RESERVE, SYMPTOMS, SEX, AND OUTCOME FOLLOWING A SINGLE SPORTS-RELATED CONCUSSION

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Abstract

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Reserve refers to the biological/cognitive differences between individuals that protect against cognitive changes following a single sports-related concussion (SRC). A single SRC can lead to brain damage and a loss of reserve. The ImPACT is a neurocognitive test which was used as a proxy for reserve. The Post-Concussion Symptom Scale (PCSS), a symptom checklist, was used to examine symptoms. It was hypothesized that pre-SRC reserve would affect post-SRC reserve, so that those with higher pre-SRC reserves would demonstrate less change in their reserve after a single SRC compared to those with low pre-SRC reserves. It was also hypothesized that females would report more emotional, cognitive, and total symptoms than males, and that cognitive symptoms would be reported more frequently than other symptoms across participants. This study used data collected by the North Coast Concussion Program, which administers the ImPACT test and the PCSS to athletes at Humboldt State University prior to each athletic season. In the event of an SRC, the test is re-administered. It was found that participants (N = 129) with low pre-SRC reserves had better outcomes compared to those with high pre-SRC reserves, and that females reported more symptoms than males. This study is the first to examine the role of reserve in

predicting outcome following a single SRC using a pretest-posttest design. The validity of the ImPACT test as a proxy for reserve as well as the test structure's influence on administrative decisions was examined. The current study also expanded on research relating to sex's influence on symptomatology following a single SRC.

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Literature Review

Sports-related concussions (SRCs) are a leading cause of brain injury. SRCs range in severity from mild to traumatic. About 300,000 SRCs are documented annually in the United States (Gessel, Fields, Collins, & Comstock, 2007; Sosin & Sniezek, 1996). However, SRCs often go unreported (Emery et al., 2011; McCrea, Hammeke, Olsen, Leo, & Guskiewicz, 2004). The Centers for Disease Control endorses the estimate that as many as 3.8 million SRCs occur in the United States each year (Centers for Disease Control, 2007; Langlois, Rutland-Brown, & Wald, 2006). Despite the high incident rate of SRCs, the factors that influence individual outcome following a single SRC are poorly understood.

Reserve is one factor that influences outcome following a traumatic brain injury like an SRC (Fay et al., 2009; Oldenburg, Lundin, Edman, Boussard, & Bartfai, 2015). Reserve refers to the quantifiable neurophysiological and cognitive differences between individuals that contribute to everyday functioning and protect against cognitive changes following brain injury. Neurocognitive tests like the Immediate Post-Concussion Assessment and Cognitive Test Version 2 (ImPACT) are used as proxies for reserve. Symptomatology is also important piece of everyday functioning which the ImPACT measures via the Post-Concussion Symptoms Scale (PCSS). The current study aims to evaluate the role of reserve in shaping what kind of outcomes following a single SRC.

In addition, the current study addresses symptomatology following an SRC and how it is influenced by biological sex.

Reserve

Reserve is a major component of everyday functioning that is compromised following a sports-related concussion. Reserve refers to the neurophysiological (i.e., neuroanatomical and cognitive) factors that influence everyday functioning. Those with high baseline reserve show more consistency in everyday functioning following a brain injury compared to those with low reserve (Habeck, Eich, Razlighi, Gazes, & Stern, 2018; Stern et al., 2013; Tucker & Stern, 2011). Thus, reserve explains why some individuals are more resilient against symptoms of brain injury than others. According to the reserve theory, those with high reserve are less affected by symptoms of brain injury, but those with high reserve may still show neuroanatomical signs of injury (Barbey et al., 2014; Barulli & Stern, 2013; Katzman et al., 1988). The reserve theory is investigated in this thesis by comparing outcomes of those with high and low reserve following a sports-related concussion.

The reserve theory is the modern composite of two earlier theories: brain and cognitive reserve. The brain and cognitive reserve theories arose as explanations for the discrepancy observed between clinical and neurophysiological symptoms of neurodegeneration. In a landmark study, it was observed that some elderly adults who sustained independent, everyday functioning through life displayed the neuroanatomical signs associated with Alzheimer's (e.g., plaques and tangles) upon autopsy (Katzman et

al., 1988). This study spurred an interest in the role of pre-injury neuroanatomical and cognitive functioning in predicting post-injury functioning. Once similar findings validated this discrepancy (Baltes & Kühl, 1992; Baltes, Kühl, Gutzmann, & Sowarka, 1995; Katzman, 1993; Stern et al., 1994) the theories of brain and cognitive reserve came into fruition.

Brain reserve held that neuroanatomical differences in brain structure accounted for differences in clinical outcomes following brain injury. Given this, brain reserve viewed brain injuries as passive (Satz, 1993). This view contradicted research on brain plasticity, which asserts that the brain is subject to neuroanatomical change and repair throughout the lifetime (Barulli & Stern, 2013; Kliegl, Smith, & Baltes, 1989; Mahncke et al., 2006). Cognitive or neural reserve holds that neurocognitive differences (i.e. differences in neural connections within and between anatomical structures) accounted for differences in clinical outcomes following brain injury (Bigler & Stern, 2015; Fay et al., 2009; Kesler, Adams, Blasey, & Bigler, 2003; Mathias & Wheaton, 2015; Oldenburg et al., 2015; Ropacki & Elias, 2003; Stern, 2002). The neuroanatomical and neurocognitive components that contribute to everyday functioning are now known to be integrated. The reserve theory reflects this integration and is neurophysiological in nature.

Reserve theory is an evolving concept which explains the discrepancy between clinical and neurophysiological symptoms following neurodegeneration. It has been used to explain individual differences in everyday functioning in those with neurodegenerative diseases such as Alzheimer's (Alexander et al., 1997; Arenaza-Urquijo, Wirth, &

Chételat, 2015; Liberati, Raffone, & Belardinelli, 2011; Oh, Razlighi, & Stern; 2017; Sobral, Pestana, & Paúl, 2015), Parkinson's (Barulli & Stern, 2013; Bigler & Stern, 2015; Koerts, Tucha, Lange, & Tucha, 2012; Poletti, Emre, & Bonuccelli, 2011; Rouillard et al., 2016) and Huntington's (Bonner-Jackson et al., 2013; Soloveva, Jamadar, Poudel, & Georgiou-Karistianis, 2018). Neurocognitive tests like the ImPACT are intended to reflect neurophysiological factors that contribute to everyday functioning (i.e., reserve). The reserve theory has also been applied to explain individual differences in everyday functioning in many types of brain injury, including sports-related concussions (SRCs). However, the reserve theory has seldom, if ever, been applied to explain differences in individual functioning following a single SRC. One of the purposes of the current study is to apply the reserve theory to single SRCs.

Reserve in a single sports-related concussion (SRC). Compelling evidence suggests that a single brain injury, including sports-related concussion (SRC), can lead to permanent neurophysiological damage, and thus a loss of reserve (Fay et al., 2009; Mez et al., 2017; Oldenburg et al., 2015; Tagge et al., 2017). This suggestion is controversial. It was once thought that permanent damage from a single SRC was improbable (Pellman, Viano, Casson, Arfken, & Feuer, 2005). Some individuals have been shown to develop the neurodegenerative disorder chronic traumatic encephalopathy (CTE) following a single SRC.

Chronic traumatic encephalopathy (CTE) is a neurodegenerative disorder caused by prolonged microstructural damage resulting from concussion. CTE is typically

associated with repeated concussive and subconcussive blows (Gavett, Stern, Cantu, Nowinski, & McKee, 2010; McKee et al., 2012; McKee et al., 2009; Omalu et al., 2005). Like other neurodegenerative disorders, those with CTE experience cognitive decline, personality changes and loss of independent functioning. CTE is biologically, cognitively and clinically similar to other neurodegenerative diseases (Gavett et al., 2010; McKee et al., 2012; McKee et al., 2009; Mez et al., 2017; Omalu et al., 2005; Stern et al., 2011; Tagge et al., 2017). Recent studies have suggested that the functional and microstructural injuries associated with CTE can result from a single concussion (Johnson et al., 2013; Johnson, Stewart, & Smith, 2012; Mez et al., 2017; Tagge et al., 2017). The theory of reserve may explain, in part, individual differences in outcome following a single SRC.

In order to illustrate how reserve can be applied to a single SRC, it is important to understand the related neuroanatomical and cognitive components of reserve. SRCs are brain injuries caused by biomechanical forces. Paralleling the components of reserve, two types of related injuries, functional and microstructural, occur during an SRC. Functional injury affects the neuroanatomical structures which facilitate everyday functioning (Clauss, 2010; Giza & Hovda, 2014; Ivancevic, 2009; Smith, Meany, & Shull, 2003). Functional injury may go on to cause microstructural injury. Microstructural injury is associated with the loss of neural networks that facilitate cognitive everyday functioning (Hashim et al., 2017; Huey et al., 2015; Miller, 2001; Nithianantharajah, 2004; Tomassy et al., 2014). Together, functional and microstructural injuries account for reserve loss following an SRC. Neurocognitive tests like the ImPACT are intended to measure cognitive performance. The ImPACT may be sensitive to detecting changes in reserve

brought upon by functional and microstructural injury following a single SRC. The current study seeks to use the ImPACT to encapsulate individual differences in neuropsychological functioning that are affected by functional and microstructural injury.

Functional injury. Functional injury directly jeopardizes the functioning of important neuroanatomical structures. Those with high reserve may be more resistant to functional injury compared to those with low reserve. For example, low brain volume is associated with increased experiences of loss of consciousness during a traumatic brain injury (MacKenzie et al., 2002; Sundman & Hall, 2014). However, brain volume alone is a crude way of measuring reserve following an SRC. Functional injuries brought upon by SRCs can cause permanent damage to neuroanatomical structures associated with reserve.

In sports-related concussions (SRCs), functional injury results from the transfer of energy from an initial acceleration force to the brain. The transfer of energy brought upon by an SRC damages neurons. Pyramidal neurons are a family of neurons found chiefly in the cerebral cortex (Elston, 2003), as well as in the amygdala and hippocampus (Coleman et al., 2018; Nakatomi et al., 2002). Repeated SRCs are associated with atrophy of pyramidal neurons in the hippocampus (Tagge et al., 2017). Metabolic changes brought upon by biomechanical forces ultimately contribute to loss in reserve.

Functional injury and reserve loss from an SRC begins with metabolic disruption brought upon by acceleration and deceleration forces. If acceleration and deceleration forces are not gradual, physical impact is experienced as weight. This acceleration is measured by g-force (Meaney & Smith, 2011). In sports, a rapidly accelerating player is

forced to a sudden halt at the moment of impact. This collision usually does not result in a skull fracture. However, many SRCs have a g-force significant enough to push the less-dense and more rapidly accelerating brain against the denser skull. Within the brain, a similar process causes areas of differing densities to decelerate at conflicting paces. This energy transfer causes metabolic disruption (Giza & Hovda, 2014). The chemical shifts that coincide with these metabolic disruptions are responsible for shifts in neurophysiological functioning, leading to changes in cognition and symptomatology.

The sudden transfer of kinetic energy forces the opening of voltage-gated ion channels. The opening of these channels allows an uninhibited influx of neurotransmitters to pass through the blood-brain barrier. The rapid release of neurotransmitters, particularly dopamine, GABA and glutamate, contribute to a variety of physical and psychological symptoms immediately following SRC (Clauss, 2010; Giza & Hovda, 2014). Many of the physical and psychological symptoms associated with metabolic disruption are measured on-site, however, the expression of these symptoms varies between individuals. Some functional injuries, like axonal tearing, follow a relatively stereotyped course. Axonal damage can lead to neurophysiological damage which goes on to affect reserve.

Axonal tearing is another type of functional injury that can occur following a single brain injury (Johnson et al., 2013). Axonal tearing occurs when the g-force is great enough to cause the axons that connect areas in the brain of varying densities to tear, resulting in loss of consciousness or death (Clauss, 2010; Giza & Hovda, 2014; Ivancevic, 2009). Axonal tearing may be diffuse (occurring throughout the brain) or

localized (occuring at the point of impact). Localized axonal tearing is often associated with swelling in the cerebral cortex (Blennow, Hardy, & Zetterberg, 2012; Langlois et al., 2006). Axonal tearing in SRCs is relatively rare, while axonal damage may be more common (Giza & Hovda, 2014; Prins, Hales, Reger, Giza, & Hovda, 2010). Both axonal tearing and axonal damage lead to neuroanatomical changes and a loss of reserve, and occur along with injury, leading to immediate symptoms (Bigler & Stern, 2015; Prins et al., 2010). However, the immediate symptoms and biomechanical processes involved in a functional injury are not independently predictive of outcome. Reserve considers the neuroanatomical changes that influence neurophysiological and cognitive functioning. Functional injury is a potential consequence of a single SRC. Functional injury coincides with and/or goes on to cause neurodegeneration through microstructural injury. Functional and microstructural injury contribute to a loss of reserve.

Microstructural injury. Microstructural injury is more subtle than functional injury. Microstructural injury accounts for damage in neural networks which allow different brain regions to communicate (Gray & Thompson, 2004). Some neuroimaging techniques including diffusion tensor imaging (DTI) have assisted in identifying microstructural injury in neurodegenerative disorders (Hartikainen et al., 2010; Inglese et al., 2005; Lancaster et al., 2016; Maruyama et al., 2013), but little is known about their etiology or repercussions. Differences in gray and white matter morphology, as well as differences in neuronal density/structure in gray matter, have been observed between individuals with high and low reserve (Barulli & Stern, 2013; Benedict, Morrow, Guttman, Cookfair, & Schretlen, 2010; Stern, Gazes, Razlighi, Steffener, & Habeck,

2018; Stern & Habeck, 2018). Evidence is presented which highlights differences in clinical outcome as a function of physiological factors that have been shown to relate directly to reserve.

Gray matter is a visible collection of neuronal cell bodies while white matter is a visible collection of tissue that primarily facilitates transport between different areas of the brain (Paus, Pesaresi & French, 2014). Microstructural injury in gray and white matter has been repeatedly observed through DTI and post-mortem autopsy in those with neurodegenerative disorders. Decreased gray and white matter volume is associated with clinical symptoms of dementia in life in individuals with Alzheimer's disease (Kopeikina et al., 2011; Maruyama et al., 2013), in CTE and single traumatic brain injury (Blennow et al., 2012; Holleran et al., 2017; Lancaster et al., 2016; Meier et al., 2015a). In individuals who had sustained concussion, DTI suggested that those who displayed decreased white matter tended to score low on tests of fluid intelligence (Niogi et al., 2008). Likewise, differences in gray and white matter density and formation are seen in individuals with a number of disorders, including schizophrenia, depression and obsessive-compulsive disorder (Fields, 2008). In addition to brain damage, environmental and genetic influences affect white and gray matter formation, and thus reserve (Hinton, 1992; Lee & Seo, 2016; Paus et al., 2014; Wallin & Sjögren, 2001).

White and gray matter are known to develop along with reserve during childhood, and early childhood neglect is associated with disrupted white matter growth (Fields, 2008; Hanson et al., 2013; Nagy, Westerberg & Klingberg, 2004). Given that the white matter is developed over time, its formation and functional capacity vary between

individuals (Hinton, 1992; Kapitein & Hoogenraad, 2015; Lee & Seo, 2016; Wallin & Sjögren, 2001; Wolfe, 2012). Individuals with rich learning experiences are suspected to have more structurally complex gray and white matter (Arenaza-Urquijo et al., 2013). Individuals with more structurally complex intracranial gray and white matter score high on standardized neurocognitive tests (Oh et al., 2017; Lancaster et al., 2016; Narr et al., 2006).

Microstructural injury is associated with neurodegeneration and the loss of neural networks which facilitate the cognitive aspects of everyday functioning (Giza, & Hovda, 2010; Lipton et al., 2013). Neuroimaging has assisted in assessing the severity of functional injury following an SRC. However, neuroimaging alone cannot adequately predict outcome following brain injury (Hashim et al., 2017; Hofman et al., 2001). When assessing clinical outcome, current neuroimaging techniques may lack predictive validity. Thus, neurocognitive testing is a useful tool in assessing clinical outcome. The current study uses the computerized neurocognitive test, ImPACT, as a proxy for reserve.

Neurocognitive tests and reserve. The use of the ImPACT to measure reserve is motivated by its relationship to validated neurocognitive measures. Neurocognitive tests typically act as proxies for intelligence, which is related to reserve. General intelligence refers to an individual's ability to acquire knowledge and problem solve. General intelligence is theoretically comprised of crystallized and fluid intelligence (Zaval, Li, Johnson, & Weber, 2015). Crystallized intelligence refers to knowledge acquisition, while fluid intelligence refers to problem solving abilities (Gray & Thompson, 2004).

Neurocognitive tests like the Wechsler Adult Intelligence Scale Version 4 (WAIS-IV) and the ImPACT attempt to measure both crystallized and fluid intelligence (Saklofske & Schoenberg, 2011; Tuokko et al., 2003). Reserve is related to general intelligence, although crystallized and fluid intelligence may contribute to reserve in different ways. Understanding the components of intelligence and how they relate to reserve justifies the use of neurocognitive tests like the ImPACT as a proxy for reserve.

It is typically accepted that general intelligence is composed of crystallized and fluid intelligence. However, reserve may relate more to fluid intelligence. Measures of fluid intelligence have been shown to be more sensitive to brain injury compared to measures of crystallized intelligence (Barbey et al., 2014; Gray & Thompson, 2004). Loss of brain volume (i.e., loss of reserve) is associated with decreased scores on measures of fluid intelligence over time (Rabbitt et al., 2008). More specifically, loss of volume in the frontal lobe in the prefrontal cortex is linked to decreased scores on fluid intelligence, but not crystallized intelligence (Roca et al., 2010). Neurocognitive tests which estimate fluid intelligence using tasks that measure processing speed and reaction time are correlated with meaningful neurophysiological differences, indicating that fluid intelligence is related to reserve (Gray & Thompson, 2004; Meiran & Shahar, 2018; Niogi et al., 2008; Sheppard & Vernon, 2008). Neurocognitive tests have been shown to predict clinical outcome better than biomechanical tests in SRCs (Breedlove et al., 2012; Broglio, Eckner, Surma & Kutcher, 2011). Similarly, current neuroimaging techniques are unable to reliably detect microstructural injury resulting from a single SRC (Eierud et al., 2014). In addition, neurocognitive exams are cheaper and more accessible than

neuroimaging exams (Kantarci & Jack, 2003). Computer-based neurocognitive tests like the ImPACT may account for functional and microstructural damage that influences reserve. The availability of these tests makes them useful tools in estimating reserve. This thesis will use the ImPACT to measure reserve.

ImPACT as a Proxy for Reserve

Neurocognitive tests like the ImPACT can be used as a proxy for reserve. The ImPACT is widely used to assess neurophysiological functioning following an SRC. However, the theory of reserve has been sparsely applied to explain individual differences in outcome following a single SRC. It has been suggested that baseline reserve influences outcome following a single concussion, but these findings relied on retrospective data to estimate baseline reserve (Fay et al., 2009; Oldenburg et al., 2015). By using the ImPACT as a proxy for reserve, a baseline measure of reserve was made available. The current study proposes the use of the ImPACT as a proxy for reserve in individuals who have sustained a single concussion.

The use of ImPACT is widespread, and it is the only computer-based test endorsed by the FDA (U.S. Food and Drug Administration, 2016). The application of the reserve theory may assist in the interpretation of neurocognitive tests like the ImPACT. The ImPACT test is used to inform return-to-play decisions following SRCs. Due to functional injury following a brain injury, cognitive testing within 72 hours of an SRC is unreliable. When properly administered, the ImPACT could act as a neurophysiologically

meaningful proxy for reserve which estimates cognitive changes resulting from functional and microstructural injury.

The ImPACT test is structurally similar to other neurocognitive tests like the Wechsler Adult Intelligence Scale. The WAIS-IV measures four components of cognitive functioning — verbal memory, working memory, perceptual (or visual) memory and processing speed (Flanagan & McDonough, 2018). The ImPACT measures the same components as the WAIS-IV, but also includes reaction time and impulse control. The components of the ImPACT, as related to the WAIS-IV and similar neurocognitive tests, are presented below.

Verbal memory composite. The verbal memory composite of the ImPACT is intended to evaluate memory, learning and attention in the verbal domain (ImPACT Technical Manual, 2016). Accuracy on the Word Memory, Symbol Match and Three Letters modules contribute to the verbal memory composite score. Subtests in the verbal memory domain bear similarity to subtests used in the WAIS-IV and other neurocognitive tests.

The subtests which make up the verbal memory composite score on the ImPACT are similar to those used in the WAIS-IV to measure Processing Speed. The verbal memory composite scores correlate with scores on Processing Speed subtests on the WAIS-IV (Thoma et al., 2018). The subtests which contribute to the ImPACT's verbal memory composite score appear to reflect visual motor processing as well as verbal memory (Thoma et al., 2018). Scores on the verbal memory module of the ImPACT were

shown to be sensitive in detecting differences between concussed and non-concussed athletes (Arrieux, Cole, & Ahrens, 2017). The verbal memory composite of the ImPACT may also be sensitive in estimating pre and post-concussion differences in reserve.

The ImPACT test battery as a whole has been shown to detect change within 72 hours following brain injury (Arrieux et al., 2017). Unlike the other composites, the verbal memory portion of the ImPACT detected significant differences between concussed and non-concussed groups up to eight days following an SRC (Nelson et al., 2016). Similarly, it was demonstrated that concussed athletes deviated furthest from their baseline scores on the verbal memory domain compared to other domains (Schatz, Pardini, Lovell, Collins, & Podell, 2006). The verbal memory domain may be more sensitive than other tests of verbal memory. The Hopkins Verbal Learning Test-Revised (HVLT-R) is a neurocognitive test intended to assess verbal memory. Athletes who completed the HVLT-R prior to brain injury were shown to return to their baseline scores within seven days of injury (McCrea et al., 2003). The verbal memory composite of the ImPACT may be more sensitive in detecting neurocognitive changes associated with the loss of reserve for seven to eight days following brain injury compared to the HVLT-R (Arrieux et al., 2017; Nelson et al., 2016; Schatz et al., 2006). Other studies have demonstrated that verbal memory is an aspect of reserve that is affected by brain injury (Fay et al., 2009; Oldenburg et al., 2015). Given this, the verbal memory composite of the ImPACT may reflect a portion of neurophysiological functioning that is compromised by brain injury like SRCs. Visual memory is another aspect of reserve that is compromised by SRCs.

Visual memory composite. The visual memory composite score of the ImPACT is intended to represent memory, learning and attention in the visual domain. The Design Memory and X's and O's subtests contribute to the ImPACT's visual memory composite score (ImPACT Technical Manual, 2016). A task similar to the Design Memory subtest has been shown to be sensitive to changes in reserve in young adults (Stern et al., 2003). The ImPACT Visual memory composite relates to other assessments of visual memory better than tasks which contribute to perceptual (or visual) memory scores on the WAIS-IV (Thoma et al., 2018). Visual memory is an important aspect of reserve, and changes in visual memory may coincide with changes in everyday functioning. Deficits in visual memory are associated with decreased reserve (Mason et al., 2017; Stern, 2002; Stern et al., 2003). It has been demonstrated that individuals with low reserve are less able to recognize novel changes in complex visual stimuli compared to those with high reserve (Mason et al., 2017). The ImPACT uses complex visual stimuli in this module to assess visual memory. Visual motor speed, which relates to processing speed and fluid intelligence, is also sensitive to meaningful changes in reserve.

Visual motor speed composite. The visual motor speed composite of the ImPACT test is intended to evaluate visual processing and visual-motor response speed, as well as visual memory and learning (ImPACT Technical Manual, 2016). Accuracy on the distractor task of the X's and O's subtest contributes to the visual motor speed composite score (ImPACT Technical Manual, 2016). As a measure of visual learning and memory, scores on the visual motor speed composite are correlated with scores on the

WAIS-IV Digit Span Backward task. The WAIS-IV Digit Span Backward tasks requires the participant to memorize an increasing string of numbers and repeat them backward to the administrator (Flanagan & McDonough, 2018). The WAIS-IV Digit Span Backward task bears similarity to the Three Letters distractor task. The WAIS-IV Digit Span Backward tasks measure fluid intelligence (Benson, Hulac, & Kranzler, 2010). The WAIS-IV Digit Span Backward tasks have been shown to be significantly high in those without brain injury compared to those with brain injury (Hashim et al., 2017). Like the visual motor speed composite, Processing Speed scores are related to fluid intelligence and reserve.

Processing speed. Processing speed scores contribute to the visual motor speed composite score. Processing speed refers to the rate at which cognitive tasks are completed, and is a measure of fluid intelligence (Nilsson, Thomas, Obrien, & Gallagher, 2014). On the ImPACT, processing speed is determined based on the accuracy on interference tasks in the X's and O's task along with accuracy on the Symbol Match subtest. The Symbol Match subtest in the ImPACT is modeled after the Symbol Digit Modalities Test (SDMT), and processing speed scores on the ImPACT are highly correlated with scores on the SDMT (Iverson, Lovell, & Collins, 2005). The Digit-Symbol Coding subtest of the WAIS-IV is also modeled after the SDMT (Logue et al., 2015). The SDMT alone has been used as a proxy for reserve (Roldán-Tapia, García, Cánovas, & León, 2012; Benedict et al., 2010). Past research has demonstrated the role of processing speed in reserve.

Processing speed may be an especially important indicator of reserve. One study suggested that those with high reserve scored high on the SDMT compared to those with low reserve (Benedict et al., 2010). These individuals also deviated less from their baseline reserve five years later (Benedict et al., 2010). In individuals who sustained traumatic brain injury, high scores on a task similar to the SDMT were significantly related to genetic indicators of high reserve (Barbey et al., 2014). Processing speed is also related to low white matter volume (i.e., reserve) (Gray & Thompson, 2004; Niogi et al., 2008). Reaction time is similarly related to reserve, as both estimate fluid intelligence.

Reaction time composite. The reaction time composite of the ImPACT measures the average response speed on portions of the X's and O's, Symbol Match and Color Match subtests (ImPACT Technical Manual, 2016). The X's and O's as well as the Symbol Match subtests also contribute to the visual memory and visual motor speed composites, respectively. The Color Match subtest is intended to measure response time alone. The Color Match subtest utilizes the widely used Stroop Color and Word task to gauge response time (Stroop, 1935). Tasks similar to those used in the Color Match subtest have been widely used as a proxy for reserve (Koerts et al., 2012; Le Carret et al., 2005). Scores on the Stroop Color and Word task differed significantly in those with brain injury compared to those without brain injury (Ropacki & Elias, 2003). This suggests that the Color Match subtest is a useful addition to the ImPACT. This is due to the relationship between reaction time and reserve.

Reaction time is an aspect of fluid intelligence and an indicator of reserve. Like processing speed, reaction time is related to the rate at which cognitive tasks can be completed, although reaction time is less concerned with accuracy than processing speed (Nilsson et al., 2014). Still, reaction time alone has been shown to correlate with general intelligence (Sheppard & Vernon, 2008). Faster reaction times may be associated with complexity of neural networks, and thus reserve (Habeck et al., 2018; Habeck et al., 2003; Stern, 2009). The reaction time composite of the ImPACT test captures an important aspect of reserve.

As a whole, the ImPACT test is a measure of crystallized and fluid intelligence and thus can act as a meaningful proxy for reserve. However, cognitive functioning alone cannot determine an individual's post-concussion functioning. Concussions are individualized injuries, and symptoms associated with SRC's provide meaningful subjective information. The Post-Concussion Symptom Scale (PCSS) is a measure of post-concussion symptom presence and severity. The PCSS is administered to athletes prior to the ImPACT cognitive assessment to achieve a more complete profile of an individual's mental state following an SRC.

Symptoms and Reserve

Symptomatology is an important aspect of everyday functioning that relates to reserve. SRCs are highly individualized, and changes in symptomatology reflect changes in reserve (Barnett, Salmond, Jones, & Sahakian, 2006; Ross et al., 2012). Decreased white matter resulting from microstructural injury was linked to persistent post-

concussion symptoms (Cubon, Putukian, Boyer, & Dettwiler, 2011; Smits et al., 2010). In addition, symptomatic concussed athletes were shown to differ in their neurophysiological responses compared to non-concussed controls matched in age and sex (Chen et al., 2004). Measures of symptomatology like the Post-Concussion Symptom Scale (PCSS) assess symptomatology following an SRC (Barlow, Schlabach, Peiffer, & Cook, 2011).

The ImPACT test battery includes the Post-Concussion Symptom Scale (PCSS). The PCSS a self-report measure intended to assess the presence and severity of common post-concussion symptoms. Unlike the ImPACT, which is a test of cognitive functioning, the PCSS attempts to capture more general aspects of everyday functioning. An individual's PCSS score is typically correlated with their ImPACT score, and the PCSS contributes a sizable amount of unique variance to an individual's overall ImPACT test battery score (Lau, Collins & Lovell, 2011; Schatz et al., 2006). Items on this scale are typically evaluated together as an individual's total PCSS score. However, clustering items on the PCSS based on symptom type may provide a richer understanding of an individual's symptoms following an SRC. Each items on the PCSS can be conceptualized as belonging to one of four symptom clusters: somatic/migraine, cognitive, emotional and sleep symptoms (Covassin, Elbin, Larson, & Kontos, 2012; Lau, Lovell, Collins, & Pardini, 2009; Lau et al., 2011). It has been demonstrated that framing the PCSS by cluster increases the sensitivity and specificity of the PCSS (Lau et al., 2011). The current study applies these clusters to PCSS scores in order to obtain a more nuanced

understanding of symptomatology. The prevalence of each cluster and its interaction with biological sex is observed.

Sex has repeatedly been demonstrated to influence scores on the PCSS. Specifically, females tend to have high total PCSS scores compared to males (Covassin, Schatz, & Swanik; 2007; Frommer et al., 2011; Sunderman et al., 2016). The application of clusters as a means of interpreting total PCSS suggests that sex differences vary by cluster (Covassin et al., 2012). This thesis seeks to provide more information regarding this relationship. A description of each cluster is presented, followed by a review of findings related to sex and symptom clusters.

Somatic/migraine symptoms cluster. Somatic/migraine symptoms are physical symptoms. Headache, visual problems, dizziness, sensitivity to light and noise, nausea/vomiting, balance problems and numbness/tingling are physical symptoms that belong in the somatic/migraine symptom cluster of the PCSS (Lau et al., 2011). An individual's score on the somatic/migraine cluster of the PCSS is related to reserve. Those who experienced physical symptoms following a brain injury were shown to have low post-injury reserve compared to those who did not report physical symptoms (Bigler & Stern, 2015; MacKenzie et al., 2002; Maxwell, Mackinnon, Stewart, & Graham, 2010). Somatic/migraine symptoms assist in determining outcomes following SRCs. Similarly, other items on the PCSS appear to provide unique contributions to an individual's post-injury ImPACT battery score when analyzed by cluster. Cognitive symptoms differ from somatic/migraine symptoms, although both contribute to reserve.

Cognitive symptoms cluster. Items on the PCSS which belong in the cognitive symptom cluster include those related to fatigue, drowsiness, difficulty concentrating and cognitive slowing (Lau et al., 2011). Those with longer lengths of recovery following an SRC were shown to report more cognitive symptoms compared to somatic/migraine, emotional or sleep symptoms (Lau et al., 2011). In addition, persistent cognitive symptoms were shown to relate to microstructural injury and impaired cognitive functioning (Hartikainen et al., 2010). Thus, an individual's score on items belonging to the cognitive symptom cluster of the PCSS may relate to their reserve. The PCSS also estimates the presence and severity of emotional symptoms.

Emotional symptoms cluster. Emotional symptoms are neuropsychiatric in nature. Items on the PCSS that assess sadness, nervousness, irritability and changes in emotionality belong in the emotional symptom cluster (Lau et al., 2011). It has been observed that symptoms belonging in the emotional cluster of the PCSS are reported the least among individuals who sustained an SRC (Lau et al., 2011). Nevertheless, emotional symptoms following an SRC may provide important information when reported. It may be beneficial to break the emotional cluster of the PCSS down further in order to focus on the influence of specific neuropsychiatric symptoms. Some emotional/neuropsychiatric symptoms like neuroticism have been shown to be related to low baseline reserve and poorer outcomes following brain injury (Bigler & Stern, 2015; Parker & Rosenblum, 1996). Emotional symptoms due to SRCs have been noted in cases of CTE (McKee et al., 2009). Microstructural injury within areas of the brain implicated

in emotion regulation have been observed in individuals with CTE. It has been suggested that emotional symptoms may appear before other symptoms in males with CTE (McKee et al., 2009). Emotional symptoms may uniquely reflect changes in reserve brought upon by SRCs. This notion bolsters the practice of separating symptoms by cluster. Symptoms relating to sleep also contribute to changes in reserve.

Sleep symptoms cluster. Items on the PCSS that belong in the sleep symptom cluster include those that assess difficulty falling asleep and changes in sleep pattern (i.e. sleeping more or less than usual) (Lau et al., 2011). Changes in sleep patterns are related to changes in reserve. Axonal damage resulting from SRCs can influence gray matter in areas of the brain that regulate sleep-wake cycles, such as the pons (Jaffee, Winter, Jones & Ling, 2015). In addition, the atrophy of hypocretin neurons is associated with brain injury. Hypocretin neurons produce the neuropeptide hypocretin, which plays a role in sleep-wake cycles (Lavigne, Khoury, Chauny & Desautels, 2015; Baumann et al., 2009; Baumann, Werth, Stocker, Ludwig & Bassetti, 2007). The same biological marker which contribute to lowed reserve is linked to an increased risk of concussion as well as persistent sleep disturbances (Lavigne et al., 2015). Those with sleep disturbances were also shown to perform significantly worse on neurocognitive tests compared to those without sleep disturbances (Macera, Aralis, Rauh, & Macgregor, 2013; Nebes, Buysse, Halligan, Houch, & Monk, 2009). In addition, symptoms belonging in the sleep cluster may persist longer than symptoms in other clusters following brain injury (Jaffee et al., 2015). This suggests that sleep is an important aspect of reserve. The PCSS gauges

symptoms relating to sleep disturbances. The presence and severity of sleep and other symptom clusters has been shown to vary as a function of sex.

Sex differences. Sex has been shown to influence the expression of symptoms following an SRC. In general, females tend to score slightly high on the PCSS compared to males (Covassin et al., 2007; Frommer et al., 2011; Sunderman et al., 2016). On the PCSS, females were shown to be more likely to report cognitive and emotional symptom clusters compared to males, although items on the somatic/migraine and sleep clusters of the PCSS did not significantly differ between sexes (Covassin et al., 2012). This relationship appears to hold true for other symptom scales (Mollayeva, El-Khechen-Richandi, & Colantonio, 2018). Past research has posited that biological factors as well as sociocultural factors may contribute to differences in symptom reporting between sexes (Brown, Elsass, Miller, Reed, & Reneker, 2015; Frommer et al., 2011; Gessel et al., 2007).

Given that PCSS scores contribute significantly to an individual's composite ImPACT test battery score, differences in symptom reporting on the PCSS between sexes is an issue of particular interest (Lau et al., 2011; Schatz et al., 2006). A more complex relationship between sex and symptomatology is revealed when interpreting PCSS scores in terms of clusters. This study seeks to add to the body of research by determining if differences in symptom reporting between sexes is consistent in the current population.

The Current Study

Reserve and symptomatology are important aspects of everyday functioning that are affected by brain injury. The purpose of the current study was to identify individual differences in reserve and symptomatology that contribute to distinct outcomes following a single SRC. The current study compared baseline reserve scores to post-SRC reserve scores in order to gauge a relationship between existing reserve and outcome. In addition, the current study examined the prevalence of particular symptoms by clustering symptoms by type. The relationship between symptom cluster and sex was also examined. The ImPACT test battery was used as a proxy for reserve, while symptomatology was evaluated using the PCSS.

Hypotheses

Hypothesis 1: Baseline and post-concussion reserve. If one's level of reserve before an SRC (i.e. pre-concussion reserve) affects one's level of reserve after an SRC (i.e. post-concussion reserve), then those with high baseline reserve would demonstrate less of a change in their reserve scores after an SRC compared to those with low baseline reserve. This prediction was consistent with previous findings, which suggest that those with high baseline reserve tended to show less change in reserve following a brain injury compared to those with low baseline reserve (Oldenburg et al., 2015; Fay et al., 2009; Kesler et al., 2003; Ropacki & Elias, 2003; Satz, 1993; Wright et al., 2016).

Hypothesis 2: Sex and symptom cluster interaction. If one's sex affects the type of post-concussion symptom clusters reported, then females would score higher on symptoms belonging to cognitive and emotional clusters compared to males. No significant difference in somatic/migraine and sleep cluster scores was expected between sexes. This relationship between sex and post-concussion symptom cluster was observed by Covassin et al. (2012).

Hypothesis 2b: Main effect of sex. If one's sex affects the number of post-concussion symptoms reported, then scores on the post-concussion symptom scale would differ between sexes. It was expected that females would report more post-concussion symptoms than males, however, the findings supporting this prediction are mixed. Some studies have found that that females tended to report more overall post-concussion symptoms compared to males (Covassin et al., 2012; Frommer et al., 2011; Gessel et al., 2007), while others found that males tended to report more overall post-concussion symptoms compared to females (Covassin et al., 2007).

Hypothesis 2c: Main effect of symptom cluster. If one's post-concussion symptoms differ by cluster, then higher scores from the cognitive cluster and lower scores from the emotional, sleep and somatic/migraine clusters would be reported. No significant differences between scores of symptoms reported from emotional, sleep or somatic/migraine clusters were expected. This prediction is supported by findings from Covassin et al. (2012), which suggest that symptoms from the cognitive cluster are reported more than symptoms from other clusters.

Method

Materials

The ImPACT is a self-paced, computerized test battery. It is composed of eight modules. The first module, demographic information, includes age, sex, concussion history and disability status. Participants then completed the Post-Concussion Symptom Scale (PCSS). The Post-Concussion Symptom Scale (PCSS) contains 22 items assessing the presence and severity of somatic/migraine, cognitive, emotional, and sleep-related symptoms. Each item on the PCSS was measured on a likert-type scale ranging from zero (*none*) to six (*severe*). Number of items belonging to each cluster and descriptive statistics for the PCSS are presented in Table 1.

Table 1. *Descriptive Statistics and Number of Items on the PCSS*

Symptom	No. Items	Males (n = 70)	Females (n = 59)	Total (n = 129)
		M (*SD*)	*M* (*SD*)	*M* (*SD*)
Somatic/Migraine	9	6.42 (7.76)	8.71 (7.70)	7.75 (7.80)
Cognitive	6	6.28 (6.40)	7.92 (6.30)	7.18 (6.37)
Emotional	4	1.98 (3.31)	3.69 (4.86)	2.91 (4.30)
Sleep	3	2.14 (2.61)	3.30 (3.19)	2.78 (2.99)
Total	22	16.83 (17.49)	23.79 (18.49)	20.60 (18.31)

Note. Values represent descriptive statistics prior to z-score and square root transformations.

The remaining six modules (Word Memory, Design Memory, X's and O's, Symbol Match, Color Match and Three Letters) are neurocognitive portions of the ImPACT test. Participant's responses on these modules produce five index scores (verbal memory, visual memory, visual motor/processing speed, reaction time, and impulse control). Each index score is measured using one or more modules. For the purpose of this study, the impulse control composite was not included as it is not neurocognitive in nature.

The Word Memory module assessed verbal memory. The Word Memory module required the participant to memorize 12 target words at the beginning of the test battery. The participant was prompted to identify the 12 target words out of 24 total words near the end of the test battery.

The Design Memory module assessed visual memory. The Design Memory module was similar to the Word Memory module. In this module, participants memorized 12 target designs at the beginning of the test which are presented along with 12 foil designs at the end of the test battery.

The X's and O's module measured visual memory, visual motor speed and reaction time. In the X's and O's module, participants were presented a screen of X's and O's and asked to memorize their placement. Three X's or O's were yellow while the remainder are black. The X's and O's module then presented a distractor task. During the X's and O's distractor task, participants were primed to associate a target shape (i.e., a red circle and a blue square) with a corresponding letter (e.g., N and F) by keying in that

letter when a target shape was presented. Following the distractor task, participants indicate which X's or O's were previously yellow.

The Symbol Match module assessed verbal memory and reaction time. In the Symbol Match module, participants first practiced pairing distinct symbols with numbers one through nine with a guide. Participants then repeated this task without a guide.

The Color Match module assessed reaction time. During the Color Match module, participants were shown a word associated with a color written in capital letters (i.e., RED, GREEN, BLUE). These words were written in color consistent (e.g., RED written in red) or color inconsistent (e.g., RED written in green) text. Participants were presented with one word at a time, and were instructed to click if the word was written in color consistent text.

The Three Letters module measured verbal memory as well as visual motor speed. In the Three Letters module, participants were shown a 5x5 grid with 25 randomized quadrants labeled one through 25. Participants were required to select quadrants in descending order. Three consonants were then presented, interrupting the grid task. The grid then reappears and participants continued the grid task for 18 seconds. Following this, participants were prompted to key in the three consonants that appeared during the grid task (ImPACT Technical Manual, 2016).

Participants

Subject data was obtained with permission from the NCPP. The NCPP provides pre and post-concussion ImPACT testing as well as post-concussion management for residents of Humboldt and Del Norte counties in Northern California.

Participants (N = 129) were National Collegiate Athletic Association (NCAA) Division II or club athletes enrolled in an athletic activity at Humboldt State University (HSU) between the years of 2008-2018. All enrolled athletes were required to take the ImPACT test prior to the beginning of the athletic season. Athletes who experienced a sports-related concussion (SRC) during play took the ImPACT test 24-72 hours after injury. For athletes who completed multiple pre-season ImPACT tests, the most recent score was used. Male and female participants aged 18 and over were included in the analysis. Participants analyzed sustained a single SRC and reported no prior history of concussion. Participants with complete pre and post-SRC ImPACT scores were included in the current study.

Exclusion criteria. Individuals with disabilities and/or invalid test scores were excluded from the current study. ImPACT scores may not accurately reflect reserve for individuals with disabilities, including Attention Deficit Disorder (ADD)/hyperactivity, dyslexia, autism, anxiety, epilepsy/seizure, depression and/or history of substance/alcohol abuse (Covassin et al., 2012; ImPACT Technical Manual, 2016; Yang, Peek-Asa, Covassin, & Torner, 2015; Elbin et al., 2013). For this reason, only individuals without disabilities were included in the analysis. In addition, individuals whose ImPACT scores

were invalid due to intentional underperformance were not included in the analysis. The ImPACT includes covert mechanisms intended to identify individuals who intentionally underperform on the test.

Procedures

Participants completed the pre and post-SRC ImPACT test batteries on HSU's campus. The ImPACT test battery was self-administered. However, in order to standardize administration, trained examiners were present in order to ensure the test is completed properly. Tests were administered indoors in a quiet environment. Prior to the test, participants were told to read all instructions carefully and perform their best at a semi-isolated computer terminal. All responses were recorded via computer and stored on the ImPACT company's data server. The ImPACT test battery was administered in the following sequence: demographic information, the Post-Concussion Symptom Scale (PCSS), the Word Memory module, the Design Memory module, the X's and O's module, the Symbol Match module, the Color Match module, and the Three Letters module.

Results

Data Analysis

Data was received from the North Coast Concussion Program (NCCP) via Microsoft Excel, version 15.37. The raw data received used unique participant IDs in order to protect the anonymity of participants in the current study. All data were cleaned and analyzed using R (R Core Team, 2018). Data were first cleaned according to exclusion criteria prior to analyses.

Mixed-effects models for interactions. Mixed-effect models were utilized in order to test both hypotheses. The mixed-effect models were used to predict change in the dependent variable based on both between-subjects and within-subjects fixed predictor variables while considering random effects. The random effect of participant ID was included for all mixed-effects models, as the data used to test both hypotheses included multiple observations of the same participant. It was assumed that scores attained by the same participants were non-independent. Therefore, variance due to differences in individual participant's performance was addressed. An interaction between predictor variables was expected for both hypotheses. In order to assess the fitness of the mixed-effects models which included interaction terms, likelihood ratio tests were used.

Likelihood ratio comparison tests. Likelihood ratio tests were used to compare the fitness of different possible models. All models used included participant ID as a random effect. As the interaction models were of interest for all hypotheses, the

significance of the interaction in the relevant model was observed first. If the interaction was shown to be insignificant, reduced models were constructed and compared in order to find the most likely model. Null models were also used in order to determine the fitness of the most likely model. The null models used reflected the null hypothesis that the predictor variables had no relationship with the dependent variable. The null model used in both hypotheses included the random effect of participant ID as the sole predictor variable.

ANOVAs were used to compare the likelihood of a reduced model should the interaction model show an insignificant interaction effect. ANOVAs were also used to compare the most likely model to the relevant null model. If the interaction term was shown to be insignificant, then the interaction model would be compared to the first reduced model. The first reduced model included both between and within-subjects predictor variables, but did not include an interaction term. If no significant difference between the interaction model and the first reduced model was found, it was concluded that the first reduced model was more the likely model. The first reduced model was then examined. If a significant effect for only one predictor variable was found in the first reduced model, then the first reduced model was compared to a second reduced model which included only the significant predictor variable. If no significant difference between the first reduced model and the second reduced model was found, it was concluded that the second reduced model was more likely. The model which was shown to be the most likely was then then compared to the relevant null model in order to determine the most likely model's fitness. If the most likely model differed significantly

from the null model, then that model was considered a good fit and was used to draw conclusions for the relevant hypothesis. Simple effect models were used to address the effect of a single level within the predictor variable of interest if the interaction model displayed a significant interaction and was a good fit.

Simple effects. Simple effects models were used in the presence of a significant interaction for each hypothesis. Simple effects models analyzed the significant interaction by the levels of the predictor variable of interest in order to determine how the interaction differed by level. Mixed-effects models were used to examine simple effects. Simple effects models for each level of the variable of interest were constructed. For each simple effects model, the dependent variable reflected that used in the interaction model. However, the dependent variable for each simple effects model only reflected scores obtained by one level of the predictor variable of interest. A null model for each simple effects model was constructed in order to determine the fitness of the model. Simple effects models that differed from their respective null models were determined to reflect the levels of the predictor variable of interest which drove the interaction.

Assumptions. Skewness and kurtosis for the dependent variables in all hypotheses were examined using a qq plot, density plot, and statistical tests. Diagnoses for deviations from normality were assessed using Kline's parameters. According to Kline (2005), skewness and/or kurtosis can be diagnosed using confidence intervals. If the confidence interval for the skewness and kurtosis value both pass through zero, than the distribution is considered normal. Bootstrapping was used to calculate confidence

intervals, where 1,000 bootstrapped samples were produced in order to estimate the most likely bounds of skewness and kurtosis. Transformations were applied to dependent variables that demonstrated a significant skewness and/or kurtosis. Qq plots, density plots, and statistical tests were then re-ran on transformed variables in order to determine if transformations corrected the dependent variables normality.

Hypothesis 1: Baseline and Post-Concussion Reserve

The first hypothesis held that those with high baseline reserve would demonstrate less change in their reserve after a single SRC compared to those with low baseline reserve. A 2 (baseline reserve) x 2 (test type) mixed-effects model was used in order to address this hypothesis. Baseline reserve was the between-subjects predictor variable with two levels: high and low. Test type was the within-subjects predictor variable with two levels: baseline and post-injury. An interaction between baseline reserve and test type was expected, so that those with high baseline reserve would show less of a decrease in reserve scores between their pre and post-injury tests compared to those with low baseline reserve. Total ImPACT score, which acted as a proxy for reserve, was used as the dependent measure.

Results of the mixed-effects model with interaction terms suggested a significant interaction between baseline reserve and test type (see Table 2), marginal $R^2 = .35$. When compared to the null model, the mixed-effects model with interaction terms was shown to be a good fit, $\chi^2(1) = 93.01$, $p < .001$. Simple-effects follow-up tests were conducted in order to examine the significant interaction. Two simple-effects models were used, each

assessing one level of the baseline reserve predictor variable (high and low). The high reserve simple-effects model was shown to differ significantly from its null model, suggesting a good fit, $\chi^2(1) = 18.05$, $p < .001$. The low reserve simple-effects model did not differ significantly from its null model, suggesting that the model was not a good fit, $\chi^2(1) = 2.41$, $p = .121$. Summaries of the simple-effects models suggested that those with high baseline reserve displayed a greater decrease in reserve scores compared to those with low baseline reserve (see Table 2 and Figure 1). These findings were opposite of the proposed hypothesis.

Baseline reserve classification. Participants were divided into two groups based on baseline ImPACT scores (i.e. high and low reserve). High and low reserve scores were categorized based on the median group ImPACT score, Mdn = 203.58. Individuals with scores above the median were classed as possessing high reserve (n = 69) while those below the median were classed as possessing low reserve (n = 60).

Baseline and post-concussion reserve assumptions. The dependent variable, total ImPACT score, was not normally distributed. Total ImPACT score displayed a skewness of -0.50, 99% CI [-0.75, -0.24] and a kurtosis of -0.44, 99% CI [-0.57, 0.04]. A reflected square root transformation was applied to total ImPACT scores in order to normalize the dependent variable. The total ImPACT score transformation displayed a skewness of -0.25, 99% CI [-0.54, 0.05] and a kurtosis of -0.15, 99% CI [-0.57, 0.48]. The reflected square root transformation reversed the direction of ImPACT total scores, so that low values reflected high scores while high values reflected low scores. The

values reported in Hypothesis 1 and in Table 2 as well as Figure 1 were reversed in order to assist in interpretation, so that the direction of the relationships reported are consistent with the true direction of the dependent variable.

Table 2. *Mixed-Effects Model Predicting Reserve Score from Baseline Reserve and Test Type*

	*b**	Std. Error	CI	z-value
Main effects				
Baseline reserve (low)	-.73	.07	[-.87, -.58]	-10.13***
Test type (post-injury)	-.26	.05	[-.36, -.16]	-4.93***
Interaction effect				
Baseline reserve (low) x test type (post-injury)	.28	.07	[.16, .41]	4.36***
Simple effects				
Baseline reserve (high)	-.28	.06	[-.40, -.16]	-4.51***
Baseline reserve (low)	.29	.07	[-.25, .03]	1.55***
Random effect	σ^2	τ_{00}	ICC	
Subject ID	1.37	1.01	.42	

Note. *p < .05, ** p < .01, ***p < .001.

Model = reserve score ~ (baseline reserve x test type) + (1 | subject ID). High baseline reserves were used as the reference level for baseline reserve. Baseline tests were used as the reference level for test type. A reflected square root transformation was applied to reserve scores. *b**, std. error and CI values were standardized. CI = 95% confidence interval around *b**. σ2 = within-subjects variance, τ00 = between-subjects variance, ICC = intra-class correlation.

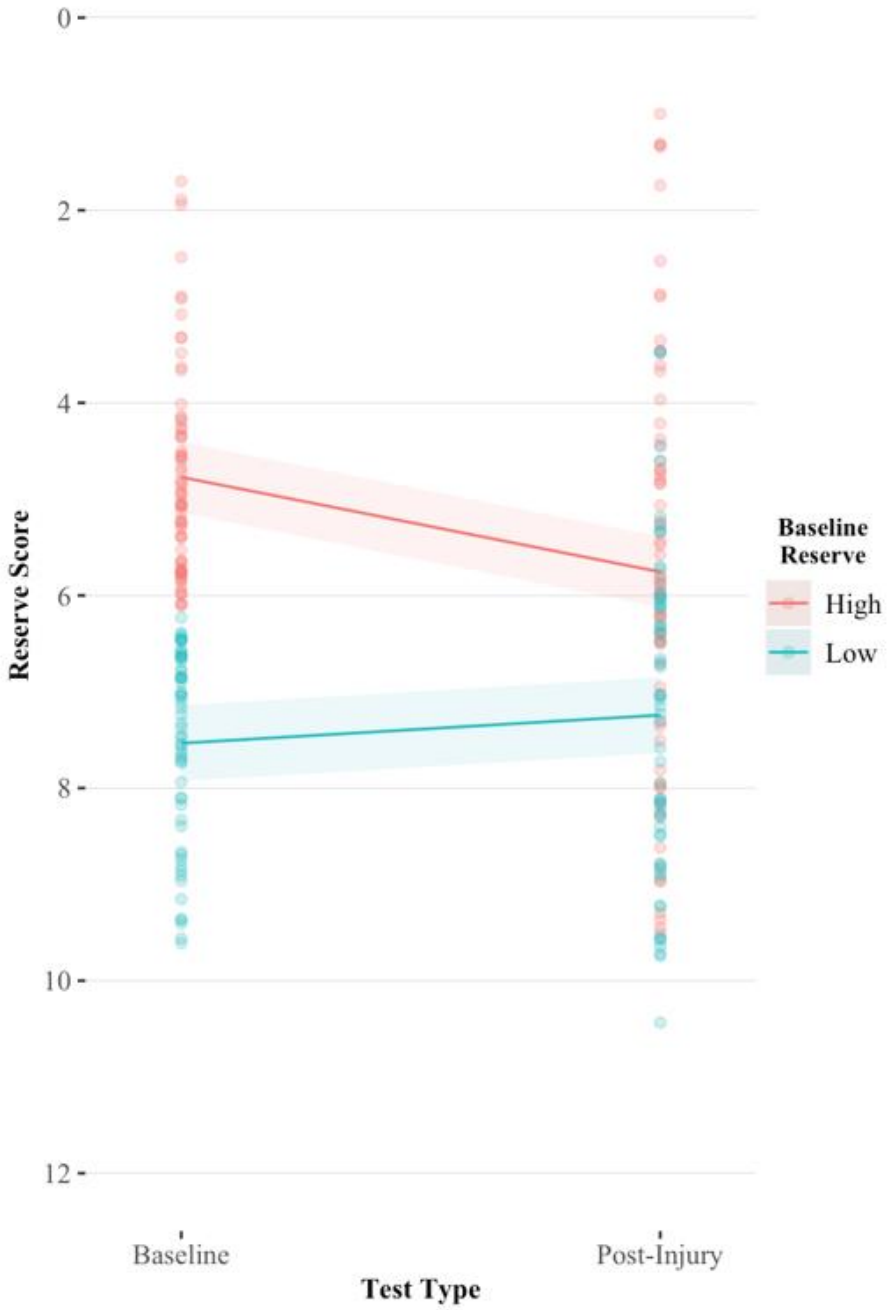

Figure 1. *Reserve score by baseline reserve and test type.* A reflected square root transformation was applied. Model = reserve score ~ (baseline reserve x test type) + (1 | subject ID). Smaller values on the y-axis represent larger scores. Shaded area around slope represents standard error.

Follow-up analyses. Several supplementary analyses relating to baseline and post-concussion reserve were carried out to further explore the results of the relevant hypothesis. In order to examine the components which contributed to total reserve, change in the composite scores which make up the total ImPACT (reserve) scores were examined. The previously established method of classifying reserve based on baseline ImPACT score was used. Finally, an additional method of reserve classification based on the distribution of ImPACT scores was explored.

Verbal memory composite score change. Verbal memory composite score change based on baseline reserve classification and test type was examined. For the interaction model, verbal memory composite score acted as the dependent variable while baseline reserve classification and test type acted as the predictor variables. Subject ID was included as a random effect. Results of the mixed-effects model with the interaction terms suggested a significant interaction between baseline reserve and test type for verbal memory scores (see Table 3), marginal R2 = .17. When compared to the null model, the mixed-effects model with interaction terms was shown to be a good fit, $\chi2(1) = 40.28$, $p < .001$ Simple-effects follow-up tests were conducted in order to examine the significant interaction for verbal memory scores. Two simple-effects models were used, each assessing one level of the baseline reserve variable (high and low). The high reserve simple-effects model was shown to differ significantly from its null model, suggesting a good fit $\chi2(1) = 6.38$, $p = .012$. The low reserve simple-effects model did not differ significantly from its null model, suggesting that the model was not a good fit $\chi2(1) = 1.88$, $p = .170$. Summaries of the simple-effects models suggested that those with high

baseline reserve displayed a greater decrease in verbal memory scores compared to those with low baseline reserve (see Table 3 and Figure 2).

Verbal memory composite score assumptions. Verbal memory composite scores were not normally distributed. The dependent variable, verbal memory composite score, displayed a skewness of -0.81, 99% CI [-1.19, -0.51] and a kurtosis of 0.24, 99% CI [-0.44, 1.37]. The verbal memory composite score variable was normalized using a reflected square root transformation, fixing the negative skew. The verbal memory composite score transformation displayed a skewness of -0.02, 99% CI [-0.23, 0.25] and a kurtosis of -0.49, 99% CI [-0.83, 0.03]. The kurtosis of the verbal memory composite score increased following the application of a reflected square root transformation, however, the kurtosis still met normality assumptions. The reflected square root transformation reversed the direction of verbal memory composite scores. The values reported in this additional analysis and in Table 3 as well as in Figure 2 were reversed in order to assist in interpretation.

Table 3. *Mixed-Effects Model Predicting Verbal Memory Score from Baseline Reserve and Test Type*

	*b**	Std. Error	CI	z-value
Main effects				
Baseline reserve (low)	-.52	.08	[-.68, -.36]	-6.40***
Test type (post-injury)	-.18	.06	[-.31, -.06]	-2.83***
Interaction effect				
Baseline reserve (low) x test type (post-injury)	.22	.08	[.07, .38]	2.80**
Simple effects				
Baseline reserve (high)	-.19	.07	[-.33, -.04]	-2.57***
Baseline reserve (low)	.10	.07	[-.04, .23]	1.37**
Random effect	σ^2	τ_{00}	ICC	
Subject ID	1.11	0.50	.31	

Note. *$p <$ .05, ** $p <$ .01, ***$p <$ .001.

Model = verbal memory score ~ (baseline reserve x test type) + (1 | subject ID). A reflected square root transformation was applied to verbal memory scores. *b**, std. error and CI values were standardized. CI = 95% confidence interval around *b**. σ2 = within-subjects variance, τ00 = between-subjects variance, ICC = intra-class correlation.

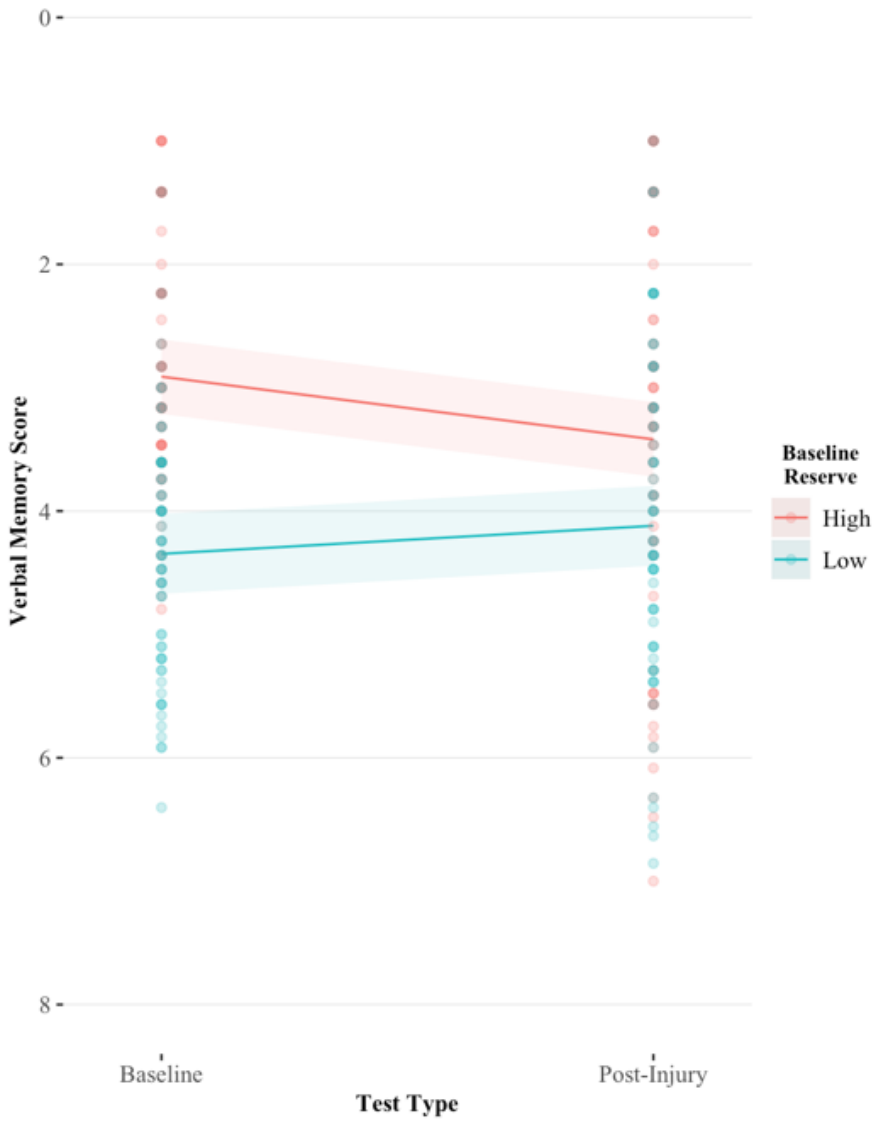

Figure 2. *Verbal memory score by baseline reserve and test type* . A reflected square root transformation was applied. Model = verbal memory score ~ (baseline reserve x test type) + (1 | subject ID). Smaller values on the y-axis represent larger scores. Shaded area around slope represents standard error.

Visual memory composite score change. Visual memory composite score change based on baseline reserve classification and test type was examined. Visual memory composite score acted as the dependent variable while baseline reserve classification and test type acted as the predictor variables in the interaction model. Subject ID was included as a random effect. The mixed-effects model with the interaction terms suggested a significant interaction between baseline reserve and test type for visual memory scores (see Table 4), marginal R2 = .29. The mixed-effects model with interaction terms was shown to be a good fit when compared to the null model, $\chi 2(1) = 80.15$, $p < .001$. Simple-effects follow-up tests were conducted so that the significant interaction for visual memory composite scores could be examined. Each level of the baseline reserve variable (high and low) was examined using two simple-effects models. The high reserve simple-effects model was shown to be a good fit compared to its null model, $\chi 2(1) = 26.64$, $p < .001$. The low reserve simple-effects model did not significantly from its null model, suggesting that the model was not a good fit $\chi 2(1) = 0.23$, $p = .635$. Summaries of the simple-effects models suggested that those with high baseline reserve displayed a greater decrease in visual memory composite scores compared to those with low baseline reserve (see Table 4 and Figure 3).

Table 4. *Mixed-Effects Model Predicting Visual Memory Score from Baseline Reserve and Test Type*

	*b**	Std. Error	CI	z-value
Main effects				
Baseline reserve (low)	-.67	.07	[-.81, -.52]	-8.93***
Test type (post-injury)	-.31	.06	[-.43 -.20]	-5.36***
Interaction effect				
Baseline reserve (low) x test type (post-injury)	.29	.07	[.15, .43]	4.02***
Simple effects				
Baseline reserve (high)	.37	.06	[.24, .49]	5.66***
Baseline reserve (low)	-.04	.07	[-.18, .11]	-0.47****
Random effect	σ^2	τ_{00}	ICC	
Subject ID	77.21	40.09	.34	

Note. *p < .05, ** p < .01, ***p < .001.
Model = visual memory score ~ (baseline reserve x test type) + (1 | subject ID). *b**, std. error and CI values were standardized. CI = 95% confidence interval around *b**. σ2 = within-subjects variance, τ00 = between-subjects variance, ICC = intra-class correlation.

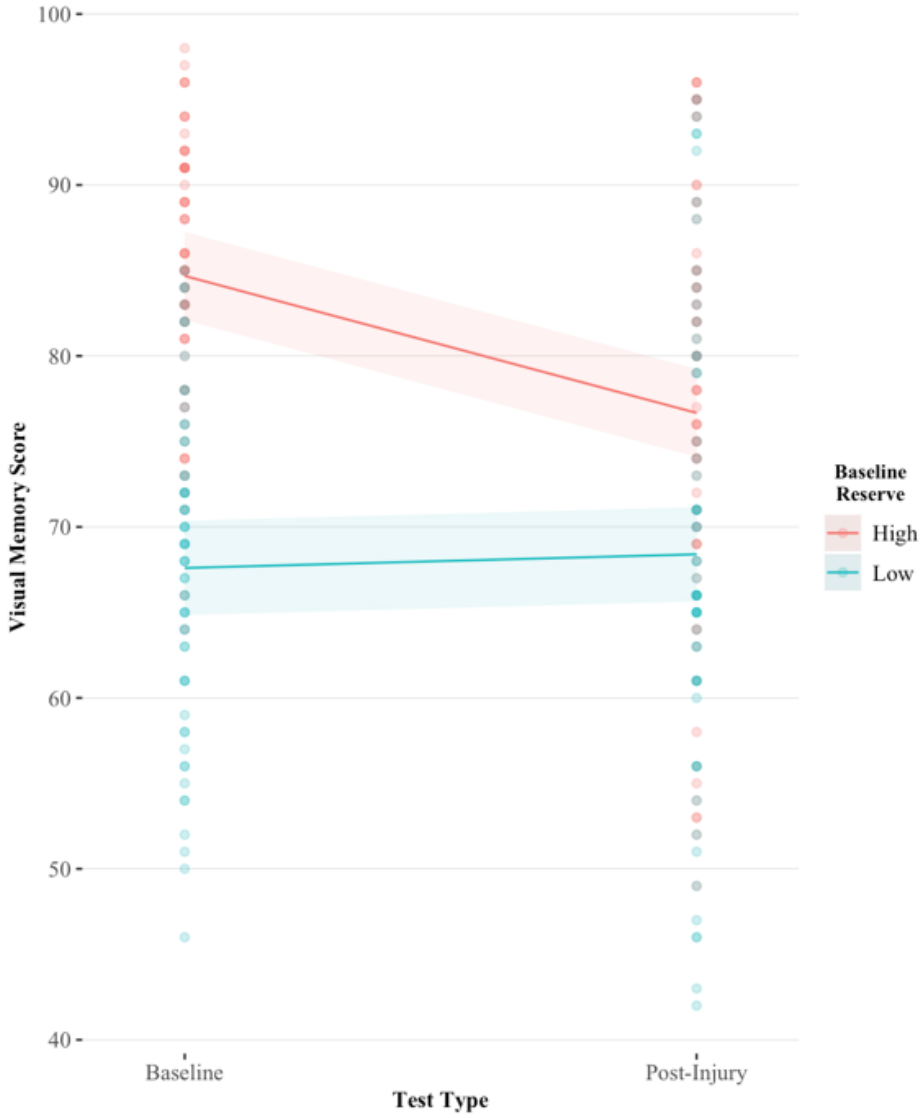

Figure 3. *Visual memory score by baseline reserve and test type*. Model = visual memory score ~ (baseline reserve x test type) + (1 | subject ID). Shaded area around slope represents standard error.

Visual memory composite score assumptions. The dependent variable, visual memory composite score, was not normally distributed. Visual memory composite scores displayed a skewness of -0.28, 99% CI [-0.54, -0.02] and a kurtosis of 0.62, 99% CI [-0.92, -0.11]. However, the application of reflected square root, log and inverse transformations did not improve skewness or kurtosis. Therefore, untransformed visual memory composite scores were used.

Visual motor speed composite score change. Visual motor speed composite score change based on baseline reserve classification and test type was also examined. The dependent variable was visual motor speed composite score, while baseline reserve classification and test type acted as the predictor variables. Subject ID was included as a random effect. The interaction model found no significant interaction between baseline reserve classification and test type for visual motor speed scores (see Table 5). Likelihood ratio tests demonstrated that the second reduced mixed-effects model was the most likely model. The first reduced model, which included both baseline reserve and test type as predictor variables but did not include an interaction term, did not differ significantly from the interaction model, $\chi2(1) = 3.81$, $p = .051$. The first reduced model suggested a main effect for baseline reserve, but no main effect for test type. Therefore, a second reduced model was constructed with baseline reserve acting as the predictor variable. The second reduced model did not differ significantly from the first reduced model, $\chi2(1) = 0.40$, $p = .536$. The second reduced model was shown to differ significantly from the null model, $\chi2(1) = 33.14$, $p < .001$. The second reduced model suggested that those with high baseline reserve scored higher on visual motor speed

scores compared to those with low baseline reserve, b* = -.43, SE = .07, z = -6.10, p < .001, 95% CI around b* = [-.57, -.29]. These main effects were also found in the interaction model (see Table 5). The mixed-effects model with the interaction term suggested that visual motor speed scores did not drop following a single SRC (see Table 5 and Figure 4). As no significant interaction was found for visual motor speed scores, simple-effects analyses were not conducted.

Visual motor speed composite score assumptions. Visual motor speed scores were normally distributed. The visual motor speed score variable displayed a skewness of -0.25, 99% CI [-0.55, 0.01] and a kurtosis of -0.45, 99% CI [-0.85, 0.34]. Thus, no transformations were applied to the visual motor speed composite score variables.

Table 5. *Mixed-Effects Model Predicting Visual Motor Speed Score from Baseline Reserve and Test Type*

	*b**	Std. Error	CI	z-value
Main effects				
Baseline reserve (low)	-.50	.08	[-.66, -.35]	-6.31***
Test type (post-injury)	-.09	.05	[-.19, .01]	-1.80****
Interaction effect				
Baseline reserve (low) x test type (post-injury)	.12	.06	[.00, .24]	1.95****
Random effect	σ^2	τ_{00}	ICC	
Subject ID	14.17	19.07	.57	

Note. *$p <$ .05, ** $p <$ .01, ***$p <$ .001.

Model = visual motor speed score ~ (baseline reserve x test type) + (1 | subject ID). *b**, standard error and CI values were standardized. CI = 95% confidence interval around *b**. σ2 = within-subjects variance, τ00 = between-subjects variance, ICC = intra-class correlation.

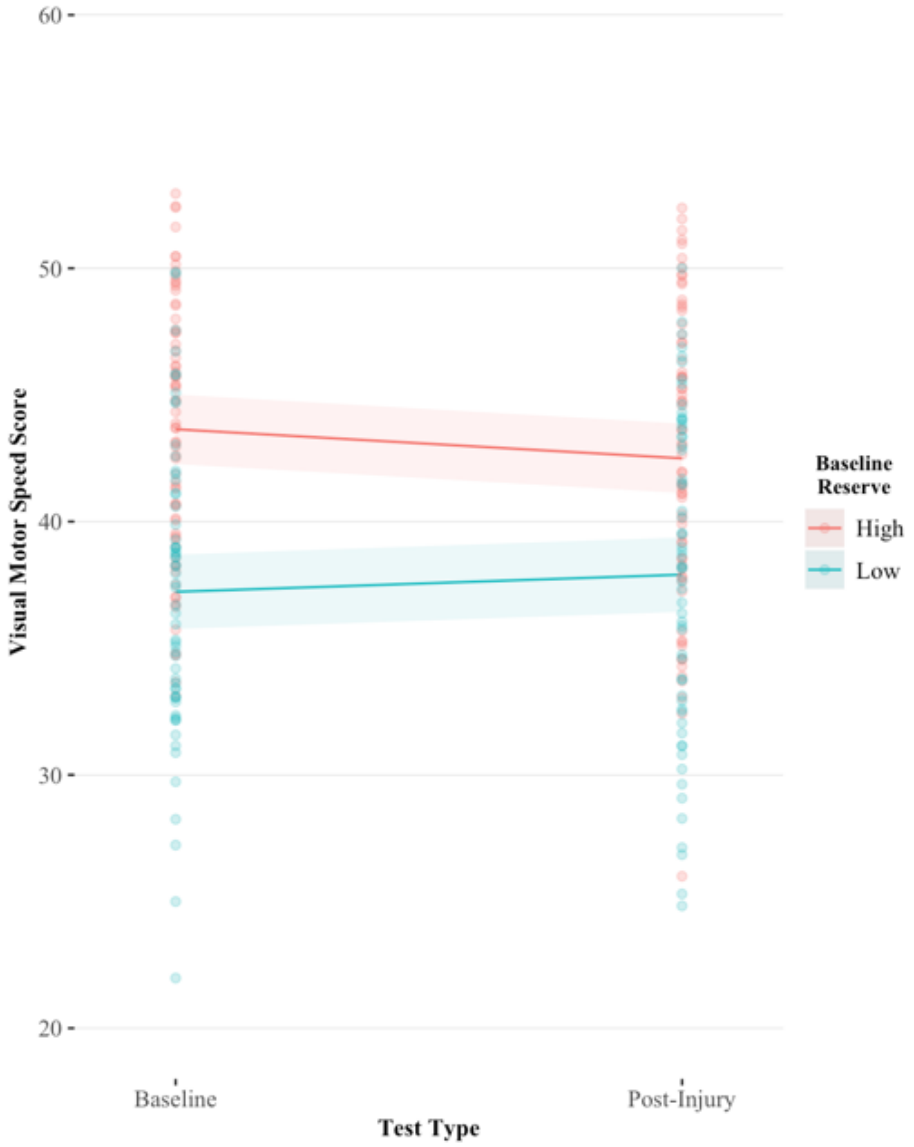

Figure 4. *Visual motor speed score by baseline reserve and test type*. Model = visual motor speed score ~ (baseline reserve x test type) + (1 | subject ID). Shaded area around slope represents standard error.

Reaction time composite score change. Finally, reaction time composite score change based on baseline reserve classification and test type was examined. The dependent variable was reaction time composite score, while baseline reserve classification and test type acted as the predictor variables. Subject ID was included as a random effect. Results from the interaction model suggested no interaction between baseline reserve and test type for reaction time scores (see Table 6). Likelihood ratio comparison tests showed that the first reduced model was the most likely model for reaction time score change. The first reduced model did not differ significantly from the interaction model, $\chi 2(1) = 2.35$, $p = .126$. The first reduced model which did not include the interaction terms was shown to significantly differ from the null model, suggesting a good fit $\chi 2(1) = 34.15$, $p < .001$. A main effect for baseline reserve was found in the first reduced model, so that those with high baseline reserve scored high on reaction time composite scores compared to those with low baseline reserve, b* = -.31, SE = .07, z = -4.38, p < .001, 95% CI around b* = [-.45, -.17]. A main effect for test type was also found in the first reduced model, so that baseline reaction time composite scores were higher than post-injury scores, b* = -.17, SE = .04, z = -4.11, p < .001, 95% CI around b* = [-.25, -.09], marginal R2 = .13. The interaction model also suggested these main effects (see Table 6 and Figure 5). No simple-effects analyses were conducted as the interaction was not significant.

Table 6. *Mixed-Effects Model Predicting Reaction Time Scores from Baseline Reserve and Test Type*

	*b**	Std. Error	CI	z-value
Main effects				
Baseline reserve (low)	-.38	.08	[-.54, -.21]	-4.56***
Test type (post-injury)	-.23	.06	[-.34, -.12]	-4.06***
Interaction effect				
Baseline reserve (low) x test type (post-injury)	.11	.01	[-.03, .24]	1.53
Random effect	σ^2	τ_{00}	ICC	
Subject ID	0.00	0.00	.50	

Note. *$p <$ .05, ** $p <$ .01, ***$p <$ .001.
Model = reaction time score ~ (baseline reserve x test type) + (1 | subject ID). A square root transformation was applied to reaction time scores. *b**, std. error and CI values were standardized. CI = 95% confidence interval around *b**. σ2 = within-subjects variance, τ00 = between-subjects variance, ICC = intra-class correlation.

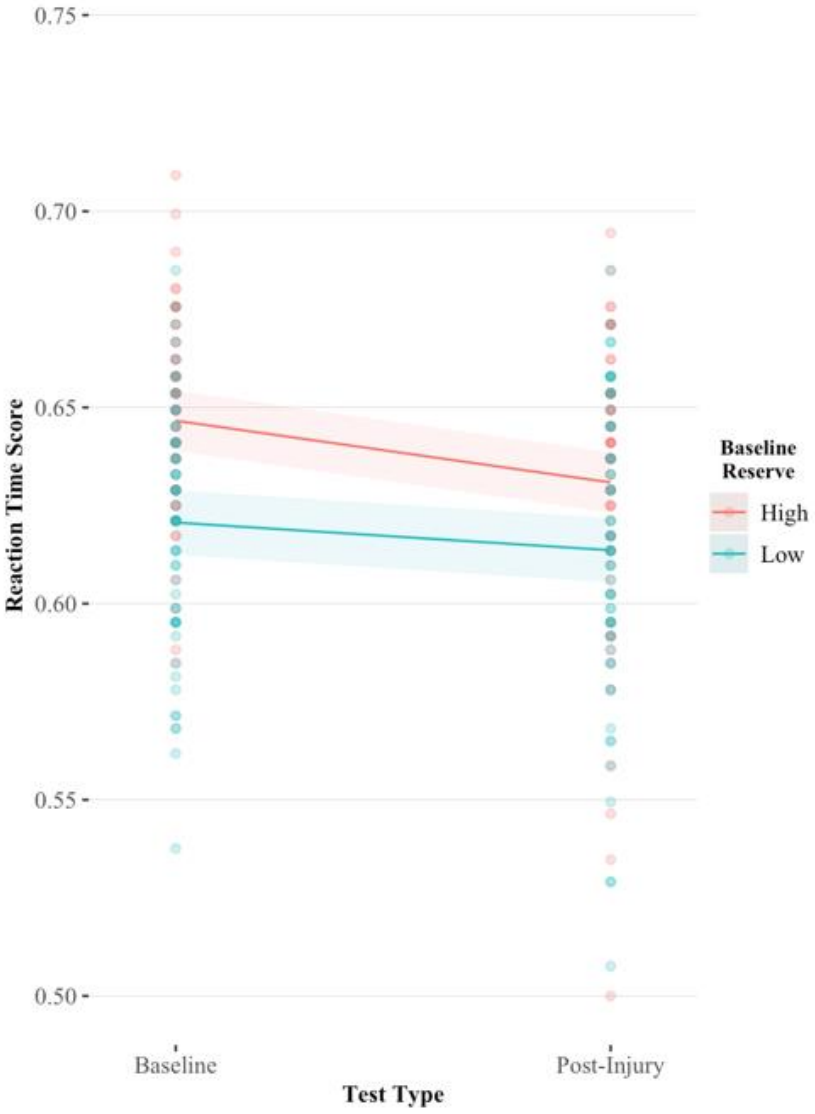

Figure 5. *Reaction time score by baseline reserve and test type*. An inverse transformation was applied. Model = reaction time score ~ (baseline reserve x test type) + (1 | subject ID). Shaded area around slope represents standard error.

Reaction time composite score assumptions. Reaction time composite scores were not normally distributed, displaying a skewness of 1.23, 99% CI [0.74, 1.88] and a kurtosis of 2.42, 99% CI [0.54, 4.77]. Square root, log and inverse transformations were applied to reaction time composite scores. Although no transformations normalized the skewness of the reaction time composite score variable, the inverse transformation improved both skewness and kurtosis. When the inverse transformation was applied to reaction time composite scores, the variable displayed a skewness of -0.80, 99% CI [-1.28, -0.36] and a kurtosis of 1.01, 99% CI [-0.10, 2.78].

Reserve classification. Due to the first hypothesis not being supported using the initial method of classing reserve, a second method of classing reserve was also tested. Using this method, individuals with baseline reserve above one standard deviation of the median were classed as possessing high reserve while individuals with baseline reserve below one standard deviation of the median were classed as possessing low reserve. Those with baselines reserve within one standard deviation of the median were removed. However, this second method of classifying baseline reserve did not change the results found in Hypothesis 1. Therefore, the method of classifying baseline reserve according to the group median was used.

Hypothesis 2: Sex and Symptom Cluster Interaction

Prior to analyzing Hypotheses 2, 2b, and 2c, symptom cluster scores were isolated and converted to z-scores. Items containing questions pertaining to each symptom cluster were identified based on prior research (Covassin et al., 2012; Lau et al., 2011). Scores

on each item belonging to a cluster were summed, creating four symptom cluster scores. As the items belonging to each symptom cluster varied (see Table 1), summed scores belonging to each symptom cluster were converted to z-scores. Summed scores belonging to each symptom cluster were then transposed into a single variable, symptom cluster score, which was used as the dependent measure in Hypotheses 2, 2b and 2c. The symptom cluster to which each score belonged was also transposed into a single variable, symptom cluster. Symptom cluster acted as the within-subjects predictor variable for the relevant hypotheses. Transposing the data resulted in multiple observations from the same individual, so a mixed-effects model was used.

The second hypothesis proposed an interaction between sex and post-SRC symptom cluster. A 2 (sex) x 4 (symptom cluster) mixed-effects model was used in order to test this hypothesis. Sex was the between-subjects predictor variable with two levels: male and female. Symptom cluster was the within-subjects predictor variable with four levels: somatic/migraine, cognitive, emotional and sleep symptoms. An interaction between sex and symptom type was expected, so that females would score high on symptoms belonging to cognitive and emotional clusters compared to males. No significant difference in somatic/migraine and sleep cluster scores was expected between sexes. Symptom cluster score was used as the dependent measure.

Results from the interaction model suggested no interaction between sex and symptom cluster for symptom cluster scores (see Table 7). Likelihood ratio comparison tests showed that the second reduced model was the most likely model for assessing the relevant hypothesis. The first reduced model, which included both sex and symptom

cluster as predictor variables but did not include an interaction term, did not significantly differ from the interaction model, $\chi^2(1) = 0.26$, $p = .957$. The first reduced mixed-effects model suggested a main effect for sex, but no main effect for symptom cluster. Therefore, a second reduced model was constructed with sex acting as the predictor variable. The second reduced model did not differ significantly from the first reduced model, $\chi^2(1) = 3.13$, $p = .372$. The second reduced model was shown to significantly differ from the null model, suggesting a good fit, $\chi^2(1) = 5.28$, $p = .021$. A main effect for sex was also shown in the interaction model (see Table 7 and Figure 6). As a significant interaction was not found, no simple-effects follow up tests were conducted. These results did not support Hypothesis 2.

Hypothesis 2b: Main effect of sex. Hypothesis 2b held that a main effect of sex would be present, so that females would report higher symptom cluster scores compared to males. The second reduced model was shown to be the more likely model. The second reduced model omitted symptom cluster and included sex as the predictor variable. The second reduced model suggested that males reported lower symptom cluster scores compared to females, b* = -.17, SE = .07, z = -2.30, p = .021, 95% CI around b* = [-.31, -.03], marginal R2 = .03. These findings supported hypothesis 2b.

Table 7. *Mixed-Effects Model Predicting Symptom Score from Sex and Symptom Type*

	*b**	Std. Error	CI	z-value
Main effects				
Symptom type (emotional)	.06	.05	[-.03, .15]	1.27
Symptom type (physical)	.01	.05	[-.08, .10]	0.22
Symptom type (sleep)	.03	.05	[-.06, .12]	0.65
Sex (male)	-.15	.09	[-.32, -.03]	-2.30*
Interaction effect				
Sex (male) x symptom type (emotional)	-.01	.05	[-.11, .09]	-0.25
Sex (male) x symptom type (physical)	-.02	.05	[-.12, .08]	-0.39
Sex (male) x symptom type (sleep)	-.02	.05	[-.12, .08]	-0.48

Random effect	σ^2	τ_{00}	ICC
Subject ID	0.11	0.16	.59

Note. *$p <$ .05, ** $p <$ .01, ***$p <$ .001.

Model = symptom score ~ (sex x symptom type) + (1 | subject ID). Cognitive symptoms were used as the reference level for symptom type. Females were used as the reference level for sex. A z-score and square root transformations were applied to symptom scores. *b**, std. error and CI values were standardized. CI = 95% confidence interval around *b**. σ^2 = within-subjects variance, τ_{00} = between-subjects variance, ICC = intra-class correlation.

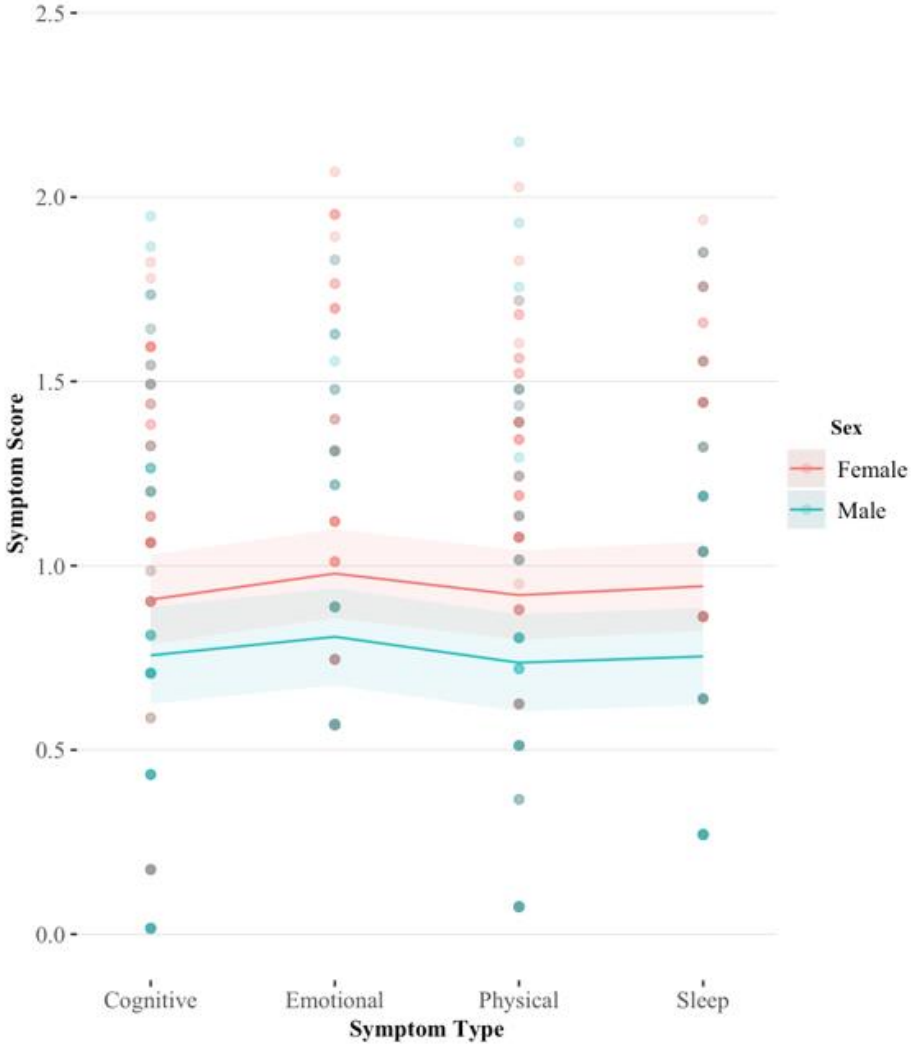

Figure 6. *Symptom score by sex and symptom type*. A z-score and square root transformation was applied. Model = symptom score ~ (sex x symptom type) + (1 | subject ID). Shaded area around slope represents standard error.

Hypothesis 2c: Main effect of symptom cluster. Hypothesis 2c held that a main effect of symptom cluster would be present, so that symptom cluster scores would be high for cognitive symptoms than for somatic/migraine, emotional and sleep symptoms. No significant differences in symptom scores for somatic/migraine, emotional and sleep symptoms were expected. The results of the likelihood ratio comparison tests suggested that the addition of cluster type as a predictor variable did not influence symptom cluster scores. In addition, the mixed-effect model which included an interaction between sex and symptom cluster suggested no main effect for symptom cluster (see Table 7). Thus, Hypothesis 2c was not supported.

Sex and symptom cluster assumptions. Symptom cluster scores were not normally distributed. The dependent variable for hypotheses 2, 2b and 2c displayed a skewness of 1.08, 99% CI [0.87, 1.35] and a kurtosis of 0.45, 99% CI [-0.18, 1.50]. Square root, log and inverse transformations were applied to the symptom cluster scores, but no transformations normalized the variable. However, a square root transformation improved the variable's positive skewness. When a square root transformation was applied to symptom cluster scores, the variable displayed a skewness of 0.22, 99% CI [0.70, 0.41] and a kurtosis of -0.08, 99% CI [-0.06, 0.59].

Discussion

Reserve and symptomatology are both crucial components of everyday functioning that are affected by a brain injury, including a single concussion. The current study aimed to explore the role of baseline reserve and symptomatology in determining outcome following a single SRC. Baseline reserve was compared to post-SRC reserve in order to identify how baseline reserve influenced post-SRC outcome. Symptomatology following a single SRC was examined by analyzing somatic/migraine, cognitive, emotional and sleep symptoms and their relationship with participant's sex. The ImPACT test battery was used as an estimate of reserve, and the PCSS was used to examine symptomatology. The results of the current study suggest a counterintuitive and nuanced relationship between baseline reserve and post-SRC reserve. Results also suggested that sex contributes to symptomatology following a single SRC, however, no distinction in the types of symptoms reported amongst participants was found.

Hypothesis 1: Baseline and Post-Concussion Reserve

The first hypothesis explored the role of baseline reserve on post-SRC reserve following a single SRC. Total ImPACT scores were used as proxies for reserve. It was hypothesized that individuals with high baseline reserve would demonstrate less change in reserve compared to those with low baseline reserve, but this hypothesis was not supported. Results indicated that those with low baseline reserve demonstrated significantly less change in reserve scores following a single SRC compared to those with

high baseline reserve scores, which was the opposite of what was predicted. This relationship persisted amongst verbal and visual memory scores. However, those with high and low baseline reserve did not differ in visual motor speed and reaction time scores following a single SRC. In addition, when reserve was classified by participants who scored in the first and third quartiles as having low and high reserve, respectively, this relationship persisted.

High reserve and rates of decline. While these findings were not consistent with the reserve theory as a whole, some research supports the notion that high premorbid reserve is linked to poor clinical outcome following the onset of neurodegeneration. Stern & Tang (1995) found that individuals with high reserve prior to the onset of Alzheimer's demonstrated a more rapid decline and a higher mortality rate compared to those with low reserve. Stern & Tang (1995) suggested that those with high premorbid reserve may be more sensitive to changes in reserve following the onset of neurodegeneration compared to those with low premorbid reserve. This finding was echoed in similar studies (Scarmeas, Albert, Manly, & Stern, 2005; Stern, Albert, Tang, & Tsai, 1999; Teri, Mccurry, Edland, Kukull, & Larson, 1995). A subsequent study also found that, in addition to high premorbid reserve, participation in leisure activities contributed the onset of neurodegeneration (Helzner, Scarmeas, Cosentino, Portet, & Stern, 2007). Two of these studies found that those with high premorbid reserve displayed a rapid decline in reserve prior to a diagnosis of Alzheimer's disease, suggesting that those with high premorbid reserve are susceptible to a sudden decrease in reserve when

neurodegeneration is present. In contrast, those with low premorbid reserve displayed a steady decline in reserve before the clinical threshold for Alzheimer's disease was met (Helzner et al., 2007; Scarmeas et al., 2005).

High reserve and PCS. It has been suggested that those with high premorbid reserve are more likely to be diagnosed with post concussion syndrome (PCS) following a TBI (Meares et al., 2008). PCS is associated with fatigue, memory problems, and difficulty concentrating (World Health Organization, 1992). These types of symptoms are noted in the cognitive cluster of the PCSS. Although the current study found that those with low baseline reserve reported less cognitive symptoms than those with high baseline reserve following a single brain injury, these results were not significant. However, the legitimacy of PCS as a diagnosis is controversial. The definition of PCS is broadly defined, and there is no universally accepted clinical tool used to diagnose PCS (McCrea, 2008; Snell, Macleod, & Anderson, 2016). Though PCS was recognised in the fourth revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM), it was removed in the fifth revision (American Psychiatric Association, 1994; American Psychiatric Association, 2013). Despite these issues, it has been argued that PCS is a complex but legitimate diagnosis that may be influenced by multiple personal factors (Broshek, Marco, & Freeman, 2014). Those with high reserve may be more sensitive to the clinical manifestations of symptoms following a brain injury, and thus better equipped to report them to a clinician. It has been shown that individuals who report more symptoms are more likely to perform poorly on neurocognitive tests following a

brain injury (Fazio, Lovell, Pardini, & Collins, 2007). Although no relationship between reserve and PCSS scores were examined in the current study, the PCSS may lack the sensitivity to detect PCS. No prior research has used the PCSS as a tool for diagnosing PCS.

ImPACT sensitivity. Floor and ceiling effects may have contributed to the finding that those with high baseline reserve demonstrated a larger drop in reserve scores compared to those with low baseline reserve. The ImPACT may have high test ceilings than other clinical measures. High test ceilings permit those with high baseline reserve to display greater changes on the measure used to estimate reserve (Stern, 2013). If the ImPACT has a higher ceiling than other proxies of reserve, then the ImPACT should show greater sensitivity in detecting reserve change for high-reserve individuals. The ImPACT may be unable to adequately detect reserve changes in those with low reserve.

Those with low baseline reserve may have required a lower test ceiling in order to detect changes in their reserve scores. Those with low baseline reserve scored at the bottom threshold of the ImPACT during both pre and post-testing. Those with low reserve would be unable to penetrate this bottom threshold further following an SRC in the presence of a high test ceiling, and results would indicate a lack of change in reserve as a result (Giza & Choe, 2015). In contrast, those with high baseline reserve scored far above the bottom threshold than their counterparts, allowing room for a decrease in ImPACT scores that appear substantial in the presence of a high test ceiling. Results indicated that despite displaying a greater change in ImPACT scores, the mean post-SRC

scores of individuals with high reserve would still classified them as possessing high reserve according to the criteria used. Although those with low baseline reserve showed less change in reserve following a single SRC, their post-SRC scores still classified them as possessing low reserve. However, administrators of the ImPACT interpret impairment relativistically.

Follow-up analyses. Follow-up analyses examined the relationship between baseline reserve and change in the four composite scores which make up total ImPACT scores. Results suggested that those with high baseline reserve demonstrated a greater decline in verbal and visual memory composite scores following a single SRC compared to those with low baseline reserve. Those with high and low baseline reserve did not differ in their rates of decline for visual motor speed and reaction time composite scores. For all participants, scores on verbal memory, visual memory and reaction time decreased following a single SRC. However, visual motor speed scores did not significantly decrease following a single SRC.

Crystallized and fluid intelligence. The follow-up analyses suggested that verbal and visual memory composite scores drove the significant decrease in total reserve scores for those with high baseline reserve found in Hypothesis 1. Verbal and visual memory both represent components of crystallized intelligence (i.e., knowledge acquisition), while visual motor speed and reaction time are components of fluid intelligence (i.e., problem solving abilities). The differences in crystallized and fluid intelligences and their relation to reserve may help explain the current study's findings.

The cognitive investment model suggests that crystallized and fluid intelligence are closely related (Cattell, 1987; Kvist & Gustafsson, 2008; Sheppard & Vernon, 2008). It has been suggested that those with high fluid intelligences tend to acquire high rates of crystallized intelligence, as those with high fluid intelligences are able to attain more factual knowledge as a result of faster processing speeds (Ackerman, 1996). Adhering to this view, it can be speculated that crystallized intelligence is a residual outcome of fluid intelligence. Thus, the cognitive investment model supports the notion that measures fluid intelligence are more appropriate proxies for reserve. The cognitive investment model partially conflicts with the findings of the current study. If high fluid intelligence leads to increases in crystallized intelligence, then it would be expected that those with high baseline reserve would demonstrate a decrease in fluid intelligence analogous to the decrease in crystallized intelligence found in the current study. However, these results could be explained by the possibility of a high test ceiling present in the ImPACT test.

Prior studies have demonstrated the presence of high test ceilings in neurocognitive tests which evaluate crystallized intelligence (Busch et al., 2005; Cardenas et al., 1994; Light & Zelinski, 1983; Williams et al., 1998). Tasks which evaluate crystalized intelligence, including verbal and visual memory, may be more prone to ceiling and floor effects due the nature of their construction. The verbal and visual memory composites assess accuracy while the visual motor speed and reaction time composites depend on measures of time (e.g., duration and latency). Tests of memory accuracy (e.g., crystallized intelligence) can vary greatly in difficulty based on their construction. If the items used to evaluate memory accuracy are too difficult and the

distractor tasks separating the presentation and recall stages of the subtests are too long, then a high test ceiling may be present. However, tests of visual motor speed (i.e., processing speed) and reaction time, which depend on measures of time, may be less prone to manipulation by the creators of the test. Hypothesis 1's findings may be due to artifacts of a high test ceiling in the construction of the verbal and visual memory subtests. If the visual motor speed and reaction time composite scores (i.e., measures of fluid intelligence) are less prone to ceiling and floor effects, they may provide an accurate estimation of reserve change. Previous studies have demonstrated that fluid intelligence is a more appropriate proxy for reserve compared to crystallized intelligence (Barbey et al., 2014; Gray & Thompson, 2004; Habeck et al., 2018; Habeck et al., 2003; Stern, 2009). Prior research has shown no relationship between baseline scores of fluid intelligence and post-injury outcome following a TBI (Green et al., 2008; Greiffenstein & Baker, 2003). When isolating the composite scores of the ImPACT test which measure fluid intelligence, it appears that those with high and low reserve do not differ in their loss of reserve following a single SRC.

Hypotheses 2, 2b & 2c: Sex and Symptom Cluster

Hypothesis 2 predicted that participant's scores on the PCSS would reveal an interaction between sex and post-SRC symptom clusters. It was proposed that females would score higher on symptoms belonging to cognitive and emotional clusters compared to males, while no difference between sexes were expected on somatic/migraine and sleep cluster scores. However, no significant interaction between sex and symptom

cluster was found. Hypothesis 2b posited a main effect for sex, so that females would report more post-concussion symptoms compared to males. Results of the current study supported Hypothesis 2b. Hypothesis 2c stated that a main effect of symptom cluster would be present, so that participants would report more cognitive symptoms than emotional, sleep or somatic/migraine symptoms. Results of the current study did not support Hypothesis 2c, and suggested that all symptom clusters were reported equally amongst participants.

Few studies have examined the method of clustering symptoms by type on the PCSS. Prior studies have all demonstrated a significant interaction between sex and symptom cluster, but the current study did not. Similarly, the absence of a main effect for symptom cluster type cannot be accounted for. The current study found that symptom clusters are reported similarly among participants, while prior studies suggested that symptom clusters are reported differently amongst participants. However, several of these studies, which used the same method of clustering symptoms as the current study, did not examine the normality of symptom scores (Covassin et al., 2012; Lau et al., 2009). In one such study, it was unclear if summed cluster scores were converted to z-scores in order to allow for objective comparison (Lau et al., 2011). Lau et al., 2011 found that somatic/migraine symptoms were reported more than other symptoms, but this result may be inflated due to the amount of items belonging to the somatic/migraine cluster (see Table 1). In addition, Kontos et al., 2012 found that several items on the PCSS were equally represented by multiple clusters, and dropped five items for their analysis. Given

this, examining the PCSS as a whole may be more appropriate than examining the PCSS by cluster.

Previous studies support the finding that females reported more symptoms compared to males (Covassin et al., 2012; Frommer et al., 2011; Gessel et al., 2007; Kontos et al., 2012). Biological differences as well as sociocultural differences may account for the differences in symptom reporting between males and females. From the biological perspective, sex influences symptom reporting differences between males and females. From the sociocultural perspective, gender influences symptom reporting differences between males and females.

Biological differences between sexes contributes in part to differences in symptom reporting. For example, neck strength tends to differ between males and females. Biomechanical forces may impact those with weaker necks (i.e. females) more than those with stronger necks (i.e. males) (Tierney et al., 2008; Gessel et al., 2007; Barnes et al., 1998). This may be why females have been observed to sustain high rates of concussion compared to males in sports like soccer, where participation is relatively equal amongst sexes (Gessel et al., 2007). Hormones may also influence how symptoms are reported. Females who sustained a concussion during their menstrual cycles reported more symptoms compared to females who were not menstruating or taking contraceptives (Brown et al., 2015; Wunderle, Hoeger, Wasserman, & Bazarian, 2014).

Sociocultural influences may also affect how symptoms are reported between sexes. Sociocultural influences, like sports participation and disclosure, may lead to differences in symptom reporting between genders. Males tend to participate more often

in football, which has the highest incidence rate of concussion in high school and collegiate sports alike (Frommer et al., 2011; Gessel et al., 2007). The culture surrounding high-collision sports like football and the normalization of injury may lead males to underreport symptoms following an SRC (Benson, 2017; Jones, 2011). Similarly, males have been shown to participate in more risk-taking behaviors which lead to brain injury compared to females (Finch, McIntosh, & McCrory, 2001; Love, Tepas, Wludyka, & Masnita-Iusan, 2009; Mollayeva et al., 2018). In addition, females may be more likely to express vulnerability compared to males, which could result in females being more likely to report symptoms following an SRC (Kroshus, Baugh, Stein, Austin, & Calzo, 2017; Mollayeva et al., 2018). From the sociocultural perspective, it is gender rather than sex that contributes to differences in symptom reporting. However, biological and sociocultural factors cannot be separated. Both sex and gender likely contribute to differences in symptom reporting between sexes.

Implications

Hypothesis 1: Baseline and post-concussion reserve. Pre and post-SRC scores on the ImPACT test are used to inform return-to-play time. Athletes whose ImPACT scores return to baseline following an SRC and who report no symptoms on the PCSS may be recommended to gradually return-to-play. However, the NCPP also utilizes semi-structured interviews in order to inform return-to-play decisions. Although different recommendations for informing return-to-play decisions based on ImPACT scores have been proposed, the return-to-baseline method remains dominant (Schatz et al., 2006). If

those with low baseline reserve are unable to demonstrate change in their reserve following an injury due to the presence of a high test ceiling in the ImPACT, then these individuals may be prematurely returned to play. Conversely, those with high baseline reserve scores may be required to refrain from activity longer than needed. The change in reserve scores demonstrated by those with high baseline reserve could more accurately represent the actual change in reserve of the sample as a whole. While the ImPACT is not a replacement for clinical diagnosis and administrators are instructed to err on the side of caution, many traumatic brain injuries that appear mild may not raise sufficient alarm if ImPACT results appear satisfactory. The consequence of low-reserve individuals prematurely returning to play following an SRC are potentially devastating. This is especially true when considering the theory of reserve, which holds that those with low baseline reserve are more likely to experience deleterious effects following injury than their high baseline reserve counterparts.

Although several studies suggest that those with high baseline reserve may exhibit more immediate cognitive declines, these studies were conducted on those with Alzheimer's disease (Helzner et al., 2007; Scarmeas et al., 2005). While Alzheimer's disease has a similar neurophysiological and clinical profile than that of traumatic brain injury, their etiologies are distinct, and reserve theory can account for these findings. The onset of Alzheimer's disease is gradual and cannot be linked to specific event, unlike traumatic brain injury. Therefore, an individual may display the neurophysiological markers of the disease before they reach the clinical threshold which diagnoses them with Alzheimer's. In individuals with low reserve, these neurophysiological markers would

manifest themselves into the gradual onset of clinical symptoms until the threshold for a diagnosis of Alzheimer's disease is reached. In individuals with high reserve, these neurophysiological markers would worsen while the individual continues to show no clinical symptoms until a threshold is reached, at which point the neurophysiological markers give way to what appears to be a sudden decline (Scarmeas et al., 2005; Stern, Tang, Denaro, & Mayeux, 1995). In a single traumatic brain injury, neurophysiological markers of disruption occur immediately following injury, and clinical symptoms have been shown to arise 24-72 hours following injury and improve over time (McCrory et al., 2017). When accounting for the relatively acute display of clinical symptoms following a brain injury and the notion that clinical testing is administered in close temporal proximity to a known event, the results of the current study go unexplained.

Only a handful of studies have demonstrated the absence of a relationship between baseline reserve and post-injury outcome (Fuentes, Mckay, & Hay, 2010; Johnstone, Hexum, & Ashkanazi, 1995). No studies to date, aside from the current study, have suggested that high baseline reserve could be detrimental to post-injury reserve changes following a brain injury. Additionally, no studies to date, aside from the current study, have used the ImPACT as a proxy for reserve. If the reserve theory holds true and the findings of reserve changes in the current study are due to the design of the ImPACT, then premature return-to-play decisions based on low-reserve individuals' results would be a major cause for concern.

Follow-up analyses. The follow-up analyses conducted for Hypothesis 1 suggested that measures of fluid intelligence such as visual motor speed (i.e., processing

speed) and reaction time may be less susceptible to floor and ceiling effects. High test ceilings on verbal and visual memory composites may be a product of test construction. These high test ceilings could be avoided by evaluating item difficulty and varying the inclusion of each item based on difficulty. Ho & Yu (2014) suggest that item-level analyses could assist in item selection, which would result in tests producing normalized distributions and quell the presence of ceiling and floor effects. Item-level analysis consists of examining the distribution of scores obtained on a single item, ideally across a variety of populations. The majority of items included in a measure should show a normal distribution, while an even number items showing a positively or negatively skewed distribution should be added if needed. This practice may assist in bolstering the validity of measures of crystallized intelligence such as those which contribute to the verbal and visual memory composite scores in the ImPACT.

In addition, measures of fluid intelligence have been shown to be more valid proxies of reserve compared to measures of crystallized intelligence (Barbey et al., 2014; Gray & Thompson, 2004; Habeck et al., 2018; Habeck et al., 2003; Stern, 2009). The cognitive investment model suggests that measures of crystallized intelligence may be indirect measures of fluid intelligence, as knowledge acquisition results from the ability to apply faster processing speeds (Ackerman, 1996). Given these findings, neurocognitive tests like the ImPACT may benefit from adding additional measures which assess fluid intelligence.

Hypothesis 2, 2b & 2c: Sex and symptom cluster. The current study found that symptom cluster type did not differ between sexes, nor did scores on each symptom cluster significantly differ from one another amongst all participants. However, this finding may be due to the lack of item representation amongst symptom clusters. For example, nine items contribute to the somatic/migraine cluster, while only three items contribute to the sleep cluster (see Table 1). If an equal number of items belonging to each cluster were included in the PCSS, a significant interaction or main effect for symptom cluster may have been found. The method of clustering scores on the PCSS was done post-hoc, i.e., the PCSS was not constructed in order to evaluate symptom scores by cluster. The PCSS may benefit from including an equal number of items belonging to each cluster based on post-hoc analyses.

The finding that females report more symptoms than males following a single SRC has mixed implications. Inherent sex-related bias in symptom reporting following an SRC has been widely reported. However, highlighting sex differences in symptom reporting may result in further bias from test administrators and clinicians. Symptomatology is highly individualized, and administrators and clinicians should be encouraged to prioritize within-group factors (e.g., prior symptomatology) rather than between-group factors (e.g., sex/gender). The contribution of biological factors which contribute to differential symptomatology, such as neck strength and time of menstrual cycle in females, should be evaluated on a case-by-case basis. If gender is salient as a factor which influences symptom reporting, then administrators and clinicians may be prone to make decisions for an individual based on group trends. The belief that females

are falsely reporting more symptoms or that males are falsely reporting less symptoms could potentially lead to an underestimation of symptom severity in females and an overestimation of symptom severity in males. This could contribute to return-to-play decisions, so that females may be prematurely returned-to-play while males may be held from play for longer than needed. The individualized nature of symptomatology should be prioritized over the sex/gender of the individual.

Limitations

Hypothesis 1: Baseline and post-concussion reserve. The current study presented several limitations in terms of the relationship between baseline and post-concussion reserve following a single SRC. Firstly, participants' concussion history was self-reported. Prior research has demonstrated that SRCs often go unreported (Kroshus, Garnett, Hawrilenko, Baugh, & Calzo, 2015; Llewellyn, Burdette, Joyner, & Buckley, 2014). Llewellyn et al. (2014) examined participants who reported symptoms of concussion and their likelihood of acknowledging the presence of a concussion. The researchers found that 11.8% of participants with possible concussions did not acknowledge the presence of a concussion due to pressure from teammates and/or coaches. Kroshus et al. (2015) and Llewellyn et al. (2014) suggested that the prospect of being pulled out of play and letting teammates/coaches down contributed to the social pressure which influences concussion under-reporting. Llewellyn et al. (2014) also found that 26.1% of participants with possible concussions did not recognize that their symptoms were indicative of a concussion. In addition, there is no consensus regarding

the diagnosis of concussion (McCrory et al., 2013; Patricios et al., 2017). The lack of consensus on how concussions are diagnosed may also contribute to unrecognized concussions. Although pre-season ImPACT testing may make athletes at HSU more cognizant of the symptoms of concussion, unreported and unrecognized concussions pose a threat to the validity of current study. Given this, the findings presented in the current study may not accurately reflect baseline reserve's influence on participants who have sustained a single concussion.

In addition, the ImPACT test may not be a valid proxy for reserve. No prior studies have used the ImPACT as a proxy for reserve, and the findings regarding reserve change following a single SRC may not be valid based on the method used. If the ImPACT test has a high test ceiling, then the ImPACT test would be unable to adequately measure change in reserve following concussion. Although the ImPACT test displays good convergent validity with other established measures of reserve such as the WAIS-IV (Thoma et al., 2018), a high test ceiling would influence the ImPACT's ability to detect reserve changes in individuals with low baseline reserve.

Finally, the age of the sample used in the current study may not accurately depict the age at which reserve is solidified. The age of the current sample ranged from 18 - 27 (M = 19.80, SD = 1.67). Prior research has demonstrated that the neurophysiological characteristics of the brain may not fully mature until age 22 (Dosenbach et al., 2010). Tamnes et al., 2009 found that some areas of the brian had not reached maturity by age 30. If the neurophysiological architecture of the brain was continuing to mature while the

sample's change in reserve was being evaluated, then changes in reserve cannot be attributed to concussion alone.

Hypotheses 2, 2b & 2c: Sex and symptom cluster. Several limitations may have influenced the findings in Hypotheses 2, 2b & 2c. In one study, a structured interview was used to evaluate the prevalence of symptoms following an SRC similar to those targeted on the PCSS. Scores on these interviews were compared to scores on the PCSS. Results suggested that participants reported more symptoms during the structured interview than on the PCSS (Meier et al., 2015b). These findings suggest that participants in the current study may have under-reported post-concussion symptoms, as the PCSS was used to evaluate symptomatology. In addition, the PCSS does not have a method of detecting meandering like that found in the ImPACT test. Given this, the PCSS may not be an accurate measure of symptomatology following a single SRC.

The method of evaluating symptoms by cluster may have also limited the validity of the current study's findings. As stated previously, the number of items belonging to each cluster varied. Clusters with less items may have lacked sensitivity and specificity. Similarly, the separation of the PCSS by cluster was based on post-hoc analyses. Therefore, items on the PCSS were not constructed in order to fit into a clustered model. Some items may not be adequately described by a single cluster, and could have demonstrated significant overlap as found by Kontos et al., 2015. This overlap could have also threatened the sensitivity and specificity of cluster scores.

Future Directions

Hypothesis 1: Baseline and post-concussion reserve. The finding that those with high baseline reserve demonstrated a greater decrease in reserve scores following a single SRC compared to those with low baseline reserve suggests a need for further research. No prior studies have examined the role of reserve in protecting and/or compensating for neurophysiological decline following a single SRC. In addition, no prior studies have used the ImPACT test as a proxy for reserve. Both of these factors need to be further explored in order to draw conclusions regarding reserve's influence on a single concussion or the validity of the ImPACT test as a proxy for reserve. Namely, prior research has not demonstrated that high reserve may play a deleterious role in outcome following a single concussion. Other proxies for reserve should be used in order to further examine the relationship between baseline reserve and outcome following a single concussion. In addition, other methods of advising return-to-play decisions based on ImPACT scores should be explored. Administrators of the ImPACT test may be able to make more informed decisions regarding return-to-play by examining between-subjects factors, such as where an individual's scores fall in relation to a normative sample, in addition to within-subjects factors, such as how an individual's post-injury scores compare to their baseline score.

The validity of the ImPACT test for informing return-to-play decisions based on between-subjects factors also needs to be studied further. The current findings suggest that the ImPACT test may have a high test ceiling, especially on subtests which

contribute to verbal and visual memory composite scores. This may contribute to premature return-to-play decisions for individuals with low baseline reserve. By administering the ImPACT test alongside other proxies for reserve, floor and ceiling effects in the ImPACT could be examined and corrected. It was also suggested that measures of fluid intelligence, such as visual motor speed and reaction time, may be better proxies for reserve. Additional proxies for reserve administered alongside the ImPACT should be targeted toward either crystallized or fluid intelligence in order to determine if more subtests which target fluid intelligence should be included in the ImPACT.

Hypothesis 2, 2b & 2c: Sex and symptom cluster. Future research should also focus on sex and symptom cluster's influence on symptom reporting following concussion. Current research on symptomatology following an SRC is largely focused on between-subjects factors, such as sex. Within-subject factors, such as baseline symptomatology, should be emphasized in future studies. In addition, administrator and clinician bias based on sex when informing return-to-play decisions should also be examined. However, further research on the biological and sociocultural influences which may underlie differential symptom reporting by sex and gender would assist unbiased administrators and practitioners in making return-to-play decisions. The separation of biological and sociocultural influences is a major hurdle in current research. Cross-cultural studies may assist in determining the how sociocultural influences alter symptom reporting between genders.

In terms of symptom clustering, a modified version of the PCSS which includes an equal number of items relating to each symptom cluster would assist in examining the validity of the clustering method. Clustering symptoms on the PCSS by type may help administrators and clinicians target certain types of symptoms in order to expedite recovery following concussion. However, the current method of clustering items on the PCSS based on symptom type may not be sensitive nor specific enough for administrators and clinicians to target certain symptoms with confidence. The current method of clustering should be examined alongside a modified version of the PCSS in order to determine if clustering symptoms by type is appropriate.

Conclusions

It was hypothesized that baseline reserve would affect post-SRC reserve, so that those with high baseline reserve would demonstrate less change in their reserve after a single SRC compared to those with low baseline reserve. In addition, it was hypothesized that females would report more emotional, cognitive, and total symptoms compared to males. It was also hypothesized that cognitive symptoms would be reported more frequently than other symptoms across participants. The results of the current study only partially supported these hypotheses. Results suggested an inverse relationship between baseline reserve and post-injury reserve, so that those with high baseline reserve demonstrated a greater change in their reserve following a single SRC compared to those with low baseline reserve. It was also found that females and males did not differ in the amount of somatic/migraine, cognitive, emotional or sleep symptoms, and that scores

belonging to each symptom cluster did not differ in the sample as a whole. However, the current study's results did suggest that females reported more symptoms overall compared to males.

Few studies have examined the relationship between baseline reserve and post-injury outcome following concussion, and no studies to date have utilized the ImPACT test as a proxy for reserve. Although some studies have found that those with high baseline reserve demonstrate better outcomes following concussion than those with low baseline reserve, the current study demonstrated the opposite effect (Fay et al., 2009; Oldenburg et al., 2015). However, these studies estimated baseline reserve retrospectively. Several studies have found that sex influences the types of symptoms reported on the PCSS (Covassin et al., 2012; Kontos et al., 2012) and that the rate at which symptoms are reported differ in all participants (Kontos et al., 2012; Lau et al., 2011). The current study did not support these significant findings. The current study does add to the existing body of literature which demonstrates that females report more overall symptoms compared to males (Frommer et al., 2011; Kontos et al., 2012; Sunderman et al., 2016). Explanations for these findings were put forth, such as the presence of floor and ceiling effects in the ImPACT test and the clustering method's lack of sensitivity and specificity. Future studies would benefit from examining these factors, and should focus on the use of additional proxies for reserve in concussion research as well as the validity of using clustering to isolate symptoms by type on the PCSS.

The current study was a novel exploratory analyses of the relationship between baseline reserve and outcome following a single SRC. In addition, the current study

added to the body of research on sex in symptom reporting following a single SRC and the clustering method of the PCSS. A single brain injury like an SRC can have detrimental effects in terms of reserve and symptomatology. SRCs are one of the most common types of brain injury (Gessel et al., 2007), and further research needs to be conducted in order to assist in the management of this public health issue.

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