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# A Novel Tablet Based System To Measure The Effect Of Subconcussive Blows On Sensorimotor And Cognitive Functioning

Stuart D. Red

A NOVEL TABLET BASED SYSTEM TO MEASURE THE EFFECT OF SUBCONCUSSIVE BLOWS ON SENSORIMOTOR AND COGNITIVE FUNCTIONING

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# A NOVEL TABLET BASED SYSTEM TO MEASURE THE EFFECT OF SUBCONCUSSIVE BLOWS ON SENSORIMOTOR AND COGNITIVE FUNCTIONING

A

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By

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## Dedication

To my grandfather, Richard “Dickiebird” Schissler Jr., who always encouraged me to enjoy life and follow whatever made me happy. His love and support throughout my education have been absolutely critical to my success.

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Concussions have become a major societal concern with studies showing detrimental short and long-term effects on cognitive and sensory functioning. More recently, research has begun to focus on “subconcussive” blows to the head. Subconcussive blows, which are common in many sports (soccer, boxing, football, etc), do not result in the more obvious symptoms of a concussion but have the potential to cause severe brain injury. In our lab and others, eye movements have been used as a sensitive marker of cognitive and sensory changes related to specific diseases and treatments. We have developed a novel measure based on eye movement tasks that can be administered on a tablet computer. This tablet-based system allows us to study individuals (sports players on the field, patients in ER, etc) that had proven difficult to study previously. My project first aims to determine if our technique is capable of detecting brain related behavioral changes from subconcussive head blows. Utilizing this novel technique, my project also aims to better understand the short and long term effects of subconcussive blows. This project is at the forefront of developing standardized methods to help diagnose and monitor treatments in any individuals (car accidents, military combat, falls, etc) receiving subconcussive head blows.

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# Chapter 1

# General Introduction

## Head trauma is a major problem in society

Head trauma is a large problem for society today, with an estimated 10 million cases of traumatic brain injury (TBI) resulting in death or hospitalization each year (Langlois, Rutland-Brown, & Wald, 2006). Menon et al. (2010) defined traumatic brain injury as "an alteration in brain function or other evidence of brain pathology caused by an external force" (Menon, Schwab, Wright, & Maas, 2010). Mild traumatic brain injury (mTBI) or concussion refers to the most mild form of diagnosed TBI and accounts for 80% of all TBIs (Ruff, 2011; Slobounov & Sebastianelli, 2014). Concussion is defined as a "transient neurological event that occurs following a blow to or twisting of the head and may be characterized by confusion, disorientation, and retrograde or anterograde amnesia" (Terrell et al., 2014). Typical symptoms include: headache, difficulty concentrating, fatigue, and/or nausea.

Sports and recreational activities are a major cause of concussions with an estimated 1.6 million to 3.8 million occurring each year; although these numbers are likely underestimated as many individuals do not seek medical attention or receive an appropriate diagnosis (Langlois et al., 2006). Further, the rate of concussions has increased 16.5% annually in high school sports (Lincoln et al., 2011). Despite the increased attention paid to concussions, much confusion still exists in terms of diagnosis and recovery (Chrisman, Schiff, & Rivara, 2011; McCrea, Prichep, Powell, Chabot, & Barr, 2010). The most obvious symptom of a concussion is loss of consciousness, however over 90% of sports related concussions do not result in loss of consciousness (Cantu, 2014). Thus, making diagnosis extremely difficult as clinicians must mostly rely on subjective testing of the patient.

While concussive head blows are frequent in sports with over 1.6 million concussions annually, subconcussive head blows occur at a much higher rate. Recent work has shown that individual high school football players sustain an average of 774 head impacts per season with the average player sustaining 10.5 impacts per practice and 24.1 impacts per game (Martini, Eckner, Kutcher, & Broglio, 2013). Soccer players who regularly play are estimated to incur over 1,000 head impacts per year (Lipton et al., 2013). While many previous studies have shown that individuals that incur multiple concussions are at a higher risk for having more persistent brain related deficits, recently the spotlight shifted to the long term effect of repetitive subconcussive head blows (McKee et al., 2009; Roberts, Allsop, & Bruton, 1990). Specifically, Mckee et al. (2009) as well as multiple studies that followed, have found evidence of Chronic Traumatic Encephalopathy (CTE) in individuals who played contact sports involving repetitive head blows but had no history of concussion (Baugh et al., 2012; Gavett, Stern, & McKee, 2011; McKee et al., 2009; Omalu, Hamilton, Kamboh, DeKosky, & Bailes, 2010). CTE is a neurodegenerative disease that develops following head trauma, often with a delayed onset of years or even decades (Gavett et al., 2011). Symptoms include difficulties with executive functioning, memory, irritability, and even suicidality (Omalu et al., 2010). More recent work has actually indicated that the accumulation of subconcussive blows may be a better predictor of brain related changes and long-term cognitive deficits, such as CTE, than individual concussive events (Breedlove et al., 2012). As most sports related concussion are preceded by multiple subconcussive head blows, recent research has aimed to understand potential interactions ( Schmidt, Heyde, Ertel, & Stahel, 2005). Studies using animal models have shown mixed results with some studies showing repetitive subconcussive head blows preceding increased vulnerability to concussive events (Barkhoudarian, Hovda, & Giza, 2011), while others indicate a protective effect (Johnson, 2014). More recent work in humans has shown that higher rates of subconcussive head blows prior to a concussive event are associated with a delayed diagnosis (Beckwith et al., 2013). Thus indicating repetitive subconcussive head blows prior to a concussive event may mask initial symptoms and complicate diagnosis. Further, individuals with delayed diagnosis often have more persistent symptoms (Beckwith et al., 2013). Clearly, there is mounting evidence for brain injury and brain related changes from subconcussive head blows, and with widespread participation in contact sports, the development of a further understanding of the effects of these subconcussive head blows is of the utmost importance.

## Problems with current measures of brain related changes from head blows

<u>Neuroimaging</u>

Computed Tomography (CT) and structural magnetic resonance imaging (MRI) have shown extremely limited use in assessing more mild traumatic head blows as they lack the sensitivity to monitor subtle structural differences. Most clinically relevant findings on CT scans indicate more complicated or severe pathology than mTBI or concussion (Slobounov, Gay, Johnson, & Zhang, 2012). Many of the damaging effects of concussion occur at the microscopic level and therefore are not accessible at the macroscopic view of CT and MRI techniques (Slobounov et al., 2012). Findings in MRI have implicated specifically the susceptibility of the frontal lobe to damage from more severe head injuries (Wilde et al, 2005).

Recently, more advanced imaging techniques, such as diffuse tensor imaging (DTI), have been shown to be sensitive enough to measure subtle axonal injuries (Kou & Haacke, 2014). While DTI has shown sufficient sensitivity to measure changes related to concussive head blows, results have been inconsistent (Kou & Haacke, 2014). Some studies in sports related concussion have indicated increases in fractional anisotropy (FA) values in particular brain regions while others indicate decreases in those same regions (Arfanakis et al., 2002; Bazarian, Zhu, Blyth, Borrino, & Zhong, 2012). Only recently has work in DTI shown changes related to subconcussive head blows in soccer players from before to after an entire season (Koerte, Ertl-Wagner, Reiser, Zafonte, & Shenton, 2012; Lipton et al., 2013). Koerte et al. (2012) also showed a significant difference in FA values between soccer players with no diagnosed concussion and swimmers. Consistent with findings in diagnosed concussion, these changes occurred specifically in the frontal lobes of the brain. While DTI appears promising, these changes seem to only occur or be detectable in long-term players.

The imaging technique of functional magnetic resonance imaging (fMRI), has shown some promise in the immediate measure of concussive as well as subconcussive head blows (Kou & Haacke, 2014). The technique of fMRI uses changes in blood oxygenated-level dependent response as a measure of brain region specific changes in neuronal activity under a specific set of conditions or in response to specific tasks or stimuli (Huettel, Song, & McCarthy, 2004). Research in concussed athletes has shown increases in activation in the prefrontal cortex, especially the dorsal lateral prefrontal cortex (McAllister et al., 2001; McAllister, Flashman, et al., 2011; McAllister, McDonald, et al., 2011). This increased activation relative to non-concussed controls is thought to be related to a “neural inefficiency” (Chang et al., 2004; Chiaravalloti et al., 2005; Hillary & Schultheis, 2003; Perlstein et al., 2004). Interestingly in the study of subconcussive head blows, Breedlove et al 2012, showed that the number of head impacts across the season was related to a reduction of activity in the dorsal lateral prefrontal cortex, middle frontal and superior frontal gyri during a working memory task (Breedlove et al., 2012). In agreement with previous animal studies, brain related changes from head blows are most apparent in the frontal lobe (Marmarou, Foda, & Brink, 1994; McIntosh, Noble, Andrews, & Faden, 1987; Shultz, MacFabe, Foley, Taylor, & Cain, 2011).

Findings of structural and functional changes of the frontal lobe coincide with the deficits in executive functioning that are common in some forms of traumatic brain injury (Bales, Wagner, Kline, & Dixon, 2009; Baugh et al., 2012; Halterman et al., 2006). While some of these neuroimaging studies exhibit potential, the conclusions and clinical relevance remain questionable. More importantly, these methods are costly, require extensive data analysis, and are not feasible for monitoring of all sports players or even for acute monitoring in sports with repeated subconcussive head blows.

Behavioral testing

While behavioral research of concussion has seen a rapid increase in the recent past, a definitive objective measure of concussion does not exist. Research on subconcussive blows has shown mixed results with many previous studies only finding effects resulting from chronic subconcussive head blows (Rutherford, Stephens, & Potter, 2003). Further, many of these studies have been called into question, as they were unable to account for other important factors such as concussion history or alcohol and drug use (Rutherford et al., 2003). Many of these previous studies have used formal complicated behavioral testing that is highly susceptible to practice effects and therefore has limited value for repeated testing (Resch et al., 2013). Further, formal neuropsychological testing requires administration by a trained clinician and is often time consuming (Randolph, McCrea, & Barr, 2005).

More recently, clinicians and researchers have turned to computer and tablet based testing systems as they allow for easier administration. The Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) system is the most widely used computerized test for management of concussion in athletes (Collie, Darby, & Maruff, 2001; Dykes et al., 2009; Resch et al., 2013).

Early results indicate that ImPACT is sensitive to the effects of concussion and it has been a useful tool for clinicians making decisions on when an athlete is ready to return to play. While the ImPACT test has shown sensitivity to concussion, recent work by Kontos et al 2012, has shown that ImPACT lacks the sensitivity to measure changes related to subconcussive head blows (Kontos, Dolese, Elbin, Covassin, & Warren, 2011). Further, recent work has indicated that the ImPACT test suffers from weak test-retest reliability in healthy controls (Resch et al., 2013).

Eye tracking research has been shown to be more sensitive at detectiing changes or differences in cognitive and motor functioning than more formal behavioral tests (Gooding, Mohapatra, & Shea, 2004; Heitger, Jones, Frampton, Ardagh, & Anderson, 2007; Hill, Reilly, Harris, Khine, & Sweeney, 2008). The King-Devick Test is a reading test that measures eye movement function. Recently is has become available in a portable tablet version and has been used as a more accurate and reliable concussion screening test (Galetta, Barrett, et al., 2011; Galetta, Brandes, et al., 2011; Galetta et al., 2013). A recent study by Leong et al (2014), has shown that the King-Devick Test can be easily and successfully administered by a lay person, thus allowing for a suggested diagnosis without the need of medical personnel (Leong, Balcer, Galetta, Liu, & Master, 2014). While the King-Devick Test has shown great promise for monitoring diagnosable concussion, it may lack the sensitivity to detect more subtle injuries (Galetta, Barrett, et al., 2011). It is clear that an objective tool capable of monitoring more subtle differences from subconcussive head blows is greatly needed.

## Goal directed measures of frontal lobe functioning

Previous work has indicated the frontal lobes and their related functions are particularly susceptible to damage from head blows (Kilbourne et al., 2009; Lindner, Plone, & Cain, 1998; Wilde et al., 2005). While previous imaging and behavioral studies have implicated changes in the frontal lobe and executive functioning in concussion and more severe TBI, they appear to lack the necessary sensitivity and specificity necessary to consistently detect subtle changes related to subconcussive head blows (Resch et al., 2013). Goal directed behaviors are known to involve very specific brain regions, namely the prefrontal cortex, thus offering a potential behavioral method for monitoring brain related changes from head blows.

Goal directed or voluntary movements require extensive input from the frontal cortex, whereas more stimulus driven or sensorimotor movements remain intact even with loss of frontal function (Guitton, Butchel, & Douglass, 1985; Petrides, 1982; Wise & Murray, 2000). Goal directed behavior experiments involving a visual cue and arbitrarily associated motor action have been used in human and non-human primate studies to better understand the involved brain regions ( Khatoon, Briand, & Sereno, 2002; Wise & Murray, 2000). Using elegantly designed experiments, researchers have been able to show how physiological activity in specific areas may be involved at different steps in a goal directed action (Hoshi, 2013; Nakayama, Yamagata, Tanji, & Hoshi, 2008).

Specifically the dorsal lateral prefrontal cortex is thought to be highly involved in the formation of goals and behavioral planning. These two processes are at the foundation of many executive functions and are likely to be affected in head trauma.

Tasks involving goal directed behavior have been previously used to measure post concussive symptoms and have shown superior sensitivity to standard neuropsychological testing (Heitger et al., 2007). Animal studies of mild TBI have shown specifically, cognitive deficits with intact sensorimotor performance (Shultz et al., 2011a; Xiong, Mahmood, & Chopp, 2013). Cognitive deficits are the most robust and common deficits following human and animal TBI (Dixon, Kraus, Kline, & Ma, 1999; Lindner et al., 1998; Salmond & Sahakian, 2005; Shear, Tate, Archer, & Hoffman, 2004). The following work aims to test and implement a novel tablet based set of tasks, including a goal directed task, to measure the effects of subconcussive head trauma on cognitive performance (Aim 1). Further, this work aims to compare the sensitivity and specificity of these novel tablet based tasks to other tablet based tasks, specifically the King-Devick Test (Aim 3).

## Biomechanics of primary head injury

Traumatic brain injury is typically divided into primary and secondary phases. The primary phase involves the initial insult from the impact incurred on the head. This primary injury results in cell death, shearing and tearing of blood vessels, neurons, glia and axons as well as the initiation of the secondary injury, which will be discussed in the subsequent section. While contusions or structural changes may occur focally at the site of impact, the shearing and tearing of axons can occur in a more diffuse manner thus affecting more widespread brain regions (Dashnaw, Petraglia, & Bailes, 2012; Levin & Robertson, 2013; Rabinowitz, Li, & Levin, 2014). Research into understanding the biomechanics of a head blow spans crash dummy, human, and non-human animal models (Duma & Rowson, 2014). Most of this work has aimed at understanding the forces necessary to induce both focal and diffuse brain injury and further to test methods for limiting these forces.

Cadaver and crash dummy models

Research into the biomechanics of head injury using cadavers and crash test dummies has focused on the distinction between the effects of linear and rotational forces on brain injury (Duma & Rowson, 2014). Brain injuries from linear forces are thought to occur from changes in intracranial pressure; while injury from rotational forces is likely related to strain placed on neural tissue (Hardy, Khalil, & King, 1994). Although these mechanisms have been studied independently, all head impacts involve both linear and rotational forces. Thus, it is likely that both linear and rotational forces contribute to brain injury (Duma & Rowson, 2011). Researchers have further substantiated these claims by using film of professional football games to reproduce concussive and non-concussive impacts with crash test dummies, and have subsequently found that both linear and rotational forces were correlated with concussion (Pellman, Viano, & Tucker, 2003). Rotational forces on the brain are thought to impact more subcortical structures such as the mesencephalon, corpus callosum, and fornix. Further, these effects are thought to be present in subconcussive blows as well (Pellman et al., 2003). Along with shearing injuries, rotational forces can also result in injuries at the point of contact between the skull and the brain (Hovda, Giza, Bergsneider, & Vespa, 2014). Often these injuries occur in the frontal regions of the brain, thus explaining some cognitive deficits (Hovda et al., 2014; Slobounov et al., 2014).

Humans

Biomechanical studies into subconcussive head blows are extremely limited with some indicating that a significant amount of forces are distributed to the deep midbrain and brainstem structures (Pellman et al., 2003; Viano et al., 2005). Recent work using technology, such as the Head Impact Telemetry System, has attempted to monitor the magnitude of forces of head impacts (Beckwith et al., 2013; Broglio, Eckner, & Kutcher, 2012; Fife, O'Sullivan, & Pieter, 2013). So far this research has failed to establish consistent thresholds of concussion (Broglio et al., 2012; Greenwald, Gwin, Chu, & Crisco, 2008; Rowson & Duma, 2013); however, it has provided an accurate measure for the frequency of head blows in various sports (Beckwith et al., 2013; Beckwith, Greenwald, & Chu, 2012; Greenwald et al., 2008). This research is most easily applied in sports where helmets are worn, such as American football. Most of this work has indicated that the number of head blows rather than the magnitude is the best predictor of brain related changes (Dashnaw et al., 2012).

Non-human animal models

Many non-human models of head trauma have been developed in an effort to not only recreate the biomechanical effects, but to take advantage of the plethora of techniques available to study the underlying chemical, physiological, and structural changes. While some of these models have been used in larger animals such as cats, rabbits, dogs, sheep, swine, and monkeys; the majority of research uses rats and mice due to their lower cost and well-established behavioral tests (Xiong et al., 2013).

Current models include fluid percussion injury (fpi), controlled cortical impact (cci), weight-drop, and blast TBI (Wang & Ma, 2010). The weight drop and fpi models are two of the most widely used and are successful in recreating the biomechanical mechanisms related to human TBI, but they do suffer from high mortality rates (Xiong et al., 2013). Different versions of the weight drop model exist, with some creating more focal injury and others creating mainly diffuse injury (Albert-Weißenberger, Várrallyay, Raslan, Kleinschnitz, & Sirén, 2012; Chen, Constantini, Trembovler, Weinstock, & Shohami, 1996; Feeney, Boyeson, & Linn, 1981; Marmarou et al., 1994); while fluid percussion injury models create a mix of diffuse and focal injury and thus are more representative of human injury (Armstead, 2001; Carbonell, Maris, McCall, & Grady, 1998; McIntosh, Noble, Andrews, & Faden, 1987; Schmidt & Grady, 1993). Fluid percussion injury models also allow for the fine-tuning of injury severity and are highly reproducible (Armstead, 2001; Shultz et al., 2011).

With the vast increase in sports related brain trauma, recent work has focused on developing models that best simulate head blows in sports (Creeley, Wozniak, Bayly, Olney, & Lewis, 2004; DeFord et al., 2002; DeRoss et al., 2002; Kilbourne et al., 2009; Raghupathi & Margulies, 2002; Wang et al., 2011). Specifically, Kilbourne et al. (2009), modified a previous weight drop model by applying the impact force at the anterior part of the cranium to more accurately recreate the linear and rotational accelerations most typically experienced from frontal impact in sports (Kilbourne et al., 2009). While initial results indicating diffuse axonal injury are promising, this relatively new method still requires additional study (Kilbourne et al., 2009; Xiong et al., 2013). While there is extensive non-human animal research in concussion or mTBI, few studies have focused on subconcussive head trauma. Recent work by Shultz et al. (2012), showed brain related changes without observable behavioral differences following a low force "subconcussive" mild fpi (Shultz, MacFabe, Foley, Taylor, & Cain, 2012).

Recent animal models have also adapted to the needs of sports related head blows by developing models of repetitive head trauma, as is common in contact sports (DeFord et al., 2002; DeRoss et al., 2002; Raghupathi & Margulies, 2002; Y. Wang et al., 2011). Both the weight drop and fpi models have been adapted to be used in repetitive head injury paradigms (Creeley et al., 2004; DeFord et al., 2002; DeRoss et al., 2002). This work has indicated that repeated head injury results in significantly worse short and long term impairments when compared to individual head impacts (Shultz, Bao, et al., 2012). Further, Shultz et al. (2012), also indicated a cumulative effect in which increases in the number of head blows is related to worse and longer lasting deficits. Other research has begun to explore the effect of time between head blows and has indicated that shorter time intervals between blows result in more devastating impairments (Friess, Ichord, & Ralston, 2009). While there is much promise in these models of repetitive head injury, much work still needs to be done to more accurately represent the frequency of sports related head impacts. However, these various models of individual as well as repeated head trauma show many similarities with results from human studies, and offer the great advantage to study the underlying pathophysiology of the primary and secondary phases of injury.

## Pathophysiology of Secondary injury in head trauma

Secondary injury occurs from a cascade of biochemical and brain related changes stemming from the initial insult; and can last for hours to weeks after the trauma. As mentioned above, the initial forces on the brain likely lead to shear stress on neurons thus causing axonal strain and ultimately diffuse axonal injury (DAI) (Dashnaw, Petraglia, & Bailes, 2012; Maruta, Lee, Jacobs, & Ghajar, 2010). As opposed to complete cell death, DAI is thought to be mediating the behavioral injuries in more mild head trauma (Browne, Chen, Meaney, & Smith, 2011; Lipton et al., 2012; Niogi et al., 2008; Rubovitch et al., 2011). Accompanying this axon strain is a host of detrimental biochemical responses including the increased presence of excitatory amino acids, subsequent disruption of ionic balances, and activation of inflammatory responses (Signoretti, Lazzarino, Tavazzi, & Vagnozzi, 2011). Much of the work that will be discussed below is based on studies of concussive head blows, however many of the microstructural and biochemical changes are thought to be similar in subconcussive blows (Hovda et al., 2014;

Khurana & Kaye, 2012).

Specifically, mechanical damage to the neurons results in massive increases of the excitatory amino acid glutamate into the synapse, thus causing massive increases in intracellular calcium through stimulation of N-methyl-D-asparate (NMDA) receptors (Katayama, Becker, Tamura, & Hovda, 1990). Accumulation of intracellular calcium can be related to many destructive processes including blood-brain barrier disruption and altered signal transduction that can potentially alter neuronal function for extended periods of time (Hovda et al., 1995; Schmidt et al., 2005; Schmidt & Grady, 1993). Along with multiple other changes, the increases in calcium lead to a state of ionic imbalance (Signoretti et al., 2011). In response to this ionic imbalance, increases in glucose uptake occur to provide the ionic pumps with the ATP necessary for operation (Hovda et al., 2014). Co-occurring with this increased need for glucose and ATP, is a decrease in their availability likely due to decreased cerebral blood flow and mitochondrial resources being dedicated to the sequestration of calcium (Giza & Hovda, 2001). This so called “energy crisis” is thought to be a major contributor to the underlying brain related changes from head trauma (Giza & Hovda, 2001).

Along with increases in excitatory amino acids, the primary impact and subsequent cellular changes can lead to neuroinflammatory responses (Ramlackhansingh et al., 2011; Shultz et al., 2011). Specifically, microglia are thought to mediate much of the neuroinflammatory response as they are activated by the axonal injury as well as subsequent ionic imbalance and disruption of the blood brain barrier (Gehrmann, Matsumoto, & Kreutzberg, 1995;

Schmidt et al., 2005). The activated microglia respond by secreting multiple pro-inflammatory signaling molecules. These increases in neuroinflammation have been previously associated with cognitive impairments and brain function alterations in both human and non-human animals ( Schmidt et al., 2005; Shultz et al., 2011; Uchida et al., 2012). Shultz et al. (2011), showed specifically that inflammation in the frontal regions is associated with decreases in performance on cognitive tasks. In a subsequent study, the authors have now shown a similar increase in inflammation in response to a single subconcussive head blow in the frontal areas of the brain but failed to find any cognitive deficits (Shultz, MacFabe, et al., 2012). It is possible that following repetitive subconcussive hits and/or with more sensitive behavioral testing cognitive changes will be measurable. Further, the underlying changes in neuroinflammation may provide a mechanism for long-term deficits such as CTE in individuals without previous concussion history (Shultz, MacFabe, et al., 2012).

While single mild head injuries have been shown to result in short term behavioral and neuropathological changes with limited neuronal cell loss, repeated mild head injuries have been shown to result in long-term behavioral deficits and neuropathological changes (Broglio et al., 2014; Guskiewicz et al., 2005; Notebaert & Guskiewicz, 2005). Repetitive subconcussive head blows may lead to the similar but more minor biochemical and cellular changes that may result in more long term or even chronic damage (Giza & Hovda, 2001; Hovda et al., 2014; Levy et al., 2012). Increases in the number of concussive head blows have been shown to increase not only the amount of neuroinflammation but also the persistence of it (Shultz, Bao, et al., 2012). Further, these changes in neuroinflammation co-occurred with more pronounced and persistent cognitive deficits (Shultz, Bao, et al., 2012).

While the aforementioned cellular changes are known to underlie some clinical symptoms such as poor concentration, short term memory loss, headache, and dizziness (Hovda et al., 2014); the current clinical utility of this research is limited due to lack of applicable techniques in humans. It is clear from above mentioned animal studies that brain related changes from head impacts extend beyond the initial moment of injury. Research in humans has confirmed this by showing that while most symptoms from head trauma peak on the day of injury; others may occur hours to days later (Hovda et al., 2014). Research into the time course of the effects of subconcussive head blows is extremely limited. This project aims to implement a novel tablet based task to measure potential changes in cognitive performance across time following sessions of subconcussive head blows (Aim 2).

## Central hypothesis and specific aims:

We hypothesize that there may be small cognitive changes with subconcussive head blows. We also hypothesize, based on human reports and known changes in biochemical cascades in the animal literature across time, that it is possible that these changes may be more detectable after multiple hours and may recover 48 hours following sessions of subconcussive head blows. Finally, we hypothesize that our test will show superior sensitivity to other currently available tablet based tasks.

_Aim 1_. To test if tablet-based behavioral measures are able to detect differences between soccer and non-soccer players that may arise from subconcussive trauma on (a) sensorimotor performance (b) cognitive performance; and (c) to test whether any differences are associated with short-term (e.g., number of headers) or long-term (e.g., number of years played) variables. We hypothesize that female high school soccer players incurring subconcussive head trauma will show deficits in cognitive performance but not sensorimotor control. Thus, we expect that following a practice involving soccer heading, they will show no difference from age-matched controls in performance on a sensorimotor task, but slowing in the cognitive task, thus indicating a decrement specific to cognitive functioning. Further, we hypothesize that increased rates of soccer ball heading will be related to slowing on the more cognitively demanding task.

_Aim 2._ *We* aim to measure the effects of subconcussive head trauma on sensorimotor and cognitive functioning in professional boxers performing boxing workouts with (Spar-workout) and without (Bag-workout) head blows. We will use the novel tablet based tasks developed by our lab. We will compare performance changes at three different time intervals: (1) immediate- before and after workout; (2) short- before workout and 2-4 hours after workout; and (3) long-before workout and 48 hours after. For all time points, we will measure sensorimotor and cognitive performance. We hypothesize that professional boxers tested before and immediately after “Sparring”, a workout session involving head blows, will show deficits on cognitive tasks. We hypothesize that boxers tested 2-4 hours after a Sparring session will be incurring additional costs from biochemical cascades. Thus, they will show more apparent deficits specifically in the cognitive task, indicative of a cognitive dysfunction related to the subconcussive head trauma. Finally, we hypothesize that boxers tested 48 hours following a session of subconcussive head blows will most likely show no deficit as they have functionally recovered from this subclinical head trauma.

Aim 3. We aim to see if the tablet version of the King-Devick Test, the most widely used tablet based measure of concussion, is able to detect changes related to subconcussive head blows. Further, we aim to test the sensitivity and specificity of the King-Devick, Pro-point, and Anti-point tasks in detecting and correctly categorizing the presence of subconcussive head blows. We hypothesize that our Anti-point task will out perform both the King-Devick and Pro-point tasks given the similarity of the Anti-point task to other established frontal lobe tasks, and the fact that frontal lobe deficits are most apparent after brain injury.

**Project Significance:** This study will help us gain a better understanding of the effects and time course of repetitive subconcussive head blows. Many popular sports involve regular sessions of repetitive head blows (e.g. soccer, boxing, football). While the long and short-term deficits related to concussions and repeated concussions are well documented, little research has studied the effects of repeated subconcussive head blows on brain function. Using this tool we can begin to better understand the immediate, short-term, and long-term effects of subconcussive head blows as well as potentially monitor and help predict increased risk of concussion or potential long-term deficits in brain function. By using such a portable inexpensive approach we also have the potential to go beyond research and apply this technology to a wide range of individuals in a variety of situations (e.g. sports field, emergency room, etc.).

# Chapter 2

# Novel tablet task for monitoring effects of subconcussive head blows

***Following text and Figures based on:***

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## Introduction:

Concussive brain injuries in head-jarring sports such as American football, hockey, and boxing, where repeated loss of consciousness often occur, could lead to long-term cognitive dysfunctions (Kelly, Amerson, & Barth, 2012). However, whether less violent head impacts such as heading a soccer ball could lead to subconcussive brain injury is unclear (Matser, Kessels, & Lezak, 1999; Rutherford et al., 2003). A recent imaging study (Lipton et al., 2013) showed detectable structural differences in brain areas, consistent with traumatic brain injury (TBI), between amateur adult (mean age of 31 yrs, played soccer since childhood) soccer players with self-reported high and low heading frequencies. Similar findings were also obtained in another recent imaging study (Koerte, Ertl-Wagner, Reiser, Zafonte, & Shenton, 2012) which found differences in white matter integrity in a small sample of professional male soccer players (mean age of 20 yrs, who played soccer since childhood) compared with a control group of swimmers (mean age of 21 yrs). Previous imaging studies have failed to find structural brain differences directly related to heading balls (Autti, Sipilä, Autti, & Salonen, 1997). Previous studies using formal cognitive testing have also failed to detect changes with ball heading in young adults (Rieder & Jansen, 2011) or in 13- to 16-year-old soccer players

Previous studies that did not find significant changes in higher level cognitive tasks associated with soccer ball heading (Rieder & Jansen, 2011) have often tested for cognitive changes using more formal but complicated cognitive testing (e.g., visual memory retention, addition, logic, and other tasks that occur at the level of seconds and minutes). Moreover, several studies have now demonstrated that standard neuropsychological testing is less sensitive than eye tracking tasks in detecting differences in cognitive or executive function (Broerse, Crawford, & den Boer, 2001; Gooding, Mohapatra, & Shea, 2004; Hill, Reilly, Harris, Khine, & Sweeney, 2008). For example, Hill et al. (2008) showed that eye tracking (or oculomotor) biomarkers were more sensitive to treatment-related changes in neurocognitive function than traditional neuropsychological measures (Hill et al., 2008). Here we use a new touch based method, with tasks similar to those used in eye tracking research, which are simple, straightforward, and less sensitive to interfering issues such as second language differences. Our method with its relatively short response latencies and high temporal resolution may be a more sensitive test of executive function and hence be able to dectect more subtle cognitive changes in high school soccer players, deficits that were previously undetected because of lack of sensitive measurement techniques.

Frontal lobes are among the brain regions most susceptible to injury in traumatic brain injury (Wilde et al., 2005). Using a variant on a well-established frontal-lobe task of executive function (antisaccade task), we developed a simple iPad-based application to detect the cognitive effects of soccer ball heading. Prior research shows that the antisaccade task, a voluntary eye movement task, can be used to determine deficits in executive functioning (Munoz & Everling, 2004; A. B. Sereno & Holzman, 1995; A. Sereno et al., 2009; Wilde et al., 2005). Point responses by the hand towards a target (Pro-point) are similar to prosaccade eye movements in that they both involve a more reflexive motor movement directly to a target; while point responses away from a target (Anti-point) are more similar to antisaccade movements as they involve inhibition of the reflexive movement towards the target and generation of a voluntary or goal directed motor movement in the opposite direction of the target location (Everling & Fischer, 1998; Khatoon et al., 2002; Wise & Murray, 2000). The following experiments are the first to test the ability of this novel tablet based task to measure changes related to subconcussive head blows. We hypothesize that ball heading causes cognitive dysfunctions as measured by soccer player's slower responses and more errors in Anti-point tasks, indicating disruption of their voluntary brain function.

## Methods:

Participants:

All participants gave informed consent before enrolling in the study, and this study was approved by the Committee for the Protection of Human Subjects at the University of Texas Health Science Center at Houston, in accordance with the Declaration of Helsinki. Twelve soccer players and 12 age-matched controls were recruited from a local high school in an approved location, and the study was explained to them by a research assistant. All soccer players participating in the study, performed head balls in a coach controlled practice session prior to the testing. Subjects were administered a questionnaire during the course of the study which asked questions about medical and sports history. Header related data was not included for two soccer participants because they responded with qualitative answers. Participants were only included if they had normal or corrected-to normal vision and no previous head injury or neurological condition.

*Stimuli*: The experiment was performed on an iPad 2 (**Figure 1**) with a video frame refresh rate of 60 Hz. The onset and offset of stimuli were synchronized with the frame refresh signal with a precision of 1.6 msec. The visual display consisted of a filled center fixation circle (diameter subtending 2.4° visual angle from a 33 cm viewing distance, 1.4 cm) surrounded by four square boxes (1.4°, 0.8 cm) 7.0° (4.0 cm) from the fixation circle indicating possible response locations. Participants started a trial by placing their index finger on the center circle. A visual target (white square, 0.8 cm) appeared randomly 480 ms later, at one of the four locations. For the Pro-point task, the participant was instructed to touch the response box containing the target as fast as possible without making errors. For the Anti-point task, the participant was to touch the response box opposite to the target location.

*Touch responses*: The spatial locations of the touches were captured by the iPad's capacitive touch screen and exact coordinates calculated using its touch-screen interface with resolution of 52 pixels per cm. A response was counted as an error if the distance between the target location and the iPad-calculated location was greater than 3.3° (1.9 cm).

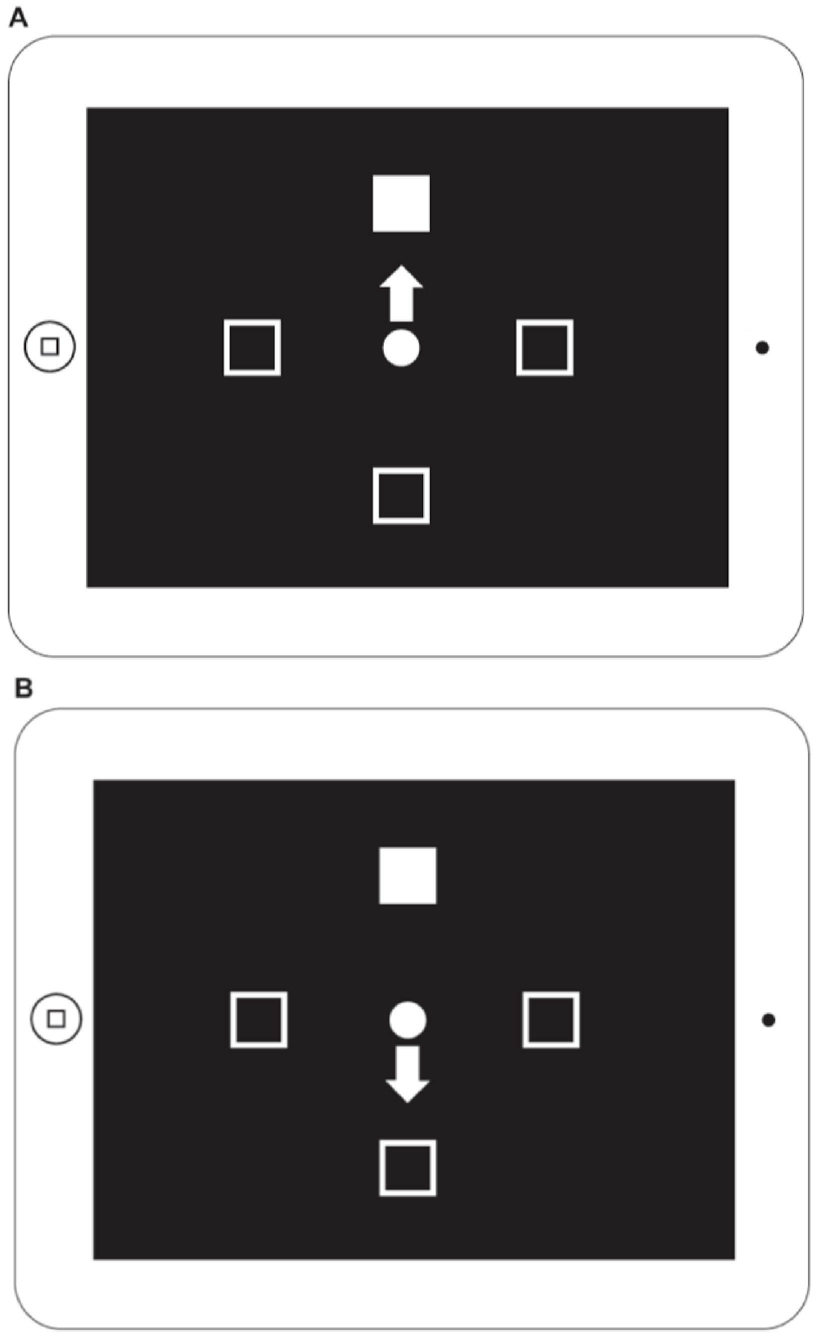


**Figure 1 Tablet based tasks**

A. Pro-point task on tablet with arrow indicating direction of correct response of direction (towards target). B. Anti-point task with white arrow indicating direction of correct response (opposite of target).

*Design and Procedure*: There were 3 dependent variables: (1) Initiation Time - the duration between when the visual cue appears and when the finger is lifted, (2) Reaction Time - the duration between when the visual cue appears and when the target goal is touched, and (3) Error - when the finger touched more than 3.3° (1.9 cm) from the target goal center.

Each participant performed two blocks of trials until they obtained 48 correct trials in each Pro-point and Anti-point block (mean total trials 48.3 and 49.4, respectively). Within each participant group, half started with the Pro-point block followed by the Anti-point block, and the other half received the reversed order. Both groups were tested after school academic activities were over. Soccer players went to practice right after school academic activities and then were tested in the field immediately following their afternoon practice. To match the environmental conditions, Non-soccer players were also tested outdoors after school academic activities were over at approximately the same time in the afternoon (4-5 pm).

*Analysis*: Error trials were excluded from the analyses of response times. Outlier trials with times more than 2.5 SD away from the mean of each subject for each task were excluded iteratively until all remaining trails were within 2.5 SD, removing, for initiation times, 6.86% (Pro-point) and 3.91% (Anti-point) and, for reaction times, an additional 0.95% and 2.60% of the total trials, respectively. A mixed effect model was performed for response time data and a logit-link generalized linear model with repeated measurements for error data. The logit-link transforms error percentage, p, to logit(p) by log[p/(1-p)]. All models assumed that measurements obtained within each subject have an autoregressive correlation structure, AR(1). Group (soccer vs. non-soccer players) was the between-subject variable for each task (Pro-point and Anti-point) and group difference was calculated and tested by constructing the contrasts from the mixed effect models or logit-link generalized linear model. In addition, to test if the Anti-point response time slowing in the soccer group found in the first group analysis was related to ball heading, years of soccer, or current weekly hours of soccer playing, we performed a similar mixed effect model (with repeated measurements and autoregressive correlation structure) on the Anti-point response time data from the soccer players with the independent variables of heading rate (n=10), years of soccer playing (n=12), and hours of soccer per week (n=12). Due to missing data, analyses were run separately. Data were analyzed using a significance level of $p<0.05$ and a marginal significance level of $.05 \leq p < 0.10$.

## Results:

Initiation time results

**Figure 2** shows mean initiation times for Pro and Anti-point tasks performed by both groups. Estimated mean and significance values can be found in **Table 1**. As can be seen in **Figure 2** there were no significant differences in initiation time between non-soccer players and soccer players on the Pro-point task. However, soccer players were marginally slower than non-soccer players in initiation time on the Anti-point task (see **Figure 2**).

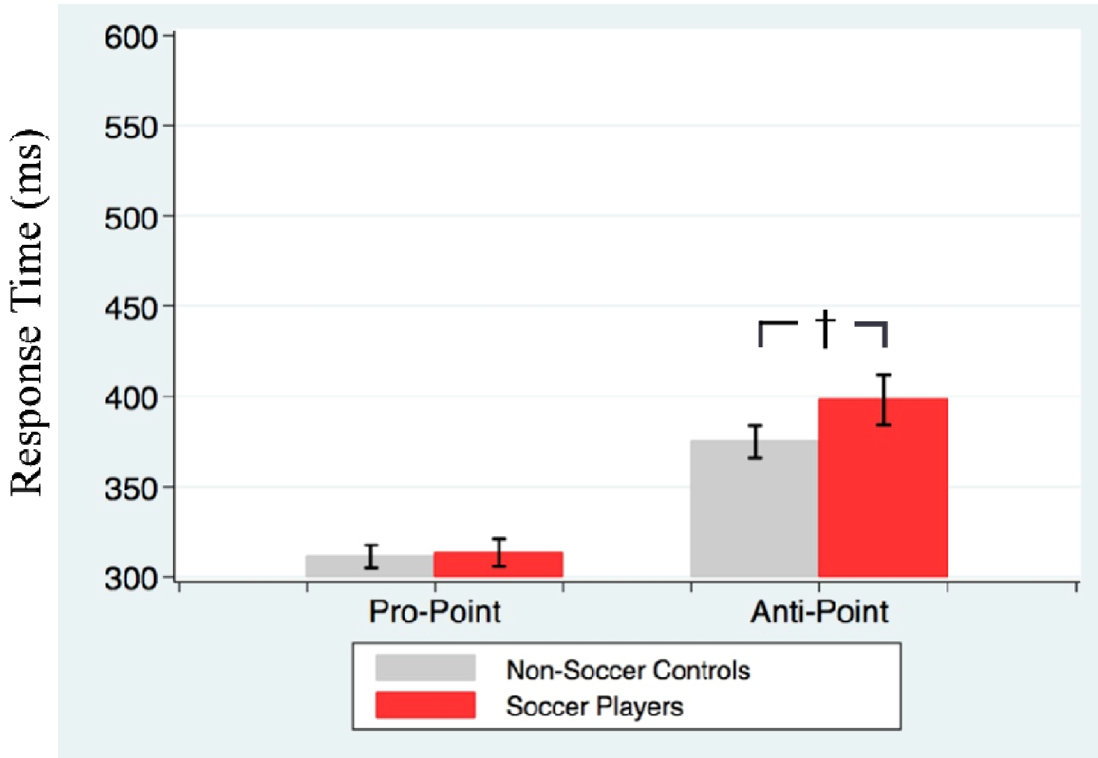


**Figure 2 Estimated mean initation time for soccer and non-soccer subjects.**

Gray bars represent non-soccer control subjects, and red bars represent soccer players. Errors bars represent standard error. Signifcance levels: (†) for p<0.1. Soccer players showed a marginal slowing when compared to non-soccer players.

| | Non-soccer controls | Soccer players | | |
|---|---|---|---|---|
| | *Estimated Mean (ms)* | *Estimated Mean (ms)* | *t-value* | *p-value* |
| Pro-point | 313 | 312 | 0.16 | .87 |
| Anti-point | 378 | 394 | 1.86 | .08 |

**Table 1 Estimated means for initation times of non-soccer controls and soccer players.**

Table displays means for non-soccer controls and soccer players initiation times in milliseconds (ms). T and p-values from the mixed models analysis are also included. There is a marginal slowing for soccer players compared to non-soccer controls in the Anti-point task.

In a follow up mixed model analysis, the relationship of Anti-point initiation slowing and ball heading, years of soccer, and current weekly hours of soccer playing was tested. These findings are summarized in **Table 2**. Slowing in the initiation time on the Anti-point tasks was marginally related to heading ball rate and years of soccer played. Further, Anti-point slowing was significantly related to hours of soccer per week.

| | t-value | p-value |
|---|---|---|
| Heading Ball Rate (n=10) | 1.88 | 0.0976 |
| Hours of Soccer Per Week (n=12) | 3.51 | 0.0056 |
| Years of Soccer (n=12) | 2.03 | 0.0697 |

**Table 2 Results of fixed effects of soccer related variables relationship to Anti-point initiation time slowing.**

Hours of soccer per week were significantly related to Anti-point slowing. Heading ball rate and years of soccer were marginally related to Anti-point slowing.

<u>Reaction time results</u>

The reaction time results for Pro and Anti-point tasks performed by both groups are shown in **Figure 3** and **Table 3**. The results from the mixed models analysis indicate no significant differences in reaction time between groups on the Pro-point task. In contrast, soccer players were significantly slower than non-soccer players in reaction time on the Anti-point task.

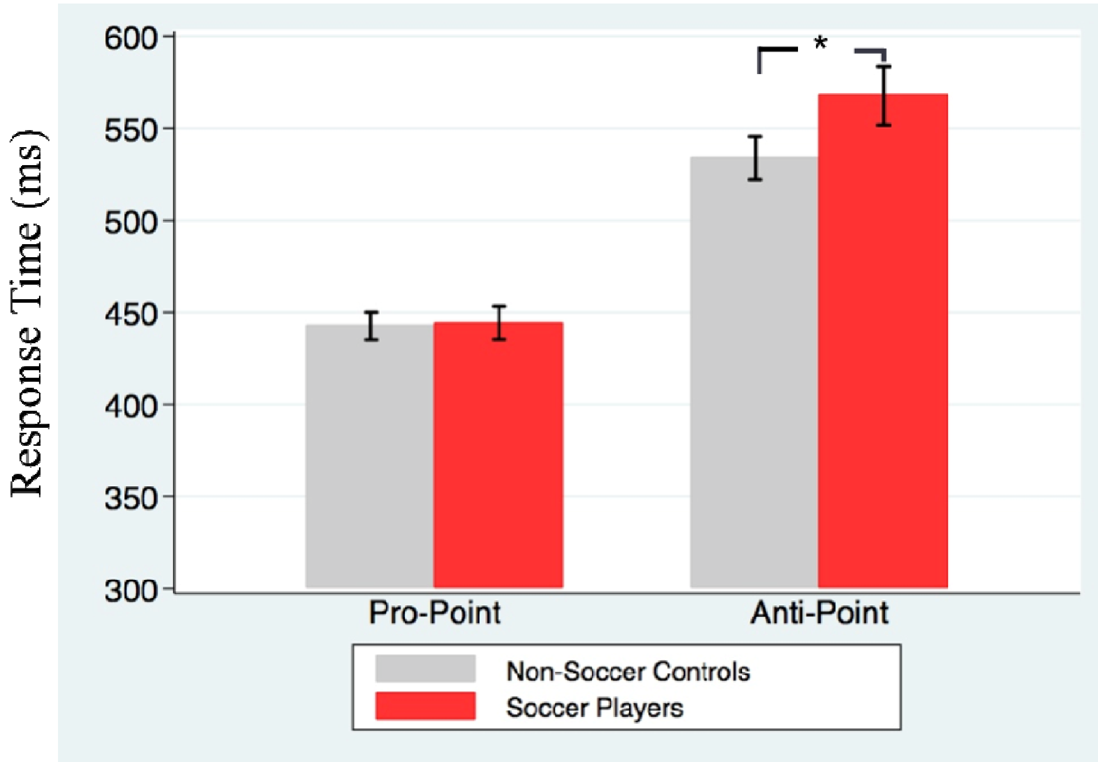


**Figure 3 Estimated mean reaction time for soccer and non-soccer subjects.**

Gray bars represent non-soccer control subjects, and red bars represent soccer players. Errors bars represent standard error. Signifcance levels: (*) for $p<0.005$. Soccer players showed a significant slowing in the Anti-point task when compared to non-soccer players.

| | Non-soccer controls | Soccer players | | |
|---|---|---|---|---|
| | *Estimated Mean (ms)* | *Estimated Mean (ms)* | *t-value* | *p-value* |
| Pro-point | 439 | 445 | 1.18 | .25 |
| Anti-point | 531 | 561 | 3.69 | .004 |

**Table 3 Estimated means for reaction times of non-soccer controls and soccer players.**

Table displays means for non-soccer controls and soccer players reaction times in milliseconds (ms). T and p-values from the mixed models analysis are also included. There is a significant slowing for soccer players compared to non-soccer controls in the Anti-point task.

The relationship of Anti-point reaction time slowing to ball heading, years of soccer, or current weekly hours of soccer playing was tested in a follow up mixed model analysis. These findings are summarized in **Table 4**. The independent variables of years of soccer and weekly hours of soccer were significantly related to slowing in Anti-point reaction time. However, heading ball rate did not show a significant relationship to Anti-point slowing.

| | t-value | p-value |
|---|---|---|
| Heading Ball Rate (n=10) | 1.86 | 0.1165 |
| Hours of Soccer Per Week (n=12) | 2.27 | 0.0470 |
| Years of Soccer (n=12) | 2.71 | 0.0065 |

**Table 4 Results of fixed effects of soccer related variables relationship to Anti-point reaction time slowing.**

Hours of soccer per week were significantly related to Anti-point slowing. Heading ball rate and years of soccer were marginally related to Anti-point slowing.

Error analysis

There were no significant differences in errors in either Pro-point tasks (0.3% vs. 1.0%, z=0.83, p=0.41, logit-link generalized model) or Anti-point (3.1% vs. 2.5%, z=1.13, p=0.26, logit-link generalized model) for soccer and non-soccer players.

## Discussion:

Our results indicate that frontal lobe functioning as measured through our Anti-point task is slowed in soccer players following a practice involving ball heading. This deficit appears to be specific to frontal lobe function as results from our Pro-point task show intact sensorimotor functioning. Further, our findings also indicate that Anti-point slowing is marginally related to number of headers and significantly related to hours and years of soccer played. Finally, our results indicated that our novel tablet based tasks have the necessary sensitivity to measure changes related to subconcussive head blows.

Though the changes we report were robust, they do not necessarily imply sustained changes or brain injury. Further study is needed to track soccer players for longer periods to evaluate if these changes are transient or longer-lasting, if they are dependent upon repeated subconcussive blows, and if they generalize to male soccer players. To our knowledge, these results provide the first evidence that even subconcussive blows in soccer could lead to measureable, even if possibly transient, cognitive changes in young soccer players.

In sum, the cognitive changes that we report were measured with a simple iPad based application. A simple tool such as this iPad application may be a quick and effective method to screen for and track cognitive deficits in sports players. It could potentially be used to detect, screen, and track other populations for mild traumatic brain injury and development of cognitive comorbidities.

# Chapter 3

# Effects of subconcussive head blows and exercise across time

## Introduction:

As has been emphasized in chapter 1, gaining a better understanding of the brain and behavioral related effects of subconcussive head blows is being realized as an important goal. We have already shown that our novel tablet based task is tool capable of measuring the subtle brain behavior changes related to subconcussive head blows (Chapter 2). Our initial studies, indicate that individuals incurring subconcussive head blows can show slowing specifically in frontal lobe function. As emphasized in Chapter 1, brain injury from head impact involves a secondary phase with brain related changes occurring hours and days following the initial impact (Giza & Hovda, 2001; Slobounov et al., 2014). In this chapter, we aim to study the time course of changes in sensorimotor and cognitive functioning related to subconcussive head blows.

The time course of brain changes related to subconcussive head blows has received limited attention in human studies, likely due to time consuming nature and lack of sensitivity of current behavioral tests (Lau, Collins, & Lovell, 2011; Resch et al., 2013). As was indicated in Chapter 1, subconcussive head blows are repetitive and frequent in many contact sports (Lipton et al., 2008; Martini, Eckner, Kutcher, & Broglio, 2013). One recent study has indicated that repetitive subconcussive hits prior to a concussive blow can lead to a delay in the peak of concussive symptoms (Beckwith et al., 2013). Separately, studies in both animals and humans have indicated that repetitive head blows lead to more persistent changes (Bailes, Petraglia, Omalu, Nauman, & Talavage, 2013; Marchi et al., 2013; Prins, Alexander, Giza, & Hovda, 2013; Shultz, Bao, et al., 2012). Together, these findings indicate repetitive head impacts may lead to delayed or more persistent changes in cognitive function.

Exercise alone has been shown to improve cognition in short and long term studies (Joyce, Graydon, McMorris, & Davranche, 2009; Lambourne & Tomporowski, 2010; Tsai et al., 2014). Further, higher fitness level has been shown to be potentially protective of cognitive decline in many neurodegenerative diseases and even in normal aging (Frazzitta et al., 2013; Griesbach, Hovda, & Gomez-Pinilla, 2009; Tarumi & Zhang, 2014). Other studies have indicated that the increased arousal from intense exercise in sports may serve to mask potential cognitive deficits from subconcussive head blows (Beckwith et al., 2013; Zhang, Red, Lin, Patel, & Sereno, 2013). In this chapter, we investigate the time course of changes in sensorimotor and cognitive functioning following subconcussive head blows, as wells as examine and control for potential effects related to exercise.

## Methods:

Participants:

All participants gave informed consent before enrolling in the study, and this study was approved by the Committee for the Protection of Human Subjects at the University of Texas Health Science Center at Houston, in accordance with the Declaration of Helsinki. Eight male and 1 female professional boxers were recruited from a local boxing gym that was approved as a study location. A research assistant explained the study to all participants.

Stimuli

The Pro and Anti-point tasks, stimuli presentation, and touch response recording are identical to those in chapter 2. Briefly, the experiments were performed on an iPad 2 (**Figure 1**). Participants began each trial by placing a finger on a center circle. A visual target appeared randomly at one of the four locations. For the Pro-point task, participants were instructed to touch the box with the target as fast as possible without making an error. In contrast, participants were instructed to touch the box opposite of the target in the Anti-point task.

Definition of workout conditions:

Data was collected from participants in 2 workout conditions. Subjects participated in “Spar” sessions in which they would train for upcoming boxing matches by boxing another individual. During these sessions, participants always incurred multiple subconcussive head blows. As opposed to real boxing matches, participants wear head-gear, protective girdle, and heavier gloves (20 oz. vs 10 oz.). Sparring sessions were regulated by at least one coach and would include multiple rounds each of 3 minutes duration with 1 minute of rest between rounds. The number of rounds differed in each session (range 2-10 rounds).

Subjects also participated in “Bag” sessions where they would perform boxing related drills that included punching bags and moving as they would in a boxing match. These sessions were regulated by at least one coach and included multiple rounds of 3 minutes of vigorous exercise with 1 minute of rest between rounds.

Procedure:

The boxers were tested multiple times across the day (maximum 3 testing sessions per day) depending on their availability (9 boxers, mean per boxer: 15.78 testing sessions, range: 8-31 testing sessions). They were tested before beginning a workout session (pre), and after (post) workout. Post workout data was collected immediately after a workout, 2-4 hours (short-term) and 48 hours (long-term) following the end of the workout (see **Table 5**). Data analysis for the long-term time point included a subset of the data in an effort to control for potential confounds of current activity (Bag or Spar) as well as the activity that was performed the following day or day preceding the post (long-term) data collection (5 boxers, mean per boxer: 5.8 sessions, range: 4-8). For example, data for the long-term analysis of Sparring included pre data from individuals before a Spar workout and post data 48 hours after from individuals again before a Spar workout (see **Table 6**). Further, this post session (48 hours later pre spar) was always preceded on the previous day by a Bag session. Conversely, data for the long-term time point analysis in the Bag condition includes pre data from individuals before Bag sessions and post data 48 hours later from before another Bag session. Additionally, post data (48 hours later, pre Bag workout) for the long-term Bag analysis was only included if it was preceded by a Bag session 24 hours prior (see **Table 6**).

For each of the three testing sessions, subjects completed the Pro-point, and Anti-point tasks in a randomized order. Subjects were also administered the tablet based version of the King-Devick Test in randomized order before or after the administration of Pro- and Anti-point tasks. The results from the King-Devick Test will be discussed in Chapter 4. In their first data collection session subjects were administered a questionnaire, which asked questions about medical and sports history. Each subsequent data collection session lasted approximately 5-10 minutes.

| | | ***Time Point*** |
|---|---|---|
| Pre: | | <20 minutes before |
| Post: | *Immediate* | <20 minutes after |
| | *Short-Term* | 2-4 hours after |
| | *Long-Term* | 48 hours after |

**Table 5 Table of Time Points.**

Table displays intervals when data was collected as well as terms (pre, post, immediate, short-term, long-term) that will be used to describe data gathered at those intervals.

| Workout Condition | Data Collection for Pre 48 | | Data Collection for Post 48 |
|---|---|---|---|
| | Day 1 | Day 2 | Day 3 |
| *Spar* | Spar | Bag | Spar |
| *Bag* | Bag | Bag | Bag |

**Table 6. Data collection for long-term data analysis.**

Note all data for long-term data analysis was collected immediately before either spar or bag workout.

Data analysis

For the analysis of response time (initiation and reaction time), error trials were excluded (1.70%). Data was trimmed iteratively to exclude responses beyond 2.5 sd from the mean for each subject in each testing session for each task (3.3% for Pro-point, 4.8% for Anti-point). As in previous analyses (Zhang et al, 2013), a mixed effect model was performed on the response time data and the fixed effect was time point (pre, immediate, short, or long), while subject was a random effect with an autoregressive correlation structure, AR(1). The dependent variable was response time (initiation and reaction time). Similarly, to examine differences between workout conditions (Spar vs Bag), we combined data from Bag and Spar sessions and performed an analysis for each dependent variable (initiation and reaction time) with the fixed effects of workout condition (Bag and Spar) and time point (pre, immediate, short, and long) as well as the interaction of workout condition and time point. The interaction term was used as the measure of differences in workout condition across time in the Spar vs Bag analysis. The long-term analysis was only performed on a subset of data as described in Table 6.

## Results:

<u>Initiation time results</u>

*Immediate*

**Figure 4** shows the mean initiation time data for Pro and Anti-point tasks by workout condition. The analysis revealed that participants Pro-point performance improved immediately following Bag (-13.91 ms, p<.001) and Spar (-15.05 ms, p<.001) workouts. Subjects also showed improved performance on the Anti-point task immediately following Bag (-18.0175 ms, p<.001) and Spar (-27.71 ms, p<.001) workouts.

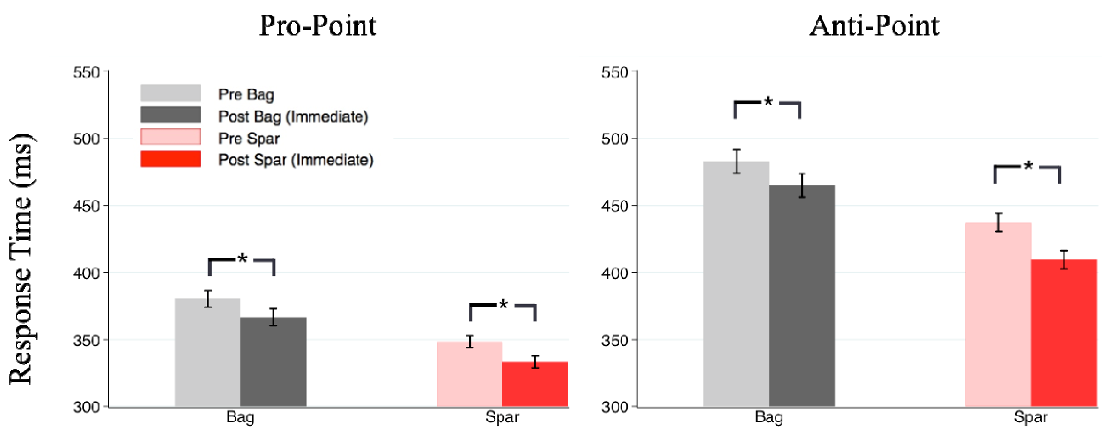


**Figure 4 Estimated mean initiation times at immediate timepoint.**

Significant improvements were seen immediately following Gray bars represent data collected in the Bag condition. Red bars represent data collected in the Spar condition. Lighter gray and red bars represent data collected at the pre time point for Bag and Spar. Darker gray and red bars represent data collected at the immediate time point following Bag and Spar sessions. Error bars represent confidence intervals for within condition mixed model analysis. Significance levels: (*) for p<0.05. Significant improvements were seen immediately following Bag and Spar sessions for both Pro and Anti-point initation times.

*Short-Term (2-4 hour)*

For the short-term time point, 2-4 hours following workouts, the initiation time results are shown in **Figure 5**. When compared to pre workout response times, participants showed significant improvement on the Pro-point task 2 to 4 hours after Bag (-25.63 ms, p<.001) and Spar (-4.86 ms, p<.05) workouts. In the Anti-point task participants showed improvement 2-4 hours following Bag workouts (-23.54 ms, p<.001), however they showed a significant slowing 2-4 hours following a Spar (+8.38 ms, p<.001) workout with subconcussive head blows.

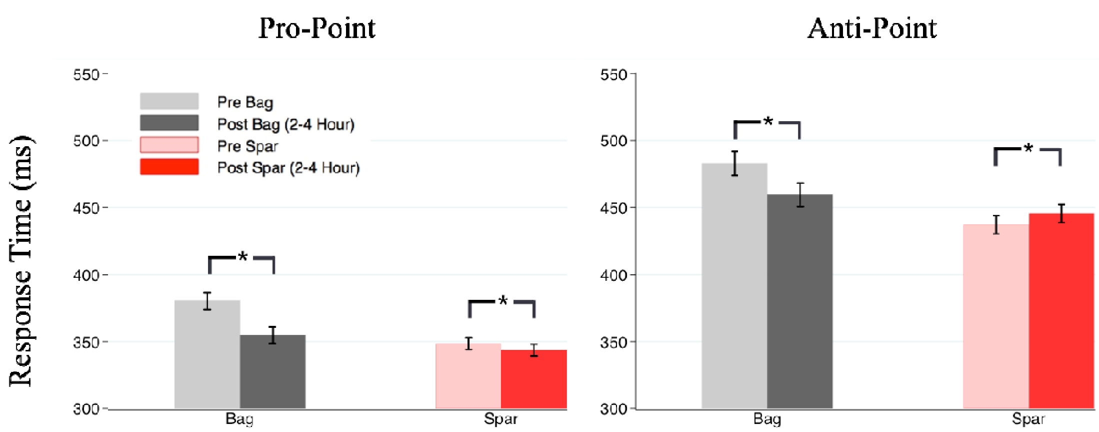


**Figure 5 Estimated mean initiation times at short-term timepoint.**

Gray bars represent data collected in the Bag condition. Red bars represent data collected in the Spar condition. Lighter gray and red bars represent data collected at the pre time point for Bag and Spar. Darker gray and red bars represent data collected at the short-term time point following Bag and Spar sessions. Error bars represent confidence intervals for within condition mixed model analysis. Significance levels: (*) for p<0.05. Significant deficits were seen in Anti-point initation time 2-4 hours following a Spar session.

*Long-Term (48 hour)*

**Figure 6** shows the initiation time results for 48 hours following Bag and Spar workouts. In the Pro-point task, no significant differences were found for initiation time 48 hours following Bag (+0.91 ms, p=.685) or Spar (+2.52 ms, p=.293) workout sessions. In the Anti-Point task no significant differences were found 48 hours following Bag workouts (-5.27ms, p=.291); however participants showed a significant slowing 48 hours following Spar workouts (+15.53 ms, p<.05).

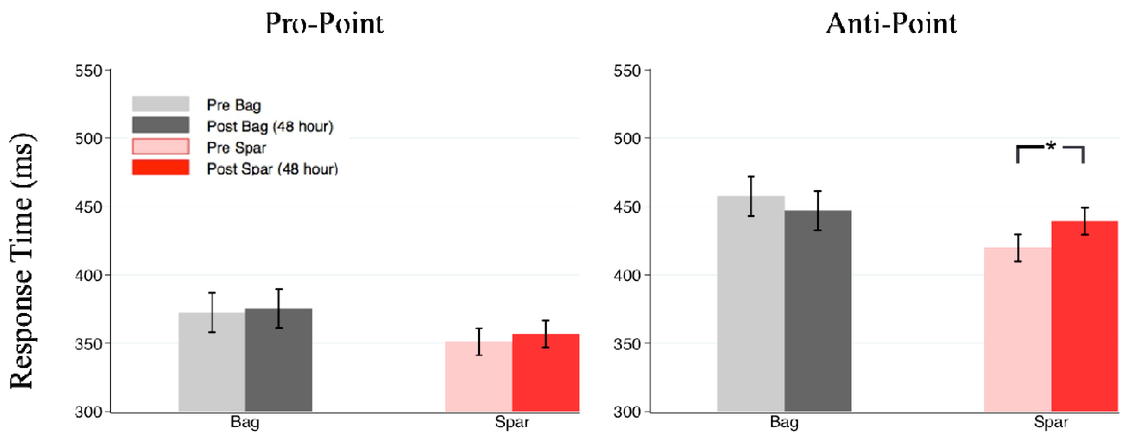


**Figure 6 Estimated mean initiation times at long-term timepoint.**

Gray bars represent data collected in the Bag condition. Red bars represent data collected in the Spar condition. Lighter gray and red bars represent data collected at the pre time point for Bag and Spar. Darker gray and red bars represent data collected at the long term time point following Bag and Spar sessions. Error bars represent confidence intervals for within condition mixed model analysis. Significance levels: (*) for p<0.05. Significant deficits in Anti-point initation were seen 48 hours following Spar sessions.

*Spar vs Bag analysis*

Results from the Spar vs Bag analysis for the Pro-point and Anti-point tasks are displayed in **Figures 7** and **8**, respectively. In the Pro-point task, no significant differences were seen at the immediate time point (-2.02 ms, p=.38; **Figure 7**). The results show a smaller improvement (reduction) in response time in Pro-point for the Spar condition when compared to the Bag condition at the short-term time point (+20.72 ms, p<.03; **Figure 7**). In the Pro-Point task, no significant differences between workout conditions were seen at the long-term time point (+1.61 ms, p=.78; **Figure 7**). For the Anti-point task, the analysis indicated a larger improvement in response time for the Spar condition at the immediate time point (-11.65 ms, p<.001; **Figure 8**). However, at the short and long-term time points in the Anti-point task, the results indicate a slowing in reaction time in the Spar condition (+33.42 ms, p<.001; +20.81ms, p<.01; **Figure 8**).

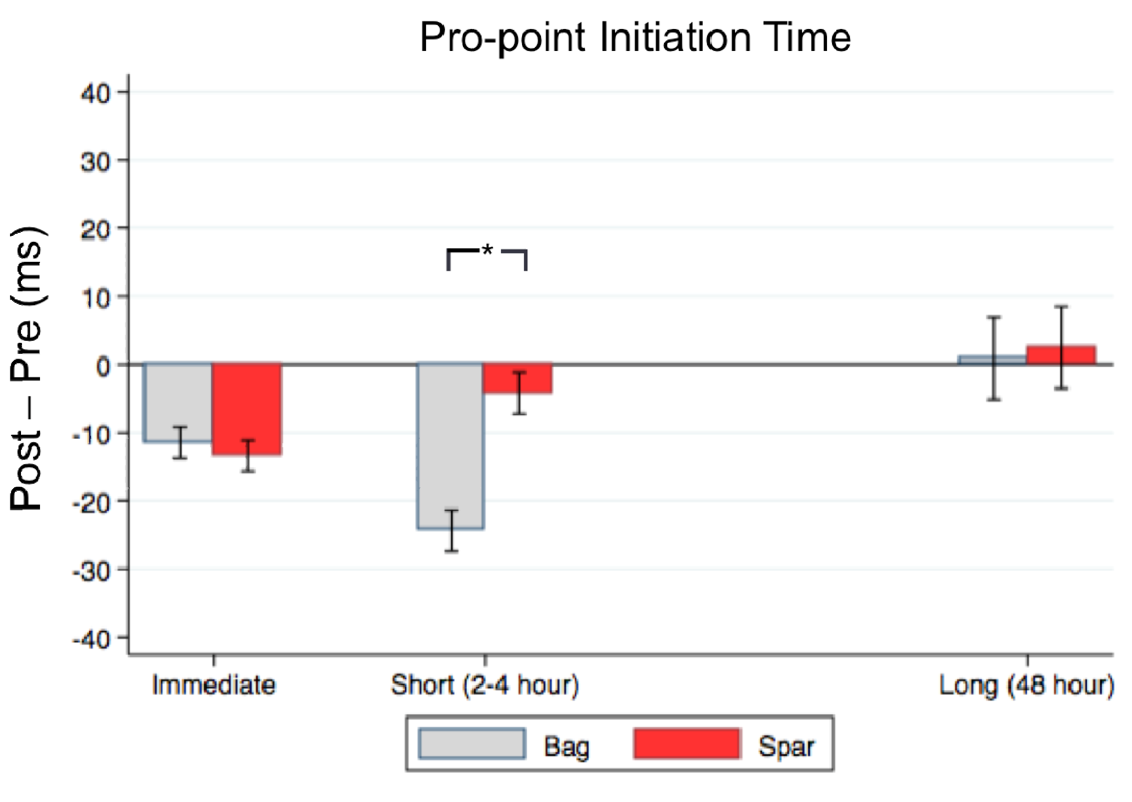


**Figure 7 Estimated pre and post difference for Pro-point initiation time.**

Gray bars represent data collected in the Bag condition. Red bars represent data collected in the Spar condition. Error bars represent confidence intervals for Spar vs Bag mixed model analysis. Significance levels: (*) for $p<0.05$. Pro-point initation showed a significant reduction 2-4 hours following Bag compared to Spar sessions.

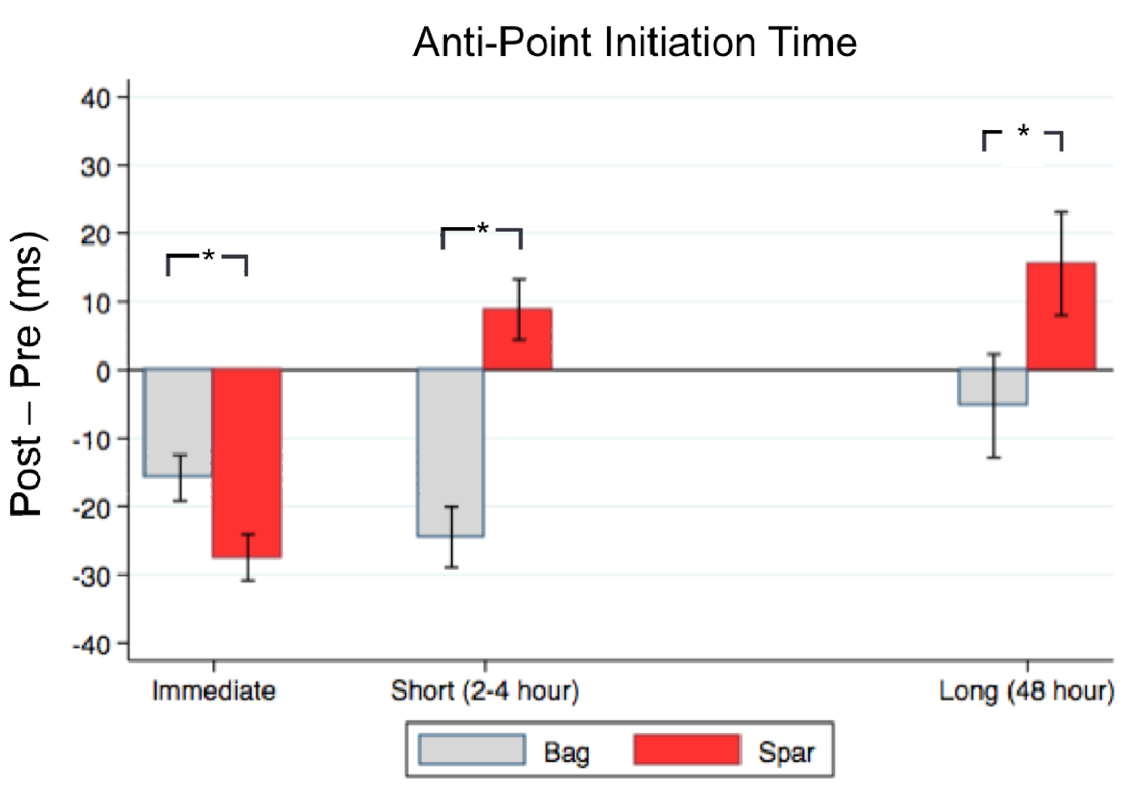


**Figure 8 Estimated pre and post difference for Anti-point initiation time.**

Gray bars represent data collected in the Bag condition. Red bars represent data collected in the Spar condition. Error bars represent confidence intervals for Spar vs Bag mixed model analysis. Significance levels: (*) for $p<0.05$. Anti-point initation showed a significant reduction immediately following Spar compared to Bag sessions. Significant slowing was apparent 2-4 and 48 hours following Spar as compared to Bag sessions.

<u>Reaction time results</u>

*Immediate*

The reaction time results are shown in **Figure 9**. As in the initiation time results, Pro-point performance at the immediate time point was significantly improved following both Bag (-29.73 ms, $p<.001$) and Spar (-25.06 ms, $p<.001$) workouts. Further, the Anti-point response times were also improved following both Bag (-28.30 ms, $p<.001$) and Spar (-38.95 ms, $p<.001$) workouts.

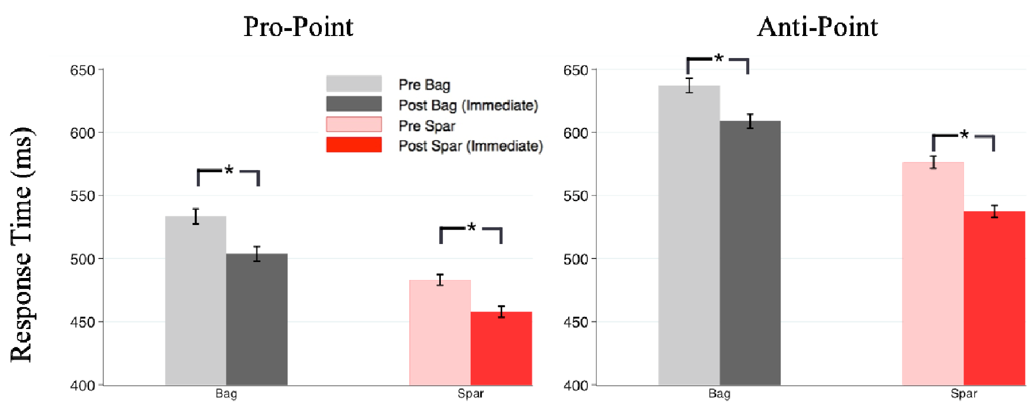


**Figure 9 Estimated mean reaction times at immediate timepoint.**

Gray bars represent data collected in the Bag condition. Red bars represent data collected in the Spar condition. Lighter gray and red bars represent data collected at the pre time point for Bag and Spar. Darker gray and red bars represent data collected at the immediate time point following Bag and Spar sessions. Error bars represent confidence intervals for within condition mixed model analysis. Significance levels: (*) for p<0.05. Significant improvements were seen immediately following Bag and Spar sessions for both Pro and Anti-point reaction times.

*Short-term time point (2-4 hours)*

**Figure 10** displays the reaction time data for the short-term time point. As in the initiation time analysis in the Pro-point task, subjects showed significant improvement 2-4 hours following Bag (-20.52 ms, p<.001) and Spar (-12.53 ms, p<.001) workouts. While on the Anti-point task, subjects showed significant improvement 2-4 hours following Bag workouts (-19.72 ms, p<.001), and no change was seen 2-4 hours following a Spar (-2.96 ms, p=.35) workout.

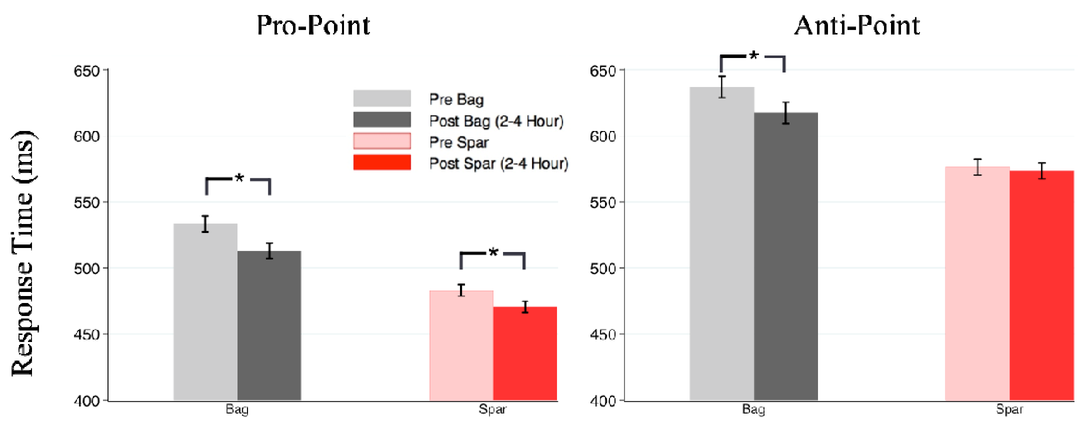


**Figure 10 Estimated mean reaction times at short-term timepoint.**

Gray bars represent data collected in the Bag condition. Red bars represent data collected in the Spar condition. Lighter gray and red bars represent data collected at the pre time point for Bag and Spar. Darker gray and red bars represent data collected at the short-term time point following Bag and Spar sessions. Error bars represent confidence intervals for within condition mixed model analysis. Significance levels: (*) for p<0.05. Significant improvements were seen 2-4 hours following Bag sessions for both Pro and Anti-point reaction times. Significant improvements were apparent 2-4 hours following in Pro-point reaction time, however no change following Sparring sessions.

*Long-term (48 hour)*

The reaction time results for 48 hours following Bag and Spar workouts are shown in **Figure 11**. Participants showed no significant differences in the Pro-point 48 hours following Bag (+3.61 ms, p=.737) and Spar (-1.92 ms, p=.356) workouts. Results in the Anti-point task indicated no change 48 hours following Bag workouts (+2.12 ms, p=.525), but a significant slowing 48 hours following Spar workouts (+22.84 ms, p=.027).

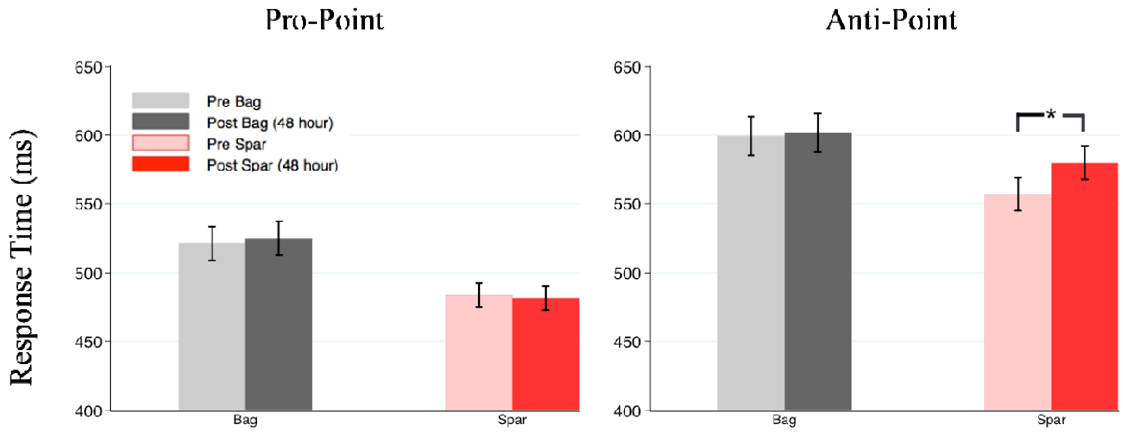


**Figure 11 Estimated mean reaction times at long-term timepoint.**

Gray bars represent data collected in the Bag condition. Red bars represent data collected in the Spar condition. Lighter gray and red bars represent data collected at the pre time point for Bag and Spar. Darker gray and red bars represent data collected at the long-term time point following Bag and Spar sessions. Error bars represent confidence intervals for within condition mixed model analysis. Significance levels: (*) for p<0.05. Significant anti-point reaction time slowing was apparent 48 hours following Sparring session.

*Spar vs Bag analysis*

The results from the Spar vs Bag analysis can be seen in **Figures 12** and **13**.

The analysis indicated that the improvements seen in the Pro-point task for the Spar condition were significantly smaller at the immediate (+5.76 ms, p<.05) and short-term (+10.93 ms, p<.01) time points. In the Pro-point task, No difference between conditions was seen at the long-term time point (-5.53 ms, p=.73). In the Anti-point task, a larger improvement occurred in the Spar condition when compared to the Bag condition at the immediate time point (-9.98 ms, p<.01).

Further, the Anti-point results indicate a smaller reduction in response time at the short-term time point in the Spar condition when compared to the Bag condition (+21.77 ms, p<.001). Additionally in the Anti-point task, a larger increase in reaction time occurred at the long-term time point for Spar when compared to Bag condition (+20.72 ms, p<.03).

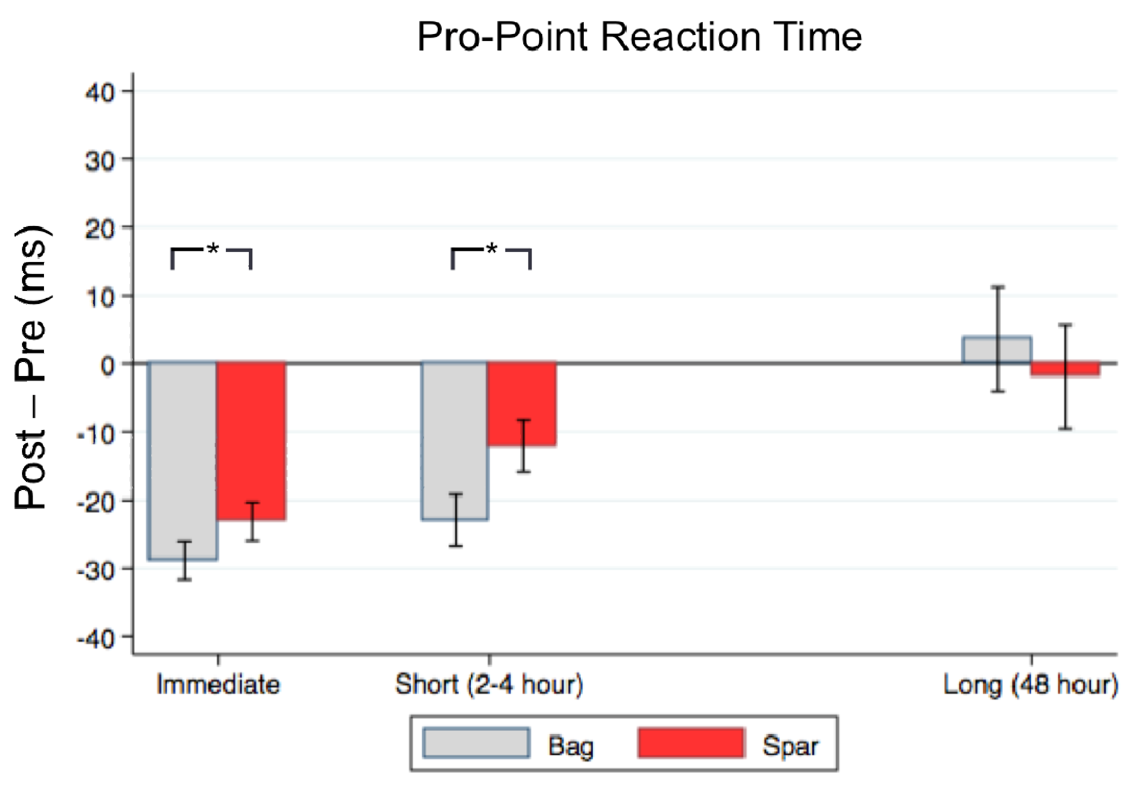


**Figure 12 Estimated pre and post difference for Pro-point reaction time.**

Gray bars represent data collected in the Bag condition. Red bars represent data collected in the Spar condition. Error bars represent confidence intervals for Spar vs Bag mixed model analysis. Significance levels: (*) for p<0.05. Significant Pro-point reaction time slowing was apparent immediatley and 2-4 hours following Spar as compared to Bag sessions.

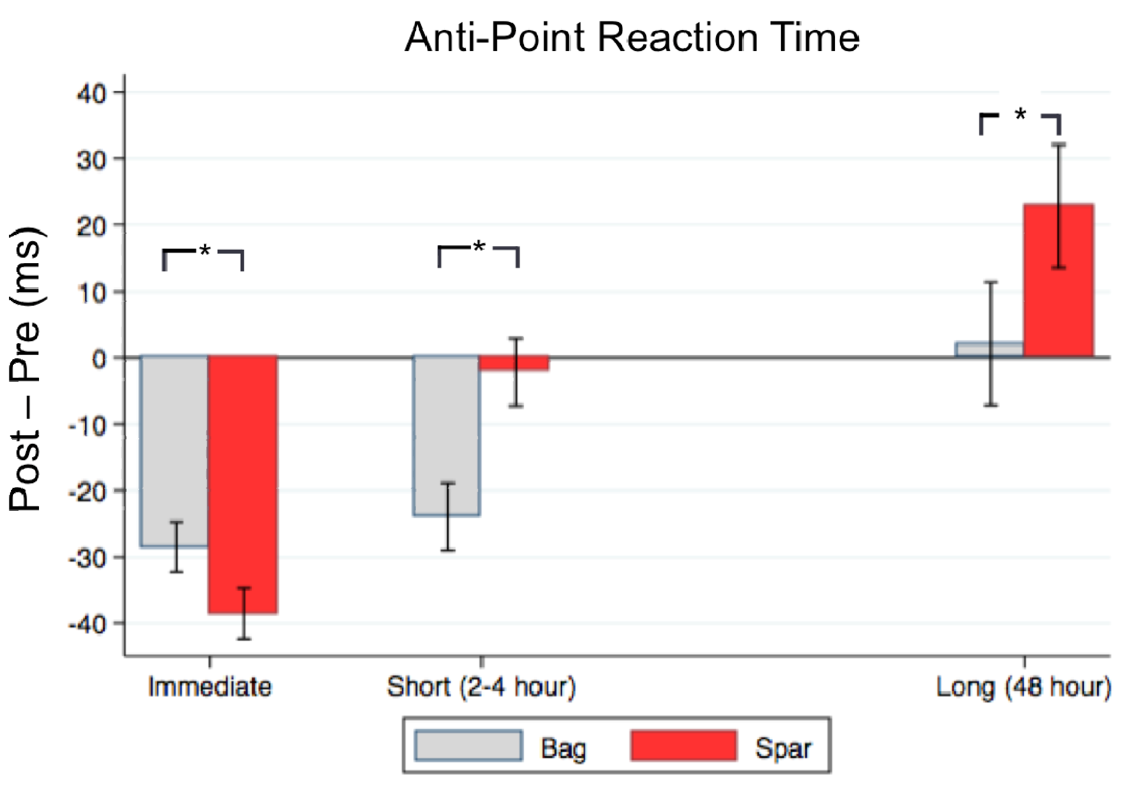


**Figure 13 Estimated pre and post difference for Anti-point reaction time.**

Gray bars represent data collected in the Bag condition. Red bars represent data collected in the Spar condition. Error bars represent confidence intervals for Spar vs Bag mixed model analysis. Significance levels: (*) for $p<0.05$. Anti-point reaction time showed a significant reduction immediately following Spar compared to Bag sessions. Significant slowing was apparent 2-4 and 48 hours following Spar as compared to Bag sessions.

## Discussion:

In professional boxers we found mixed changes at different time points following sessions of exercise (Bag) and exercise with subconcussive head blows (Spar). Specifically, we found significant improvements in Anti-point performance immediately following Bag and Spar sessions. However, we find a cognitive slowing 2-4 hours and 48 hours following Sparring sessions. We also find significant improvements in performance 2-4 hours following exercise sessions with no head blows (Bag).

Our results also indicate potential differences in subconcussive effects on our different response time variables (initiation time and reaction time). While most of the effects followed a similar pattern in the Spar vs Bag comparison, the reaction time results indicate a smaller reduction in response for the Spar compared to the Bag condition at the immediate time point. As the reaction time measurement includes the movement of the finger, it is possible that suboncussive head blows are having an immediate negative effect on the execution of the motor movement as opposed to a motor plan. Previous work in animal models of head injury, has suggested temporary negative effects on motor performance that quickly resolve (Shultz, MacFabe, Foley, Taylor, & Cain, 2011; Shultz, Bao, et al., 2012). However, as a clear improvement in reaction time is evident in both workout conditions, it is a relative negative effect.

Overall, these results indicate that the effects of subconcussive head blows vary across time in this population of professional boxers. As has been shown in previous animal studies, brain related changes following head blows have a variable time course (Giza & Hovda, 2001; Hovda et al., 2014; Wilde et al., 2012). Further, we indicate that improvements in cognitive performance are apparent following sessions of exercise alone (Bag). The cognitive benefits of exercise have been seen in previous studies (Joyce et al., 2009; Lambourne & Tomporowski, 2010). Previous studies have also suggested that benefits from exercise or arousal may limit potential deficits from head blows (Griesbach et al., 2009; Zhang, Red, Lin, Patel, & Sereno, 2013), thus the lack of deficits immediately following subconcussive head blows may also be related to the co-occurring benefits from the vigorous exercise involved in sparing sessions.

# Chapter 4

# Comparison of novel tablet based tasks to current measures

## Introduction:

As is clear from the previous chapters, in order to properly monitor the effects of head blows on brain behavior functioning requires measurements capable of detecting subtle differences. Current computer based tests and standard neuropsychological tests have failed to find effects for subconcussive head blows related to subconcussive blows likely due to a lack of sensitivity (Kontos, Dolese, Elbin, Covassin, & Warren, 2011; Resch et al., 2013).

More recently the tablet version of the King-Devick Test has been suggested as a more accurate and reliable sideline-screening test for concussion (Galetta, Brandes, et al., 2011; Galetta et al., 2013). The King-Devick Test is efficient to administer and has recently been shown to accurately diagnose concussed individuals when administered by non-medical personnel (Leong et al., 2014). While the King-Devick has shown great promise in the testing of concussion, recent work indicates that it is incapable of measuring differences in a population of emergency room concussed patients when compared to non-head injury patients (Silverberg, Luoto, Ohman, & Iverson, 2014). Thus, the King-Devick may lack the necessary sensitivity to measure changes related to subconcussive head blows as well. As indicated in Zhang et al. (2013), and in the previous chapters the Anti-point task is capable of measuring the subtle changes from subconcussive blows and therefore will likely have superior sensitivity to the King-Devick Test (Zhang, Red, Lin, Patel, & Sereno, 2013).

The following analyses were performed to first test the ability of the King-Devick to monitor changes related subconcussive head blows in the same professional boxing population from chapter 3. Further, Receiver Operating Characteristic (ROC) analyses were performed to compare the sensitivity and specificity of the Pro-point, Anti-point, and King-Devick tasks to subconcussive head blows. We hypothesized that the King-Devick would fail to detect subtle the subtle changes from subconcussive head blows and that our Anti-point task would have superior sensitivity and specificity to subconcussive head blows.

## Methods:

Procedure

Data for the King-Devick Test was collected in the same sessions as data from Chapter 3. The Pro and Anti-point tasks were counterbalanced with the King-Devick Test for a given subject being administered before or after the administration of the Pro and Anit-point tasks.

The King-Devick is a brief rapid number naming test, and was administered using the tablet version. Examples of the tablet version of the King-Devick Test cards are shown in **Figure 14**. For this task, subjects are asked to read each number, beginning on the top line, from left to right. The subjects are also instructed to touch the screen after reading the last number (bottom line). The subjects completed two sets of cards for each session. Each set of cards included a demonstration card and 3 test cards (**Figure 14**). King-Devick timing scores are based on the sum of the set of 3 test cards. If a subject said the wrong number, an error was recorded by the experimenter. As has been done in previous studies the best score (least errors and faster time) out of the sets of cards was used as the King-Devick Test score (Silverberg et al., 2014).

Data analysis

As in chapter 3, Response time data from the King-Devick Test was analyzed using a mixed effect model. As in the analysis for the Pro and Anti-point tasks, the effect of time point was analyzed separately for each condition. As in the analysis from chapter 3, the effect of condition (Spar vs Bag) was analyzed for differences across Time Points.

For the sensitivity and specificity analysis, the differences in mean response time from pre to post (immediate, short, long-term) were calculated for each individual in each task (Pro-point, Anti-point, and King-Devick Test). Then a ROC analysis was performed separately for each time point and for each task (Pro-point, Anti-point, and King-Devick Test) to evaluate the sensitivity and specificity of changes in response time to sessions of exercise with subconcussive head blows (Spar) and exercise alone (Bag). The area under the ROC curve (AUROC) will be reported, as it is a summary of the sensitivity and specificity of a measure with values above .8 being considered good.

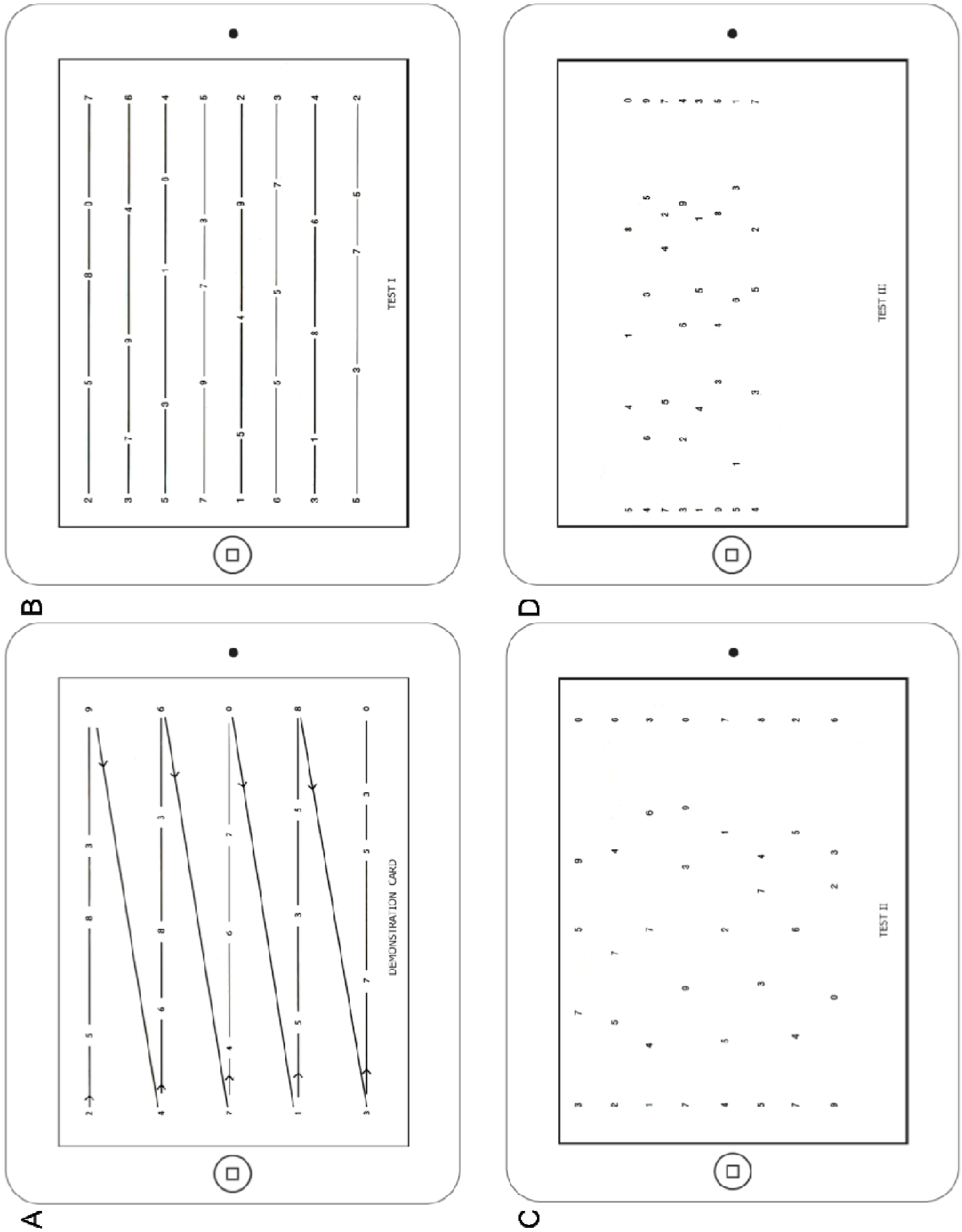


**Figure 14 King-Devick stimuli.**

Example set of demonstration and test screens from tablet version of King-Devick Test. Example screens are shown in order as presented to subjects from A-D. For procedure details see text.

**Results:**

*Immediate*

**Figure 15** displays the results of the King-Devick Test. The analysis indicated that there was no significant change (-2.43 s, p=.17) in performance following the Bag workout. However, individuals showed a significant improvement (-2.86 s, p<.01) in performance (faster times) following Spar workouts.

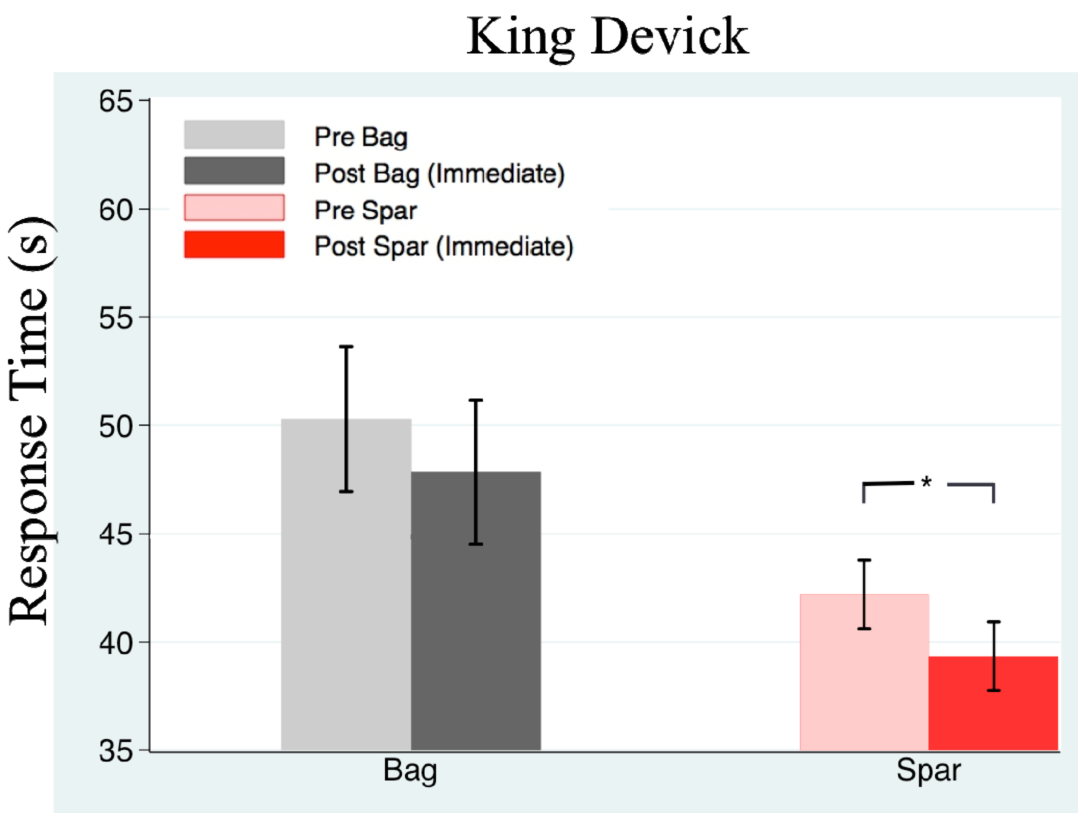


**Figure 15 Estimated King-Devick Test scores at immediate timepoint.**

Gray bars represent data collected in the Bag condition. Red bars represent data collected in the Spar condition. Lighter gray and red bars represent data collected at the pre time point for Bag and Spar. Darker gray and red bars represent data collected at the immediate time point following Bag and Spar sessions. Error bars represent confidence intervals for within condition mixed model analysis. Significance levels: (*) for p<0.05. Significant improvements in King-Devick response time immediately following Sparring sessions.

*Short-term (2-4 hour)*

The results for the King-Devick Test at the short-term point can be seen in **Figure 16**. Participants showed no change 2-4 hours following Bag (+1.14 s, p=.60) or Spar (.26 s, p=.80) workouts

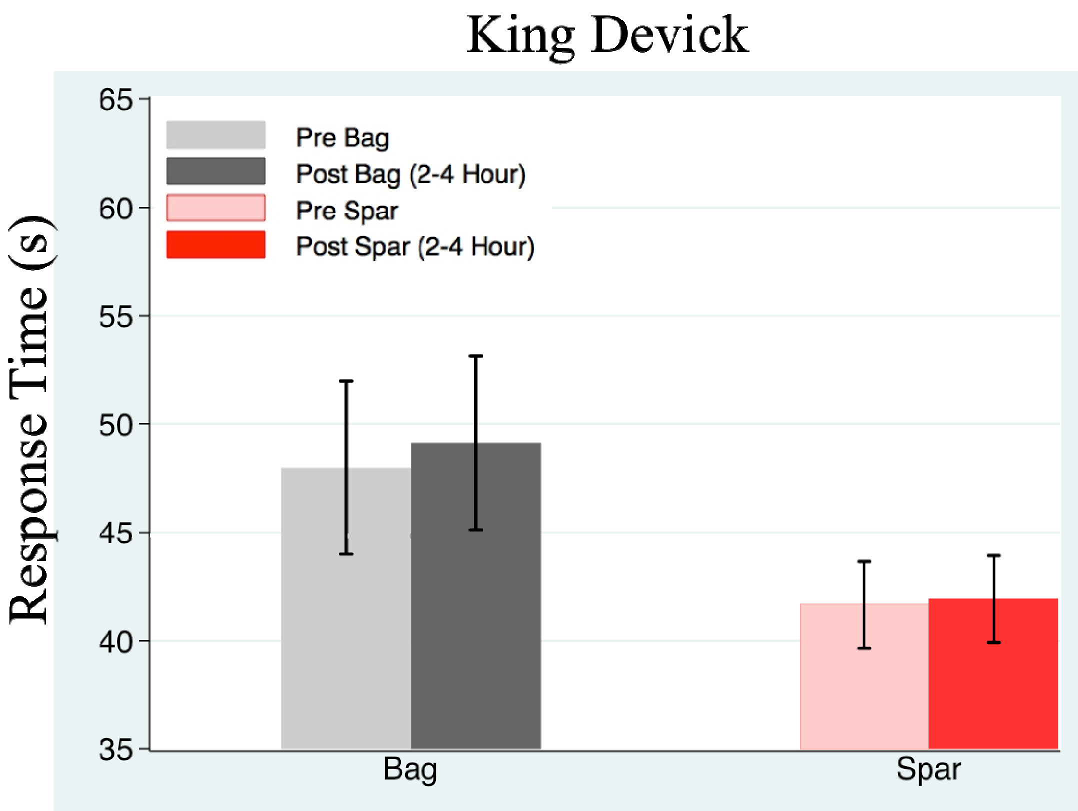


**Figure 16 Estimated King-Devick Test scores at short-term timepoint.**

Gray bars represent data collected in the Bag condition. Red bars represent data collected in the Spar condition. Lighter gray and red bars represent data collected at the pre time point for Bag and Spar. Darker gray and red bars represent data collected at the short-term time point following Bag and Spar sessions. Error bars represent confidence intervals for within condition mixed model analysis. Significance levels: (*) for p<0.05. No significant differences 2-4 hours following Spar or Bag.

*Long-term (48 hour)*

The results for the King-Devick Test at the long-term time point can be seen in **Figure 17**. Participants showed no change 48 hours following Bag (-2.90 s, p=.38) or Spar (+.68 s, p=.72) workouts.

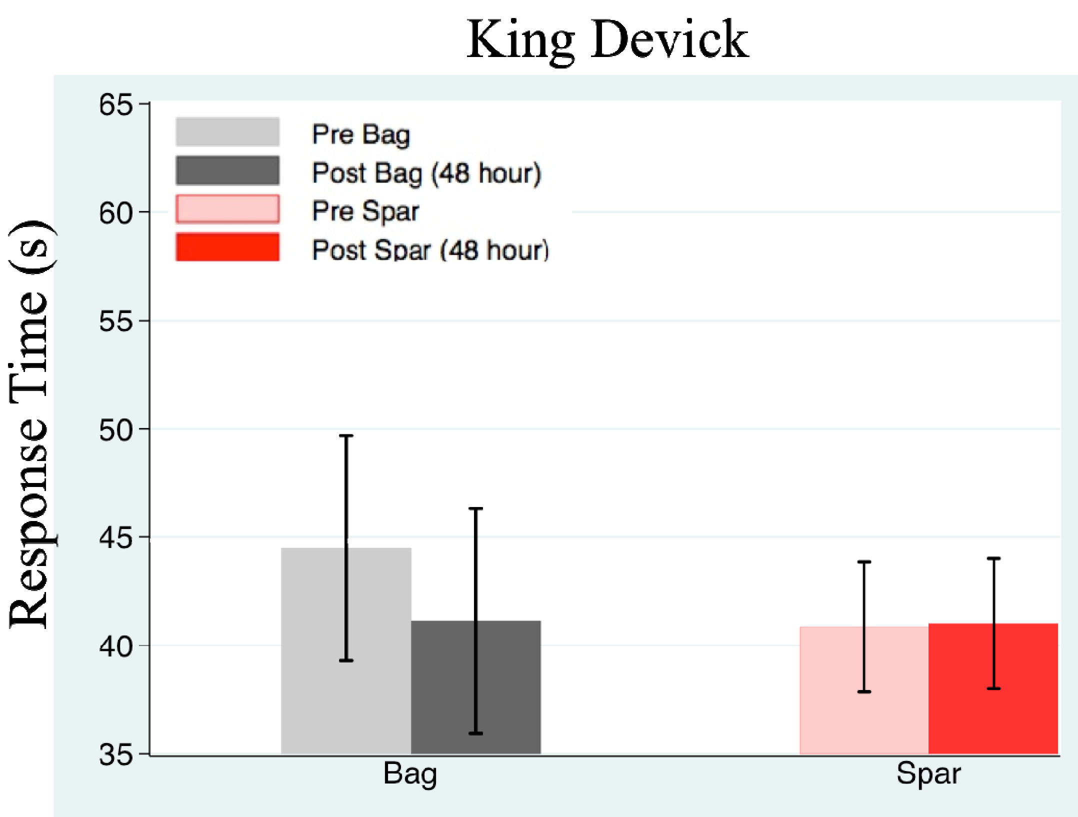


**Figure 17 Estimated King-Devick Test scores at long-term timepoint.**

Gray bars represent data collected in the Bag condition. Red bars represent data collected in the Spar condition. Lighter gray and red bars represent data collected at the pre time point for Bag and Spar. Darker gray and red bars represent data collected at the long-term time point following Bag and Spar sessions. Error bars represent confidence intervals for within condition mixed model analysis. Significance levels: (*) for p<0.05. No significant differences 2-4 hours following Spar or Bag.

*Spar vs Bag analysis*

The results for the Spar vs Bag analysis of the King-Devick Test can be seen in **Figure 18.** There was no significant differences between condtions at the immediate (-.39 s, p=.81), short-term (-.45 s, p=.82), or long-term time-point (+2.2 s, p=.24).

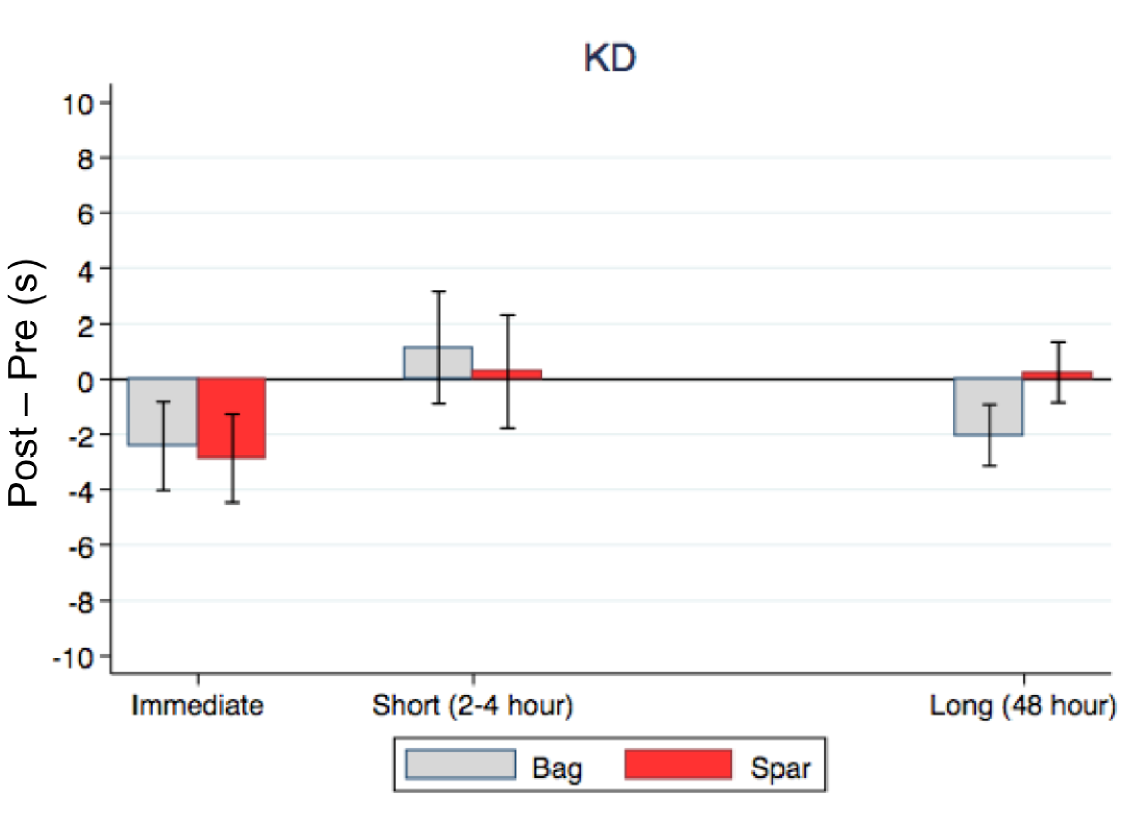


**Figure 18 Estimated pre and post difference for King-Devick Test score.**

Gray bars represent data collected in the Bag condition. Red bars represent data collected in the Spar condition. Error bars represent confidence intervals for Spar vs Bag mixed model analysis. Significance levels: (*) for p<0.05. No significant between Bag and Spar at any time point.

Sensitivity and specificity analysis

*Immediate*

The results from the ROC analysis for each task at the immediate time point are shown in **Table 7**. As was expected from the results above and in the previous chapter, none of the tasks showed high sensitivity at the immediate time point. The results indicate the Pro and Anti-point reaction times have the best sensitivity and specificity of all these tasks.

| | Area under the ROC curve |
|---|---|
| Pro-point initiation time | .53 |
| Anti-point initiation time | .60 |
| Pro-point reaction time | .64 |
| Anti-point reaction time | .66 |
| King Devick Test score | .54 |

**Table 7 AUROC for all tasks at immediate time point.**

Area under the ROC (AUROC) values are shown for each task. Initation and reaction times are included separately for Pro-and Anti-point tasks.

*Time point 2*

**Table 8** shows the results from the ROC analysis for each task at the short-term time point. Anti-point initiation time shows the largest area under the ROC curve, thus indicating it has superior sensitivity to the other measures (**Table 8**). **Figures 19** and **20** show the ROC curves for the ROC analysis of initiation and reaction time, respectively.

| | Area under the ROC curve |
|---|---|
| Pro-point initiation time | .76 |
| Anti-point initiation time | **.90** |
| Pro-point reaction time | .48 |
| Anti-point reaction time | .78 |
| King-Devick Test score | .62 |

**Table 8 AUROC for all tasks at short-term time point.**

Area under the ROC (AUROC) values are shown for each task. Initation and reaction times are included separately for Pro-and Anti-point tasks. By convention, AUROC values above .80 are considered highly sensitive and specific; therefore, they are bolded.

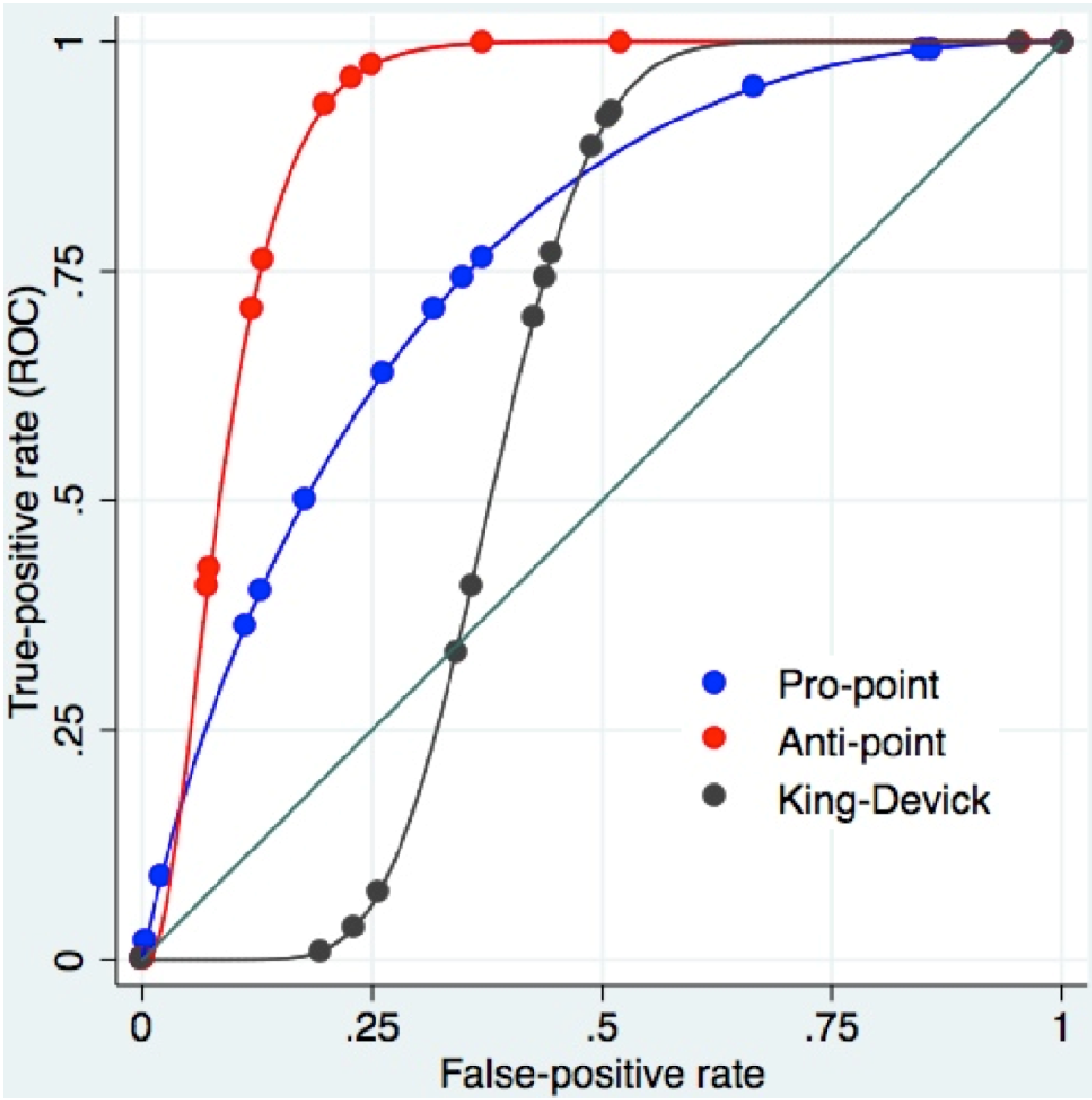


**Figure 19 ROC curves for initation time and King-Devick Test at short-term timepoint.**

Blue markers and line represent ROC curve for pro-point initation time. Red markers and line represent ROC for anti-point initation time. Gray makers and line represent ROC curve for King-Devick Test. Anti-point initation time has the best sensitivity and specificity.

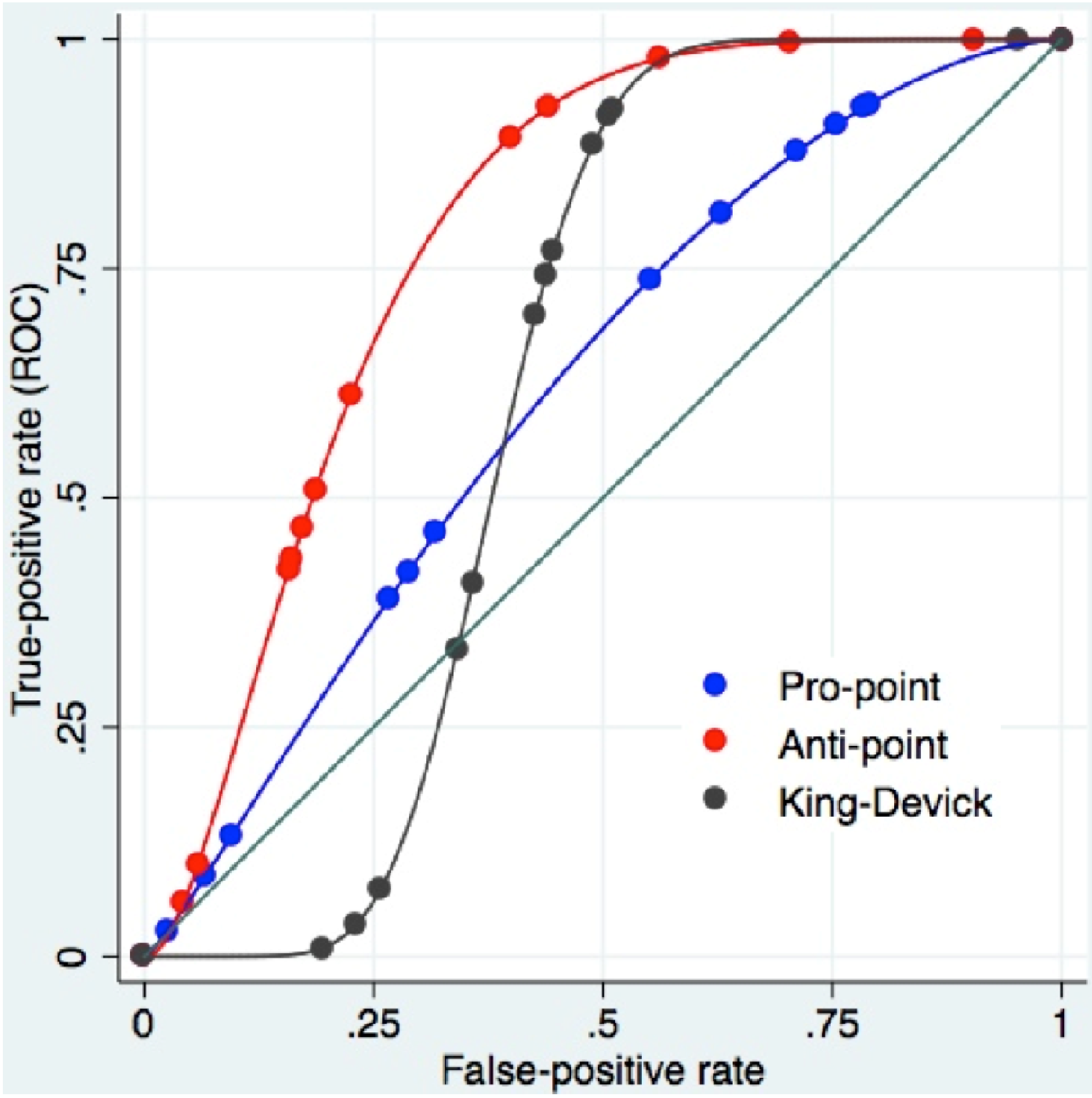


**Figure 20 ROC curves for reaction time and King-Devick Test at short-term timepoint.**

Blue markers and line represent ROC curve for pro-point initation time. Red markers and line represent ROC for anti-point initation time. Gray makers and line represent ROC curve for King-Devick Test. Anti-point reaction time has the best sensitivity and specificity.

*Long-term time point*

The results for the ROC analysis of the long-term time point are shown in **Table 9**. None of the tasks exhibited high sensitivity at the long-term time point, however Anti-point initiation and reaction time were the highest.

| | Area under the ROC curve |
|---|---|
| Pro-point initiation time | .51 |
| Anti-point initiation time | .59 |
| Pro-point reaction time | .51 |
| Anti-point reaction time | .59 |
| King-Devick Test score | .53 |

**Table 9 AUROC for all tasks at long-term time point.**

Area under the ROC (AUROC) values are shown for each task. Initation and reaction times are included separately for Pro-and Anti-point tasks.

## Discussion:

The current results show that all the tasks (King-Devick, Pro- and Anti-point) fail to reliably detect performance changes immediately following sessions of repetitive head blows, however the Anti-point task shows high sensitivity 2-4 hours following. More specifically, our results show that Anti-point initiation time is a more sensitive measure of behavioral changes related to subconcussive head blows in the same population of professional boxers then the current gold standard of tablet based concussion testing, the King-Devick Test. Further, we show that no task showed high sensitivity or specificity at the long-term time point. Additionally, we show that the King-Devick Test is unable to detect subtle changes related to subconcussive head blows.

In line with results from the previous chapter, none of the tasks were able to monitor deficits related to subconcussive head blows immediately following a Sparring session. It is possible that the positive benefits of exercise and/or adrenaline may be masking symptoms immediately following sets of subconcussive head blows. Further, biochemical changes related to the secondary phase of injury are known to be delayed in their onset (Barkhoudarian et al., 2011; Giza & Hovda, 2001), and may be delayed in their effect on performance in the tasks (King-Devick, Pro- and Anti-point) from this set of experiments. Finally, the lack of sensitivity and specificity at the long-term time point, may indicate possible recovery of function 48 hours following subconcussive head blows.

Overall, these results indicate that while the King-Devick Test has been proven as a ideal monitor of diagnosable concussive head blows (Dziemianowicz et al., 2012; Galetta, Brandes, et al., 2011; Leong et al., 2014), it appears to lack the ability to monitor changes related to subconcussive head blows. The superior sensitivity and specificity of the Anti-point task at the short-term time point further indicate that it may be a better behavioral measure for monitoring changes related to subconcussive head blows.

# Chapter 5

# Summary of findings and discussion

## Summary of findings:

As shown in Chapter 2, our results indicate that this novel tablet based task was capable of measuring subtle differences between a group of soccer players participating in heading drills and age matched controls. Although sensorimotor behavior was intact, the group of high school soccer players showed slowing in the Anti-point task. This slowing indicates that immediately following a practice session involving subconcussive head blows, these individuals are experiencing some deficit in cognitive functioning. Additionally, we showed that slowing in the Anti-point task was related to long-term soccer variables (hours of soccer played per week, and years of soccer participation).

In chapter 3, the results show that subconcussive head blows result in cognitive changes that vary across time. In a population of professional boxers, immediately following a Sparring session, cognitive performance is improved. However, cognitive slowing is evident 2-4 hours and 48 hours following a workout session including subconcussive blows (Spar). Further we show improvements in cognitive performance immediately and 2-4 hours following exercise sessions without subconcussive blows (Bag), thus indicating benefits from exercise.

In chapter 4 we demonstrated that the King-Devick Test was unable for the most part to detect these subtle changes related to subconcussive head blows in the same population of professional boxers. Further, we showed that our Anti-point task had superior sensitivity and specificity in detecting changes related to subconcussive head blows at the short-term time point. Additionally, our results indicate that none of the tasks have high sensitivity and specificity immediately or 48 hours following sessions of subconcussive head blows in this population of professional boxers.

## Discussion:

*Aim 1*

In Aim 1, we showed that our Anti-point task was able to detect subtle cognitive differences related to subconcussive head blows in a group of high school soccer players as compared to age matched controls. An alternative conclusion could be that this cognitive slowing is not due specifically to the subconcussive head blows, but rather it could be an effect of fatigue from exercising during the soccer practice. However, previous studies have indicated that aerobic exercise actually improves cognitive performance (Budde, Voelcker-Rehage, Pietrabyk-Kendziorra, Ribeiro, & Tidow, 2008; Lambourne & Tomporowski, 2010). Further, it is possible that the benefits from exercise may have actually reduced deficits related to subconcussive head blows in the soccer players.

In Aim 1, we also showed that slowing in the Anti-point task was related to more long-term soccer variables (hours per week of soccer, years of soccer participation). Data for the soccer experiments was gathered immediately following practice; therefore it is possible that this slowing is only evident immediately following a practice involving headers. However, another explanation could be that long-term brain changes are stable and that the cognitive changes occurred across the days and years of soccer participation.

*Aim 2*

In Aim 2, we have showed that the cognitive effects of subconcussive head blows vary across time in a group of professional boxers. Alternatively, these results could be interpreted as changes in arousal or adrenaline. Following this hypothesis, one might attribute the immediate benefit in cognitive performance following a Sparring session to increases in arousal or adrenaline following participation in a high intensity combative sports event. Further, as increases in arousal are known to precede combative events, deficits at the 2-4 hour time point would be attributed to a return to normal baseline of adrenaline as has been seen in other combative sports (Barbas et al., 2011). However, the improvement seen in exercise without head blows was not evident 2-4 hours following the Sparring session. Further, deficits at the long-term time point cannot be attributed purely to changes in adrenaline or arousal due to the upcoming combative event. In the analysis of the long-term effect of Sparring, only data from participants before a Sparring match was included. By doing this we have aimed to control for any increase in adrenaline that may be seen prior to a combative sports event. In this case, we still see deficits 48 hours following a spar workout. Hence, we do not think the deficits we report can be interpreted as a change in arousal or adrenaline.

*Aim 3*

In Aim 3, we have shown that the Anti-point task shows superior sensitivity and specificity to subconcussive head blows when compared to the King-Devick Test in the same population of professional boxers at the short-term time point. Another possible conclusion is that our test is specific to the effects of exercise and not subconcussive head blows. To fully test such a hypothesis would require a situation in which subconcussive head blows were not co-occurring (before or after) exercise. Future experiments could try and take advantage of sport specific drills that include head blows but little to no exercise component. These sorts of experiments would require extensive cooperation from the players involved. Further, such experiments may be able to clearly separate out the effects of head blows from exercise, but would not accurately portray the typical situations in which subconcussive head blows are incurred.

Additionally, these results indicate that all tasks, including the Anti-point, lack sensitivity to changes in performance 48 hours following subconcussive head blows. Data for this analysis was based on a subset of boxers who met the necessary conditions; therefore, the small subject number makes it difficult to determine if the tasks lack sensitivity or if it would improve with an increased number of subjects. However, it is also possible that individuals are showing recovery from these subconcussive head blows by 48 hours. There is indication that cognitive deficits are apparent 48 hours following subconcussive head blows based on the results in chapter 3, and well-controlled studies focused on the sensitivity of these tasks to the long-term (across days) effects of subconcussive head blows are definitely warranted.

*Differences in Aim 1 and 2*

Our results from Chapter 2 indicate a slowing immediately following a session of subconcussive head blows in a group of non-professional high school soccer players. However, in Chapter 3, we show a cognitive benefit immediately following a session of subconcussive head blows in a population of professional boxers. There are several differences that may have influenced these contradictory findings.

*Higher intensity exercise in professional athletes*

Previous research has indicated that increased arousal from exercise can improve cognitive performance, especially on reaction time experiments (Audiffren, Tomporowski, & Zagrodnik, 2008; Lambourne & Tomporowski, 2010). Some have even suggested that this increased arousal could potentially mask cognitive deficits from head blows (Griesbach, Hovda, & Gomez-Pinilla, 2009; Zhang, Red, Lin, Patel, & Sereno, 2013). The results obtained for Chapter 2 were in a group of non-professional soccer players, while results in Chapter 3 included a population of professional boxers. Previous work has shown that individuals at higher fitness levels, such as the professional boxers, experience larger cognitive benefits from intense exercise (Budde et al., 2008; Lambourne & Tomporowski, 2010; Tsai et al., 2014). Further, higher intensity exercise is known to induce larger and more immediate improvements on cognitive performance (Budde, Voelcker-Rehage, Pietrabyk-Kendziorra, Ribeiro, & Tidow, 2008; Joyce et al., 2009; Lambourne & Tomporowski, 2010). Thus indicating that the professional boxers may be seeing larger benefits of exercise than the population of non-professional high school soccer players. This increased benefit could be based on higher intensity exercises performed as well as the increased level of fitness in these professional athletes. Further, this increased benefit from exercise may be delaying or masking symptoms from subconcussive head blows.

*Effect of adrenaline*

Beyond just an effect of fitness level and higher intensity exercise, further increases in adrenaline from involvement in a combative sport such as boxing may additionally enhance some of the effects of exercise. Previous work has indicated that exercise induced increases in adrenaline may be related to increases in arousal and improved performance on cognitive tasks (Davis, Loiacono, & Summers, 2008; Leuenberger & Sinoway, 1993; Zouhal, Jacob, Delamarche, & Gratas-Delamarche, 2008). Increases in adrenaline are known to accompany combative sports, and thus may result in cognitive benefit beyond just exercise (Barbas et al., 2011). Further, individuals that are high level athletes, such as the professional boxers in our study, show an increased adrenaline response to exercise possibly due to growth in their adrenal gland (Zouhal et al., 2008). Thus large increases in adrenaline related to the combative nature of sparring and increased adrenal response in high-level athletes may contribute to the large benefits seen immediately following sparring sessions. These large adrenaline related benefits could potentially mask cognitive deficits from the subconcussive head blows immediately following Sparring sessions. Further, levels of adrenaline in combative sports have been shown to return to baseline 90 minutes following a combative sport event (Barbas et al., 2011). Thus, the professional boxers are no longer experiencing the benefits of adrenaline 2-4 hours following sparring sessions. Therefore, this may account for the presence of cognitive slowing, as there is no longer a cognitive benefit of adrenaline. However, this explanation cannot account for the slowing seen at 48 hours (pre

Spar).

To specifically test if adrenaline may affect performance on the Anti-point task, we compared the Anti-point response times prior to a Bag and Spar session. Previous studies have shown increases in adrenaline prior to the start of a combative sport event (Barbas et al., 2011). In order to control for effects of activity from the previous days, we selected a subset of the data (same as used for 48 hour analysis) that was preceded by at least 2 days of no subconcussive head blows. The results show that prior to the beginning of a Sparring session (Pre Spar), individuals show improved cognitive (-35.08 ms, $p<.005$; **Figure 21**) and sensorimotor (-21.45 ms, $p<.05$; **Figure 21**) performance when compared to performance prior to a Bag session (Pre Bag). Thus indicating that both sensorimotor and cognitive benefits occur prior to the onset of a sparring match. As increases in adrenaline may be fueling these improvements, it is also possible that the known large increases immediately following combative sports participation may be masking deficits related to subconcussive head blows in this population of professional boxers. Further, these pre activity differences in cognitive performance have implications for potential confounds in standard baseline testing. For example, a baseline test performed prior to the beginning of a sports season may not provide the proper baseline for comparison on the day of a practice or game session involving head blows where exercise and adrenaline alter baseline levels.

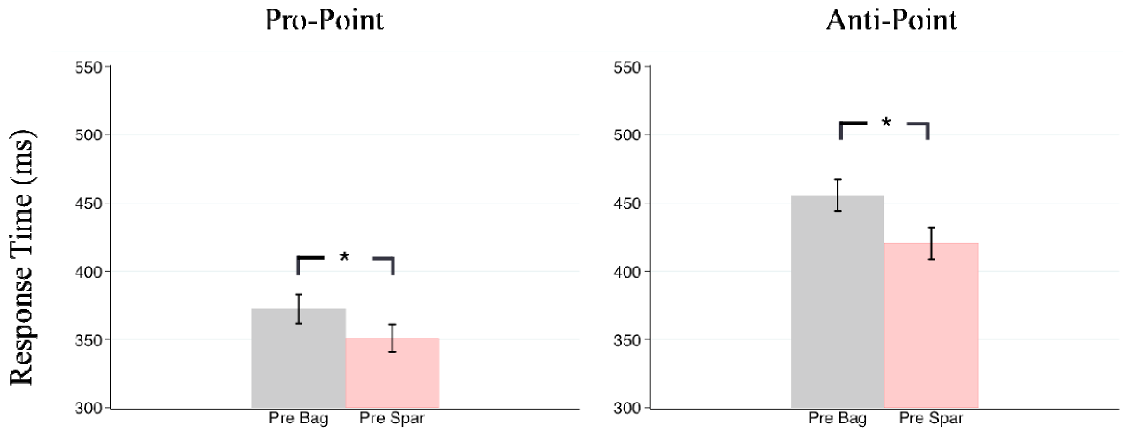


**Figure 21 Estimated mean initiation times for pre session in each condition.**

Gray bars represent data collected in the Bag condition. Red bars represent data collected in the Spar condition. Error bars represent confidence intervals for Spar vs Bag mixed model analysis. Significant improvement in Pro and Ant-point initaiton time performance in Pre Spar compared to Post Spar.

Future cognitive testing for head blows

While the scope of this project was limited to subconcussive head blows, the results have indication for the future testing of both subconcussive and concussive head blows. We have established that cognitive changes related to even subconcussive head blows can differ across time. As mentioned above, increases in exercise and adrenaline may be underlying some of these differences. Current work in sideline assessment, has aimed to better assess brain functioning immediately following possible concussive events (Broglio & Guskiewicz, 2009; Galetta, Brandes, et al., 2011; Terrell et al., 2014). Results obtained immediately following participation in sporting events should be interpreted with caution and future testing of head blows must factor in time since injury as well as current activity. Further, our results indicate that baseline tests should take into account the activities (exercise, exercise with subconcussive blows, competition, etc) that may be affecting the cognitive performance of individuals.

The work presented here also indicates that our novel tablet based tasks, specifically the Anti-point, offers the necessary sensitivity and specificity to measure the subtle changes related to subconcussive head blows. Such a task has great use as it is portable, inexpensive, and can be potentially administered by a lay person because of their simplicity. Other tablet based tasks, such as the King-Devick Test, have been shown to be effectively administered by lay persons and therefore show great promise in gaining an understanding of the various aspects of cognitive functioning in a wide variety of special populations including head trauma patients (Leong, Balcer, Galetta, Liu, Master, 2014). However, as the Anti-point test shows superior sensitivity it appears to be a better monitor of subconcussive head blows.

Finally, this work may also have importance in the monitoring and prediction of future symptoms in individuals who experience head blows. Following a concussive event or a substantial decline in functioning from a subconcussive head blow, these tasks could be used to continually and objectively monitor an individual's behavior. Clinicians or other medical professionals could use results from the Anti-point task to help determine appropriate treatments for individuals incurring subconcussive and concussive head blows.

Conclusions

In sum, goal directed tablet based tasks seem to have the necessary sensitivity to detect subtle cognitive changes related to subconcussive head blows as well as changes related to exercise. Further, the tablet based Anti-point task is capable of measuring changes across time. Even showing deficits 2-4 and 48 hours following sessions of subconcussive head blows. Finally, we have demonstrated that the Anti-point task exhibits superior sensitivity and specificity to subconcussive head blows as compared to the King-Devick Test.

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