

PEER-REVIEWED PUBLICATIONS (in reverse chronological order)

- Raikes, A. C.**, Duran, L., & Schaefer, S.Y. (In preparation). Cultural and ethnic diversity in concussion-focused neurocognitive research: a review of the literature.
- Villanueva, I., Campbell, B., & **Raikes, A. C.** (In revision). Towards a real-time assessment of physiological collaborative learning in engineering. *Journal of Engineering Education*.
- Studenka, B. E., & **Raikes, A. C.** (in press). Gender differences in non-linear motor performance following concussion. *Journal of Sport and Health Science*.
- Raikes, A. C.**, & Schaefer, S. Y. (2016). Sleep quantity and quality during acute concussion: A pilot study. *SLEEP*, 39(12), 2141-2147.
- Lohse, K., Schaefer, S. Y., **Raikes, A.**, Boyd, L., & Lang, C. E. (2016). Asking new questions with old data: The Centralized Open-Access Rehabilitation database for Stroke (SCOAR). *Frontiers in Neurology*, 7, 153.
- Raikes, A. C.**, & Schaefer, S. Y. (2016). Phasic Electrodermal Activity During the Standardized Assessment of Concussion (SAC). *Journal of Athletic Training*, 51(7), 533–539.
- Jha N, Cantu R, Gennarelli TA, Tator CH, Bailes JE, Giza C, et al. International concussion consensus 2015. *Current Research: Concussion*. 2015;2(3).
- Pierce, J. R., **Raikes, A. C.**, & Schaefer, S. Y. (2015). Is a visual-based balance assessment reliable under potentially distracting conditions? *Current Research: Concussion*, 2(2), 43–48.
- Raikes, A. C.**, & Smart, J. (2015). The effects of sport-related concussions sustained during childhood and adolescence, and the need for educational accommodation. *Current Research: Concussion*, 2(1), 25–28.

Peer-reviewed conference proceedings

- Villanueva, I., **Raikes, A.**, Ruben, N., Schaefer, S., & Gunther, J. (2014). The use of physiological tools to identify changes in affective responses for graduate students recently admitted into a scientific discipline. Presented at the 2014 FIE Conference under the “Student Beliefs, Motivation, and Persistence Through the College Years” session, Madrid, Spain.

Statistical Consultation

- Duran, L., Wackerle-Hollman, A., & **Raikes, A. C.** (In preparation). Determining the language groups of Spanish-English bilingual preschoolers
- Wackerle-Hollman, A., Duran, L., Palma, J., & **Raikes, A. C.** (In preparation). Home and classroom language exposure and the language performance of Spanish-speaking preschoolers in English and Spanish
- Duran, L., Schalla, L., Pratt, A., & **Raikes, A.** (Under review). Exploring the home literacy environments of young children in Mexico. *International Journal of Early Childhood*.

REFEREED ABSTRACTS (in reverse chronological order)

- Raikes, A. C.**, & Schaefer, S. Y. (2016). Measurement of Sleep Quantity and Quality During Acute Concussion via Actigraphy. Presented at the National Athletic Trainer's Association Clinical Symposium, Baltimore, MD.
- Gardner, J. E., Raikes, A. C., & Schaefer, S. Y. (2014). Changes in electrodermal activity during motor learning: A proxy for attention? Presented at the Society for Neuroscience Annual Meeting, Washington DC.

PRESENTATIONS

- Raikes, A. C.**, & Schaefer, S. Y. (2016, June). Measurement of Sleep Quantity and Quality During Acute Concussion via Actigraphy. Presented at the National Athletic Trainer's Association Clinical Symposium, Baltimore, MD.
- Raikes, A. C.**, & Schaefer, S. Y. (2016, April). Measurement of Sleep Quantity and Quality During Acute Concussion via Actigraphy. Presented at Student Research Symposium, Utah State University.
- Raikes, A. C.**, & Studenka, B. (2016, February). Non-linear assessment of motor variability following concussion. Poster presented at the Big Sky Athletic Training and Sports Medicine Conference, Big Sky, MT.
- Raikes, A. C.** (2015, April). Phasic Electrodermal Activity during the Standardized Assessment of Concussion. Oral Presentation presented at the Student Research Symposium, Utah State University.
- Raikes, A. C.**, & Schaefer, S. Y. (2013, June). Typical Electrodermal Responses During SAC Performance. Poster presented at the National Athletic Trainer's Association Clinical Symposium, Las Vegas, NV.
- Raikes, A. C.**, & Schaefer, S. Y. (2013, April). Typical Electrodermal Responses During SAC Performance. Poster presented at the Student Research Symposium, Utah State University.
- Raikes, A. C.**, & Dolny, D. (2012, June). The Diagnostic Efficacy of the USU Modified BESS. Poster presented at the National Athletic Trainer's Association Clinical Symposium, St. Louis, MO.

TEACHING EXPERIENCE

- 2011-Present Instructor, PEP 3100: Athletic Injuries, Undergraduate Curriculum, Utah State University
- 2014-2016 Instructor, PEP 4400: Performance Evaluation in Physical Education, Undergraduate Curriculum, Utah State University

PROFESSIONAL AND SERVICE ACTIVITIES

Ad hoc reviewer for:

Journal of Athletic Training
Journal of Sport Rehabilitation

Conference reviewer for:

8th International Conference on University Learning and Teaching

Multi-Disciplinary Advisory Team, The Konkussion Retreat (2015)

AWARDS

2013-Present	Graduate Research and Teaching Assistantship, Utah State University
2016	Rick Q. Lawson Scholarship (\$3000)
2016	Outstanding Graduate Student, Special Education and Rehabilitation Department
2015	Rick Q. Lawson Scholarship (\$3000)
2015	Travel Award, Utah State University (\$1089.75)
2013	Travel Award, Utah State University (\$400)
2013	Rick Q. Lawson Scholarship (\$3200)
2012	Outstanding Graduate Student, Health, Physical Education, and Recreation Department
2009-2012	Graduate Athletic Training Assistantship, Utah State University
2008	NATA Research and Education Foundation Scholarship (\$2500)

PROFESSIONAL MEMBERSHIPS/CERTIFICATIONS

National Athletic Trainer's Association (NATA) – Athletic Trainer Certified: Member #1013271, Certification #2000001235

American College of Sports Medicine