APPROVAL SHEET

Title of Dissertation: The Relation between Traumatic Brain Injury and

Neuropsychological Functioning: Sociodemographic Moderators and Biopsychosocial

and Behavioral Mediators

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Abstract

Traumatic brain injury (TBI) has been shown to have known acute cognitive effects, but less is known about more distal cognitive correlates and whether these vary as a function of sociodemographic factors. Additionally, even less is known about the potential biopsychosocial and behavioral mediators of these relations. Thus, the purpose of this study was, first, to examine whether sex and race moderate the relations between TBI history and cognition. We further evaluated clusters of biopsychosocial and behavioral variables as potential mediators of theses associations. Participants were 250 adults with a self-reported history of TBI (62% male, 57% White, 50% above the 125% poverty line, mean age = 47.6 years, mean education 12.2 years) and 500 age-matched adults without a history of TBI (61% male, 63% White, 36% above the 125% poverty line, mean age = 47.0 years, mean education 12.5 years) from the Healthy Aging in Neighborhoods of Diversity Across the Life Span (HANDLS) Study. TBI history and sociodemographic information (age, sex, race, poverty status, and education) were self-reported by participants. Cognitive function was measured across a variety of domains including verbal memory (California Verbal Learning Test Total Recall, Learning Curve, Short Delay Free Recall, and Long Delay Free Recall), visual memory (Benton Visual Retention Test), perceptuo-motor speed and manual dexterity (Trail Making Test, Part A), attention/working memory (Digit Span Forward and Backward), language/executive function (Category Fluency), and executive function (Trail Making Test, Part B). Biopsychosocial and behavioral clusters were identified using principal components analysis for the biological (systolic blood pressure, fasting glucose level, and body mass index), psychological (post-traumatic stress disorder symptomatology, depressive

symptomatology, and trait anger), social (emotional and instrumental support), and behavioral (alcohol status, smoking status, and a composite drug use variable) domains. Mixed-effect models were used to examine the interaction of sex and TBI history on a variety of neuropsychological measures covarying for education, poverty status, and race. These models were repeated for the interaction of race and TBI history, and a 3-way interaction of sex, race, and TBI history. For each significant interaction, the biopsychosocial and behavioral components were incrementally added to each model as potential explanatory factors. Results showed that African-Americans with a history of TBI performed significantly worse on CVLT total, a measure of verbal memory (F (1, 695) = 6.161, p = .013), than African-Americans without a TBI history, and that men with a TBI history performed significantly worse on Digits Forward and Backward, measures of attention (F (1, 480.902) = 4.045, p = .045) and working memory (F (1, 478.600) = 5.952, p = .014), respectively. The relation of race and TBI history to memory was partially mediated by the cluster of psychological variables, and the relation of sex and TBI history to attention was partially mediated by the biological cluster. The sex, TBI history, and working memory association was not significantly mediated by any cluster. Overall, these findings suggest that distal cognitive effects, particularly verbal memory and attention/working memory, from TBI may be most pronounced in African-Americans and men, and these relations may be mediated by psychological and biological factors respectively. However, further exploration is needed to clarify these relations. These biopsychosocial factors should be an important focus in clinical practice, particularly for African-Americans and men, to aid in the recovery of cognitive deficits.

The Relation between Traumatic Brain Injury and Neuropsychological Functioning:

Sociodemographic Moderators and Biopsychosocial and Behavioral Mediators

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Copyright Statement

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Table of Contents

List of Tables

List of Figures

Introduction

Known as one of the leading causes of death (Greve & Zink, 2009), traumatic brain injury (TBI) causes a wide variety of symptoms from headaches to coma (Ghajar, 2000). It is also well documented that TBI is associated with lower levels of cognitive performance even years after an individual sustained the injury (Benedictus, Spikman, & Van Der Naalt, 2010). Several domains of functioning such as memory, psychomotor abilities, executive functioning, and overall cognition are negatively impacted by moderate to severe TBI (Brenner, 2011), although the effects of mild TBI is still debated (Cullum & Thompson, 1997).

Select sociodemographic subgroups of individuals may be particularly vulnerable to risk for TBI and its various consequences. In that regard, older adults sustain more severe TBIs and undergo a longer recovery process (Katz & Alexander, 1994). In terms of sex, men are more likely to sustain an injury (Faul, Xu, Wald, & Coronado, 2010), but women typically have worse functional outcomes (Bazarian, Blyth, Mookerjee, He, & McDermott, 2010). With respect to race, African-Americans are more vulnerable to the ill effects of TBI (e.g., functional dependence and disability in home, work, school, and other environments) when compared to Whites (Arango-Lasprilla & Kreutzer, 2010; Kennepohl, Shore, Nabors, & Hanks, 2004). Both poverty status and education also negatively affect TBI sequelae such that more affluent and educated individuals have better cognitive outcomes (Dan Hoofien, Vakil, Gilboa, Donovick, & Barak, 2002; Kesler, Adams, Blasey, & Bigler, 2003). One the primary aims of the present investigation was to examine whether the relation of history of head injury to cognitive performance is moderated by sex and race, the most well-documented sociodemographic

moderator variables in the TBI literature, while controlling for age, poverty status, and education.

A second aim was to explore potential mediators of the relation of TBI to cognitive function. Multiple biopsychosocial and behavioral factors may, in part, mediate the relation between TBI and cognition. However, to my knowledge, no prior studies have examined such associations. In the biological realm, blood pressure, body mass index (BMI), and glucose levels are associated with TBI and can negatively affect patient outcomes; both high and low levels of all variables have been associated with higher rates of death in the acute post-injury phase (Baccouche, Arous, Sellami, & Elloumi, 2014; Griesdale, Tremblay, McEwen, & Chittock, 2009; Werner & Engelhard, 2007). Higher levels of these biological factors have also been associated with poorer long-term TBI outcomes (Griesdale et al., 2009; Tagliaferri, Compagnone, Yoganandan, & Gennarelli, 2009; Zafar et al., 2011), and lower levels of cognitive function in the general population (Gunstad et al., 2007; Sommerfield, Deary, & Frier, 2004; Waldstein, Giggey, Thayer, & Zonderman, 2005). Therefore, blood pressure, body mass index, and glucose levels were examined as partial mediators of the relation of TBI to neuropsychological outcomes in the present investigation.

Psychological variables are also associated with various outcomes among individuals who have sustained a TBI. Specifically, depression, post-traumatic stress disorder (PTSD), and anger have a higher prevalence in the TBI (than general) population, and higher levels of associated symptoms negatively affect individuals' functional status and cognitive outcomes (Carlson et al., 2011; Hoofien, Gilboa, Vakil, & Donovick, 2001; Kreutzer, Seel, & Gourley, 2001). Furthermore, each of these

psychological factors has been associated with neuropsychological test scores such that more symptoms are negatively associated with performance in the general population (Foster, Hillbrand, & Silverstein, 1993; Gordon, Fitzpatrick, & Hilsabeck, 2011; Horner & Hamner, 2002; Levin et al., 2001; Satz et al., 1998). Given the demonstrated prevalence and associations of symptoms of depression, PTSD, and anger in health-related TBI outcomes, and their known relations to cognitive function in the general population, they were explored as partial mediators of TBI-cognition associations in the present study.

Behavioral factors such as alcohol, nicotine, and illicit drug use are highly prevalent in the TBI population. These factors, even in small amounts, are extremely detrimental to individuals with TBI in terms of poorer post-injury neurological, behavioral, vocational, and life-satisfaction outcomes (Taylor, Kreutzer, Demm, & Meade, 2003). Alcohol, nicotine, and a variety of other substances have largely negative associations with cognitive functions in non-TBI samples (Durazzo et al., 2013; Kelly, Johnson, Knoller, Drubach, & Winslow, 1997; Richardson, Powell, & Curran, 2003). However, little is known about the relation of these behavioral factors to neuropsychological performance in TBI samples (Jong, Zafonte, Millis, & Yavuzer, 1999). Thus, they were explored as potential mediators of the relation of TBI to cognitive function in the present investigation.

Social support is another factor that is significantly effected in those with TBI, with post-TBI decrements in social support commonly reported (Rauch & Ferry, 2001). While lower levels of emotional support have been associated with a number of poorer functional outcomes in TBI such as rates of employment, physical functioning, social

functioning, and general health (MacMillan, Hart, Martelli, & Zasler, 2002; Tomberg, Toomela, Pulver, & Tikk, 2005), instrumental support has not been studied as thoroughly (Douglas & Spellacy, 2000). Higher levels of social support have generally been associated with better neuropsychological functioning in the general population (Seeman, Lusignolo, Albert, & Berkman, 2001). However, it is unknown whether social support affects neuropsychological performance within the TBI population. Social support was therefore examined as a potential mediator of TBI-cognition associations in the present investigation.

In sum, the proposed study used a case-control design to examine whether the cognitive function of those with TBI varies as a function of race and sex. Those with TBI and non-TBI adults were matched for age, and influences of poverty status and education were adjusted. The investigation examined whether multiple biopsychosocial and behavioral factors partially explain the relations of TBI to cognitive function. In this document, I first provide an overview of the literature pertaining to the various severities of TBI and neuropsychological outcomes. The overview is followed by a discussion of various sociodemographic variables and how they affect TBI outcomes. Then a discussion of potential biological, psychological, social, and behavioral mediators of the relation of TBI to cognitive function is provided. Next, the aims, hypotheses, methodology, and data analytic procedures for the current study are outlined. The results of the current study are then presented, followed by a discussion of the results as they relate to the current literature. Finally, strengths, limitations, and future directions for the current study and the field are discussed.

Literature Review

Traumatic Brain Injury

TBI is one of the leading causes of death and disability in the world, especially among the young (Greve & Zink, 2009). According to the Centers for Disease Control, each year 52,000 people in the US die from a head injury, 275,000 are hospitalized, and about 1.4 million are treated and released from an emergency department (Faul, Xu, Wald, & Coronado, 2010). These numbers have steadily increased over time, even in a four-year period (Faul, Xu, Wald, & Coronado, 2010). The causes of TBIs vary greatly, including but not limited to vehicular accidents, violent crimes, combat, and sports injuries (Faul, Xu, Wald, & Coronado, 2010). From the expansive epidemiology of TBIs and the continuing growth of these incidences, head injury research has been receiving increased attention as a major public health concern.

The consequences of a TBI can vary greatly as a function of several factors. Depending on the severity of the injury, most commonly measured by the Glasgow Coma Scale (Teasdale & Jennett, 1974), patients' symptoms may range from absent to death. Severity of TBIs are judged predominantly by loss of consciousness, with mild TBIs causing a loss of consciousness less than 30 minutes, moderate TBIs causing a loss of consciousness 30 minutes to 24 hours, and severe TBIs causing a loss of consciousness greater than 24 hours (Department of Defense, 2010). Mild TBIs may cause short-term memory loss or concentration difficulties, moderate injuries may result in lethargy or stupor, and severe TBIs typically result in a coma for varying amounts of time post-injury (Ghajar, 2000). Most clinical correlates of mild TBI are seen as temporary, and many

patients make a full recovery from the injury, whereas moderate-severe injuries have more lasting effects that require rehabilitation.

Measuring TBI, though, has been difficult, and there is no gold standard for measurement. While many hospital-based studies can use the Glasgow Coma Scale (Brooks, Fos, Greve, & Hammond, 1999; Draper & Ponsford, 2008), studies using the general population have used various interview questions (Benedictus et al., 2010; Brenner et al., 2010) and others have used structured questionnaires such as the Brain HELPS (Picard, Scarisbrick, & Paluck, 1991), the Brief Traumatic Brain Injury Screen (Schwab et al., 2006), and the Veteran Traumatic Brain Injury Screen Tool (Donnelly et al., 2011).

TBI and Neuropsychology

Neuropsychological tests are commonly used among those with TBI to assess the degree of impairment and functionality of the individual. These tests typically span multiple domains of cognitive function and are used to further understanding of the exact nature of the injury, including speculation on which brain and cognitive domains may be most affected, and how to best proceed with treatment and rehabilitation. There are numerous studies that have examined different types of head injuries and neuropsychological outcomes, all of which have varying results which are described below.

Moderate-Severe TBI

The majority of research on TBI and cognitive outcomes has been conducted in samples with moderate-severe TBI. This body of literature, while heterogeneous, generally illustrates that a moderate-severe injury negatively impacts several cognitive

domains (Brenner, 2011). In aggregate, the literature shows the domains of attention, processing speed, visual and verbal memory, executive functions, and working memory can all be significantly impaired, but none of these domains was consistently impaired across all studies. This is to be expected as TBI is a heterogeneous condition affected by length of loss of consciousness, area of injury, and a variety of other factors. Other studies have shown more specific deficits in several types of attention including attention span, focused/selective attention, sustained attention, and supervisory attentional control (Mathias & Wheaton, 2007), and verbal memory (Vanderploeg, Crowell, & Curtiss, 2001).

Several studies have examined the self-report of "global cognition" and persisting functional and cognitive problems in individuals that have sustained a moderate to severe head injury. In a group of participants with varying degrees of head injury severity ($n = 343$, mean age = 34.8 years, 72% men) it was found that despite a favorable outcome for functional abilities, individuals with a TBI still experienced persisting cognitive problems (Benedictus et al., 2010). After a one-year follow-up, up to 50% of those individuals studied in an inpatient level one trauma center still had some persisting cognitive difficulties.

Multiple TBIs

Other research has investigated the associations of multiple head injuries on cognitive performance. Although all found a negative association with neuropsychological test performance, some research found the relations of each injury to be cumulative (Maroon et al., 2000), whereas others noted that specific domains were affected, such as working memory (Erlanger, Kutner, Barth, & Barnes, 1999), executive

functioning (Brenner, 2011), visuospatial abilities (Belanger, Spiegel, & Vanderploeg, 2009), and motor function (Belanger, Spiegel, & Vanderploeg, 2010). While there is importance in investigating how multiple TBIs affect cognition, the current study does not have sufficient statistical power (or range in number of injuries) to address this issue.

In summary, moderate to severe head injuries and multiple head injuries have been studied thoroughly and both show lasting associations on several domains of cognitive and other types of functioning (e.g., physical, social). There have been mixed results about which domains of cognitive function are most affected and the severity of the effects, which is expected with the heterogeneity of TBI. But, in general, all studies found significant negative associations of moderate to severe TBI, and/or multiple head injuries on at least a single domain of function.

Mild TBI

While multiple head injuries of any magnitude have shown lasting effects on cognitive function, singular mild head injuries are often seen as inducing temporary deficits, with effects lasting up to only a few months after the injury, but this is debated in the literature (Cullum & Thompson, 1997). This generalization has some backing in the neuropsychological literature. According to one recent review, small, immediate difficulties were found in the domains of processing speed, working memory, attention, short-term memory, and executive functioning in patients with mild TBI, but these effects did not last upon follow-up, approximately 42 weeks post-injury (Brenner, 2011). Another study corroborated these results, finding no differences between controls and mild TBI patients across several neuropsychological domains, on average 10 months after injury (Brenner et al., 2010; Maroon et al., 2000). A review of the literature regarding

mild head injury and the recovery process suggested that after only one to three months following the injury, all cognitive functioning was comparable to controls, unlike the lasting effects found in moderate to severe injuries (Schretlen & Shapiro, 2003).

In contrast, other studies have found that there are some lingering cognitive effects from mild TBI. A meta-analysis on mild TBI by Binder, Rohling, and Larrabee (1997) revealed that while memory acquisition, delayed recall, manual dexterity, performance skills, cognitive flexibility, and verbal skills did not differ significantly from controls, attention was worse in those with mild TBI at least 3 months post-injury. Draper and Ponsford (2008) examined hospital head injury databases ($n = 103$, mean age = 42 years old, 55% men) and found that processing speed, memory, and executive functioning were negatively associated with any degree of TBI; they also noted that the more severe the TBI, the worse the outcome. Similarly, in a review of the literature on children, Ewings-Cobbs and Barnes (2002) examined the impact of TBI on expressive language, finding that while those with a moderate-severe TBI displayed worse expressive language than children with mild TBI. However, both sets of patients still had negative associations with their injury.

Throughout the adult and child TBI literature, studies have shown that various cognitive domains can indeed be impacted by mild TBI beyond three months post-injury and up to two years. There has been evidence to suggest that the domains of visual memory (Moore, Ashman, Cantor, Krinick, & Spielman, 2010), verbal memory (Babikian et al., 2011), psychomotor abilities (Babikian et al., 2011; Frencham, Fox, & Maybery, 2005), language (Babikian et al., 2011; Raskin, Mateer, & Tweeten, 1998), divided attention (Frencham et al., 2005), complex attention (Raskin et al., 1998),

working memory (Frencham et al., 2005; Raskin et al., 1998), concentration (Frencham

et al., 2005), cognitive vigilance (Frencham et al., 2005), and response inhibition

(Frencham et al., 2005) may show significant changes from premorbid abilities following

mild head injury. Even in persons with very mild TBI, significant neuropsychological

outcomes have been found, wherein verbal memory, reaction time, and arithmetic

abilities were hindered compared to controls ($n = 26$, mean age = 25 years old, 57.7%

men; Voller et al., 1999). It is therefore possible that individual outcomes are

heterogeneous, and select persons may be vulnerable to poor outcomes.

Executive Functioning

A further subsection of the neuropsychological literature has focused explicitly on

executive functioning after mild head injuries in both children and adults. When

examining children immediately after sustaining a mild TBI ($n = 30$, mean age = 8.3

years, 33% men), a recent study showed that, compared to controls, children with a head

injury performed less accurately on selective attention and updating tasks than those

without (Catale, Marique, Closset, & Meulemans, 2009). Others have examined children

in inpatient hospitals longitudinally after a head injury ($n = 285$, mean age = 11.9 years,

68.8% men), and found that there were no behavioral or cognitive deficits related to

executive function after a 12-month follow up (Maillard-Wermelinger et al., 2009). These

studies in children corroborate the postulation that mild TBIs, while causing acute

cognitive dysfunction, do not leave lasting effects beyond the first few months of

recovery.

Similar studies were also conducted in adult samples immediately after they had

sustained a head injury. The prevalence of executive dysfunction measured by the

Wisconsin Card Sorting Test was 21.7%, which was noted by the researchers to be a high

rate for a mild TBI ($n = 60$, mean age = 29.5 years old, 80% men; Tunvirachaisakul,

Thavichachart, & Worakul, 2011). When testing a larger range of executive functions,

Brooks and colleagues found that performance on multiple tests including Trails A and B,

Controlled Oral Word Association Test, and subtests two-four of the Paced Auditory

Serial Addition Task, discriminated between controls and those with a mild TBI in an

inpatient level one trauma center ($n = 24$, mean age = 32 years old, 62.5% men; Brooks,

Fos, Greve, & Hammond, 1999).

While much of the literature on executive function has shown immediate deficits

and no prolonged dysfunction, the literature is not consistent. Another study examined 52

mild, closed head injury patients (mean age = 35.2 years old, 92.3% men) and found that

executive functioning was significantly lower in adults but not in children (Stablum,

Mogentale, & Umilta, 1996). Deficits were still noted two years after the injury, thus

indicating that the injury had a sustained relation with executive functioning.

In summary, the body of literature on mild traumatic brain injuries shows not only

the heterogeneity of traumatic brain injury itself, but also the varying degrees of

association that such injuries may have with neuropsychological performance. The exact

nature of this impact is extremely diverse, ranging from negative effects on memory,

attention, and executive functioning to no impairments at all. Consistency in the literature

is lacking, possibly from studying head injuries involving different areas of the brain, or

possibly from confounding or moderating variables that influence the injury and recovery

process. Furthermore, potential vulnerability and resilience factors have not been

examined. Other issues of concern include practice effects with repeated testing and lack

of consideration of subgroups that may show trajectories of improvement, versus no change, versus further decrement.

TBI and Sociodemographics

TBIs occur at different rates among various sociodemographic groups, with known yearly incidence rates varying by age, sex, and race (Faul, Xu, Wald, & Coronado, 2010). However, little research has examined the lifetime prevalence rates of TBI by various sociodemographic groups or the associations of brain injury on cognitive (or other types of) function across these groups. Specifically, no known research has investigated the relation of TBI to neuropsychological function among various sociodemographic groups despite known differences in yearly TBI incidence rates and neuropsychological outcomes in the general population. The vast majority of studies in the TBI neuropsychological literature have examined white affluent men in select age ranges (most typically young or old). Below is the literature examining known differential effects of TBI across age, sex, race, poverty status, and education.

Age

TBI disproportionately affects individuals across the lifespan, with the most at-risk groups being the young and the old (Faul, Xu, Wald, & Coronado, 2010). It is postulated that the reasons for these differences may depend on the reckless behaviors of the youth and the risk of falls in the elderly. Not only are the proportions of head injury different across these groups, but also the recovery process following a TBI varies across the lifespan.

One study examining younger and elderly TBI patients ($n = 235$, 19% older than 65, 49% White, 18% African-American, 76% male) found that upon admittance to the hospital, the Glasgow Coma Scale for older patients (M = 14.1) was significantly higher than that of their younger counterparts (M = 12.5), indicating that younger individuals on average had more severe head injuries (Mosenthal et al., 2004). Despite lesser severity in elderly patients, their mean score on the Functional Independence Measure (FIM) at discharge was significantly lower (M = 10.4) when compared to the young (M = 11.4; Mosenthal et al., 2004). A follow-up completed six-months after discharge showed that the differences in the FIM remained, with a mean score of 11.0 in the elderly and 11.7 in the young (Mosenthal et al., 2004). This study illustrates that while younger individuals have worse injuries, their elderly counterparts tend to take longer to recover from their TBI.

Similarly, another study was conducted examining individuals with varying degrees of head injury upon hospital admission and one year post-injury ($n = 411$, age range: 18-89 years, 73% male; Rothweiler, Temkin, & Dikmen, 1998). Older individuals sustained more severe injuries as reflected by a longer period of time in a coma and a greater number of complications and surgeries (Rothweiler et al., 1998). This study also found that with increasing age, there were greater levels of psychosocial limitations, as indicated by a more dependent living situation (e.g., assisted living) and a pending employment status (Rothweiler et al., 1998). As in the previous study, the elderly generally had more severe and complicated TBI and worse outcome measures even after a full year of recovery.

A third study followed TBI patients ($n = 243$, age range: 8-89 years, 71% below 40 years of age, 77% male) that were admitted to a rehabilitation unit and were followed at six and 12 months to examine their Glasgow Outcome Scale (GOS; Katz & Alexander, 1994). While the study's main outcome examined posttraumatic amnesia, a secondary analysis examined age and the recovery process (Katz & Alexander, 1994). Despite the severity of the injury, older individuals (those above the age of 40 years) had significantly longer posttraumatic amnesia while in the hospital and had worse GOS scores (Katz & Alexander, 1994). The results from all of these articles illustrate longer and less efficient recovery processes in older individuals that have sustained a TBI. To my knowledge, though, neuropsychological outcomes have not been examined specifically in the TBI population across various age groups.

In summary, age differences have been shown in the TBI population on various outcomes, including severity of injury, time to recovery, functional independence and overall functional outcome. All associations revealed that older adults were at a greater disadvantage, especially if over 60 years of age. Because of these known age differences in the TBI and neuropsychological literature, and the multitude of outcome differences across the lifespan favoring different age groups, the present investigation matched head injury cases and controls with respect to age. However, age was not examined as a moderator variable because the current sample does not include youth or elderly individuals, the most vulnerable populations.

<u>Sex</u>

Sex differences in TBI have been well-documented, with yearly incidence rates for men being more than double that of women (Faul, Xu, Wald, & Coronado, 2010). Similarly, lifetime prevalence rates are twice as high in men (16.68%) than in women (8.55%; Frost, Farrer, Primosch, & Hedges, 2013). Despite higher rates in men, however, several studies have shown worse outcomes in their female counterparts who have sustained a TBI. These outcomes range from physical symptomatology (e.g., headaches, photosensitivity), recovery length, and select motor and cognitive processes.

A meta-analysis of eight studies of TBI patients examined men and women separately to investigate potential sex differences in outcomes (Farace & Alves, 2000). Of the 20 outcome measures (e.g., severity of injury, return to work, psychiatric symptoms), women fared worse in 17 outcomes with the average effect size being $r = -0.15$ (Farace & Alves, 2000). The authors noted that these findings are contradictory to popular clinical opinion, and also emphasized that there are only a small number of articles that actually analyze outcomes from TBI in men and women separately (Farace & Alves, 2000).

Despite the limitations of the meta-analysis, other researchers have continued to see worse outcomes in women following a TBI. One study examined outcomes from a large sample of individuals who had been admitted to the emergency department after a mild TBI ($n = 1425$, 54.9% male, mean age = 30.1 years, 69.3% white; Bazarian, Blyth, Mookerjee, He, & McDermott, 2010). Logistic regression analyses examined sex differences in the odds of having a higher post-concussive symptom score, number of

days to return to normal activities, and number of days missed of work (Bazarian et al., 2010). The researchers found that men had lower odds of being in a higher post-concussive symptom score category than women ($OR = 0.62$), which appeared to be more prominent during child-bearing years for women (Bazarian et al., 2010). The researchers postulated that the hormone fluctuations present in women during child-bearing years may significantly impact symptomatology and recovery from mild TBI (Bazarian et al., 2010).

Another study examined a sample of male and female high school and collegiate athletes who later went on to develop a sports-related concussion ($n = 155$, 76% men; Broshek et al., 2005). When examining neurocognitive computerized testing results from baseline to post-concussive status, women were 1.7 times more likely to be classified as cognitively impaired than men following concussion, with the most notable difference found for simple and complex reaction times (Broshek et al., 2005). Women also reported significantly more objective and subjective adverse effects from the concussion when compared to men (Broshek et al., 2005). Despite the rudimentary nature of the neurocognitive computerized testing, these findings corroborate the meta-analytic findings, illustrating that women experience worse outcomes following TBI.

Similarly in the realm of cognitive performance in athletes, another study examined baseline and post-concussion computerized neuropsychological test scores in men and women ($n = 79$, 51.9% male; Covassin, Schatz, & Swanik, 2007). When analyzing specific cognitive domains, the researchers found that concussed women performed slightly worse than men on visual memory tasks (Covassin et al., 2007). Conversely though, men reported more post-concussive symptoms than women,

including vomiting and sadness (Covassin et al., 2007). Overall then, women tended to perform worse on objective measures of visual memory, while men reported more subjective post-concussive symptomatology.

While the majority of the literature demonstrates that women have worse symptoms, functional outcomes, and neuropsychological performance than their male counterparts following a TBI, there is some literature that shows contradictory findings. A study examining both young boys and girls ($n = 60$, mean age = 13.5 years, 50% male, 80% white) one-year following a TBI found that boys performed significantly worse on the California Verbal Learning Test- Children's Version than girls ($\eta^2 = .09$; Donders & Hoffman, 2002). Although this was a relatively small effect, it may still represent a notable difference in the performance of young men on verbal memory following a TBI.

In summary, while the preponderance of literature shows significant sex differences in recovery from TBI such that women are more vulnerable than men to post-concussive symptomatology, recovery, and cognitive outcomes, the findings are mixed. Additionally, many of the studies did not include controls without TBI to examine if the sex differences are unique to TBI or artifacts of known sex differences in cognitive function in the general population. There are also very few studies that look at both men and women independently as they recover from a TBI, so additional research is needed. Given that the majority of the literature suggests sex differences in head injury and its sequelae including cognitive function (Moore et al., 2010; Strauss, Sherman, & Spreen, 2004), and the unknown *interaction* of sex and head injury on neuropsychological outcomes, sex was included as a moderator in my data analyses.

Race

Another sociodemographic variable that has significant implications on TBI outcomes is race. While yearly incidence rates are similar among Whites and African-Americans, African-Americans are more likely to die as a consequence of their TBI (Centers for Disease Control and Prevention, 2013). Among children who reported to an Emergency Department in the United States with a TBI ($n = 475,000$, age range 0-14 years), African-American children were more likely to be hospitalized and were also more likely to die as a result of their injury (Langlois, Rutland-Brown, & Thomas, 2005). To my knowledge, though, no studies have examined lifetime prevalence rates in different racial groups. For those who survive TBI, there are additional race differences documented in the literature.

Within the TBI literature, one review examined psychosocial outcomes in African-Americans and Whites (Arango-Lasprilla & Kreutzer, 2010). Although head injury significantly predicted worse psychosocial outcomes (e.g., marital status, life satisfaction, emotional symptoms) and fewer social connections in both African-Americans and Whites, African-Americans had significantly worse outcomes than their White counterparts (Arango-Lasprilla & Kreutzer, 2010). The authors of this review concluded that there may also be racial differences in functional outcomes following head injury, such as functional dependence and disability in home, work, school, and other environments (Arango-Lasprilla & Kreutzer, 2010).

Another study investigated various community outcomes one-year after a moderate or severe TBI in African-Americans and Whites ($n = 94$, mean age = 39.4

years, 82% male, 59% White, mean education = 12.2 years; Hart, Whyte, Polansky,

Kersey-Matusiak, & Fidler-Sheppard, 2005). Despite being relatively equal on measures

of community integration, life satisfaction, neurobehavioral functioning, and employment

prior to their injury, African-Americans reported significantly lower social integration

than Whites one-year post-injury (Hart et al., 2005). Additionally, the researchers found

that African-Americans may have lost more income than Whites due to their TBI (Hart et

al., 2005). Overall, the researchers concluded that the longstanding effects of TBI vary

based on race across different social and functional variables (Arango-Lasprilla &

Kreutzer, 2010).

Other studies have specifically examined post-TBI productivity (defined as being

employed or in school at least part-time) among African-Americans, Whites, and other

racial minorities (n = 1083, 77% male, 58% White, 32% African-American, 58% had 12

or more years of education, median age = 34 years; Sherer, Nick, Sander, Hart, Tessa,

Robin, Rosenthal, High, & Yablon, 2003). The researchers found that African-Americans

were 2.76 times more likely to be nonproductive than Whites (Sherer, et al., 2003).

Additionally, after adjusting for pre-injury productivity, education level, and cause of the

injury, African-Americans remained twice as likely to be nonproductive than Whites (R^2-

Nagelkerke = .02; Sherer, et al., 2003). This research demonstrates that African-

Americans are more likely to be negatively impacted in their post-TBI productivity than

Whites.

Few studies have examined the relation of TBI to neuropsychological outcomes in

African-Americans, and even fewer studies have compared African-Americans to

Whites. One study investigated the association of acculturation of African-Americans and

Whites with neuropsychological performance following a TBI. In a sample of African-Americans and Whites (n = 71, mean age = 42.2 years, 82% male, mean education = 11.8 years, 44% in the lowest SES bracket), lower levels of acculturation were associated with poorer performance on the Galveston Orientation & Amnesia Test, Multiaphasic Examination: Token Test, Wechsler Adult Intelligence Scale- Revised (WAIS-R) Block Design, Rey Auditory Verbal Learning Test, Symbol Digit Modalities Test, and a composite indicator of overall neuropsychological test performance (Kennepohl, Shore, Nabors, & Hanks, 2004). Furthermore, irrespective of acculturation, African-Americans performed worse on Block Design and Trail Making Test (Kennepohl, Shore, Nabors, & Hanks, 2004). This study demonstrates an association of both race and level of acculturation with neuropsychological performance and cognitive recovery following a TBI.

In summary, race differences are prevalent in the TBI literature, illustrating more disadvantages for African-Americans than Whites. Outcomes span functional indices, social integration, productivity, and a number of neuropsychological tests. However, few studies have compared African-Americans and Whites with and without a TBI, so limited conclusions can be drawn from these finding. Because of the well-documented differences in TBI outcomes and neuropsychological performance by race (Heaton, Miller, Taylor, & Grant, 2004), and the preponderance of associations noted in the prior literature, I included race as an additional moderator variable in the present investigation.

Poverty Status

Socioeconomic status (SES), commonly measured by income, is another sociodemographic variable that has a significant associations with various outcomes in the TBI literature. Individuals having a lower SES have an elevated risk of sustaining a TBI (Kraus & McArthur, 2006). This association holds true even while accounting for racial differences, indicating that SES independently increases the risk for TBI (Kraus & McArthur, 2006).

SES further influences return to work post-TBI. One review found that after three months following a mild TBI, SES was a significant predictor of return to work (Evans, 2006). When separated by type of work,100% of executives and business managers had returned to work while only 68% of skilled laborers and 57% of unskilled laborers had successfully returned to work (Evans, 2006). While this may represent an artifact of premorbid functioning or the type of employment demands of the position, these results may also represent a delayed recovery among those with a lower SES.

Other studies have investigated children from various SES backgrounds to understand behavior and achievement outcomes following TBI (Taylor et al., 2002). A sample of 109 children with a TBI and 80 children with orthopedic injuries (43% male, 43% White, mean age = 9.5 years) were assessed shortly after their injury and three additional times across a four year span with the Child Behavior Checklist, Vineland Adaptive Behavior Scales, and subscales of the Woodcock-Johnson Tests of Achievement-Revised (Taylor et al., 2002). Using the Socioeconomic Composite Index (SCI) for SES, the researchers found that low SCI predicted worse scores on the Child

Behavior Checklist Behavior Problem scale in the TBI children only (Taylor et al., 2002).

The researchers also found significant interactions between TBI group status and SCI

such that lower SCI predicted lower scores on the Vineland Socialization, Academic

Performance, and Woodcock-Johnson Calculations among those with TBI (Taylor et al.,

2002). These trends also held true across the four year span with the exception of the

Woodcock-Johnson Calculations (Taylor et al., 2002), illustrating that socialization and

select aspects of cognition are differentially related to SES among children with TBI .

A second study by the same group looked more in-depth into the cognitive

differences between children who had sustained a TBI based on their SES. The same

sample of children (43% male, 43% White, mean age = 9.5 years) also completed

neuropsychological testing at baseline, six-months, and 12-months post injury (Yeates et

al., 2002). The researchers found that, among those children who had sustained a TBI,

lower SCI score predicted worse performance on CVLT-C Total Recall (Yeates et al.,

2002). Therefore, not only is general academic achievement negatively associated with

TBI in lower SES children, but their verbal memory performance is also significantly

lower than higher SES children with TBI.

When turning to the adult TBI literature, there have been mixed findings with

respect to the relation of SES to neuropsychological test performance. In one study

examining the long-term effects of TBI based on pre-injury SES, a sample of individuals

($n = 76$, mean age = 38.6 years) was measured on cognitive, psychiatric, vocational, and

activities of daily living (Hoofien et al., 2002). The researchers found that even after 14

years, SES significantly predicted worse performance on the WAIS-R (Full scale, Verbal,

and Performance Intelligence Quotients) as well as the Global Severity Index of the

Psychiatric Symptoms Checklist-90, employment level, and stability of work among those with TBI (Hoofien et al., 2002).

While these neuropsychological and neuropsychiatric results are compelling, other researchers have found no relation between SES and post-TBI cognitive recovery. A study examining narratives of 55 closed head injury patients and 47 non-brain-injured patients (mean age = 30.3 years, 70% male, mean months since TBI = 10.5) split evenly as professional, skilled worker, or unskilled worker (a proxy for SES) were tested on the Wisconsin Card Sorting Test, a test of executive function (Coelho, 2002). When examining the TBI group based on SES, there were no significant differences in performance on the Wisconsin Card Sorting Test (Coelho, 2002). These results suggest that SES may not significantly impact more complex executive functioning following a TBI.

In summation, SES significantly affects numerous outcomes as an individual recovers from a TBI. Those who are from a higher SES typically recover more quickly, are more likely to be employed and return to work, and have higher IQs after the TBI when compared to those in lower SES. Although some studies did not find SES differences in post-TBI neuropsychological performance, these studies serve as a minority in the field. Because SES has not received as much attention as other sociodemographic variables (i.e. sex and race), but literature tends to suggest effects on head injury outcomes and cognition, SES was included as a covariate in my analyses.

Education

Although education has been shown to be a significant predictor of general neuropsychological performance (Lezak, Howieson, Loring, Hannay, & Fischer, 2004), few studies have investigated the relation of education to TBI outcomes, with even fewer specifically looking at neuropsychological outcomes. One review of the literature found that pre-injury educational level significantly predicted return to work three-months following the injury, such that those with less education were more likely to still be out of work (Evans, 2006).

Another study corroborated that more highly educated individuals were more likely to have returned to work one to three years following their TBI (Gollaher et al., 1998). This study sampled individuals that had sustained a TBI (69% male, mean age = 29.4 years, mean education = 12.4 years) and measured their disability rating, overall outcome, as well as their employment and productivity one and three years following their TBI (Gollaher et al., 1998). While those with higher levels of education were more likely to return to work, these individuals also reported not working "at full capacity" or that "colleagues were covering up" their mistakes due to incapacity, indicating that there were still some residual effects from the TBI that significantly affected their job performance (Gollaher et al., 1998).

Studies have also examined the association between education and long-term functioning in multiple aspects of persons' lives following a TBI. One study investigated the need for physical, cognitive, and behavioral supervision in a sample of TBI patients (n = 76, mean age = 32 years, mean education level = 13 years) approximately nine

months post-injury (Sherer, Bergloff, High, & Nick, 1999). Results indicated that premorbid educational level was correlated with productivity as well as cognitive and behavioral supervision such that those with higher education were more productive and needed less supervision (Sherer et al., 1999). These results support the idea that educational level may benefit TBI patients in their return to pre-morbid function and independence, or may be protective against some of the detrimental effects of the injury.

One study investigated whether the Cognitive Reserve Hypothesis (Katzman et al., 1988) held true in a TBI sample. The Cognitive Reserve Hypothesis proposes that the detrimental effects of acquired brain injury, such as dementia, may have fewer ill effects in individuals with greater pre-morbid abilities because they may have more "reserve" to lose before functioning is impacted (Katzman et al., 1988) The study investigated a small group of TBI patients (n = 25, mean age = 25.8 years, mean education = 13.1 years, 52% male) who underwent brain magnetic resonance imaging and completed the WAIS-R as an estimate of premorbid intellectual functioning (Kesler et al., 2003). The sample was divided based on estimated premorbid intelligence quotient (IQ; above or equal to 90 and below 90). Results indicated that those with a higher premorbid IQ and greater level of education demonstrated higher post-injury IQ scores as compared to their premorbid IQ (perhaps suggesting benefit from practice effects), while those with lower premorbid IQ and lower level of education had lower IQ than their premorbid standardized test (Kesler et al., 2003). Consistent with the cognitive reserve hypothesis, these findings suggest that higher levels of education and IQ are protective against the negative effects of a TBI.

Overall, the literature suggests that education serves as a protective factor for individuals who sustain a TBI. Those having more education tend to have an increased

likelihood of returning to work, are more productive, need less supervision, and have lesser decrements in IQ as a result of the TBI. Yet, some researchers have found that despite returning to work more quickly, highly educated individuals may still experience symptoms that negatively affect their work. Overall, since education has not received as much attention as other sociodemographic variables (i.e. sex and race), but literature tends to suggest significant effects on head injury outcomes and cognition, education was also included as a covariate in my analyses.

<u>Summary</u>

Within the TBI literature as a whole, an abundance of evidence suggests that sociodemographic factors impact TBI recovery. However few studies have specifically investigated neuropsychological outcomes. Even fewer studies have included non-TBI control participants who varied as a function of the same sociodemographic variables. The present study therefore makes a novel contribution to the literature by examining those with a history of TBI to those without across a spectrum of neuropsychological outcomes as a function of sex and race (while matching for age and adjusting for poverty status and education). While there would be utility to examine all of these sociodemographic variables as potential moderator variables, the present study did not have sufficient power to do so. To my knowledge, the study is also the first to evaluate potential biopsychosocial mediators of the relation of TBI to neuropsychological outcomes. This latter body of literature is described below.

Potential Mediating Factors of TBI-Cognition Associations

Throughout the TBI literature, there are multiple biological, psychological, social, and behavioral factors that have been examined as post-TBI outcomes per se or as predictors of additional favorable/unfavorable outcomes. Each of these factors has been linked to neuropsychological outcomes in the general population. However, to my knowledge, no one has examined whether these factors partially explain the relation of TBI to neuropsychological performance. The available literature for each relevant factor is discussed below.

Biological Factors

Blood Pressure

Blood pressure has received a large amount of attention as it relates to brain health outcomes. Hypertension has been linked to stroke (Sacco, et al. 1997), dementia (Oveisgharan & Hachinski, 2010), and lower levels of cognitive function (Waldstein, Manuck, Ryan, & Muldoon, 1991). However, the importance of cardiovascular health in TBI outcomes has received minimal attention. Both high and low post-TBI blood pressure have been linked to poorer outcomes (e.g., length of recovery, rate of death) and prognoses in a group of individuals with varying degrees of TBI severity ($n = 1,613$; Butcher, et al., 2007). For example, in a large study examining TBI patients' in-hospital blood pressure, moderate to severe TBI patients ($n = 7,238$, 64% male, 68% White, 7% African-American) were found to have the highest mortality rate when their Emergency Department systolic blood pressure was below 120 mmHg (2.6 times) or above 140

mmHg (1.6 times) as compared to those who presented with blood pressures between 120 and 140 mmHg (Zafar et al., 2011).

Additional outcomes have been studied as they relate to blood pressure and TBI. In a sample of children who had sustained a severe TBI ($n = 172$, mean age = 7.0 years), low blood pressure [age-appropriate systolic blood pressure (SBP) < 75th percentile and SBP < 90 mmHg] predicted greater odds of having a Glasgow Outcome Scale < 4 (*OR* = 3.5; Vavilala et al., 2003). This study demonstrated that low SBP in TBI patients can significantly affect functional status and outcomes beyond survival.

To my knowledge, my master's thesis research is the only study to investigate the association of blood pressure to cognitive function in a select (predominantly male and white) sample of older adults with history of TBI (Kisser, 2014). Results of this study found no significant interactions between SBP and mild TBI history with a variety of neuropsychological outcomes. However, a preponderance of research in the general population has shown that hypertension is negatively associated with cognitive function across multiple major domains of function (Lezak et al., 2004). One early review of the literature revealed that tests of memory (*d* ranging from 0.08 to 1.13), abstract reasoning (0.33 to 1.41), and attention (0.17 to 0.93) were most frequently and significantly negatively associated with hypertension, followed by tests of perception (0.47 to 1.97), constructional skills (0.02 to 1.13), mental flexibility (0.12 to 0.62), and psychomotor speed (0.10 to 1.50), but the findings (and effect sizes) were mixed (Waldstein, Manuck, Ryan, & Muldoon, 1991). However, low blood pressure has also been associated with poorer cognitive performance (Maule et al., 2008). Other research has examined both

high and low blood pressure, finding that blood pressure at both extremes is associated with lower levels of cognitive function (Waldstein et al., 2005).

Overall, low and high blood pressure have been shown to be significantly associated with outcomes in TBI populations and cognitive function in the general population. However, the majority of studies to date have only examined blood pressure assessed while in the hospital and have not looked at long-term outcomes such as cognition. Given the strong relation between hypertension and cognition in the general population, it remains plausible that blood pressure levels in those with TBI could negatively impact cognition. Because SBP (rather than diastolic blood pressure) is more consistently associated with outcomes in the TBI literature, the present investigation examined SBP as a potential mediator of the relation of TBI to cognitive function

Body Mass Index

Another possible mediator of the relation between TBI and neuropsychological outcomes is body mass index (BMI). With a growing obesity epidemic in the United States and the world, concerns over the long-term implications of higher BMI have become increasingly important. BMI has been linked to severe neurological conditions such as stroke (Jood, Jern, Wilhelmsen, & Rosengren, 2004) and vascular dementia (Kivipelto et al., 2005), in addition to lower levels of cognitive function (McDonald, Flashman, & Saykin, 2002).

Several studies have begun to connect BMI with TBI outcomes. In a sample of individuals involved in motor vehicle accidents (n = 5,918, mean age = 37 years, 61% men), obese individuals were more likely to sustain the maximum head injury severity

when compared to those who were not obese (Tagliaferri, Compagnone, Yoganandan, & Gennarelli, 2009). Additionally, one study found that 42% of post-TBI patients (75.7% male, mean age = 36 years, mean BMI = 23.3 kg/m^2) reported weight gain (mean gain = 9 kg) at 38 months post-injury which, in turn, was associated with behavioral dysexecutive syndrome, greater oral food intake, and higher pre-injury BMI (Crenn et al., 2014). In children (mean age = 8.6 years, 59% male), one year following a TBI there was an average weight gain of 0.9 kg/m^2 with a mean z-score gain of 0.4 (Jourdan et al., 2012).

Executive dysfunction is indeed a common correlate of TBI and can confer some of the most disabling symptomatology (McDonald et al., 2002). It is plausible that TBI-related executive difficulties (e.g., behavioral inhibition) could generally alter patterns of food intake. Other studies using the general population have also linked BMI to executive function. In one sample (*n* = 408, 48.5% overweight/obsess, mean age = 38.0 years, 48% male), researchers found that overweight and obese adults exhibited poorer executive function than those with BMIs below 25 (Gunstad et al., 2007).

The possibility that BMI may partially mediate the relation of TBI to neuropsychological outcomes has not been explored. Aside from executive functioning (Gunstad et al., 2007), higher BMI has been linked to lower scores in list learning (Cournot et al., 2006), verbal and visual memory (Baccouche et al., 2014), visual motor speed (Baccouche et al., 2014), and general cognition (Kerwin et al., 2011; Sabia, Kivimaki, Shipley, Marmot, & Singh-Manoux, 2009). Additionally lower BMI has also been associated with greater decline in cognition in the elderly (Cronk, Johnson, &

Burns, 2009). Thus, BMI was examined as a potential mediator of the relation of TBI to cognitive function in the present investigation.

Glucose

Glucose metabolism may be negatively affected by TBI with resulting hyper- or hypoglycemia (Barkhoudarian, Hovda, & Giza, 2011). Increased post-TBI glucose metabolism in animal models has been associated with slower cellular metabolism and recovery from the TBI (Prins & Hovda, 2009). The author posited that these findings may be generalizable to humans with TBI.

In a study examining severe TBI patients in an Intensive Care Unit (ICU; $n =$ 170, mean age = 38 years, 62% male), researchers monitored daily morning glucose levels during the first 10 days of hospitalization (Griesdale et al., 2009). Hyperglycemia (> 11 mmol/l or 200 mg/dl) was associated with significantly higher odds of mortality ($OR = 3.6$) while hypoglycemia (< 4.5 mmol/l or 80 mg/dl) was not (Griesdale et al., 2009). In another related investigation of a large sample of moderate to severe TBI patients ($n = 51,585$, mean age = 52.5 years, 71% male, 3.3% diabetic), those who had diabetes mellitus prior to their TBI were more likely to rate higher on the Glasgow Coma Scale and were more likely to die from the TBI (Ley et al., 2011). While these studies show the importance of pre-TBI and inpatient glucose in the TBI recovery process, no studies have examined the long-term effects of glucose dysregulation in TBI patients following discharge from the hospital. Yet, given the known long-term associations of TBI and BMI, it is plausible that glucose levels (which are highly correlated with BMI) may also remain dysregulated in TBI patients following their discharge.

In extreme cases, higher glucose levels may lead to diabetes mellitus, which has known neuropsychological effects. The domains of working memory (Knopman et al., 2001; Ryan & Geckle, 2000), psychomotor speed (Knopman et al., 2001; Ryan & Geckle, 2000), verbal memory (Perlmuter et al., 1984), language (Wahlin, Nilsson, & Fastbom, 2002), and executive functioning (Gregg et al., 2000) have all been shown to be significantly associated with diabetes. Even pre-diabetes levels of glucose have been related to worse cognitive performance on measures of global cognition (Vanhanen et al., 1998), long-term memory (Vanhanen et al., 1998), and verbal fluency (Kanaya, Barrett-Connor, Gildengorin, & Yaffe, 2004), and higher rates of dementia (Kuusisto et al., 1997). Plus, acute periods of hyperglycemia have significant relations with cognitive performance (Sommerfield et al., 2004). It is therefore possible that glucose dysregulation in TBI may lead to worse cognitive performance, but this relation has not been explored in the literature.

Summary

Overall, there are a variety of biological factors that have serious implications for the well-being of TBI patients. Blood pressure, BMI, and glucose levels are all critical components of the post-TBI recovery process while a patient is in the hospital. These risk factors may also be impacted in a more long term manner among those with TBI. Additionally each biological factor has known neuropsychological implications in the general population. It is therefore possible that each factor may play a significant role in relation of TBI to cognitive function. Blood pressure, BMI, and glucose levels were therefore examined as partial mediators of the relation of TBI to cognitive function in the present investigation.

Psychological Factors

Depression

Various psychological factors are also negatively associated with TBI and may, at least in part, mediate the relation of TBI to cognitive function. Perhaps the most significant of these factors is depression. Prevalence rates of depression in the TBI population are significantly higher than in the general population, with rates as high as 42% in some samples (Kreutzer et al., 2001). It is widely accepted in the literature that a variety of interconnected and complex mechanisms are involved in these increased prevalence rates (Ownsworth & Oei, 1998). Indeed, a review of the literature postulates the importance of a combination of neuroanatomic, neurochemical, and psychosocial factors (Rosenthal, Christensen, & Ross, 1998).

Greater depression in TBI patients has been linked to outcome measures in various domains of life. In a sample of patients with mild TBI (n = 50, 14 had major depressive disorder following the TBI, mean age = 38.0 years, 82% White, 74% male), those individuals that qualified as having major depressive disorder reported more post-concussion symptoms as well as being more impaired in self-reported emotional role functioning, mental health, and general health perceptions (Fann, Katon, Uomoto, & Esselman, 1995). Other studies have corroborated these results by finding poorer social functioning (Fedoroff et al., 1992) and overall functional outcomes (Hudak, Hynan, Harper, & Diaz-Arrastia, 2012) among TBI patients with greater depressive symptoms

With respect to the outcome of cognitive function, depression may significantly affect attention, reasoning, memory, processing and motor speed, language, and

visuospatial abilities in the general population (Gotlib & Joormann, 2010). When comparing a sample of mild to moderate TBI patients (n = 69, 17% depressed, mean age = 35.06 years, 71% male) to a sample of general trauma patients (n = 52), individuals with major depressive disorder were more disabled in their Glasgow Outcome Scale and community integration, and had worse performance on tests of psychomotor speed, visuospatial abilities, memory, and executive functioning (Levin et al., 2001).

While some researchers have found a link between depression and neuropsychological outcomes in TBI, other studies have found no significant differences. In one study comparing TBI patients (n = 100, mean age = 32.0 years, mean education = 12.3 years, 83% male) and matched controls that had an injury to another part of the body (n = 30), depression predicted a worse Glasgow Outcome Scale, but did not predict worse performance on neuropsychological tests, including the domains of psychomotor speed and memory (Satz et al., 1998). In a second study of patients with closed head injury (n = 64, 27% depressed, mean age = 29.2 years, 54% male, 75% White) followed three, six, and 12 months after their hospital admission, researchers also found no quantitative differences in measures of either physical or cognitive impairment between those who met criteria for major depression and those who did not (Jorge et al., 2004). Although findings have been mixed, a fairly large body of literature suggests that depression is associated with poorer cognitive performance in the general population as well as those with TBI. It's therefore plausible that depressive symptoms may partially mediate neuropsychological outcomes in the TBI population.

Post-Traumatic Stress Disorder

Post-traumatic stress disorder (PTSD) is another common psychological condition found in TBI. While TBI and PTSD are often linked based on a single traumatic experience causing damage to the brain, especially in the military population, the general co-occurrence of PTSD and TBI is actually heavily debated. A recent review of the literature found the co-occurrence of mild TBI and PTSD ranged from 0-89% (Carlson et al., 2011). This review cited three large studies of war veterans, estimating a frequency of 5-7% of all veterans having both PTSD and a mild TBI, with 33-39% of all individuals with a mild TBI suffering from PTSD (Carlson et al., 2011). Other studies have estimated PTSD prevalence rates of 18% in moderate-severe TBI (Williams, Evans, Wilson, & Needham, 2002).

Similarly, the effect of PTSD on TBI outcomes is heavily debated in the literature. Some researchers have found no relation between PTSD and neurocognition in TBI patients. One study examined veterans with mild TBI ($n = 82$, mean age = 49.8 years, 88% male, 51% White, 10% African-American) and compared those with PTSD, those with another psychiatric condition, and those without any psychiatric condition (Gordon et al., 2011). When examining the domains of psychomotor speed, executive functioning, visuospatial abilities, and verbal and visual memory, they found no significant group differences in performance (Gordon et al., 2011). In contrast, other studies have indeed found significant associations with PTSD (even below the threshold of diagnosis) in TBI. When looking at a range of PTSD symptomatology, one study found that in a sample of Army soldiers ($n = 760$, mean age = 25.1 years, 57.1% White, 40% men) studied before and after mild TBI, greater PTSD symptomatology was

associated with more pronounced decreases in visuospatial skills and learning pre- to post-TBI (Vasterling et al., 2012).

In a review of the literature on the interactive relations of TBI and PTSD to neuropsychological outcomes, Horner & Hamner (2002) concluded that PTSD exacerbates mild TBI symptoms of inattention and/or immediate memory deficits as assessed by both subjective complaints and neuropsychological test scores. These findings are corroborated in the PTSD-cognitive function literature of the general population. In that regard, a meta-analysis found that PTSD is most significantly associated with the domains of verbal learning, speed of information processing, attention/working memory, and verbal memory (Scott et al., 2015). Despite the existing controversies in this field, the literature suggests that PTSD is likely associated with neuropsychological outcomes following a TBI. Accordingly, symptoms of PTSD were examined as a potential mediator of TBI –cognitive function associations in the present study.

Anger

Anger and aggression are very common sequelae of TBI that often co-occur with major depressive disorder (Jorge et al., 2004). Clinically significant aggression has been identified in 25-33% of individuals with a severe TBI (Baguley, Cooper, & Felmingham, 2006). These aggressive behaviors have been noted even 10 years post- TBI (Dan Hoofien et al., 2002). In a military sample, researchers found that TBI patients ($n = 661$, mean age = 27.9 years, 97% male, 73% White, 9% African-American), as compared to those without TBI ($n = 1204$), had clinically elevated problems with experience,

expression, and control of anger, with greater time since their TBI yielding lower scores (Bailie, Cole, Ivins, Boyd, Lewis, Neff, & Schwab, 2015). In contrast, other studies have found that anger worsens throughout the first year of recovery (Hanks, Temkin, Machamer, & Dikmen, 1999).

Research has also found that problems with anger in the TBI population have led to negative life outcomes. When examining moderate to severe TBI survivors ($n = 228$, 79% male, mean age of injury = 34.4 years) longitudinally over five years, higher aggression scores were related to lower satisfaction with life (Baguley et al., 2006). Another study examined severe TBI survivors ($n = 44$, average years since TBI = 8.8, mean age = 36.8 years) and found that lower levels of "challenging behavior," which included aggressive behavior, significantly predicted higher levels of community integration (Winkler, Unsworth, & Sloan, 2006). Both of these studies illustrate that aggressive behavior in TBI can have detrimental effects on patients' well-being and ultimately their recovery.

No study, to my knowledge, has examined the cognitive implications of anger in TBI. However, there is research in the general population linking anger to executive dysfunction. In a sample of male prison inmates who had committed acts of aggression ($n = 57$, 26% White, 49% African-American, mean age = 26.3 years) matched to non-inmate controls ($n = 44$), researchers found that inmates who had committed more impulsive acts of aggression performed worse on tests of comprehension, information processing, vocabulary, processing speed, visuoconstruction, and verbal memory (Barratt, Stanford, Kent, & Felthous, 1997). Another study found that tests of visual perception, response inhibition, and emotional perception significantly predicted the

frequency of aggression (57% of the variance) for a sample of violent male forensic patients (n = 23, mean age = 29 years, 65% White, 35% African-American; Foster, Hillbrand, & Silverstein, 1993). These findings suggest that anger in TBI may be linked to cognitive dysfunction, but this relation has not been examined.

Summary

In sum, depression, PTSD, and anger are all more prevalent in TBI than in the general population. Additionally, each of these psychological variables has been associated with less favorable outcomes for TBI patients and their families. While these factors have all been studied in non-TBI samples as to their effects on cognition, no definitive conclusions have been drawn as to their associations with cognitive function among TBI patients. Given the cognitive effects in the general population and the numerous effects that depression, PTSD, and anger have on functional outcomes in TBI, it is possible that these factors also impact cognitive outcomes in TBI patients. They were therefore explored as partial mediators of TBI-cognition association in the present investigation

Social Factors

Emotional Support

Directly related to the various psychological effects of TBI are the social impacts. While social support is one of the dominant concerns in TBI, it receives relatively little research focus when compared to other domains of function (Ylvisaker, Turkstra, & Coelho, 2005). Multiple studies have found that TBI patients are significantly less satisfied with the social and emotional support that they receive than controls who have

not sustained a TBI (Tomberg et al., 2005), and that these perceptions may negatively affect multiple functional outcomes.

One review of the available social support literature found that, in general, TBI patients have a smaller network size compared to controls, which has, in turn, been related to higher levels of emotional distress (Rauch & Ferry, 2001). Overall, individuals receiving more social support had faster recoveries as well. In a sample of adults who had sustained a severe head injury ($n = 36$, mean age = 27.5 years, 72% male, mean education = 11.7 years), an individual's satisfaction with their social support (primarily emotional support) indicated how likely they were to be employed (Kaplan, 1990).

Other studies have found similar benefits to increased social support. A study examining moderate-severe TBI patients longitudinally ($n = 31$, 81% male, mean age = 43.8 years) revealed that individuals who were more satisfied with their social and emotional support had higher rates of employment, as well as better physical functioning, social functioning, and generally better health (Tomberg, Toomela, Ennok, & Tikk, 2007). Another sample of adult, moderate-severe TBI patients ($n = 45$, 64% male, 89% White) had fewer neurobehavioral symptoms if they had more social interactions (MacMillan et al., 2002), illustrating that emotional support can play a critical role in the recovery and functional status of an individual.

Little to no research has linked social support to neuropsychological functioning in TBI patients. However, in the general neuropsychological literature, there have been strong links between emotional support and cognition, as those with more support perform better on measures of incidental recall, story recall, and abstraction (Seeman et

al., 2001). One study found that, in a sample of older adults (n = 838, mean age = 80.2 years, mean education = 14.4 years, 25% men, 91% White), greater social support, especially emotional support, as well as greater social activity predicted better performance in working memory, perceptual speed, and visuospatial abilities (Krueger et al., 2009).

Other studies have found no relation between social support and cognition. One study following a sample of older adults (n = 1,869; mean age = 82.4 years; 34.1% male) over time found that perceived emotional support was not associated with changes in cognition across multiple domains (Eisele et al., 2012). Overall though, given that the majority of literature supports benefits of social support on cognition, and the general importance of social support in the TBI population, it was included as a potential mediator of TBI-cognition associations in this investigation.

Instrumental Support

Receiving perhaps even less attention in the TBI literature is instrumental support, defined as tangible support, such as providing transportation, financial assistance, or physical aid (Seeman et al., 2001). Instrumental support is particularly important for TBI patients due to their sudden and often pronounced dependence on family and loved ones in multiple areas of their life. When sampling TBI patients, a study found that 61% were concerned about being a burden to others and 38% felt as though they should get what they need without the help of others (Farmer, Clark, & Sherman, 2003).

Very little attention has been given to the influence of instrumental support on outcomes in TBI patients. Most studies instead focus on the instrumental support and

burden of the caregiver (Kolakowsky-Hayner, Miner, & Kreutzer, 2001; Serio, Kreutzer, & Witol, 1997). One study examined both severe TBI patients ($n = 35$, 60% male, mean age = 29.9 years) and their caregivers and found that instrumental factors (e.g., lack of money and lack of involvement) significantly predicted depression for TBI patients (40% of the variance) as well as for caregivers (15% of the variance; Douglas & Spellacy, 2000).

The relations of instrumental support in the neuropsychological literature is also sparse with one study finding non-significant differences across the domains of language, incidental recall, story recall, spatial recognition, visuospatial skills, and abstraction (Seeman et al., 2001). However, several studies investigating social support did not separate instrumental and emotional support and so the relations of each type of support on cognition cannot be delineated.

Summary

Overall, social factors have grossly been understudied in the TBI population. Despite the prevalence of deficits in social support and patients' concerns about receipt of support, few studies have investigated their effect on recovery. Additionally no studies have examined the neuropsychological relations with emotional and instrumental support in TBI patients. Given the importance of social support in the TBI population and the relation of social support to cognitive function in the general population, it was examined as a potential mediator of TBI-cognitive function in the present investigation.

<u>Behavioral Factors</u>

　　Substance abuse is not only a risk factor for TBI, but it also plays a significant role post-injury. The prevalence of substance abuse in the post-TBI population is not well documented. However, one study of soldiers found that, compared to non-TBI controls, those who had sustained a mild TBI were 2.6 times more likely, and those with a moderate TBI were 5.4 times more likely, to be discharged for alcoholism or drug abuse (Ommaya, Salazar, Dannenberg, Chervinsky, & Schwab, 1996). Much of the TBI literature shows that those who abuse substances after a TBI have worse outcomes (Parry-Jones, Vaughan, & Miles Cox, 2006), including poorer neurological, behavioral, vocational, and life-satisfaction outcomes (Taylor, Kreutzer, Demm, & Meade, 2003). Thus, substance abuse in a post-TBI population is of significant concern. Most studies group alcohol, nicotine, and illicit substance together in their outcomes, but this review focuses on individual substances.

Alcohol

　　Parry-Jones and colleagues (2006) estimated that 7-26% of post-TBI individuals drink heavily. Another study showed that persons with TBI are four times more likely to be heavy drinkers when compared to the general population (Kreutzer, Witol, & Marwitz, 1996). Additionally, those individuals who sustained a TBI and who abused alcohol were more likely to be unemployed and have various medical complications, including intracranial hemorrhaging and greater brain atrophy (Rönty, Ahonen, Tolonen, Heikkilä, & Niemelä, 1993).

A multitude of domains of neuropsychological function have been associated with alcohol use/abuse in the general population, but the literature is controversial. The neuropsychological literature has shown that chronic alcohol abuse is negatively associated with attention, memory, language, visuospatial abilities, and executive functioning (Grant, 1987). In the TBI population, researchers have found that amongst in-patients with severe, closed TBI (n = 119, 44% with positive alcohol screen, mean age = 36.5 years), those who had a positive alcohol screen performed significantly worse on Full Scale IQ, Verbal IQ, and all five memory indices of the Wechsler Memory Scale-Revised (Kelly, Johnson, Knoller, Drubach, & Winslow, 1997). However, a second study looking at patients one year after mild TBI (n = 44, mean age = 35.1 years, 73% Caucasian, 74% male) found no significant associations between hazardous alcohol consumption and the neurocognitive domains of processing speed, learning and memory, visuospatial skills, and global cognition (Durazzo et al., 2013). These studies illustrate the discrepancies in the literature and the need for additional studies to clarify how alcohol use influences cognitive recovery in TBI. Additionally, to my knowledge, no study has examined the effects of non-abusive, post-TBI alcohol consumption on functional or cognitive outcomes.

Smoking

Smoking has also been found to be more prevalent among those with a history of TBI. Compared to 17.8% of the general population (CDC, 2013), the odds of being a smoker are 2.15 times higher for adults who had a TBI (Ilie, Adlaf, et al., 2014) and 2.5 for adolescents who had a TBI (Ilie, Mann, et al., 2014). While an increased prevalence of smoking in TBI is well documented, the outcomes from smoking are more variable.

One study examined the Glasgow Outcome Scale in a large sample of TBI patients (n = 689, mean age = 49.1 years, 65% male) and found no significant differences in outcome between smokers and non-smokers (Östberg & Tenovuo, 2014). However, when specifically analyzing neuropsychological outcomes, other research has found significant relations with smoking.

When looking at a full battery of neuropsychological tests among smokers (n = 19, mean age = 35.7 years, 74% White, 72% male) and non-smokers (n = 25, mean age = 34.6 years, 72% White, 76% male) one-month and eight-months post mild TBI, nonsmokers significantly improved on tests of processing speed, learning and memory, visuospatial skills, and global neurocognition when compared to smokers (Durazzo et al., 2013). Conversely, smokers significantly improved on tests of executive skills when compared to non-smokers over this same interval (Durazzo et al., 2013). Interestingly, a review of the neuropsychological literature for the general population shows that nicotine has acute enhancing effects for reaction time, selective attention, recognition memory, and working memory (Swan & Lessov-Schlaggar, 2007). However, this review also shows that chronic smoking can lead to cognitive deficits in the domains of processing speed, memory, and executive function (Swan & Lessov-Schlaggar, 2007). Overall then, smoking may have beneficial acute effects but chronic detrimental effects in both the general population and in the TBI population, but further clarification of these effects need to be researched.

Illicit Substances

In addition to alcohol and nicotine, illicit substance use has also been examined in the TBI population. Adults with TBI are 2.8 times more likely to use marijuana and 2.9 times more likely to use nonmedical opioids when compared to non-TBI individuals (Ilie, Adlaf, et al., 2014). In addition, 55% of heroin users have suffered a TBI, with 37% suffering multiple injuries and 15% having suffered a moderate-severe injury (Darke, McDonald, Kaye, & Torok, 2012). Amongst adolescents, TBI patients are 2.4 times more likely to have a cannabis problem and 2.1 times more likely to have a drug problem other than cannabis (Ilie, Mann, et al., 2014). Regarding cocaine, prevalence amongst the TBI population is not well documented, but 29.5% of cocaine-dependent individuals have sustained a TBI (Ramesh et al., 2015).

The neuropsychological correlates of drug use after a TBI have received little attention in the literature. Amongst the general population, some have found that marijuana has no neurocognitive effects (Carlin & O'Malley, 1996) while a review of the literature has shown mixed-effects of attention and aspects of executive function for acute and longstanding use (Crean, Crane, & Mason, 2011). Cocaine and opiate users have shown slowed mental processing, memory deficits, and reduced mental flexibility and visuospatial deficits respectively (Carlin & O'Malley, 1996; Strickland, Miller, Kowell, & Stein, 1998). In a sample of TBI patients ($n = 119$, 14% drug users, mean age = 36.5 years), those who had a positive drug screen ($n = 17$: nine cocaine users, seven opiate users) performed worse on Full Scale IQ, Verbal IQ, and four memory indices on the Wechsler Memory Scale-Revised (Kelly, Johnson, Knoller, Drubach, & Winslow, 1997).

There have been mixed findings in the area of post-TBI cocaine use and cognitive function. In a study of rats with TBI, cocaine did not affect cognitive performance on the Morris water maze (Muir, Lyeth, Hamm, & Ellis, 1995). However, among humans admitted to a trauma center who had tested positive or negative for cocaine (and matched on age and education; $n = 50$, age range 16-70 years; Jong, Zafonte, Millis, & Yavuzer, 1999), the cocaine group scored lower on a test of verbal memory (Jong et al., 1999). In sum, the cognitive consequences of cocaine use amongst the TBI population are still debated. Additionally the effects of opiates and marijuana are not represented in the TBI literature and need to be investigated.

Summary

Overall, alcohol, nicotine, and illicit substance use in the TBI population is a serious problem. Prevalence rates are relatively high, with a variety of negative outcomes. While the effects of each substance on cognition are well known in the general population, there is controversy in the TBI literature about whether the substances cause deficits beyond the TBI itself. The present investigation explored whether use of alcohol, smoking, and illicit drug use partially mediates the relation of TBI to cognitive function

Potential Mediating Factors Summary

TBI is a serious, pervasive condition with very serious consequences. The neuropsychological sequelae of moderate-severe TBI are well documented while the long-term cognitive outcome of mild TBI is still debated. Various sociodemographic variables play significant roles in the prevalence and outcomes of TBI and specifically have relations with cognitive function. Additionally, while various biological,

psychological, behavioral, and social variables have received some attention as they relate to TBI outcomes, few studies have examined whether they partially mediate the relation between TBI and neuropsychological outcomes. While many of the potential mediators reviewed could also potentially be moderators with TBI, this study only focused on these variables as potential mediators. While there is a benefit to examining the unique variance for each mediator domain independently, this study focused on the non-unique variance to analyze the variance accounted for in the context of the other domains. The behavioral components were entered first. Next the psychological components were examined in the context of the behavioral components because of the known influences of psychological factors in substance use (RachBeisel, Scott, & Dixon, 1999). Next the biological components were analyzed because of the known influences of psychological factors (Newcomer, 2007) and substance use (Lezak et al., 2004). Finally, the social components were examined due to their exploratory nature.

The Current Study

TBI is a debilitating condition that can significantly impact an individual's cognitive functioning. When examining sociodemographic differences in TBI outcomes, the literature has shown that the young are more likely to have a severe injury (Mosenthal et al., 2004) while the old have a longer recovery time (Katz & Alexander, 1994). Similarly there are sex differences in TBI such that men are more likely to sustain an injury (Faul, Xu, Wald, & Coronado, 2010), but women are more likely to have lasting effects from the injury (Farace & Alves, 2000). While the literature has shown no differences in incidence rates across races (Centers for Disease Control and Prevention, 2013), African-Americans are most likely to have lasting functional impairments

(Arango-Lasprilla & Kreutzer, 2010). Additionally, SES and education have been shown to influence TBI outcomes such that lower SES (Taylor et al., 2002) and less education (Gollaher et al., 1998) are related to worse outcomes. While individual sociodemographic variables have been studied as to their associations with TBI outcomes, no single investigation has taken all variables into consideration. The present investigation examined the potential interactions among TBI, race, and sex with respect to multiple cognitive outcomes. Those with a history of TBI were age-matched to controls, and education and poverty status served as adjustment variables.

Biopsychosocial and behavioral variables have also received a moderate amount of attention as they relate to various TBI outcomes. Yet, very little is known about their association with cognitive outcomes among persons with TBI. Biological variables such as blood pressure, BMI, and glucose levels have ill effects on cognitive function, particularly at high levels, in the general population (Bhambhani, Rowland, & Farag, 2005; Griesdale et al., 2009; Vavilala et al., 2003) and have been linked to poor functional outcomes in TBI (Baccouche et al., 2014; Knopman et al., 2001; Waldstein, 2003). Greater psychological symptoms of depression, PTSD, and anger have been correlated with worse functional outcomes following TBI (Hanks et al., 1999; Hudak et al., 2012; Vasterling et al., 2012) and poorer cognitive performance in the general population (Foster et al., 1993; Satz et al., 1998; Scott et al., 2015). Social support, in the form of emotional and instrumental support, has received little attention in the neuropsychological and TBI literature. Current findings suggest a link between greater social support and favorable outcomes in TBI (Douglas & Spellacy, 2000; Tomberg et al., 2005), but mixed-effects on cognition in the general population (Seeman et al., 2001).

Substance use, such as alcohol, nicotine, and illicit drugs, has been linked to longer recovery time in TBI (Ilie, Mann, et al., 2014; Östberg & Tenovuo, 2014; Parry-Jones et al., 2006), albeit mixed-effects on cognition in the general population (Durazzo et al., 2013; Kelly et al., 1997). Thus, multiple biological, psychological, social, and behavioral factors have relations with TBI, are associated with various TBI outcomes (including cognitive function), and are associated with cognitive functioning in the general population. However, to my knowledge, no studies have investigated these factors as potential mediators of neuropsychological outcomes in the TBI population.

The present study provides a unique opportunity to understand the relations between history of head injury and neuropsychological outcomes in a racially and socioeconomically diverse sample, including potential biopsychosocial mediators that may partially explain these associations. Understanding these relations may have clinical implications relevant to the process of recovery from head injury. Resulting information may be useful to clinicians in helping patients understand the importance of factors that may influence their cognitive outcomes. The present study addresses the following study aims and hypotheses:

Aim 1: To examine the moderating effects of race with history of head injury on neuropsychological outcomes using mixed-effects regression analyses adjusting for poverty status and education.

Hypothesis 1: Race will significantly moderate the relation of history of head injury to neuropsychological outcomes such that African-Americans who have a history of head

injury will display lower levels of performance on neuropsychological tests than the other subgroups of individuals.

Aim 2: To examine the moderating effects of sex with history of head injury on neuropsychological outcomes using mixed-effects regression analyses adjusting for poverty status and education.

Hypothesis 2: Sex will significantly moderate the relation of history of head injury to neuropsychological outcomes such that women who have a history of head injury will display lower levels of performance on neuropsychological tests than the other subgroups of individuals.

Aim 3: To explore the moderating effects of race and sex with history of head injury on neuropsychological outcomes using mixed-effects regression analyses adjusting for poverty status and education.

Hypothesis 3: Race and sex will significantly moderate the relation of history of head injury to neuropsychological outcomes such that African-American women will perform most poorly.

Aim 4: To examine potential biological, psychological, social, and behavioral factors that may partially mediate the relations of history of head injury to neuropsychological outcomes using mixed-effects regression analyses adjusting for poverty status and education.

Hypothesis 4: Biological (higher SBP, BMI, and fasting glucose levels), psychological (higher PTSD symptomatology, depressive symptomatology, and trait anger), behavioral

(positive history of smoking, alcohol consumption, and illicit drug use), and social factors (lower emotional and instrumental support) will partially mediate the relation between history of head injury and neuropsychological outcomes.

Method

Participants

Participants are community-dwelling adults who completed the first wave of the Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) study. HANDLS is an ongoing longitudinal study of race and SES-related health disparities amongst African-American and White adults between the ages of 30 and 64 years (at baseline) who live in one of 13 neighborhoods in Baltimore City (Evans et al., 2010). Individuals were pre-selected based on their likelihood to yield representative distributions of race and sex across different socioeconomic states (Evans et al., 2010). While a total of 3,724 participants were enrolled in the entire first wave of the HANDLS study, only 2,802 participants completed both phases. Phase I consisted of screening, recruitment, and a household interview. Following inclusion, Phase II was then carried out on mobile medical research vehicles (MRV) parked in the participant's neighborhood, where a medical history, physical examination, cognitive testing, and other diagnostic procedures were performed.

Participants were excluded from the HANDLS study if they were pregnant, were within six months of active treatment for cancer (chemotherapy, radiation, or biological treatments), had been diagnosed with AIDS, were unable to provide informed consent due to drug or alcohol intoxication, had severe developmental disability, were currently using illicit or illegal drugs (methadone was acceptable), had uncontrolled high blood

pressure (>160/100), could not provide government issued identification, or were without

a verifiable address at the time of consent. Additionally for this study, participants were

further excluded if they have a history of stroke, any type of dementia or other

neurological conditions (e.g., multiple sclerosis, brain cancer, epilepsy), congestive heart

failure, or were on dialysis.

Procedure

Beginning in 2004 with Phase I, participants were recruited and administered

surveys by a federal contractor trained in NIH and NIA informed consent procedures

including the Health Insurance Portability and Accountability Act (HIPPA) and specialty

training in obtaining consent from individuals with low literacy. Field interviewers went

door to door in each census tract to gather sociodemographic data such as age, sex, race,

and family income. This information was then used to obtain a random sample that was

representative of the 2000 census.

From the randomly selected sample, up to two participants per household were

offered the opportunity to participate. The study was described and the Household and

Nutritional Survey Consent Form, the HIPPA Consent Form, the NIA Privacy Statement,

and the Medical Release of Information Form were then presented and signed by the

participant. The household survey was then administered, consisting of

sociodemographic questions regarding the household and the neighborhood and a dietary

recall questionnaire.

Following Phase I, participants were scheduled for Phase II of testing on the

MRV unit, with time between phases varying from one to 42 days. Before coming to

their appointment, participants were asked to fast after 10pm and avoid smoking and

intense physical activity for at least 30 minutes. Upon arrival, participants watched a consent video and were then asked to sign the Consent Booklet, Informed Consent for Clinical Research Consent Form, and an Informed Consent for Genetic Testing Research Form. Additionally, trained NIA staff reviewed the information in all of the forms with the participant, and the staff member and a second staff member (serving as the witness) signed all forms. Medical staff then performed a medical history and physical exam, where fasting blood samples were collected and blood pressure, height and weight, and waist circumference were measured. Additionally, neuropsychological assessment was conducted by trained neuropsychometrists. Breakfast and lunch were provided for participants as well as $100 compensation for the completion of Phase II. The last participant completed Phase II in 2009.

Measures

Head Injury and Loss of Consciousness

Head injury was assessed by asking the participant if they had ever had a head injury that had resulted in a loss of consciousness in a semi-structure interview by physician or nurse practitioner. If the participants responded yes, they were then asked to report the number of head injuries they had sustained and what year they had sustained the injury. Wording was altered to the participant to maximize understanding. While self-reported loss of consciousness has relatively low reliability and validity, there remains no standardized measure of head injury, and therefore this remains the standard method of inquiry in the literature (Warner, Schenker, Heinen, & Fingerhut, 2005).

Sociodemographics

Age was measured continuously in years. Sex was coded 1 as male and 0 as female. Race was coded as self-identified "White" as 0 or "African-American" as 1.

Poverty status was assessed via family income as a function of household size. The variable was then dichotomized using the 2004 Federal poverty threshold line (e.g. $18,850 per year for a family of four). "Poverty" was defined as having a family income below or just above (between 100% and 124%) the poverty threshold, while "not poverty" was defined as having a family income above 125% of the poverty threshold. Education was quantified as years of formal education.

Biological factors

Participants had blood samples drawn after a 12-hour fast. Serum levels of glucose were assayed using standard laboratory methods at Quest Diagnostics (Chantilly, VA; www.questdiagnostics.com). Additionally, blood pressure was obtained from the brachial artery using the auscultation method, implementing an aneroid manometer, a stethoscope, and an inflatable cuff. Blood pressure was measured both in the left and right arm and then averaged for these analyses. Specifically, systolic blood pressure was used in these analyses. Height and weight were also measured and used to calculate body mass index (BMI = weight in kg/ height in m^2).

Psychological factors

Depression symptomatology was measured by the Center for Epidemiological Studies-Depression Scale (CES-D; Radloff & Radloff, 1977). The CES-D is a 20 item self-report measure using a four-point Likert-scale, asking the participant to rate symptom frequency over the past week. Response options for each question range from

"Rarely or none of the time (less than one day)" to "Most or all of the time (five-seven days)." Total scores range from zero to 60. Internal consistency is estimated to be .85 for the general population and .90 in patient samples, and test-retest reliability from two weeks to 12 months is in the moderate range (.45-.70; Radloff & Radloff, 1977). Radloff (1977) notes that given the intention of the scale to measure current affective symptoms, there is some expectation for fluctuations of scores over time. The CES-D has been shown to have moderate sensitivity, specificity, and positive predictive value for samples with major depressive disorder (sensitivity 85%, specificity 64%, and positive predictive value 63%) and clinically relevant depression (sensitivity 84%, specificity 60%, and positive predicted value 77%; Haringsma, Engels, Beekman, & Spinhoven, 2004).

PTSD symptomatology was measured by the PTSD Checklist-Civilian Version (PCL-C), a 17-item self-report measure using a five-point Likert-scale established to evaluate clinically significant and sub-clinical symptoms of post-traumatic stress (Weathers, Litz, Huska, & Keane, 1994). Participants were asked to answer based on how much they had been bothered by each stressful life experience in the last month, ranging from "Not at all" to "Extremely." Total scores range from 17-85. Test-retest reliability for PCL-C has been shown to be high, with correlation coefficients between $r = .75-.88$ (Wilkins, Lang, & Norman, 2011). Internal consistency ranges from .65-.96, with most articles finding consistencies above .90 (Wilkins et al., 2011). Convergent validity ranged from $r = .63-.90$ and discriminant validity ranged from moderate to high with various measures of depression (Beck Depression Inventory-II, $r = .71-.76$; Brief Symptom Inventory- Depression Subscale, $r = .51$; Mental Health Index 5 Depression Scale, $r = .78$; Wilkins et al., 2011).

The "Anger" subscale of the Buss-Perry Aggression Questionnaire was used to measure trait anger (Buss & Perry, 1992). The self-report subscale consists of seven questions which participants answer using a five-point Likert-scale from "Extremely uncharacteristic" to "Extremely characteristic." Scores range from zero to 28. The anger subscale has high test-retest reliability, with a correlation coefficient of $r = .91$ (Webster et al., 2014), and high internal consistency with the total Buss-Perry Aggression Questionnaire score, with a correlation coefficient of $r = .89$ (Buss & Perry, 1992). Additionally in a confirmatory factor analysis of the entire Buss-Perry Aggression Questionnaire, the anger subscale loaded onto a single factor with loadings ranging from .58-.70 (Gerevich, Bácskai, & Czobor, 2007).

Behavioral factors

Participants were asked if they ever drank alcohol, and if they currently drink alcohol. Participants were then classified as "Never" if they had never consumed an alcoholic beverage, "Former" if they had drank alcohol but not currently, and "Current" if they currently drink alcohol. This variable was further dichotomized into two groups ("Current" and "Not Current" = Former or Never). Similarly, participants were asked whether they have ever smoked and if they currently smoke. This was similarly divided into "Never," "Former," and "Current," and then dichotomized to "Current" and "Not Current." Participants additionally were asked if they had ever tried opiates, cocaine, and marijuana, and if they currently use each substance. Each substance was also divided into "Never," "Former," and "Current," and then dichotomized with 1 being coded as "Current" and 0 being coded as "Not Current." These three variables were then summed to generate a count variable for ever using illicit drugs.

Social factors

Perceived emotional support was measured using the Emotional Support Questionnaire, taken from the MacArthur Aging Study (Seeman et al., 2004). Participants self-reported their perceived emotional support by answering six questions using a four-point Likert-scale. Each question targeted a specific source of support (i.e. spouse or partner, children, and family and relatives), and answers ranged from "Never" to "Frequently." Participants could also answer "N/A" if they did not have a spouse/partner or children. An average score was then generated based on the number of items answered that were not "N/A," creating scores ranging from zero to three. Cronbach's alpha for the emotional support scale was shown to be .66 and test-retest reliability over a two-month period was shown to be .73 (Seeman et al., 2004).

Perceived instrumental support was measured using the Instrumental Support Questionnaire, a scale also taken from the MacArthur Aging Study (Seeman et al., 2004). Similar to the Emotional Support Questionnaire, participants answered six questions using a four-point Likert scale targeting different sources of support. An average score was also then generated based on the number of items answered that were not "N/A" creating scores ranging from zero to three. Cronbach's alpha for the instrumental support was .45 and test-retest reliability over a two-month period was shown to be .44 (Seeman et al., 2004). The authors of the scale also conducted a Spearman rank correlation, showing $r = .55$ (Seeman et al., 2004).

Neuropsychological Tests

Neuropsychological measures spanning multiple cognitive domains were selected. Trained psychometrists under the supervision of a neuropsychologist administered all

neuropsychological tests. Extensive training was conducted with the neuropsychologist or other previously trained examiners including several practice sessions to guarantee accurate and reliable administration of the measures in an appropriate manner. Provided below are the descriptions of the included measures and associated administration procedures. Reliability and validity evidence is particularly difficult and may be limited for neuropsychological measures. Testing environment, nonstandard administration, practice effects, and cooperation and effort from the examinee can all affect the stability of performance (Strauss, Sherman, & Spreen, 2004). Additionally, validity for a measure on a specific construct can potentially be confounded by other cognitive domains because neuropsychological tests commonly span multiple domains of functioning. Despite these limitations, reliability and validity measures for each test are also provided below by cognitive domain.

Memory

California Verbal Learning Test

The California Verbal Learning Test is a multi-trial list learning task designed to measure verbal learning and memory (Delis, Kramer, Kaplan, & Ober, 1987). In a shortened version of the original CVLT, participants are read a list (List A) of 16 words from four separate categories and then asked to recall as many words as possible. This process is repeated over three trials (as opposed to five trials from the original). A total is calculated from the total number of correctly named items over the three trials as the CVLT Total Correct for List A. Additionally a learning slope is calculated by a least squares regression of the linear model of the total correct over the three trials. Following the three trials of List A, an interference list of 16 items is read to the participant and they

are asked to recall as many words as possible. Immediately after the recall of the interference list, participants are asked to recall the original list that was presented as the short delay free recall. Participants are then given the four category cues to generate as many words as possible as the short delay cued recall. Following a 20-25 minute delay where other tasks are performed, participants are then asked to recall as many words from List A as possible (long delay free recall) and then given category cues to generate as many words (long delay cued recall).

Internal consistency on total word scores across trials were high for clinical samples ($r = .83$) and for the standardization sample ($r = .82$; Strauss, Sherman, & Spreen, 2004). Split-half reliability comparing List A trials was also high, ranging from $r = .77$-$.86$ (Delis, Kramer, Kaplan, & Ober, 1987). Test-retest reliability over the course of a year was also found to be high, with $r = .76$ (Paolo, Troster, & Ryan, 1997). When factor analyses have been conducted on 19 scores generated from the CVLT, six factors emerged labeled as general verbal learning, response discrimination, primacy-recency effects, organization strategies, recall efficiency, and acquisition rate (Strauss, Sherman, & Spreen, 2004). Additionally when compared to age- and education-matched controls, patients with focal frontal lesions showed overall poorer recall, more intrusions, reduced semantic clusters, and worse recognition (Baldo, Delis, Kramer, & Shimamura, 2002). For the present study, Total Correct for List A, Learning Slope, Short Delay Free Recall, and Long Delay Free Recall were used as outcome measures.

Benton Visual Retention Test

Also known as the BVRT-5, the Benton Visual Retention Test measures visual perception, visual constructive abilities, and visual memory (Sivan, 1992). Participants

are presented 10 designs, one at a time, for five seconds and then the designs are withdrawn. Following each design, participants are then asked to draw what they remember from the design. The first two designs consist of a single geometric shape, while the following eight contain two major figures and a third, smaller figure. Figures are scored using manualized instructions (Sivan, 1992) and a total number of errors from the 10 figures is calculated. Errors include omissions, distortions, perseverations, rotations, misplacements, and size errors. Figures are scored by two examiners to verify scoring validity.

For various forms of the BVRT, internal consistency is high, with Cronbach's alpha ranging from .71-.82 (Steck, Beer, Frey, Fruhschutz, & Korner, 1990). Interrater reliability is very high for both number correct ($r = .96$) and error codes ($r = .97$; Swan, Morrison, & Eslinger, 1990). Coefficients of concordance between scores obtained for separate administrations were also high, with $r = .74$ for total correct and $r = .77$ for errors (Lezak et al., 2004). In a factor analysis with other neuropsychological tests, BVRT loaded primarily on visuospatial factor (.55) but also loaded significantly on memory (.45) and concentration (.42) factors (Larrabee, Kane, Schuck, & Francis, 1985). Additionally, impairments were seen in individuals with head injury (Levin et al., 1990), relapsing-remitting form of multiple sclerosis (Ruggieri et al., 2003), polydrug abusers (Amir & Bahri, 1999), and older men with both apolipoprotein E allele and magnetic resonance imaging showing signs of brain atrophy (Carmelli et al., 2000). For this study, total number of errors from all 10 figures was used.

Perceptuo-Motor Speed and Manual Dexterity

Trail Making Test, Part A

Adapted from its original part in the *Army Individual Test Battery* (1944), the Trail

Making Test is a stand-alone test of visuomotor tracking and scanning, divided attention,

and mental flexibility (Reitan, 1992). Participants first completed the Trails A sample

where they were told to draw lines connecting the numbers in order, as quickly as

possible, without making mistakes. The sample consisted of six circles, numbered 1

through 6, randomly placed throughout the page. The participant was then given the

Trails A test, consisting of the numbers 1 through 25, but following the same concept as

the sample. If participants made an error, they were instructed by the examiner to return

to the last correct circle and correct their mistake. The trial was timed, and the time to

complete the entire trial was then recorded with the number of errors.

Practice effects readily occur in repeated administrations of Trail Making Test,

making reliability difficult to measure. Regardless, much of the literature shows that

reliability is often in the .80s and .90s (Strauss, Sherman, & Spreen, 2004). Additionally

alternative form reliability coefficients are also high, ranging between .80 and .92 for

both parts A and B, and inter-rater reliability is .94 and .90 for parts A and B respectively

(Strauss, Sherman, & Spreen, 2004). Research has also shown that the tests are sensitive

to cognitive inflexibilities (cognitive flexibility predicted a significant amount of Trails B

test performance, $R^2 = .07$) and brain injuries (82-88% correctly identified against

controls; Kortte, Horner, & Windham, 2002; Spreen & Benton, 1965). Others have found

that Trails A and B correctly classify brain-damaged individuals 96% and 98% of the

time, respectively, using cut-off time scores (Mitrushina, Boone, & D'Elia, 1999). The

Trail Making Test also correlates highly with other measures of attention-switching, executive control, psychomotor speed, and visuomotor scanning (Strauss, Sherman, & Spreen, 2004).

Attention/Working Memory

Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Span Forward and Backward

The Digit Span subtest, another component of the WAIS-R battery, requires attention, concentration, and working memory (Lezak et al., 2004). In Digit Span Forward, a span of numbers was read to the participants, beginning with three digits, and then participants were asked to repeat the numbers back to the examiner immediately. Two trials of a specific digit length were administered, and then the examiner moved on to the next set of trials which had an additional digit, up through 10 digits. Participants received one point for each trial for a maximum total score of 14 points. After both trials of a specific digit length were incorrect, the test was discontinued. Digit Span Backward was administered in a similar fashion, except participants had to immediately recall the span of digits in the opposite order they were read. The test began with a span of two digits and continued up through spans of nine numbers. Each trial was also worth a single point for a maximum score of 14 points. This study utilized both Digit Span Forward and Backward scores independently.

Test-retest reliability is high for Digit Span, with coefficients spanning from .66 to .89 (Matarazzo & Herman, 1984; Snow, Tierney, Zorzitto, Fisher, & Reid, 1989), and internal consistency is very high (greater than .90; Strauss, Sherman, & Spreen, 2004). In a confirmatory factor analysis in a clinical sample and a standardized sample, Digit Span

was found to have factor loadings of .67 and .71 on the Working Memory factor,

respectively (Burton, Ryan, Axelrod, & Schellenberger, 2002).

Language/Executive Function

Category Fluency

As part of several neuropsychological batteries, semantic fluency is used to

measure the number of words a participant can generate spontaneously in a set amount of

time corresponding to a specific category, the most common of which is animals (Strauss,

Sherman, & Spreen, 2004). Participants are told to generate as many animals as possible

within a 60 second interval, and the total number of unique animals named is summed to

generate a category fluency score.

Test-retest reliability shows high correlations for short and long intervals, with

coefficients greater than .70 (Strauss, Sherman, & Spreen, 2004). One study noted

minimal practice effects after a one-month interval for 99 healthy adults, with on average

a 1.3 word increase (Bird, Papadopoulou, Ricciardelli, Rossor, & Cipolotti, 2004).

Patients with frontal lobe lesions (Baldo & Shimamura, 1998), Alzheimer's disease

(Fama, Sullivan, & Shear, 1998), and Parkinson's disease (Fama, Sullivan, & Shear,

1998) show reduced category fluency when compared to letter fluency. Specifically in

Alzheimer's disease, category fluency had very high sensitivity (100%) and specificity

(90.9%; Fama, Sullivan, & Shear, 1998). Animal fluency also helped discriminate effects

of dementia and depression, with depressed individuals performing better on the task

(Hart, Kwentus, Taylor, & Hamer, 1988).

Executive Function

Trail Making Test, Part B

Trails Sample B and Test B from the second half of the Trail Making Test is completed in similar fashion to part A. Trails Sample B and Test B, though, have both numbers and letters, and participants must alternate between numbers and letters (1 to A, A to 2, 2 to B, etc.). Time to complete Trails B and the number of errors were both recorded.

Data Analyses

Power Analysis

G*Power statistical power software was used to conduct power analysis based on an estimated sample size of 768. With a power of .80, an alpha of .05, and 14 (history of head injury, race, sex, their interactions, biopsychosocial and behavioral factors, and three covariates) factors and predictors the proposed study should be able to detect a small effect f^2 estimate of 0.018. This demonstrates adequate power to detect small effects in this study.

Participant Matching

To compare individuals with histories of head injury to comparable individuals without histories of head injuries, participants with histories of head injuries (n = 256) were each matched to two participants without a history of head injury (n = 512) based on age (±4 years). Participants were matched by the "Match" function in the "Matching" package (Sekhon, 2011) using R 3.2.1 (R Development Core Team, 2015). Pearson's chi-squared test with Yates' continuity correct tested differences in age between the head

injury and control groups. A verification of the match checked the feasibility and accuracy of the match using Pearson's chi-squared test with Yates' continuity correction for sex, race, and poverty status and a Welch two-sample t-test for age and years of education between the two groups.

Diagnostics and Descriptive Statistics

Descriptive statistics and distributions were examined for all variables. Normality, skewness, outliers, and any other discrepancies between variables and the requirements of the statistical analyses were investigated to verify the appropriateness of the analyses. If a variable was found to be skewed, the variable was log-transformed in order to normalize the distribution. Outlier scores were verified with raw data, and decisions were made whether to drop or include values.

Correlations

Preliminary correlation tables were generated to examine zero-order correlations among the predictor, moderators, mediators, outcomes, and covariates. Correlations not only illustrated associations among variables in the same mediator domain (e.g. SBP and BMI), but also demonstrated preliminary associations between the predictor and outcomes.

Principal Components Analysis (PCA)

A principal components analysis (PCA) was used to derive clusters of variables for the biological mediator domain (SBP, BMI, fasting glucose level). Components with eigenvalues greater than one were retained for each PCA. This was then repeated for the

psychological mediator domain (PTSD symptomatology, depression symptomatology, trait anger), the behavioral mediator domain (weekly alcohol consumption, history of cigarette use, history of illicit drug use), and the social mediator domain (emotional support, instrumental support). Based on prior analyses with the HANDLS data, a single component was expected for each group of measures.

Mixed-Effect Models

To address Aim 1, 2, and 3, mixed-effect regression analyses were computed. The group match of head injury to controls served as the random effect, and race, sex, and all of the interactions between the predictors were entered as fixed effects with education and poverty status as fixed covariates. Each of the neuropsychological outcomes identified (Benton Visual Retention Test total score; California Verbal Learning Test total score, learning slope, short and long delay free recall score; Digit Span Forward and Backward score; Trail Making Test, Part A and B time; Category Fluency score) were used as a separate criterion variable for each analysis. While global cognitive index or domain scores would yield more parsimonious analyses, many individuals in the neuropsychological literature assert that the complexity of cognitive abilities make it extremely difficult to summarize with composite measures (Elias, Elias, Sullivan, Wolf, & D'Agostino, 2003; Lezak et al., 2004; Waldstein, 2000) and some advise against it (Waldstein, 2000). For these reasons we chose to use individual neuropsychological test scores as outcome measures. Family-wise error correction was not used due to the unique nature of each test.

If the three-way interaction of head injury, race, and sex was not significant for any analysis, the interaction was removed from the analysis to explore the two-way interactions of race and head injury and sex and head injury. If a three-way interaction was significant for any mixed-effect model analyses, the effect was probed by plotting head injury at the four interactive levels of race and sex (i.e. African-American men, African-American women, etc.). If only a two-way interaction was significant for any mixed-effect model analysis, the effect was probed by plotting head injury at the two levels of the interactive variable (race or sex). From these plots I was able to determine the nature of the interaction for the specific neuropsychological outcome. If two-way interactions were not significant for any mixed-effect model analysis, the interactions were removed from the analysis to explore the main effects of race, sex, and head injury. These procedures were repeated for each non-significant interaction effect.

To explore Aim 4 and understand the possible mediating effects of various biopsychosocial and behavioral variables, nested mixed models were employed. For each analysis, the group match of head injury to controls served as the random effect, and race, sex, and all of the interactions between the predictors were entered as fixed effects with education and poverty status as fixed covariates, and an Akaike information criterion (AIC) was obtained to measure the model's fit. Next, the component(s) from the behavioral mediator PCA were entered in as a fixed effect, and a new AIC was determined. Subsequently, the psychological mediator component, the biological mediator component, and the social mediator component, were entered as fixed variables and AICs were obtained for each addition. As the literature has no agreement on appropriate criteria for significant changes in AIC, significant mediation was determined

if the AIC changed from the previous iteration by at least two units, accompanied by the

interaction head injury term becoming non-significant (G. Diao, personal communication,

March 7, 2015). This procedure was then repeated for each neuropsychological outcome

identified above as the criterion variable.

Results

Description of Sample

For sample characteristics in tabular form, please refer to Table 1. After

accounting for missing data, the analysis sample included 750 individuals. Of these

participants, 250 had sustained a head injury, of which 62 were White men, 45 were

White women, 93 were African-American men, and 50 were African-American women.

On average, for those that sustained a head injury, White men had 1.1 head injuries (SD =

0.3, Min = 1, Max = 3), White women had 1.2 head injuries (SD = 0.9, Min = 1, Max =

6), African-American men had 1.1 head injuries (SD = 0.3, Min = 1, Max = 3), and all

African-American women reported a single head injury.

For those with and without a head injury respectively, the analysis sample was

62% and 61% male, and 57% and 63% White. The sample had 50% and 36% of

individuals above the 125% poverty line for those with and without a head injury

respectively. On average, participants were similar in age, with a mean age of 47.6 years

(SD = 8.3, Min = 30, Max = 64) for those with a head injury and 47.01 years (SD = 8.3,

Min = 30, Max = 64) for those without. Similarly participants were close in educational

background as well, with a mean of 12.2 years of education (SD = 3.0, Min = 1, Max =

21) for those with and 12.5 years (SD = 3.0, Min = 2, Max = 21) for those without a head injury.

Amongst the individuals who sustained a head injury, the average number of years from the head injury was 23.4 years (SD = 14.7, Min = 0, Max = 54) for African-American men, 22.4 years (SD = 15.7, Min = 0, Max = 49) for African-American women, 20.8 years (SD = 14.1, Min = 0, Max = 53) for White men, and 17.5 years (SD = 14.0, Min = 0, Max = 53) for White women (see Figure 1). Additionally there was a small correlation between race and poverty status for individuals without a history of head injury ($r = .196$, $p < .001$) and those with a history of head injury ($r = .165$, $p < .001$).

For those with a history of head injury, 66% reported current alcohol use, 57% current smoking, and had a mean substance use count of 0.34 (SD = 0.69, Min = 0, Max = 3) while, amongst those without a head injury, 63% reported current alcohol use, 48% current smoking, and had a mean substance use count of 0.25 (SD = 0.60, Min = 0, Max = 3). Individuals reporting a history of head injury scored a mean of 16.8 on the CES-D (SD = 11.5, Min = 0, Max = 59), 32.8 on the PCL-C (SD = 15.6, Min = 17, Max = 82), and 10.6 on the Buss-Perry Aggression Questionnaire (SD = 6.4, Min = 0, Max = 26) while those reporting no history of head injury scored a mean of 13.7 on the CESD (SD = 10.4, Min = 0, Max = 52), 28.3 on the PCL-C (12.3, Min = 17, Max = 77), and 10.2 on the Buss-Perry Aggression Questionnaire (SD = 6.5, Min = 0, Max = 28). For individuals with and without a head injury respectively, systolic blood pressure was 120.6 (SD = 16.6, Min = 80, Max = 186) and 119.7 (SD = 17.8, Min = 83, Max = 194.5), fasting glucose was 99.2 (SD = 28.2, Min = 42, Max = 306) and 103.4 (SD = 41.3, Min = 56,

Max = 430), and body mass index was 28.7 (SD = 6.8, Min = 16.9, Max = 55.0) and 29.3

(SD = 75, Min = 16.4, Max = 59.9). For the emotional support questionnaire, those with a

head injury had a mean score of 2.1 (SD = 0.6, Min = 0.5, Max = 3) while those without

had a mean score of 2.3 (SD = 0.7, Min = 0.5, Max = 3), while on the instrumental

support questionnaire, those with a head injury had a mean score of 1.4 (SD = 0.7, Min =

0, Max = 3) and those without had a mean score of 1.5 (SD = 0.7, Min = 0, Max = 3).

Reliability was also calculated for all psychological and social scales (see Table

2). The Cronbach's alpha for MacArthur's Instrumental Support Questionnaire was

slightly below the acceptable range (α = .635) but all other scales had acceptable to high

reliability.

All outliers were judged to be accurate representations of participants in the

parent study and therefore were included in our sample.

Normality

Among the variables included in our analyses, time to complete Trail Making

Test, Part B had a right-skewed distribution (refer to Figure 2). Therefore the natural log

of time to complete Trail Making Test, Part B was computed and used in all analyses. All

other variables were relatively normally distributed.

Principal Components Analysis

Behavioral

A principal components analysis was run with smoking status, alcohol drinking status, and the recreational drug count variable. All variables loaded onto a single variable with only one component having an eigenvalue greater than 1 (Table 3).

Psychological

A principal components analysis was run with depressive symptomatology, PTSD symptomatology, and trait anger variables. All variables loaded onto a single variable with only one component having an eigenvalue greater than 1 (Table 4).

Biological

A principal components analysis was run with fasting glucose level, body mass index, and systolic blood pressure as included variables. All variables loaded onto a single variable with only one component having an eigenvalue greater than 1 (Table 5).

Social

A principal components analysis was run with a mean emotional support and mean instrumental support variables. All variables loaded onto a single variable with only one component having an eigenvalue greater than 1 (Table 6).

Hypothesis 1-3

A series of mixed-effect models were computed to examine the 2-way interactive associations of race and head injury and sex and head injury, the 3-way interaction of

race, sex, and head injury, and main effects of race, sex, and head injury with various neuropsychological outcomes. Covariates included sex, poverty status, and education. Complete results are outlined in Tables 7 through 16.

<u>Memory</u>

CVLT Total Correct for List A

For CVLT List A total, there was not a significant interaction between sex, race, and head injury, $F (1, 689.964) = 0.096$, $p > .050$. While there was not a significant interaction between sex and head injury, $F (1, 504.425) = 0.040$, $p > .050$, there was a significant interaction between race and head injury status, $F (1, 695) = 6.161$, $p = .013$. There was no main effect of head injury, $F (1, 498.887) = 2.607$, $p > .050$.

The estimates of fixed effects were then obtained and used to graph the interaction between race and head injury (Figure 3). From this graph it can be seen that African-Americans obtained lower CVLT List A total scores if they had a history of head injury than African-Americans without a history of head injury. Conversely for White, those who had a head injury performed better on CVLT List A total than their counterparts who had no history of head injury. Further the analysis was repeated for each racial group to test significance of each trend. Stratified analyses revealed that the trend in African-Americans was significant, $F (1, 385) = 4.012$, $p = .046$, while the trend in Whites was not significant, $F (1, 309) = 1.628$, $p = .203$.

CVLT Learning Slope

For CVLT Learning slope, there was not a significant interaction between sex, race, and head injury, $F(1, 532.390) = 0.079$, $p > .050$. Additionally there was not a significant interaction between race and head injury status, $F(1, 535.971) = 0.075$, $p > .050$, or between sex and head injury status $F(1, 406.639) = 0.171$, $p > .050$, and there was no main effect of head injury status, $F(1, 406.002) = 0.321$, $p > .050$.

CVLT Short Delay Free Recall

For CVLT Short Delay Free Recall, there was not a significant interaction between sex, race, and head injury, $F(1, 526.601) = 0.126$, $p > .050$. Additionally there was not a significant interaction between race and head injury status, $F(1, 527.872) = 0.628$, $p > .050$, or between sex and head injury status $F(1, 383.369) = 0.119$, $p > .050$, and there was no main effect of head injury status, $F(1, 384.962) = 0.095$, $p > .050$.

CVLT Long Delay Free Recall

For CVLT Long Delay Free Recall, there was not a significant interaction between sex, race, and head injury, $F(1, 520.901) = 0.646$, $p > .050$. Additionally there was not a significant interaction between race and head injury status, $F(1, 522.981) = 0.525$, $p > .050$, or between sex and head injury status $F(1, 387.901) = 0.00$, $p > .050$, and there was no main effect of head injury status, $F(1, 389.761) = 0.013$, $p > .050$.

Benton Visual Retention Test

For Benton Visual Retention Test, there was not a significant interaction between sex, race, and head injury, $F(1, 692.727) = 0.677$, $p > .050$. Additionally there was not a

significant interaction between race and head injury status, F (1, 693.993) = 0.583, $p >$ .050, or between sex and head injury status F (1, 486.020) = 1.676, $p > .050$, and there was no main effect of head injury status, F (1, 482.780) = 0.025, $p > .050$.

Perceptuo-Motor Speed and Manual Dexterity

Trail Making Test, Part A

For Trail Making Test, Part A, there was not a significant interaction between sex, race, and head injury, F (1, 689.964) = 0.096, $p > .050$. Additionally there was not a significant interaction between race and head injury status, F (1, 693.651) = 2.417, $p >$ .050, or between sex and head injury status F (1, 504.425) = 0.040, $p > .050$, and there was no main effect of head injury status, F (1, 498.887) = 2.607, $p > .050$.

Attention/Working Memory

Digit Span Forward

For Digit Span Forward, there was not a significant interaction between sex, race, and head injury, F (1, 692.990) = 0.239, $p > .050$. While there was not a significant interaction between race and head injury, F (1, 694.755) = 1.010, $p > .050$, there was a significant interaction between sex and head injury status, F (1, 480.902) = 4.045, $p =$ .045. There was no main effect of head injury, F (1, 476.084) = 1.174, $p > .050$.

The estimates of fixed effects were then obtained and used to graph the interaction between sex and head injury (Figure 4). From this graph it can be seen that men obtained lower Digit Span Forward scores if they had a history of head injury than men without a history of head injury. Conversely for women, those who had a head injury performed better on Digit Span Forward than their counterparts who had no history

of head injury. Further the analysis was repeated for each sex group to test significance of each trend. Stratified analyses revealed that the trend in men was significant, F (1, 290.296) = 4.101, p = .044, while the trend in women was not significant, F (1, 181.599) = 1.679, p = .197.

Digit Span Backward

For Digit Span Backward, there was not a significant interaction between sex, race, and head injury, F (1, 692.646) = 0.004, p > .050. While there was not a significant interaction between race and head injury, F (1, 693.580) = 0.013, p > .050, there was a significant interaction between sex and head injury status, F (1, 478.600) = 5.952, p = .014. There was no main effect of head injury, F (1, 472.515) = 1.964, p > .050.

The estimates of fixed effects were then obtained and used to graph the interaction between sex and head injury (Figure 5). From this graph it can be seen that men obtained lower Digit Span Backward scores if they had a history of head injury than men without a history of head injury. Conversely for women, those who had a head injury performed better on Digit Span Backward than their counterparts who had no history of head injury. Further the analysis was repeated for each sex group to test significance of each trend. Stratified analyses revealed that the trend in men was significant, F (1, 295.996) = 5.717, p = .017, while the trend in women was not significant, F (1, 182.342) = 2.471, p = .118.

Language/Executive Function

Category Fluency

For Category Fluency, there was not a significant interaction between sex, race, and head injury, F (1, 689.459) = 0.155, p > .050. Additionally there was not a significant interaction between race and head injury status, F (1, 689.169) = 0.039, p > .050, or between sex and head injury status F (1, 480.962) = 0.045, p > .050, and there was no main effect of head injury status, F (1, 476.973) = 0.032, p > .050.

Executive Function

Trail Making Test, Part B

For Trail Making Test, Part B, there was not a significant interaction between sex, race, and head injury, F (1, 654.136) = 0.821, p > .050. Additionally there was not a significant interaction between race and head injury status, F (1, 658.102) = 0.001, p > .050, or between sex and head injury status F (1, 468.311) = 0.313, p > .050, and there was no main effect of head injury status, F (1, 470.310) = 0.415, p > .050.

Hypothesis 4

Mixed-effect models were computed to examine the potential mediating effects of the behavioral, psychological, biological, and social components on the significant interaction relations from Hypothesis 1 and 2 (race by head injury on CVLT total, sex by head injury on Digit Span Forward, and sex by head injury on Digit Span Backward). Covariates included poverty status and education, and when not a main effect, sex or race. The main effects of head injury and either race or sex, as well as the interaction

variable of the appropriate two were also included. Complete results are outlined in Tables 17 through 19.

CVLT Total List A

For the interaction of race and head injury with CVLT Total List A score, after adding the behavioral component, the AIC significantly changed (ΔAIC = -56.637), however the race by head injury interaction remained significant, F (1, 686) = 6.800, p =.009. When the psychological component was added, the AIC significantly changed (ΔAIC = -1400.79), and the race by head injury interaction was no longer significant, F (1, 496) = 2.968, $p > .050$, indicating that the psychological component accounted for a significant amount of the variance in CVLT Total List A score that was previously accounted for by the interaction of sex and head injury. When the biological component was added, the AIC significantly changed (ΔAIC = -294.289), and the race by head injury interaction remained non-significant, F (1, 443) = 1.686, $p > .050$. Additionally when the social component was added, the AIC significantly changed (ΔAIC = -548.427), and the race by head injury interaction remained non-significant, F (1, 366) = 2.445, $p > .050$.

Digit Span Forward

For the interaction of sex and head injury with Digit Span Forward score, after adding the behavioral component, the AIC significantly changed (ΔAIC = -25.752), however the sex by head injury interaction remained significant, F (1, 476.909) = 4.357, p =.037. When the psychological component was added, the AIC significantly changed (ΔAIC = -858.882), however the sex by head injury interaction remained significant, F

(1, 374.153) = 4.136, p = .050. When the biological component was added, the AIC

significantly changed (ΔAIC = -167.354), and the sex by head injury interaction lost its

significance, F (1, 360.259) = 3.340, p > .050, indicating that the biological component

accounted for a significant amount of the variance in Digit Span Forward that was

previously accounted for by the interaction of sex and head injury. Additionally when the

social component was added, the AIC significantly changed (ΔAIC = -362.674), and the

sex by head injury interaction remained non-significant, F (1, 366) = 2.252, p > .050.

Digit Span Backward

For the interaction of sex and head injury with Digit Span Backward score, after

adding the behavioral component, the AIC significantly changed (ΔAIC = -35.925),

however the sex by head injury interaction remained significant, F (1, 474.168) = 6.128,

p =.006. When the psychological component was added, the AIC significantly changed

(ΔAIC = -827.610), however the sex by head injury interaction remained significant, F

(1, 375.311) = 6.728, p = .010. When the biological component was added, the AIC

significantly changed (ΔAIC = -156.163), however the sex by head injury interaction

remained significant, F (1, 364.133) = 6.762, p = .010. Additionally when the social

component was added, the AIC significantly changed (ΔAIC = -338.146), however the

sex by head injury interaction remained significant, F (1, 300.677) = 4.058, p = .009.

Discussion

To my knowledge, this was the first study to investigate the interactive relations

of race, sex, and TBI history to cognitive function in an age-matched sample of

community-dwelling adults. The project was also the first to examine a multi-level

spectrum of biological, psychological, social, and behavioral variables as potential mediators of these associations. Discussed in detail below, results generally indicated that African-Americans with a history of head injury performed significantly worse on a measure of verbal memory than African-Americans without an injury, and men with a history of head injury performed significantly worse on measures of attention and working memory than men without a head injury. Additionally, results showed that the interactive association of race and head injury to memory may be mediated by psychological factors and the association of sex and head injury to attention may be mediated by biological factors.

While TBI preventative measures should be taken across all populations, results of the present investigation suggest a need to focus these efforts on African-Americans and men, who may be particularly vulnerable to the long-term neuropsychological sequelae of TBI. Additionally, by demonstrating that the biological and psychological clusters examined herein may partially mediate the relation between TBI and cognition, this study highlights the need to utilize a multifactorial and holistic approach to TBI recovery. As the fields of behavioral medicine and neuropsychology begin to merge, results of this study provide evidence for the need of further integration in the treatment of TBI to maximize recovery for patients.

Hypothesis 1: Interaction of Race and TBI

It was posited that race would significantly moderate the relation of history of head injury to neuropsychological outcomes such that African-Americans with a history of head injury would perform more poorly on neuropsychological tests than the other

subgroups. This hypothesis was only partially supported, as African-Americans with a history of head injury performed significantly worse than African-Americans without a history of head injury on CVLT Total Recall, a test of verbal memory. It was also unexpected within the interaction that for individuals without a history of head injury African-Americans performed better than Whites. There was no significant association between history of head injury and CVLT Total Recall performance for Whites. Additionally, all other neuropsychological outcomes were not significant.

To my knowledge, no prior studies have directly examined the moderating effects of race and TBI history on neuropsychological outcomes. Indeed, results of the only study that compared African-Americans to Whites following a TBI showed that the African-Americans fared significantly more poorly on two of 20 neuropsychological tests -Block Design and the Trail Making Test, Part A, while all other measures of visuospatial abilities, processing speed, verbal memory, attention, working memory, language, and executive function did not differ between groups (Kennepohl et al., 2004). Similarly, the present findings revealed an absence of interactive relations of race and head injury to 9 of 10 of the neuropsychological outcomes measures examined. Thus, it is possible that the majority of negative findings in our study represent a true lack of interactive relations of race and TBI to cognitive function. However, there are various other possible explanations for these largely negative results.

One potential explanatory factor could be that proximity to TBI plays a significant role in the potential presence or absence of race and TBI interactions. Depending on the severity of the injury, the brain may take one month to several years to maximally recover (Brenner, 2011). It is possible that race differences in cognition following a TBI

are only noted within the acute recovery process, but not reflected in more distal outcomes. Given that a large proportion of the present sample was over a decade post-TBI, it is likely that all of these individuals are beyond any additional brain recovery

Another possible explanatory factor hindering potential findings could be TBI severity. Race differences may only be present within a particular severity of injury. In this study, severity of injury was not known and therefore was not considered in the present analyses. If, in theory, race differences were present only among those with moderate to severe TBI, the results may have been diluted by grouping together all individuals with varying severities of TBI.

Despite the numerous negative findings, results of the present investigation did include a significant interaction of race with history of TBI on a single measure of memory. This finding is partially supported by prior literature on the neuropsychological sequelae of TBI. Throughout the literature, individuals with a history of TBI, no matter the magnitude of the injury, display worse memory performance than their non-TBI counterparts (Babikian et al., 2011; Draper & Ponsford, 2008; Vanderploeg et al., 2001; Voller et al., 1999). Additionally within the general neuropsychology literature, African-Americans have been shown to perform more poorly than Whites on multiple CVLT measures (Norman, Evans, Miller, & Heaton, 2000), as well as other measures of verbal memory (Manly et al., 1998). Thus, while it is possible that this single significant finding for memory performance is spurious given the large amount of analyses conducted, it is also possible that there is a true interaction of race and TBI history for performance on CVLT total recall.

There are several possible explanations for the significant relation of history of TBI to CVLT total recall for African-Americans. In previous literature outside of the TBI field, African-Americans have been shown to have a particular vulnerability to poor clinical brain health outcomes such as stroke (Lloyd-Jones et al., 2009) and dementia (Fitzpatrick et al., 2004). African-Americans have also been shown to be particularly vulnerable to cognitive deficits from dementia (Welsh et al., 1995). Oftentimes memory is the first domain to show an initial decline in early Alzheimer's disease, the most common form of dementia (Petersen et al., 1999). Given the connection between TBI history and dementia onset (Jellinger, 2004), it is possible that our sample of African-Americans with a history of TBI are at a greater risk for developing a dementia such as Alzheimer's disease, hallmarked by their worsened delayed memory performance.

Additionally the severity of the injuries in our sample may differ between Whites and African-Americans. Although the incident rates of TBI are relatively equal for Whites and African-Americans, African-Americans tend to have more serious outcomes such as death (Faul et al., 2010). These differential outcomes may extend to the realm of cognition, with the complex brain network of memory and encoding being particularly vulnerable to post-TBI dysfunction.

African-Americans also may not have had the same resources as their White counterparts who sustained a TBI. While poverty status based on household income (and size) was used as a covariate in our study, it may not have accurately captured other resources such as access to, or utilization of, medical care and ability to take time off from work, all of which can affect TBI recovery. Previous TBI research has shown that African-Americans reported having lost more income than Whites with the same

magnitude of injury (Hart et al., 2005). Thus, for African-Americans, a TBI of equal magnitude depletes more of their financial resources, placing a larger burden and more pressure to return to work for this group. There are also known racial disparities in health care utilization for African-Americans (Betancourt, Green, Carrillo, & Ananeh-Firempong, 2003), which, in the context of TBI, can lead to delay in, or lack of, treatment and increases in secondary injuries.

There may also be factors present in African-Americans prior to the injury that confer vulnerability to their memory performance. Unique stressors to African-Americans such as discrimination may make these individuals particularly vulnerable to lasting effects from a brain injury. In general, chronic stress has been linked to diminished plasticity in the hippocampus and amygdala, ultimately leading to decreased memory performance (Roozendaal, McEwen, & Chattarji, 2009; Wingenfeld & Wolf, 2014). Specific to African-Americans, research has shown that greater perceived discrimination can lead to poor performance on measures of memory (Barnes et al., 2012). Therefore baseline memory for African-Americans may be weaker than Whites from chronic stressors such as perceived discrimination. This vulnerability coupled with TBI may then be a reason why African-Americans with a head injury showed significantly worse performance on a memory measure than African-Americans without a TBI history.

In the current study, CVLT total recall was the only significant finding, despite inclusion of multiple other verbal memory measures, including CVLT learning slope and long and short delay free recall. Assuming this is a true finding, it could potentially suggest a specific area of memory that was affected by TBI and race. Memory is typically

conceived of having three components: encoding, storage, and retrieval (Tulving, Markowitsch, Craik, Habib, & Houle, 1996). CVLT total recall particularly examines the aspect of encoding, assessing how much information a person can take into their memory from a list of words across several trials (Lezak et al., 2004). Even if storage and retrieval are impaired, an individual conceivably could still perform within normal limits on CVLT total recall, whereas short and long delay free recall test storage and retrieval, as well as retroactive interference from List B, could reveal diminished performance (Lezak et al., 2004). Therefore since only CVLT total recall was significantly affected by the interaction of race and TBI history, it is possible that these associations reflect encoding differences.

Although CVLT learning slope, which is also measure of verbal encoding, was not significantly associated with TBI and race, it is important to note that CVLT total recall is considered a more valid measure. While learning slope shows patterns of learning and memory performance, individuals who perform poorly on all trials (e.g., scores of 1, 2, and 3 across trials) could have the same value as those who performed very well (e.g., scores of 14, 15, and 16 across trials). Additionally many individuals within the HANDLS sample have variable performance across trials which may significantly influence learning slope while only modestly affecting CVLT total recall.

In summary, the majority of neuropsychological outcomes were not significantly associated with a race by TBI history interaction. This may be attributable to true negative findings or may, in part, reflect methodological differences in our study as compared to prior research (e.g., individuals with a more distal history of TBI, mixed severity of TBI). However, we also found that African-Americans with a history of head

injury performed significantly worse on a measure of verbal memory than African-Americans without a head injury. While this is a novel finding in the literature, it is generally corroborated by both the TBI-specific and general neuropsychology literature. Additionally, there are several proposed reasons to suggest the vulnerability of African-Americans to TBI-verbal memory associations, including increased risk of dementia, greater severity of injury, fewer resources, and unique stressors.

Hypothesis 2: Interaction of Sex and TBI

Hypothesis 2 posited that sex would significantly moderate the relation of history of head injury to various neuropsychological outcomes such that women with a history of head injury would perform worse on neuropsychological tests than the other subgroups. This hypothesis was not supported, as men with a history of head injury performed significantly worse than men without a history of head injury on Digit Span Forward and Backward, tests of attention and working memory. TBI history was not associated significantly with performance on Digit Span Forward or Backward for women. For all other outcomes, the interaction between sex and TBI history did not predict neuropsychological performance.

There are several studies that have examined the interactive relations between sex and TBI history to neuropsychological outcomes. However, the majority of previous studies have shown that women with TBI performed worse than their male counterparts (Broshek et al., 2005; Covassin et al., 2007). To my knowledge, all previous studies investigating sex differences in cognition following a TBI have found one or two domains being associated, with no differences in all other domains (Bazarian et al., 2010;

Broshek et al., 2005; Covassin et al., 2007). However, all of these studies examined the acute effects of TBI on neurocognitive recovery, with no other study examining individuals more than a year after their injury.

While the large number of negative findings from my analyses are corroborated by similar, largely negative findings in the literature, there have also been significant results in the literature for tests of verbal memory (Donders & Hoffman, 2002), visual memory (Covassin et al., 2007), and reaction time (Broshek et al., 2005) that were not supported by my results. There are several methodological factors that may have prevented this study from detecting true sex by TBI history interactions for certain cognitive domains.

Similar to the relative lack of race by TBI interactions, the negative findings for sex and TBI history on many cognitive domains could be related to inclusion of individuals who had completed their post-TBI recovery and who had injuries of varying severity. Indeed, perhaps the most salient factor for potential sex differences could be TBI severity. The majority of studies analyzing sex differences in post-TBI cognitive function were done in college athletes who had oftentimes sustained a concussion or mild TBI (Broshek et al., 2005; Covassin et al., 2007; Donders & Hoffman, 2002), and almost all of which found that women had worse cognitive performance than men. However, prior literature has more generally shown that men have more severe injuries than women (Faul et al., 2010) which are, in turn, linked to greater cognitive impairments (Brenner, 2011). As such, it is possible that the majority of men in our study had more severe TBIs compared to the women. Furthermore, findings may have been different had we directly compared men and women with only a mild TBI.

Results of this study did reveal that men with a TBI history performed worse on tests of attention and working memory as compared to men without a TBI. Only a single study to my knowledge has noted worse performance (specifically verbal memory) in boys than girls with a TBI history (Donders & Hoffman, 2002). However, all prior studies of sex differences in post-TBI cognitive function only examined measures of memory and reaction time, without studying other cognitive domains such as attention or working memory. Prior neuropsychological research has demonstrated a female advantage in measures of attention (Estes, 1974; Smith, 1982; Yeudall & Fromm, 1986). In addition, prior literature suggests that attentional abilities may be particularly vulnerable to TBI (Brenner, 2011; Erlanger et al., 1999; Frencham et al., 2005; Mathias & Wheaton, 2007; Raskin et al., 1998). Thus, prior literature provides some support for the present finding that history of TBI was associated with poorer attention and working memory performance in men only.

While my two significant findings in attention and working memory may be spurious effects, they could also represent true differences in men and women who sustained a TBI. It is possible that men, rather than women, performed worse on the measures of attention and working memory due to the severity of injury. While this study did not have information about severity of head injury, the TBI literature shows that men are not only more likely to have a TBI, but that their TBI is likely to be greater in severity than women's (Faul et al., 2010). Given that attention is the most frequently affected domain of function in the TBI literature, especially in more severe injuries (Mathias & Wheaton, 2007), it may represent one of the domains that is most vulnerable to head injury. Thus, it is conceivable that the men in this study had more severe TBIs, therefore

making them more likely to have poorer performance in the vulnerable domains of attention and working memory.

Conversely women may have protective factors that men do not. Authors have speculated that women's hormone fluctuations during child-bearing years may influence their recovery from a TBI (Bazarian et al., 2010). However, whereas some authors posit that hormone fluctuations are damaging to TBI recovery (Bazarian et al., 2010), others propose it as neuroprotective to the female brain (Ratcliff et al., 2007). Preliminary findings from studies of other neurological conditions affecting the brain (e.g., multiple sclerosis) show that female sex hormones do indeed have the potential to exert anti-inflammatory and protective effects on brain tissue (Tomassini & Pozzilli, 2009). Therefore, if female sex hormones can protect brain tissue from damage associated with primary or secondary injuries, then hormones may serve as a mechanism for women to fare better cognitively following TBI than their male counterparts, who lack this level of protection.

Another possible explanation for the present findings related to attention and working memory is the disproportionate prevalence of Attention Deficit Hyperactivity Disorder (ADHD) - a premorbid condition more commonly found in men. ADHD, characterized by deficits in attention as well as hyperactivity, has prevalence rates nearly twice as high in men as they are in women (Polanczyk, Silva de Lima, Horta, Biederman, & Rohde, 2007). Additionally, individuals with ADHD are more likely to sustain a TBI, attributed to the hyperactivity and risk-taking behavior more commonly found in these individuals (Keenan, Hall, & Marshall, 2008). While a history of ADHD was not explicitly measured in our sample, it is possible that, amongst the individuals who had a

history of TBI, more men had a history of ADHD. Therefore, these individuals may having already had attention difficulties that were exacerbated by (and/or particularly vulnerable to) their TBI.

In sum, the interaction of sex and head injury was not associated with the majority of neuropsychological outcomes. This may be due to a variety of methodological considerations, with TBI severity of particular importance. However, we also found that men with a history of head injury performed significantly worse on measures of attention and working memory than those without. While our results are not supported by previous explorations of sex differences in cognition following TBI, there is evidence in the general neuropsychology and TBI literatures to corroborate these findings. There are also several possible mechanisms that may explain our results, including severity of injury, sex hormones, and prior ADHD.

Hypothesis 3: Interaction of Race, Sex, and TBI

Hypothesis 3 postulated that both sex and race would significantly moderate the relation of history of head injury to various neuropsychological outcomes such that African-American women with a history of head injury would perform worse on neuropsychological tests than the other subgroups. This hypothesis was not supported, as there were no significant interactions among sex, race, and history of TBI on any of the neuropsychological measures. To my knowledge this was the first study that specifically examined the three way interaction of sex, race and TBI with respect to neuropsychological outcomes. Previous studies have examined sex interactions alone, showing mostly that women with TBI have performed worse than men with TBI

(Broshek et al., 2005; Covassin et al., 2007), or have looked at race interactions alone, showing that African-Americans with TBI performed worse than Whites with TBI (Kennepohl et al., 2004).

There are several possible explanations for why I did not find significant interactions among sex, race, and TBI history. First, it is possible that the present study was underpowered for detection of a three-way interaction. Second, within the TBI population, race and sex generally affect different cognitive outcomes. Therefore, a true interaction between sex and race with TBI history may not exist. This is supported by my previous results from hypothesis 1 and 2, showing that race was associated with memory while sex was associated with attention and working memory among those with a history of TBI. This explanation is also corroborated within the general neuropsychological literature. Racial differences, while spanning many domains, are most frequently associated with the domains of memory (Norman et al., 2000), academic achievement (Kareken, 1995), and reasoning (Kaufman, McLean, & Reynolds, 1988), while sex differences exist predominately in language and visuospatial tasks (Schaie, 1994), further illustrating a lack of overlapping domains.

Some may argue, however, that many neuropsychological tests, while predominantly testing one domain, also involve components of other domains which overlap among known sex and race differences (e.g., verbal memory including a language component and reasoning involving a visuospatial component). In these instances, an alternative explanation may be warranted for the lack of sex by race by head injury interactions. Specifically, it is possible that the underlying mechanisms for sex and racial differences in post-TBI cognitive performance are not synergistic and instead

represent completely independent pathways. As discussed above, several disparate mechanisms have indeed been proposed for sex by TBI and race by TBI interactions.

Additionally there may have been other more important sociodemographic variables that interact with sex and/or race and TBI to impact cognition. While poverty status and education were both covariates in this study, they may have had important interactive effects with TBI (and the other moderator variables). Several studies in the neuropsychological literature that have found race differences in TBI-related cognitive outcomes suggest that these findings may be explained by the lack of adjustment for education or SES (Kareken, 1995).

In summary, there were no significant interactions among sex, race, and history of head injury on any neuropsychological outcomes. While this is the first study to examine this three-way interaction, both the TBI and neuropsychology literature do not corroborate the present lack of findings. Possible explanations may be that different domains of function are affected by sex and race (which are driven by different underlying mechanisms), that other sociodemographic variables that may have been better suited for exploring potential interactions, and/or a lack of power for our analyses.

Hypothesis 4: Biopsychosocial Mediation of Interactions

I proposed that the significant interactions between sex and/or race and history of head injury would be mediated by clusters of biological, psychological, social, and behavioral factors. This hypothesis was partially supported, as the race by TBI interaction on CVLT total recall was mediated by the cluster of psychological variables and the sex by TBI interaction on Digit Span Forward was mediated by the biological cluster.

However, the sex by TBI interaction on Digit Span Backward was not mediated by any of the clusters of variables examined. To my knowledge this is the first evidence to show a potential mediational role of any biopsychosocial explanatory factors pertaining to TBI-cognition associations, and highlights the importance of an integrative approach to understanding TBI and cognitive outcomes.

The relations among TBI, cognition, and the biopsychosocial and behavioral clusters examined here is likely complex. While the present study does show that a significant portion of the variance in select cognitive tests is accounted for by these clusters of variables, formal mediation analyses were not conducted (Baron & Kenny, 1986) and so the extent of this relation is unknown. According to the criteria we adopted in the present study (i.e., increase in AIC > 2 in addition to a notable decrease in the association of the TBI term of interest to a cognitive outcome measure), only the psychological cluster emerged as a candidate mediator of the relation between the race by TBI history interaction for CVLT Total Recall, and only the biological cluster was a potential mediator of the relation between TBI history and sex for Digit Span Forward. This approach has inherent limitations as it does not explicitly assess if a significant change in AIC accompanied by reduced significance of the interaction term (e.g., p changing from .001 to .04) is attributable to mediation per se. Additionally, our approach yields challenges regarding the order of entry of potential mediators; it does not adequately assess whether subsequent clusters of variables may also serve as partial mediators if it is has been entered after the TBI term of interest has already been "explained" (i.e., rendered non-significant) by a cluster of variables entered previously. In an attempt to explore this problem, results were also corroborated by examining each

individual cluster of variables in separate analyses. When using this approach to examine the clusters of biopsychosocial and behavioral variables, results were the same. As discussed further below, only the psychological cluster was a candidate mediator for the race, TBI, CVLT total recall association, and only the biological cluster emerged for the sex, TBI, and Digit Span Forward relation, whereas none were significant for Digit Span Backward. Additionally, since our analyses were cross-sectional analyses, the directionality of the mediation cannot be determined. For example, the neuropsychological domain could mediate the relation between the interaction and the biopsychosocial factor.

For the interactive relation of race and TBI history to memory performance, the biological, social, and behavioral domains explained a significant amount of the variance of CVLT total recall. However, the race by TBI interaction was not diminished suggesting that none of the clusters served as potential mediators. It is possible that other factors within the domains explored, but not explicitly examined in this study, could potentially mediate these relations. It is also possible that factors outside of these realms (e.g., access to health care) could mediate the interactive relation between race and TBI history on memory.

In contrast, results of the present analyses did show that the cluster of psychological variables was indeed a potential mediator of the interactive relation of race and TBI history to memory performance. While no study to my knowledge has looked at the relations of PTSD, depression, and anger to post-TBI cognitive function in African-Americans, related literature partially corroborates our finding. Lifetime prevalence of PTSD has been shown to be higher in African-American as compared to Hispanic,

Whites, and Asians (Roberts, Gilman, Breslau, Breslau, & Koenen, 2011). Additionally, PTSD in TBI has been shown to be negatively associated with learning and verbal memory (Horner & Hamner, 2002; Scott et al., 2015; Vasterling et al., 2012). Therefore it is possible that in our sample, African-Americans had greater PTSD symptomatology prior to or following their TBI, perhaps making them more vulnerable to any associated cognitive changes from the injury.

When examining post-TBI depression and anger in African-Americans the relation is more complex. Depressive symptomatology has been found to be greater in African-Americans following a TBI (Seel et al., 2003), but to my knowledge the specific emotion of anger has not been examined in African-Americans post-TBI. Given known links between greater depression (Hamilton et al., 2014; Turner, Capuano, Wilson, & Barnes, 2015) and anger (Barratt et al., 1997) and poorer memory, it is also possible that African-Americans in our study were more vulnerable to the psychological effects of the TBI, which then led to a change in their cognition. In sum, any of these psychological variables (PTSD symptomatology, depression, and trait anger) or combinations thereof may partially explain the interactive relations of race and TBI to CVLT total recall performance.

Similarly, when turning to the interaction of sex and TBI on attention, the psychological, social, and behavioral domains accounted for a significant amount of the variance of Digit Span Forward, but the relation between the interaction term and the outcome was not diminished. Other factors within the domains explored, but not explicitly examined in this study, or other domains not explored in this study could

potentially serve as alternative mediators of these relations. The biological cluster,
however, emerged as a potential mediator of the relation of sex and TBI to attention.

When considering the specific variables included in the biological cluster, it is important
to note that, on average, men have greater systolic blood pressure (Reckelhoff, 2001),
greater fasting plasma glucose (Faerch et al., 2010), and greater body mass indexes
(Eurostat, 2008; Li et al., 2006) than women. Greater values for each of these biological
variables have also been shown to predict worse cognitive performance in multiple
domains including attention (Blumenfeld, 2010; Cournot et al., 2006; Gunstad et al.,
2007; Kerwin et al., 2011; Knopman et al., 2001; Momjian-Mayor & Baron, 2005; Ryan
& Geckle, 2000). It is possible that men had greater values for each biological variable
prior to their injury, making them more vulnerable to TBI effects on cognition.
Alternatively, TBI has been shown to have significant negative relations with each of
these biological variables (Bouma & Muizelaar, 1992; Jourdan et al., 2012; Prins &
Hovda, 2009). Men may be more vulnerable to such biological changes post-TBI, which
may, in turn, negatively affect attention. Any of these individual biological variables
(blood pressure, fasting glucose, and body mass index) or their combinations may explain
the interactive relation of sex and TBI to Digit Span Forward.

For Digit Span Backward, despite all biopsychosocial and behavioral domains
explaining a significant amount of the variance of the outcome (according to AIC
criteria), the interactive relation of sex and TBI to working memory was not diminished
by entry of any of the clusters of variables. It is possible that variables outside of those
explored, such as severity of injury (Faul et al., 2010) or sex hormones (Ratcliff et al.,
2007), account for the relation between TBI, sex, and working memory. It is also possible

that other factors within the domains explored, but not explicitly examined in this study, significantly mediate these relations. Examples of these potential variables could include cerebral blood flow in the biological domain (Werner & Engelhard, 2007), discrimination in the psychological domain (Barnes et al., 2012), social network size in the social domain (Rauch & Ferry, 2001), and addiction in the behavioral domain (Ommaya et al., 1996).

In sum, the race by TBI interaction on memory was partially mediated by the psychological component and the sex by TBI interaction of attention was partially mediated by the biological component. Additionally the pathways for these relations are complex and the directionality could be reversed due to the nature of the cross-sectional analyses. While no previous studies have investigated these mediating relations, there are several disparate bodies of literate that partially corroborate these findings and provide preliminary evidence for future research and clinical implications (discussed below). However, the sex by TBI interaction on working memory was not mediated by any biopsychosocial or behavioral domain, and the race by TBI interaction on memory and the sex by TBI interaction of attention were not mediated by any of the other domains. It may be that these relations are mediated by variables from other domains not explored or variables within the domains measures but not included in the study.

Limitations

This study had several limitations. First, this was a sample of African-Americans and Whites living in Baltimore. It is possible that samples of individuals from different sociodemographic backgrounds or different geographic locations may have been

differentially affected by TBI and the candidate mediating factors. The current sample

size also limited the statistical power of analyses and did not allow detection of any small

effects that might be present. The sample size also limited the types of analyses

conducted, preventing exploration of the moderating effects of other sociodemographic

variables such as poverty status, age, and education. The moderating effects were also

only explored in a single interpretation (TBI vs. non-TBI) rather than exploring from

alternative stances (e.g., African-Americans vs. Whites). Also, examining clusters of

mediating factors limited interpretation of results, and may have masked significant

mediation for individual factors. Another potential limitation was that clusters of

individual measures were utilized rather than component scores. Importantly, traditional

mediation analyses were not conducted, and the criteria for significant mediation were

not well established or outlined in the study (e.g., unclear magnitude of decrease in

association of TBI term of interest to cognitive outcome), which also limits the

interpretation of results as discussed previously. The reliability of MacArthur's

Instrumental Support Questionnaire was also slightly below the acceptable range for our

sample. Also, the potential mediating clusters chosen for inclusion in these analyses may

not have represented the most significant factors. The data obtained were cross-sectional,

limiting any temporal inferences that could be drawn from this study. Analyses only

included individuals who self-reported a TBI rather than using medical records or a

formal questionnaire (e.g., Picard, Scarisbrick, & Paluck, 1991). Individuals could be

inaccurate in their self-reported history. Also, there was limited knowledge of specific

characteristics of participants' TBI history; those who self-reported TBI likely constituted

a heterogeneous group in regards to their severity of injury, length of loss of

consciousness, area of injury, and time since injury, which could confound our results. Finally, participants who sustained a TBI were also relatively distal from their injury, thus precluding understanding of more proximal recovery from TBI. This however is also a strength of our study though as it is the first to my knowledge to investigate the potential long-term effects of TBI on individuals.

Strengths

Despite the numerous limitations of the current study, there are also several strengths. Our sample is unique, being relatively diverse in sociodemographic variables, which allowed both moderation analyses addressing potential subgroup difference and covariation of other important factors. Additionally this is a community-based sample, allowing these results to represent individuals who are not explicitly seen in a medical setting. The study was also unique by utilizing age-matching of TBI and non-TBI individuals, thus controlling for age. This study also utilized multiple neuropsychological outcomes that represented most major cognitive domains. A variety of mediating variables were explored that typically are not available in many studies. Finally, this study is the first of its kind, to my knowledge, giving the field a novel area of research. This study can serve as a foundation for others to continue exploring biopsychosocial and behavioral factors that may impact TBI and recovery. The study also provides a foundation for implementing more holistic approaches to TBI recovery in clinical practice.

Implications and Future Directions

The current study represents the first steps in fully understanding the moderating and mediating factors of TBI and cognition. Our findings highlight that certain demographic groups may be particularly vulnerable to the cognitive effects of TBI. Prevention and intervention should be targeted towards African-Americans and men in helping minimize any long term cognitive effects from a TBI. Our findings also show that interventions should be multifocal across the biopsychosocial and behavioral realms, with particular importance of psychological factors in African-Americans and biological factors in men. Because the effect sizes were relatively small in this study, they suggest that interventions may confer population level significance rather than for individuals.

To further understand these complex interactions, this study should be expanded to separately examine different levels of severity of TBI. Additionally, the proximal effects of TBI should be assessed including whether select mediating factors are more likely to negatively influence the acute cognitive recovery process and the length of time for recovery. Further exploration of the interaction of different moderating sociodemographic factors with TBI should also be explored, including age, poverty status, and education. Future studies should also utilize neuroimaging measures such as functional magnetic resonance imaging and measures of cerebral perfusion to understand changing in brain functioning that may correlate with neuropsychological test results. Other potential mediating factors should also be explored individually to understand how they impact TBI and cognition.

Conclusion

Results of the present study represent an important step for the field in understanding the complex relation between the effect of TBI on cognition in different sociodemographic groups, and what factors may help or hinder these relations. Our study showed significant moderating effects of TBI and race on a measure of verbal memory and interacting effects of TBI and sex on measures of attention and working memory that were partially mediated by psychological clusters and biological clusters respectively. These findings suggest not only that TBI has longstanding cognitive effects on different subgroups, but also that these effects can be explained by different biopsychosocial factors. These biopsychosocial factors should be an important focus in clinical practice, particularly for African-Americans and men, to aid in the recovery of cognitive deficits.

Table 1

Sample Characteristics

	With Head Injury				Without Head Injury			
	Mean	SD	Percent	Range	Mean	SD	Percent	Range
Age (Years)	47.60	8.30		30-64	47.04	8.29		30-64
% Male			62				61	
% White			57				63	
% Above 125% Poverty Line			50				36	
Education (years)	12.18	2.98		1-21	12.52	3.04		2-21
% Current Alcohol Drinker			66				62.5	
% Current Smoker			57.4				48.2	
Substance Use Count	0.34	0.69		0-3	0.25	0.60		0-3
Depression Symptomatology	16.84	11.53		0-59	13.71	10.35		0-52
PTSD Symptomatology	32.79	15.55		17-82	28.33	12.27		17-77
Trait Anger	10.64	6.36		0-26	10.22	6.48		0-28
Systolic Blood Pressure	120.63	16.64		80-186	119.70	17.76		83-194.5
Fasting Glucose	99.18	28.20		42-306	103.38	41.28		56-430
Body Mass Index	28.68	6.83		16.9-55.0	29.34	7.52		16.41-59.94
Emotional Support	2.10	0.63		0.5-3.0	2.28	0.67		0.5-3.0
Instrumental Support	1.44	0.66		0-3.0	1.53	0.70		0-3.0
Scores of Neuropsychological Test								
Benton Visual Retention Test (total errors)	6.16	4.93		0-23	5.89	5.04		0-30
CVLT List A Total	21.26	10.04		0-45	21.08	10.78		0-43
CVLT Learning Slope	1.64	1.07		-2.5-4.5	1.63	1.09		-2.5-4.5
CVLT Short Delay	7.00	2.93		1-16	7.18	3.18		1-15
CVLT Long Delay	7.13	2.83		1-15	7.36	3.25		1-16
Digit Span Forward (total score)	7.01	2.85		0-14	6.95	2.74		0-14
Digit Span Backward (total score)	5.40	2.67		0-13	5.36	2.64		0-14
Trail Making Test, Part A (time)	45.48	72.62		12-600	36.46	29.78		11-600
Trail Making Test, Part B (time)	160.83	164.25		30-600	146.77	153.95		25-600
Category Fluency (total score)	19.05	5.15		9-39	19.26	5.43		7-38

	Men			Women		
Proximity from Head Injury for African-Americans (in years)	23.39	14.72	0-54	22.38	15.66	0-49
Proximity from Head Injury for Whites (in years)	20.78	14.12	0-53	17.49	14.00	0-53
Number of Head Injuries for African-Americans	1.09	0.32	1-3	1	0.00	1-1
Number of Head Injuries for Whites	1.09	0.34	1-3	1.21	0.93	1-6

Table 2. *Reliability of psychological and social measures*

Scale	Cronbach's Alpha
Center for Epidemiological Studies: Depression Scale	.784
Post-Traumatic Stress Disorder Checklist	.948
Buss-Perry Aggression Questionnaire Anger Subscale	.752
MacArthur Emotional Support Questionnaire	.745
MacArthur Instrumental Support Questionnaire	.635

Table 3. *Factor loadings of a principal components analysis for biological mediators*

Biological Variable	Biological Factor
Systolic Blood Pressure	.669
Body Mass Index	.731
Fasting Glucose Level	.652

Table 4. *Factor loadings of a principal components analysis for psychological mediators*

Psychological Variable	Psychological Factor
Depression Symptomatology	.861
Post-Traumatic Stress Disorder Symptomatology	.880
Trait Anger	.700

Table 5. *Factor loadings of a principal components analysis for social mediators*

Social Variable	Social Factor
Emotional Support	.836
Instrumental Support	-.836

Table 6. *Factor loadings of a principal components analysis for behavioral mediators*

Behavioral Variable	Behavioral Factor
Alcohol Use	.650
Cigarette Use	.683
Drug Count	.750

Table 7.

Summary of Mixed-Effect Model Analysis for Sex, Race, Head Injury, and their Interactions Predicting California Verbal Learning Test List A Total

	Final Model			
Variable	F	*Numerator df*	Denominator df	Akaike Information Criterion
Race	5.628	1	697	5240.043
Sex	16.815*	1	697	
Poverty Status	0.610	1	697	
Education	38.586**	1	697	
Head Injury	2.608	1	697	
Sex X Head Injury	1.988	1	695	5231.219
Race X Head Injury	6.161*	1	695	
Race X Sex	0.966	1	693	5224.947
Head Injury X Sex X Race	0.012	1	693	

 * p < .05
**p < .01

Table 8.

Summary of Mixed-Effect Model Analysis for Sex, Race, Head Injury, and their Interactions Predicting California Verbal Learning Test Learning Slope

Variable	Final Model			
	F	*Numerator df*	Denominator df	Akaike Information Criterion
Race	0.089	1	531.688	1650.548
Sex	0.989	1	260.240	
Poverty Status	0.044	1	538.563	
Education	5.395*	1	526.915	
Head Injury	0.321	1	406.002	
Sex X Head Injury	0.171	1	406.639	1653.058
Race X Head Injury	0.075	1	535.971	
Race X Sex	1.190	1	534.294	1653.091
Head Injury X Sex X Race	0.079	1	532.390	

 * p < .05
**p < .01

Table 9.
Summary of Mixed-Effect Model Analysis for Sex, Race, Head Injury, and their Interactions Predicting California Verbal Learning Test Short Delay Free Recall

	Final Model			
Variable	F	*Numerator df*	Denominator df	Akaike Information Criterion
Race	15.461**	1	510.178	2676.666
Sex	14.949**	1	261.567	
Poverty Status	0.023	1	529.511	
Education	36.788**	1	505.947	
Head Injury	0.095	1	384.962	
Sex X Head Injury	0.119	1	383.369	2674.697
Race X Head Injury	0.628	1	527.872	
Race X Sex	3.626	1	517.881	2665458
Head Injury X Sex X Race	0.126	1	526.601	

 * p < .05
**p < .01

Table 10.

Summary of Mixed-Effect Model Analysis for Sex, Race, Head Injury, and their Interactions Predicting California Verbal Learning Test Long Delay Free Recall

Variable	Final Model			
	F	*Numerator df*	Denominator df	Akaike Information Criterion
Race	22.548**	1	515.145	2660.377
Sex	13.623**	1	255.736	
Poverty Status	0.034	1	524.921	
Education	24.438**	1	506.028	
Head Injury	0.013	1	389.761	
Sex X Head Injury	0.000	1	387.901	2658.566
Race X Head Injury	0.525	1	522.981	
Race X Sex	1.500	1	517.626	2651.123
Head Injury X Sex X Race	0.646	1	520.901	

 * p < .05
**p < .01

Table 11.
Summary of Mixed-Effect Model Analysis for Sex, Race, Head Injury, and their Interactions Predicting Benton Visual Retention Test

| Variable | Final Model | | | |
	F	*Numerator df*	Denominator df	Akaike Information Criterion
Race	0.049	1	689.597	4226.502
Sex	2.255	1	283.578	
Poverty Status	0.000	1	696.123	
Education	40.533**	1	670.423	
Head Injury	0.025	1	482.780	
Sex X Head Injury	1.676	1	486.020	4220.345
Race X Head Injury	0.583	1	693.993	
Race X Sex	0.063	1	691.949	4216.883
Head Injury X Sex X Race	0.677	1	692.727	

 * p < .05
**p < .01

Table 12.
Summary of Mixed-Effect Model Analysis for Sex, Race, Head Injury, and their Interactions Predicting Trail Making Test, Part A

Variable	Final Model			
	F	*Numerator df*	Denominator df	Akaike Information Criterion
Race	7.943**	1	694.891	7446.559
Sex	3.318	1	295.749	
Poverty Status	9.778**	1	696.900	
Education	0.928	1	681.687	
Head Injury	2.607	1	498.887	
Sex X Head Injury	0.040	1	504.425	7432.097
Race X Head Injury	2.417	1	693.651	
Race X Sex	0.268	1	692.947	7418.516
Head Injury X Sex X Race	0.096	1	689.964	

 * p < .05
**p < .01

Table 13.

Summary of Mixed-Effect Model Analysis for Sex, Race, Head Injury, and their Interactions Predicting Digit Span Forward

Variable	Final Model			
	F	*Numerator df*	Denominator df	Akaike Information Criterion
Race	8.716**	1	685.978	3403.956
Sex	0.003	1	493.852	
Poverty Status	0.119	1	693.982	
Education	13.803**	1	664.647	
Head Injury	1.174	1	476.084	
Sex X Head Injury	4.045*	1	480.902	3402.775
Race X Head Injury	1.010	1	694.755	
Race X Sex	0.360	1	690.909	3400.673
Head Injury X Sex X Race	0.239	1	692.990	

  * p < .05
**p < .01

Table 14.

Summary of Mixed-Effect Model Analysis for Sex, Race, Head Injury, and their Interactions Predicting Digit Span Backward

Variable	*F*	*Numerator df*	Denominator df	Akaike Information Criterion
		Final Model		
Race	24.574**	1	680.991	3311.375
Sex	1.535	1	485.998	
Poverty Status	1.129	1	691.298	
Education	28.948**	1	657.244	
Head Injury	1.964	1	472.515	
Sex X Head Injury	5.952*	1	478.600	3311.322
Race X Head Injury	0.013	1	693.580	
Race X Sex	0.035	1	688.494	3309.797
Head Injury X Sex X Race	0.004	1	692.646	

 * p < .05
**p < .01

Table 15.
Summary of Mixed-Effect Model Analysis for Sex, Race, Head Injury, and their Interactions Predicting Category Fluency

	Final Model			
Variable	F	*Numerator df*	Denominator df	Akaike Information Criterion
Race	11.518**	1	672.685	4275.959
Sex	2.976	1	260.678	
Poverty Status	0.008	1	685.986	
Education	59.075**	1	647.134	
Head Injury	0.032	1	476.973	
Sex X Head Injury	0.045	1	480.962	4273.121
Race X Head Injury	0.039	1	689.169	
Race X Sex	0.690	1	681.994	4268.216
Head Injury X Sex X Race	0.155	1	689.459	

 * p < .05
**p < .01

Table 16.

Summary of Mixed-Effect Model Analysis for Sex, Race, Head Injury, and their Interactions Predicting Trail Making Test, Part B

	Final Model			
Variable	*F*	*Numerator df*	Denominator df	Akaike Information Criterion
Race	37.420**	1	656.170	1404.827
Sex	1.654	1	275.205	
Poverty Status	6.225*	1	659.784	
Education	69.271**	1	640.766	
Head Injury	0.415	1	470.310	
Sex X Head Injury	0.313	1	468.311	1409.576
Race X Head Injury	0.001	1	658.102	
Race X Sex	0.007	1	656.993	1411.886
Head Injury X Sex X Race	0.821	1	654.136	

 * p < .05
**p < .01

Table 17.
Summary of Mixed-Effect Model Analysis for Sex, Race, Head Injury, and their Interactions Predicting California
Verbal Learning Test List A Total and the Potential Behavioral, Psychological, Biological, and Social Mediators

	Variable	F	Numerator df	Denominator df	Akaike Information Criterion	Δ Akaike Information Criterion
			Final Model			
Step 1	Race	6.008	1	697	5249.411	-
	Sex	17.168**	1	697		
	Poverty Status	0716	1	697		
	Education	28.972**	1	697		
	Head Injury	2.626	1	697		
	Race X Head Injury	6.902**	1	697		
Step 2	Race X Head Injury	6.800**	1	686	5192.774	-56.637
	Behavioral Component	0.914	1	686		
Step 3	Race X Head Injury	2.968	1	496	3791.984	-1400.79
	Psychological Component	0.932	1	496		
Step 4	Race X Head Injury	1.686	1	443	3497.695	-294.289
	Biological Component	0.726	1	443		
Step 5	Race X Head Injury	2.445	1	366	2949.268	-548.427
	Social Component	1.084	1	366		

 * $p < .05$
** $p < .01$

Table 18.

Summary of Mixed-Effect Model Analysis for Sex, Race, Head Injury, and their Interactions Predicting Digit Span Forward and the Potential Behavioral, Psychological, Biological, and Social Mediators

	Variable	*F*	*Numerator df*	Denominator df	Akaike Information Criterion	Δ Akaike Information Criterion
Step 1	Race	8.720**	1	687.454	3403.792	-
	Sex	0.003	1	494.537		
	Poverty Status	0.122	1	694.972		
	Education	13.816**	1	665.669		
	Head Injury	1.175	1	477.502		
	Sex X Head Injury	4.047*	1	482.226		
Step 2	Sex X Head Injury	4.357*	1	476.909	3378.04	-25.752
	Behavioral Component	1.117	1	681.388		
Step 3	Sex X Head Injury	4.136*	1	374.153	2519.158	-858.882
	Psychological Component	1.076	1	489.099		
Step 4	Sex X Head Injury	3.340	1	360.259	2351.804	-167.354
	Biological Component	0.920	1	438.870		
Step 5	Sex X Head Injury	2.252	1	366.000	1989.130	-362.674
	Social Component	1.074	1	366.000		

 * p < .05
**p < .01

Table 19.
Summary of Mixed-Effect Model Analysis for Sex, Race, Head Injury, and their Interactions Predicting Digit Span
Backwards and the Potential Behavioral, Psychological, Biological, and Social Mediators

	Variable	*F*	*Numerator df*	Denominator df	Akaike Information Criterion	Δ Akaike Information Criterion
				Final Model		
Step 1	Race	24.898**	1	684.114	3315.935	-
	Sex	1.628	1	490.409		
	Poverty Status	1.033	1	693.169		
	Education	29.282**	1	660.737		
	Head Injury	1.966	1	476.611		
	Sex X Head Injury	6.128*	1	481.168*		
Step 2	Sex X Head Injury	7.589**	1	474.814	3280.010	-35.925
	Behavioral Component	2.221*	1	681.789		
Step 3	Sex X Head Injury	6.728**	1	375.311	2452.400	-827.610
	Psychological Component	0.732	1	494.150		
Step 4	Sex X Head Injury	6.762**	1	364.133	2296.237	-156.163
	Biological Component	0.830	1	441.605		
Step 5	Sex X Head Injury	4.058**	1	300.677	1958.091	-338.146
	Social Component	1.280	1	362.773		

 * p < .05
**p < .01

Figure 1.

Distribution of traumatic brain injury (TBI) proximity split by race and sex

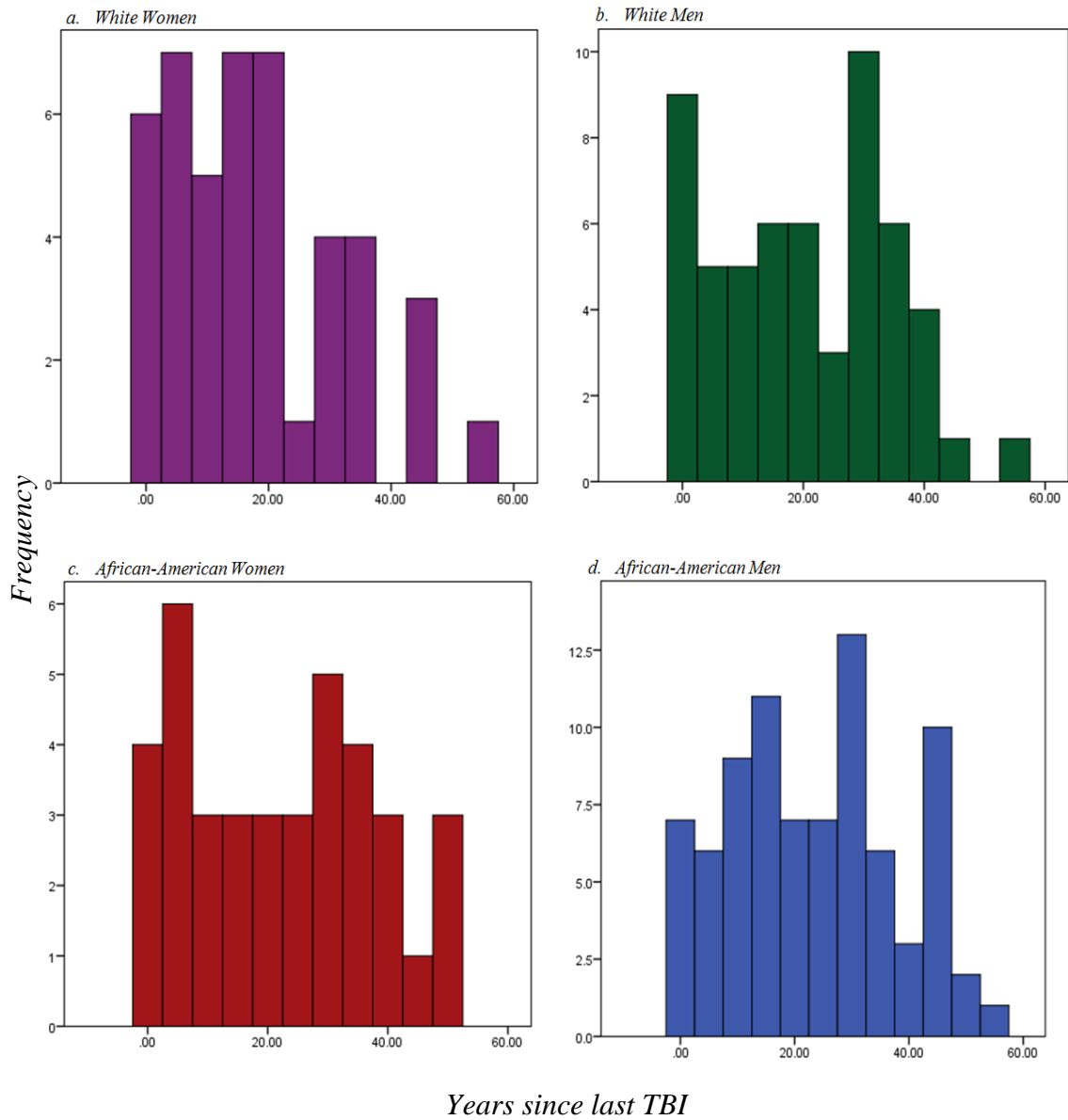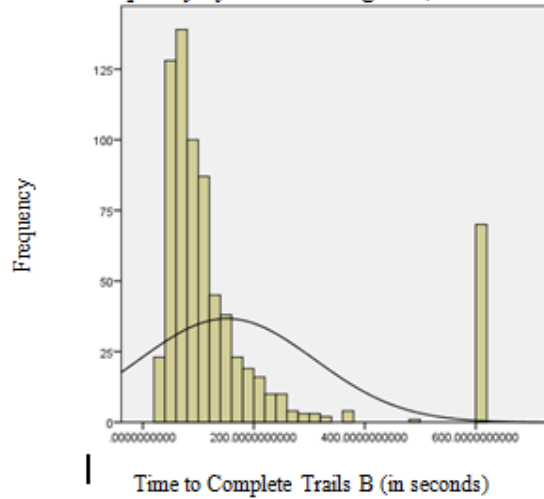*Frequency*

Years since last TBI

Figure 2.

Frequency and distribution curves of Trail Making Test, Part B Before and After Natural Log Transformation

Frequency of Trail Making Test, Part B time to complete

Time to Complete Trails B (in seconds)

Frequency of Log of Trail Making Test, Part B time to complete

Natural Log of Time to Complete Trails B (In ln seconds)
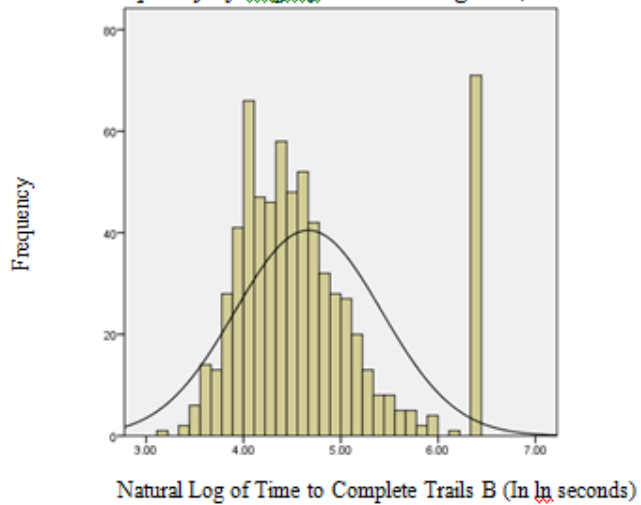
Figure 3.
The Interaction Graph of Race and Head Injury with California Verbal Learning Test (CVLT) List A Total
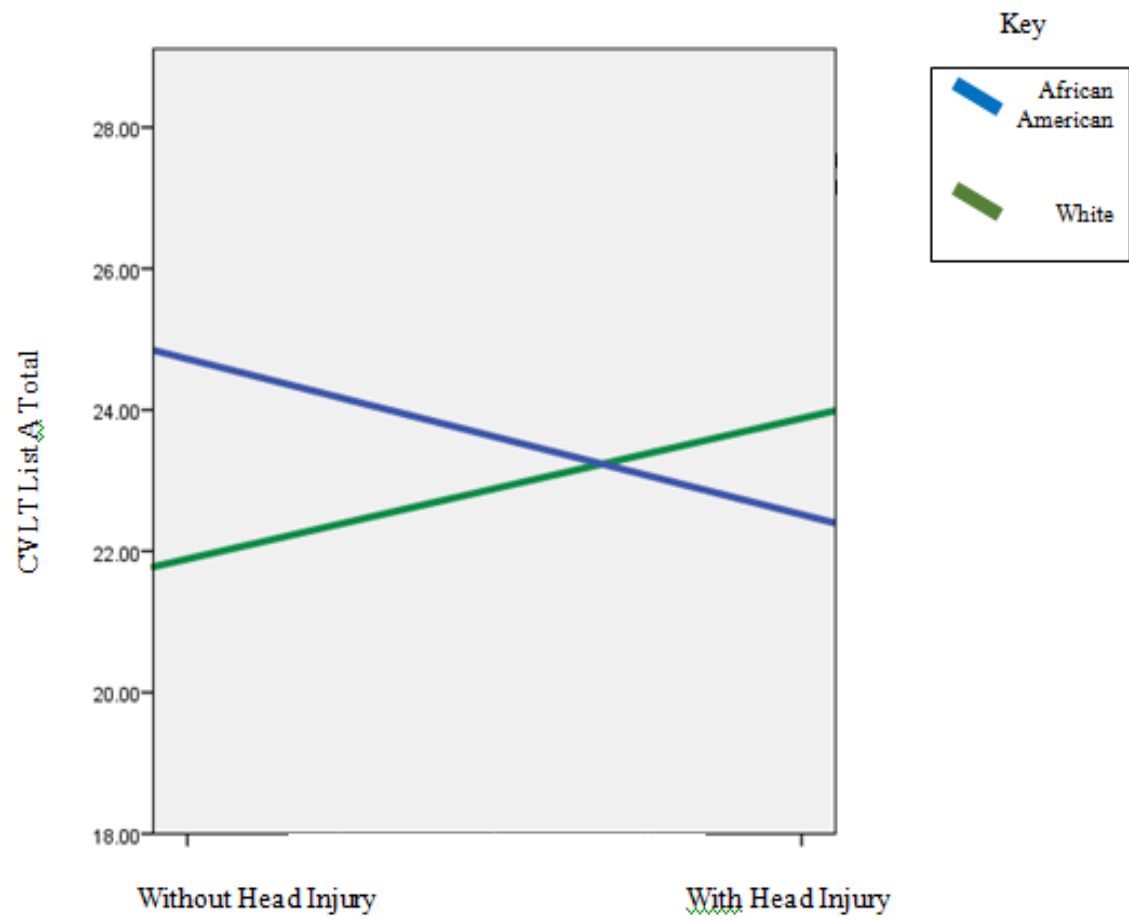
Figure 4.
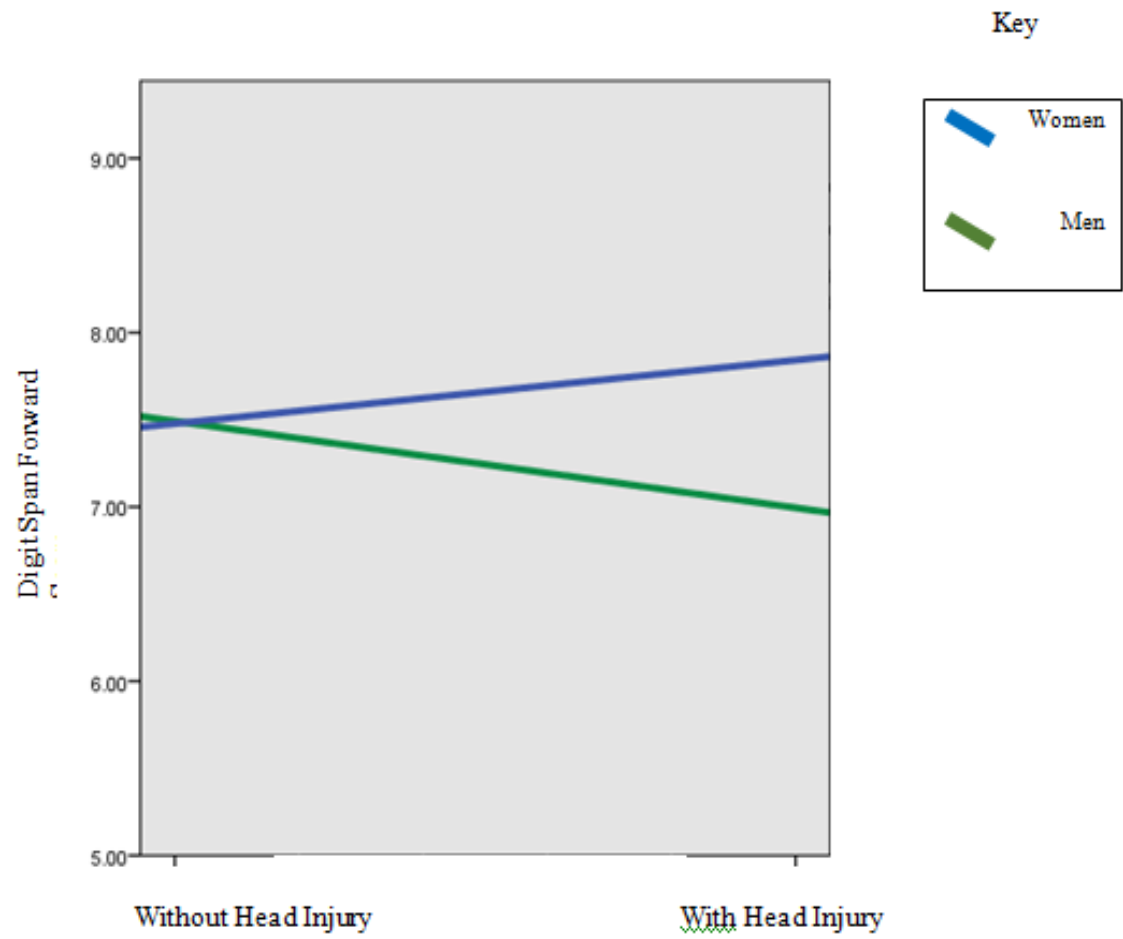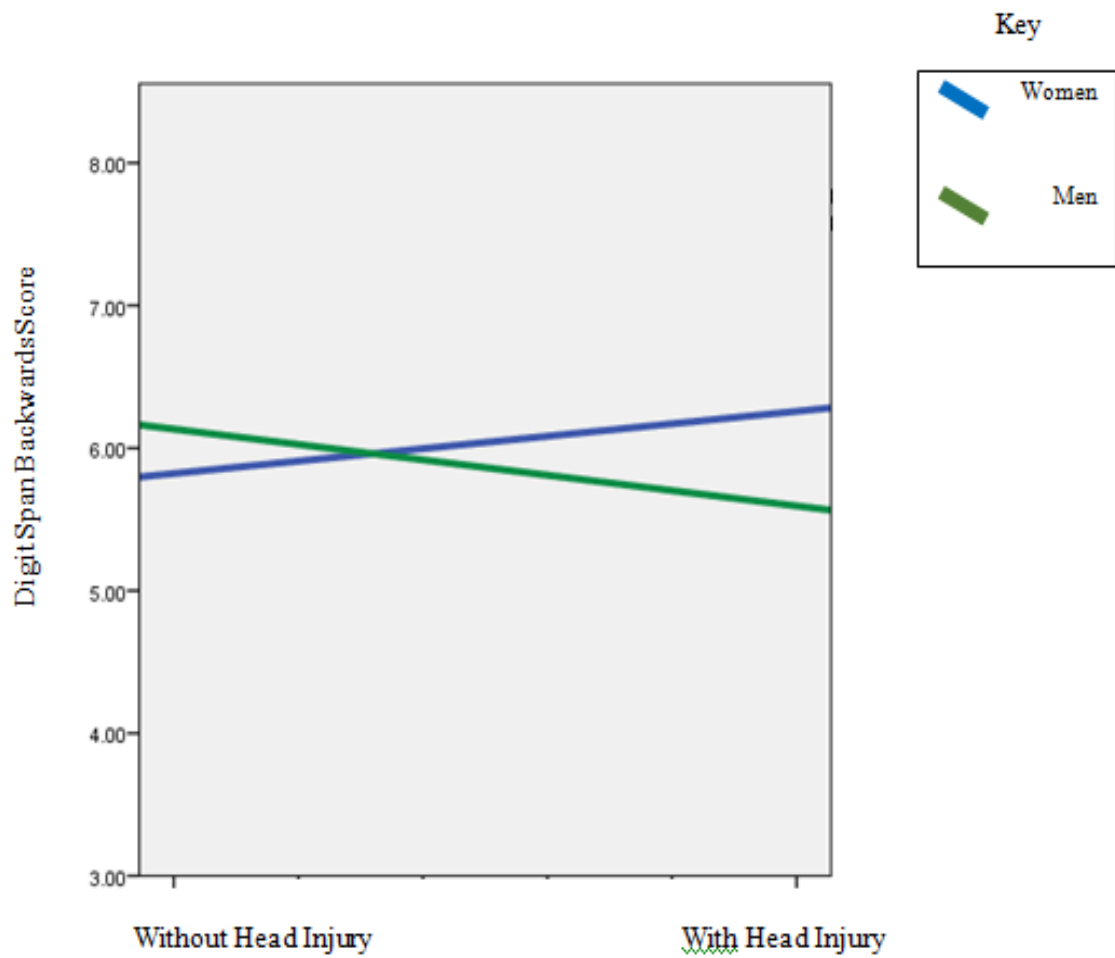The Interaction Graph of Race and Head Injury with Digit Span Forward Score

Figure 5.
The Interaction Graph of Race and Head Injury with Digit Span Backwards Score

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