APPROVAL SHEET

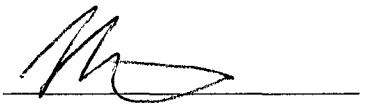
Title of Thesis: Developing a Novel Eye Tracking Paradigm to Assess Mild Traumatic Brain Injury: A Feasibility Study of the Bethesda Eye & Attention Measure (BEAM)

Name of Candidate: David M. Barry

Master of Science

October, 2012

Thesis and Abstract Approved:



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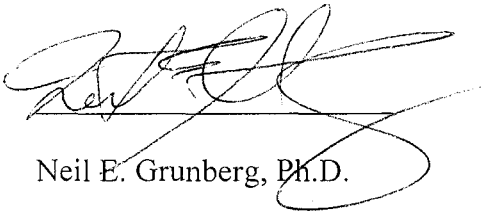

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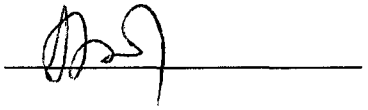

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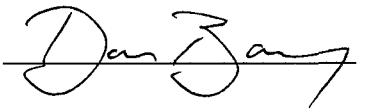

David M. Barry

Department of Medical and Clinical Psychology

Uniformed Services University of the Health Sciences

ABSTRACT

Title of Thesis: Developing a Novel Eye Tracking Paradigm to Assess Mild Traumatic Brain Injury: A Feasibility Study of the Bethesda Eye & Attention Measure (BEAM)

Author: David M. Barry, Master of Science, 2012

Thesis directed by: Mark L. Ettenhofer, Ph.D., Assistant Professor
Department of Medical and Clinical Psychology

The Bethesda Eye & Attention Measure (BEAM), a computer-based eye tracking paradigm, was designed to assess visual (i.e., saccadic) and manual (i.e., button press) reaction times to stimuli that appear on a screen. A developmental phase and two studies were conducted to assess the feasibility of the BEAM for the assessment of cognitive performance in humans with a history of mild TBI. It was determined that the BEAM could elicit multiple cognitive processes in a small sample ($N = 11$) of adult men and women without a history of brain injury. Orienting, alerting, executive, and gap effects were found in both visual and manual reaction times. The results suggest the BEAM is capable of assessing cognitive performance. Future studies comparing visual and manual reaction times between individuals and groups with and without a history of TBI are needed to evaluate the BEAM's viability as a clinical measure of cognitive impairment.

TITLE PAGE

Developing a Novel Eye Tracking Paradigm to Assess Mild Traumatic Brain Injury:

A Feasibility Study of the Bethesda Eye & Attention Measure (BEAM)

by

David M. Barry

Master's Thesis submitted to the Faculty of the

Department of Medical and Clinical Psychology

Graduate Program of the Uniformed Services University

of the Health Sciences in partial fulfillment

of the requirements for the degree of

Master of Science, 2012

ACKNOWLEDGEMENTS

First and foremost, I'd like to thank my wife Erin for her limitless support and dedication. She has been and will always be instrumental to my happiness and success. I thank my son Bradley for giving me the priceless gift of fatherhood. I wholeheartedly thank my family and Erin's family for supporting all I do. I'd also like to thank my friends—from those met at USUHS to lifelong friends from Tennessee—for continuously providing sources of humor and fun. I thank you all for being there for me.

I am eternally grateful to Mark Ettenhofer for his mentorship. In two years, Dr. Ettenhofer has dedicated countless hours to my development as a clinician and a researcher. He gave me a tremendous amount of responsibility and several difficult tasks, but he provided me with the resources—equipment, personal communication, and his time—necessary to enable success. I look forward to many more years of mentorship and partnership with him.

I enthusiastically thank Neil Grunberg and Andrew Waters for not only serving on my Master's committee, but for their mentorship, guidance, and support. I appreciate not only their time and wisdom with coursework, research, statistics, and presentations, but also with life and professional enhancement. Quite simply, I am a better clinical psychologist, researcher, and person because of them.

A special thanks goes to Doug Girard, our lab's programmer. I cannot imagine how different graduate school would have been thus far without serendipitously meeting Doug at a baseball game during my first month at USUHS. His ability to take my conceptual frameworks for the BEAM programs and scoring software and put it into code helped us accomplish our goals in months rather than years.

Of course, I would like to thank the members of the Ettenhofer Neurocognitive Research Laboratory for their support and help with the eye tracking research. In particular, I want to thank Dmitry Mirochnitchenko and Angie Landenburger for their countless hours helping me with data entry and administration. Their presence has made the lab more productive and more enjoyable.

I'd like to thank the faculty and support staff of the USUHS Medical and Clinical Psychology Department for all they have done for me in the past two years. I thank the faculty for taking a chance on someone without much psychology, research, or clinical experience, for their willingness to help me whenever I needed it, and for their professional development. I am light years ahead of where I was in 2010 because of the quality of training I have received. Tricia Crum, Mindy Sheinberg, and Natalie Rosen deserve special thanks for their assistance with literally everything. Lastly, I want to thank Corinne Simmons. I thank her for her dedication to the department's mission, for her commitment to the students, and, above all, for being my friend. I will always treasure the time we shared.

DEDICATION

This work is dedicated to the Soldiers of Easy Company, 1st Battalion, 66th Armor Regiment, 1st Brigade Combat Team, 4th Infantry Division, to the men and women who served alongside them in Operation Iraqi Freedom 07-09, and to the United States Service Members who risk their lives to find and eliminate explosive devices.

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INTRODUCTION

The following Master's thesis describes the process of developing and refining the Bethesda Eye & Attention Measure (BEAM), a novel computer-based eye tracking paradigm for the assessment of cognitive function. The primary goal for the project was to develop a tool sensitive enough to detect cognitive deficits associated with mild traumatic brain injury (mild TBI), deficits that often go undetected. Key tasks for the project were to identify and evaluate how to optimally use a high-speed, remote eye-tracking system to measure oculomotor performance, to design a standard protocol using the eye-tracking system to assess oculomotor performance as an index of neurocognitive functioning, and to refine the eye-tracking protocol to elicit several neurocognitive functions in healthy volunteers.

To introduce the topics relevant to the project, this manuscript first reviews the impact of mild TBI on American Service Members and civilians, the functional outcomes of mild TBI, and methods used to assess mild TBI events. The manuscript then transitions to the topics of oculomotor functioning and cognitive processes associated with eye movement.

Because of the developmental nature of this project, it is important to describe the process of how the measure was created. The hardware used, software programmed, and data calculation procedures employed all relate to the overarching goals of the project, and they are described in detail. The methods of this project—from the design of the paradigm to the completion of the final experiment—represent the core of this Master's thesis. Accordingly, the methods section describes the initial planning and developmental phase of the BEAM, and then presents two studies conducted on two

different versions of the measure. The first study represents an exploratory, inductive approach to assess the utility of the measure, while the second study represents a more traditional experimental design, complete with formal hypotheses and statistical analyses. The developmental phase, Study 1, and Study 2 in their entirety represent the feasibility study of the Bethesda Eye & Attention Measure.

Traumatic Brain Injury and the US Military

Traumatic brain injury (TBI) is often called the "silent epidemic" because the problems associated with these injuries are not always visible to the people who suffer them or to healthcare providers (Centers for Disease Control and Prevention, 2003). TBI has long been a serious public health problem in the United States (McCrea, 2008), and recent, high-profile research detailing the physical and psychological impact of TBI on American Service Members (Hoge et al., 2008) and professional football players (Cantu, 2007) has brought increased attention to the importance of TBI research for military and civilian populations. In fact, TBI has widely been called a "signature wound" of the wars in Iraq and Afghanistan (Okie, 2006; Tanielian & Jaycox, 2008) because of the spike in TBI incidence among American Service Members during the past decade of conflict.

Traumatic brain injury may be classified by severity into "mild," "moderate," or "severe" categories. "Penetrating" TBI, in which the dura mater is penetrated by another object, is a type of severe TBI. The vast majority of treated TBI (~70-90%) are considered "mild" based on diagnostic criteria and acute injury characteristics (Bazarian et al., 2005; Cassidy et al., 2004; Centers for Disease Control and Prevention, 2003). It is important to note that the terms "concussion" and "mild traumatic brain injury" are

interchangeable, because many studies use either term to relate to the same phenomenon (Defense and Veterans Brain Injury Center, 2011c).

The Department of Veterans Affairs (VA) and the Department of Defense (DoD; 2009) define traumatic brain injury as:

- A traumatically induced structural injury and/or physiological disruption of brain function as a result of an external force that is indicated by new onset or worsening of at least one of the following clinical signs immediately following the event:
    - Any period of loss of or a decreased level of consciousness (LOC)
    - Any loss of memory for events immediately before or after the injury (post-traumatic amnesia [PTA])
    - Any alteration in mental state at the time of the injury (confusion, disorientation, slowed thinking, etc.; alteration of consciousness/mental state [AOC])
    - Neurological deficits (weakness, loss of balance, change in vision, praxis, paresis/plegia, sensory loss, aphasia, etc.) that may or may not be transient
    - Intracranial lesion
- External forces may include any of the following events: the head being struck by an object, the head striking an object, the brain undergoing an acceleration/deceleration movement without direct external trauma to the head, a foreign body penetrating the brain, forces generated from events such as a blast or explosion, or other forces yet to be defined.

Consistent with the standard medical definitions of the World Health Organization (WHO), the Centers for Disease Control and Prevention (CDC), the American Academy of Neurology (AAN), and the American Congress of Rehabilitation Medicine (ACRM), the VA and DoD define traumatic brain injury as an *event* (2009). Stated otherwise, any person who experiences the aforementioned signs and symptoms immediately after an "external force" can be said to have had a TBI (Department of Veterans Affairs & Department of Defense, 2009).

Regardless of the external event causing the injury, concussion is believed to occur when there is a sufficiently rapid transfer of kinetic energy that results in an absorption (acceleration) or release (deceleration) of kinetic energy inside the head (Shaw, 2002). This transfer of energy occurs via two processes of inertial loading of forces: linear (translational) acceleration/deceleration and rotational (angular) acceleration/deceleration (Shaw, 2002). While several studies indicate the minimum threshold for mild TBI is a linear gravitational acceleration between 80-100 g, the influence of rotational forces, duration of inertial loading, and location of impact all influence the chances of reaching the minimum biomechanical threshold of concussion (McCrea, 2008).

The duration of one's loss of consciousness (LOC), post-traumatic amnesia (PTA), or alteration of consciousness (AOC) following a TBI event determines whether the TBI will be classified as mild, moderate, or severe. Concussion/mild TBI is characterized by an AOC (i.e., a confused or disoriented state) lasting less than 24 hours, an LOC lasting up to 30 minutes, PTA (i.e., memory loss) lasting up to 24 hours, and structural neuroimaging (MRI/CT scan) yielding normal results (Department of Veterans Affairs & Department of Defense, 2009). According to VA/DoD guidelines (2009), observed signs of neurological or neuropsychological dysfunction, such as headache, dizziness, irritability, fatigue, or poor concentration can be used to support a diagnosis of mild TBI if made soon after the injury, but cannot be used to make the diagnosis in the absence of observed or self-reported LOC or AOC. Moderate TBI is characterized by AOC > 24 hours, LOC > 30 minutes but < 24 hours, and/or PTA lasting > 24 hours but < 7 days, and/or structural brain imaging yielding normal or abnormal results (Department

of Veterans Affairs & Department of Defense, 2009). Severe TBI is characterized by AOC > 24 hours, LOC > 24 hours, PTA > 7 days, and structural neuroimaging yielding normal or abnormal results (Department of Veterans Affairs & Department of Defense, 2009).

The CDC estimates that approximately 1.7 million Americans sustain a TBI each year; of them, 1.365 million (about 80% of all TBI cases) are treated and released from an emergency department, 275,000 are hospitalized, and 52,000 die (Department of Veterans Affairs & Department of Defense, 2009; Faul, Xu, Wald, & Coronado, 2010). According to population-based data obtained between 2002-2006, TBI contributes to nearly one-third of all injury-related deaths in the United States (Faul, et al., 2010).

Among US civilians, children aged 0-4 years, older adolescents aged 15-19 years, and adults aged 65 years and older are most likely to sustain a TBI, with falls being the most common cause of TBI across all age groups (Faul, et al., 2010). After falls (35.2% of all TBI incidents), the next leading causes of TBI are motor vehicle accidents (17.3%), struck by/against events (16.5%), and assaults (10%; Faul, et al., 2010). Motor vehicle accidents result in the greatest percentage of TBI-related deaths across all age groups (31.8%; Faul, et al., 2010). Regardless of age group, males have higher rates of TBI than females (Faul, et al., 2010). Multiple studies report adults aged 75 years or older have the highest rates of TBI-related hospitalization and death, at least three times the rate of any other age group (Centers for Disease Control and Prevention, 2006; Faul, et al., 2010; Thompson, McCormick, & Kagan, 2006).

Among US Service Members deployed to combat environments, the leading causes of TBI are explosive blasts, fragments/shrapnel, falls, and vehicle accidents

(Defense and Veterans Brain Injury Center, 2011c; Hoge, et al., 2008). Improvised explosive devices (IEDs) in particular pose an acute threat of brain injury to US Service Members deployed to combat environments (Tanielian & Jaycox, 2008). IEDs are commonly used by enemy insurgents to maim, kill, and disrupt coalition forces. IEDs can take many forms, from 500-pound explosive charges buried in the middle of the road to tripwire-initiated landmines. Suicide bombers, vehicle-borne IEDs, and mortars also contribute to the estimated two-thirds of US Army war zone evacuations due to blast-related injuries (Warden, 2006).

From January 1, 2000 through the first quarter of 2011, there have been 212,742 documented cases of all-severity TBI in the DoD; of those, 163,181 (76.7%) were mild; 35,661 (16.7%) were moderate; 3,573 (1.7%) were penetrating; 2,235 (1.1%) were severe; and 8,092 (3.8%) were not classifiable (Defense and Veterans Brain Injury Center, 2011b). Among the service branches in the DoD, the Army has sustained over 57% of all TBI, followed by the Marine Corps (14.4%), the Navy (14.3%), and the Air Force (14%; Defense and Veterans Brain Injury Center, 2011a). Since 2005, the incidence of mild TBI among US Service Members has increased more than 250% (Defense and Veterans Brain Injury Center, 2011a). It has been estimated that approximately 15-20% of all US Service Members who deploy to Iraq or Afghanistan sustain a mild TBI (Hoge, et al., 2008; Tanielian & Jaycox, 2008; Terrio et al., 2009).

The considerable economic impact of these 200,000+ TBI in the US military poses a significant and far-reaching problem. Using a standard cost-of-illness approach to assess the costs of deployment-related TBI, the RAND Corporation (2008) took data from a 2005 sample of Service Members that suffered TBI while deployed to combat

operations and estimated costs based on treatment and rehabilitation, TBI-caused death, suicide (including both attempts and completions), and productivity losses. In 2005 dollars, the estimated average cost of a deployment-related TBI to the US economy ranged from $148,573 to $222,000, with the total economic cost of deployment-related TBI from 2001-2005 ranging from $90,629,389 to $135,419,773 (Tanielian & Jaycox, 2008). For moderate-to-severe TBI, costs came primarily from mortality (70-80%), followed by loss of productivity (8-13%), treatment (7-10%), and suicide (0-12%; Tanielian & Jaycox, 2008). The costs of mild TBI, by contrast, are associated more with treatment (43-53%) and loss of productivity (47-57%; Tanielian & Jaycox, 2008).

With advances in modern medicine and neuroimaging, more Service Members and civilians are surviving TBI. As a result of reduced mortality rates, an ever-increasing number of people are living with major functional and cognitive disabilities (McCrea, 2008). In fact, between 3.17 and 5.3 million US citizens (roughly 10% of all disabled Americans) are estimated to be living with permanent TBI-related disability (Langlois, Rutland-Brown, & Wald, 2006; Thurman, Alverson, Dunn, Guerrero, & Sniezek, 1999; Zaloshnja, Miller, Langlois, & Selassie, 2008).

The prevalence, incidence, and cost of mild traumatic brain injury (mild TBI) make it a major societal and economic problem in America. Using existing research and adjusting for inflation and health care costs, McCrea (2008) estimates TBI to have a $100 billion annual impact on the US economy in terms of medical costs and lost productivity. Making matters worse, the majority of people who sustain mild TBI delay consulting with medical professionals until several days after the initial injury or do not seek medical attention at all (Kay, Newman, Cavallo, Ezrachi, & Resnick, 1992; Langlois et

al., 2003; Ruff et al., 2009). Because of this lack of reporting, the Centers for Disease Control and Prevention (CDC) warned in a 2003 report to the US Congress that mild TBI's true incidence and actual public health impact may be vastly underestimated (Centers for Disease Control and Prevention, 2003).

Based on incidence and prevalence of TBI among American Service Members and civilians, and the subsequent economic and societal impact the injuries have on the United States, it is not surprising that TBI is viewed as a major public health problem. At the forefront of this crisis is mild traumatic brain injury, the most prevalent yet under-diagnosed type of traumatic brain injury (Bazarian, et al., 2005; McCrea, 2008). To better understand the problems associated with mild TBI, it is important to understand the physical and functional impacts associated with concussion.

Neuropsychiatric Sequelae of Mild TBI

While each mild traumatic brain injury event is unique, these injuries often result in predictable neuropsychiatric cognitive, physical, emotional, and behavioral sequelae (Iverson, 2005; Silver, McAllister, & Arciniegas, 2009). Cognitive and physical symptoms are common among mild TBI patients, with the most severe symptoms usually emerging within a few minutes of the injury (McCrea, 2008). Common cognitive symptoms that emerge after mild TBI include deficits in delayed memory, verbal fluency, language, attention, visuospatial skills, memory acquisition, global functioning, and executive function (Belanger, Curtiss, Demery, Lebowitz, & Vanderploeg, 2005). Visual memory and verbal fluency are most susceptible to change after mild TBI (Belanger, et al., 2005; McCrea, 2008; Rohling et al., 2011). Headache, dizziness, fatigue, and light/noise sensitivity are common physical symptoms after mild TBI (Department of

Veterans Affairs & Department of Defense, 2009; McCrea, 2008), and depression, anxiety, agitation, irritability, impulsivity, and aggression are common behavioral/emotional symptoms after mild TBI (Department of Veterans Affairs & Department of Defense, 2009).

Rapid symptom improvement normally occurs within 72 hours of a mild TBI (Giza & Hovda, 2001; Iverson, 2005), and 80-90% of mild TBI patients report drastic symptom improvement after just 7-10 days (McCrea, 2008). Several meta-analyses have reported that the vast majority of mild TBI cases recover completely within 90 days of injury (Belanger, et al., 2005; Binder, Rohling, & Larrabee, 1997; Frencham, Fox, & Maybery, 2005; Rohling, et al., 2011; Schretlen & Shapiro, 2003). Unfortunately, 1-5% of people who experience mild TBI will have their symptoms persist months to years after the injury (Iverson, 2005; McCrea, 2008). This "miserable minority" experiences persistent postconcussive symptoms across cognitive, physical, and behavioral/emotional domains (Ruff, 2005; Ruff, Camenzuli, & Mueller, 1996). Using DoD figures of diagnosed mild TBI since 2001 (Defense and Veterans Brain Injury Center, 2011b), it is estimated that 1,600-8,200 US Service Members suffer from persistent post-concussive symptoms.

Signs and symptoms of mild TBI are not unique to mild TBI; headache, irritability, fatigue, and difficulty concentrating are quite common in the general, healthy population and are frequent among individuals with chronic pain, depression, and PTSD (Department of Veterans Affairs & Department of Defense, 2009; Hoge, et al., 2008). For any given individual who has suffered a mild TBI, the cognitive, physical, and emotional/behavioral signs and symptoms of their "mild TBI" may be better explained by

pre-existing conditions or other medical, neurological, or psychological causes (Department of Veterans Affairs & Department of Defense, 2009). Patients often present with a heterogeneous mixture of symptoms unique to the person's injury and premorbid conditions, making it difficult to differentiate "normal" complaints from symptoms specific to mild TBI (Department of Veterans Affairs & Department of Defense, 2009; Silver, et al., 2009).

In addition to injury characteristics (location, type, and severity of injury), pre-injury characteristics such as age, gender, genetics, baseline cognitive function, psychiatric conditions, substance abuse, socioeconomic environment, and risk-taking behaviors affect the development of cognitive, physical, emotional, and behavioral disturbances after head injury (Silver, et al., 2009). The resulting neuropsychiatric sequelae of mild TBI may interact with each other, with each symptom domain interacting with the other domains to produce the post-traumatic neuropsychiatric symptoms commonly to mild TBI (Silver, et al., 2009). The non-specific presentation of signs and symptoms associated with mild TBI coupled with their relatively brief presentation make accurate assessment of mild TBI very difficult.

Assessing Mild TBI

Compared to moderate and severe TBI, mild TBI is more difficult to assess and diagnose (Ruff, et al., 2009). The initial signs and symptoms of mild TBI are especially difficult to identify in deployed settings where resources are low and Service Members tend to underreport symptoms (Coldren, Russell, Parish, Dretsch, & Kelly, 2012). A lack of consensus diagnostic criteria adds to the problem. As recently as 2003, mild traumatic brain injury lacked a consensus definition, and only recently have the American Congress

of Rehabilitation Medicine, the World Health Organization, the DoD/VA, and the Centers for Disease Control and Prevention adopted a tentative agreement on what constitutes a mild traumatic brain injury (Cassidy, et al., 2004; Centers for Disease Control and Prevention, 2003; Department of Veterans Affairs & Department of Defense, 2009; Ruff, et al., 2009). A universally-held definition of mild traumatic brain injury is still being debated (Menon, Schwab, Wright, & Maas, 2010).

Objective measures used to assess mild TBI often lack the sensitivity and specificity to ensure reliable and valid diagnoses. Despite the wide use of neuroimaging to determine the extent of head injuries in US military populations (French & Parkinson, 2008), CT and MRI scans from patients with mild TBI often appear normal (Flanagan, Cantor, & Ashman, 2008). In fact, for patients presenting with possible mild TBI, CT scans are the "gold standard" for ruling *out* more severe injuries rather than ruling *in* the mild TBI (Cushman et al., 2001). Advanced neuroimaging techniques like diffuse tensor imaging (DTI), magnetoencephalography (MEG), functional MRI (fMRI), and magnetic resonance spectroscopy (MRS) have not yet been clinically validated for mild TBI diagnosis and are often unavailable, impractical, or financially cumbersome to mild TBI patients (Heitger et al., 2009).

While neuropsychological assessments can evaluate the cognitive and functional outcomes from mild traumatic injury, the measures alone cannot be used for the basis of initial diagnosis (Ruff, et al., 2009). Neuropsychological measures can be influenced by premorbid functioning, age, education, employment status, socioeconomic status, depression, malingering, and litigation (Iverson, 2005). Furthermore, critics contend that neuropsychological assessment has questionable real-world validity for mild TBI

(particularly beyond the sub-acute phase), variable capability to detect malingering/faking bad, and over-reliance on the personnel administering the tests (Zasler & Martelli, 2003).

For all of these reasons, the current "gold standard" of mild TBI diagnosis consists of self-report, clinical interviews, collateral interviews, and record reviews to evaluate the signs and symptoms immediately following the injury (Corrigan & Bogner, 2007; Ruff, 2005; Ruff, et al., 2009). Patients are typically diagnosed with having incurred a mild TBI hours, days, or months after the injury actually occurred, forcing clinicians to rely upon retrospective data (Ruff, 2005; Ruff, et al., 2009). Importantly, the ability to accurately detect mild TBI diminishes with time as the recovery takes place (Iverson, 2005). Even when first responders arrive at the scene of the injury, various acute symptoms of mild TBI may have subsided by the time medical help arrives. As such, clinicians must integrate retrospective data from patients, witnesses of the injury, first responders, and other sources of information. Obtaining early and precise information regarding the symptoms immediately following the injury is important for accurate mild TBI identification (Terrio, et al., 2009). Failure to identify and treat mild TBI when it occurs could lead to suboptimal recovery and persistent postconcussive symptoms if additional concussions are sustained (McCrea et al., 2009). Persistent postconcussive symptoms absent of concussion diagnosis can lead to psychological stress in addition to physical suffering.

Unfortunately, retrospective reports are fraught with confounding factors that may lead to misdiagnosis of potential mild TBI (Zasler & Martelli, 2003). Financial incentives through injury lawsuits and/or disability evaluations also may impact the

severity of symptoms reported in mild TBI cases (Binder & Rohling, 1996; Lees-Haley & Brown, 1993; Lees-Haley, Fox, & Courtney, 2001). Response bias in symptom report can take many forms on both sides of a continuum: denial or unawareness of impairments and/or symptom minimization on one side, and sensitization to minor symptoms, symptom magnification, and clear malingering on the other (Zasler & Martelli, 2003). According to Millis and Volinsky (2001), response bias may be influenced by initial injury severity, preexisting emotional or social distress, history of neurological or psychiatric disorder, physical injuries unrelated to TBI, and preinjury substance abuse.

Clinicians working with US Service Members face unique challenges with regard to collecting diagnostic information for mild TBI. While deployed to combat environments, medical systems are constrained and assessment of non-life threatening illnesses can be delayed (Schwab et al., 2007). Service Members may minimize symptom report (or not report symptoms at all) for fear of being removed from the battlefield and their unit (Marion, Curley, Schwab, & Hicks, 2011). Neuropsychological assessment and neuroimaging are often unavailable in deployed settings, forcing military clinicians to rely on screeners such as the Military Acute Concussion Evaluation (MACE), which lack the sensitivity and specificity to be clinically useful 12 or more hours post-injury (Coldren, Kelly, Parish, Dretsch, & Russell, 2010). Despite DoD guidelines mandating that deployed Service Members take the computer-based Automated Neuropsychological Assessment Metrics (ANAM) before and after deployment, the ANAM lacks the sensitivity required to detect cognitive impairment just 10 days after a single, uncomplicated brain injury (Coldren, et al., 2012). In fact, the

ANAM is most useful within 72 hours; assessment afterwards loses sensitivity to detect cognitive impairment (Coldren, et al., 2012). Whether deployed or in secured environments, several factors complicate assessment of mild TBI for Service Members: misinformation regarding TBI, delayed clinical presentation of symptoms, exposure to numerous potentially injurious events, nonspecificity of concussion-like symptoms due to deployment-related stress, and psychiatric comorbidities like PTSD and depression (Brenner, Vanderploeg, & Terrio, 2009; Hoge, et al., 2008).

In both civilian and military populations, assessment of mild TBI is complicated, difficult, and subject to error. After reviewing patient charts and independently interviewing emergency room patients at a level 1 trauma center and an academic nontrauma hospital, Powell and colleagues (2008) found over *half* of the emergency department patients meeting CDC criteria for mild traumatic brain injury were not diagnosed. Ruff and colleagues (2009) assert that every medical provider in the patient's chain of care should use a thoughtful, deliberate approach to assessing the presence of LOC, AOC, PTA, and focal neurologic signs, being careful not to assume that the patient's previous caretakers had done the same. To help clinicians make accurate diagnostic choices, Corrigan and Bogner (2007) designed a semi-structured interview called the Ohio State University TBI Identification Method (OSU TBI-ID). The OSU TBI-ID has been utilized in prison (Bogner & Corrigan, 2009), veteran (Olson-Madden et al., 2010), and substance abuse (Corrigan & Bogner, 2007) samples, showing considerable promise as a diagnostic tool. However, the possibility of response bias will always accompany these subjective measures.

In August 2010, subject matter experts from a wide spectrum of concussion-related clinical and research disciplines met with active duty Army, Navy, and Air Force TBI researchers to discuss the development of objective tests for mild TBI in military populations (Marion, et al., 2011). The military mild TBI working group identified several clinical categories of interest for the acute (< 3 hours post-injury) diagnosis of mild TBI, including advanced imaging techniques, biomarkers obtained from blood and urine samples, and objective measurements of oculomotor functioning and attention (Marion, et al., 2011).

As discussed above, attention is a cognitive domain that is negatively impacted by traumatic brain injury. While mild TBI also can impact cognitive domains such as memory, verbal fluency, and language (Belanger, et al., 2005), attention measures may be the most sensitive indicators of dysfunction associated with mild TBI (Cicerone & Azulay, 2002). Measures with good sensitivity will minimize false negatives, a useful tool for ruling out the presence of impairment (Cicerone & Azulay, 2002). Furthermore, quantitative measurements of oculomotor function also have been demonstrated to be sensitive markers of cerebral dysfunction (Heitger et al., 2004). As such, objective assessments that combine attention and oculomotor functioning measurements may provide sensitive and specific tools to identify mild TBI better than existing subjective measures.

Oculomotor Functioning and Eye Tracking Research

Oculomotor functioning is a blend of cognition and perception; each eye movement is not simply a random survey of the visual world, but a representation of one's cognitions, expectations, and motivations for comprehension (Exton & Leonard,

2009). Visually guided eye movements incorporate neural activity in the afferent visual system, central visuomotor structures, and the efferent oculomotor system, which includes the retina, lateral geniculate nucleus, striate cortex, superior colliculus, parietal cortex, frontal eye fields, supplementary eye fields, prefrontal cortex, basal ganglia, and the brain stem (Fischer, Gezeck, & Huber, 1995). These oculomotor pathways, particularly in the frontal eye fields, supplementary eye fields, prefrontal cortex, and parietal cortex, overlap considerably with cognitive processes such as attention, working memory, and learning, suggesting that these systems are functionally interrelated (Middleton & Strick, 2001).

Common processes associated with eye movements include fixations, saccades, and pursuit movements. Fixations refer to a person focusing on a specific stimulus and stabilizing his or her gaze it. When one is "looking" at a given object, that person is said to be "fixating" on that object. Fixations are controlled by voluntary and involuntary fixation mechanisms (Guyton & Hall, 2006, 2011). Voluntary fixation movements allow a person to willfully move their eyes onto a given object, and they are controlled in bilateral cortical fields in the premotor cortex of the frontal lobes (Guyton & Hall, 2006, 2011). Involuntary fixation movements, on the other hand, enable the eyes to "lock" onto the object once it has been found; these fixation movements are controlled by secondary visual areas in the occipital cortex (Guyton & Hall, 2006, 2011). Involuntary and voluntary fixation movements work in concert with each other; as either the voluntary or involuntary fixation movement ceases, the other begins.

Saccades are quick, jerky eye movements that occur between fixations during the search for visual targets (Barrett, 2010; Johnson, 2003). As a person disengages from

one object to fixate upon a new object, a saccadic movement is initiated towards the new object. Regulated by the superior colliculus (Barrett, 2010), saccades occur very rapidly, lasting 20-50 ms (Van De Graaff, Fox, & Thouin, 1999). In the duration of a normal eye movement from saccadic initiation to final fixation, the saccadic movement itself takes only 10% of the time while the fixation on a target encompasses the other 90% (Guyton & Hall, 2006, 2011). Saccadic movements are ballistic; no corrections in the speed or direction of the saccade can be made after a saccade is initiated (Johnson, 2003). In addition, the brain blocks visual input during saccades, rendering people unaware of any changes in the visual environment in the many brief periods between fixations (Guyton & Hall, 2006, 2011).

Pursuit movements, or fixations on moving objects, are another type of eye movement. Also known as smooth pursuit eye movements (SPEM), these movements occur when a person follows or maintains gaze on a moving stimulus by matching its direction and velocity (Duchowski, 2007). When patterns of movement can be predicted, as in circular or sinusoidal movements, subconscious, cortical computations enable finer and finer saccades to closely approximate the object's movement (Guyton & Hall, 2006, 2011).

These eye movement processes—fixations, saccades, and pursuit movements—all fall within a relatively narrow range of measurements for most individuals, making them highly reliable for comparisons between groups with and without a history of TBI (Exton & Leonard, 2009). Researchers have utilized eye tracking systems to obtain precise measurements of eye movements. Eye tracking systems, which use high speed cameras and processing equipment, can measure oculomotor activity to determine where and how

long a person gazes at a given point during a visual task (Duchowski, 2007). Eye tracking analysis software can take the raw opticokinetic data and extract information about fixations, saccades, and smooth pursuit eye movements.

Cognitive neuroscientists have used eye movement paradigms to study attention, response inhibition, working memory, processing speed, and executive function (Barnes, 2008; Gooding & Basso, 2008; Hutton, 2008; Müri & Nyffeler, 2008; Olk & Kingstone, 2003; Pierrot-Deseilligny, Milea, & Müri, 2004). Studies incorporating neural injuries and neurodegenerative disorders have indicated that eye movement control relates closely to brain functioning (Müri & Nyffeler, 2008; Pierrot-Deseilligny, et al., 2004; Sharpe, 2008).

Studies of brain function in multiple neuropathological populations have incorporated eye tracking equipment into their research. Crawford and colleagues (2005) used eye tracking technology to record visual attention via saccadic eye movements in delirium patients, finding that specific cognitive operations such as memory, attention, and comprehension were impaired. Eye movement abnormalities have been found in schizophrenia (Schwartz et al., 1995), Parkinson's disease (van Stockum, MacAskill, Anderson, & Dalrymple-Alford, 2008), and mild TBI patients three-to-five months after injury (Heitger, et al., 2009). Additionally, eye tracking measures appear to be resistant to the effects of depression, intelligence, or malingering (Heitger, et al., 2009).

A rapidly growing body of evidence suggests that eye movements and fixations directly correspond to attention and executive functions, two cognitive processes commonly disrupted by TBI (Exton & Leonard, 2009; Kraus, Little, Wojtowicz, & Sweeney, 2010). Kapoor and Ciuffreda (2002) reported that 40% of individuals with

some form of TBI experience visual dysfunction. In a study conducted with 192 veterans with mild-to-severe TBI, Brahm and colleagues (2009) found that combat troops suffering a mild TBI from blast trauma are at risk for oculomotor and other visual dysfunctions. Therefore, studying eye movements in a military population may yield important clues to aid the detection of mild TBI.

Attention, Saccades, and the Gap Effect

Attention has been described as a cognitive process sensitive enough to detect TBI (Cicerone & Azulay, 2002). Conceptually, attention serves as a basic set of mechanisms that facilitates one's awareness of the world and the voluntary regulations of thoughts and emotions (Posner & Rothbart, 2007). Aspects of attention can be manipulated and controlled experimentally, providing researchers and clinicians with a window into the underlying neuroanatomical functioning of a patient.

A wide swatch of research suggests three specific "networks" uniquely contribute to different aspects of attention (Fan, McCandliss, Fossella, Flombaum, & Posner, 2005; Posner & Rothbart, 2007). Attention can be divided into subsystems that perform separate but related functions: orienting to sensory events (orienting network), detecting signals for conscious focusing (executive network), and maintaining a state of alertness (alerting network; Fan, et al., 2005; Posner & Petersen, 1990).

Orienting describes the process where attention aligns with one or more sources of sensory signals (Posner & Rothbart, 2007) or where information is selected from sensory input (Posner, 2008). Orienting can occur "covertly" without eye movement or "overtly" with eye movement (Posner & Rothbart, 2007). Orienting can be reflexive (i.e., exogenous), as when sudden events draw attention, or voluntary (i.e., endogenous),

as when a person scans a field of vision looking for something (Fan et al., 2009). The orienting system of attention has been associated with the superior parietal cortex, the temporal parietal junction, the frontal eye fields, and the superior colliculus (Corbetta & Shulman, 2002). Studies with rhesus monkeys indicate that acetylcholine modulates the orienting network (Davidson & Marrocco, 2000; Posner, 2008; Posner & Rothbart, 2007).

Alerting describes the process of tonically achieving and maintaining a state of high sensitivity to new stimuli and phasically responding to warning signals or other cues (Fan, et al., 2009; Posner, 2008). The alerting system of attention has been associated with the right frontal cortex, the parietal cortex, and the locus coeruleus in the pons (Fan, et al., 2005). Studies with monkeys indicate that norepinephrine modulates the neural activity of the alerting network (Marrocco, Witte, & Davidson, 1994; Posner, 2008; Posner & Rothbart, 2007). This finding is consistent with the alerting network's association with the locus coeruleus, the principal site for brain synthesis of norepinephrine (Posner, 2008). The norepinephrine pathway includes major nodes in the frontal lobes and dorsal parietal regions associated with visual pathways (Posner, 2008). Damage to the posterior parietal lobe impairs the ability to disengage attentional focus on a target located in the visual field opposite to the side of the lesion (Posner & Cohen, 1984).

The executive network of attention describes mechanisms that monitor and resolve conflict among thoughts, emotions, and responses (Posner & Rothbart, 2007). The functions of the executive attention network include planning, decision-making, detecting errors, responding to novel situations, and overcoming habitual actions (Fan, et

al., 2009). The anterior cingulate cortex, lateral ventral cortex, prefrontal cortex, and basal ganglia have been associated with the executive network (Fan, Hof, Guise, Fossella, & Posner, 2008; Fan et al., 2007; Posner & Rothbart, 2007). The anterior cingulate cortex and lateral prefrontal cortex are both associated with the ventral tegmental dopamine system (Benes, 2000), and evidence suggests that dopamine modulates the executive attention network (Posner & Rothbart, 2007).

Vision involves continuous engagement and disengagement of attention, where people fixate their attention on an object, then disengage their attention in order to fixate on a new object. According to Fischer's "three-loop" model (1986, 1987; Fischer, et al., 1995), three processes occur before a saccade is made: disengagement of visual attention, decision to execute a saccade, and calculation of saccade "metrics" (direction, amplitude, velocity) needed to reach the target.

A person's visual attention can be influenced by cues. Cues of all types—biological, psychological, and environmental—provide information to individuals that influence the focus of their attention. Predictive cues (e.g., cues that point or indicate target location) greatly reduce the latency of saccades made towards the target (Cavegn, 1996). Invalid cues, or cues that incorrectly predicted target appearance, increase latencies of saccades towards a target (Walker, Kentridge, & Findlay, 1995). These findings suggest a functional, cognitive relationship between saccades and spatial attention, where cues orient a person's attention to a presumed target location (Hutton, 2008).

While cues can influence an individual breaking a fixation on an object to generate a saccade towards another object, fixated objects themselves can facilitate

disengagement by disappearing during the fixation. A brief "gap" occurs after a fixated-upon object suddenly disappears, and an individual can shift his or her attentional focus without the need for active, deliberate disengagement. Forced visual disengagements, or "gaps," are common for experiments measuring saccades, although researchers debate what processes are actually being measured (Hutton, 2008). In an experimentally manipulated "gap" condition, the fixated object disappears for a brief time (usually around 200 ms) before a new object appears in the participant's field of view. Conversely, in "overlap" conditions, new objects appear before the fixated object disappears.

Saccadic latencies are shorter (i.e., faster) in gap conditions and longer (i.e., slower) in overlap conditions (Fischer & Breitmeyer, 1987; Weber & Fischer, 1995). Researchers believe the "gap effect" is moderated by attention and mediated by a "fixation release" component (Hutton, 2008). Simply put, gap conditions appear to "release" a subject's fixation on an object, "freeing" the subject's attention and resulting in a more rapid fixation on a new object. Conversely, in overlap conditions, a subject must "break" his or her own fixation on an object and generate a saccade towards a new object. Researchers have hypothesized that gaps enable disinhibition of saccadic movement while overlap conditions inhibit new fixations (Hutton, 2008).

Summary

Mild TBI represents a major economic concern and health risk to US Service Members and civilians Unfortunately, identifying the mild TBI when it occurs is often difficult, especially in deployed settings. New tools combining oculomotor functioning and attention may be sensitive enough to detect the cognitive deficits that manifest after

mild TBI. A new measure, the Bethesda Eye & Attention Measure (BEAM), was designed to identify cognitive performance in people with and without mild TBI. The following methods section will describe the development and feasibility testing of the BEAM.

METHODS

The feasibility study of the Bethesda Eye & Attention Measure (BEAM) consisted of a developmental phase and two studies. The developmental phase included all BEAM hardware, software, and conceptual development before studies using human subjects. After the developmental phase, Studies 1 and 2 used exploratory/correlational methods with consented participants to assess the feasibility of the BEAM. The following Methods and Results section will be broken into the following components:

1) Developmental Phase, where the process of incorporating hardware, software, and conceptual assessment design merged to produce a testable version of the BEAM,

2) Study 1, where consented individuals took an early version of the BEAM and exploratory data analysis was conducted, and

3) Study 2, where results from Study 1 guided improvements to the BEAM paradigm that was subsequently evaluated with additional consented participants.

Developmental Phase

The developmental phase of the BEAM consisted of selecting and refining eye tracking hardware, conceptually designing the first and second versions of the paradigm (BEAM Versions 0.1 and 0.2), developing the coding structure for the paradigm, and developing a data parser (i.e., scoring program) for the BEAM. The goals of the developmental phase were to design an engaging measure that was relatively brief (< 20 minutes) with a coding structure that enabled a parser program's rapid and automated pre-processing and scoring of key variables.

Equipment: Selection and Setup. Two computers were used during the feasibility testing of the BEAM: a stimulus computer and a control computer. The stimulus

computer presented the BEAM to the subject, while the examiner used the control computer to record the data from the eye tracker. The stimulus computer was a Dell Precision T1500 with an Intel Core i7 860 CPU, 2.80 GHz processing speed. Subjects viewed the BEAM on a 15" Asus VW193 flat-screen monitor set to 1440 x 900 pixel resolution. The control computer was a custom-built PC with a Pentium Dual-Core E5400 CPU, 2.70 GHz processing speed. See Pictures 1, 2, and 3 in Appendix C for images of the equipment.

When selecting the response hardware to be used in this eye tracking study, participant characteristics and psychometrics were given high priority. The end-state users of the BEAM were intended to be Service Members in both deployed and garrison environments. To maximize participant comfort, an eye tracking system that allowed participants to move their head while still maintaining ocular data collection was needed. Essentially, an inconspicuous eye-tracking system that gave the impression of normal computer use (e.g., sitting in front of a monitor, pressing buttons on a keyboard-like apparatus) was sought to diminish potential response bias.

To meet requirements for participant comfort and data collection precision, the Applied Science Laboratories (ASL) D6 high speed remote optic system and Cedrus RB-530 response pad were chosen. See Pictures 1 and 2 in Appendix C for images of the equipment. The D6 used a two-computer interface. Participants took the assessment at the stimulus computer, where the eye tracker and response pad recorded oculomotor activity and manual responses (i.e., button presses), respectively. Examiners sat at a control computer with video monitors and an ASL data processing unit. Cables connected the two computers, synchronizing participant responses, eye movements, and

assessment events, enabling examiners to calibrate participants and monitor their gaze in real time.

The desktop-mounted D6 system did not require chinrests or other head stabilizers. Participants sat at eye level 24" away from the monitor, level with the center of the monitor. The D6 was placed below the computer monitor, and used multiple cameras to record eye and head movement. To record eye movement, the system first determined the participant's eye location. The D6 used facial recognition software to identify and lock onto a person's face and eye location. Once locked onto the right eye, the cameras followed participants as they moved their heads. This ability to compensate for head motion allowed participants to turn their head and look away from the computer monitor and back again without losing calibration. When the eye location was established, ASL software determined the center of the pupil. Simultaneously, an infrared light emitted from the D6 created a corneal reflection on the participant's eye. After calibrating a participant to the eye tracking system, the D6 used pupil and corneal reflection location to calculate a gaze vector, producing a continuous stream of coordinates representing the screen location upon which the subject was looking (i.e., gaze position).

The high-speed D6 recorded eye movements at 120 Hz (e.g., 120 times per second or every 8.33 ms). The Cedrus RB-530 response pad was used to record button press response time with 1 ms time resolution. The pad had five buttons, with four 0.75" x 1.5" rectangular buttons forming a crosshair shape around a 0.87" diameter circle in the center. The Cedrus response pad was chosen to allow a much higher level of time resolution relative to a standard computer keyboard.

Eye Tracker Calibration. Each participant's points of gaze were calibrated to the D6 eye tracker system using ASL calibration software. The goal of the calibration was to determine the pupil and corneal reflection locations of the individual participant as he or she looked at multiple predefined areas on the screen. Participants looked at each of nine points on a computer monitor that were arranged in the configuration of a telephone pad. Once examiners obtained a good lock (e.g., continuous pupil and corneal reflection) on each of the nine points, the subject was considered to be successfully calibrated to the eye tracker. The calibration process took approximately 2 minutes to complete.

Coding the BEAM Paradigm. E-Prime 2.0 software, a suite of applications used in computerized experiment design, data collection, and analysis, was used to program and run the BEAM. E-Prime software also enabled paradigm developers to use signal codes called "XDATs" to add markers to the eye tracking data file, identifying events that occur throughout the computer-based measure. By marking certain events (e.g., trial begins, target appears, button is pressed), developers could synchronize participant responses with paradigm activity.

A parallel cable connecting the stimulus computer and control computer enabled BEAM paradigm events to be synchronized in real time with manual and oculomotor data collection. In a given trial, the stimulus computer sent XDAT codes that indicated when the trial began, when visual stimuli were presented on screen, when buttons were pressed, and when the trial ended. Because every data segment collected during the BEAM used a specific XDAT code, ASL software could perform trial-by-trial analysis after the participant completed the BEAM. The data output was designed so that examiners could know what was happening during a given trial, where a person was

looking throughout a given trial, and whether/when the button was pressed before the trial ended.

Conceptual Framework for the BEAM

The Bethesda Eye & Attention Measure (BEAM) was conceptualized as a computer-based, continuous performance task to elicit oculomotor and manual (i.e., button press) responses to visual stimuli on a monitor. As such, the BEAM was initially designed to have several unique blocks, or sets, of similar trials. A multiple trial design was chosen to evaluate a large number of trials in a short amount of time while manipulating and counterbalancing the timing, location, and circumstances under which the visual stimuli would appear on the screen.

Each trial began with a fixation cross that appeared at the center of the screen. On select trials, the fixation cross would offset (i.e., disappear) and be immediately replaced with a "cue." This cue would be a diamond or an arrow pointing up, down, left, or right. On every trial, a target circle would appear at one of four locations above, below, left, or right of the cross (see Figure 1). When the target circle disappeared, the trial ended and a new trial immediately began. Sequential trials continued to run until the block of trials ended, and the participants were given an opportunity to take a break.

The BEAM was designed to measure visual reaction time and manual reaction time. Visual reaction time was defined as the time it took a person to fixate on the target circle after it appeared. In other words, visual reaction time corresponded to the time it took a person to break his or her fixation on the center of the screen, initiate and complete a saccade towards the target circle, and fixate on the target circle. Manual reaction time

was defined as the time it took a person to press a button on the response box after the target circle appeared.

Parsing BEAM Data. By using E-Prime to specifically code when trials began and ended, ASL software was able to parse each trial into a discrete "event." Once the trials were separated from each other, ASL software found fixations that occurred in a given trial. The eye tracker collected one point-of-gaze data segment every 8.33 ms in the 120 Hz setting, and continuously calculated standard deviations for horizontal and vertical gaze position. A fixation was considered to "start" when ASL software determined a cluster of horizontal and vertical point-of-gaze coordinate samples occurred within two standard deviations of one degree visual angle (1° horizontal by 1° vertical) within a 100 ms span. In other words, ASL software considered a fixation to "start" when the gaze data it received was sufficiently stable for 100 ms. Once the ASL software found a series of sequential sample points that had a small enough standard deviation to meet fixation criteria, the software retroactively considered the fixation to start with the first point-of-gaze in the sequence. The software recorded the average point-of-gaze value for the cluster of data points as the "fixation start position" (Applied Science Laboratories, 2009).

ASL software used two criteria to determine the end of a fixation. First, a fixation could end when the average location of three sequential data points (i.e., three sequential points-of-gaze) deviated from the fixation start position by more than one degree visual angle (horizontal or vertical). ASL software considered the data point preceding the three sequential samples to be the last data sample in the fixation. The second criterion to "end" a fixation was a continuous loss of eye recognition for more than 200 ms. Shorter

losses were assumed to be blinks and did not cause the fixation to end (Applied Science Laboratories, 2009).

The "final fixation position" was calculated as the average of all the points-of-gaze from the fixation start position to the last data sample in the fixation, excluding any points-of-gaze the software considered to be outliers. To prevent brief measurement noise spikes from prematurely ending a fixation, ASL software allowed up to two points-of-gaze to vary greater than one degree visual angle from the fixation start position and still continue the fixation. Any point farther than 1.5 degrees visual angle from the fixation start position were considered outliers and were excluded from the final fixation position calculation (Applied Science Laboratories, 2009).

Once fixations were found in all the trials, ASL analysis software allowed examiners to plot the fixations on a 2D graph. For a typical BEAM evaluation, the fixations generally congregated into five main areas corresponding to the locations of the targets presented during the BEAM: the center of the screen, and above, below, left, and right of the center. Examiners identified each of the five areas of concentrated fixations as "Areas of Interest," and then ran the ASL software to find fixation sequences; ASL then combined fixation data with the defined Areas of Interest. This process allowed examiners to determine which areas of the screen a participant looked during a given trial. The possible fixation locations were "Center," "Up," Down," Left," "Right," or "Outside" if fixations did not fall inside any of the defined areas of interest.

To measure manual and visual reaction time, the primary variables of interest, the following information was required: time of button press, the time of the first correct fixation on the target, and the time that the target appeared on the screen. ASL software

did not have the capability to calculate reaction time on its own; the software could indicate when button presses and fixations were made but could not determine which fixations were "correct" or subtract the fixation times from the time of target onset. Therefore, a custom computer program, a data parser, was designed to meet these specifications and separate fixations of interest from other fixations which occur during completion of the BEAM.

BEAM Version 0.1. The first version of the BEAM, also known as BEAM Version 0.1, was comprised of a simple "reaction time block" of 20 trials followed by 12 "experimental blocks," each with 20 similar trials of a given independent variable condition. Within the measure, trial conditions were systematically manipulated to elicit directional and temporal effects to evaluate the orienting, alerting, and executive networks of attention (Posner & Rothbart, 2007). The independent variables manipulated were cue type (three levels: Nondirectional Cues only in the block [NDC], both Directional and Nondirectional Cues in the block [DANDC], and Misdirectional Cues only in the block [MDC]), interstimulus interval (two levels: fixed interstimulus interval [FISI] and variable interstimulus interval [VISI]), and gap condition (two levels: gap [G] and overlap [O]), rendering a full 3 x 2 x 2 factorial design to compare manual and visual reaction times across the 12 possible independent variable condition combinations. Each block was pseudorandomly counterbalanced by target circle location and arrow direction, if applicable. See Table 1 for the BEAM Version 0.1 block design. The dependent variables in BEAM Version 0.1 were manual and visual reaction times, calculated as described previously.

Three cue types were used in BEAM Version 0.1. On every trial, a fixation cross would appear at the center of the screen. The fixation cross would offset and be replaced by a cue. In BEAM Version 0.1, the cues were either solid, white diamonds or solid, white arrows. The diamonds were called "Nondirectional Cues," and the arrows that pointed to the location where the target circle would appear were called "Directional Cues." In contrast, the arrows that pointed to a direction *other than* where the target circle would appear were called "Misdirectional Cues." The location of the target circle on Misdirectional Cue trials was randomized to mitigate prediction effects.

The cue types were designed to elicit effects of directional predictiveness (i.e., the orienting effect of knowing where a target circle would appear; Posner & Rothbart, 2007) on reaction time. It was expected that more accurate directional predictiveness might elicit faster reaction times. To compare the effects of directional predictiveness, cues that could isolate the phenomenon through direct comparison were used. The diamond shaped, Nondirectional Cue did not indicate where the target circle would appear; it was not useful for directional prediction. The Directional Cue, on the other hand, indicated where the target circle would appear. The Misdirectional Cue created directional "interference" by pointing to a direction other than where the target circle would appear. Misdirectional Cues were believed to engage the executive network of attention (Posner & Rothbart, 2007), forcing participants to inhibit looking at an expected direction and redirect their gaze to a different area of the screen. It was expected that TBI patients in future studies using the BEAM would take significantly longer to redirect their attention in Misdirectional Cue trials than would participants without a history of head injury.

The gap condition referred to whether or not the trial had a gap—a manipulated, forced visual disengagement—between the cue disappearing and the target circle appearing. In "gap" trials, the diamond or arrow cue would disappear, 250 ms would elapse where nothing would be on the screen, and then the target circle would appear. In "overlap" trials, the target circle appeared while the diamond or arrow cue remained on screen; there was no manipulated visual disengagement on overlap trials. During these overlap trials, a participant needed to break his or her fixation on the center cue and initiate a saccade towards the target circle. By contrast, the gaps between cues and target circles in gap trials broke the fixation on the central cue *for* the participant, eliminating the cognitive prerequisite of disengagement before saccade initiation. As such, gap trials were believed to elicit faster reaction times than overlap trials.

The interstimulus interval (ISI) was defined as the time between the fixation cross disappearing and target circle appearing. The interstimulus interval included the duration of the cue on the screen and the 250 ms gap, if applicable. In BEAM Version 0.1, the fixed interstimulus interval (FISI) was 2000 ms, and the variable interstimulus interval (VISI) was pseudorandomly counterbalanced to be 1000 ms, 2000 ms, or 3000 ms. The ISI conditions were designed to compare the effects of temporal predictiveness (i.e., the alerting effect of knowing when the target circle would appear; Posner & Rothbart, 2007). It was believed that temporal reliability in the FISI trials, where the target circle always appeared 2000 ms after the fixation cross offsets, would elicit faster reaction times than VISI trials.

BEAM Version 0.1 was designed to test not only the main effects of independent variable conditions but also interactions between the conditions. It was predicted that

DANDC, G, and FISI trials in Block 1C would have the fastest reaction times, and that MDC, O, and VISI trials in Block 1M would have the slowest reaction times. It was believed that visual and manual reaction times would share the same trends on similar blocks, but that visual reaction times would be faster than manual reaction times. Table 2 presents the predicted cognitive difficulty in each of the independent variable conditions.

On every trial, the fixation cross remained on screen for 2000 ms. When the fixation cross disappeared, the cue would appear. On gap trials, the cue disappeared 250 ms before the target circle appears. On overlap trials, the cue remained on the screen until the trial ended. In all conditions, the target circle remained on the screen for 1000 ms. When the target circle disappeared, the trial was over. See Figure 2 for example trial orders for BEAM Version 0.1.

After coding BEAM Version 0.1, developers in the lab conducted beta-testing with the paradigm. The development team, which consisted of this writer and a clinical psychologist with five years of post-doctoral neuropsychology research experience, identified several design flaws in BEAM Version 0.1 that were believed to limit reliability, validity, and amount of participant engagement. First, BEAM Version 0.1 had no practice block to familiarize participants with the paradigm, rendering the validity of data from the first several trials questionable. Furthermore, the 13 blocks of trials and independent variable conditions were believed to be overly redundant, limiting statistical power to detect within- and- between-group differences. Including Directional Cues and Nondirectional Cues in the same blocks, rather than using them in separate blocks, weakened the ability to assess directional predictiveness. The development team also believed the trial duration lasted too long to sufficiently maintain one's attention. Based

on these limitations, it was decided that the BEAM design needed to be updated prior to formally running participants in a study.

BEAM Version 0.2. In an attempt to increase overall reliability and the corresponding power of future statistical tests involving the BEAM, the block design was consolidated and independent variable conditions were reconfigured. For simplification purposes, BEAM Version 0.2 was comprised of one practice block and four experimental blocks. There were six trials in the practice block and 144 trials in the experimental blocks, giving BEAM Version 0.2 a total of 150 trials. To make the measure more engaging, multiple trials types were pseudorandomly interspersed throughout the five blocks instead of having the same trial condition repeated 20 times. Trials were pseudorandomized and counterbalanced by arrow direction, fixation cross duration, cue type, gap condition, and target circle location.

The ISI independent variable condition was removed for several reasons. In BEAM Version 0.1, the effect of temporal predictiveness (i.e., knowing when a target would appear) was assessed by comparing fixed and variable interstimulus intervals. It was determined that a more efficient and statistically powerful method of assessing temporal predictiveness would be to vary fixation cross duration and add an "Uncued" (UC) cue type. The previously constant fixation cross durations were changed to have variable duration among 1500 ms, 2000 ms, and 2500 ms across all trial types. In UC trials, no arrow or diamond appeared before the target circle appeared; no information about when or where the target circle would appear was given. The development team believed that comparing Uncued trials (without *when* or *where* information) to

Nondirectional Cue trials (with *when* but not *where* information) would assess temporal predictiveness better than the previous version of the BEAM.

The gap condition was changed slightly from the previous version. Beta-testing from BEAM Version 0.1 indicated that the gap duration of 250 ms was too long; participants were likely to look at places other than the center of the screen before the target circle appeared. To reduce this potential while maintaining the gap effect (i.e., breaking the fixation and freeing a participant to look at the target circle), the gap duration was changed to 200 ms.

In BEAM Version 0.1, cues remained on screen for a minimum of 750 ms and a maximum of 4000 ms. After beta-testing, it was believed that directional, temporal, and gap effects were being diluted by having multiple cue durations. Additionally, long cue durations increased the likelihood that participants would make anticipatory saccades prior to target onset. For BEAM Version 0.2, the cue duration was set to 100 ms to elicit more standardized cue effects. In cued overlap trials, the target circle appeared 100 ms after the cue appeared, and the cue would remain onscreen until the end of the trial. In cued gap trials, the cue would appear, disappear after 100 ms, and would then be followed by the 200 ms gap before the target circle appeared.

To measure influence of competing cognitive processes and interference effects, two new independent variable conditions were added: the "task type" condition and the "presence of Misdirectional Cues" condition. With the addition of the "Uncued" cue type, the BEAM Version 0.2 had a full 4 x 2 x 2 x 2 factorial design. See Table 3 for the BEAM Version 0.2 block design.

The "task type" condition compared the effects of dual task (i.e., having to look at the target circle and press the button) and single task (i.e., only looking at the target circle with no button press) on visual reaction time. It was predicted that dual task trials would have slower reaction times than single task trials.

Instead of running blocks consisting entirely of Misdirectional Cue (MDC) trials, two blocks were designed to include MDC trials intermixed with Directional Cue (DC), Nondirectional Cue (NDC), and Uncued (UC) trials. This design would determine what effects, if any, the presence of MDC cues—interference cues—has on reaction time. In contrast to BEAM Version 0.1, MDC trials in BEAM Version 0.2 were designed so that the target circle would always appear *opposite* of where the arrow was pointing. This decision was made to standardize and enhance the executive/interference effect. It was predicted that the presence of MDC trials would slow the block's overall reaction times and the reaction times of the DC trials in those blocks. To increase power for this comparison, the total number of trials in blocks with MDC trials was doubled from 24 to 48.

The BEAM Version 0.2 design was intended to allow comparisons of blocks and individual trials across several predicted levels of cognitive difficulty (see Table 4). It was believed that the new design would enhance the following comparisons with regard to visual and manual reaction times:

1) Orienting and alerting effects of directional and temporal predictability,

2) Effects of target circle overlap vs. gap,

3) Effects of dual task (i.e., looking at the target circle and pressing the button) vs. single task (i.e., only looking at the target circle), and

4) Effects of Misdirectional Cue presence.

On every trial for BEAM Version 0.2, the fixation cross remained on screen for either 1500, 2000, or 2500 ms. When the fixation cross disappeared, either the cue (for DC, NDC, or MDC trials) or target circle (for UC trials) would appear. In gap conditions, the fixation cross/cue disappeared 200 ms before the target circle appeared. In overlap conditions, the fixation cross/cue remained on screen when the target circle appeared. Cue durations on DC, NDC, and MDC were fixed at 100 ms. The target circle remained on the screen for 1000 ms. When the target circle disappeared, the trial was over.

The dependent variables in BEAM Version 0.2 were manual and visual reaction times. Manual reaction time was calculated by taking the time of the button press on the Cedrus response pad and subtracting the time of the target circle onset. Manual reaction time was only calculated in dual task condition blocks (Blocks 2C and 2E). Visual reaction time was calculated by taking the time of first fixation on the target circle and subtracting the time of the target circle onset. Visual reaction time was calculated for every block.

Once BEAM Version 0.2 was programmed in E-Prime, lab developers beta-tested the paradigm. By using a fixed, pseudorandom, counterbalanced design, it was believed that the updates produced a more engaging assessment, and that psychometric data for BEAM Version 0.2 were ready to be obtained from participants. Recruitment for Study 1 began after beta-testing was complete. With a coded paradigm, data parser, and assessment design that was believed to efficiently collect data while maximizing statistical power, the developmental phase was complete.

STUDY 1

Using BEAM Version 0.2 and a custom-made data parser (i.e., scoring) program, Study 1 was ready to begin. The goals of Study 1 were to obtain descriptive statistics for manual and visual reaction time on each of the trial conditions, perform preliminary reliability analyses, and evaluate specific comparisons of trials among various independent variable conditions. Furthermore, direct feedback from participants was sought to optimize the instructions and test delivery methods of the BEAM.

Study 1 IRB Approval

Study 1 was approved by the Uniformed Services University Institutional Review Board. Participants were recruited via IRB-approved flyers. All subjects received and signed informed consent documents prior to study participation. See Pictures 4, 5, and 6 in Appendix C for IRB-approved documents. Data collection for Study 1 was conducted between April 2011 and May 2011.

Study 1 Protocol

Once a participant was calibrated and ready to begin the BEAM paradigm, the examiner read a series of instructions the following instructions: "You are about the take the Bethesda Eye and Attention Measure, the BEAM. The BEAM consists of a series of trials with visual stimuli appearing on the screen. On all trials, a target circle will appear above, below, left, or right of the center of the screen. When a target circle appears, look at it as fast as you can. We will now begin with a practice set." When the participant completed the practice set, he or she was given the opportunity to ask questions or retake the practice set. When the participant was ready to proceed, he or she received one of two instruction sets, depending on the button press condition. If the block did not require

a button press, then participants were given these instructions, “On the next block of trials, a target circle will appear above, below, left, or right of the center of the screen. When a target circle appears, look at it as fast as you can.” If the block required a button press, then participants were given these instructions, “On the next block of trials, a target circle will appear above, below, left, or right of the center of the screen. When a target circle appears, look at it and press the button as fast as you can.”

BEAM Version 0.2 consisted of one practice block of six trials without MDC trials, two blocks of 24 trials without MDC trials, and two blocks of 48 trials with MDC trials (see Table 3). Each trial consisted of a fixation cross appearing at the center of the screen for a fixed, pseudorandom period of time—1500 ms, 2000 ms, or 2500 ms—before disappearing. On all trials, a target circle appeared either above, below, left, or right of the center of the screen (see Figure 1). Only one target circle appeared per trial. The target circle appeared for 1000 ms before disappearing.

On cued trials (DC, NDC, or MDC), arrows or diamonds appeared in the center of the screen immediately after the fixation cross offsets. Cues were presented for 100 ms before the target circle appeared (overlap condition) or the cue disappeared (gap condition). In gap conditions, the target circle appeared 200 ms after the cue/fixation cross disappeared. In overlap conditions, the cue remained on screen until the target circle disappeared. When the target circle disappeared, a new fixation cross appeared and a new trial began. Each trial lasted between 2500 ms and 3700 ms, with the total BEAM Version 0.2 time lasting approximately 8 minutes.

Study 1 Participants

Participants included nine individuals without a self-reported history of TBI (five women and four men; *M* age = 30.8, *SD* = 4.90). The sample was 55.6% Caucasian, 33.3% Asian, and 11.1% African-American. No participants were compensated for their involvement in the study. The following inclusion criteria were required for all Study 1 participants: must be 18 years or older, must have fluency or literacy in English (per self-report), must be willing and able to provide informed consent, and must have obtained written permission from supervisor and/or brigade commander if they were a federal civilian or service member (see Picture 6 in Appendix C). Participants of all ethnicities and socioeconomic statuses were recruited. Participants were excluded from the study if examiners determined they demonstrated an impaired or fluctuating level of consciousness/arousal, if they had a medical condition that could impair cognitive abilities, if they had any visual impairment that was not corrected by glasses/contacts, or if they had motor impairment or amputation of one of both upper extremities. Because this phase of this project sought to determine the viability of the newly developed measure to differentiate hypothetical cognitive processes, Study 1 participants must not have incurred a traumatic brain injury of any kind throughout their lifetime. Demographic information for Study 1 is shown in Table 5.

Study 1 Procedure

The four independent variables for Study 1 were cue type (four levels: Uncued [UC], Nondirectional Cue [NDC], Directional Cue [DC], or Misdirectional Cue [MDC]), gap condition (two levels: gap [G] or overlap [O]), task type (two levels: single task or dual task), and misdirectional cue trial presence in the block (two levels: yes or no). Gap

condition and cue type were manipulated on all trials, meaning multiple gap and cue type independent variable levels were present in each block. By contrast, task type and MDC trial presence were manipulated by block, meaning each block used only one task type and MDC presence independent variable level. The dependent variables were manual reaction time and visual reaction time. Manual reaction time was only assessed on "dual task" blocks of trials.

Aims and Expectations. Study 1 was an exploratory, feasibility study that sought to collect data on BEAM performance. As such, there were no formal hypotheses planned or tested in Study 1. Rather, two research aims, each with expectations of BEAM performance, were evaluated.

Specific Aim 1: Assess the internal consistency of reaction times in BEAM Version 0.2 trials.

Expectation 1a: Cronbach's alpha value of .80 or higher would be obtained for visual reaction time.

Expectation 1b: Cronbach's alpha value of .80 or higher would be obtained for manual reaction time.

Rationale: Internal reliability reflects the extent to which items within an assessment measure the same cognitive construct (Strauss, Sherman, & Spreen, 2006). Reliable BEAM reaction times would support the validity of interpretations of cognitive performance. General guidelines indicate that internal reliability values of .80 or higher are desirable for measures that will be used to assess individuals (Sattler, 2001).

Specific Aim 2: Determine if BEAM Version 0.2 could elicit trends of manual and visual reaction time differences across different trial and block conditions.

Expectation 2. On all trials, visual reaction time would appear to be faster than manual reaction time.

Expectation 3. Single task trials would appear to have faster visual reaction time than dual task trials.

Expectation 4. Directional Cue (DC) trials would appear to have faster manual and visual reaction times than Nondirectional Cue (NDC) trials in similar gap conditions.

Expectation 5. Nondirectional Cue (NDC) trials would appear to have faster manual and visual reaction times than Uncued (UC) trials in similar gap conditions.

Expectation 6. Trials with gaps (G) would appear to have faster manual and visual reaction times than trials with overlaps (O) across all trial types.

Expectation 7. Trials in blocks without MDC trials (MDC- blocks) would appear to have faster visual reaction times than trials in blocks with MDC trials (MDC+ blocks).

Rationale: If BEAM Version 0.2 could accomplish Aims 1 and 2 with a sample of participants without a history of head injury, then it was believed that future experiments using between-groups analyses with uninjured and head-injured populations would produce clinically useful results. It was believed that Aim 2 would be reached by examining the following effects on manual and visual reaction time: the orienting effect (i.e., directional predictiveness), the alerting affect (i.e., temporal predictiveness), the gap effect (i.e., forced visual disengagement in gap vs. overlap), dual task (i.e., looking at target circle and pressing button) vs. single task (i.e., only looking at target circle) effect, and the executive effect (i.e., Misdirectional Cue interference present in blocks).

The orienting and alerting effects were assessed by comparing the manual and visual reaction time means on DC, UC, and NDC trials on non-MDC blocks. The gap

effect was assessed by comparing gap trials to overlap trials on non-MDC blocks. The dual task vs. single task effect was assessed by comparing Block 2B (no button press, no MDC) to Block 2C (button press, no MDC). The executive effect was assessed by comparing reaction times between MDC and non-MDC blocks.

Data Analytic Plan. Study 1 provided the first opportunity to evaluate the BEAM. As such, no formal comparisons were planned. Rather, descriptive statistics, and visual trends were examined to give the development team a preliminary indication of which aspects of the BEAM were useful and which aspects needed to be changed. Participant means for each trial type were calculated, and the group trial type means were calculated from the participant means. All expectations were evaluated by descriptive statistics, trends, and visual inspection. It was believed that descriptive statistics and trend analysis would provide an informative evaluation of BEAM Version 0.2's feasibility. To mitigate the influence of outliers on driving future improvements to the BEAM, trial type means that exceeded the group mean by three standard deviations were removed from analysis. Internal reliability was calculated using SPSS Version 19.

Study 1 Results

The results for Study 1 are comprised of preliminary reliability analyses, descriptive statistics (means, standard deviations), and trend analyses (percent differences). Reliability was excellent for overall visual reaction time, with a Cronbach's alpha value of .91 with 144 loaded items. Reliability was also excellent for overall manual reaction time, with a Cronbach's alpha value of .98 with 72 items loaded. Visual reaction time means ranged from 0.21 sec (SD = 0.053) in Dual Task, Directional Cue with Gap (DC/G) trials to 0.39 sec (SD = 0.042 sec) in Single Task, Misdirectional Cue

with Overlap (MDC/O) trials. Manual reaction time means ranged from 0.42 sec (*SD* = 0.080) in DC/G trials to 0.57 sec (*SD* = 0.047) in Uncued with Overlap (UC/O) trials. Visual and manual reaction time means and standard deviations across cue type, task type, and gap condition are reported in Tables 6 and 7. The visual and manual reaction time means and standard deviations in Tables 6 and 7 include data from blocks with and without misdirectional cues.

Because manual reaction time data were only collected in dual task conditions, Expectation 2 was examined by comparing overall visual reaction time in dual task blocks (*M* = 0.32 sec, *SD* = 0.041) with overall manual reaction time in dual task blocks (*M* = 0.50 sec, *SD* = 0.068). On all trial types in the dual task condition, visual reaction time was 22.0% faster than manual reaction time (see Figure 3).

Expectation 3 was examined by comparing overall single task reaction time with overall dual task reaction time. Omnibus single task visual reaction time mean (*M* = 0.32 sec, *SD* = 0.041) was 1.53% slower than the omnibus dual task visual reaction time mean (*M* = 0.33 sec, *SD* = 0.038) on similar trial types (see Figure 4).

Directional Cue with Gap (DC/G) trials had 37.0% faster single task visual reaction time (*M* = 0.22 sec, *SD* = 0.066), 35.3% faster dual task visual reaction time (*M* = 0.21 sec, *SD* = 0.053), and 5.61% faster manual reaction time (*M* = 0.42 sec, *SD* = 0.080) than similar Nondirectional Cue with Gap (NDC/G) trials (single task visual reaction time [*M* = 0.32 sec, *SD* = 0.060], dual task visual reaction time [*M* = 0.30 sec, *SD* = 0.075], and manual reaction time [*M* = 0.47 sec, *SD* = 0.11], respectively). Directional Cue with Overlap (DC/O) trials had 3.03% faster single task visual reaction time (*M* = 0.32 sec, *SD* = 0.030) and 3.03% dual task visual reaction time (*M* = 0.32 sec,

SD = 0.047) than similar Nondirectional Cue with Overlap (NDC/O) trials (single task visual reaction time [*M* = 0.34 sec, *SD* = 0.075] and dual task visual reaction time [*M* = 0.34 sec, *SD* = 0.042]). Unlike other DC and NDC trials, manual reaction time for NDC/O was 1.96% faster (*M* = 0.50 sec, *SD* = 0.073) than DC/O trials (*M* = 0.52 sec, *SD* = 0.073; see Figure 5).

Nondirectional Cue with Gap (NDC/G) trials had 1.81% faster single task visual reaction time (*M* = 0.32 sec, *SD* = 0.060), 1.64% faster than dual task visual reaction time (*M* = 0.30 sec, *SD* = 0.075), and 6.00% faster manual reaction time (*M* = 0.47 sec, *SD* = 0.11) than similar Uncued with Gap (UC/G) trials (single task visual reaction time [*M* = 0.33 sec, *SD* = 0.062], dual task visual reaction time [*M* = 0.31 sec, *SD* = 0.056], and manual reaction time [*M* = 0.53 sec, *SD* = 0.081]). Among the overlap trials, Nondirectional Cue with Overlap (NDC/O) trials were 5.55% faster in single task visual reaction time (*M* = 0.34 sec, *SD* = 0.075) and 4.22% faster in dual task visual reaction time (*M* = 0.34 sec, *SD* = 0.042) than similar Uncued with Overlap (UC/O) trials (single task visual reaction time [*M* = 0.38 sec, *SD* = 0.064] and dual task visual reaction time [*M* = 0.37 sec, *SD* = 0.032]). Manual reaction time for NDC/O was 6.54% faster (*M* = 0.50 sec, *SD* = 0.073) than UC/O trials (*M* = 0.57 sec, *SD* = 0.047; see Figure 6).

In single task conditions, all trials with gaps had faster visual reaction time (DC/G: *M* = 0.22 sec, *SD* = 0.066; NDC/G: *M* = 0.32 sec, *SD* = 0.060; UC/G: *M* = 0.33 sec, *SD* = 0.062; MDC/G: *M* = 0.35 sec, *SD* = 0.051) than similar single task trials with overlaps (DC/O: *M* = 0.32 sec, *SD* = 0.030; NDC/O: *M* = 0.34 sec, *SD* = 0.075; UC/O: *M* = 0.38 sec, *SD* = 0.064; MDC/O: *M* = 0.39 sec, *SD* = 0.042). Overall, single task gap trials were 7.92% faster than single task overlap trials. In dual task conditions, all trials

with gaps had faster visual reaction time (DC/G: *M* = 0.21 sec, *SD* = 0.053; NDC/G: *M* = 0.30 sec, *SD* = 0.075; UC/G: *M* = 0.31 sec, *SD* = 0.056; MDC/G: *M* = 0.36 sec, *SD* = 0.060) than similar dual task trials with overlaps (DC/O: *M* = 0.32 sec, *SD* = 0.047; NDC/O: *M* = 0.34 sec, *SD* = 0.042; UC/O: *M* = 0.37 sec, *SD* = 0.032; MDC/O: *M* = 0.36 sec, *SD* = 0.081). Overall, dual task gap trials were 8.17% faster than dual task overlap trials. Manual reaction times in all gap trials (DC/G: *M* = 0.42 sec, *SD* = 0.080; NDC/G: *M* = 0.47 sec, *SD* = 0.11; UC/G: *M* = 0.53 sec, *SD* = 0.081; MDC/G: *M* = 0.51 sec, *SD* = 0.10) than similar trials with overlaps (DC/O: *M* = 0.52 sec, *SD* = 0.073; NDC/O: *M* = 0.50 sec, *SD* = 0.073; UC/O: *M* = 0.57 sec, *SD* = 0.047; MDC/O: *M* = 0.52 sec, *SD* = 0.066). Overall, manual reaction time in gap trials was 4.46% faster than manual reaction time in overlap trials (see Figure 7).

Overall, single task trials in blocks without Misdirectional Cues (MDC-) had 9.38% faster overall visual reaction time (*M* = 0.29 sec, *SD* = 0.043) than similar trials in blocks with Misdirectional Cues (MDC+; *M* = 0.35 sec, *SD* = 0.050). Overall, trials in dual task MDC- blocks had 3.13% faster overall visual reaction time (*M* = 0.31 sec, *SD* = 0.045) than similar trials in MDC+ blocks (*M* = 0.33 sec, *SD* = 0.043). Manual reaction times in trials in MDC- blocks were 3.03% faster (*M* = 0.48 sec, *SD* = 0.071) than trials in MDC+ blocks (*M* = 0.51 sec, *SD* = 0.077; see Figure 8).

Study 1 Summary of Findings

Specific Aim 1: Assess the internal consistency of reaction times in BEAM Version 0.2 trials.

Expectation 1a. The Cronbach's alpha value for overall visual reaction time was above 0.80, **confirming Expectation 1a.**

Expectation 1b. The Cronbach's alpha value for overall manual reaction time was above 0.80, **confirming Expectation 1b.**

Specific Aim 2: Determine if BEAM Version 0.2 could elicit manual and visual reaction time differences across different trial and block conditions.

Expectation 2. Findings from Study 1 provided **preliminary evidence to support** the expectation that visual reaction time would be faster than manual reaction time on all trials types.

Expectation 3. The expectation that single task trials would have faster visual reaction time than dual task trials **was not supported**.

Expectation 4. The expectation that Directional Cue (DC) trials would have faster manual and visual reaction times than Nondirectional Cue (NDC) trials in similar gap conditions **was partially supported.**

Expectation 5. The expectation that Nondirectional Cue (NDC) trials would have faster manual and visual reaction times than Uncued (UC) trials in similar gap conditions **was partially supported.**

Expectation 6. The expectation that trials with gaps (G) would have faster manual and visual reaction times than trials with overlaps (O) across all trial types **was partially supported**.

Expectation 7. The expectation that trials in blocks without MDC trials (MDC- blocks) would have faster visual reaction times than trials in blocks with MDC trials (MDC+ blocks) **was partially supported**.

Study 1 Discussion

The results from Study 1 were mixed. BEAM Version 0.2 achieved the desired reliability metrics, and visual reaction times were consistently faster than manual reaction times on similar trials. Confirmations of Expectations 1a and 1b supported the overall feasibility of BEAM Version 0.2 to elicit reliable and useful oculomotor function data. Expectation 2 had enough preliminary evidence (visual reaction time being 22% faster than manual reaction time) to be supported. Contrary to Expectation 3, the visual reaction time was slower in single task conditions compared to dual task conditions, albeit by a small margin (less than 5% difference). Expectation 4 was partially supported, with gap conditions having a greater disparity between DC and NDC trials than overlap conditions. Expectation 5 was partially supported in the opposite manner, with overlap conditions having the greater percent difference between NDC and UC trials compared to gap conditions. In both single and dual task conditions, the gap trials had faster visual reaction time than overlap trials, supporting Expectation 6. However, the manual reaction time percent differences were only marginally (less than 5%) faster in gap trials than overlap trials, making Expectation 6 only partially supported. Trials in blocks without MDC cues were marginally faster than trials in blocks with MDC cues, partially supporting Expectation 7. In general, Study 1 provided preliminary support for several expectations among nine participants without a history of head injury. However, the large number of percent differences less than 5% indicated effects that may not be clinically or statistically useful for further exploration.

Study 1 revealed several limitations in the trial and block design that may have mitigated the expected effects. It was determined that fundamental changes in trial and

block design were needed to maximize the key effects of directional predictiveness (i.e., orienting), temporal predictiveness (i.e., alerting), interference (i.e., executive), and gaps (i.e., forced visual disengagements). Some conditions needed to be added, some conditions needed to be removed, and some conditions needed to be modified.

Conceptual Improvement of the BEAM

Based on the results from Study 1, the development team believed that the BEAM could be made more reliable and efficient by combining certain elements of the BEAM Version 0.2 design. Additionally, it was determined that a standard set of instructions needed to be presented to participants to reduce potential response bias (e.g., a bias to look at the target circle before pressing the button or vice-versa). The goals of BEAM Version 0.3 design were to improve psychometric quality and among discriminate between effects of location, timing, gap, and interference.

BEAM Version 0.3. Statistical analyses and qualitative participant feedback from Study 1 guided several changes to the design of BEAM Version 0.3. Design strengths from previous BEAM versions were combined in BEAM Version 0.3 to produce a more engaging, simplified, and psychometrically robust measure. By merging the experimental structure from BEAM Version 0.1 (i.e., block by block comparisons with fixed trial conditions) with the trial structure from BEAM Version 0.2 (i.e., trial by trial comparisons with variable block conditions), it was anticipated that BEAM Version 0.3 would provide a number of improved psychometric characteristics over BEAM Version 0.2 and produce more direct comparisons between trial types to reflect targeted aspects of cognitive performance. Specifically, changes to BEAM Version 0.3 included a reduction of independent variables, the removal of the single task condition, the removal of most

gap trial types, the addition of a "No-Go" trial, an increase in cue duration, changes to fixation cross duration, and the addition of a standardized instructional video.

To simplify statistical comparisons and increase power, the four independent variables from BEAM Version 0.2 were merged into one independent variable—"trial type"—with six levels. BEAM Version 0.3 consisted of one practice block of 24 trials and four experimental blocks of 48 trials. The practice block of 24 trials included all trial types in order to expose participants to each trial variation prior to the experimental portion of the paradigm. Each of the four experimental blocks had the same number of trial types to enable direct comparisons among blocks.

The findings of Study 1 suggested that there may not be a meaningful difference in visual reaction time between single task and dual task blocks. Therefore, the single task condition from BEAM Version 0.2 was removed; in BEAM Version 0.3, participants were instructed to look at target circles and press a response box button on every trial. This change increased the number of manual reaction time samples during the BEAM without increasing the administration time and enabled experimenters to compare manual and visual reaction time data across blocks.

Results of Study 1 suggested a strong trend for a gap effect in visual reaction time across conditions, where "gap" trials tended to be faster than "overlap" trials. Cue types did not appear to significantly impact the gap effect. To balance time/trial demands with other comparisons of interest, it was determined that the gap variants for trials with arrow or diamond cues could be removed. As such, DC, NDC, and MDC trials in BEAM Version 0.3 all had their cues overlap with the target circle onset. Uncued trials with gap and overlap conditions remained the same. This decision was justified for several

reasons. With their longer reaction times, overlap conditions were believed to be more cognitively demanding than gap conditions, making them more likely to produce an interaction between uninjured and head-injured groups in later BEAM studies. However, retention of "uncued with gap" and "uncued with overlap" trials in the BEAM would allow direct comparison with previous literature regarding the gap effect (Drew et al., 2007; Hutton, 2008). It was important to the designers of the BEAM that the measure reproduce a known effect in cognitive neuroscience, so the "uncued with gap" trial was retained in BEAM Version 0.3 as the only trial type with a 200 ms gap.

A new trial type, a "No-Go" condition, was added to directly measure disinhibition, a cognitive process which results in an individual having a reduced capacity to manage or control immediate, impulsive response(s) to a situation (Lezak, Howieson, & Loring, 2004). Previous versions of the BEAM did not measure disinhibition, a common dependent variable in TBI research (Lezak, et al., 2004). By adding a disinhibition trial type, it was believed that the BEAM could obtain an additional dependent variable to complement visual and manual reaction time data from other trial types.

Unlike other trial types, visual and manual reaction times were not assessed in the "No-Go" trial type. The new trial type was designed like a Directional Cue trial, except that the arrow cue pointing to where the target circle would appear was colored red. In the revised instructions to participants, directions stated, "When a target circle appears, look at it and press the button as fast you can. However, if you see a red arrow, do not look at the target circle and do not press the button." The new trial type was referred to as

"DCR," representing "Directional Cue-Red." As with other cued trial types in BEAM Version 0.3, DCR was an overlap, rather than a gap, trial type.

Cue duration was increased from 100 ms to 200 ms for several reasons. First, making the cue duration 200 ms equalized the overlap duration on cued trials with gap duration on "uncued with gap" trials. This change was made to increase comparability between trial types and improve overall paradigm reliability. Second, participant feedback from Study 1 indicated that 100 ms was not always long enough for participants to perceive the cue shape by the time the target circle had appeared, thereby reducing the intended predictiveness of the cue. Also, stop signal reaction time (SSRT) research indicates that a cue duration between 200-250 ms is sufficient for healthy participants to cognitively process a "no-go" cue and inhibit a response (Lipszyc & Schachar, 2010; Rieger, Gauggel, & Burmeister, 2003; Stevenson, Elsley, & Corneil, 2009). Based on this research, it was believed that 100 ms would be insufficient time for even individuals without a history of head injury to correctly inhibit a response. By comparison, allowing 200 ms to inhibit a response was believed to lead to significantly more disinhibition errors among head-injured participants than uninjured participants, improving the diagnostic utility of inhibition errors in the BEAM.

To increase the timing predictiveness of cues, the fixation cross duration was changed from three fixed times—1500 ms, 2000 ms, or 2500 ms—to a continuous, pseudorandom time between 1500 ms and 2500 ms. In BEAM Version 0.3, every trial's fixation cross appeared at the center of the screen for a pseudorandom period of time between 1500 ms and 2500 ms before offsetting. This change added a perceived randomization to the measure that both enabled direct comparisons between subjects

taking the same measure while reducing temporal predictiveness of when cues or target circles would appear.

To standardize the content and delivery of BEAM instructions, a computer-based video was created. The 2.5 minute video relayed the following instructions from a pre-recorded voice: "You are about to take the BEAM. The BEAM consists of a series of trials. On each trial, a fixation cross will appear at the center of the screen. On all trials, a target circle will eventually appear above, below, left, or right of the fixation cross. When the target circle appears, look at it and press the button in front of you as fast as you can. However, if you see a red arrow, do not look at the target circle and do not press the button." The participant is then guided through an example trial to ensure that he or she can accurately see the objects on the screen. The video ends with a final calibration of the participant's gaze to the eye tracker.

Each of the six trial types in BEAM Version 0.3 used systematically modulated cues to elicit specific neurocognitive functions. Visual and manual reaction times were measured in five of the six trial types (the sixth trial type—DCR—measured inhibition errors). More cognitively difficult trial types were estimated to have slower visual and manual reaction times because they would require more time to respond appropriately to target circle onset. Table 8 displays the hypothetical cognitive difficulty of each trial type with visual and manual reaction times.

Each of the six trial types in BEAM Version 0.3 was designed to provide participants with specific pieces of information to influence different cognitive networks, such as knowing when or where a target circle would appear. There were four "cued" trial types and two "uncued" trial types. Cues with a fixed 200 ms duration were

believed to provide information to the participants about when the target circle would appear. White, Nondirectional Cues with Overlap (NDC[1]) were diamond shaped and not predictive of where the circle stimulus would appear. NDC trials were believed to communicate *when* a target circle would appear, but not *where*. White, Directional Cues with Overlap (DC) were arrow-shaped, and they always pointed to the location where the circle stimulus would appear. DC trials were believed to convey *when* and *where* the target circle would appear. White, Misdirectional Cues with Overlap (MDC) were arrow-shaped, but the target circle always appeared in the *opposite* direction from which the arrow was pointing. MDC trials were believed to communicate the *when* but the wrong *where*.

The fourth "cued" trial type was the newly added "No-Go" task—the Red, Directional Cue with Overlap (DCR) designed to test inhibition. On DCR trials, participants were instructed to *not* look at the target circle and to *not* press the button. The red arrows on DCR trials always pointed to where the target circle would appear. Because the correct response on DCR trials was no response at all, visual and manual reaction times were not calculated for DCR trials; only visual or manual "errors" were counted. Visual errors were counted if a participant fixated on the target circle (i.e., looked when they should not have looked), and manual errors were counted if the participant pressed the button (i.e., pressed when they should not have pressed).

The two "uncued" trial types where no arrow or diamond appeared were called Uncued with Gap (UCG) and Uncued with Overlap (UC). As stated earlier, the UCG trial type was the only trial type in BEAM Version 0.3 with a gap. During UCG trials, the fixation cross would offset, and then be followed by a 200 ms "gap" before the target

[1] The trial type acronyms in BEAM Version 0.3 assume overlap unless otherwise noted.

circle appeared. This gap condition was contrasted by the UC, NDC, MDC, DC, and DCR trials, where the cue or fixation cross remained on the screen (i.e., overlap) while the circle stimulus was presented. Because all but one trial type had an overlap, only the uncued with gap (UCG) trial type had a gap (G) qualifier in its acronym, and all overlap (O) acronyms were dropped.

Other than the changes previously mentioned, the procedure of the BEAM remained the same in Version 0.3 (e.g., multiple trial types were presented continuously in multiple blocks of trials). Under the new design, each trial lasted pseudorandomly between 1500 ms and 3700 ms, with the total BEAM Version 0.3 duration lasting approximately 12 minutes.

BEAM Version 0.3 was designed to assess specific components of attention and executive functions with more reliability and larger effects for across-trial (i.e., within-individual) comparisons of cognitive processes than previous versions. Emphasis was given to standardize and counterbalance as much as possible while designing six truly unique trial types that could elicit different cognitive processes. The new version was expected to improve the psychometric quality of the data and enhance the validity of cognitive performance interpretation. Furthermore, the modification of the BEAM's trial types and structure enabled cognitive comparisons similar to Posner's (Fan, et al., 2009; Posner, 2008; Posner & Rothbart, 2007) work with the orienting, alerting, and executive networks of attention. Posner and Fan's (Fan, et al., 2009; Fan, McCandliss, Sommer, Raz, & Posner, 2002; Posner, 2008; Posner & Rothbart, 2007) work with the Attention Network Test (ANT) utilized button presses to measure manual reaction time. Applying

these comparisons to visual as well as manual reaction times, was believed to reliably elicit these well-characterized reaction time effects (Posner & Rothbart, 2007).

It was estimated that four possible cognitive processes or "effects" could be elicited and measured under the new BEAM design: the orienting effect of knowing target location (determined by comparing DC vs. NDC reaction times), the alerting effect of knowing when a target would appear (determined by comparing NDC vs. UC reaction times), the gap effect of one's perceptual flexibility with engaging and disengaging attention (determined by comparing UC vs. UCG reaction times), and the executive effect of reacting to accurate vs. inaccurate information (determined by comparing NDC vs. MDC reaction times). See Table 9 for a list of cognitive process comparisons in BEAM Version 0.3.

Because target circles consistently appeared 200 ms after cues appeared, cued trials (DC, NDC, MDC, and DCR) by design alerted the participant that a target circle was about to appear. Timing predictiveness was similar across the four cued trial types, making comparisons of directional predictiveness possible. DC trial types indicated where the target would appear, NDC trial types did not indicate where the target would appear, and MDC trial types indicated the opposite area where the target would appear. As such, DC vs. NDC comparisons were believed to elicit a response from the orienting network of attention (Posner, 1980; Posner & Dehaene, 1994; Posner & Petersen, 1990; Posner & Rothbart, 2007). Because MDC trials require a person to rapidly adjust to a surprising stimulus (i.e., the target circle appearing elsewhere from where the arrow was pointing), it was believed that an NDC vs. MDC comparison would elicit an

"interference" effect modulated by the executive network of attention (Posner & Dehaene, 1994; Posner & Petersen, 1990; Posner & Rothbart, 2007).

Unlike cued trial types, uncued trial types had no directional or timing predictiveness; the target circles would appear either after a gap (UCG trials) or while the fixation cross remained on screen (UC trials). Because NDC trials do not predict *where* the target circle will appear, but they predict *when* the target will appear, an NDC vs. UC comparison was believed to elicit a response from the alerting network of attention (Posner, 2008; Posner & Dehaene, 1994; Posner & Petersen, 1990; Posner & Rothbart, 2007).

Similar to previous research (Drew, et al., 2007; Goldring & Fischer, 1997; Pratt, Bekkering, Abrams, & Adam, 1999; Pratt, Lajonchere, & Abrams, 2006; Stevenson, et al., 2009), the gap effect (i.e., the impact of visual disengagement prior to reaction) was elicited by comparing uncued overlap (UC) trials with uncued gap (UCG) trials. Neither trial type had directional predictiveness.

A new master trial list of 216 trials was created. Each of the five blocks was counterbalanced for trial type, arrow cue direction, and target circle location. The scoring program also was updated to reflect this new trial design. Once all updates were coded and verified, examiners began recruitment for Study 2.

STUDY 2

The objective of Study 2 was to determine if the BEAM enhancements that were made improved the measure's reliability while eliciting more significant differences between key trial type comparisons among healthy individuals.

Study 2 IRB Approval

Study 2 was approved by the Uniformed Services University Institutional Review Board. Participants were recruited via IRB-approved flyers. All subjects received and signed informed consent documents prior to study participation. See Appendix C for IRB-approved documents. Data collection for Study 2 was conducted between May 2011 and June 2011.

Study 2 Protocol

Study 2 used BEAM Version 0.3. Once calibrated and ready to begin the BEAM paradigm, the subject was shown a standardized instructional video for the BEAM on their computer monitor. The 2.5 minute long video, a new addition to the BEAM protocol, explained what the participant was to do during the BEAM and gave participants practice trials to orient them to how trials would be displayed.

BEAM Version 0.3 consisted of one practice block of 24 trials and four blocks of 48 trials. Each trial consisted of a fixation cross appearing at the center of the screen for a pseudorandom period of time between 1500 ms and 2500 ms before offsetting. On all trials, a target circle appeared either above, below, left, or right of the center of the screen (see Figure 1). Only one target circle appeared per trial. The target circle appeared for 1000 ms before offsetting.

On cued trials (DC, NDC, MDC, or DCR), arrows or diamonds appeared in the center of the screen immediately after the fixation cross disappeared. Cues presented for 200 ms before the target circle appeared, and the cue remained on screen until the target circle offset. In UCG trials, the target circle would appear 200 ms after the fixation cross disappeared. In UC trials, the target circle would appear pseudorandomly between 1500

and 2500 ms with the fixation cross remaining on the screen until the trial ended. Trials ended when the target circle disappeared. Immediately after the circle disappeared, a new fixation cross would appear and a new trial would begin.

Study 2 Participants

Participants included 11 individuals without a self-reported history of TBI (eight women and three men; M = 26.1 years, SD = 3.53). The majority of the participants were highly educated (M = 17.4 years, SD = 1.36) and Caucasian (72.7%). Nearly three quarters of the sample (72.7%) were enrolled at the time of the study in a full time (36.4%) or part time (36.4%) educational program. Recruitment of Study 2 participants was conducted via flyers and word of mouth. No participants were compensated for their involvement in the study. Inclusion and exclusion criteria for Study 2 were the same as in Study 1. Because Study 2 sought to determine the viability of BEAM Version 0.3 to differentiate cognitive processes, study participants must not have incurred a traumatic brain injury of any kind throughout their lifetime. Demographic information is shown in Table 10.

Study 2 Procedure

The sole independent variable for Study 2 was cue type, and it had five levels: Directional Cue with Overlap (DC), Uncued with Gap (UCG), Nondirectional Cue (NDC), Uncued with Overlap (UC), and Misdirectional Cue (MDC). While BEAM Version 0.3 had a sixth trial type, Directional Cue-Red with Overlap (DCR), it was not included as part of this study since manual and visual reaction times were the feasibility study's primary variables of interest. The dependent variables were manual reaction time and visual reaction time. Manual reaction time was determined by taking the difference

between the time the target circle appeared on the screen and the time the participant pressed the button on the Cedrus box. Visual reaction time was determined by taking the difference between the time the target circle appeared on the screen and when the participant first fixated on the target circle.

Aims and Hypotheses. There were two specific aims of Study 2. Unlike Study 1, which was more exploratory in nature, several formal hypothesis tests were planned for Study 2.

Specific Aim 1: To determine if BEAM Version 0.3 represented an improvement in overall measure reliability from BEAM Version 0.2.

Hypothesis 1a. Internal reliability for visual reaction time will be higher in BEAM Version 0.3 than BEAM Version 0.2.

Hypothesis 1b. Internal reliability for manual reaction time will be higher in BEAM Version 0.3 than BEAM Version 0.2.

Rationale. BEAM Version 0.3 was designed to improve overall reliability from BEAM Version 0.2. Changes were made to the block and trial design to improve internal consistency.

Specific Aim 2: To determine if BEAM Version 0.3 could elicit several significant manual and visual reaction time effects of attention and executive function: orienting, alerting, executive, and gap effects.

Hypothesis 2a. Visual reaction time will be significantly faster than manual reaction times for each of the six trial types.

Hypothesis 2b. Directional Cue with Overlap (DC) trials will have significantly faster visual and manual reaction times than Nondirectional Cue with Overlap (NDC) trials, eliciting the orienting effect.

Hypothesis 2c. NDC trials will have significantly faster visual and manual reaction times than Uncued with Overlap (UC) trials, eliciting the alerting effect.

Hypothesis 2d. Uncued with Gap (UCG) trials will have significantly faster visual and manual reaction times than UC trials, eliciting the gap effect.

Hypothesis 2e. DC trials will have significantly faster visual and manual reaction times than Misdirectional Cue with Overlap (MDC) trials, eliciting the executive effect.

Rationale. The orienting effect (i.e., knowing *where* something was going to appear) was assessed by comparing manual and visual reaction time means between DC and NDC trials. The alerting effect (i.e., knowing *when* something was going to appear) was assessed by comparing manual and visual reaction time means between NDC and UC trials. The executive effect (i.e., response to interference or unpredictable events) was assessed by comparing manual and visual reaction times between DC and MDC trials. Lastly, the gap effect (i.e., engagement/disengagement of attention) was assessed by comparing manual and visual reaction time means between UCG and UC trials.

If BEAM Version 0.3 could accomplish Aims 1 and 2 with a sample of participants without a history of head injury, then it was believed that future experiments using between-groups analyses with uninjured and head-injured populations would produce clinically useful results.

Study 2 represented the first opportunity during the feasibility study of the BEAM to conduct formal statistical analyses on key comparisons. It was determined *a priori*

that dependent samples *t*-tests with 95% confidence intervals would be used to test the Study 2 hypotheses representing within-individual effects. Cohen's *d* was calculated for each *t*-test to determine effect size using the following formula:

$$d = \frac{\mu_D}{\sigma\sqrt{2(1-\rho)}},$$

where μ_D is the difference of means between groups, σ is the average standard deviation of the groups, and ρ is the correlation between scores (Morris & DeShon, 2002). Support for each of these hypotheses would provide evidence for the feasibility of the BEAM for future experiments comparing uninjured and head-injured groups.

Data Analytic Plan. Internal reliability was calculated using SPSS Version 19. Each of the five trials with reaction time dependent variables—DC, UCG, NDC, UC, and MDC—had 32 trials in BEAM Version 0.3, totaling 160 trials being loaded into the reliability analysis. Because BEAM Version 0.3 represented a fundamentally different paradigm than BEAM Version 0.2, Cronbach's alpha values greater than .98 for manual reaction time and .91 for visual reaction time were considered to be improvements in reliability over BEAM Version 0.2.

After completing BEAM Version 0.3, trial type manual and visual reaction time means were calculated for each participant ($N = 11$). Any trial type mean that exceeded the group mean by three standard deviations was considered an outlier and removed from analysis. Two repeated-measures ANOVAs were conducted on all participant means for manual and visual reaction times, where the within-subject factor was trial type with five levels: DC, UCG, NDC, UC, and MDC. Five dependent samples *t*-tests were then performed to compare the visual and manual reaction times for individual trial types. Eight additional comparisons, four for visual reaction time and four for manual reaction

time, were planned *a priori* to evaluate cognitive comparisons if significant repeated measures ANOVA results were obtained. These comparisons were made *a priori* in order to reduce the likelihood of Type 1 error, and they were based off data collected in Study 1. The planned dependent samples *t*-tests compared reaction time for DC and NDC trials (i.e., the orienting effect), NDC and UC trials (i.e., the alerting effect), UCG and UC trials (i.e., the gap effect), and DC and MDC trials (i.e., the executive effect). Dependent samples effect sizes were calculated using means, standard deviations, and correlations between means (Morris & DeShon, 2002). All tests were two tailed using alpha = .05.

Study 2 Results

Means and standard deviations for visual and manual reaction time were calculated for each of the five trial types that measured reaction times: Uncued with Overlap (UC), Uncued with Gap (UCG), Directional Cue with Overlap (DC), Misdirectional Cue with Overlap (MDC), and Nondirectional Cue with Overlap (NDC). One trial type, Directional Cue-Red (DCR), measured inhibition errors rather than reaction times; for this reason, it was not included in this analysis.

BEAM Version 0.3 had excellent internal reliability, with Cronbach alpha values of .99 for overall manual reaction time and .94 for overall visual reaction time. Individual trial type reliabilities were excellent for manual reaction time and acceptable-to-good for visual reaction time (see Tables 11 and 12). Visual reaction time means ranged from 0.26 sec in DC trials to 0.34 sec in MDC trials (see Figure 9). Visual reaction time standard deviations ranged from 0.026 sec in UCG trials to 0.034 sec in DC trials. Manual reaction time means ranged from 0.49 sec in DC trials to 0.59 sec in UC

trials. Manual reaction time standard deviations ranged from 0.12 sec in UC trials to 0.14 sec in MDC trials. Manual and visual reaction time data from BEAM Version 0.3 are represented in Table 13.

The five trial types significantly differed from each other in visual ($F(4, 40) = 29.6$, $p < 0.001$, partial $\eta^2 = 0.75$) and manual ($F(4, 40) = 37.9$, $p < 0.001$, partial $\eta^2 = 0.79$) reaction times. Individual dependent-samples *t*-tests confirmed Hypothesis 2a, where visual reaction time was significantly faster than manual reaction time on DC trials ($t(10) = 5.64$, $p < .001$), UCG trials, ($t(10) = 7.48$, $p < .001$), NDC trials ($t(10) = 5.63$, $p < .001$), UC trials ($t(10) = 6.45$, $p < .001$), and MDC trials ($t(10) = 6.45$, $p < .001$).

Dependent-samples *t*-tests also confirmed Hypotheses 2b, 2c, 2d, and 2e. As seen in Table 14, all four of the predicted cognitive effects in visual and manual reaction times reached statistical significance with large effect sizes. The orienting effect was elicited for visual ($t(10) = 10.2$, $p < .001$, $d = 3.22$) and manual ($t(10) = 7.04$, $p < .001$, $d = 2.18$) reaction times, confirming Hypothesis 2b (see Figures 10 and 11). The alerting effect was elicited for visual ($t(10) = 3.53$, $p = .005$, $d = 1.10$) and manual ($t(10) = 5.32$, $p < .001$, $d = 1.85$) reaction times, confirming Hypothesis 2c (see Figures 12 and 13). The gap effect was elicited for visual ($t(10) = 2.95$, $p = .015$, $d = 0.90$) and manual ($t(10) = 3.61$, $p = .005$, $d = 1.15$) reaction times, confirming Hypothesis 2d (see Figures 14 and 15). The executive effect also was elicited for visual ($t(10) = 12.0$, $p < .001$, $d = 3.66$) and manual ($t(10) = 9.69$, $p < .001$, $d = 3.05$) reaction times, confirming Hypothesis 2e (see Figures 16 and 17).

Study 2 Summary of Findings

Specific Aim 1: To determine if BEAM Version 0.3 represented an improvement in overall measure reliability from BEAM Version 0.2

Hypothesis 1a. The hypothesis that internal reliability for visual reaction time would be higher in BEAM Version 0.3 **was confirmed.**

Hypothesis 1b. The hypothesis that internal reliability for manual reaction time would be higher in BEAM Version 0.3 **was confirmed.**

Specific Aim 2: To determine if BEAM Version 0.3 could elicit significant manual and visual reaction time differences across four networks of attention and executive function: orienting, alerting, executive, and gap effects.

Hypothesis 2a. The hypothesis that visual reaction time would be significantly faster than manual reaction times for each of the six trial types **was confirmed.**

Hypothesis 2b. The hypothesis that Directional Cue with Overlap (DC) trials would have significantly faster visual and manual reaction times than Nondirectional Cue with Overlap (NDC) trials, eliciting the orienting effect, **was confirmed.**

Hypothesis 2c. The hypothesis that NDC trials would have significantly faster visual and manual reaction times than Uncued with Overlap (UC) trials, eliciting the alerting effect, **was confirmed.**

Hypothesis 2d. The hypothesis that Uncued with Gap (UCG) trials would have significantly faster visual and manual reaction times than UC trials, eliciting the gap effect, **was confirmed.**

Hypothesis 2e. The hypothesis that DC trials would have significantly faster visual and manual reaction times than Misdirectional Cue with Overlap (MDC) trials, eliciting the executive effect, **was confirmed.**

Study 2 Discussion

Summary. Results from Study 2 indicated that BEAM Version 0.3 elicited reliable and signficant reaction time differences in a sample of participants without a history of head injury. The updates implemented in BEAM Version 0.3 improved the measure's psychometric properties and enhanced the utility of within-group comparisons of cognitive domains. All six of the hypotheses that drove Study 2 were confirmed: reliability in BEAM Version 0.3 was higher for manual and visual reaction times than in BEAM Version 0.2, visual reaction time was faster than manual reaction time in each of the five reaction time trial types, and the orienting, alerting, executive, and gap effects were elicited with large effect sizes.

Compared to BEAM Version 0.2, which had Cronbach's alpha values of .98 and .91 for overall manual reaction time and overall visual reaction time, respectively, BEAM Version 0.3 had better reliability. While BEAM Versions 0.2 and 0.3 could not be compared directly because they were two different measures, the higher Cronbach's alpha values in BEAM Version 0.3's manual and visual reaction time support Hypothesis 1 being confirmed. All five trial types had significantly faster visual reaction times than manual reaction times, suggesting that the visual response was consistently faster than the button press. Trial type accounted for 74.8% of the variance in visual reaction time and 79.1% of the variance in manual reaction time, providing strong support that reaction time was primarily influenced by the trial types themselves. The effect sizes from the

post-hoc *t*-tests, ranging from 0.90 to 3.66, are perhaps the most striking findings from Study 2. Potentially, these very large effect sizes represent clinically significant differences between several cognitive domains: alerting, executive, gap, and orienting. Obtaining large effect sizes for each of these domains within a relatively small sample of non-head-injured participants provides encourgaing evidence for future between subject studies comparing people with and without head injury.

Limitations. The results from Study 2 were obtained from a relatively small sample size of highly educated young adults, most of whom were Caucasian females. As such, the results of Study 2 may not generalize well to populations with greater age, education, gender, and ethnic diversity. Furthermore, no measures of fatigue, depression, or anxiety were recorded during Study 2, so physical or psychiatric influences on reaction time could not be determined. In addition, the sample consisted entirely of individuals without a history of head injury, preventing any analysis of head injury effects with BEAM data. These limitations, however, are consistent with the scope of Study 2—to represent a "proof of concept" for the feasibility of the BEAM to detect multiple aspects of cognitive function. Employing nearly equivalent sample size and demographics from Study 1, Study 2 suggested that BEAM Version 0.3 represented a marked improvement in reliability and construct validity from previous BEAM versions.

The order in which people responded, either visually first or manually first, to the target circle appearing on screen represented a potential limitation from the study. The directions were written to avoid biasing one form of response over the other, specifically stating, "When a target circle appears, look at it and press the button as fast as you can." While the word order may imply that a participant should look first and press the button

later, the response pattern varied from participant to participant. Based on examiner observation, participants typically looked at the target circles first and then pressed the button, a pattern consistent with dual task paradigms (Kokubu, Ando, Kida, & Oda, 2006). This response pattern, however, did not always manifest throughout a measure or among participants, as evidenced by faster manual reaction times on some trials than visual reaction times. It may be useful for future studies with the BEAM to evaluate response patterns as a potential source of systemic error.

A potential limitation of the conculsions drawn from this feasibility study stems from reliability of difference scores in reaction times. Like other data transformations, subtracting an average reaction time from another induces systemic error into the manipulated variable, reducing its reliability. A meta-analysis conducted by MacLeod and colleagues (2010) on the Attention Network test (ANT) presented convincing evidence that reaction time difference scores lack the reliability to make clinical decisions. In congruence with that recommendation, it should be noted that the four BEAM "effects" listed in the manuscript may not be useful for clinical decision making at this time. Fortunately, the purpose of this study was to demonstrate future clinical feasibility using saccadic metrics, not to create a ready-to-use clinical decision making tool. The comparisons between trial type mean reaction times, each with acceptable-to-excellent [.75-.99] internal consistency, were made for "proof of concept" purposes. No difference scores were actually calculated for the four BEAM effects (e.g., the alerting effect was not calculated by subtracting mean NDC trial type reaction time from mean UC trial type reaction time). The trial type reaction time means in the BEAM were compared to specific trial type reaction time means, just as one group would be compared

to another, and the comparisons stopped there (e.g., alerting performance was not compared to executive performance).

Looking forward, it may be imprudent to use difference scores for clinical applications with the BEAM. The variance of each reaction time measure in the BEAM includes simple reaction time and process reaction time. In cognitive research, differences scores are used to reduce or eliminate simple reaction time variance and isolate the process reaction time. However, simple reaction time is a useful comparison tool for clinical TBI research, and it should be retained, *not* be reduced or eliminated. The BEAM's reaction time measurements by themselves demonstrated acceptable-to-excellent reliability, making them useful for comparisons to normative sets.

Difference scores and their reliabilities have always mattered to cognitive research largely because reliable difference scores can identify the processes mediating cognitive functions. In clinical research, however, what matters is usually a comparison of an individual's scores to normative data, not necessarily difference scores. Obviously, the measures used to evaluate a certain construct need to be reliable and possess good construct validity for these comparisons to be useful (Strauss, et al., 2006). Given this study's small sample size ($N = 11$), though, it would be imprudent to draw conclusions from test-retest or split-half reliability at this time. Future studies of the BEAM with larger sample sizes would benefit from these additional reliability analyses.

Using means to compare reaction times, even when excluding outliers, exposes the data to undue influence from extreme variables. Coldren and colleagues (2012) used medians to compare reaction times on the ANAM since that metric is largely resistant to outliers. A recent study using Dinges's psychomotor vigilance task (PVT; Basner &

Dinges, 2011) found that the reciprocal of mean reaction time (1/RT) was a statistically robust, sensitive, and reliable measure of alertness. Future studies using BEAM data can incorporate other indices such as medians and mean reaction time towards reliability analyses.

General Discussion. Consolidating independent variables from previous BEAM versions into one independent variable with five levels represented a major design improvement in BEAM Version 0.3. Reducing the number of independent variable conditions reduced the number of familywise comparisons, and subsequently reduced the probability of making a Type 1 error. Additionally, the five levels of Study 2's "trial type" independent variable that measured reaction time enabled direct comparisons of multiple networks of attention and executive function, a major design improvement from earlier versions of the BEAM.

Instead of randomizing the trial presentation, the BEAM was designed with a fixed trial type set to counter the effects of inhibition of return. As such, every participant took the same measure with the same trial order. The trial order was designed such that an equivalent number of non-DCR trial types followed DCR trials (e.g., roughly the same number of DC, UCG, NDC, UC, and MDC trials followed DCR trials). Any inhibition of return effect, if present, would be consistent across groups and within the individual.

The sixth trial type, DCR, measured commission errors instead of reaction time. Unlike other trial types, participants were told to *not* look at the target circle and to *not* press a button if they saw a red arrow cue. On DCR trials, visual commission errors were counted if a participant looked at the target circle, and button press commission errors

were counted if the participant pressed the button. On a given DCR trial, there could be four outcomes: no commission errors, visual commission error only, button press comission error only, or both visual and button press commission errors.

While DCR errors were not included in Study 2's *a priori* hypotheses, post-hoc analysis provided some interesting data meriting further exploration. Among the 11 participants, there were 3.50 average visual commission errors ($SD = 3.40$). The same sample averaged 0.20 button press commission errors ($SD = 0.40$). A post-hoc, dependent samples *t*-test revealed that the sample committed significantly more visual commission errors ($t(10) = 3.27$, $p < .005$, $d = 1.53$) than button press commission errors. Study 2's sample of participants without a history of TBI was significantly more prone to visual commission errors than button press errors. Since people with TBI often have greater difficulty inhibiting their responses than people without a history of TBI (DeHaan et al., 2007), it is likely that there would be an interaction between TBI status and commission errors. Future studies incorporating both reaction time and inhibitory error data may produce more robust results that could enhance the BEAM's power to detect cognitive impairment.

For this feasibility study, reaction time was defined as the time of the first fixation on the target circle minus the time of target presentation. Saccadic velocity, acceleration, and initiation latency are components of this study's reaction time worthy of additional study. For the purposes of Study 2, however, the dependent variable was chosen to reflect functional performance, e.g., quantify how quickly a participant completes a task under various conditions. In the BEAM, the task is fixating a visual target. Until the target is fixated, the information that it contains cannot be effectively used, and the

attentional process remains incomplete. Certainly, initiation of a saccade toward a correct target represents some kind of cognitive accomplishment, but it is not a completed task until the target is fixated.

The BEAM's simple reaction time measurement reflects how quickly a participant fixates on a target once it appears somewhere on a computer screen. This simple reaction time provides a reliable measurement of attention and serves as a highly useful between-group comparison (Coldren, et al., 2012). From this practical and functional perspective, BEAM variables can translate to real-life applications. For example, measurement of MDC reaction times may provide an indication of how fast one reacts to the unexpected.

Several sub-components of saccades (e.g., saccadic initiation latency, saccadic duration, saccadic accuracy, etc.) load into the reaction time variables that were measured in this study, and they likely load differently for different subjects. Specific analysis of these saccadic sub-components may provide insight into the mechanisms of functional reaction time to the research community. However, in the interest of reducing chances of making a Type 1 error, the BEAM and its parser was coded to identify the simplest and most functionally relevant reaction time.

Based on the results from Study 1 and a desire to improve the quality of the measure, the development team chose to redesign numerous components of the BEAM's paradigm and individual trial design in BEAM Version 0.3. To achieve clinical feasibility benchmarks, the development team attempted to find the trial configurations that could be as sensitive and specific as possible in the shortest possible time. In Study 2, the 12-minute BEAM Version 0.3 elicited alerting, orieting, gap, and executive effects

with large effect sizes among a relatively small sample of healthy participants. It appears that BEAM Version 0.3 succeeded in being able to rapidly elicit multiple cognitive processes in healthy individuals.

A major strength of Study 2 was consolidating and replicating known effects of attention and executive function research from multiple scientific fields, including neuroscience, psychophysics, and cognitive psychology. For example, knowing where something would appear resulted in faster BEAM Version 0.3 reaction times, supporting the orienting effect (Posner & Rothbart, 2007). Likewise, knowing when something would appear rendered faster reaction times than trials without temporal predictiveness, supporting the alerting effect (Posner, 2008). Forced visual disengagements on gap trials rendered faster visual and manual reaction times than overlap trials, supporting the idea that gaps mediate faster reaction time (Drew, et al., 2007; Pratt, et al., 1999; Stevenson, et al., 2009). Also, healthy controls were significantly slower on trials with inaccurate directional information than on trials with accurate directional information, supporting the executive effect (Fan, et al., 2009; Fan, et al., 2007).

More work is needed to further evaluate the BEAM. Future studies should compare reaction times and response variability between individuals with and without a history of head injury. Groups with a history of mild TBI should display slower overall visual and manual reaction times than healthy controls across all trial types, specifically amongst the DC and MDC trials. Van Donkelaar and colleagues (2005) found that the orienting and executive components of attention were negatively impacted by mild TBI more than the alerting component. Knowing where something would appear in DC trials (i.e., orienting) would presumably help less (i.e., longer reaction time), and reacting to

unexpected target location in MDC trials (i.e., executive) would take longer, too. Given the vast amount of research into mild TBI and frontal deficits, people with mild TBI should likely have larger (i.e., poorer) MDC reaction times.

Deficits in mild TBI often manifest heterogeneously as a result of its diffuse pathophysiology, which makes group comparisons between healthy and injured groups more difficult to make. Additionally, the nature of mild TBI deficits that manifest in diverse groups of people (e.g., people with higher premorbid IQ tend to have smaller deficits associated with mild TBI) further complicates clinical decision making. People with and without a history of mild TBI may perform well on some trial types and poorly in others.

Identification of mild TBI is only one of the BEAM's clinical goals; future studies will seek to characterize the brain systems affected by mild TBI for a given individual. A key point of interest is how the five trial types appear in different populations, such as sub-acute mild TBI, healthy fatigue, post-acute mild TBI, and healthy participants with suboptimal effort, to name a few. With large enough samples, reaction time patterns specific to certain populations may emerge.

BEAM Version 0.3 is sensitive enough to detect within-individual reaction time differences among a small sample of healthy participants; future studies are warranted to determine if these effects are maintained or enhanced in a sample of head-injured persons. Given the clinical purpose of the BEAM, more psychometric evaluation is warranted. Test-retest and split-half reliability in multiple clinical and non-clinical populations should be evaluated in future studies to determine confidence intervals of assessed performance. To determine if the BEAM is measuring intended cognitive

domains, convergent and divergent construct validity should be examined by comparing BEAM results with validated measures of attention, executive function, processing speed, memory, and psychomotor performance. Direct comparisons with the ANAM (Coldren, et al., 2012) or ANT (Fan, et al., 2009; Fan, et al., 2002) would enhance understanding of advantages, disadvantages, and similarities between the BEAM and currently used computer-based measures of cogntive processing. To explore potential confounds or sources of error, future studies should explore relationships between BEAM performance and psychosocial factors common to military poulations, such as depression, tramatic stress, and fatigue in the military population (Hoge, et al., 2008). Ultimately, more research evaluating reliability and validity across multiple injured and non-injured populations is needed to determine the BEAM's clinical utility as a measure of cognitive performance and impairment for head injured individuals. For now, the feasibility study of the BEAM provides prelimary evidence of a sensitive assessment for cognitive performance.

CONCLUSION

The feasibility study of the Bethesda Eye & Attention Measure (BEAM) represented the development, evaluation, and refinement of a computer-based eye-tracking paradigm designed to measure cognitive function. The project was divided into three phases: an in-house paradigm and data processing developmental phase, an initial study of the measure's capability, and a follow-up study to assess a refined measure. Each phase implemented conceptual and experimental improvements from previous research until a system that was believed to be viable for larger studies of convergent and divergent validity emerged.

The BEAM, a 12-minute measure, measured multiple cognitive processes (i.e., alerting, orienting, gap, and executive effects) with large effect sizes in a small sample size of participants without a history of head injury. More than 75% of the variance in reaction time was attributed to the trial design. Reliability for visual and manual reaction time was excellent. Combined, these results suggest the BEAM may be a psychometrically sound tool to assess these cognitive functions in a relatively short amount of time.

Future studies should compare BEAM performance with validated measures of attention, executive functions, and processing speed from a large, normative sample of people with and without a history of head injury in order to obtain convergent construct validity for the cognitive aspects purportedly observed in this project. While BEAM data, particularly visual reaction time data, is believed to be more sensitive to attention and executive function deficits than traditional neuropsychological measures, it is still important to determine the level to which BEAM data and neuropsychological data

correlate. Comparisons of BEAM data between people with and without a history of head injury would provide critical information about the BEAM's sensitivity, specificity, and predictive power. Neuroimaging studies using the BEAM could be compared to other studies involving the orienting, alerting, executive, and gap networks (Fan, et al., 2008; Fan, et al., 2005; Fan, et al., 2002; Fan & Posner, 2004; Fernandez-Duque & Posner, 2001; Posner & Rothbart, 2007) to identify similarities and differences of the BEAM and the Attention Network Test (ANT).

In conclusion, the feasibility study of the BEAM has shown that the BEAM has the *potential* to identify cognitive dysfunction associated with mild TBI. Given the large effect sizes obtained in this study, the BEAM may be more sensitive to cognitive deficits associated with mild TBI than existing neuropsychological measures. The feasibility study strongly supports the connections between oculomotor function and cognition, and lends support to using computer-based oculomotor assessment to assess attention and executive function. More research is needed to determine the psychometric properties of the BEAM and to evaluate any potential clinical utility.

APPENDIX A: FIGURES

FIGURE LEGEND:

DC/G = Directional Cue with Gap

DC/O = Directional Cue with Overlap

NDC/G = Nondirectional Cue with Gap

NDC/O = Nondirectional Cue with Overlap

UC/G = Uncued with Gap

UC/O = Uncued with Overlap

MDC/G = Misdirectional Cue with Gap

MDC/O = Misdirectional Cue with Overlap

MDC+ = Blocks with Misdirectional Cues

MDC- = Blocks without Misdirectional Cues

O = Overlap

G = Gap

ManRT = Manual Reaction Time

VisRT = Visual Reaction Time

FIGURE 1

Example Computer Screen with Fixation Cross and Four Possible Stimuli Locations

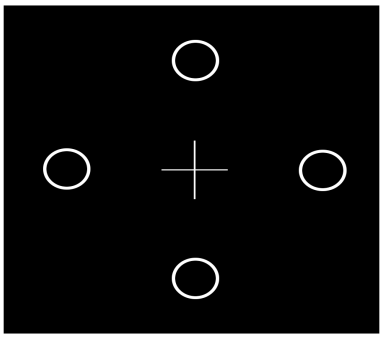


FIGURE 2

Example Trial Orders. A = Directional cue with overlap. B = Directional cue with gap.

C = Misdirectional cue with overlap. D = Nondirectional cue with overlap.

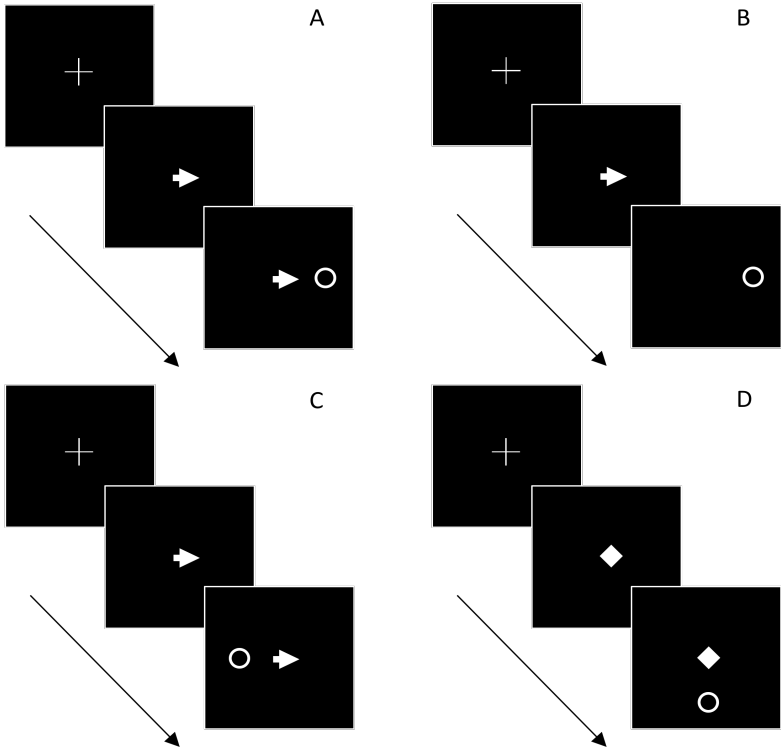


FIGURE 3

Study 1: Mean Visual and Manual Reaction Times for Trials in Dual Task Condition

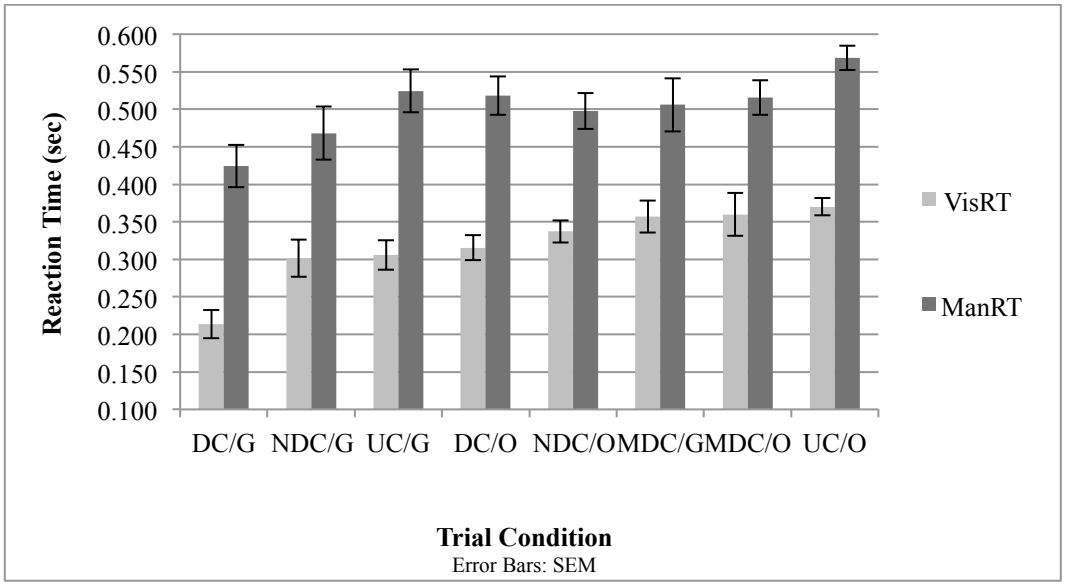


FIGURE 4

Study 1: Mean Visual Reaction Times for Trials in Single and Dual Task Conditions

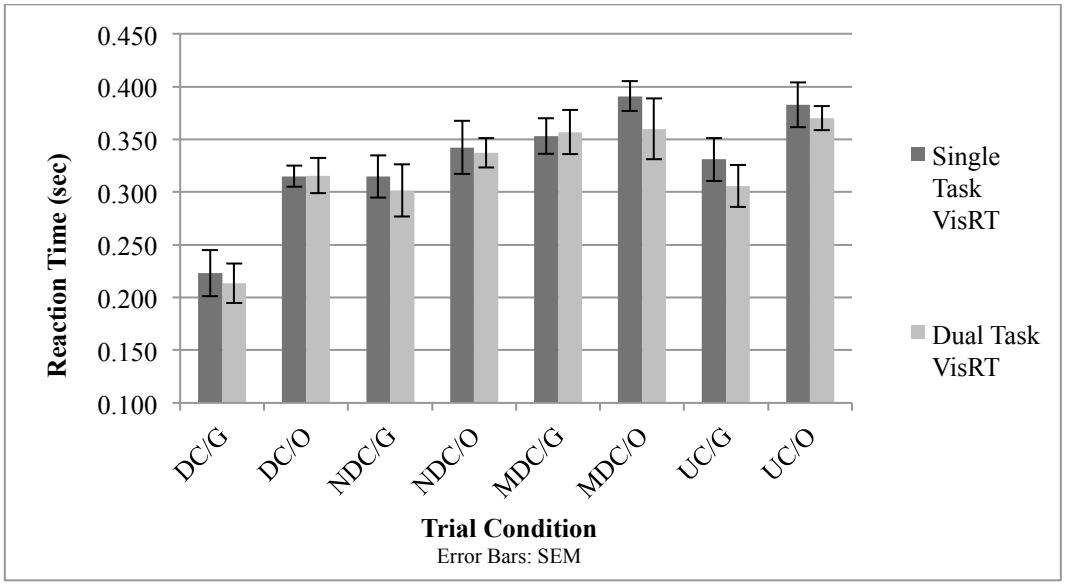


FIGURE 5

Study 1: Mean Visual and Manual Reaction Times for Directional Cue and Nondirectional Cue Trials in Gap and Overlap Conditions

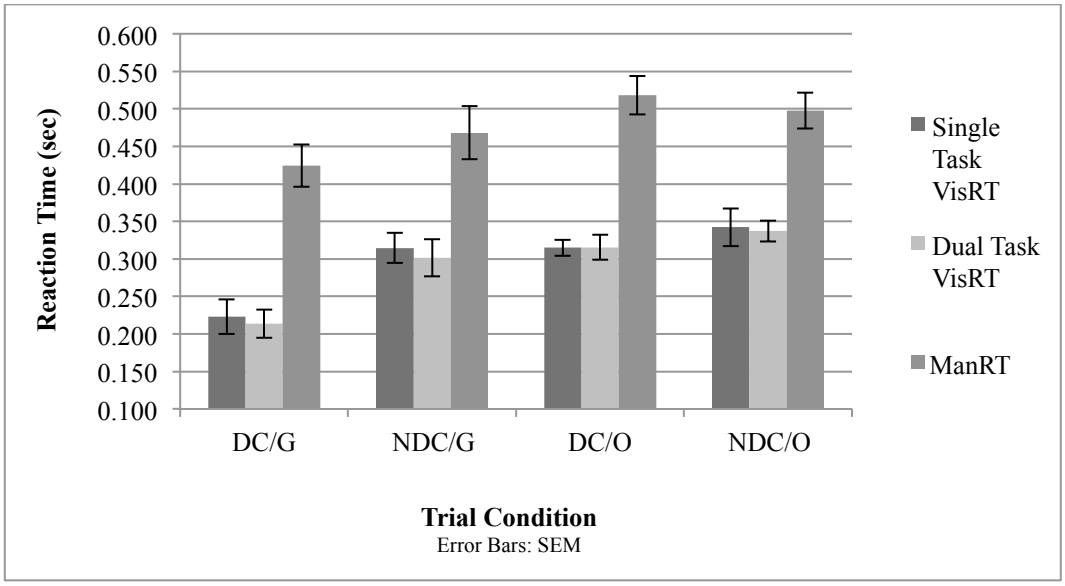


FIGURE 6

Study 1: Mean Visual and Manual Reaction Times for Nondirectional and Uncued Trials in Gap and Overlap Conditions

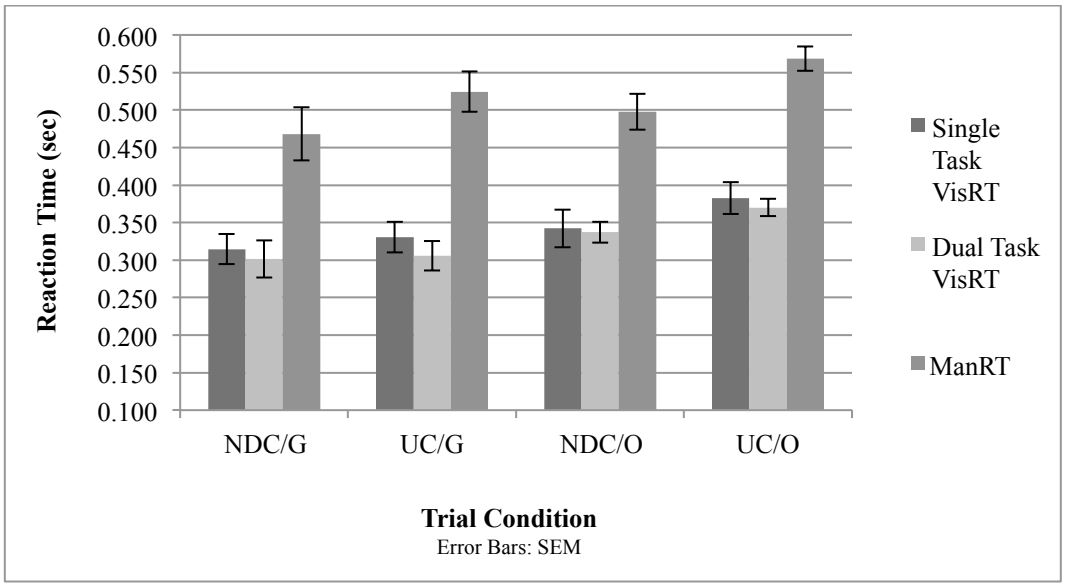


FIGURE 7

Study 1: Mean Visual and Manual Reaction Times for Trials in Gap and Overlap Conditions

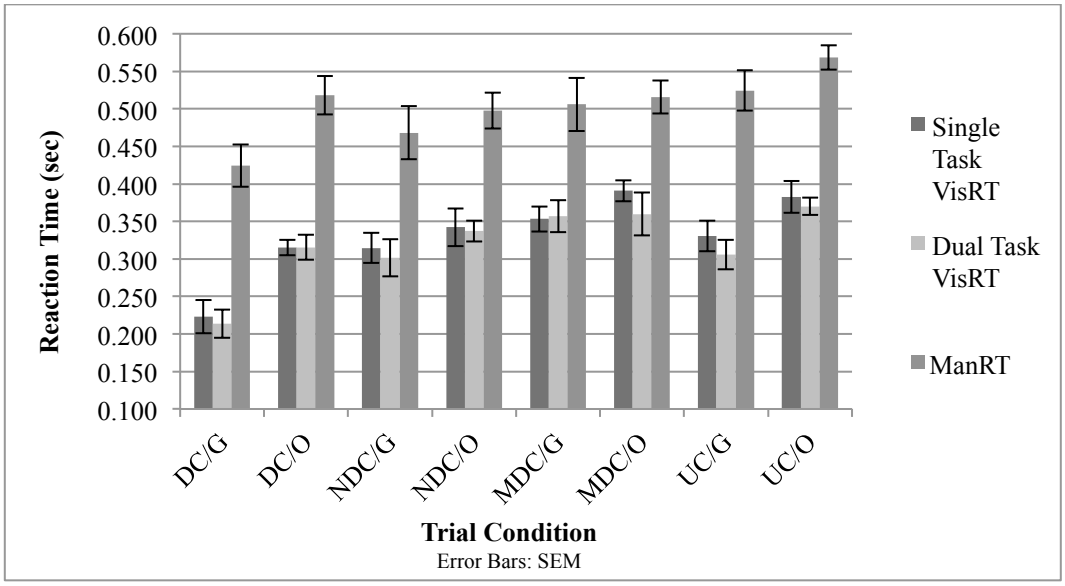


FIGURE 8

Study 1: Mean Visual Reaction Times for Trials in Blocks With and Without Misdirectional Cues in Single and Dual Task Conditions

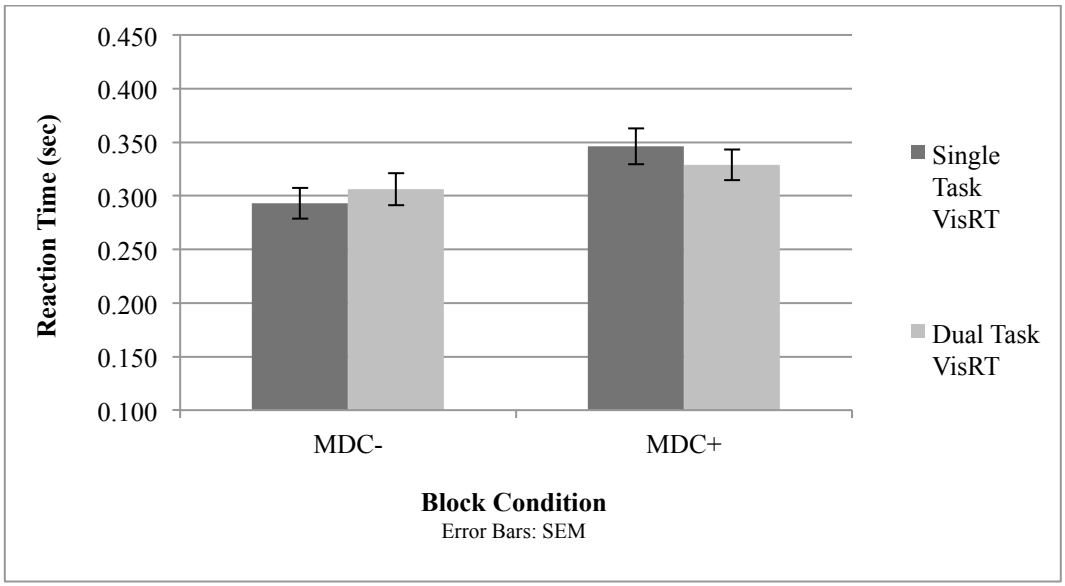


FIGURE 9

Study 2: Mean Visual and Manual Reaction Times by Trial Type

Visual Reaction Time: $F(4, 40) = 29.6$, $p < 0.001$, partial $\eta^2 = 0.75$

Manual Reaction Time: $F(4, 40) = 37.9$, $p < 0.001$, partial $\eta^2 = 0.79$

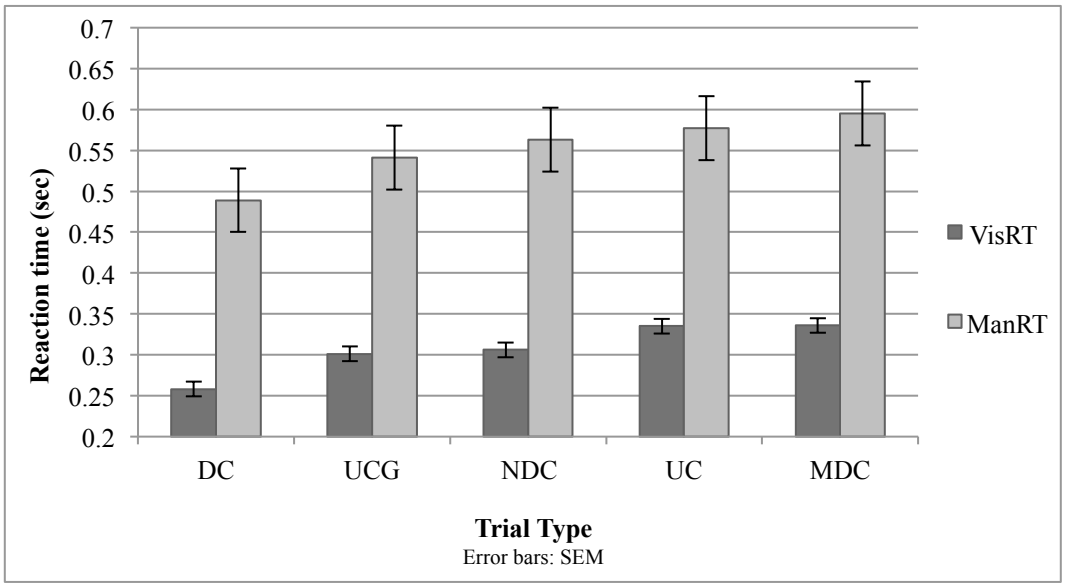


FIGURE 10

Study 2: Orienting Effect Comparison with Visual Reaction Time

$t(10) = 10.2$, $p < .001$, $d = 3.22$

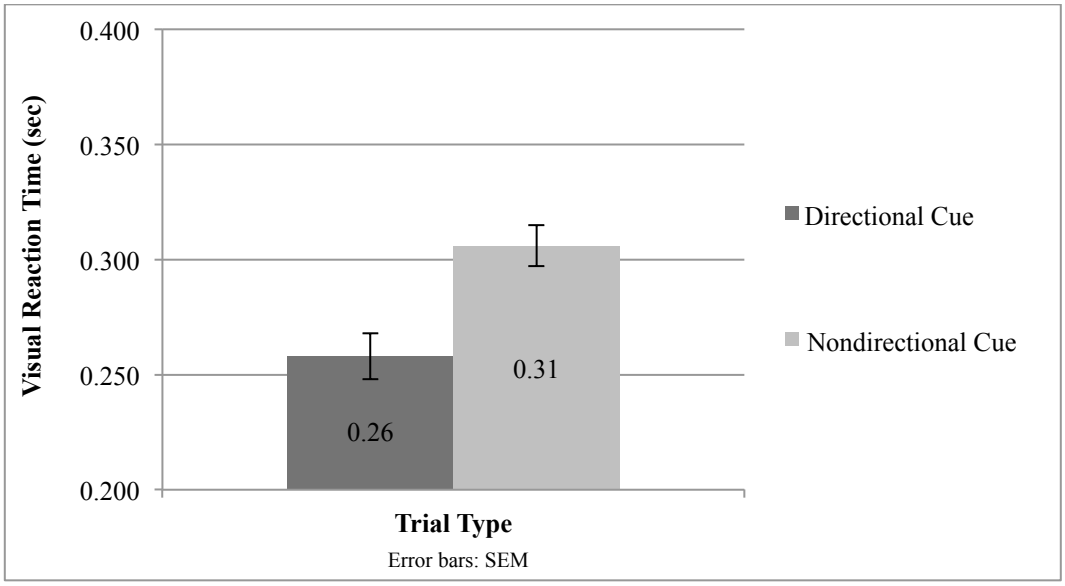


FIGURE 11

Study 2: Orienting Effect Comparison with Manual Reaction Time

$t(10) = 7.04$, $p < .001$, $d = 2.18$

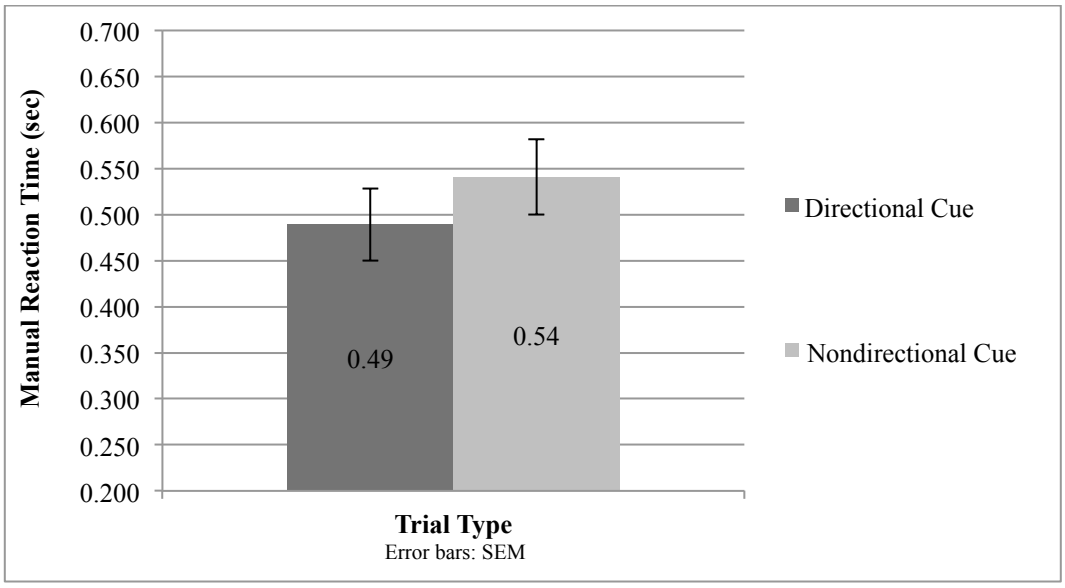


FIGURE 12

Study 2: Alerting Effect Comparison with Visual Reaction Time

$t(10) = 3.53$, $p = .005$, $d = 1.10$

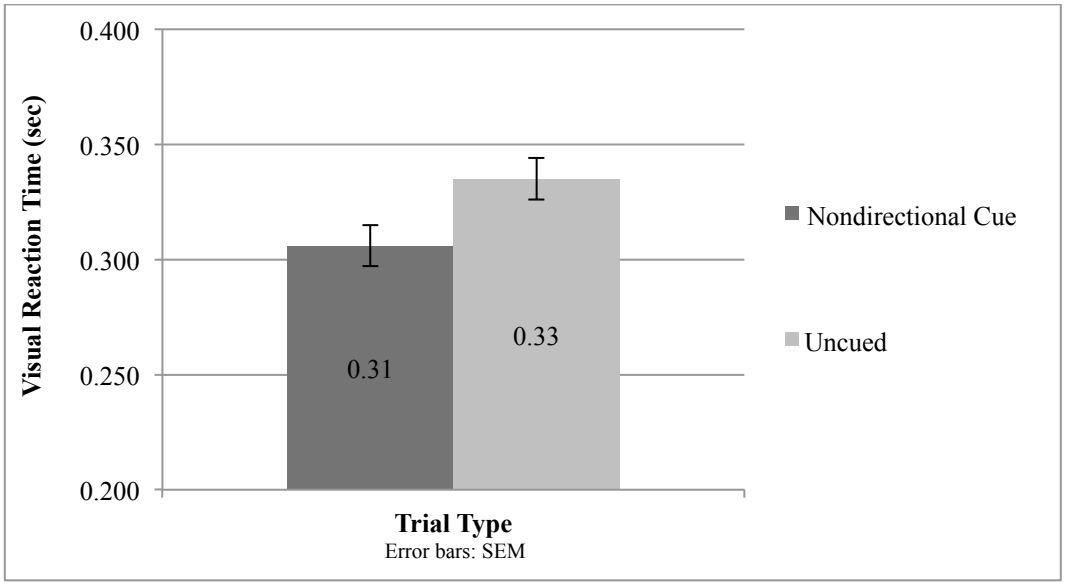


FIGURE 13

Study 2: Alerting Effect Comparison with Manual Reaction Time

$t(10) = 5.32$, $p < .001$, $d = 1.85$

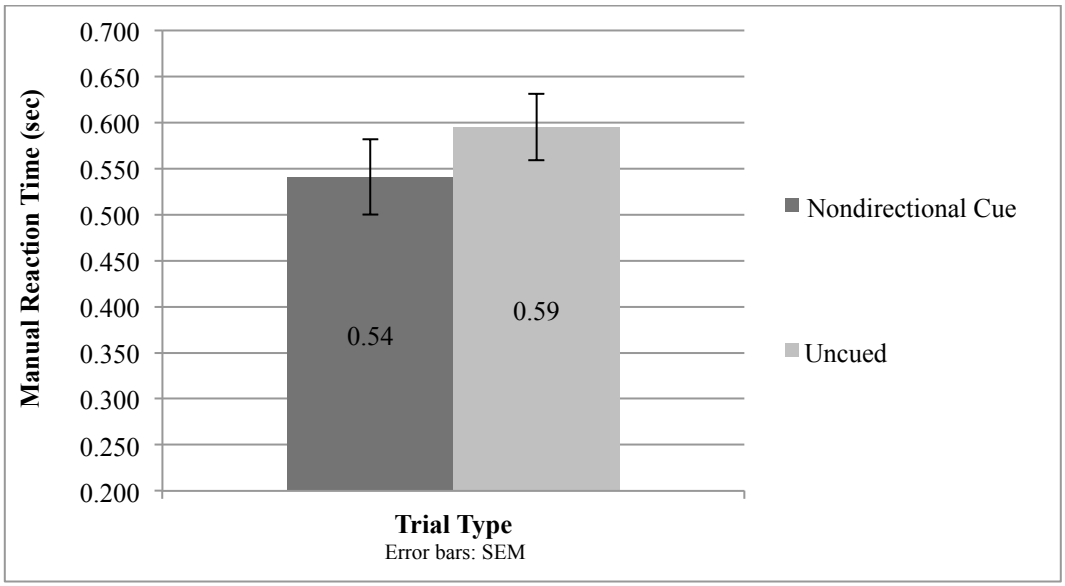


FIGURE 14

Study 2: Gap Effect Comparison with Visual Reaction Time

$t(10) = 2.95$, $p = .015$, $d = 0.90$

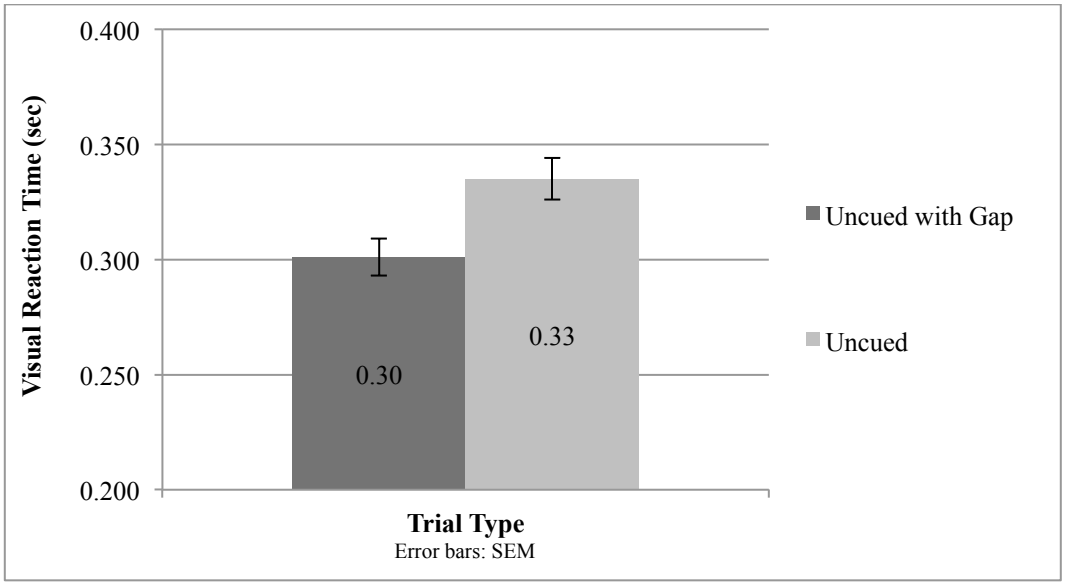


FIGURE 15

Study 2: Gap Effect Comparison with Manual Reaction Time

$t(10) = 3.61$, $p = .005$, $d = 1.15$

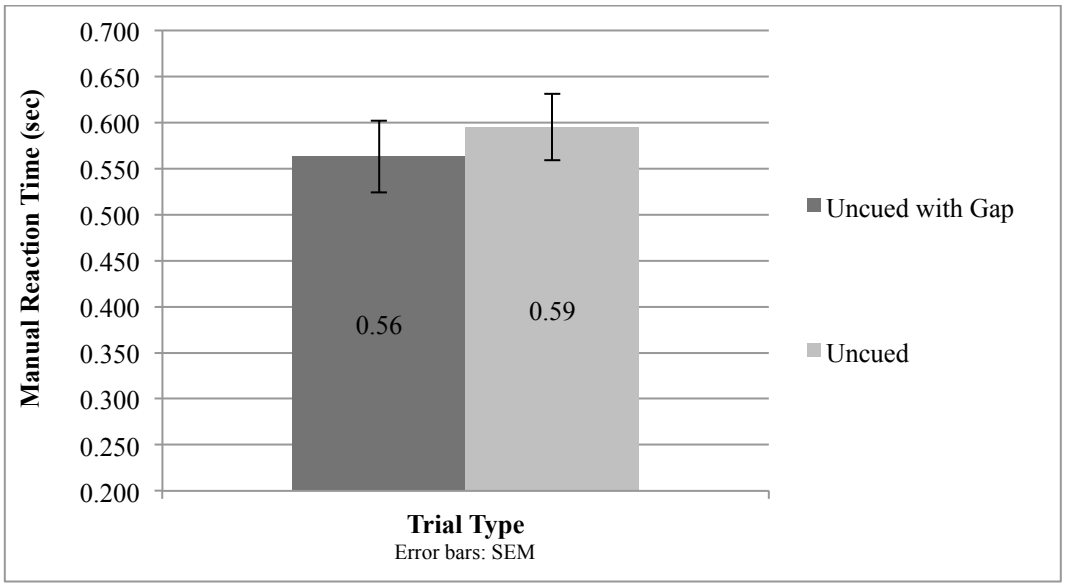


FIGURE 16

Study 2: Executive Effect Comparison with Visual Reaction Time

$t(10) = 12.0, p < .001, d = 3.66$

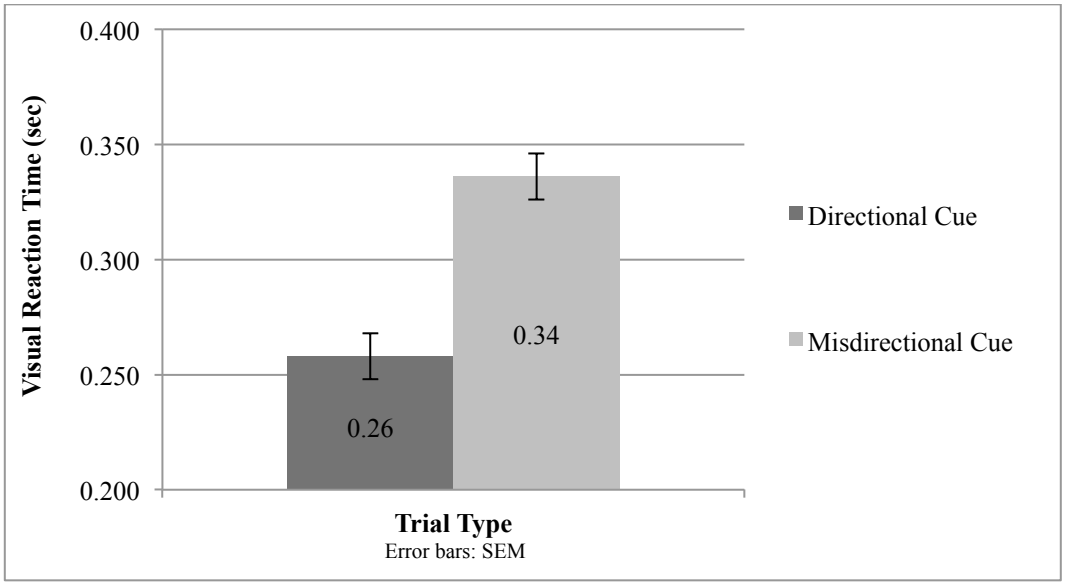
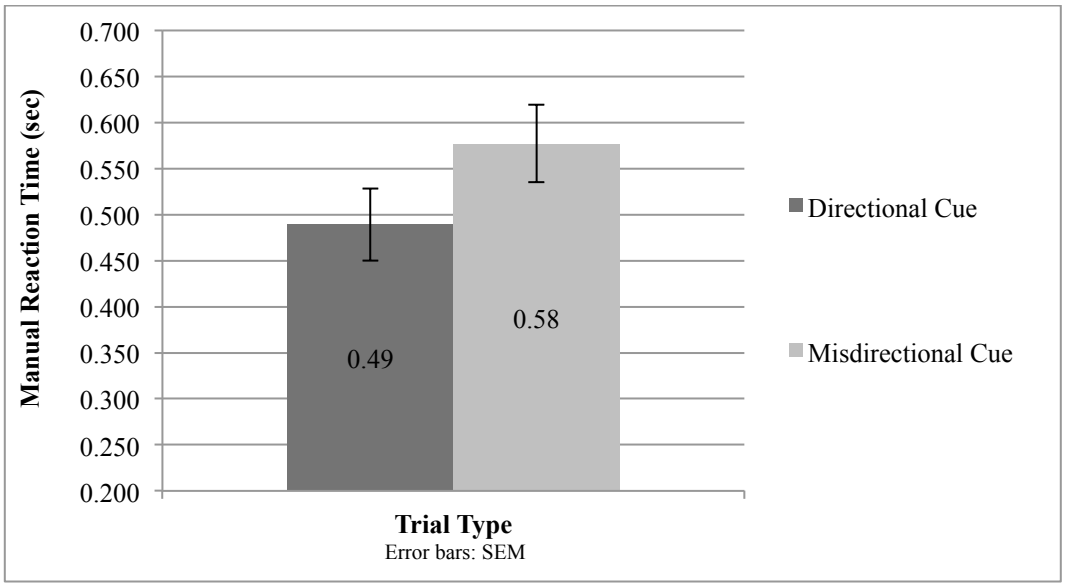


FIGURE 17

Study 2: Executive Effect Comparison with Manual Reaction Time

$t(10) = 9.69, p < .001, d = 3.05$



APPENDIX B: TABLES

TABLE LEGEND:

NDC = Nondirectional Cue

DANDC = Directional and Nondirectional Cue

MDC = Misdirectional Cue

O = Overlap

G = Gap

FISI = Fixed Interstimulus Interval

VISI = Variable Interstimulus Interval

DC/G = Directional Cue with Gap

DC/O = Directional Cue with Overlap

NDC/G = Nondirectional Cue with Gap

NDC/O = Nondirectional Cue with Overlap

UC/G = Uncued with Gap

UC/O = Uncued with Overlap

MDC/G = Misdirectional Cue with Gap

MDC/O = Misdirectional Cue with Overlap

MDC+ = Blocks with Misdirectional Cues

MDC- = Blocks without Misdirectional Cues

ManRT = Manual Reaction Time

VisRT = Visual Reaction Time

Table 1

BEAM Version 0.1 Block Design with Independent Variable Conditions								
Block	Reaction Time	Cue Type			Gap Condition		Interstimulus Interval	
		NDC	DANDC	MDC	O	G	FISI	VISI
1A	X							
1B		X				X	X	
1C			X			X	X	
1D		X				X		X
1E			X			X		X
1F		X			X		X	
1G			X		X		X	
1H		X			X			X
1I			X		X			X
1J				X		X	X	
1K				X	X		X	
1L				X		X		X
1M				X	X			X

Table 2

Predicted Cognitive Difficulty of Independent Variable Conditions in BEAM Version 0.1			
Independent Variable	IV Level	Description	Level of Difficulty Relative to Other IV Levels
Cue type	DANDC	Directional and nondirectional cues	Easiest
Cue type	NDC	Nondirectional cues	Medium
Cue type	MDC	Misdirectional cues	Hardest
Gap condition	G	Gap between cue and target circle	Easiest
Gap condition	O	Overlap between cue and target circle	Hardest
Interstimulus interval	FISI	Fixed interstimulus intervals	Easiest
Interstimulus interval	VISI	Variable interstimulus intervals	Hardest

Table 3

BEAM Version 0.2 Block Design with Number of Trials per Independent Variable Condition											
Block	Block Type	Cue Type					Gap Condition		Task Type		
		UC	NDC	DC	MDC		O	G	Single Task	Dual Task	Total Trials
2A	Practice	2	2	2	No	0	3	3	6	0	6
2B	Experimental	8	8	8	No	0	12	12	24	0	24
2C	Experimental	8	8	8	No	0	12	12	0	24	24
2D	Experimental	12	12	12	Yes	12	24	24	48	0	48
2E	Experimental	12	12	12	Yes	12	24	24	0	48	48

Table 4

Predicted Cognitive Difficulty of Independent Variable Conditions in BEAM Version 0.2			
Independent Variable	IV Level	Description	Level of Difficulty Relative to Other IV Levels
Cue type	DC	Directional cues	Easiest
Cue type	NDC	Nondirectional cues	Medium
Cue type	UC	No arrow or diamond cues	Harder
Cue type	MDC	Misdirectional cues	Hardest
Gap condition	G	Gap between cue and target circle	Easier
Gap condition	O	Overlap between cue and target circle	Harder
Button Press	Single task	No button press, just looking at target	Easier
Button Press	Dual Task	Button press and looking at target	Harder
MDC Trial Presence	MDC No	No MDC trials present in block	Easier
MDC Trial Presence	MDC Yes	MDC trials present in block	Harder

Table 5

Study 1: Participant Demographic Information

	Valid *N*	Full Sample
N	-	9
Female	5	55.6%
Mean Age in Years (SD)	9	30.8 (4.90)
Mean Years Education (SD)	9	17.3 (0.69)
Single	6	66.7%
Married/Legally Partnered	2	22.2%
Engaged	1	11.1%
Caucasian / White	5	55.6%
African American / Black	1	11.1%
Asian	3	33.3%
Right-handed	8	88.9%

Table 6

Study 1: Visual Reaction Time Data

	Single Task					
	Gap			Overlap		
Trial Type	Valid N	Mean (sec)	SEM (sec)	Valid N	Mean (sec)	SEM (sec)
DC	9	0.22	0.066	9	0.32	0.030
NDC	9	0.32	0.060	9	0.34	0.075
UC	9	0.33	0.062	9	0.38	0.064
MDC	9	0.35	0.051	9	0.39	0.042

	Dual Task					
	Gap			Overlap		
Trial Type	Valid N	Mean (sec)	SEM (sec)	Valid N	Mean (sec)	SEM (sec)
DC	8	0.21	0.053	8	0.32	0.047
NDC	9	0.30	0.075	9	0.34	0.042
UC	8	0.31	0.056	8	0.37	0.032
MDC	8	0.36	0.060	8	0.36	0.081

Table 7

Study 1: Manual Reaction Time Data

	Dual Task					
	Gap			Overlap		
Trial Type	Valid N	Mean (sec)	SEM (sec)	Valid N	Mean (sec)	SEM (sec)
DC	8	0.42	0.080	9	0.52	0.073
NDC	9	0.47	0.11	9	0.50	0.073
UC	9	0.53	0.081	8	0.57	0.047
MDC	8	0.51	0.10	9	0.52	0.066

Table 8

Hypothesized Cognitive Difficulty of Independent Variable Conditions in BEAM Version 0.3 that Measure Visual and Manual Reaction Time						
IV Level	Description	Target Timing Cue (+/-)	Target Positional Cue (+/-)	Gap (+/-)	Net (+/-)	Level of Difficulty Relative to Other Trials
DC	Directional cues	+	+	-	++	Easiest
UCG	No arrow or diamond cue with gap	N/A	N/A	+	+	Easier
NDC	Nondirectional cues	+	N/A	-	Neutral	Medium
UC	No arrow or diamond cues	N/A	N/A	-	-	Harder
MDC	Misdirectional cues	+	-	-	- -	Hardest

Table 9

Hypothesized Cognitive Effects Highlighted in Key Trial Type Comparisons of Manual and Visual Reaction Time in BEAM Version 0.3						
		Trial Type Comparisons				
Cognitive Effect	Associated Scientific Question	DC	UCG	NDC	UC	MDC
Orienting Effect	How does knowing *where* the target will appear affect reaction time?	X		X		
Gap Effect	How does visual disengagement affect reaction time?		X		X	
Alerting Effect	How does knowing *when* a target will appear affect reaction time?			X	X	
Executive Effect	How do accuracy of information affect reaction time?	X				X

Table 10

Study 2: Participant Demographic Information

	Valid *N*	Full Sample
N	-	11
Female	8	72.7%
Mean Age in Years (SD)	11	26.1 (3.53)
Mean Years Education (SD)	11	17.4 (1.36)
Single	7	63.6%
Married/Legally Partnered	3	27.3%
Divorced	1	9.10%
Caucasian / White	8	72.7%
Hispanic	1	9.10%
Asian	2	19.2%
Right-handed	8	72.7%

Table 11

BEAM Version 0.3 Visual Reaction Time Reliabilities		
Trial Type	Cronbach's Alpha	Number of Items
Overall Paradigm	.94	160
Nondirectional Cue (NDC)	.86	32
Directional Cue (DC)	.85	32
Misdirectional Cue (MDC)	.79	32
Uncued with Gap (UCG)	.78	32
Uncued (UC)	.75	32

Table 12

BEAM Version 0.3 Manual Reaction Time Reliabilities		
Trial Type	Cronbach's Alpha	Number of Items
Overall Paradigm	.99	160
Nondirectional Cue (NDC)	.99	32
Uncued with Gap (UCG)	.99	32
Misdirectional Cue (MDC)	.99	32
Directional Cue (DC)	.99	32
Uncued (UC)	.98	32

Table 13

BEAM Version 0.3 Trial Type Data

	VisRT			ManRT		
Trial Type	Valid N	Mean (sec)	SD (sec)	Valid N	Mean (sec)	SD (sec)
DC	11	0.26	0.034	11	0.49	0.13
UCG	11	0.30	0.026	11	0.56	0.13
NDC	11	0.31	0.029	11	0.54	0.14
UC	11	0.33	0.029	11	0.59	0.12
MDC	11	0.34	0.032	11	0.58	0.14

Table 14

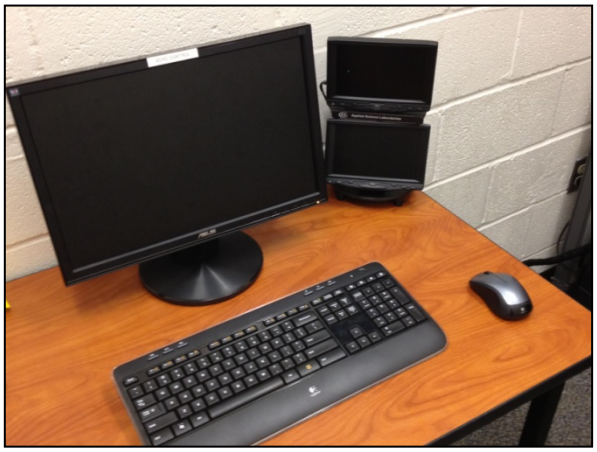
Comparison of Effects from Trial Types in BEAM Version 0.3

Trial Type Comparison	VisRT		ManRT	
	p	*d*	*p*	*d*
Orienting Effect: DC vs. NDC	< .001	3.22	< .001	2.18
Gap Effect: UC vs. UCG	.015	0.90	.005	1.15
Alerting Effect: NDC vs. UC	.005	1.10	< .001	1.85
Executive Effect: DC vs. MDC	< .001	3.66	< .001	3.05

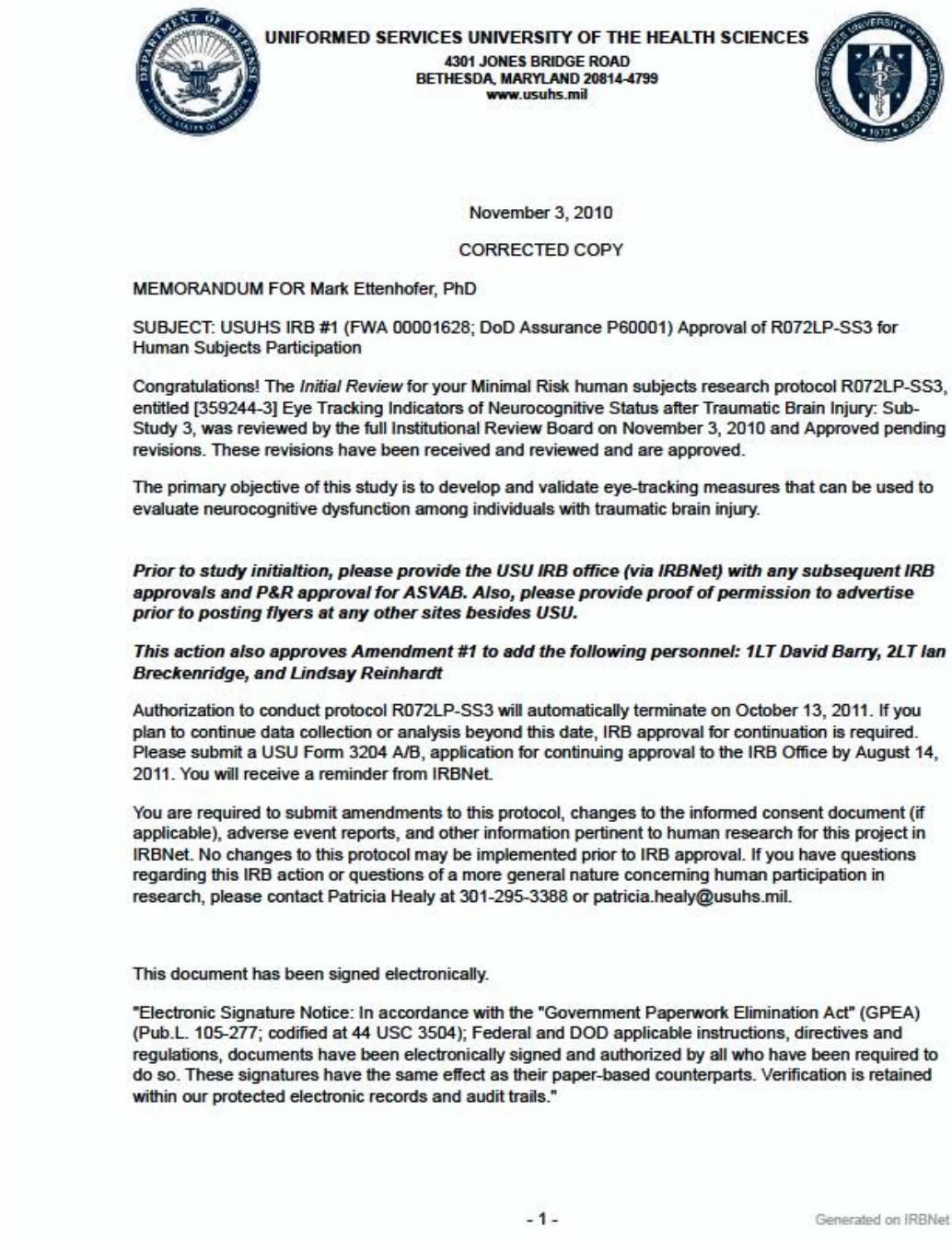
APPENDIX C: SUPPLEMENTAL MATERIALS

Picture 1: Computer Monitor, ASL D6 Eye Tracker, and Cedrus Response Pad

Picture 2: ASL EYE-TRAC 6 Control Unit, Control Computer, and Stimulus Computer



Picture 3: Examiner Station with ASL LCD Monitors



UNIFORMED SERVICES UNIVERSITY OF THE HEALTH SCIENCES
4301 JONES BRIDGE ROAD
BETHESDA, MARYLAND 20814-4799
www.usuhs.mil

November 3, 2010

CORRECTED COPY

MEMORANDUM FOR Mark Ettenhofer, PhD

SUBJECT: USUHS IRB #1 (FWA 00001628; DoD Assurance P60001) Approval of R072LP-SS3 for Human Subjects Participation

Congratulations! The *Initial Review* for your Minimal Risk human subjects research protocol R072LP-SS3, entitled [359244-3] Eye Tracking Indicators of Neurocognitive Status after Traumatic Brain Injury: Sub-Study 3, was reviewed by the full Institutional Review Board on November 3, 2010 and Approved pending revisions. These revisions have been received and reviewed and are approved.

The primary objective of this study is to develop and validate eye-tracking measures that can be used to evaluate neurocognitive dysfunction among individuals with traumatic brain injury.

Prior to study initialtion, please provide the USU IRB office (via IRBNet) with any subsequent IRB approvals and P&R approval for ASVAB. Also, please provide proof of permission to advertise prior to posting flyers at any other sites besides USU.

This action also approves Amendment #1 to add the following personnel: 1LT David Barry, 2LT Ian Breckenridge, and Lindsay Reinhardt

Authorization to conduct protocol R072LP-SS3 will automatically terminate on October 13, 2011. If you plan to continue data collection or analysis beyond this date, IRB approval for continuation is required. Please submit a USU Form 3204 A/B, application for continuing approval to the IRB Office by August 14, 2011. You will receive a reminder from IRBNet.

You are required to submit amendments to this protocol, changes to the informed consent document (if applicable), adverse event reports, and other information pertinent to human research for this project in IRBNet. No changes to this protocol may be implemented prior to IRB approval. If you have questions regarding this IRB action or questions of a more general nature concerning human participation in research, please contact Patricia Healy at 301-295-3388 or patricia.healy@usuhs.mil.

This document has been signed electronically.

"Electronic Signature Notice: In accordance with the "Government Paperwork Elimination Act" (GPEA) (Pub.L. 105-277; codified at 44 USC 3504); Federal and DOD applicable instructions, directives and regulations, documents have been electronically signed and authorized by all who have been required to do so. These signatures have the same effect as their paper-based counterparts. Verification is retained within our protected electronic records and audit trails."

- 1 -

Generated on IRBNet

Picture 4: IRB Approval Form

UNIFORMED SERVICES UNIVERSITY
OF THE HEALTH SCIENCES

INFORMED CONSENT FORM
RESEARCH STUDY

Eye Tracking Indicators of Neurocognitive Status after Traumatic Brain Injury – Phase 1a

INTRODUCTION

You are being asked to take part in a research study. Before you decide if you want to be in the study, you need to understand its risks and benefits so that you can make an informed decision. This is known as informed consent.

This consent form provides information about the research study which has been explained to you. Once you understand what it involves, you will be asked to tell the researcher if you want to take part in it. Your decision to take part in the study is entirely voluntary. This means that you are free to choose whether or not you want to be a research subject.

DESCRIPTION OF THE RESEARCH AND ITS PURPOSE

The purpose of this study is to develop and test an eye-tracking tool to accurately diagnose traumatic brain injury. This tool works by watching your eyes as you complete tasks on a computer.

In this phase of the study, you will assist with early development of the tool by testing newly-developed tasks while your eye movements are tracked.

This study is being conducted using funds from the Uniformed Services University of the Health Sciences (USUHS).

The principal investigator for this study is: Mark L. Ettenhofer, Ph.D.
Department of Medical and Clinical Psychology
Uniformed Services University of the Health Sciences
4301 Jones Bridge Road
Bethesda, MD 20814-4712
301-295-3279

Eligibility to Participate:

You are being asked to be in this study because you were previously determined to be eligible during the pre-screening procedure. During the pre-screening procedure, it was determined that you are over the age of 18, and you do not have a medical condition that would be expected to affect your eye or brain functioning or your use of your hands.

USUHS IRB APPROVED
14 Oct 2010
expires: 13 Oct 2011

Picture 5: Informed Consent Form, Pg. 1 of 5

If you are Active Duty Military or a civilian federal employee it is also required that you provide a signed Statement of Approval for Participation in Research. Active Duty Military personnel must have this approval signed by their supervisor and the Brigade Commander; Federal Civilians must have this signed by their Supervisor before any research participation.

STUDY PROCEDURE:

Your participation in this study will require 1 visit that will last about 45 minutes.

If you agree to participate, you will sign this consent form after it has been explained to you and before any study related procedures take place.

We will collect personal information about you (your name, address, phone number, and the name and phone number of two people you know). We will collect basic information about your age, education, military history, and medical history in an interview. You may refuse to answer any questions that make you feel uncomfortable.

Next, you will complete a series of computer tasks, about 30 minutes in duration, during which your eyes will be tracked by a camera. The computer will record your eye movements while you complete the tasks.

After completing the eye tracking tasks, you will give research staff feedback on your experience. For example, you will tell the research staff which parts of the task were easy or hard, and which parts were frustrating or confusing. Research staff will use this information to change or update the computer program.

POSSIBLE BENEFITS

You will not benefit from being in this study. However the information researchers get from this study may help others in the future.

COMPENSATION

You will not be compensated for participating in this study.

POSSIBLE RISKS

There are no known or expected risks for participating in this study, but you could have side effects that we do not expect or know to watch for now. Call the principal investigator if you have any symptoms or problems.

There is a risk that one or more of these questions or tasks might make you upset or uncomfortable. If this happens, remember that you will not need to respond to any questions or complete any tasks that make you feel upset or uncomfortable. You may also discontinue participation at any time without penalty.

Picture 5: Informed Consent Form, Pg. 2 of 5

Referrals

If we feel it is needed or you request it, we will provide you with referrals to a mental health care provider for evaluation or treatment at your option and your expense. These referrals may be provided up to one week from your visit if the principal investigator judges that you may benefit from these services based upon evidence of mental health difficulties. However, this study is not intended to diagnose or treat any conditions. Non-referral does not imply the absence of a mental health condition.

RIGHT TO WITHDRAW FROM THE STUDY

You may decide to stop taking part in this study at any time. This will not affect your relationship with USUHS in any way. You can agree to be in the study now and change your mind later. Your participation may also be discontinued by study personnel for reasons including, but not limited to, your potential difficulty following study procedures. If requested, we will also destroy any information we have collected about you.

PRIVACY AND CONFIDENTIALITY

All information you provide as part of this study will be confidential and will be protected to the fullest extent provided by law. Your records related to this study will be accessible to the sponsors of the study and those persons directly involved in conducting this study and members of the Uniformed Services University of the Health Sciences Institutional Review Board (IRB), which provides oversight for protection of human research volunteers. In addition, the Institutional Review Board at USUHS and other federal agencies who help protect people who are involved in research studies, may need to see the information you give us. Other than those groups, records from this study will be kept private to the fullest extent of the law. Scientific reports that come out of this study may use the information you have provided, but these reports will not use your name or identify you in any way.

Records of your participation in this study may only be disclosed in accordance with federal law, including the Federal Privacy Act, 5 U.S.C.552a, and its implementing regulations. Confidentiality of your records will be protected to the extent possible under existing regulations and laws but cannot be guaranteed. Complete confidentiality cannot be promised, particularly for military personnel, because information bearing on your health may be required to be reported to appropriate medical or command authorities.

Personal contact information may be retained for the purposes of completing this study and to notify you of future studies and assess your interest in participation. You will only be contacted regarding your current participation and future studies. Optionally, you may choose to not be contacted for future studies by notifying study personnel of your decision.

Picture 5: Informed Consent Form, Pg. 3 of 5

RECOURSE IN THE EVENT OF INJURY

This study should not entail any physical or mental risk beyond those described above. We do not expect complications to occur, but if, for any reason, you feel that continuing this study would constitute a hardship for you, we will end your participation in the study.

In the event of a medical emergency while participating in this study or medical treatment required as a result of your participation in this study, you may receive emergency treatment in the facility you are in or a nearby Department of Defense (military) medical facility (hospital or clinic). Treatment/care will be provided even if you are not eligible to receive such care. Care will be continued until the medical doctor treating you decides that you are out of immediate danger. If you are not entitled to care in a military facility, you may be transferred to a private civilian hospital. The attending doctor or member of the hospital staff will go over the transfer decision with you before it happens. The military will bill your health insurance for health care you receive which is not part of the study. You will not be personally billed and you WILL NOT be expected to pay for medical care at our hospitals. If you are required to pay a deductible you may make a claim for reimbursement through the Uniformed Services University Office of General Counsel. In case you need additional care following discharge from the military hospital or clinic, a military health care professional will decide whether your need for care is directly related to being in the study. If your need for care is related to the study, the military may offer you limited health care at its medical facilities. This additional care is not automatic.

If at any time you believe you have suffered an injury or illness as a result of participating in this research project, you should contact the Office of Research at the Uniformed Services University of the Health Sciences, Bethesda, Maryland 20814-4799 at (301) 295-3303. This office can review the matter with you, can provide information about your rights as a subject, and may be able to identify resources available to you. If you believe the government or one of the government's employees (such as a military doctor) has injured you, a claim for damages (money) against the federal government (including the military) may be filed under the Federal Torts Claims Act. Information about judicial avenues of compensation is available from the University's General Counsel at (301) 295-3028.

IF YOU HAVE QUESTIONS OR CONCERNS

If you have questions about this research, you should contact Dr. Mark Ettenhofer, the person in charge of the study. His phone number at USUHS is 301-295-3279. Even in the evening or on weekends, you can leave a message at that number. If you have questions about your rights as a research subject, you should call the Director, Human Research Protections Program at USUHS at (301) 295-9534. He is your representative and has no connection to the researcher conducting this study.

Picture 5: Informed Consent Form, Pg. 4 of 5

By signing this form you are agreeing that this study has been explained to you, that you understood that explanation, and that you want to take part in this research.

Subject — Date of signature

Witness — Date of signature

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

Investigator — Date of signature

Picture 5: Informed Consent Form, Pg. 5 of 5

LABORATORY FOR NEUROCOGNITIVE RESEARCH

UNIFORMED SERVICES UNIVERSITY OF THE HEALTH SCIENCES
4301 JONES BRIDGE ROAD, ROOM B1032
BETHESDA, MARYLAND 20814-4712
www.usuhs.mil
(301) 295-3279

Statement of Approval for Participation in Research

I would like to participate in the research study "**Eye Tracking Indicators of Neurocognitive Status after Traumatic Brain Injury: Phase 1a**" in the Laboratory for Neurocognitive Research at the Uniformed Services University of the Health Sciences. It is anticipated that this study will take **45 minutes** total. I understand that my organization may require additional information or completion of additional forms.

- I have read the informed consent form and do not believe that my participation will interfere with my normal duties.
- If scheduled visits are to be done during duty hours, my supervisor must approve my absence from my duty section.
- I understand that I need my supervisor's approval to be compensated for participation, and if compensated I must participate in a non-duty status (leave status, before/after duty hours, non-paid lunch period).
- Copies of this form will be placed in my study file.

Participant's Name: _____

Signature: _____ Date: _____

Supervisory Chain-of-Command

- I understand that participation in this study will require the service member's/federal civilian employee's time, and if compensated must be done in a non-duty status (leave status, before/after duty hours, non-paid lunch period).
- I approve the service member's/federal civilian employee's participation in the study.

Supervisor's Name: _____

Signature: _____ Date: _____

Brigade Commander (for military personnel)

Signature: _____ Date: _____

Picture 6: Military and Federal Employee Supervisor Approval Form

Healthy Volunteers Needed for
Eye Tracking Research Study

Healthy volunteers are needed to test a non-invasive, computerized eye tracking method for measuring brain functions.
Total participation time is about **45 minutes.**

Eligible volunteers will complete computer tasks while the eye tracker records their eye movements with a high-speed camera, and then provide feedback regarding its use. Future research will use the eye tracker to study traumatic brain injury.

This research is being conducted at the Uniformed Services University of the Health Sciences (USUHS), in Bethesda, MD.

You must be 18 years or older. No compensation will be provided for your participation. Active Duty Military and Federal employees must obtain permission from supervisor prior to participation.

USUHS IRB APPROVED
Expires: 13 Oct 2011

For more information please contact:
Mark Ettenhofer, Ph.D.
mark.ettenhofer@usuhs.mil 301-295-3279

Mark Ettenhofer
301-295-3279
mark.ettenhofer@usuhs.mil

Picture 7: Recruitment Advertisement

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