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An Examination of Traumatic Brain Injury and Genes for Neurotrophins and Apolipoprotein E in Predicting Cognitive Function in Older Adults: The Cache County Study

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AN EXAMINATION OF TRAUMATIC BRAIN INJURY AND GENES FOR NEUROTROPHINS AND APOLIPOPROTEIN E IN PREDICTING COGNITIVE FUNCTIONING IN OLDER ADULTS: THE CACHE COUNTY STUDY

by

Mikaela A. Drewel

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ABSTRACT

An Examination of Traumatic Brain Injury and Genes for Neurotrophins and Apolipoprotein E in Predicting Cognitive Functioning in Older Adults: The Cache County Study

by

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Sixty-nine million individuals globally (Dewan et al., 2018) experience a traumatic brain injury (TBI) in their lifetime. TBI disrupts neurological mechanisms that underlie cognition (Xiong et al., 2014) and intrinsic neuronal connectivity networks (Sharp et al., 2014). Recovery and long-term effects of TBI may be impacted by genetic factors such as the polymorphic Apolipoprotein E (APOE) gene as well as brain-derived neurotrophic factor (BDNF) and nerve-growth factor (NGF) related genes, which appear to play a role in the brain's response to injury. This study examines the effects of history of TBI on late-life cognitive decline, exploring important characteristics of TBI as well as moderating effects of sex, APOE genotype and selected genes/single-nucleotide polymorphisms (SNPs) related to BDNF and its receptors. Using extant data from the Cache County Study on Memory in Aging (CCSMA), results revealed that a history of two or more TBIs was associated with lower scores on verbal list learning than those without a TBI history. Unexpectedly, females with a history of severe TBI scored higher

on verbal recognition recall tasks compared to males with no TBI. The association of TBI history and cognitive functioning was moderated by APOE ε4 and BDNF-related SNPs. In particular, females with at least one APOE ε4 allele and two or more TBIs scored lower on global cognitive and verbal learning tasks compared to males with no TBI lacking the APOE ε4 allele. The SNP for BDNF receptor TrkB (rs2289656) moderated the association of TBI history on verbal recognition memory such that individuals with severe TBI with at least one minor allele for the TrkB (rs2289656) SNP scored lower than individuals lacking a history of TBI and the minor allele. These results underscore the importance of examining individual differences in sex and APOE and neurotrophin genes in studying long-term consequences of TBI. Lifestyle factors such as physical activity and diet, that promote BDNF neurotrophin signaling may offer a target for intervention to mitigate the effects of TBI on late-life cognitive decline. Future research is needed to examine this and other possible interventions to mitigate the effects of TBI on late-life cognitive decline.

(159 pages)

PUBLIC ABSTRACT

An Examination of Traumatic Brain Injury and Genes for Neurotrophins and Apolipoprotein E in Predicting Cognitive Functioning in Older Adults: The Cache County Study

Mikaela Drewel

Recovery from a traumatic brain injury (TBI) is influenced by a wide array of factors including age at incidence, number, and severity as well as genetic factors, some of which exhibit sex-dependent effects. This study examines how TBI history influences rate of cognitive decline in older adults, exploring the characteristics of TBI (e.g., number, severity and timing) as predictors and interactions of TBI history with genetic variants suspected to play a role in brain health and late-life cognitive functioning. These genes include the Apolipoprotein E (APOE) as well as brain derived neurotrophic factor (BDNF) and its receptors. This study analyzed extant data from the Cache County Study on Memory in Aging (CCSMA), a longitudinal, population-based study of over 5,000 adults, aged 65 years and older.

A history of two or more TBIs was associated with lower scores on verbal list learning. Unexpectantly, females with a history of severe TBI scored higher on a test of verbal recognition recall compared to males with no history of TBI. Furthermore, females with at least one APOE ε4 allele and two or more TBIs scored lower on global cognitive and verbal learning tasks compared to males lacking a history of TBI and the APOE ε4 allele. BDNF receptor TrkB (rs2289656) moderated the association of TBI severity on recognition tasks such that individuals with a history of severe TBI and at least one minor

allele for receptor TrkB (rs2289656) scored lower than individuals lacking a history of TBI and the minor allele. Overall, this study suggests that the course of late-life cognitive decline is associated with history of TBI and the associations examining severity or number of TBI may depend on sex and genotype. Although gene modification is not a viable intervention, one may consider how to enhance BDNF activity to reduce the deleterious effects of TBI on late-life cognition. For example, physical activity and diet are lifestyle factors that promote BDNF activity and may offer a target for intervention. Future research is needed to examine this and other possible interventions to mitigate the effects of TBI on late-life cognitive decline.

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CONTENTS

Page

LIST OF TABLES

Page

LIST OF FIGURES

Page

CHAPTER I

Introduction

The Centers for Disease Control and Prevention (CDC) defines a traumatic brain injury (TBI) as "a disruption in the normal function of the brain that can be caused by a bump, blow, or jolt to the head, or penetrating head injury" (Centers for Disease Control and Prevention [CDC], 2021). Clinical signs of disruption to normal brain function can present in several different forms and may include alteration in one's mental state at the time of injury, neurological deficits, loss of memory for events before or after injury, and/or any period of decreased consciousness (Menon et al., 2010). The most common causes of TBI are unintentional falls and vehicle crashes, making up to 49.1% and 24.5% of all TBI-related hospitalizations in 2017 in the United States (U.S.), respectively (Peterson et al., 2021).

In 2014, 2.87 million TBI-related emergency department visits, hospitalizations, and deaths occurred in the U.S. (Peterson et al., 2019). However, this number is considered to be a gross underestimate due to the inability to account for individuals who did not seek medical attention for their injury or who sought care at an outpatient, private office or a federal facility (Peterson et al., 2019). Additionally, the number of TBIs are expected to continually increase in the U.S. Results from a surveillance report conducted by the CDC showed that TBI-related emergency department visits between 2006 and 2014 increased by 54%. For the majority of causes, TBI-related emergency department visits increased by 80% as a result of falls; 58% as a result of being struck by or against an object; 60% as a result of intentional self-harm, 18% as a result of assault, and 24% as the result of motor vehicle accidents (Peterson et al., 2019).

Although everyone is susceptible to a TBI, the risk varies by demographic factors. For instance, TBI risk is highest among young children aged 0-4 years, followed by adolescents aged 15-19 years, and adults aged 75 years and older, with hospitalization rates being highest for those over the age of 75 (Faul et al., 2010). The leading cause of TBI-related injuries for ages 0-4 years as well as those 75 years and older are falls (Peterson et al., 2019). However, TBI-related injuries that occur in individuals aged less than 19 years are generally more likely to be associated with participation in bicycling, football, playground activities, basketball, and soccer (Gilchrist et al., 2011). In addition to one's age, TBI risk is also influenced by an individual's sex. In a meta-analysis by Frost and colleagues, a summary odds ratio from twelve studies showed that biological men are 2.22 times more likely to experience a TBI than biological women (Frost et al., 2013). However, it should be cautioned that the numbers of women with TBI may be underrepresented in these studies due to the cause of the primary injury. Women are more likely to obtain a TBI-related injury from assault or violence in interpersonal relationships (and thus less likely to report the injury), whereas men are more likely to receive work-related injuries from falls or vehicle crashes (Gupte et al., 2019a).

While TBIs are associated with a variety of short-term effects, there may be lasting long-term effects as well. It is estimated that approximately 3.2 million individuals in the U.S. are living with a TBI-related disability including 145,000 individuals between the ages of 0-19 years and 775,000 individuals older than age 75 (Zaloshnja et al., 2008). Individuals with a history of TBI also are at greater risk for delayed consequences such as the development of psychological or neurological disorders later in life (Perry et al., 2016).

Research shows that even a single TBI disrupts neurobiological mechanisms that underlie cognition (Xiong et al., 2014). In a review by Sharp et al. (2014), it is suggested that diffuse axonal injury accompanying TBI negatively impacts the functioning of intrinsic connectivity networks resulting in decreased cognitive abilities. In addition to these neurological changes, the review also suggests that TBI can trigger the misfolding of various proteins along damaged white matter tracts, thus contributing to earlier onset of neurodegenerative processes. The effects of these neurobiological changes may become more prominent later in life with the onset of aging processes in the brain. Beginning around the age of 50, the natural aging process in the brain results in increased synaptic pruning of grey matter, especially in the frontal lobe, followed by changes in white matter (Masliah et al., 2006; Raz & Rodrigue, 2006; Salat et al., 1999). Current research suggests a prolonged and intricate pathophysiology of TBI that likely interacts and influences earlier onset of age-related cognitive decline and pathological processes such as the development of neurodegenerative diseases, such as Alzheimer's disease (AD) (Sharp et al., 2014).

Recovery from TBI may be impacted by genetic factors. The polymorphic Apolipoprotein E (APOE) gene is located on chromosome 19 and is believed to be involved in maintaining structural integrity of neurons, transporting lipids, and assisting with neuronal transmission amongst its other functions within the human brain (Nathoo et al., 2003). It has been hypothesized that the ε4 allele of APOE may play a role in neural recovery following TBI through the inhibition of neurite growth, release of pro-inflammatory mediators, and the alteration of the blood brain barrier (Blanchard et al., 2022; Ferguson et al., 2010; Mahley & Huang, 2012; Main et al., 2018). However, the

results of systematic and meta-analyses exploring the role of APOE ε4 in cognitive and functional recovery after TBI are inconclusive (Lawrence et al., 2015; McFadyen et al., 2021). Follow-up times for included studies vary (between hours after injury to 24 months) with very few studies examining the effects of APOE ε4 on long term cognitive outcomes. This exposes a gap in the literature as APOE ε4 has been identified as a risk factor for accelerated cognitive decline in late life as well as for neurological disorders, in particular, AD (Fan et al., 2019).

Research also implicates neurotrophic factors as playing a role in the recovery from TBI. Broadly, neurotrophins, such as brain-derived neurotrophic factor (BDNF) and nerve-growth factor (NGF), are widely distributed in the brain and have well-established roles in neuronal development, differentiation, plasticity and survival (Huang & Reichardt, 2001). BDNF synthesis and function are regulated by several single-nucleotide polymorphisms (SNPs), some of which are associated with cognitive decline later in life, in particular, the BDNF Val66Met (rs6265) gene (Azeredo et al., 2017; Laing et al., 2012; Miyajima et al., 2008). In addition to playing a role in late-life cognitive decline, BDNF as well as NGF may also affect TBI outcomes. Research suggests that Met allele carriers of the BDNF Val66Met (rs6265) gene perform better than Val homozygotes on cognitive measures, suggesting that the Met allele may have a *protective* role in recovery following TBI (Krueger et al., 2011; Merritt et al., 2020). Note that this association differs from what has been observed in the general population of older adults, where Met allele carriers exhibit worse cognitive function (Boots et al., 2017; Merritt et al., 2020). With respect to NGF, its levels in the cerebral spinal fluid are elevated following TBI in children, with higher levels associated with more favorable outcomes (Chiaretti et al.,

2008). Apart from the studies discussed above, there is a paucity of research in humans, examining the role of BDNF/NGF in recovery from TBI. Nonetheless, animal studies support the notion that TBI alters neurotrophic signaling pathways in the brain after injury (Gustafsson et al., 2021; Rostami et al., 2014; Schober et al., 2012); this in turn may impact cognitive processes later in life, concomitant with the aging process (Shimada et al., 2014) or the onset of neurodegenerative processes (Pöyhönen et al., 2019).

Current research suggests that risk for AD following TBI is moderated by the APOE gene (Lawrence et al., 2015), however less is known about this interaction and general cognitive decline in late life. Furthermore, few studies have examined the role of neurotrophin genes (apart from BDNF (Val66Met) with respect to their interactions with history of TBI on cognitive impairment or decline. Studies examining the associations of TBI and gene interactions with cognitive outcomes in late life have examined some characteristics of TBI, such as severity or number (McFadyen et al., 2021; Zeiler et al., 2021), but few have examined recency of TBI. Moreover, an examination of TBI characteristics and neurotrophin genes with late-life cognitive outcomes has not been conducted. Finally, few studies have examined sex differences in the association of TBI and cognitive outcomes. The purpose of the present study is to examine the role of TBI history (and characteristics of TBI) in late-life cognitive decline as well as the potential moderating effects of sex, APOE genotype and genes related to the BDNF neurotrophin on these associations in a large, population-based cohort.

CHAPTER II

Literature Review

Cognitive impairment is a hallmark residual effect of Traumatic Brain Injury (TBI) (Tsai et al., 2021). While the extent and duration of cognitive impairment resulting from a TBI varies, depending on type of injury and severity, cognitive impairment is often considered the most disabling and distressing sequelae of TBI (Mollayeva et al., 2019). According to a meta-analysis by Schretlen et al. (2003), individuals who sustain a mild TBI may return to their pre-injury cognitive levels as early as three months post injury whereas those with a moderate-to-severe TBI exhibit some degree of recovery in the first two years after injury, but generally exhibit marked cognitive deficits thereafter, even 10 years after injury (Draper & Ponsford, 2008).

Cognitive deficits following a TBI are associated with diffuse axonal injury and disruption of intrinsic connectivity networks in the brain responsible for cognitive tasks (Sharp et al., 2014). In addition to damage to the brain from initial injury, referred to as primary injury, a cascade of secondary events is also triggered such as excitotoxicity, calcium overload, oxidative stress, mitochondrial dysfunction, and inflammation (Walker & Tesco, 2013). These processes not only contribute to programmed cell death and loss of neuronal networks in areas of the brain important for cognition, they are also thought to precipitate a long-term, on-going process of neurodegeneration, the mechanisms of which are largely unknown (Walker & Tesco, 2013).

Corkin et al., (1989) were the first to examine long-term effects of TBI on cognitive impairment in World War II veterans 10 years and 30 years post-injury. Their

results showed greater cognitive decline in TBI veterans compared to veterans without history of TBI between the two time points. They suggested that the greater cognitive decline exhibited in those with a history of TBI occurred as a result of secondary effects of the original injury, ongoing neurological stress, and normal age-related processes of the aging brain (Corkin et al., 1989). Natural aging of the brain in mid-life involves processes such as increased synaptic pruning and decreased plasticity (Masliah et al., 2006). Loss of brain volume in late life is seen as the result of diminished grey matter, particularly in the frontal lobe (Raz, 1997; Raz & Rodrigue, 2006; Tisserand et al., 2002) and followed by diminished white matter (Salat et al., 1999). Microglia in the aging brain are also more likely to become dystrophic and produce toxic substances that attack neurons (Brown, 2009). Senathi-Raja et al. (2010) examined the influence of age and time since TBI on cognitive performance in individuals with and without a history of TBI. Those with a history of TBI had a duration of time post injury between 5 to 22 years. Their results indicated that poorer cognitive functioning on tests of attention, processing speed, verbal learning, memory, verbal fluency, and mental flexibility was associated with both age at injury (with older individuals faring worse) and longer duration of time since injury. In addition, longer time since injury was associated with slower performance on tasks of initiation and response inhibition. The results from this study may reflect a combination of factors that occur in aging, including the brain's more limited ability to compensate for injury in adults experiencing TBI at more advanced ages as well as the ongoing processes in the aging brain itself that result in greater negative cognitive consequences later in life.

Current research supports the notion of an earlier onset of age-related cognitive decline in individuals with a history of TBI. In a sample of 609 older adults from the National Alzheimer's Coordinating Center (NACC) dataset, researchers found a significant "age-lowering effect" of 3.25 years for the onset of cognitive decline in older adults with a history of TBI [mean (SD) onset age 71.6 (11.2)] compared to controls with no history of TBI [mean (SD) onset age 74.8 (9.5)] (Iacono et al., 2021). This result was independent of education, APOE genotype, and diagnosed clinical condition (Mild Cognitive Impairment, Dementia, or non-AD cognitive impairment). Similar findings were reported in a sample of over 1,000 older adults where onset of cognitive impairment occurred two years earlier for those with a history of TBI [mean (SD) onset age 68.2 (1.1)] than those without [mean (SD) onset age of 70.9 (0.2)] (Li et al., 2016). Furthermore, there was a trend that individuals with a history of severe TBI had earlier onset of cognitive impairment than individuals with a history of mild TBI. However, neither study examined other characteristics such as number, recency or time since TBI.

The association between TBI and future risk of cognitive decline may be influenced by genetic factors. The polymorphic genetic locus, apolipoprotein (APOE), is associated with Alzheimer's disease (AD) risk for carriers of the ε4 allele (Roses, 1996). And with respect to TBI, APOE ε4 carriers with a history of TBI have increased deposition of amyloid-beta (Aβ) protein compared to non- ε4 carriers with history of head injury (Nicoll et al., 1995). This observation has led to speculation that TBI may promote AD pathogenesis among APOE ε4 carriers, and contribute to the beta-amyloid cascade associated with AD.

APOE genotype is also thought to play a role in the outcome of TBI. Ponsford et al. (2011) found that compared to non-carriers, APOE ε4 carriers had poorer long-term functional outcomes as measured by the Glasgow Outcome Scale-Extended (GOSE). This effect was notably stronger in females than in males. Other studies have found similar results in regards to poorer cognitive outcomes after TBI such as poorer memory, attention, mental flexibility, and processing speed amongst APOE ε4 carriers (Ariza, 2006; Crawford et al., 2002; Merritt et al., 2018; Müller et al., 2009). In contrast, several studies have also found no moderation by APOE genotype in cognitive outcomes after TBI (Hodgkinson et al., 2009; Pruthi et al., 2010; Rapoport et al., 2008). Possible factors contributing to the inconsistent findings across studies include small sample sizes, varying levels of TBI severity across samples as well as short follow-up times, with the majority of studies examining cognitive status within 6 months of injury.

TBI outcomes later in life may also be influenced by the activity of neurotrophins such as Brain Derived Neurotrophic Factor (BDNF) and Nerve Growth Factor (NGF) (Failla et al., 2016). Broadly speaking, neurotrophins are a class of growth factors that promote neuronal development, differentiation, and survival (Allen & Dawbarn, 2006). Studies involving humans and animals have shown that neurotrophins are upregulated following TBI with an immediate increase in BDNF and NGF messenger ribonucleic acid (mRNA) expression in the brain (Gustafsson et al., 2021; Hicks et al., 1997; Oyesiku et al., 1999; Rostami et al., 2014). In a study by Chiaretti et al. (2003), cerebrospinal fluid BDNF and plasma NGF levels were significantly higher in patients immediately post TBI (measured at 2 and 24 hours post injury) as compared to controls. However, NGF levels, but not BDNF levels, following severe TBI in children were significantly correlated with

more favorable neurological outcomes as measured by the Glasgow Outcome Scale (Chiaretti et al., 2003, 2008). Natural responses of BDNF and NGF in the brain following TBI likely contribute to a series of controlled, neuroprotective remodeling processes that improves neuronal repair and recovery (Lin et al., 2022).

BDNF has also been implicated in cognitive functioning in late life, irrespective of TBI history. For example, serum BDNF levels are correlated with rate of cognitive decline in older adults, with lower levels associated with increased severity of cognitive impairment (Siuda et al., 2017). Similarly, Buchman et al. (2016) assessed cognition and BDNF gene expression in over 500 older adults [mean (SD) age 81.4 (7.1)] annually for an average of 6 years. They found that higher levels of BDNF were associated with slower rate of cognitive decline. Furthermore, Buchman and colleagues explored whether rate of cognitive decline varied by BDNF gene expression (determined by postmortem RNA extraction) in the presence of AD pathology (determined by postmortem examination based on the National Institute on Aging criteria). Results supported a potential protective effect such that increased BDNF gene expression was associated with slower cognitive decline for participants whose brains were at the 90th percentile for AD pathology in this sample.

Variants of genes coding for neurotrophins have also been associated with cognitive outcomes in older adults (Azeredo et al., 2017; Boots et al., 2017; Laing et al., 2012; Miyajima et al., 2008). In particular, a valine to methionine substitution in the BDNF gene [BDNF Val66Met (rs6265)] (Bath & Lee, 2006), has been widely researched. Compared to homozygous Val allele carriers, minor Met allele carriers experience enhanced cognitive decline and increased risk for AD (Boots et al., 2017;

Franzmeier et al., 2021) in older adults, a relationship that was even stronger amongst APOE ε4 carriers (Gomar et al., 2016; Pietzuch et al., 2021). Cortical and hippocampal morphology also differs in minor Met allele carriers (Bath & Lee, 2006; Egan et al., 2003). Specifically, when compared to individuals homozygous for the Val allele, minor Met allele carriers have decreased volume in hippocampus and caudate nucleus as well as in the dorsolateral prefrontal cortex (Pezawas, 2004). Other BDNF-related SNPs, BDNF C270T (rs56164415) a functional promoter polymorphism and NGF/BDNF receptor p75NTR (rs2072446) have also been associated with increased risk for AD (Matyi et al., 2017). Other studies have similarly shown increased risk of AD for BDNF C270T (rs56164415) (Olin et al., 2005), with minor TT carriers having an earlier onset of about 4 years (Durmaz et al., 2019). Sex differences have been noted for various BDNF/NGF-related SNPs in risk for AD (Matyi et al., 2017) and cognitive decline (Wei et al., 2017).

To date, some studies have examined BDNF- or NGF-related SNPs in relation to history of TBI, with a paucity of studies having examined both in the risk of cognitive decline in late life. In particular, the BDNF SNP, BDNF Val66Met (rs6265), has been examined for its role in cognitive recovery following a TBI. In a sample of 168 male combat veterans [mean (SD) age = 58.2 (2.8)] with a frontal lobe lesion, Met carriers with a history of brain injury had better executive functioning (measured by the Delis-Kaplan Executive Function System battery) following TBI than non-Met carriers with a history of brain injury (Krueger et al., 2011). Furthermore, the Met allele accounted for 6.2% of the variance in executive functioning independent of preinjury intelligence scores and brain volume loss. In a similar study completed by Merritt et al. (2019) with a sample of 138 veterans [mean (SD) age = 32.6 (7.1)], Met allele carriers with a history of

TBI demonstrated better performance on measures of memory and executive functioning, than non-Met carriers with a history of TBI, independent of sex. Notably, in healthy military controls, Met allele carriers performed worse on both memory and executive functioning measures compared to healthy non-Met carriers, a finding consistent with results from other studies of BDNF Val66Met (rs6265) in the general population (Boots et al., 2017). With respect to NGF, Chiaretti et al (2008) collected cerebral spinal fluid samples from 27 children at 2 and 48 hours after TBI. NGF levels were increased and significantly correlated with more favorable neurological outcomes as measured by the Glasgow Outcome Scale.

Current Study

As discussed above, a history of TBI is associated with cognitive decline and dementia in late life (Mendez, 2017). Neurotrophins BDNF and NGF appear to play a role in the brain's response to injury, with human and animal research showcasing an immediate upregulation of BDNF and NGF levels in the brain (Gustafsson et al., 2021). The role of APOE genotype in short term cognitive outcomes following a TBI is inconclusive (McFadyen et al., 2021). However, research supports that APOE genotype influences the rate of cognitive decline in late life and increases the risk for AD (Fan et al., 2019). Moreover, in those with a history of TBI, there is even greater risk of AD among APOE ε4 carriers (Lawrence et al., 2015). Few studies, however, have examined interactions between history of TBI and cognitive decline late in life. Additionally, only a small number of studies have examined one gene in the family of neurotrophins (BDNF Val66Met (rs6265)) and history of TBI on late-life cognitive outcomes, despite the

relevance of BDNF/NGF in the recovery from TBI (Lin et al., 2022) and in late-life cognitive functioning (Siuda et al., 2017). Also largely unexplored are various characteristics of TBI, such as recency of injury, age at injury, and injury severity and their interactions with APOE and BDNF/NGF genotype in predicting late-life cognition. More broadly, studies examining the effect of TBI on cognitive decline largely have short follow-up times and have focused largely on the acute stage of recovery. Furthermore, sex differences have not been well-studied.

This current study addressed some of these gaps in the literature, by examining if TBI history influences rate of cognitive decline in late life, exploring characteristics of TBI as predictors and examining interactions of TBI history with the APOE gene and selected genes/SNPs related to BDNF and NGF. The study utilized data from the Cache County Study on Memory in Aging, a population-based study of over 5,000 adults, aged 65 years and older, followed prospectively for up to 12 years (Breitner et al., 1999). The specific research questions addressed were:

1) Whether history of TBI (none, one, two or more) was associated with the rate of cognitive decline in older adults.

2) Whether characteristics of TBI (recency of TBI, age at last TBI, or severity) were associated with the rate of cognitive decline in older adults.

3) Whether a history of TBI (or its characteristics) interacted with APOE genotype in the association with the rate of cognitive decline in older adults.

4) Whether a history of TBI (or its characteristics) interacted with SNPs related to BDNF/NGF [rs2072446 (NGF/BDNF receptor p75NTR), rs2289656 (BDNF

receptor trkB), rs56164415 (BDNF C270T), and rs6265 (BDNF Val66Met)] in the association with the rate of cognitive decline in older adults.

For each of the above research questions, interactions between sex and TBI were examined where sample size permitted.

Methods

Participants

The current study used extant data from the longitudinal, population-based Cache Country Study on Memory in Aging (CCSMA) (Breitner et al., 1999; Miech et al., 2002). A total of 5,092 permanent residents of Cache County, Utah aged 65 years or older in 1995 were enrolled into the study. Participants were followed for a maximum of four triennial waves occurring in 1995, 1998, 2002, and 2005. At each wave, researchers conducted dementia ascertainment using a multi-staged screening and assessment protocol including cognitive screening and risk factor interviews, informant interviews and clinical assessments (Breitner et al., 1999). Demographic, educational, occupational, health, family history and lifestyle information were obtained at Wave 1 and updated at each subsequent wave. Biological samples from which genotype data were obtained were collected in Waves 1, 3 and 4 (Breitner et al., 1999; Matyi et al., 2017).

Procedure

An in-depth description of the study's procedures has been previously published (Breitner et al., 1999; Miech et al., 2002). Briefly, at each wave, dementia ascertainment proceeded with cognitive screening with an adaptation of the Modified Mini-Mental State Examination (3MS) (E. L. Teng & Chui, 1987) or the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) (Jorm & Jacomb, 1989) for those participants who were unable to complete 3MS testing, scored less than 60 points on the total or less than 15 points on orientation items, or were judged as unreliable by the interviewer. In Waves 1 and 2, participants who screened positive on the 3MS or IQCODE were further screened using the Dementia Questionnaire (DQ) which consisted of a telephone interview with a knowledgeable informant. Participants with significant cognitive impairment were identified and invited to complete a clinical assessment which included neuropsychological testing, medical and neurological evaluation, and a clinical interview with a knowledgeable informant. In Waves 3 and 4, the DQ stage was eliminated, and additional cognitive measures were added but not used in the screening process. In all waves, a subsample of participants was invited to a clinical assessment regardless of screening results (see Breitner et al., 1999). Results of the clinical assessment were reviewed by the assessment team and study neuropsychologist and physician, who rendered preliminary diagnoses of dementia or other cognitive disorders. Diagnoses of dementia followed criteria of the Diagnostic Statistical Manual of Mental Disorders – 3rd Edition Revised (DSMIII-R) (American Psychiatric Association, 1987). Laboratory studies, neuroimaging, physician examination, and an 18-month follow-up clinical assessment were requested for those participants who were identified with

dementia or prodromal AD. The results of all clinical data were subsequently reviewed by an expert clinical panel who rendered final cognitive diagnoses (Breitner et al., 1999). Participants who were not assigned a dementia diagnosis at a given wave were followed at each subsequent wave. Buccal-swabs were obtained from participants in Wave 1 and blood samples were collected in Waves 3 and 4 for APOE and BDNF/NGFR genotyping as previously described (Breitner et al., 1999; Matyi et al., 2017). All procedures were approved by the Institutional Review Boards of Utah State University, Duke University, and Johns Hopkins University. To be included in the present analyses, individuals must have been deemed dementia-free at Wave 1, have completed a history of the head injury portion of the interview and not be missing APOE and BDNF/NGFR genotypes.

Outcome Variables: Cognitive Measures

Modified Mini-Mental State Exam (3MS): At each wave, cognitive status was assessed using an adapted version of the 100-point 3MS measure of global cognitive functioning. The 3MS broadly measures the following cognitive constructs: psychomotor skills, memory, orientation, naming and abstract verbal reasoning, verbal fluency, and concentration and working memory (E. L. Teng & Chui, 1987). Studies examining psychometric properties of the 3MS in older populations found high internal consistency ($\alpha = .91$) and test-retest reliability ($r = .78$) (Bassuk & Murphy, 2003). In the CCSMA, minor modifications were made such as replacing recall of personal demographic information with information items that could be verified in the field, as well as replacing aural presentation of words with a visual presentation (Tschanz et al., 2002).

Additionally, a sensory-motor adjustment was made for test items that were missed due to sensory or motor impairments. These items were discarded, and a new score was calculated based on the percentage correct from the new total possible points, with multiplication by 100 such that the adjusted score range remained 0 – 100 points (Breitner et al., 1999).

In Waves 3 and 4, additional cognitive measures were added to more fully assess working memory, short-term verbal memory and recall, and visuospatial and executive functions as follows.

Hopkins Verbal Learning Test-Revised (HVLT-R): The HVLT-R is comprised of three learning trials of a 12-item word list read to participants, a 20–25 minute delayed recall task, followed by a yes/no recognition task of the 12 items along with 12 foils. The test is designed to briefly measure verbal learning and memory (Shapiro et al., 1999). Research examining the psychometric properties of the HVLT-R found the following test-retest reliability coefficients: total recall (r = .74), learning (r = .41), delayed recall (r = .66), percentage retained (r = .39), and recognition (r = .40) (Benedict et al., 1998). Scores from this test included total from all three learning trials (0-36 points), delayed recall (0-12 points), and recognition recall (0-24 points).

Digit Span (DS): DS is a subtest of the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III) and consists of two components: Forwards and Backwards recall. The task requires participants to repeat a series of digits verbally given in separate Forwards and Backwards subtests, and measures attention, immediate auditory recall, and working

memory (Wechsler, 1997). Research examining the psychometrics of the DS found strong split half reliability (r = .90) and test retest reliability (r = .83) (Kaufman & Lichtenberger, 1999). Summary scores include total DS Forwards (0-16 points) and DS Backwards (0-14 points) scores.

Clock Drawing Test (CDT): The CDT is a measure of spatial dysfunction and neglect (Agrell and Dehlin 1998). During the task, participants were asked to "Draw the face of a clock, showing all the numbers, and set the hands to read ten after eleven." A review examining the psychometric properties of the clock drawing test found high sensitivity (85%) and specificity (85%) with excellent inter-rater reliability and good concurrent and predictive validity (Shulman, 2000). Statistical analyses were run using the CDT total score (0-21 points).

Predictor Variables: Traumatic Brain Injury

Lifetime history of TBI was obtained retrospectively as part of the risk factor interview at each wave (see Appendix). Participants were asked, "Have you had a head injury so severe that you lost consciousness, lost your memory for a period of time, or had to see a doctor?" For each incident of head trauma, the participant was asked to provide a description of the head injury, their age at injury, as well as whether there was any loss of consciousness (LOC) or post-traumatic amnesia (PTA). Endorsements of LOC or PTA were followed up with requests for duration of each. TBI status after the Wave 1 baseline was included as a time-varying variable and cumulatively grouped into

three categories across all four waves based on the distribution of the number of TBIs reported (none, one, two or more). To characterize severity and timing of TBI, exploration of LOC, PTA, and recency of last TBI were conducted. Severity of TBI was categorized according to published guidelines (Mild: 0-30 min. LOC or 0-1 day PTA; Moderate: > 30 min. and <24 hours LOC or > 1 and <7 days PTA; Severe: > 24 hours LOC or > 7 days PTA) (O'Neil et al., 2013). Ages of first and last TBI, was examined to determine developmental (first) and recency (last) effects with the following classifications: childhood (0-17), early adulthood (18-30), middle adulthood (31-64), and late life (65+). Participants who reported a head injury before baseline but did not provide a year or age at time of injury were excluded from analyses.

Genotyping

APOE genotype was obtained via buccal samples using polymerase chain reaction (PCR) as previously described (Breitner et al., 1999). APOE genotype was represented in analyses as presence or absence of the APOE ε4 allele. BDNF/NGFR SNPs were genotyped from blood DNA or if lacking, from buccal DNA using standard TaqMan® Assays (Life Technologies) (Matyi et al., 2017), yielding the following SNPs related to BDNF or its receptors: [rs6265 (BDNF Val66Met; G196A), rs56164415 (BDNF C270T), rs2289656 (receptor TrkB), and rs2072446 (receptor p75NTR)]. When minor allele frequencies allowed, analyses included codominant (A/A vs. A/a vs. a/a) comparisons, or otherwise included absence vs. presence (A/A vs A/a or a/a) of the minor alleles.

Additional Information

Demographic information was collected at baseline interviews. Participant's age was calculated from the reported date of birth. Age was centered at the sample grand mean (80 years of age) for all additional cognitive measures collected at Wave 3 and 4. Information such as sex and obtained level of education was reported by participants.

Statistical Analyses

Descriptive statistics were performed to characterize the sample. Inferential statistics, using independent sample *t* tests for continuous variables and Chi-square tests of independence for categorical variables, were used to examine demographic and baseline differences including those with a history of head injury vs. those without.

Separate linear mixed effects models were used to examine the association between the primary predictors (e.g., TBI, APOE genotype, BDNF/NGF-related receptor SNPs) and cognition across each wave. For each research question, model building proceeded from a base model consisting of the primary predictor and cognitive outcome, to more complex models that sequentially added covariate and interaction terms. Improvement in model fit at each step was determined by comparing -2Log Likelihoods of nested models using the Chi square test of independence. Significant improvement in model fit was set at Chi Square test $p < .05$. Sex, age, and education were tested for significance in all models and included as covariates in the fully adjusted model if the fit statistics for the model met significance of $p < .05$. Based on prior analyses run in the Cache County population regarding possible sex differences in BDNF/NGFR genetics

(Matyi et al., 2017), interactions between each BDNF/NGFR-related SNP and sex was tested. Furthermore, in modeling predictors of 3MS outcome, a test for non-linear (quadratic) change over time was conducted by the inclusion of a time^2 term (Fotuhi et al., 2008). Time was represented in years (baseline = time 0) and cognitive decline was assessed by including time (and time^2 for the 3MS) as an interaction term with the variable of interest [e.g., TBI history or higher-order interactions of TBI history*APOE genotype*time (and time^2)] in predicting the cognitive outcome. A linear term for time was used for outcomes assessed at Waves 3 and 4. Maximum likelihood estimation (ML) was used during the model building process, while restricted maximum likelihood estimation (REML) was used in final models to obtain parameter estimates. All statistical models were run using R Statistical Software (v4.2.1; R Core Team 2021). Models were fit using the lmerTest package (Kuznetsova et al., 2017).

Results

There were two sample subsets in the project: one that examined the association of TBI characteristics and genotype across four waves of data collection using the 3MS as the outcome and the other that examined the association of TBI characteristics and genotype on an expanded cognitive battery administered in Waves 3 and 4 only. There were 4,488 out of the 5092 participants who met eligibility criteria of not having dementia at baseline for both subsamples. Among the ineligible individuals for the 3MS outcome were 359 with dementia and 245 with unknown cognitive status (188 due to

incomplete screening and 57 lacking any cognitive data). From these eligible participants, excluded from further analyses were: 128 missing all SNPs for BDNF or its receptors, 58 missing APOE genotype, 5 missing TBI history, and 4 missing educational history, yielding the final sample of 4,293. Compared to participants excluded from the analyses, those included had significantly more follow up time (by approximately 1 year; $p < .001$) and had a slightly higher baseline 3MS score at trend level significance ($p = .052$). See Table 1 for participant characteristics of those included as compared to those excluded from the final sample.

Of the 4,488 participants who met overall eligibility criteria at Wave 1, a subsample of 2,204 participants completed at least one of the tests in the expanded cognitive battery administered at Waves 3 and 4. Further excluded from these analyses were: 67 missing all SNPs for BDNF or its receptors, 11 missing APOE genotype, and 2 missing TBI history. The final subsample of 2,124 participants included in the subsample analyses did not differ on their Wave 1 3MS scores from those excluded from the subsample; however, they had significantly higher Wave 3 3MS ($p = .006$), HVLT-R learning total ($p = .042$), and HVLT-R delayed recall ($p = .014$) scores (see Table 1) compared to those excluded from the subsample. Note that sample size numbers reported in the table are the maximum number of participants that could be included for each cognitive test. Actual sample size varied by the specific terms of each model.

Table 1

Baseline Participant Characteristics Comparing Those Included vs Excluded in Analyses

Wave 1 Participant Characteristics									
Variable	Included (n = 4293)				Excluded (n = 195)				
	M	*SD*	*n*	%	*M*	*SD*	*n*	%	*p*
BL Age (yrs)	74.93	6.87			75.55	6.62			.217
Follow-up (yrs)	5.69	4.22			4.67	3.88			<.001***
Sex									.376
Male			1857	43.3			78	39.8	
Female			2435	56.7			118	60.2	
Education									.15
Less than HS			748	17.4			40	20.4	
HS or GED			1454	33.9			72	36.7	
More than HS			2090	48.7			80	40.8	
Missing							4	2	
BL TBI									.855
None			3408	79.4			154	78.6	
One			718	16.7			29	14.8	
Two or More			166	3.9			7	3.6	
Missing							5	3.1	
APOE ε4									.199
No ε4			2993	69.7			88	44.9	
One or More ε4			1299	30.3			49	25	
Missing							59	30.1	
BL 3MS Total	90.81	6.96			89.79	7.71			.052
Wave 3 Participant Characteristics									
	Included (n = 2124)				Excluded (n = 80)				
	M	*SD*	*n*	%	*M*	*SD*	*n*	%	*p*
W3 Age (yrs)	80.01	5.42			80.66	5.75			.302
Follow-up (yrs)	3.10	0.19			3.02	0.54			.387
Sex									.675
Male			892	42			36	45	
Female			1232	58			44	55	
Education									.547
Less than HS			265	12.5			13	16.2	

HS or GED			724	34.1			28	35	
More than HS			1135	53.4			29	48.8	
W3 TBI									.236
None			1568	73.8			52	65	
One			431	20.3			22	27.5	
Two or More			125	5.9			4	5	
Missing							2	2.5	
APOE ε4									.327
No ε4			1458	68.6			43	53.8	
One or More ε4			666	31.4			26	32.5	
Missing							11	13.8	
W1 3MS Total	93.07	4.76			92.79	5.06			.623
W3 3MS Total	90.94	7.37			88.58	9.00			.006**
W3 HVLT-R Learning	23.3	5.96			21.88	5.91			.042*
W3 HVLT-R Delayed	6.81	3.91			5.68	3.94			.014*
W3 HVLT-R Recognition	20.16	5.74			20.25	5.17			.889
W3 DS Forwards	8.99	2.14			8.73	2.25			.301
W3 DS Backwards	5.38	1.85			5.19	1.84			.383
W3 CDT Total	9.83	3.97			9.70	4.21			.781

Note. BL = Baseline; HS = High School; GED = General Education Diploma; TBI = Traumatic Brain Injury; APOE ε4 = Apolipoprotein E ε4 Allele; 3MS = Modified Mini-Mental State Exam; W1 = Wave 1; W3 = Wave 3; HVLT-R = Hopkins Verbal Learning Test-Revised; DS = Digit Span; CDT = Clock Drawing Test
* p <.05. ** p <.01. *** p <.001.

With respect to sex differences, female participants were about a year older (p <.001), had fewer formal years of education (p <.001), and had fewer TBIs (p <.001) reported than males. Female participants also had higher baseline 3MS scores (p <.001) and Wave 3 HVLT-R learning (p <.001) and delayed recall (p <.001) scores, whereas

males had higher scores on CDT total (p <.001) and DS Forwards (p <.003). Table 2 shows the descriptive statistics by sex.

Table 2

Baseline Descriptive Comparisons by Sex

Wave 1 Participant Characteristics									
	Female (n = 2435)				Male (n = 1857)				
	M	*SD*	*n*	%	*M*	*SD*	*n*	%	*p*
BL Age (yrs)	75.34	6.93			74.39	6.74			<.001***
Follow-up (yrs)	5.84	4.16			5.49	4.28			.007**
Education									<.001***
Less than HS			375	15.4			373	20.1	
HS or GED			1019	41.8			435	23.4	
More than HS			1041	42.8			1049	56.5	
BL TBI									<.001***
None			2066	84.8			1342	72.3	
One			325	13.3			393	21.2	
Two or More			44	1.8			122	6.6	
APOE ε4									.617
No ε4			1706	70.1			1287	69.3	
One or More ε4			729	29.9			570	30.7	
BDNF/NGFR SNPs									
rs6265 (BDNF Val66Met)									.459
G/G			1559	64			1222	65.8	
G/a			742	30.5			538	29	
a/a			106	4.4			75	4	
Missing			28	1.1			22	1.2	
rs2289656 (receptor TrkB)									.54
C/C			1570	64.5			1229	66.2	
C/t			713	29.3			518	27.9	
t/t			90	3.7			66	3.6	
Missing			62	2.5			44	2.4	

rs2072446 (receptor p75NTR)									.334
C/C			2191	90			1664	89.6	
C/t			182	7.5			150	8.1	
t/t			11	0.5			4	0.2	
Missing			51	2.1			39	2.1	
rs56164415 (BDNF C270T)									1
C/C			2095	86			1602	86.3	
C/t			271	11.1			208	11.2	
t/t			0	0			0	0	
Missing			69	2.8			47	2.5	
BL 3MS Total	91.23	6.64			90.26	7.33			<.001***

Wave 3 Participant Characteristics									
	Female (n = 1232)				Male (n = 892)				
	M	*SD*	*n*	%	*M*	*SD*	*n*	%	*p*
W3 Age (yrs)	80.38	5.57			79.50	5.17			<.001***
Follow-up (yrs)	3.10	0.19			3.11	0.20			0.485
Education									<.001***
Less than HS			141	11.4			124	13.9	
HS or GED			528	42.9			196	22	
More than HS			563	45.7			572	64.1	
W3 TBI									<.001***
None			955	77.5			613	68.7	
One			229	18.6			202	22.6	
Two or More			48	3.9			77	8.6	
APOE ε4									.718
No ε4			850	69			608	68.2	
One or More ε4			382	31			284	31.8	
BDNF/NGFR SNPs									
rs6265 (BDNF Val66Met)									.313
G/G			769	62.4			581	65.1	
G/a			405	32.9			265	29.7	
a/a			52	4.2			40	4.5	
Missing			6	0.5			6	0.7	
rs2289656 (receptor TrkB)									.596
C/C			801	65			588	65.9	

C/t			373	30.3		261	29.3	
t/t			48	3.9		28	3.1	
Missing			10	0.8		15	1.7	
rs2072446 (receptor p75NTR)								.555
C/C			1106	89.8		787	88.2	
C/t			98	8		82	9.2	
t/t			2	0.2		2	0.2	
Missing			26	2.1		21	2.4	
rs56164415 (BDNF C270T)								.134
C/C			1092	88.6		767	86	
C/t			126	10.2		110	12.3	
t/t			0	0		0	0	
Missing			14	1.1		15	1.7	
W1 3MS Total	93.31	4.57		92.75	4.99			.007**
W3 3MS Total	91.28	7.40		90.47	7.30			.012*
W3 HVLT-R Learning	24.21	6.06		22.06	5.60			<.001***
W3 HVLT-R Delayed	7.26	4.00		6.19	3.71			<.001***
W3 HVLT-R Recognition	20.11	6.23		20.23	5.00			.633
W3 DS Forwards	8.87	2.08		9.15	2.22			.003**
W3 DS Backwards	5.43	1.80		5.32	1.92			.213
W3 CDT Total	9.37	3.47		10.47	4.50			<.001***

Note. BL = Baseline; HS = High School; GED = General Education Diploma; TBI = Traumatic Brain Injury; APOE ε4 = Apolipoprotein E ε4 Allele; BDNF/NGFR SNP= Brain Derived Neurotrophic Factor Gene/Nerve Growth Factor Receptor Single Nucleotide Polymorphism; 3MS = Modified Mini-Mental State Exam; W1 = Wave 1; W3 = Wave 3; HVLT-R = Hopkins Verbal Learning Test-Revised; DS = Digit Span; CDT = Clock Drawing Test

* p <.05. ** p <.01. *** p <.001.

For Research Question 2, there were 16 additional participants excluded from the original final sample of 4,293 due to missing head injury information, specifically age at head injury. Of the final sample (n = 4277), approximately 24.6% reported a history of

TBI, with males reporting more TBIs (30.2%) compared to females (20.4%). First TBIs were most commonly reported in childhood (33.5%) for the overall sample, but the pattern differed by sex in that females experienced their first TBIs more often in late life (46.8%) compared to males who experienced their first TBIs more often in childhood (40.1%). For last TBI, the majority were experienced in late life (36%), which was the pattern for females (49.8%) but not for males where the last TBI most commonly occurred in childhood (37.6%). For females, average age at first and last reported TBI was 48.09 (*SD* = 29.41) and 53.65 (*SD* = 28.46) years, respectively. For males, average age at first and last reported TBI was 33.27 (*SD* = 25.62) and 39.92 (*SD* = 26.58), respectively. Males and females also significantly differed on TBI severity. While majority of males and females reported mild TBIs (68.8% and 74%, respectively), males reported more moderate and severe TBIs than females. Table 3 displays TBI characteristics by sex.

With respect to gene differences by TBI history, Tables 4 and 5 display TBI characteristics by APOE and BDNF/NGF-related SNP by sex. For APOE, there were no differences in number of TBIs or TBI characteristics by presence of the ε4 allele for either males or females. Similarly, there were no differences in number of TBIs or TBI characteristics for BDNF/NGF-related SNPs BDNF Val66Met (rs6265) and receptor TrkB (rs2289656). For the p75NTR (rs2072446) SNP, participants did not differ on number of TBIs (females: $p = .355$; males: $p = .481$). A test for bivariate relationships was unable to be calculated for males with the p75NTR (rs2072446) SNP due to no participant in the sample being homozygous for the minor allele. However, female participants did not significantly differ on age of first TBI ($p = .845$), age of last TBI ($p =$

.964), or severity (p = .706). For BDNF C270T (rs56164415), participants did not significantly differ on number of TBIs (females: p = .608; males: p = .416). Males significantly differed on age of first TBI (p = .047), however females did not (p = .377). Males also significantly differed for age of last TBI (p = .022) as did females at a trend level (p = .056). Neither males nor females differed on TBI severity (females: p = .102; males: p = .180). Table 5 displays BDNF/NGFR-related SNPs and TBI characteristics by sex.

Table 3

TBI Characteristics by Sex

	Total				Female				Male				
	M	*SD*	*n*	%	*M*	*SD*	*n*	%	*M*	*SD*	*n*	%	*p*
Full Sample			*n* = 4277				*n* = 2427				*n* = 1850		
TBI History													<.001***
None			3223	75.4			1931	79.6			1292	69.8	
One			801	18.7			395	16.3			406	21.9	
Two or More			253	5.9			101	4.2			152	8.2	
Endorsed TBI			*n* = 1054				*n* = 496				*n* = 558		
Age of First TBI													<.001***
Age	40.23	28.43			48.09	29.41			33.27	25.62			<.001***
Childhood			353	33.5			129	26			224	40.1	
Early Adulthood			142	13.5			36	7.3			106	19	
Middle Adulthood			219	20.8			99	20			120	21.5	
Late Life			340	32.3			232	46.8			108	19.4	
Age of Last TBI													<.001***
Age	46.37	28.31			53.65	28.46			39.92	26.58			<.001***
Childhood			331	31.4			121	24.4			210	37.6	
Early Adulthood			140	13.3			36	7.3			104	18.6	
Middle Adulthood			204	19.4			92	18.5			112	20.1	
Late Life			379	36			247	49.8			132	23.7	
TBI Severity													.05 *
Mild			751	71.3			367	74			384	68.8	
Moderate			208	19.7			95	19.2			113	20.3	
Severe			95	9			34	6.9			61	10.9	

Note. TBI = Traumatic Brain Injury; Childhood = Ages 0-17; Early Adulthood = Ages 18-30; Middle Adulthood = Ages 31-64; Late Life = Ages 65+

* p <.05. *** p <.001.

Table 4

APOE Genotype and TBI Characteristics by Sex

	Total				No ε4				One or More ε4				
	M	*SD*	*n*	%	*M*	*SD*	*n*	%	*M*	*SD*	*n*	%	*p*
Females													
Full Sample			(*n* = 2427)				(*n* = 1701)				(*n* = 726)		
TBI History													.957
None			1931	79.6			1356	79.7			575	79.2	
One			395	16.3			275	16.2			120	16.5	
Two or More			101	4.2			70	4.1			31	4.3	
Endorsed TBI			(*n* = 496)				(*n* = 345)				(*n* = 151)		
Age of First TBI													.872
Age	48.09	29.41			48.65	29.33			46.79	29.66			.519
Childhood			129	26			89	25.8			40	26.5	
Early Adulthood			36	7.3			23	6.7			13	8.6	
Middle Adulthood			99	20			69	20			30	19.9	
Late Life			232	46.8			164	47.5			68	45	
Age of Last TBI													.955
Age	53.65	28.46			53.16	28.65			54.77	28.06			.565
Childhood			121	24.4			86	24.9			35	23.2	
Early Adulthood			36	7.3			24	7			12	7.9	
Middle Adulthood			92	18.5			63	18.3			29	19.2	
Late Life			247	49.8			172	49.9			75	49.7	
TBI Severity													.834
Mild			367	74			253	73.3			114	75.5	
Moderate			95	19.2			67	19.4			28	18.5	
Severe			34	6.9			25	7.3			9	6	
Males													
Full Sample			(*n* = 1850)				(*n* = 1282)				(*n* = 568)		
TBI History													.654
None			1292	69.8			887	69.2			405	71.3	
One			406	21.9			288	22.5			118	20.8	
Two or More			152	8.2			107	8.3			45	7.9	

	Total				No ε4				One or More ε4				
	M	*SD*	*n*	%	*M*	*SD*	*n*	%	*M*	*SD*	*n*	%	*p*
Endorsed TBI		(*n* = 558)				(*n* = 395)				(*n* = 163)			
Age of First TBI													.803
Age	33.27	25.62			33.41	25.71			32.93	25.47			.839
Childhood			224	40.1			161	40.8			63	38.7	
Early Adulthood			106	19			72	18.2			34	20.9	
Middle Adulthood			120	21.5			83	21			37	22.7	
Late Life			108	19.4			79	20			29	17.8	
Age of Last TBI													.573
Age	39.92	26.58			40.22	26.62			39.19	26.54			.678
Childhood			210	37.6			151	38.2			59	36.2	
Early Adulthood			104	18.6			71	18			33	20.2	
Middle Adulthood			112	20.1			75	19			37	22.7	
Late Life			132	23.7			98	24.8			34	20.9	
TBI Severity													.260
Mild			384	68.8			265	67.1			119	73	
Moderate			113	20.3			87	22			26	16	
Severe			61	10.9			43	10.9			18	11	

Note. TBI = Traumatic Brain Injury; APOE ε4 = Apolipoprotein E ε4 Allele; Childhood = Ages 0-17; Early Adulthood = Ages 18-30; Middle Adulthood = Ages 31-64; Late Life = Ages 65+

*** $p < .001$.

Table 5

BDNF/NGFR-Related SNPs and TBI Characteristics by Sex

	M/M				M/n				n/n				
	M	*SD*	*n*	%	*M*	*SD*	*n*	%	*M*	*SD*	*n*	%	*p*
Females													
rs6265 (BDNF Val66Met)													
Full Sample			(*n* = 1557)				(*n* = 736)				(*n* = 106)		
TBI History													.308
None			1232	79.1			587	79.8			90	84.9	
One			267	17.1			113	15.4			12	11.3	
Two or More			58	3.7			36	4.9			4	3.8	
Endorsed TBI			(*n* = 325)				(*n* = 149)				(*n* = 16)		
Age of First TBI													.673
Age	48.84	29.47			45.70	29.71			52.94	26.91			.446
Childhood			87	26.9			40	26.8			1	6.2	
Early Adulthood			23	7.1			11	7.4			1	6.2	
Middle Adulthood			62	19.1			30	20.1			5	31.2	
Late Life			152	46.9			68	45.6			9	56.2	
Age of Last TBI													.446
Age	53.14	28.93			53.95	28.41			57.44	24.10			.824
Childhood			85	26.2			33	22.1			2	12.5	
Early Adulthood			23	7.1			11	7.4			1	6.2	
Middle Adulthood			57	17.6			28	18.8			5	31.2	
Late Life			159	49.1			77	51.7			8	50	
TBI Severity													.662
Mild			246	75.7			104	69.8			12	75	
Moderate			56	17.2			35	23.5			3	18.8	
Severe			23	7.1			10	6.7			1	6.2	
rs2289656 (receptor TrkB)													
Full Sample			(*n* =1567)				(*n* = 708)				(*n* = 90)		
TBI History													.131
None			1254	80			548	77.4			80	88.9	
One			250	16			129	18.2			8	8.9	
Two or More			63	4			31	4.4			2	2.2	

	M/M				M/n				n/n				
	M	*SD*	*n*	%	*M*	*SD*	*n*	%	*M*	*SD*	*n*	%	*p*
Endorsed TBI		(*n* = 313)				(*n* = 160)				(*n* = 10)			
Age of First TBI													.541
Age	47.65	29.58			49.41	29.09			39.30	32.37			.528
Childhood			81	25.9			41	25.6			4	40	
Early Adulthood			25	8			8	5			1	10	
Middle Adulthood			61	19.5			37	23.1			0	0	
Late Life			146	46.6			74	46.2			5	50	
Age of Last TBI													.621
Age	53.81	28.43			53.71	28.41			48.40	32.30			.840
Childhood			74	23.6			40	25			4	40	
Early Adulthood			24	7.7			9	5.6			1	10	
Middle Adulthood			57	18.2			34	21.2			0	0	
Late Life			158	50.5			77	48.1			5	50	
TBI Severity													.936
Mild			231	73.8			118	73.8			8	80	
Moderate			60	19.2			30	18.8			2	20	
Severe			22	7			12	7.5			0	0	
rs2072446 (receptor p75NTR)													
Full Sample		(*n* = 2182)				(*n* =183)				(*n* = 11)			
TBI History													.355
None			1743	79.9			138	75.4			9	81.8	
One			356	16.3			33	18			2	18.2	
Two or More			0	0			0	0			0	0	
Endorsed TBI		(*n* = 439)				(*n* = 45)				(*n* = 2)			
Age of First TBI													.845
Age	48.47	29.42			47.51	29.60			39.00	45.25			.885
Childhood			114	26			10	22.2			1	50	
Early Adulthood			31	7.1			5	11.1			0	0	
Middle Adulthood			88	20			7	15.6			0	0	
Late Life			206	46.9			23	51.1			1	50	

	M/M				M/n				n/n				
	M	*SD*	*n*	%	*M*	*SD*	*n*	%	*M*	*SD*	*n*	%	*p*
Age of Last TBI													.964
Age	53.74	28.53			52.96	29.02			39.00	45.25			.758
Childhood			107	24.4			11	24.4			1	50	
Early Adulthood			32	7.3			4	8.9			0	0	
Middle Adulthood			82	18.7			7	15.6			0	0	
Late Life			218	49.7			23	51.1			1	50	
TBI Severity													.706
Mild			326	74.3			33	73.3			2	100	
Moderate			84	19.1			7	15.6			0	0	
Severe			29	6.6			5	11.1			0	0	
rs56164415 (BDNF C270T)													
Full Sample			(*n* = 2087)				(*n* = 271)				(*n* = 0)		
TBI History													.608
None			1652	79.2			221	81.5			0	0	
One			350	16.8			39	14.4			0	0	
Two or More			85	4.1			11	4.2			0	0	
Endorsed TBI			(*n* = 435)				(*n* = 50)				(*n* = 0)		
Age of First TBI													.377
Age	47.95	29.58			53.64	27.28							.195
Childhood			114	26.2			9	18			0	0	
Early Adulthood			32	7.4			3	6			0	0	
Middle Adulthood			83	19.1			14	28			0	0	
Late Life			206	47.4			24	48			0	0	
Age of Last TBI													.056 .
Age	53.15	28.69			61.32	24.49							.032 *
Childhood			110	25.3			5	10			0	0	
Early Adulthood			32	7.4			3	6			0	0	
Middle Adulthood			76	17.5			14	28			0	0	
Late Life			217	49.9			28	56			0	0	
TBI Severity													.102

	M/M				M/n				n/n				
	M	*SD*	*n*	%	*M*	*SD*	*n*	%	*M*	*SD*	*n*	%	*p*
Mild			327	75.2			34	68			0	0	
Moderate			82	18.9			9	18			0	0	
Severe			26	6			7	14			0	0	
Males													
rs6265 (BDNF Val66Met)													
Full Sample		(*n* = 1219)				(*n* = 534)				(*n* = 75)			
TBI History													.959
None			852	69.9			369	69.1			54	72	
One			269	22.1			117	21.9			15	20	
Two or More			98	8			48	9			6	8	
Endorsed TBI		(*n* = 367)				(*n* = 165)				(*n* = 21)			
Age of First TBI													.941
Age	33.39	25.77			33.40	25.78			30.62	23.06			.889
Childhood			144	39.2			68	41.2			9	42.9	
Early Adulthood			74	20.2			27	16.4			5	23.8	
Middle Adulthood			79	21.5			36	21.8			4	19	
Late Life			70	19.1			34	20.6			3	14.3	
Age of Last TBI													.691
Age	39.92	26.60			40.29	26.99			38.95	24.43			.973
Childhood			74	37.1			63	38.2			8	38.1	
Early Adulthood			74	20.2			25	15.2			5	23	
Middle Adulthood			76	20.7			31	18.8			4	19	
Late Life			81	22.1			46	27.9			4	19	
TBI Severity													.628
Mild			261	71.1			108	65.5			13	61.9	
Moderate			68	18.5			39	23.6			5	23.8	
Severe			38	10.4			18	10.9			3	14.3	
rs2289656 (receptor TrkB)													
Full Sample		(*n* = 1224)				(*n* = 518)				(*n* = 65)			
TBI History													.32
None			842	68.8			373	72			47	72.3	
One			274	22.4			112	21.6			11	16.9	
Two or More			108	8.8			33	6.4			7	10.8	

	M/M				M/n				n/n				
	M	*SD*	*n*	%	*M*	*SD*	*n*	%	*M*	*SD*	*n*	%	*p*
Endorsed TBI		(*n* = 382)				(*n* = 145)				(*n* = 18)			
Age of First TBI													.190
Age	32.52	25.24			36.22	26.77			26.28	20.50			.166
Childhood			157	41.1			51	35.2			9	50	
Early Adulthood			67	17.5			34	23.4			4	22.2	
Middle Adulthood			88	23			25	17.2			4	22.2	
Late Life			70	18.3			35	24.1			1	5.6	
Age of Last TBI													.256
Age	39.26	26.01			41.42	27.93			44.28	26.90			.556
Childhood			148	38.7			49	33.8			6	33.3	
Early Adulthood			67	17.5			33	22.8			3	16.7	
Middle Adulthood			84	22			21	14.5			4	22.2	
Late Life			83	21.7			42	29			5	27.8	
TBI Severity													.850
Mild			266	69.6			96	66.2			12	66.7	
Moderate			76	19.9			33	22.8			3	16.7	
Severe			40	10.5			16	11			3	16.7	
rs2072446 (receptor p75NTR)													
Full Sample		(*n* = 1657)				(*n* = 150)				(*n* = 4)			
TBI History													.481
None			1164	70.2			95	63.3			3	75	
One			358	21.6			40	26.7			1	25	
Two or More			135	8.1			15	10			0	0	
Endorsed TBI		(*n* = 493)				(*n* = 55)				(*n* = 1)			
Age of First TBI													NA
Age	33.14	25.29			34.62	27.93			16	NA			NA
Childhood			198	40.2			21	38.2			1	100	
Early Adulthood			94	19.1			10	18.2			0	0	
Middle Adulthood			110	22.3			9	16.4			0	0	
Late Life			91	18.5			15	27.3			0	0	

	M/M				M/n				n/n				
	M	*SD*	*n*	%	*M*	*SD*	*n*	%	*M*	*SD*	*n*	%	*p*
Age of Last TBI													NA
Age	39.50	26.11			34.93	29.65			16	NA			NA
Childhood			186	37.7			19	34.5			1	100	
Early Adulthood			92	18.7			10	18.2			0	0	
Middle Adulthood			104	21.1			7	12.7			0	0	
Late Life			111	22.5			19	34.5			0	0	
TBI Severity													NA
Mild			346	70.2			31	56.4			1	100	
Moderate			97	19.7			14	25.5			0	0	
Severe			50	10.1			10	18.2			0	0	
rs56164415 (BDNF C270T)													
Full Sample			(*n* = 1597)				(*n* = 206)				(*n* = 0)		
TBI History													.416
None			1104	69.1			151	73.3			0	0	
One			360	22.5			42	20.4			0	0	
Two or More			133	8.3			13	6.3			0	0	
Endorsed TBI			(*n* = 493)				(*n* = 55)				(*n* = 0)		
Age of First TBI													.047 *
Age	33.51	25.88			30.76	24.00							.453
Childhood			196	39.8			26	47.3			0	0	
Early Adulthood			98	19.9			5	9.1			0	0	
Middle Adulthood			99	20.1			17	30.9			0	0	
Late Life			100	20.3			7	12.7			0	0	
Age of Last TBI													.022 *
Age	39.80	26.64			37.56	25.31							.553
Childhood			184	37.3			25	45.5			0	0	
Early Adulthood			97	19.7			5	9.1			0	0	
Middle Adulthood			92	18.7			17	30.9			0	0	
Late Life			120	24.3			8	14.5			0	0	

	M/M				M/n				n/n				
	M	*SD*	*n*	%	*M*	*SD*	*n*	%	*M*	*SD*	*n*	%	*p*
TBI Severity													.180
Mild			343	69.6			36	65.5			0	0	
Moderate			100	20.3			9	16.4			0	0	
Severe			50	10.1			10	18.2			0	0	

Note. TBI = Traumatic Brain Injury; BDNF/NGFR-Related SNP= Brain Derived Neurotrophic Factor Gene/Nerve Growth Factor Receptor-Related Single Nucleotide Polymorphism; Childhood = Ages 0-17; Early Adulthood = Ages 18-30; Middle Adulthood = Ages 31-64; Late Life = Ages 65+

. p <.1. * p <.05.

RQ 1 - History of TBI (Number) on Cognition Over Time

Modified Mini-Mental State Exam. In a base model with TBI, time and time^2, 3MS scores declined in the population across the four waves in a curvilinear fashion (time^2 p <.001). In the fully adjusted model, number of TBI was not associated with either overall 3MS score (p = .170) or rate of change in 3MS (TBI*time p = .821 and TBI*time^2 p = .228). Amongst the covariates, younger age, higher educational attainment, and female sex were associated with higher overall 3MS scores and slower rates of decline for younger age and higher educational attainment. Table 6 displays the parameter estimates from the fully adjusted model.

Hopkins Verbal Learning Test-Revised. In a base model with terms for intercept and time, HVLT-R Learning scores declined by approximately 0.93 points (time p <.001) per year, HVLT-R Delayed Recall scores declined by 0.14 points (time p <.001) per year and HVLT-R Recognition scores did not significantly change in the interval between Waves 3 and 4. In the fully adjusted model, participants with two or more TBIs declined more rapidly over time on HVLT-R Learning compared to those with no TBI

history by approximately 0.39 points annually (two or more TBI*time $p = .018$). TBI history was associated with slightly higher HVLT-R Recognition recall scores at a trend level (TBI*time $p = .051$). Specifically, participants with one TBI scored on average 0.32 of a point higher per year compared to participants with no reported TBIs (one TBI*time $p = .031$). TBI history was not associated with change in HVLT-R Delayed recall scores (TBI $p = .843$) or rate of change (TBI*time $p = .491$). With respect to covariates, younger age, higher educational attainment, and female sex were associated with higher HVLT-R Learning, Delayed Recall and Recognition scores. Table 7 displays the parameter estimates for the fully adjusted models.

Digit Span. In a base model with terms for intercept and time only, DS Forwards and Backwards scores did not significantly change per year between Waves 3 and 4. In the fully adjusted model, number of TBI was not associated with change in DS Forwards score (TBI $p = .214$) or rate of change (TBI*time $p = .864$). Nor was TBI associated with change in DS Backwards score (TBI $p = .822$) or rate of change (TBI*time $p = .367$). Amongst the covariates, younger age and higher educational attainment were associated with higher DS Forwards and Backwards scores or slower rates of decline. For DS Forwards, female sex was also associated with a slower rate of decline. Table 7 displays the parameter estimates for the fully adjusted models.

Clock Drawing Test. In a base model with terms for intercept and time only, CDT total scores declined by approximately 2.35 points (time $p < .001$) annually between Waves 3 and 4. In the fully adjusted model, number of TBI was not associated with

change in CDT total scores (TBI $p = .563$) or rate of change (TBI*time $p = .817$). Amongst covariates, older age and female sex were associated with lower overall scores or faster rates of decline. Table 7 displays parameter estimates for the fully adjusted models.

Table 6

Fully Adjusted Models for History of TBI and 3MS Scores

3MS	b (SE)	*p*
Intercept	93.67 (0.24)	<.001***
Main Effects		
Time (yrs)	0.34 (0.07)	<.001***
Time^2 (yrs)	-0.03 (0.01)	<.001***
Age (Centered at 65)	-0.41 (0.01)	<.001***
Sex (Female)	1.48 (0.18)	<.001***
Education (Less than HS/GED)	-3.18 (0.27)	<.001***
Education (More than HS/GED)	2.14 (0.20)	<.001***
One TBI	0.07 (0.24)	.759
Two or More TBI	-0.71 (0.39)	.071
Interactions		
Time x Age	-0.04 (0.01)	<.001***
Time^2 x Age	-0.00 (0.00)	<.001***
Time x One TBI	0.06 (0.10)	.531
Time^2 x One TBI	-0.01 (0.01)	.471
Time x Two or More TBI	0.02 (0.16)	.884
Time^2 x Two or More TBI	-0.02 (0.01)	.099
Time^2 x Less than HS/GED	-0.03 (0.01)	<.001***
Time^2 x More than HS/GED	0.00 (0.00)	.603

Note. Reference category for sex is males. Reference category for education is HS diploma or GED. Reference category for TBI is no reported TBI.

3MS = Modified Mini-Mental State Exam; TBI = Traumatic Brain Injury; HS = High School; GED = General Education Diploma

*** p <.001.

Table 7

Fully Adjusted Models for History of TBI by Cognitive Outcomes

	HVLT-R Learning		HVLT-R Delayed		HVLT-R Recognition		DS Forwards		DS Backwards		CDT Total	
	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*
Intercept												
	21.29 (0.27)	<.001***	5.86 (0.17)	<.001***	20.32 (0.19)	<.001***	8.93 (0.10)	<.001***	4.94 (0.09)	<.001***	10.47 (0.14)	<.001***
Main Effects												
Time (yrs)	-0.96 (0.05)	<.001***	-0.17 (0.03)	<.001***	-0.74 (0.30)	.996	0.00 (0.02)	.953	0.09 (0.03)	<.01**	-2.34 (0.04)	<.001***
Age (Centered at 80 Years)	-0.34 (0.02)	<.001***	-0.23 (0.01)	<.001***	-0.32 (0.48)	<.001***	-0.05 (0.01)	<.001***	-0.05 (0.01)	<.001***	0.05 (0.01)	<.001***
Sex (Female)	2.51 (0.23)	<.001***	1.28 (0.14)	<.001***			-0.15 (0.09)	.073	0.26 (0.07)	<.001***	-1.20 (0.16)	<.001***
Education (Less than HS/GED)	-1.81 (0.37)	<.001***	-0.97 (0.23)	<.001***	0.65 (0.33)	.051	-0.81 (0.14)	<.001***	-0.61 (0.13)	<.001***		
Education (More than HS/GED)	1.59 (0.24)	<.001***	0.63 (0.15)	<.001***	0.17 (0.21)	.419	0.54 (0.09)	<.001***	0.64 (0.09)	<.001***		
One TBI	-0.39 (0.29)	.183	-11 (0.19)	.563	-0.74 (0.30)	.014*	-0.16 (0.11)	.162	0.04 (0.10)	.681	0.22 (0.22)	.313
Two or More TBI	-0.27 (0.47)	.567	-0.09 (0.30)	.769	-0.32 (0.48)	.498	-0.22 (0.18)	.209	0.08 (0.15)	.598	-0.07 (0.35)	.831

	HVLT-R Learning		HVLT-R Delayed		HVLT-R Recognition		DS Forwards		DS Backwards		CDT Total	
	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*
Interactions												
Time x Education (Less than HS/GED)									-0.10 (0.05)	.068		
Time x Education (More than HS/GED)									-0.10 (0.03)	<.01**		
Time x One TBI	0.18 (0.11)	.098	-0.01 (0.07)	.895	0.33 (0.15)	.025*	-0.00 (0.04)	.960	-0.05 (0.04)	.158	0.00 (0.09)	.990
Time x Two or More TBI	-0.39 (0.16)	.018*	-0.15 (0.11)	.176	-0.19 (0.23)	.396	0.03 (0.06)	.600	-0.02 (0.06)	.743	-0.09 (0.15)	.530

Note. Reference category for education is a HS diploma or GED. Reference category for TBI is no reported TBI.

HVLT-R = Hopkins Verbal Learning Test-Revised; DS = Digit Span; CDT = Clock Drawing Test; HS = High School; GED = General Education Diploma; TBI = Traumatic Brain Injury

* p <.05. ** p <.01. *** p <.001.

RQ 2: Age at First and Last TBI and Severity on Cognitive Outcomes Over Time

Modified Mini-Mental State Exam. In the fully adjusted model, age at first TBI was not associated with 3MS scores (age first $p = .763$) or rate of change (age first*time $p = .817$; age first*time^2 $p = .616$). Age at last TBI was also not associated with 3MS score (age last $p = .939$) or rate of change (age last*time $p = .931$; age last*time^2 $p = .419$). Furthermore, severity of TBI was not associated with 3MS score ($p = .956$) or rate of change (severity*time $p = .727$; severity*time^2 $p = .568$). Amongst the covariates, younger age, higher educational attainment, and female sex were associated with higher 3MS scores or slower rates of decline. Table 8 displays the parameter estimates for the fully adjusted model.

Hopkins Verbal Learning Test-Revised. In the fully adjusted model, age at first TBI was not associated with HVLT-R Learning score (age first $p = .765$) or rate of change (age first*time $p = .362$). Age at last TBI was also not associated with HVLT-R Learning score (age last $p = .431$) or rate of change (age last*time $p = .206$). Furthermore, severity of TBI was not associated with HVLT-R Learning score (severity $p = .376$) or rate of change (severity*time $p = .512$). For HVLT-R Delayed Recall, age at first TBI was not associated with obtained score (age first $p = .684$) or rate of change in score (age first*time $p = .582$). When interacting with sex, age at last TBI was associated with decreased HVLT-R Delayed Recall score over time at a trend level (age last*time*sex $p = .075$). Specifically, females with a reported last TBI in early adulthood scored on average 0.94 points lower (early adulthood*time*female $p = .006$) per year on

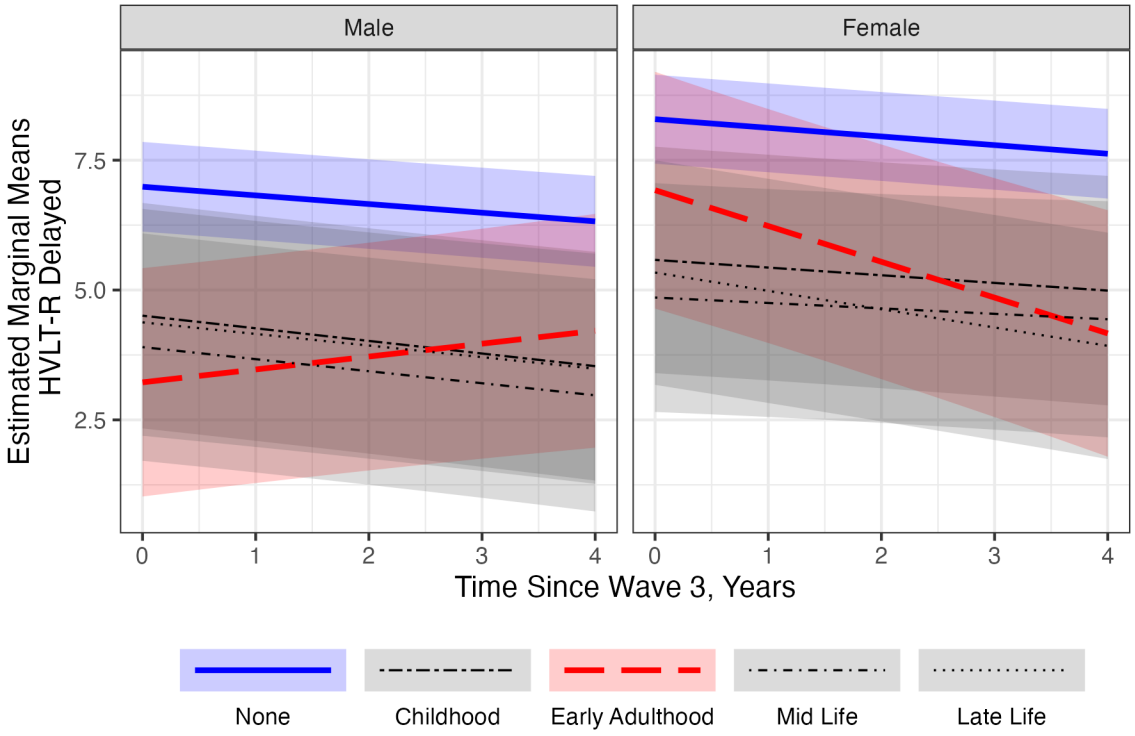
HVLT-R Delayed Recall than males with no reported TBI (see figure 1). TBI severity was not associated with changes in HVLT-R Delayed Recall scores (p = .169) or rate of change. In the fully adjusted models for HVLT-R Recognition, age at first TBI was not associated with HVLT-R Recognition score (age first p = .978) or rate of change (age first*time p = .716). Age at last TBI was also not associated with HVLT-R Recognition score (age last p = .982) or rate of change (age last*time p = .602). When interacting with sex, TBI severity was associated with increased HVLT-R Recognition recall score over time (severity*time*sex p = .030). Specifically, females with a reported severe TBI scored on average 2.35 points higher (severe*time*female p = .004) on HVLT-R Recognition compared to males without a TBI (see figure 2). Furthermore, an additional analysis which included age at last TBI as a possible confounding variable was completed, which resulted in a rank deficient model and inconclusive results. As a result, a one-way ANOVA test was completed to determine if TBI severity was associated with age at last TBI. Results indicated age at last TBI was not associated with TBI severity (p = .415).

Amongst the covariates, younger age and higher educational attainment were significantly associated with increased scores for all HVLT-R tasks. Female sex was significantly associated with higher scores for HVLT-R Learning and Delay Recall tasks. Furthermore, female sex was associated with higher scores at a trend level for HVLT-R Recognition when examining TBI severity. Table 9 presents the parameter estimates in the fully adjusted model.

Digit Span. In the fully adjusted model, age at first TBI was not associated with DS Forwards score (age first $p = .338$) or rate of change (age first*time $p = .779$). Age at last TBI was also not associated with DS Forwards score (age last $p = .177$) or rate of change (age last*time $p = .865$). Furthermore, severity of TBI was not associated with DS Forwards score (severity $p = .083$) or rate of change (severity*time $p = .548$). For DS Backwards, age at first TBI was not associated with obtained score (age first $p = .687$) or rate of change in score (age first*time $p = .521$). Age at Last TBI was also not associated with DS Backwards score (age first $p = .438$) or rate of change in score (age first*time $p = .246$). However, age at last TBI was associated with lower DS Backwards score when modified by sex at a trend level (age last*sex $p = .081$). Specifically, females with a most recent TBI reported in late life declined on average 0.54 points compared to males with no reported TBI (late life*female $p = .031$). Severity of TBI was not associated with DS Backwards score (severity $p = .862$) or rate of change (severity*time $p = .434$). Amongst the covariates, younger age and higher educational attainment were significantly associated with higher scores for DS Forwards and Backwards. For DS Backwards, sex was also a significant covariate with female sex associated with higher scores. Female sex was associated with lower scores at a trend level for DS Forwards when examining TBI severity. Table 9 presents the parameter estimates in the fully adjusted model.

Figure 1

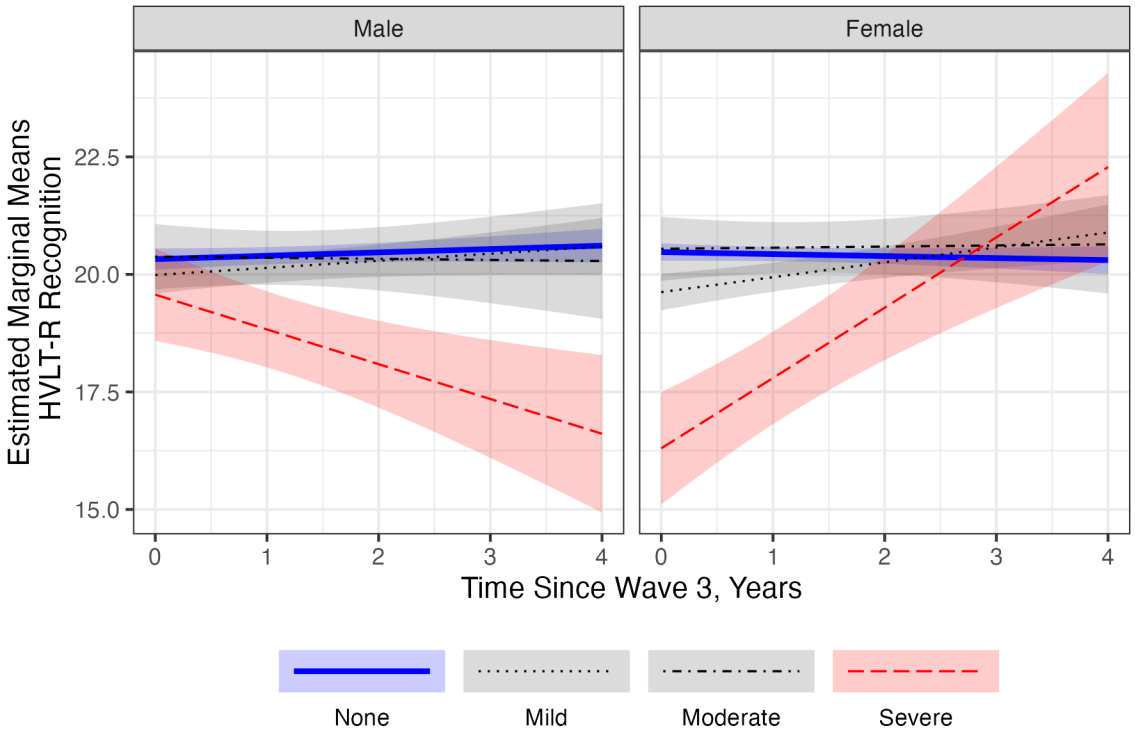
HVLT-R Delayed Recall: Age at Last TBI by Sex Over Time



Note. When interacting with sex, age at last TBI was associated with decreased HVLT-R Delayed Recall score over time at a trend level (age last*time*sex $p = .075$). Specifically, females with a reported last TBI in early adulthood scored on average 0.94 points lower (early adulthood*time*female $p = .006$) per year on HVLT-R Delayed Recall than males with no reported TBI. Shaded region represents one standard error of the mean. HVLT-R = Hopkins Verbal Learning Test-Revised; TBI = Traumatic Brain Injury.

Figure 2

HVLT-R Recognition: TBI Severity by Sex Over Time



Note. When interacting with sex, TBI severity was associated with increased HVLT-R Recognition recall score over time (severity*time*sex p = .030). Specifically, females with a reported severe TBI scored on average 2.35 points higher (severe*time*female p = .004) on HVLT-R Recognition compared to males without a TBI. Shaded region represents one standard error of the mean.

HVLT-R = Hopkins Verbal Learning Test-Revised; TBI = Traumatic Brain Injury.

Clock Drawing Test. In the fully adjusted model, age at first TBI was associated with rate of change in CDT total score at a trend level (p = .057). Specifically, individuals

with a first reported TBI in late life scored on average 0.28 points higher (late life*time p = .035) per year on CDT total compared to individuals without a TBI. Age at last TBI was not associated with CDT Total score (age last p = .580) or rate of change (age last*time p = .361). Furthermore, severity of TBI was also not associated with CDT Total score (severity p = .815) or rate of change (severity*time p = .358). With respect to covariates younger age and male sex were associated with higher CDT total scores. Table 9 presents the parameter estimates in the fully adjusted model.

Table 8

Fully Adjusted Models for Characteristics of TBI and 3MS Scores

3MS	b (SE)	***p***
Age at First TBI		
Intercept	93.68 (0.25)	<.001***
Main Effects		
Time (yrs)	0.34 (0.07)	<.001***
Time^2 (yrs)	-0.03 (0.01)	<.001***
Age (Centered at 65)	-0.41 (0.01)	<.001***
Sex (Female)	1.47 (0.19)	<.001***
Education (Less than HS/GED)	-3.19 (0.27)	<.001***
Education (More than HS/GED)	2.14 (0.20)	<.001***
Childhood	-0.30 (0.34)	.385
Early Adulthood	0.18 (0.52)	.724
Middle Adulthood	-0.38 (0.42)	.361
Late Life	0.10 (0.34)	.765
Interactions		
Time x Age (Centered at 65)	-0.04 (0.01)	<.001***
Time^2 x Age (Centered at 65)	-0.00 (0.00)	<.001***
Time^2 x Less than HS-GED	-0.03 (0.01)	<.001***
Time^2 x More than HS-GED	0.00 (0.00)	.642
Time x Childhood	0.06 (0.14)	.691
Time^2 x Childhood	-0.01 (0.01)	.625
Time x Early Adulthood	0.25 (0.22)	.259

3MS	b (SE)	*p*
Time^2 x Early Adulthood	-0.02 (0.02)	.249
Time x Middle Adulthood	0.07 (0.18)	.679
Time^2 x Middle Adulthood	-0.02 (0.02)	.360
Time x Late Life	-0.02 (0.14)	.892
Time^2 x Late Life	-0.01 (0.01)	.380
Age at Last TBI		
Intercept	93.67 (0.25)	<.001***
Main Effects		
Time (yrs)	0.35 (0.07)	<.001***
Time^2 (yrs)	-0.03 (0.01)	<.001***
Age (Centered at 65)	-0.41 (0.01)	<.001***
Sex (Female)	1.48 (0.19)	<.001***
Education (Less than HS/GED)	-3.20 (0.27)	<.001***
Education (More than HS/GED)	2.14 (0.20)	<.001***
Childhood	-0.19 (0.35)	.593
Early Adulthood	0.15 (0.52)	.774
Middle Adulthood	-0.28 (0.43)	.520
Late Life	-0.07 (0.33)	.822
Interactions		
Time x Age (Centered at 65)	-0.04 (0.01)	<.001***
Time^2 x Age (Centered at 65)	-0.00 (0.00)	<.001***
Time^2 x Less than HS-GED	-0.03 (0.01)	<.001***
Time^2 x More than HS-GED	0.00 (0.00)	.679
Time x Childhood	0.03 (0.15)	.850
Time^2 x Childhood	0.00 (0.01)	.868
Time x Early Adulthood	0.19 (0.22)	.391
Time^2 x Early Adulthood	-0.02 (0.02)	.278
Time x Middle Adulthood	0.06 (0.18)	.742
Time^2 x Middle Adulthood	-0.01 (0.02)	.523
Time x Late Life	0.03 (0.13)	.793
Time^2 x Late Life	-0.02 (0.01)	.109
Severity of TBI		
Intercept	93.66 (0.24)	<.001***
Main Effects		
Time (yrs)	0.35 (0.07)	<.001***
Time^2 (yrs)	-0.03 (0.01)	<.001***
Age (Centered at 65)	-0.41 (0.01)	<.001***
Sex (Female)	1.48 (0.18)	<.001***
Education (Less than HS/GED)	-3.20 (0.27)	<.001***
Education (More than HS/GED)	2.14 (0.20)	<.001***

3MS	b (SE)	*p*
Mild	-0.09 (0.24)	.724
Moderate	-0.20 (0.43)	.640
Severe	-0.10 (0.63)	.876
Interactions		
Time x Age (Centered at 65)	-0.04 (0.01)	<.001***
Time^2 x Age (Centered at 65)	-0.00 (0.00)	<.001***
Time^2 x Less than HS/GED	-0.03 (0.01)	<.001***
Time^2 x More than HS/GED	0.00 (0.00)	.642
Time x Mild	0.09 (0.10)	.389
Time^2 x Mild	-0.01 (0.01)	.222
Time x Moderate	0.04 (0.18)	.799
Time^2 x Moderate	-0.01 (0.02)	.398
Time x Severe	-0.18 (0.27)	.508
Time^2 x Severe	-0.01 (0.03)	.760

Note. Reference category for sex is males. Reference category for education is a HS diploma or GED. Reference category for TBI characteristics is no reported TBI.

3MS = Modified Mini-Mental State Exam; TBI = Traumatic Brain Injury; HS = High School; GED = General Education Diploma; Childhood = Ages 0-17; Early Adulthood = Ages 18-30; Middle Adulthood = Ages 31-64; Late Life = Ages 65+

*** p <.001.

Table 9

Fully Adjusted Models for Characteristics of TBI by Cognitive Outcomes

	HVLT-R Learning		HVLT-R Delayed		HVLT-R Recognition		DS Forwards		DS Backwards		CDT Total	
	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*
Age at First TBI												
Intercept												
	21.29 (0.27)	<.001***	5.89 (0.17)	<.001***	20.33 (0.19)	<.001***	8.81 (0.08)	<.001***	5.02 (0.09)	<.001***	10.48 (0.14)	<.001***
Main Effects												
Time (yrs)	-0.96 (0.05)	<.001***	-0.17 (0.03)	<.001***	0.00 (0.07)	.978	0.00 (0.02)	.945	0.02 (0.02)	.199	-2.34 (0.04)	<.001***
Age (Centered at 80 Years)	-0.34 (0.02)	<.001***	-0.23 (0.01)	<.001***	-0.16 (0.02)	<.001***	-0.05 (0.01)	<.001***	-0.05 (0.01)	<.001***	0.05 (0.01)	<.001***
Sex (Female)	2.53 (0.23)	<.001***	1.27 (0.15)	<.001***					0.26 (0.08)	<.001***	-1.22 (0.16)	<.001***
Education (Less than HS/GED)	-1.84 (0.37)	<.001***	-1.00 (0.24)	<.001***	-0.65 (0.33)	.053 .	-0.76 (0.14)	<.001***	-0.72 (0.12)	<.001***		
Education (More than HS/GED)	1.56 (0.24)	<.001***	0.59 (0.15)	<.001***	0.14 (0.21)	.510	0.58 (0.09)	<.001***	0.52 (0.08)	<.001***		
Mild			2.98 (3.00)	.320	1.67 (4.06)	.682						

	HVLT-R Learning		HVLT-R Delayed		HVLT-R Recognition		DS Forwards		DS Backwards		CDT Total	
	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*
Moderate			2.47 (2.98)	.408	2.06 (4.03)	.610						
Severe			1.88 (3.03)	.534	-0.02 (4.10)	.997						
Childhood	-0.30 (0.42)	.465	-2.71 (3.00)	.366	-2.29 (4.07)	.574	-0.08 (0.16)	.612	0.19 (0.14)	.160	0.52 (0.31)	.094 .
Early Adulthood	-0.39 (0.66)	.555	-2.89 (3.02)	.339	-2.08 (4.10)	.613	0.09 (0.25)	.729	0.07 (0.22)	.742	-0.33 (0.49)	.505
Middle Adulthood	-0.38 (0.51)	.460	-3.18 (3.01)	.292	-2.11 (4.08)	.606	-0.26 (0.19)	.169	-0.01 (0.17)	.958	0.07 (0.39)	.859
Late Life	-0.39 (0.42)	.352	2.82 (3.00)	.348	-2.27 (4.07)	.577	-0.26 (0.16)	.102	-0.04 (0.14)	.762	0.01 (0.31)	.975
Interactions												
Time x Childhood	0.09 (0.15)	.523	-0.04 (0.10)	.699	0.19 (0.20)	.357	0.04 (0.05)	.412	-0.06 (0.05)	.199	-0.14 (0.13)	.291
Time x Early Adulthood	0.06 (0.23)	.797	0.11 (0.16)	.498	0.25 (0.32)	.430	-0.08 (0.09)	.330	-0.04 (0.08)	.616	-0.15 (0.20)	.454
Time x Middle Adulthood	0.28 (0.19)	.146	-0.02 (0.13)	.905	0.23 (0.26)	.371	0.01 (0.07)	.911	-0.08 (0.07)	.197	-0.25 (0.17)	.140
Time x Late Life	-0.18 (0.15)	.238	-0.15 (0.10)	.142	0.12 (0.21)	.560	0.01 (0.05	.926	-0.00 (0.05)	1.00	0.28 (0.13)	.035*
Age at Last TBI												
Intercept												

	HVLT-R Learning		HVLT-R Delayed		HVLT-R Recognition		DS Forwards		DS Backwards		CDT Total	
	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*
	21.28 (0.27)	<.001***	5.87 (0.18)	<.001***	20.34 (0.19)	<.001***	8.81 (0.08)	<.001***	5.02 (0.09)	<.001***	10.49 (0.14)	<.001***
Main Effects												
Time (yrs)	-0.96 (0.05)	<.001***	-0.17 (0.05)	.002**	0.00 (0.07)	.981	0.00 (0.02)	.943	0.02 (0.02)	.199	-2.34 (0.04)	<.001***
Age (Centered at 80 Years)	-0.34 (0.02)	<.001***	-0.23 (0.01)	<.001***	-0.16 (0.02)	<.001***	-0.05 (0.01)	<.001***	-0.05 (0.01)	<.001***	0.05 (0.01)	<.001***
Sex (Female)	2.56 (0.23)	<.001***	1.30 (0.19)	<.001***					0.26 (0.07)	<.001***	-1.23 (0.16)	<.001***
Education (Less than HS/GED)	-1.86 (0.37)	<.001***	-1.00 (0.24)	<.001***	-0.65 (0.34)	.052*	-0.77 (0.14)	<.001***	-0.72 (0.12)	<.001***		
Education (More than HS/GED)	1.56 (0.24)	<.001***	0.59 (0.15)	<.001***	0.14 (0.21)	.514	0.58 (0.09)	<.001***	0.52 (0.08)	<.001***		
Mild			2.99 (3.00)	.319	1.66 (4.06)	.683						
Moderate			2.45 (2.98)	.411	2.06 (4.04)	.610						
Severe			1.93 (3.03)	.525	-0.01 (4.11)	.998						
Childhood	0.12 (0.43)	.779	-2.48 (3.02)	.411	-2.33 (4.07)	.568	-0.01 (0.16)	.938	0.07 (0.18)	.713	0.37 (0.32)	.254

	HVLT-R Learning		HVLT-R Delayed		HVLT-R Recognition		DS Forwards		DS Backwards		CDT Total	
	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*
Early Adulthood	-0.45 (0.66)	.497	-3.77 (3.04)	.215	-2.12 (4.11)	.606	0.13 (0.25)	.590	0.08 (0.25)	.743	-0.24 (0.49)	.620
Middle Adulthood	-0.44 (0.52)	.402	-3.09 (3.03)	.308	-2.18 (4.09)	.594	-0.27 (0.20)	.179	-0.05 (0.22)	.840	-0.21 (0.40)	.597
Late Life	-0.65 (0.39)	.097 .	2.61 (3.03)	.388	-2.17 (4.07)	.594	-0.31 (0.15)	.037*	-0.33 (0.21)	.125	0.28 (0.29)	.338
Interactions												
Time x Childhood	0.11 (0.16)	.473	-0.08 (0.14)	.594	0.27 (0.21)	.209	0.03 (0.06)	.600	-0.09 (0.05)	.081	-0.13 (0.14)	.329
Time x Early Adulthood	0.11 (0.24)	.634	0.41 (0.20)	.034*	0.24 (0.32)	.456	-0.08 (0.09)	.388	-0.05 (0.08)	.525	-0.16 (0.21)	.443
Time x Middle Adulthood	0.34 (0.20)	.087 .	-0.07 (0.18)	.711	0.27 (0.27)	.320	-0.00 (0.07)	1.00	-0.10 (0.07)	.154	-0.14 (0.17)	.404
Time x Late Life	-0.19 (0.14)	.186	-0.06 (0.16)	.727	0.06 (0.20)	.774	0.02 (0.05)	.670	0.02 (0.05)	.708	0.16 (0.12)	.193
Time x Sex (Female)			0.00 (0.07)	.997								
Sex (Female) x Childhood			-0.23 (0.56)	.686					0.42 (0.26)	.109		
Sex (Female) x			2.40 (0.93)	.010**					-0.14 (0.43)	.738		

	HVLT-R Learning		HVLT-R Delayed		HVLT-R Recognition		DS Forwards		DS Backwards		CDT Total	
	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*
Early Adulthood Sex (Female) x Middle Adulthood Sex (Female) x Late Life Time x Sex (Female) x Childhood Time x Sex (Female) x Early Adulthood Time x Sex (Female) x Middle Adulthood Time x Sex (Female) x Late Life			-0.35 (0.67)	.606					0.08 (0.32)	.795		
			-0.34 (0.54)	.526					-0.54 (0.25)	.031*		
			0.09 (0.21)	.652								
			-0.94 (0.34)	.006**								
			0.13 (0.27)	.634								
			-0.13 (0.20)	.517								

	HVLT-R Learning		HVLT-R Delayed		HVLT-R Recognition		DS Forwards		DS Backwards		CDT Total	
	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*
TBI Severity												
Intercept												
	21.32 (0.27)	<.001***	5.89 (0.17)	<.001***	20.25 (0.28)	<.001***	8.93 (0.10)	<.001***	5.03 (0.09)	<.001***	10.46 (0.14)	<.001***
Main Effects												
Time (yrs)	-0.96 (0.05)	<.001***	-0.17 (0.03)	<.001***	0.07 (0.11)	.522	0.00 (0.02)	.950	0.02 (0.02)	.192	-2.34 (0.04)	<.001***
Age (Centered at 80 Years)	-0.34 (0.02)	<.001***	-0.23 (0.01)	<.001***	-0.16 (0.02)	<.001***	-0.05 (0.01)	<.001***	-0.05 (0.01)	<.001***	0.05 (0.01)	<.001***
Sex (Female)	2.49 (0.23)	<.001***	1.26 (0.14)	<.001***	0.15 (0.30)	.613	-0.16 (0.09)	.067 .	0.26 (0.07)	<.001***	-1.18 (0.16)	<.001***
Education (Less than HS/GED)	-1.84 (0.37)	<.001***	-1.01 (0.23)	<.001***	-0.66 (0.34)	.052*	-0.80 (0.14)	<.001***	-0.72 (0.12)	<.001***		
Education (More than HS/GED)	1.56 (0.24)	<.001***	0.60 (0.15)	<.001***	0.13 (0.22)	.537	0.54 (0.09)	<.001***	0.52 (0.08)	<.001***		
Mild	-0.23 (0.31)	.452	0.17 (0.20)	.375	-0.34 (0.45)	.457	-0.07 (0.12)	.560	0.08 (0.10)	.400	0.14 (0.23)	.538
Moderate	-0.40 (0.50)	.422	-0.44 (0.32)	.164	0.05 (0.73)	.943	-0.46 (0.19)	.014*	-0.00 (0.16)	.982	0.30 (0.37)	.422
Severe	-1.16 (0.76)	.130	-1.33 (0.49)	.006**	-0.76 (1.01)	.455	-0.25 (0.29)	.382	-0.02 (0.25)	.942	-0.05 (0.57)	.925

	HVLT-R Learning		HVLT-R Delayed		HVLT-R Recognition		DS Forwards		DS Backwards		CDT Total	
	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*
Interactions												
Time x Mild	-0.03 (0.11)	.773	-0.11 (0.07)	.142	0.08 (0.22)	.717	-0.02 (0.04)	.692	-0.03 (0.04)	.399	0.02 (0.10)	.812
Time x Moderate	0.15 (0.19)	.411	0.03 (0.13)	.781	-0.09 (0.39)	.806	0.09 (0.07)	.181	-0.07 (0.06)	.281	-0.26 (0.16)	.110
Time x Severe	0.36 (0.29)	.224	0.30 (0.20)	.128	-0.81 (0.52)	.119	0.00 (0.11)	.978	-0.11 (0.10)	.256	0.16 (0.25)	.522
Time x Sex (Female)					-0.11 (0.14)	.428						
Sex (Female) x Mild					-0.51 (0.62)	.410						
Sex (Female) x Moderate					0.02 (1.01)	.986						
Sex (Female) x Severe					-3.42 (1.58)	.030*						
Time x Sex (Female) x Mild					0.28 (0.30)	.356						
Time x Sex (Female) x					0.16 (0.51)	.755						

	HVLT-R Learning		HVLT-R Delayed		HVLT-R Recognition		DS Forwards		DS Backwards		CDT Total	
	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*
Moderate Time x Sex (Female) x Severe					2.35 (0.81)	.004**						

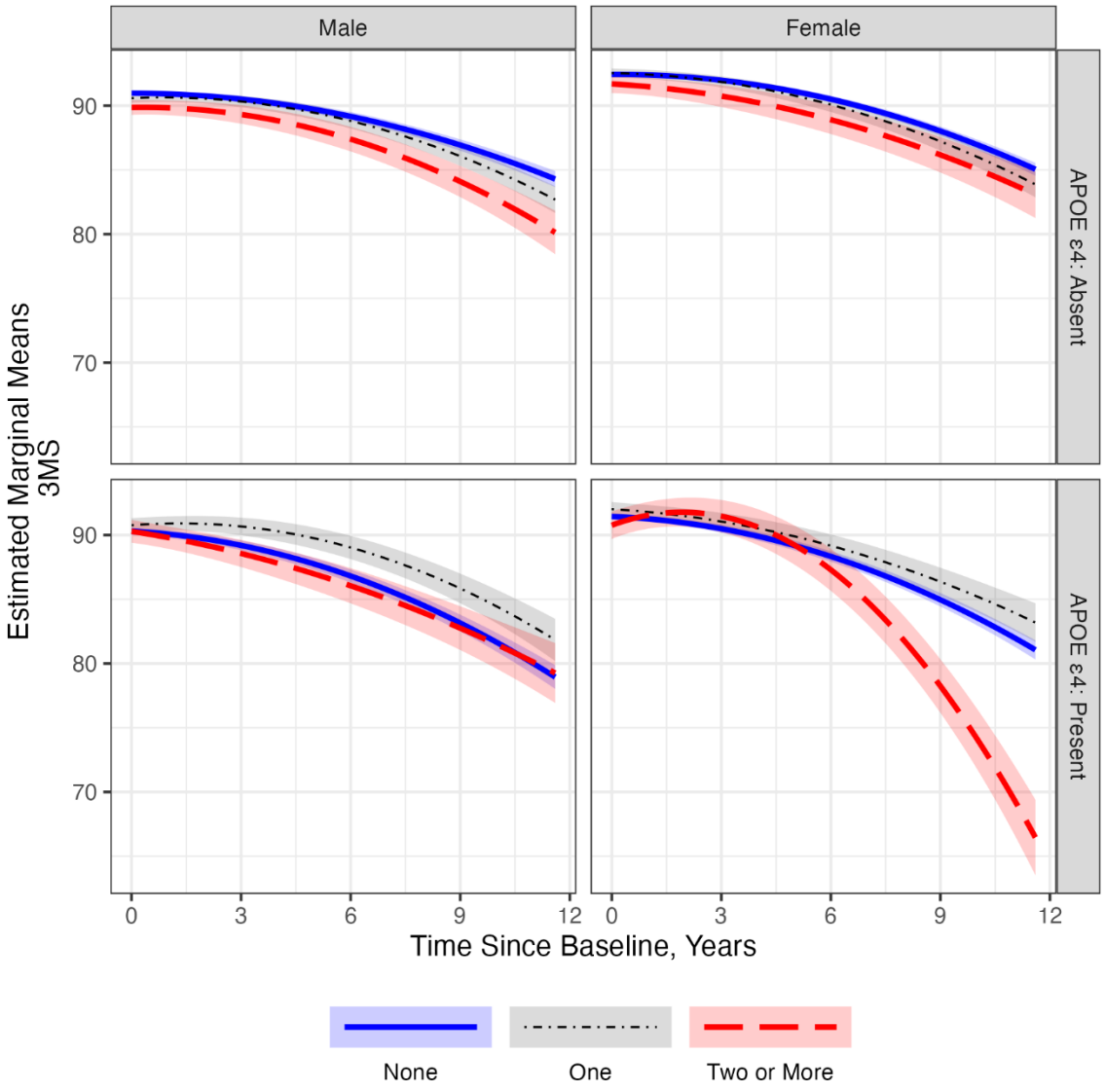
RQ 3: The Moderation of APOE Genotype on TBI and Cognitive Outcomes Over Time

In this series of analyses, the final models with a significant TBI effect for each cognitive outcome from RQ1 and RQ2 were re-examined to test for an interaction between TBI characteristics (number, age at first and last TBI, and/or severity) and APOE genotype.

Modified Mini-Mental State Exam. In the fully adjusted model, APOE ε4 significantly modified the association between number of TBI and change in 3MS score over time when examining sex differences (TBI*APOE ε4 *sex*time^2 p <.001). Specifically, females with at least one APOE ε4 allele and two or more reported TBIs declined on average 0.26 points per year more on the 3MS compared to males with no APOE ε4 allele and without a history of TBI (two or more TBI*APOE ε4 *female*time^2 p <.001; see figure 3). Amongst the covariates, younger age and higher educational attainment were associated with higher 3MS scores or slower rates of decline. Table 10 displays the parameter estimates for the fully adjusted model.

Figure 3

APOE Genotype Moderation of TBI History on 3MS Score Over Time by Sex



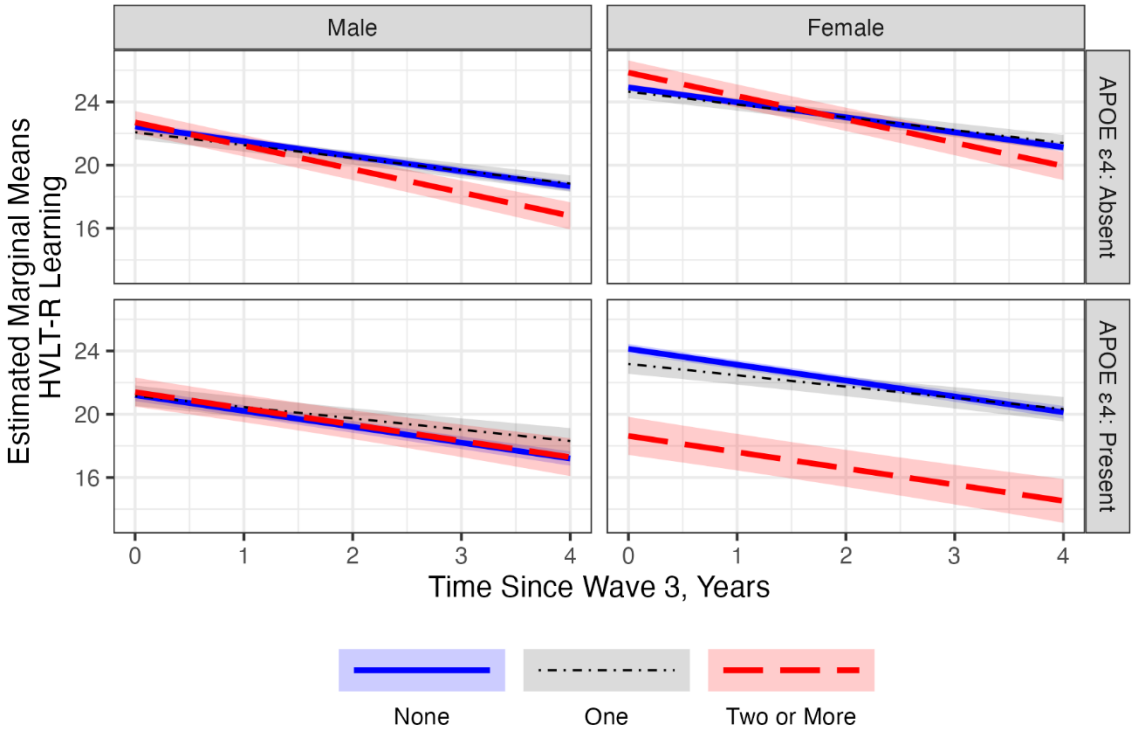
Note. APOE ε4 significantly modified the association between number of TBI and change in 3MS score over time when examining sex differences (TBI*APOE ε4 *sex*time^2 p <.001). Specifically, females with at least one APOE ε4 allele and two or more reported TBI declined on average 0.26 points per year on the 3MS compared to

males with no APOE ε4 allele and without a history of TBI (two or more TBI*APOE ε4 *female*time^2 p <.001). Shaded region represents one standard error of the mean. APOE = Apolipoprotein E; 3MS = Modified Mini-Mental State Exam; TBI = Traumatic Brain Injury.

Hopkins Verbal Learning Test-Revised. In the fully adjusted model, APOE ε4 significantly modified the association between number of TBI and change in HVLT-R Learning score when examining sex differences (TBI*APOE ε4*sex p = .002). Specifically, females with at least one APOE ε4 allele and two or more reported TBIs declined on average 6.38 points on the HVLT-R Learning compared to males with no APOE ε4 allele and without a history of TBI (two or more TBI*APOE ε4*female p <.001; see figure 4). APOE genotype did not moderate the association between age at last TBI on HVLT-R Delayed Recall score (age last*APOE ε4 p = .652) or rate of change (age last*APOE ε4*time p = .794). Furthermore, APOE ε4 did not significantly modify the association between number of TBIs and HVLT-R Recognition score (TBI*APOE ε4 p = .508) or rate of change (TBI*APOE ε4 *time p = .169) nor did the presence of APOE ε4 allele moderate the association between TBI severity and HVLT-R Recognition score (severity*APOE ε4 p = .094) or rate of change (age last*APOE ε4*time p = .429). Younger age and higher educational attainment were associated with higher scores on HVLT-R Delayed Recall and Recognition. Furthermore, female sex was associated with a higher score on HVLT-R Learning and Delayed Recall. Table 11 displays the parameter estimates for the fully adjusted model.

Figure 4

APOE genotype Moderation of TBI History on HVLT-R Learning Score by Sex



Note. APOE ε4 significantly modified the association between number of TBI and change in HVLT-R Learning score when examining sex differences (TBI*APOE ε4*sex p = .002). Specifically, females with at least one APOE ε4 allele and two or more reported TBI declined on average 6.38 points on the HVLT-R Learning compared to males with no APOE ε4 allele and without a history of TBI (two or more TBI*APOE ε4*female p <.001). Shaded region represents one standard error of the mean. APOE = Apolipoprotein E; TBI = Traumatic Brain Injury; HVLT-R = Hopkins Verbal Learning Test-Revised.

Digit Span. APOE genotype did not moderate the associations between age at last TBI on DS Backwards score (age last*APOE ε4 $p = .705$) or rate of change (age last*APOE ε4*time $p = .843$) in the fully adjusted models. Younger age, higher educational attainment, and female sex were associated with higher scores. Table 11 displays the parameter estimates for the fully adjusted model.

Clock Drawing Test. Presence of APOE ε4 allele did not moderate the associations between age at first TBI on CDT total score (age first*APOE ε4 $p = .806$) or rate of change (age first*APOE ε4*time $p = .390$). Older age and female sex were associated with lower CDT total scores or faster rates of decline. Table 11 displays the parameter estimates for the fully adjusted model.

Table 10

Fully Adjusted Models of APOE Genotype Moderation on History of TBI and 3MS Scores

3MS	b (SE)	*p*
Intercept	94.00 (0.28)	<.001***
Main Effects		
Time (yrs)	0.39 (0.10)	<.001***
Time^2 (yrs)	-0.02 (0.01)	.072 .
Age (Centered at 65)	-0.41 (0.01)	<.001***
Sex (Female)	1.46 (0.26)	<.001***
Education (Less than HS/GED)	-0.03 (0.01)	<.001***
Education (More than HS/GED)	0.00 (0.00)	<.001***
One TBI	-0.38 (0.41)	.349
Two or More TBI	-1.11 (0.61)	.070
APOE ε4	-0.67 (0.36)	.063
Interactions		
APOE ε4 x Sex (Female)	-0.32 (0.47)	.492
Time x Age (Centered at 65)	-0.05 (0.01)	<.001***
Time^2 x Age (Centered at 65)	-0.00 (0.00)	<.001***
Time^2 x Education (Less than HS/GED)	-0.03 (0.01)	<.001***
Time^2 x Education (More than HS/GED)	0.00 (0.00)	.854
Time x Sex (Female)	0.02 (0.11)	.836
Time^2 x Sex (Female)	-0.01 (0.01)	.503
Time x APOE ε4	-0.15 (0.16)	.349
Time^2 x APOE ε4	-0.02 (0.02)	.151
Time x One TBI	0.12 (0.17)	.479
Time^2 x One TBI	-0.02 (0.02)	.232
Time x Two or More TBI	0.05 (0.26)	.838
Time^2 x Two or More TBI	-0.03 (0.02)	.274
One TBI x Sex (Female)	0.48 (0.57)	.393
Two or More TBI x Sex (Female)	0.37 (0.95)	.698
One TBI x APOE ε4	0.84 (0.75)	.260
Two or More TBI x APOE ε4	1.10 (1.12)	.326
Time x One TBI x Sex (Female)	-0.19 (0.24)	.428
Time^2 x One TBI x Sex (Female)	0.02 (0.02)	.484
Time x Two or More TBI x Sex (Female)	-0.24 (0.39)	.542
Time^2 x Two or More TBI x Sex (Female)	0.03 (0.04)	.344
Time x One TBI x APOE ε4	0.26 (0.32)	.422
Time^2 x One TBI x APOE ε4	0.00 (0.03)	.880
Time x Two or More TBI x APOE ε4	-0.34 (0.46)	.453
Time^2 x Two or More TBI x APOE ε4	0.05 (0.04)	.203
Time x APOE ε4 x Sex (Female)	0.02 (0.20)	.929
Time^2 x APOE ε4 x Sex (Female)	0.01 (0.02)	.576

3MS	b (SE)	*p*
One TBI x APOE ε4 x Sex (Female)	-0.37 (1.04)	.721
Two or More TBI x APOE ε4 x Sex (Female)	-1.04 (1.73)	.550
Time x One TBI x APOE ε4 x Sex (Female)	-0.25 (0.44)	.570
$Time^2$ x One TBI x APOE ε4 x Sex (Female)	0.02 (0.04)	.713
Time x Two or More TBI x APOE ε4 x Sex (Female)	1.69 (0.69)	.015*
$Time^2$ x Two or More TBI x APOE ε4 x Sex (Female)	-0.26 (0.07)	<.001***

Note. Reference category for sex is males. Reference category for education is a HS diploma or GED. Reference category for TBI is no reported TBI. Reference category for APOE ε4 is no alleles.

3MS = Modified Mini-Mental State Exam; TBI = Traumatic Brain Injury; HS = High School; GED = General Education Diploma; APOE ε4 = Apolipoprotein E ε4 allele

. p <.1. * p <.05. *** p <.001.

Table 11

Fully Adjusted Models of APOE Genotype Moderation on Significant Characteristics of TBI by Cognitive Outcomes

	HVLT-R Learning: Number of TBI		HVLT-R Delayed: Age at Last		HVLT-R Recognition: Number of TBI		HVLT-R Recognition: Severity		DS Backwards: Age at Last		CDT Total: Age at First	
	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*
Intercept												
	21.67 (0.31)	<.001***	6.15 (0.18)	<.001***	20.39 (0.22)	<.001***	20.41 (0.22)	<.001***	5.10 (0.09)	<.001***	10.49 (0.16)	<.001***
Main Effects												
Time (yrs)	-0.95 (0.06)	<.001***	-0.16 (0.04)	<.001***	0.00 (0.08)	.958	0.01 (0.09)	.939	0.01 (0.02)	.626	-2.33 (0.05)	<.001***
Age (Centered at 80 Years)	-0.35 (0.02)	<.001***	-0.24 (0.01)	<.001***	-0.16 (0.02)	<.001***	-0.16 (0.02)	<.001***	-0.06 (0.01)	<.001***	0.05 (0.02)	<.001***
Sex (Female)	2.46 (0.32)	<.001***	1.28 (0.14)	<.001***					0.25 (0.08)	<.001***	-1.22 (0.16)	<.001***
Education (Less than HS/GED)	-1.90 (0.37)	<.001***	-1.02 (0.23)	<.001***	-0.64 (0.34)	.055 .	-0.67 (0.33)	.045*	-0.73 (0.12)	<.001***		
Education (More than HS/GED)	1.51 (0.24)	<.001***	0.57 (0.15)	<.001***	0.16 (0.21)	.458	0.12 (0.21)	.575	0.51 (0.08)	<.001***		
One TBI	-0.37 (0.50)	.455			-0.78 (0.36)	.030 *						
Two or More TBI	0.25 (0.75)	.735			0.03 (0.59)	.954						

	HVLT-R Learning: Number of TBI		HVLT-R Delayed: Age at Last		HVLT-R Recognition: Number of TBI		HVLT-R Recognition: Severity		DS Backwards: Age at Last		CDT Total: Age at First	
	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*
Mild							-0.37 (0.38)	.329				
Moderate							-0.07 (0.60)	.910				
Severe							-3.20 (0.91)	<.001***				
Childhood			0.03 (0.33)	.931					0.32 (0.17)	.062 .	0.53 (0.37)	.153
Early Adulthood			-0.69 (0.52)	.181					0.09 (0.27)	.742	-0.74 (0.60)	.216
Middle Adulthood			-0.49 (0.41)	.229					0.12 (0.21)	.565	0.09 (0.46)	.847
Late Life			-0.23 (0.30)	.445					-0.07 (0.15)	.633	-0.09 (0.37)	.804
APOE ε4	-1.24 (0.45)	.006**	-0.79 (0.19)	<.001***	-0.21 (0.31)	.503			-0.20 (0.10)	.042*	-0.02 (0.22)	.923
Interactions												
Time x APOE ε4	-0.06 (0.11)	.614	-0.03 (0.08)	.699	-0.01 (0.15)	.923	-0.02 (0.15)	.920	0.04 (0.04)	.302	-0.05 (0.10)	.621
Time x One TBI	0.14 (0.13)	.289			0.37 (0.18)	.035 *						
Time x Two or More TBI	-0.53 (0.20)	.008 **			-0.46 (0.28)	.102						
Time x Childhood			-0.06 (0.12)	.647					-0.10 (0.06)	.092 .	-0.12 (0.15)	.421

	HVLT-R Learning: Number of TBI		HVLT-R Delayed: Age at Last		HVLT-R Recognition: Number of TBI		HVLT-R Recognition: Severity		DS Backwards: Age at Last		CDT Total: Age at First	
	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*
Time x Early Adulthood			0.20 (0.20)	.326					0.00 (0.10)	.968	0.15 (0.25)	.544
Time x Middle Adulthood			0.07 (0.16)	.656					-0.12 (0.08)	.140	-0.25 (0.20)	.215
Time x Late Life			-0.09 (0.11)	.436					0.01 (0.06)	.808	0.33 (0.16)	.035*
One TBI x Sex (Female)	0.10 (0.65)	.873										
Two or More TBI x Sex (Female)	0.68 (1.04)	.510										
Sex (Female) x APOE ε4	0.46 (0.56)	410										
One TBI x APOE ε4	0.34 (0.90)	.708			0.22 (0.65)	.739						
Two or More TBI x APOE ε4	-0.06 (1.25)	.959			-1.06 (1.01)	.291						
Childhood x APOE ε4			0.47 (0.59)	.424					-0.28 (0.31)	.352	-0.04 (0.66)	.948
Early Adulthood x APOE ε4			0.98 (0.89)	.266					-0.16 (0.46)	.724	1.20 (1.02)	.240

	HVLT-R Learning: Number of TBI		HVLT-R Delayed: Age at Last		HVLT-R Recognition: Number of TBI		HVLT-R Recognition: Severity		DS Backwards: Age at Last		CDT Total: Age at First	
	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*
Middle Adulthood x APOE ε4			0.17 (0.70)	.807					-0.38 (0.37)	.298	-0.07 (0.84)	.931
Late Life x APOE ε4			0.55 (0.55)	.321					0.10 (0.28)	.727	0.33 (0.67)	.624
Time x One TBI x APOE ε4	0.15 (0.24)	.520			-0.18 (0.32)	.578						
Time x Two or More TBI x APOE ε4	0.51 (0.36)	.154			0.84 (0.49)	.089 .						
Time x Childhood x APOE ε4			0.09 (0.23)	.705					0.05 (0.12)	.651	-0.07 (0.29)	.809
Time x Early Adulthood x APOE ε4			-0.18 (0.33)	.590					-0.15 (0.17)	.369	-0.83 (0.42)	.050 .
Time x Middle Adulthood x APOE ε4			-0.20 (0.28)	.476					0.07 (0.14)	.602	0.01 (0.36)	.968
Time x Late Life x APOE ε4			-0.19 (0.21)	.378					0.02 (0.11)	.814	-0.18 (0.29)	.520

	HVLT-R Learning: Number of TBI		HVLT-R Delayed: Age at Last		HVLT-R Recognition: Number of TBI		HVLT-R Recognition: Severity		DS Backwards: Age at Last		CDT Total: Age at First	
	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*
One TBI x Sex (Female) x APOE ε4	-1.02 (1.17)	.384										
Two or More TBI x Sex (Female) x APOE ε4	-6.38 (1.84)	<.001***										
Time x Mild							0.16 (0.18)	.381				
Time x Moderate							-0.05 (0.30)	.869				
Time x Severe							0.53 (0.47)	.261				
Mild x APOE ε4							-0.73 (0.66)	.270				
Moderate x APOE ε4							0.38 (1.13)	.734				
Severe x APOE ε4							3.72 (1.74)	.032*				
Time x Mild x APOE ε4							0.22 (0.33)	.501				
Time x Moderate x APOE ε4							0.19 (0.56)	.740				

	HVLT-R Learning: Number of TBI		HVLT-R Delayed: Age at Last		HVLT-R Recognition: Number of TBI		HVLT-R Recognition: Severity		DS Backwards: Age at Last		CDT Total: Age at First	
	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*
Time x Severe x APOE ε4							-1.27 (0.88)	.152				

Note. Reference category for sex is males. Reference category for education is a HS diploma or GED. Reference category for TBI characteristics is no reported TBI. Reference category for presence of APOE ε4 is no ε4 alleles. HVLT-R = Hopkins Verbal Learning Test-Revised; DS = Digit Span; CDT = Clock Drawing Test; TBI = Traumatic Brain Injury; HS = High School; GED = General Education Diploma; APOE ε4 = Apolipoprotein E ε4 Allele; Childhood = Ages 0-17; Early Adulthood = Ages 18-30; Middle Adulthood = Ages 31-64; Late Life = Ages 65+

. p <.1. * p <.05. ** p <.01. *** p <.001.

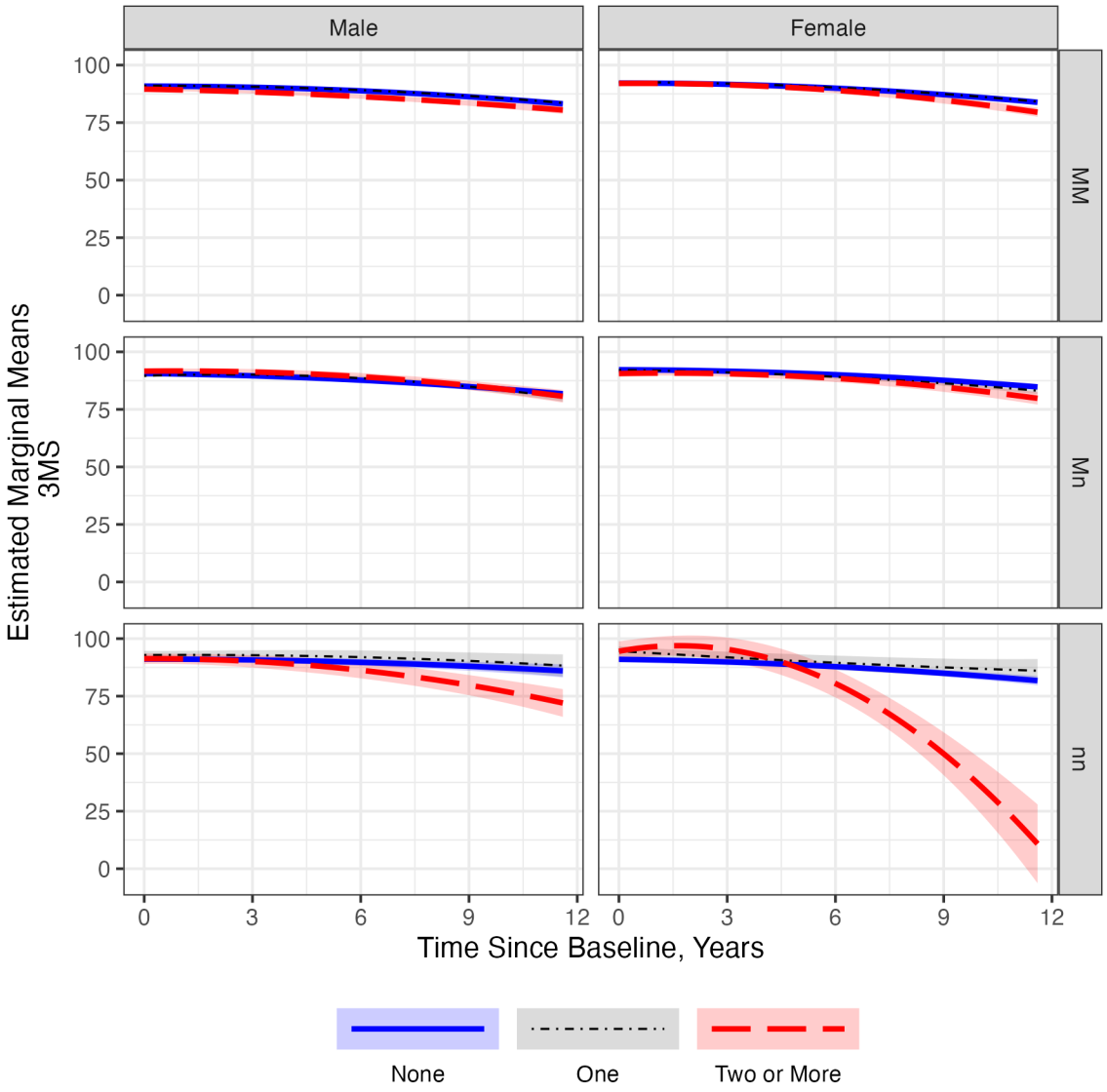
RQ 4: The Modification of SNPs for BDNF or its receptors on TBI and Cognitive Outcome Over Time

In this series of analyses, the final models with a significant TBI effect for each cognitive outcome from RQ1 and RQ2 were re-examined to test for an interaction between TBI characteristics (number, age at first and last TBI, and/or severity) and SNPs for BDNF or its receptors. For receptor TrkB (rs2289656), receptor p75NTR (rs2072446) and BDNF C270T (rs56164415) Wave 3 analyses included absence vs. presence (A/A vs A/a or a/a) of the minor alleles due to lower minor allele frequencies.

Modified Mini-Mental State Exam. In the fully adjusted models, neither receptor p75NTR (rs2072446) nor BDNF Val66Met (rs6265) exhibited a significant interaction with number of TBIs in modeling 3MS score (receptor p75NTR*TBI: p = .148 and BDNF Val66Met*TBI p = .500) or rate of change over time (receptor p75NTR*TBI*Time p = .656; receptor p75NTR*TBI*Time^2 p = .898 and BDNF Val66Met*TBI*Time p = .574; BDNF Val66Met*TBI*Time^2 p = .120, respectively). However, receptor TrkB (rs2289656) exhibited a trend level interaction with number of TBI and sex in modeling 3MS trajectory (receptor TrkB *TBI*Sex*Time^2 p = .072; see figure 5). BDNF C270T (rs56164415) exhibited a trend level interaction with number of TBI in modeling 3MS trajectory (BDNF C270T*TBI*Time^2 p = .065; see figure 6). Amongst the covariates, younger age, higher educational attainment, and female sex were associated with higher 3MS scores or slower rates of decline. Table 12 displays the parameter estimates for the fully adjusted model.

Figure 5

SNP Rs2289656 (Receptor TrkB) Moderation of Number of TBI and Time on 3MS Score by Sex



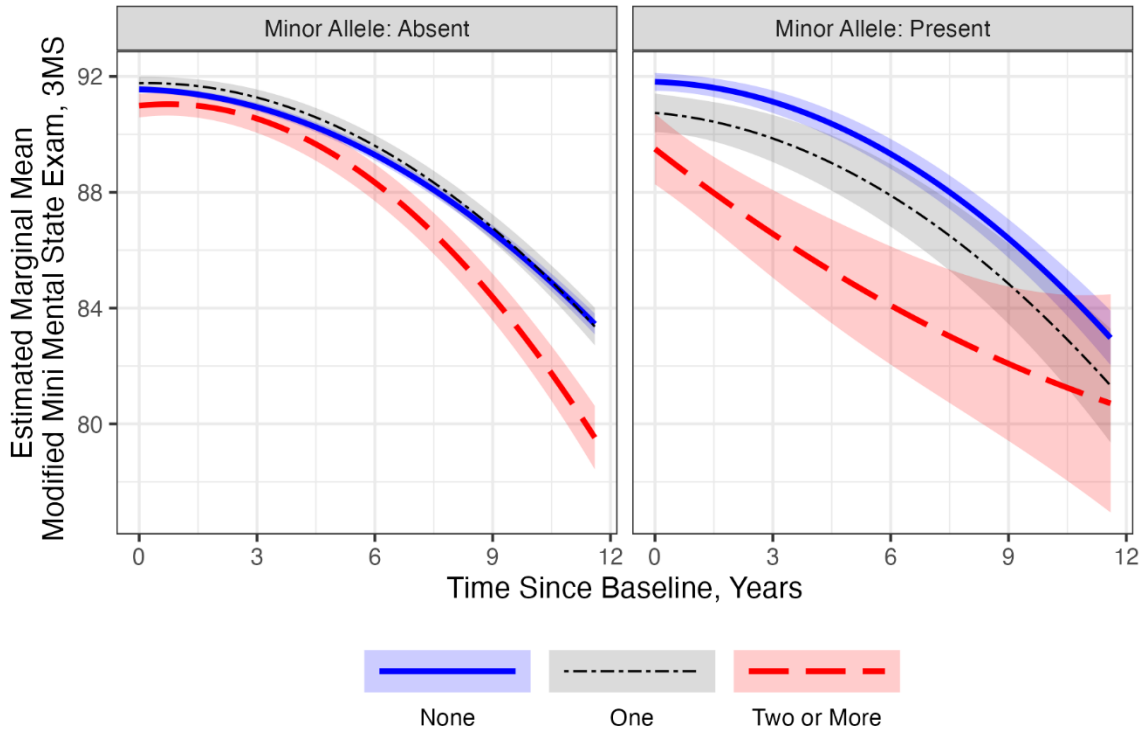
Note. Receptor TrkB (rs2289656) exhibited a trend level interaction with number of TBI and sex in modeling 3MS trajectory (receptor TrkB*TBI*Sex*Time^2 p = .072). Specifically, females homozygous for the receptor TrkB (rs2289656) minor allele with

two or more reported TBIs declined more rapidly over time on the 3MS compared to males homozygous for the dominant allele without a TBI history (receptor TrkB*two or more TBI*female*Time^2 p = .022). Shaded region represents one standard error of the mean.

SNP = Single Nucleotide Polymorphism; TBI = Traumatic Brain Injury; 3MS = Modified Mini-Mental State Exam.

Figure 6

SNP Rs56164415 (BDNF C270T) Moderation of Number of TBI on 3MS Score Over Time



Note. BDNF C270T (rs56164415) exhibited a trend level interaction with number of TBI in modeling 3MS trajectory (BDNF C270T*TBI*Time^2 p = .065). Specifically, participants with a history of two or more TBIs with at least one BDNF C270T (rs56164415) minor allele scored on average 5.18 points less than individuals with a minor allele and no TBI (p = .007) at five years post baseline. Furthermore, individuals with a history of two or more TBIs and no BDNF C270T (rs56164415) minor allele scored on average 2.82 and 2.89 points less than individuals with a history of no TBI (p = .002) and one TBI (p = .005), respectively, at 10 years post baseline. Shaded region represents one standard error of the mean.
SNP = Single Nucleotide Polymorphism; TBI = Traumatic Brain Injury; 3MS = Modified Mini-Mental State Exam.

Hopkins Verbal Learning Test-Revised

Learning. In the fully adjusted models, BDNF Val66Met (rs6265) modified the association between number of TBI and rate of change in HVLT-R Learning score at a trend level (BDNF Val66Met*TBI*time p = .059; see figure 7). No other BDNF/NGFR-related SNPs significantly moderated the relationship between number of TBI and HVLT-R Learning score (SNP*TBI receptor p75NTR (rs2072446): p = .175; receptor TrkB (rs2289656): p = .536; BDNF C270T (rs56164415): p = .690) or rate of change (SNP*TBI*time receptor p75NTR (rs2072446): p = .635; receptor TrkB (rs2289656): p = .390; BDNF C270T (rs56164415): p = .599; BDNF Val66Met: p = .285).

Delayed Recall. None of the SNPs for BDNF/NGF receptors exhibited a significant interaction with age at last TBI on HVLT-R Delayed Recall score (SNP*age last receptor p75NTR (rs2072446): $p = .572$; receptor TrkB (rs2289656): $p = .691$; BDNF C270T (rs56164415): $p = .192$; BDNF Val66Met (rs6265): $p = .553$) or rate of change (SNP*age last*time receptor p75NTR (rs2072446): $p = .476$; receptor TrkB (rs2289656): $p = .729$; BDNF C270T (rs56164415): $p = .732$; BDNF Val66Met (rs6265): $p = .671$).

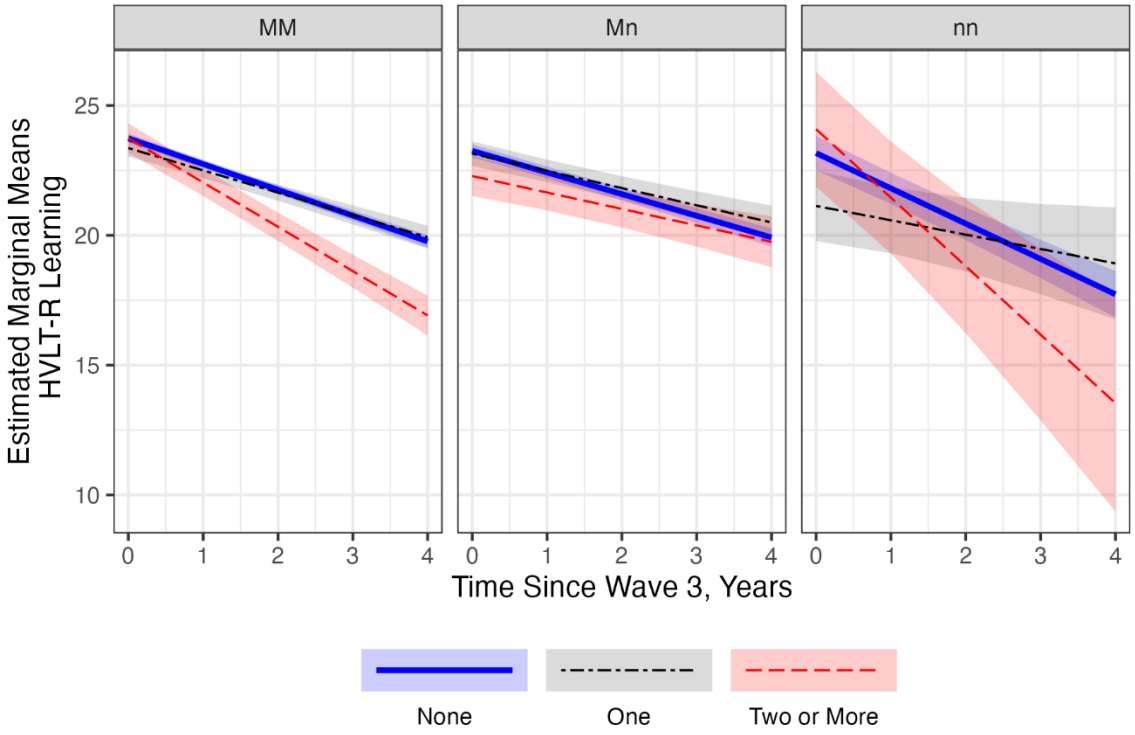
Recognition. SNP for receptor p75NTR (rs2072446) moderated the association between number of TBI and rate of change of HVLT-R Recognition scores at a trend level (Receptor p75NTR*TBI*time $p = .054$). Specifically, individuals with a least one minor allele and two or more reported TBI scored on average 1.73 points lower on HVLT-R Recognition compared to individuals with no minor allele and no reported TBI (Receptor p75NTR*two or more TBI*time $p = .020$; see figure 8). SNP for receptor TrkB (rs2289656) moderated the association between number of TBI and HVLT-R Recognition score at a trend level (receptor TrkB*TBI $p = .094$). Specifically, individuals with one reported TBI and at least one minor allele scored on average 1.39 points lower than individuals with no TBIs or minor alleles (receptor TrkB*one TBI $p = .030$). However, SNP for receptor TrkB (rs2289656) did not significantly moderate rate of change in HVLT-R Recognition score (receptor TrkB*TBI*time $p = .369$). No other BDNF/NGF-related receptor SNPs significantly moderated the relationship between number of TBI and HVLT-R Recognition score (SNP*TBI BDNF C270T (rs56164415): $p = .325$; BDNF Val66Met (rs6265): $p = .495$) or rate of change (SNP*TBI*time receptor BDNF C270T (rs56164415): $p = .263$; BDNF Val66Met (rs6265): $p = .837$).

SNP for receptor TrkB (rs2289656) did significantly moderate the association between TBI severity and HVLT-R Recognition score (receptor TrkB*severity $p = .016$). Specifically, individuals with a severe TBI and at least one minor allele scored on average 4.76 points lower than individuals with no reported TBI and no minor alleles (TrkB*severe $p = .005$). However, receptor TrkB (rs2289656) did not significantly moderate rate of change in HVLT-R Recognition score (receptor TrkB*severity*time $p = .338$). Other BDNF/NGFR-related SNPs did not moderate the association between TBI severity and HVLT-R Recognition score (SNP*severity receptor p75NTR (rs2072446): $p = .332$; BDNF C270T (rs56164415): $p = .328$; BDNF Val66Met (rs6265): $p = .402$) or rate of change in score (SNP*severity*time receptor p75NTR (rs2072446): $p = .248$; BDNF C270T (rs56164415): $p = .522$; BDNF Val66Met (rs6265): $p = .914$).

Amongst the covariates in the above models for HVLT-R subtests, younger age and higher educational attainment were associated with higher scores on HVLT-R Delayed Recall and Recognition. Female sex was associated with higher scores on HVLT-R Learning and Recognition when examining number of TBIs but not TBI severity. Table 13 displays the parameter estimates for the fully adjusted model.

Figure 7

SNP Rs6265 (BDNF Val66Met) Moderation of Number of TBI on HVLT-R Learning Score Over Time



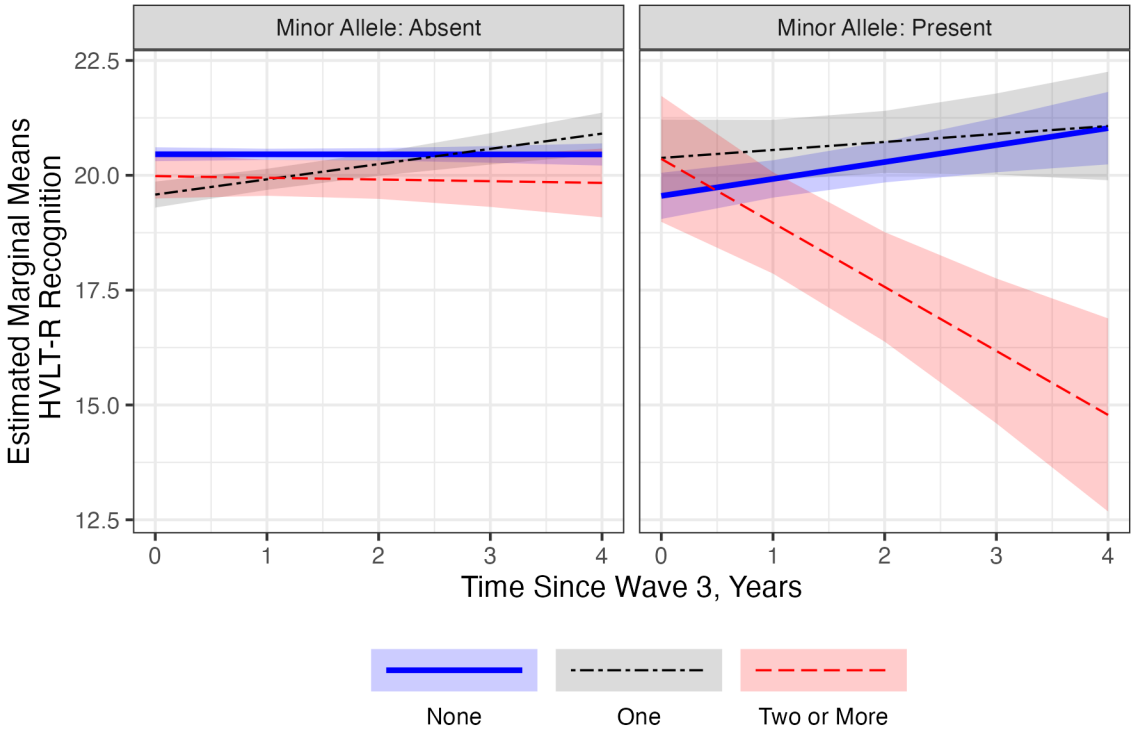
Note. BDNF Val66Met snp (rs6265) modified the association between TBIs and rate of decline in HVLT-R Learning score at a trend level (snp*TBI*time $p = .059$). Specifically, individuals homozygous for the major allele (left panel) and a reported history of two or more TBIs declined more rapidly ($b = -1.70$, $p < .001$) compared to those with no history of TBI ($b = -0.99$, $p < .001$) or a single TBI ($b = -0.86$, $p < .001$). Similarly, individuals homozygous for the minor allele (right panel) and a reported history of two or more TBIs declined more rapidly ($b = -2.64$, $p = .013$) compared to those with no history of TBI ($b = -1.36$, $p < .001$) or a single TBI ($b = -0.55$, $p < .319$). Decline in scores for heterozygous

individuals (center panel) was similar regardless of TBI history. Shaded region represents one standard error of the mean.

SNP = Single Nucleotide Polymorphism; TBI = Traumatic Brain Injury; HVLT-R = Hopkins Verbal Learning Test-Revised.

Figure 8

SNP Rs2072446 (Receptor p75NTR) Moderation of Number of TBI on HVLT-R Recognition Score Over Time



Note. SNP for receptor p75NTR (rs2072446) moderated the association between number of TBI and rate of change of HVLT-R Recognition scores at a trend level (Receptor p75NTR*TBI*time $p = .054$). Specifically, individuals with a least one minor allele and

two or more reported TBI scored on average 1.73 lower per year on HVLT-R Recognition compared to individuals with no minor allele and no reported TBI (Receptor p75NTR*two or more TBI*time $p = .020$). Shaded region represents one standard error of the mean.

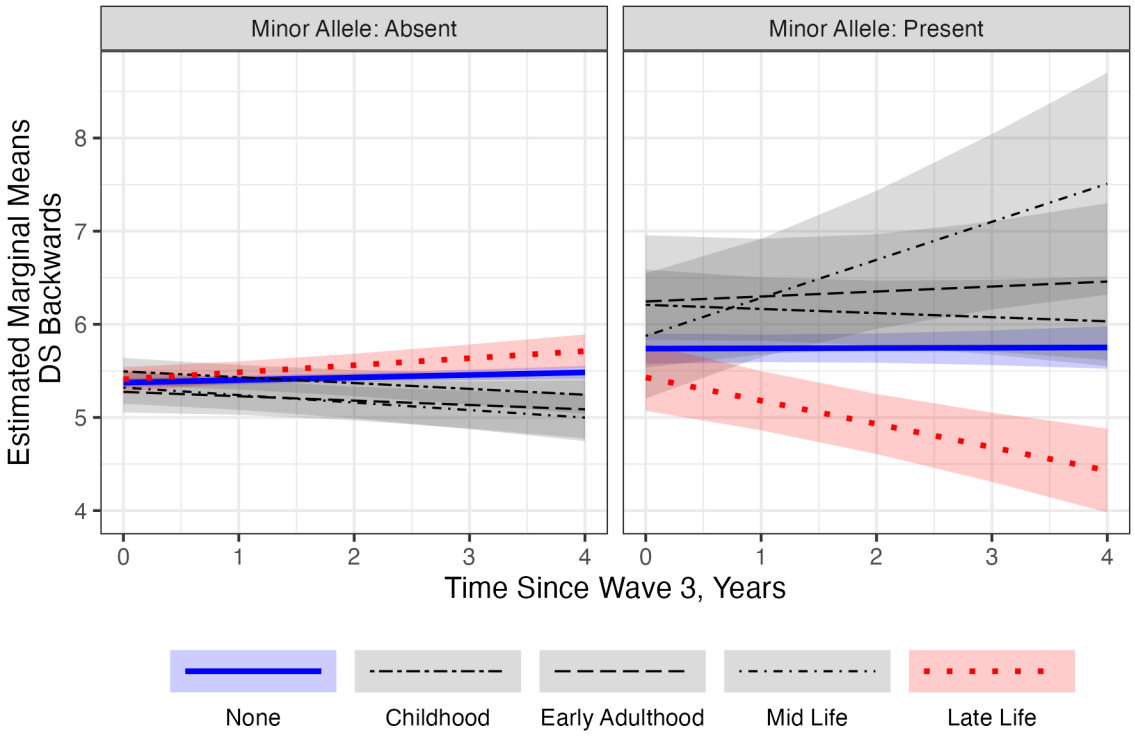
SNP = Single Nucleotide Polymorphism; TBI = Traumatic Brain Injury; HVLT-R = Hopkins Verbal Learning Test-Revised.

Digit Span. In the fully adjusted models, receptor p75NTR (rs2072446) moderated the association between age at last TBI and rate of change in DS Backwards score at a trend level (receptor p75NTR*age last*time $p = .095$) Specifically, individuals with a reported last TBI in late life with at least one minor allele scored on average 0.30 points per year lower on DS Backwards compared to individuals lacking a TBI history and the minor allele for receptor p75NTR (rs2072446) (receptor p75NTR*late life*time $p = .041$; see figure 9). Receptor TrkB (rs2289656), BDNF C270T (rs56164415), and BDNF Val66Met (rs6265) did not significantly modify the association between age at last TBI and DS Backwards score (SNP*age first receptor TrkB (rs2289656): $p = .109$; BDNF C270T (rs56164415): $p = .157$; BDNF Val66Met (rs6265): $p = .901$) or rate of change (SNP*age last*time receptor TrkB (rs2289656): $p = .607$; BDNF C270T (rs56164415): $p = .925$; BDNF Val66Met (rs6265): $p = .236$). Younger age and higher educational attainment were associated with higher scores for all BDNF/NGF related receptor SNPs. Female sex was also associated with higher scores for receptor TrkB (rs2289656). Table 13 displays the parameter estimates for the fully adjusted model.

Clock Drawing Test. In the fully adjusted model, the SNP for receptor TrkB (rs2289656) moderated the association between age at first TBI and rate of change in CDT total score at a trend level (receptor TrkB*age first*time $p = .077$). Specifically, individuals with at least one minor allele and a reported first TBI in early adulthood scored on average 1.20 points higher per year on CDT total compared to individuals lacking a TBI history and a minor allele (receptor TrkB*early adulthood*time $p = .006$; see figure 10). No other BDNF/NGFR-related SNPs moderated CDT total score (SNP*age first receptor p75NTR (rs2072446): $p = .757$; BDNF C270T (rs56164415): $p = .927$; BDNF Val66Met (rs6265): $p = .195$) or rate of change (SNP*age first*time receptor p75NTR (rs2072446): $p = .112$; BDNF C270T (rs56164415): $p = .774$; BDNF Val66Met (rs6265): $p = .285$). Amongst covariates, older age was associated with higher CDT total scores whereas female sex was associated with lower CDT total scores. Table 13 displays the parameter estimates for the fully adjusted model.

Figure 9

SNP Rs2072446 (Receptor p75NTR) Moderation of Age at Last TBI on DS Backwards Score Over Time

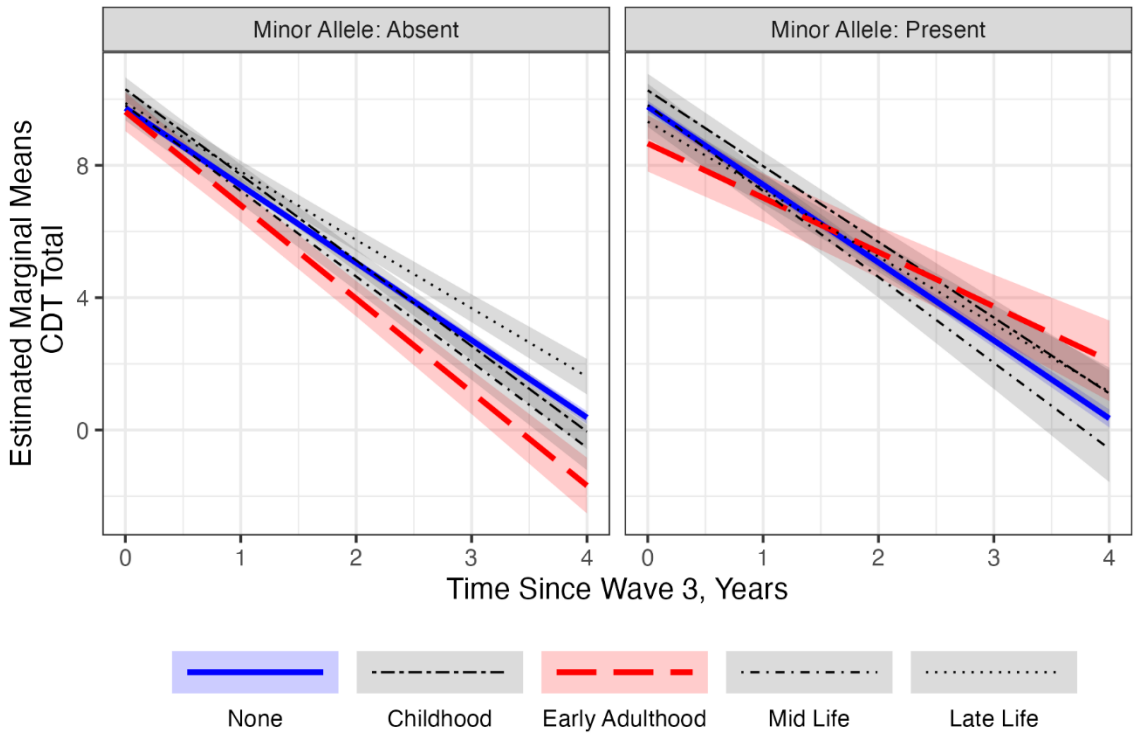


Note. SNP for receptor p75NTR (rs2072446) moderated the association between age at last TBI and rate of change in DS Backwards score at a trend level (receptor p75NTR*age last*time $p = .095$) Specifically, individuals with a reported last TBI in late life with at least one minor allele scored on average 0.30 points per year lower on DS Backwards compared to individuals lacking a TBI history and the minor allele for receptor p75NTR (rs2072446) (receptor p75NTR*late life*time $p = .041$). Shaded region represents one standard error of the mean.

SNP = Single Nucleotide Polymorphism; TBI = Traumatic Brain Injury; DS = Digit Span.

Figure 10

SNP Rs228965 (Receptor TrkB) Moderation of Age at First TBI on CDT Total Score Over Time



Note. Receptor TrkB (rs2289656) polymorphism moderated the association between age at first TBI and rate of change in CDT total score at a trend level (receptor TrkB*age first*time p = .077). Specifically, individuals with at least one minor allele and a reported first TBI in early adulthood scored on average 1.20 points higher per year on CDT total compared to individuals with no TBI history and lacking a minor allele (receptor TrkB*early adulthood*time p = .006). Shaded region represents one standard error of the mean.

SNP = Single Nucleotide Polymorphism; TBI = Traumatic Brain Injury; CDT = Clock Drawing Test.

Table 12

Fully Adjusted Models of BDNF/NGF-Related Receptor SNPs Moderation on History of TBI and 3MS Scores

	rs2072446 (receptor p75NTR)		rs2289656 (receptor TrkB)		rs56164415 (BDNF C270T)		rs6265 (BDNF Val66Met)	
	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*
Intercept								
	93.70 (0.25)	<.001***	93.84 (0.28)	<.001***	93.62 (0.25)	<.001***	93.58 (0.26)	<.001***
Main Effects								
Time (yrs)	0.36 (0.07)	<.001***	0.39 (0.11)	<.001***	0.35 (0.07)	<.001***	0.36 (0.08)	<.001***
Time^2 (yrs)	-0.03 (0.01)	<.001***	-0.03 (0.01)	.005**	-0.03 (0.01)	<.001***	-0.03 (0.01)	<.001***
Age (Centered at 65)	-0.41 (0.01)	<.001***	-0.41 (0.01)	<.001***	-0.41 (0.01)	<.001***	-0.41 (0.01)	<.001***
Sex (Female)	1.48 (0.19)	<.001***	1.34 (0.27)	<.001***	1.51 (0.19)	<.001***	1.50 (0.18)	<.001***
Education (Less than HS/GED)	-3.23 (0.27)	<.001***	-3.28 (0.27)	<.001***	-3.27 (0.27)	<.001***	-3.24 (0.27)	<.001***
Education (More than HS/GED)	2.10 (0.21)	<.001***	2.09 (0.20)	<.001***	2.18 (0.20)	<.001***	2.10 (0.20)	<.001***
One TBI	-0.06 (0.25)	.796	0.18 (0.42)	.672	0.21 (0.25)	.403	0.08 (0.29)	.775
Two or More TBI	-0.72 (0.42)	.089	-1.30 (0.61)	.034*	-0.56 (0.42)	.183	-0.17 (0.50)	.728
SNP (Presence)	-0.33 (0.40)	.403			0.26 (0.33)	.432		
SNP (Mn)			-0.26 (0.37)	.485			0.32 (0.23)	.176
SNP (nn)			0.26 (0.90)	.770			0.03 (0.51)	.960

	rs2072446 (receptor p75NTR)		rs2289656 (receptor TrkB)		rs56164415 (BDNF C270T)		rs6265 (BDNF Val66Met)	
	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*
Interactions								
Time x Age (Centered at 65)	-0.04 (0.01)	<.001***	-0.04 (0.01)	<.001***	-0.04 (0.01)	<.001***	-0.04 (0.01)	<.001***
Time^2 x Age (Centered at 65)	-0.00 (0.00)	<.001***	-0.00 (0.00)	<.001***	-0.00 (0.00)	<.001***	-0.00 (0.00)	<.001***
Time x Sex (Female)			-0.00 (0.12)	.995				
Time^2 x Sex (Female)			-0.01 (0.01)	.652				
Time^2 x Education (Less than HS/GED)	-0.03 (0.01)	<.001***	-0.03 (0.01)	<.001***	-0.03 (0.01)	<.001***	-0.03 (0.01)	<.001***
Time^2 x Education (More than HS/GED)	0.00 (0.00)	.488	0.00 (0.00)	.712	0.00 (0.00)	.579	0.00 (0.00)	.605
Time x One TBI	0.05 (0.11)	.660	0.03 (0.18)	.882	0.06 (0.11)	.549	0.13 (0.12)	.303
Time^2 x One TBI	-0.01 (0.01)	.471	-0.00 (0.02)	.967	-0.01 (0.01)	.445	-0.01 (0.01)	.303
Time x Two or More TBI	-0.06 (0.17)	.734	-0.30 (0.26)	.252	0.18 (0.17)	.305	0.07 (0.20)	.743
Time^2 x Two or More TBI	-0.02 (0.02)	.204	0.02 (0.02)	.529	-0.04 (0.02)	.012*	-0.03 (0.02)	.175
Time x SNP (Presence)	-0.03 (0.17)	.869			-0.01 (0.14)	.943		
Time^2 x SNP (Presence)	0.01 (0.02)	.653			-0.00 (0.01)	.737		

	rs2072446 (receptor p75NTR)		rs2289656 (receptor TrkB)		rs56164415 (BDNF C270T)		rs6265 (BDNF Val66Met)	
	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*
Time x SNP (Mn)			-0.20 (0.16)	.228			-0.03 (0.10)	.753
Time^2 x SNP (Mn)			0.01 (0.02)	.582			-0.00 (0.01)	.863
Time x SNP (nn)			-0.02 (0.40)	.953			-0.07 (0.22)	.747
Time^2 x SNP (nn)			0.02 (0.04)	.587			-0.00 (0.02)	.865
Sex (Female) x SNP (Mn)			0.30 (0.48)	.531				
Sex (Female) x SNP (nn)			-1.45 (1.13)	.202				
One TBI x Sex (Female)			0.20 (0.59)	.733				
Two or More TBI x Sex (Female)			1.14 (0.98)	.247				
One TBI x SNP (Presence)	1.46 (0.83)	.077 .			-1.28 (0.78)	.097 .		
Two or More TBI x SNP (Presence)	1.39 (1.28)	.280			-1.75 (1.33)	.187		
One TBI x SNP (Mn)			-1.20 (0.77)	.120			0.00 (0.53)	.997
Two or More TBI x SNP (Mn)			2.32 (1.25)	.064 .			-1.24 (0.84)	.142
One TBI x SNP (nn)			1.54 (2.05)	.451			-0.77 (1.28)	.550

	rs2072446 (receptor p75NTR)		rs2289656 (receptor TrkB)		rs56164415 (BDNF C270T)		rs6265 (BDNF Val66Met)	
	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*
Two or More TBI x SNP (nn)			1.47 (2.50)	.557			-2.33 (2.01)	.248
Time x Sex (Female) x SNP (Mn)			0.14 (0.21)	.512				
$Time^2$ x Sex (Female) x SNP (Mn)			0.00 (0.02)	.867				
Time x Sex (Female) x SNP (nn)			-0.23 (0.50)	.649				
$Time^2$ x Sex (Female) x SNP (nn)			-0.01 (0.05)	.898				
Time x Sex (Female) x One TBI			-0.05 (0.25)	.846				
$Time^2$ x Sex (Female) x One TBI			0.00 (0.02)	.929				
Time x Sex (Female) x Two or More TBI			0.40 (0.40)	.313				
$Time^2$ x Sex			-0.06 (0.04)	.139				

	rs2072446 (receptor p75NTR)		rs2289656 (receptor TrkB)		rs56164415 (BDNF C270T)		rs6265 (BDNF Val66Met)	
	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*
(Female) x Two or More TBI								
Time x One TBI x SNP (Presence)	0.19 (0.34)	.586			-0.14 (0.33)	.682		
Time^2 x One TBI x SNP (Presence)	-0.01 (0.03)	.411			0.01 (0.03)	.761		
Time x Two or More TBI x SNP (Presence)	0.42 (0.51)	.786			-1.19 (0.57)	.038*		
Time^2 x Two or More TBI x SNP (Presence)	-0.02 (0.05)	.674			0.13 (0.05)	.019*		
Time x One TBI x SNP (Mn)			0.69 (0.33)	.040*			-0.19 (0.22)	.385
Time^2 x One TBI x SNP (Mn)			-0.07 (0.03)	.036*			0.01 (0.02)	.551
Time x Two or More TBI x SNP (Mn)			0.66 (0.51)	.198			-0.21 (0.34)	.530
Time^2 x Two or More TBI x SNP (Mn)			-0.06 (0.05)	.193			0.02 (0.03)	.527
Time x One TBI			0.11 (0.84)	.900			-0.44 (0.56)	.430

	rs2072446 (receptor p75NTR)		rs2289656 (receptor TrkB)		rs56164415 (BDNF C270T)		rs6265 (BDNF Val66Met)	
	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*
x SNP (nn)								
Time^2 x One TBI x SNP (nn)			-0.01 (0.08)	.932			0.05 (0.05)	.312
Time x Two or More TBI x SNP (nn)			0.36 (1.01)	.720			0.86 (0.85)	.311
Time^2 x Two or More TBI x SNP (nn)			-0.13 (0.09)	.183			-0.18 (0.08)	.029*
One TBI x Sex (Female) x SNP (Mn)			0.72 (1.05)	.496				
Two or More TBI x Sex (Female) x SNP (Mn)			-3.83 (1.84)	.037*				
One TBI x Sex (Female) x SNP (nn)			1.65 (3.04)	.588				
Two or More TBI x Sex (Female) x SNP (Mn)			2.21 (5.05)	.662				
Time x One TBI x SNP			-0.81 (0.45)	.070 .				

	rs2072446 (receptor p75NTR)		rs2289656 (receptor TrkB)		rs56164415 (BDNF C270T)		rs6265 (BDNF Val66Met)	
	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*
(Mn) x Sex (Female)								
Time^2 x One TBI x SNP			0.07 (0.04)	.121				
(Mn) x Sex (Female)								
Time x One TBI x SNP			-0.80 (1.18)	.498				
(nn) x Sex (Female)								
Time^2 x One TBI x SNP			0.07 (0.11)	.505				
(nn) x Sex (Female)								
Time x Two or More TBI x SNP			-0.43 (0.73)	.561				
(Mn) x Sex (Female)								
Time^2 x Two or More TBI x SNP			0.05 (0.07)	.475				
(Mn) x Sex (Female)								
Time x Two or More TBI x SNP			2.67 (2.40)	.268				
(nn) x Sex (Female)								

	rs2072446 (receptor p75NTR)		rs2289656 (receptor TrkB)		rs56164415 (BDNF C270T)		rs6265 (BDNF Val66Met)	
	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*
Time^2 x Two or More TBI x SNP (nn) x Sex (Female)			-0.66 (0.29)	.022*				

Note. Reference category for sex is males. Reference category for education is a HS diploma or GED. Reference category for TBI characteristics is no reported TBI. Reference category for SNP is individuals homozygous for the major allele.

3MS = Modified Mini-Mental State Exam; TBI = Traumatic Brain Injury; HS = High School; GED = General Education Diploma; BDNF/NGFR-Related SNP = Brain Derived Neurotrophic Factor Gene/Nerve Growth Factor Receptor-Related Single Nucleotide Polymorphism

. p <.1. * p <.05. ** p <.01. *** p <.001.

Table 13

Fully Adjusted Models of BDNF/NGFR-Related SNPs Moderation on Significant Characteristics of TBI by Cognitive Outcome

	rs2072446 (receptor p75NTR)		rs2289656 (receptor TrkB)		rs56164415 (BDNF C270T)		rs6265 (BDNF Val66Met)	
	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*
HVLT-R Learning: Number of TBI								
Intercept								
	21.27 (0.27)	<.001***	21.48 (0.29)	<.001***	21.34 (0.27)	<.001***	21.46 (0.29)	<.001***
Main Effects								
Time (yrs)	-0.97 (0.05)	<.001***	-1.02 (0.06)	<.001***	-0.97 (0.05)	<.001***	-0.99 (0.06)	<.001***
Age (Centered at 80)	-0.34 (0.02)	<.001***	-0.34 (0.02)	<.001***	-0.34 (0.02)	<.001***	-0.99 (0.06)	<.001***
Sex (Female)	2.51 (0.23)	<.001***	2.48 (0.23)	<.001***	2.47 (0.23)	<.001***	2.51 (0.23)	<.001***
Education (Less than HS/GED)	-1.87 (0.37)	<.001***	-1.86 (0.37)	<.001***	-1.90 (0.38)	<.001***	-1.89 (0.37)	<.001***
Education (More than HS/GED)	1.59 (0.24)	<.001***	1.57 (0.24)	<.001***	1.62 (0.24)	<.001***	1.56 (0.24)	<.001***
One TBI	-0.52 (0.31)	.098 .	-0.61 (0.36)	.093 .	-0.40 (0.31)	.196	-0.38 (0.37)	.304
Two or More TBI	-0.18 (0.50)	.727	-0.40 (0.59)	.501	-0.36 (0.49)	.462	0.01 (0.60)	.993
SNP (Presence)	0.07 (0.52)	.885	-0.49 (0.30)	.010 .	-0.49 (0.43)	.258		
SNP (Mn)							-0.48 (0.30)	.112
SNP (nn)							-0.57 (0.68)	.405
Interactions								
Time x SNP (Presence)	0.09 (0.19)	.632	0.17 (0.11)	.119	0.16 (0.16)	.308		

	rs2072446 (receptor p75NTR)		rs2289656 (receptor TrkB)		rs56164415 (BDNF C270T)		rs6265 (BDNF Val66Met)	
	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*
Time x SNP (Mn)							0.16 (0.11)	.156
Time x SNP (nn)							-0.37 (0.24)	.133
Time x One TBI	0.19 (0.12)	.097 .	0.28 (0.13)	.035 *	0.21 (0.11)	.068 .	0.13 (0.13)	.307
Time x Two or More TBI	-0.33 (0.18)	.069 .	-0.37 (0.21)	.071 .	-0.44 (0.17)	.011 *	-0.71 (0.21)	<.001 ***
One TBI x SNP (Presence)	1.85 (1.01)	.066 .	0.70 (0.63)	.268	0.04 (0.98)	.965		
Two or More TBI x SNP (Presence)	-0.03 (1.51)	.985	0.29 (0.99)	.767	1.57 (1.82)	.389		
One TBI x SNP (Mn)							0.27 (0.65)	.679
Two or More TBI x SNP (Mn)							-0.98 (1.00)	.330
One TBI x SNP (nn)							-1.66 (1.55)	.285
Two or More TBI x SNP (nn)							0.91 (2.38)	.702
Time x One TBI x SNP (Presence)	-0.20 (0.35)	.560	-0.31 (0.23)	.177	-0.34 (0.36)	.346		
Time x Two or More TBI x SNP (Presence)	-0.45 (0.53)	.395	0.01 (0.35)	.970	0.18 (0.66)	.788		
Time x One TBI x SNP (Mn)							0.04 (0.23)	.875
Time x Two or							0.92 (0.35)	.008 **

	rs2072446 (receptor p75NTR)		rs2289656 (receptor TrkB)		rs56164415 (BDNF C270T)		rs6265 (BDNF Val66Met)	
	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*
More TBI x SNP (Mn)								
Time x One TBI x SNP (nn)							0.67 (0.62)	.276
Time x Two or More TBI x SNP (nn)							-0.56 (1.11)	.612
HVLT-R Delayed: Age at Last TBI								
Intercept								
	5.88 (0.17)	<.001***	5.90 (0.18)	<.001***	5.89 (0.17)	<.001***	5.96 (0.18)	<.001***
Main Effects								
Time (yrs)	-0.18 (0.04)	<.001***	-0.17 (0.04)	<.001***	-0.17 (0.04)	<.001***	-0.19 (0.04)	<.001***
Age (Centered at 80)	-0.23 (0.01)	<.001***	-0.23 (0.01)	<.001***	-0.23 (0.01)	<.001***	-0.23 (0.01)	<.001***
Sex (Female)	1.28 (0.15)	<.001***	1.29 (0.15)	<.001***	1.28 (0.15)	<.001***	-0.40 (0.60)	<.001***
Education (Less than HS/GED)	-1.01 (0.24)	<.001***	-1.05 (0.24)	<.001***	-1.01 (0.24)	<.001***	-1.04 (0.24)	<.001***
Education (More than HS/GED)	0.62 (0.16)	<.001***	0.61 (0.15)	<.001***	0.63 (0.16)	<.001***	0.59 (0.15)	<.001***
Childhood	0.06 (0.30)	.832	0.33 (0.34)	.338	0.19 (0.29)	.515	0.33 (0.34)	.334
Early Adulthood	-0.47 (0.45)	.290	-0.57 (0.51)	.263	-0.49 (0.43)	.257	0.14 (0.51)	.777
Middle Adulthood	-0.60 (0.35)	.087 .	-0.41 (0.40)	.308	-0.30 (0.36)	.408	-0.40 (0.43)	.346
Late Life	-0.19 (0.27)	.480	0.15 (0.32)	.627	-0.12 (0.27)	.647	-0.01 (0.32)	.975
SNP (Presence)	-0.16 (0.33)	.624	-0.10 (0.19)	.585	-0.30 (0.28)	.278		

	rs2072446 (receptor p75NTR)		rs2289656 (receptor TrkB)		rs56164415 (BDNF C270T)		rs6265 (BDNF Val66Met)	
	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*
SNP (Mn)							-0.32 (0.20)	.104
SNP (nn)							0.38 (0.44)	.382
Interactions								
Time x SNP (Presence)	0.10 (0.13)	.408	0.02 (0.07)	.755	0.02 (0.11)	.842		
Time x SNP (Mn)							0.12 (0.08)	.103
Time x SNP (nn)							-0.15 (0.17)	.378
Time x Childhood	-0.00 (0.11)	.997	-0.01 (0.13)	.969	-0.03 (0.11)	.795	-0.09 (0.13)	.466
Time x Early Adulthood	0.19 (0.17)	.264	0.23 (0.19)	.230	0.14 (0.16)	.393	-0.02 (0.19)	.896
Time x Middle Adulthood	0.00 (0.14)	.983	-0.03 (0.16)	.864	-0.02 (0.14)	.861	0.01 (0.17)	.958
Time x Late Life	-0.08 (0.10)	.454	-0.25 (0.12)	.033*	-0.12 (0.10)	.231	-0.14 (0.12)	.239
Childhood x SNP (Presence)	0.80 (0.86)	.353	-0.47 (0.58)	.420	-0.47 (0.97)	.629		
Early Adulthood x SNP (Presence)	1.16 (1.42)	.412	0.86 (0.92)	.349	3.83 (2.49)	.124		
Middle Adulthood x SNP (Presence)	1.53 (1.39)	.270	-0.09 (0.72)	.903	-1.25 (0.97)	.198		
Late Life x SNP (Presence)	0.82 (0.83)	.319	-0.43 (0.54)	.424	1.07 (0.88)	.222		
Childhood x SNP (Mn)							-0.40 (0.60)	.504

	rs2072446 (receptor p75NTR)		rs2289656 (receptor TrkB)		rs56164415 (BDNF C270T)		rs6265 (BDNF Val66Met)	
	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*
Early Adulthood x SNP (Mn)							-1.63 (0.94)	.084 .
Middle Adulthood x SNP (Mn)							-0.17 (0.71)	.815
Late Life x SNP (Mn)							0.16 (0.56)	.777
Childhood x SNP (nn)							-1.43 (1.64)	.382
Early Adulthood x SNP (nn)							-2.60 (2.53)	.304
Middle Adulthood x SNP (nn)							1.32 (1.83)	.472
Late Life x SNP (nn)							-1.32 (1.17)	.259
Time x Childhood x SNP (Presence)	-0.08 (0.31)	.799	-0.06 (0.21)	.776	0.01 (0.36)	.971		
Time x Early Adulthood x SNP (Presence)	-0.50 (0.49)	.309	-0.14 (0.35)	.682	-0.30 (0.82)	.710		
Time x Middle Adulthood x SNP (Presence)	0.42 (0.65)	.516	0.08 (0.29)	.773	0.11 (0.48)	.818		
Time x Late Life x SNP (Presence)	-0.42 (0.29)	.146	0.25 (0.20)	.212	-0.42 (0.31)	.182		
Time x Childhood							0.14 (0.22)	.538

	rs2072446 (receptor p75NTR)		rs2289656 (receptor TrkB)		rs56164415 (BDNF C270T)		rs6265 (BDNF Val66Met)	
	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*
x SNP (Mn)								
Time x Early Adulthood x SNP (Mn)							0.61 (0.36)	.096 .
Time x Middle Adulthood x SNP (Mn)							-0.08 (0.28)	.786
Time x Late Life x SNP (Mn)							0.01 (0.20)	.976
Time x Childhood x SNP (nn)							0.81 (0.79)	.303
Time x Early Adulthood x SNP (nn)							-0.31 (1.05)	.768
Time x Middle Adulthood x SNP (nn)							0.09 (0.69)	.898
Time x Late Life x SNP (nn)							-0.59 (0.54)	.271
HVLT-R Recognition: Number of TBI								
Intercept	20.35 (0.20)	<.001***	20.27 (0.22)	<.001***	20.37 (0.20)	<.001***	20.44	<.001***
Main Effects								
Time (yrs)	-0.00 (0.07)	.986	0.06 (0.09)	.464	-0.03 (0.08)	.652	0.03 (0.09)	.735

	rs2072446 (receptor p75NTR)		rs2289656 (receptor TrkB)		rs56164415 (BDNF C270T)		rs6265 (BDNF Val66Met)	
	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*
Age (Centered at 80)	-0.16 (0.02)	<.001***	-0.15 (0.02)	<.001***	-0.15 (0.02)	<.001***	-0.16 (0.02)	<.001***
Education (Less than HS/GED)	-0.60 (0.34)	.078 .	-0.64 (0.34)	.058 .	-0.68 (0.34)	.044	-0.60 (0.34)	.072 .
Education (More than HS/GED)	0.18 (0.21)	.406	0.23 (0.21)	.280	0.20 (0.21)	.358	0.16 (0.21)	.448
One TBI	-0.88 (0.32)	.006 **	-0.22 (0.37)	.551	-0.83 (0.32)	.008 **	-0.58 (0.37)	.119
Two or More TBI	-0.48 (0.51)	.352	-0.18 (0.59)	.757	-0.43 (0.50)	.390	-0.74 (0.60)	.222
SNP (Presence)	-0.91 (0.53)	.085 .	0.02 (0.30)	.951	-0.55 (0.44)	.208		
SNP (Mn)							-0.34 (0.31)	.276
SNP (nn)							-0.45 (0.70)	.516
Interactions								
Time x SNP (Presence)	0.37 (0.26)	.149	-0.11 (0.15)	.440	0.37 (0.22)	.088 .		
Time x SNP (Mn)							-0.02 (0.15)	.914
Time x SNP (nn)							-0.10 (0.34)	.767
Time x One TBI	0.33 (0.16)	.036 *	0.15 (0.18)	.412	0.35 (0.16)	.025 *	0.24 (0.18)	.190
Time x Two or More TBI	-0.04 (0.25)	.884	-0.16 (0.29)	.579	-0.13 (0.24)	.578	-0.40 (0.29)	.177
One TBI x SNP (Presence)	1.70 (1.03)	.097 .	-1.39 (0.64)	.030 *	0.99 (0.99)	.320		
Two or More TBI	1.28 (1.55)	.408	-0.30 (1.01)	.767	2.26 (1.85)	.222		

	rs2072446 (receptor p75NTR)		rs2289656 (receptor TrkB)		rs56164415 (BDNF C270T)		rs6265 (BDNF Val66Met)	
	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*
x SNP (Presence)								
One TBI x SNP (Mn)							-0.48 (0.66)	.465
Two or More TBI x SNP (Mn)							1.38 (1.02)	.174
One TBI x SNP (nn)							0.47 (1.57)	.764
Two or More TBI x SNP (nn)							-1.08 (2.41)	.655
Time x One TBI x SNP (Presence)	-0.53 (0.48)	.273	0.41 (0.31)	.196	-0.32 (0.50)	.522		
Time x Two or More TBI x SNP (Presence)	-1.73 (0.74)	.020 *	-0.18 (0.49)	.709	-1.49 (0.96)	.119		
Time x One TBI x SNP (Mn)							0.20 (0.32)	.538
Time x Two or More TBI x SNP (Mn)							0.38 (0.48)	.434
Time x One TBI x SNP (nn)							-0.02 (0.83)	.978
Time x Two or More TBI x SNP (nn)							1.20 (1.46)	.409
HVLT-R Recognition: TBI Severity								
Intercept								

	rs2072446 (receptor p75NTR)		rs2289656 (receptor TrkB)		rs56164415 (BDNF C270T)		rs6265 (BDNF Val66Met)	
	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*
	20.37 (0.20)	<.001***	20.28 (0.22)	<.001***	20.40 (0.20)	<.001***	20.45 (0.22)	<.001***
Main Effects								
Time (yrs)	-0.00 (0.07)	.996	0.06 (0.09)	.457	-0.03 (0.08)	.669	0.03 (0.09)	.739
Age (Centered at 80)	-0.16 (0.02)	<.001***	-0.15 (0.02)	<.001***	-0.15 (0.02)	<.001***	-0.16 (0.02)	<.001***
Education (Less than HS/GED)	-0.64 (0.34)	.057 .	-0.64 (0.33)	.054 .	-0.73 (0.34)	.031*	-0.64 (0.34)	.057 .
Education (More than HS/GED)	0.14 (0.21)	.525	0.21 (0.21)	.324	0.15 (0.21)	.475	0.14 (0.21)	.504
Mild	-0.76 (0.33)	.022*	-0.18 (0.38)	.635	-0.74 (0.33)	.024*	-0.65 (0.38)	.089 .
Moderate	-0.11 (0.54)	.831	-0.05 (0.64)	.939	-0.12 (0.52)	.825	0.05 (0.65)	.936
Severe	-2.49 (0.84)	.003**	-0.80 (0.93)	.388	-2.35 (0.88)	.007**	-1.91 (0.97)	.049*
SNP (Presence)	-0.90 (0.53)	.087 .	0.01 (0.30)	.969	-0.55 (0.44)	.211		
SNP (Mn)							-0.34 (0.31)	.265
SNP (nn)							-0.45 (0.70)	.518
Interactions								
Time x SNP (Presence)	0.37 (0.26)	.149	-0.11 (0.15)	.448	0.37 (0.22)	.089		
Time x SNP (Mn)							-0.01 (0.15)	.925
Time x SNP (nn)							-0.10 (0.34)	.768
Time x Mild	0.27 (0.16)	.093 .	0.08 (0.18)	.684	0.28 (0.16)	.074	0.16 (0.18)	.400
Time x Moderate	0.12 (0.28)	.657	0.14 (0.33)	.664	0.05 (0.26)	.863	-0.24 (0.33)	.476

	rs2072446 (receptor p75NTR)		rs2289656 (receptor TrkB)		rs56164415 (BDNF C270T)		rs6265 (BDNF Val66Met)	
	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*
Time x Severe	0.15 (0.43)	.733	-0.14 (0.47)	.762	0.10 (0.44)	.825	0.11 (0.49)	.814
Mild x SNP (Presence)	1.53 (1.06)	.146	-1.14 (0.66)	.086	1.71 (1.05)	.104		
Moderate x SNP (Presence)	1.59 (1.75)	.364	0.22 (1.05)	.835	2.33 (2.33)	.317		
Severe x SNP (Presence)	2.53 (2.29)	.271	-4.46 (1.70)	.005 **	-0.03 (1.98)	.989		
Mild x SNP (Mn)							0.03 (0.68)	.967
Moderate x SNP (Mn)							-0.03 (1.07)	.981
Severe x SNP (Mn)							0.17 (1.69)	.922
Mild x SNP (nn)							0.93 (1.61)	.563
Moderate x SNP (nn)							1.00 (2.62)	.702
Severe x SNP (nn)							-9.29 (4.04)	.022 *
Time x Mild x SNP (Presence)	-0.74 (0.50)	.135	0.35 (0.32)	.271	-0.71 (0.51)	.158		
Time x Moderate x SNP (Presence)	-1.30 (0.81)	.110	-0.39 (0.52)	.459	-0.49 (1.47)	.737		
Time x Severe x SNP (Presence)	-0.18 (1.11)	.871	1.06 (0.87)	.225	0.41 (1.24)	.743		
Time x Mild x SNP (Mn)							0.20 (0.33)	.541
Time x Moderate x SNP (Mn)							0.52 (0.53)	.323

	rs2072446 (receptor p75NTR)		rs2289656 (receptor TrkB)		rs56164415 (BDNF C270T)		rs6265 (BDNF Val66Met)	
	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*
Time x Severe x SNP (Mn)							-0.16 (0.84)	.847
Time x Mild x SNP (nn)							-0.12 (0.81)	.882
Time x Moderate x SNP (nn)							0.98 (2.08)	.639
Time x Severe x SNP (nn)								
DS Backwards: Age at Last TBI								
Intercept								
	5.17 (0.07)	<.001***	5.10	<.001***	5.24 (0.07)	<.001***	5.17 (0.08)	<.001***
Main Effects								
Time (yrs)	0.03 (0.02)	.135	0.03 (0.02)	.103	0.03 (0.02)	.099 .	0.03 (0.02)	.225
Age (Centered at 80)	-0.05 (0.01)	<.001***	-0.05 (0.01)	<.001***	-0.05 (0.01)	<.001***	-0.05 (0.01)	<.001***
Sex (Female)			0.24 (0.08)	.001 **				
Education (Less than HS/GED)	-0.75 (0.12)	<.001***	-0.73 (0.12)	<.001***	0.77 (0.12)	<.001***	-0.77 (0.12)	<.001***
Education (More than HS/GED)	0.48 (0.08)	<.001***	0.52 (0.08)	<.001***	0.45 (0.08)	<.001***	0.47 (0.08)	<.001***
Childhood	0.12 (0.15)	.429	-0.02 (0.18)	.915	0.25 (0.15)	.104	0.20 (0.18)	.262
Early Adulthood	-0.10 (0.23)	.661	-0.17 (0.26)	.520	-0.08 (0.22)	.701	0.16 (0.26)	.545
Middle Adulthood	-0.05 (0.18)	.769	-0.13 (0.21)	.525	-0.02 (0.19)	.914	0.07 (0.22)	.756
Late Life	0.04 (0.14)	.799	-0.12 (0.16)	.463	-0.08 (0.14)	.551	0.02 (0.16)	.909

	rs2072446 (receptor p75NTR)		rs2289656 (receptor TrkB)		rs56164415 (BDNF C270T)		rs6265 (BDNF Val66Met)	
	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*
SNP (Presence)	0.37 (0.17)	.032*	-0.19 (0.10)	.051 .	-0.10 (0.14)	.463		
SNP (Mn)							0.11 (0.10)	.284
SNP (Mn)							0.19 (0.23)	.403
Interactions								
Time x SNP (Presence)	-0.02 (0.06)	.699	-0.03 (0.04)	.410	-0.06 (0.05)	.305		
Time x SNP (Mn)							0.00 (0.04)	.995
Time x SNP (nn)							-0.08 (0.08)	.338
Time x Childhood	-0.09 (0.06)	.116	-0.06 (0.07)	.374	-0.09 (0.06)	.090 .	-0.14 (0.07)	.038*
Time x Early Adulthood	-0.07 (0.09)	.387	-0.09 (0.10)	.370	-0.06 (0.08)	.449	-0.11 (0.10)	.244
Time x Middle Adulthood	-0.11 90.07)	.118	-0.08 (0.08)	.299	-0.12 (0.07)	.095 .	-0.12 (0.09)	.185
Time x Late Life	0.05 (0.05)	.350	-0.01 (0.06)	.856	0.01 (0.05)	.830	0.04 (0.06)	.459
Childhood x SNP (Presence)	0.35 (0.44)	.427	0.74 (0.30)	.015 *	-0.90 (0.50)	.074 .		
Early Adulthood x SNP (Presence)	0.61 (0.76)	.428	0.57 (0.48)	.233	1.05 (1.29)	.414		
Middle Adulthood x SNP (Presence)	0.19 (0.71)	.791	0.37 (0.38)	.338	-0.43 (0.50)	.387		
Late Life x SNP (Presence)	-0.34 (0.42)	.409	0.15 (0.27)	.577	0.55 (0.44)	.211		

	rs2072446 (receptor p75NTR)		rs2289656 (receptor TrkB)		rs56164415 (BDNF C270T)		rs6265 (BDNF Val66Met)	
	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*
Childhood x SNP (Mn)							0.03 (0.31)	.919
Early Adulthood x SNP (Mn)							-0.59 (0.49)	.227
Middle Adulthood x SNP (Mn)							-0.32 (0.37)	.378
Late Life x SNP (Mn)							-0.06 (0.28)	.830
Childhood x SNP (nn)							-0.67 (0.85)	.426
Early Adulthood x SNP (nn)							-1.19 (1.31)	.363
Middle Adulthood x SNP (nn)							-0.41 (0.95)	.668
Late Life x SNP (nn)							-0.16 (0.60)	.786
Time x Childhood x SNP (Presence)	0.04 (0.15)	.780	-0.09 (0.11)	.427	0.11 (0.18)	.535		
Time x Early Adulthood x SNP (Presence)	0.12 (0.26)	.633	0.12 (0.18)	.504	0.09 (0.41)	.833		
Time x Middle Adulthood x SNP (Presence)	0.51 (0.32)	.113	-0.06 (0.15)	.695	0.17 (0.24)	.478		
Time x Late Life x	-0.30 (0.15)	.041*	0.11 (0.10)	.272	0.05 (0.16)	.771		

	rs2072446 (receptor p75NTR)		rs2289656 (receptor TrkB)		rs56164415 (BDNF C270T)		rs6265 (BDNF Val66Met)	
	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*
SNP (Presence)								
Time x Childhood x SNP (Mn)							0.12 (0.11)	.280
Time x Early Adulthood x SNP (Mn)							0.13 (0.19)	.506
Time x Middle Adulthood x SNP (Mn)							-0.02 (0.14)	.884
Time x Late Life x SNP (Mn)							-0.09 (0.10)	.406
Time x Childhood x SNP (nn)							0.31 (0.40)	.436
Time x Early Adulthood x SNP (nn)							1.12 (0.53)	.035*
Time x Middle Adulthood x SNP (nn)							0.64 (0.35)	.068 .
Time x Late Life x SNP (nn)							-0.05 (0.27)	.847
CDT Total: Age at First TBI								
Intercept								
	10.45 (0.15)	<.001***	10.47 (0.16)	<.001***	10.44 (0.15)	<.001***	10.44 (0.16)	<.001***
Main Effects								

	rs2072446 (receptor p75NTR)		rs2289656 (receptor TrkB)		rs56164415 (BDNF C270T)		rs6265 (BDNF Val66Met)	
	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*
Time (yrs)	-2.36 (0.05)	<.001***	-2.34 (0.05)	<.001***	-2.32 (0.05)	<.001***	-2.32 (0.06)	<.001***
Age (Centered at 80)	0.06 (0.02)	<.001***	0.05 (0.02)-	<.001***	0.05 (0.02)	<.001***	0.05 (0.02)	<.001***
Sex (Female)	-1.19 (0.16)	<.001***	-1.22 (0.16)	<.001***	-1.23 (0.16)	<.001***	-1.19 (0.16)	<.001***
Childhood	0.73 (0.33)	.027*	0.57 (0.38)	.132	0.62 (0.33)	.058 .	0.41 (0.38)	.281
Early Adulthood	-0.31 (0.51)	.545	-0.11 (0.60)	.853	-0.22 (0.50)	.663	-1.04 (0.58)	.075 .
Middle Adulthood	0.09 (0.41)	.820	0.08 (0.47)	.862	0.17 (0.42)	.690	-0.18 (0.49)	.718
Late Life	-0.05 (0.34)	.893	0.15 (0.39)	.693	0.09 (0.33)	.788	0.02 (0.39)	.952
SNP (Presence)	0.13 (0.38)	.732	0.04 (0.22)	.846	0.19 (0.32)	.545		
SNP (Mn)							-0.04 (0.22)	.871
SNP (nn)							0.43 (0.51)	.392
Interactions								
Time x SNP (Presence)	0.20 (0.16)	.230	-0.02 (0.09)	.856	-0.06 (0.14)	.662		
Time x SNP (Mn)							-0.08 (0.10)	.440
Time x SNP (nn)							-0.05 (0.21)	.805
Time x Childhood	-0.07 (0.14)	.596	-0.25 (0.16)	.122	-0.20 (0.14)	.143	-0.09 (0.16)	.566
Time x Early Adulthood	-0.30 (0.21)	.164	-0.49 (0.25)	.052 .	-0.15 (0.21)	.489	-0.03 (0.24)	.894
Time x Middle Adulthood	-0.28 (0.18)	.114	-0.25 (0.20)	.225	-0.27 (0.18)	.128	-0.09 (0.21)	.674
Time x Late Life	0.28 (0.14)	.055 .	0.27 (0.16)	.098 .	0.27 (0.14)	.053 .	0.43 (0.16)	.008**

	rs2072446 (receptor p75NTR)		rs2289656 (receptor TrkB)		rs56164415 (BDNF C270T)		rs6265 (BDNF Val66Met)	
	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*
Childhood x SNP (Presence)	-1.17 (0.98)	.232	-0.08 (0.65)	.905	-0.56 (1.03)	.591		
Early Adulthood x SNP (Presence)	0.15 (1.73)	.930	-1.00 (1.05)	.340	-0.35 (2.86)	.903		
Middle Adulthood x SNP (Presence)	-0.96 (1.59)	.547	-0.04 (0.82)	.964	-0.33 (1.12)	.769		
Late Life x SNP (Presence)	0.18 (0.95)	.846	-0.61 (0.66)	.359	-0.84 (1.06)	.430		
Childhood x SNP (Mn)							0.44 (0.66)	.508
Early Adulthood x SNP (Mn)							2.89 (1.09)	.008**
Middle Adulthood x SNP (Mn)							1.03 (0.82)	.212
Late Life x SNP (Mn)							0.17 (0.68)	.808
Childhood x SNP (nn)							0.37 (1.88)	.844
Early Adulthood x SNP (nn)							-1.55 (2.90)	.594
Middle Adulthood x SNP (nn)							-2.06 (2.10)	.326
Late Life x SNP (nn)							-1.29 (1.40)	.356
Time x Childhood x SNP (Presence)	-0.43 (0.39)	.270	0.31 (0.27)	.246	0.53 (0.44)	.227		

	rs2072446 (receptor p75NTR)		rs2289656 (receptor TrkB)		rs56164415 (BDNF C270T)		rs6265 (BDNF Val66Met)	
	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*
Time x Early Adulthood x SNP (Presence)	1.41 (0.69)	.043*	1.20 (0.44)	.006 **	-0.55 (1.07)	.610		
Time x Middle Adulthood x SNP (Presence)	0.94 (0.77)	.224	0.01 (0.36)	.984	0.13 (0.58)	.829		
Time x Late Life x SNP (Presence)	-0.13 (0.39)	.735	0.04 (0.28)	.872	0.05 (0.46)	.912		
Time x Childhood x SNP (Mn)							-0.06 (0.27)	.839
Time x Early Adulthood x SNP (Mn)							-0.45 (0.46)	.322
Time x Middle Adulthood x SNP (Mn)							-0.47 (0.36)	.190
Time x Late Life x SNP (Mn)							-0.43 (0.29)	.134
Time x Childhood x SNP (nn)							-2.89 (1.30)	.027*
Time x Early Adulthood x SNP (nn)							-0.11 (1.34)	.935
Time x Middle							0.03 (0.89)	.974

	rs2072446 (receptor p75NTR)		rs2289656 (receptor TrkB)		rs56164415 (BDNF C270T)		rs6265 (BDNF Val66Met)	
	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*	b (SE)	*p*
Adulthood x SNP (nn)								
Time x Late Life x SNP (nn)							-0.61 (0.65)	.350

Note. Reference category for sex is males. Reference category for education is a HS diploma or GED. Reference category for TBI characteristics is no reported TBI. Reference category for SNP is individuals homozygous for the major allele.

3MS = Modified Mini-Mental State Exam; TBI = Traumatic Brain Injury; HS = High School; GED = General Education Diploma; BDNF/NGFR-Related SNP = Brain Derived Neurotrophic Factor Gene/Nerve Growth Factor Receptor-Related Single Nucleotide Polymorphism

. p <.1. * p <.05. ** p <.01. *** p <.001.

Summary

In summary, several significant associations were found between TBI characteristics (number, severity, and age of occurrence) and cognition in late life as well as moderation of by a number of individual difference variables (i.e., sex, genetic factors). Tables 14 and 15 display the overall significant and trend-level associations across research questions.

Table 14

Summary of Significant and Trending Associations for Research Question 1 and 2

	TBI Characteristics			
	Number of TBI	Age at First	Age at Last	TBI Severity
3MS	X	X	X	X
HVLT-R				
Learning	TBI x Time (p = .018*)	X	X	X
Delayed	X	X	Last x Time x Sex (p = .075 **.**)	X
Recognition	TBI x Time (p = .051 **.**)	X	X	Severity x Time x Sex ((p = .030 *)
DS				
Forward	X	X	X	X
Backward	X	X	Last x Sex (p = .081 **.**)	X
CDT Total	X	First x Time (p = .057 **.**)	X	X

Note. X denotes no significant result.

TBI = Traumatic Brain Injury; 3MS = Modified Mini-Mental State Exam; HVLT-R = Hopkins Verbal Learning Test-Revised; DS = Digit Span; CDT = Clock Drawing Test

. p <.1. * p <.05.

Table 15

Summary of Significant and Trending Moderation Effects for Research Question 3 and 4

	Genetic Variables				
	APOE ε4	rs2072446 (Receptor p75NTR)	rs2289656 (Receptor TrkB)	rs56164415 (BDNF C270T)	rs6265 (BDNF Val66Met)
3MS: Number of TBI	APOE x TBI x Sex x Time^2 (p <.001 ***)	X	SNP x TBI x Sex x Time^2 (p = .072 .)	SNP x TBI x Time^2 (p = .065 .)	X
HVLT-R					
Learning: Number of TBI	APOE x TBI x Sex (p = .002**)	X	X	X	SNP x TBI x Time (p = .059.)
Delayed: Age at Last	X	X	X	X	X
Recognition: Number of TBI	X	SNP x TBI x Time (p = .054 .)	SNP x TBI (p = .094 .)	X	X
Recognition: TBI Severity	X	X	SNP x Severity (p = .016*)	X	X
DS Backwards: Age at Last	X	SNP x Age Last x Time (p = .095 .)	X	X	X
CDT Total: Age at First	X	X	SNP x Age First x Time (p = .077 .)	X	X

Note. X denotes no significant result.

TBI = Traumatic Brain Injury; 3MS = Modified Mini-Mental State Exam; HVLT-R = Hopkins Verbal Learning Test-Revised; DS = Digit Span; CDT = Clock Drawing Test

. p <.1. * p <.05. ** p <.01. *** p <.001.

Discussion

In a large population-based sample of older adults, differential effects of history of TBI on late life cognitive decline varied by TBI characteristics, which were further modified by APOE ε4 genotype and SNPs related to BDNF signaling. Sex differences in TBI frequency and age of occurrence as well as sex-dependent effects were observed in the present study. Specifically, females reported lower frequency of TBI overall and the majority of reported TBIs occurring in late life (e.g., after age 65) whereas males endorsed a higher frequency of TBIs but with the majority occurring in childhood (e.g., ages 0-17). Two or more reported TBIs was significantly associated with lower scores on verbal learning. This association was not modified by sex. However, history of TBI was moderated by presence of APOE ε4 allele in that females with a history of multiple TBIs and the APOE ε4 allele scored lower on global cognition and verbal learning than males.

These results are largely consistent with prior studies. Literature examining the role of APOE ε4 in cognitive outcome following TBI is largely conflicting, however, the majority of meta-analyses and literature reviews support an overall negative influence of APOE ε4 on cognitive outcomes following a TBI (Lawrence et al., 2015; McFadyen et al., 2021), consistent with the current study's results. Notably however, the interaction between APOE genotype and TBI history was stronger for females than in males. In a review of 156 published studies examining TBI neurocognitive outcomes between males and females across the lifespan, 47% of the studies reported worse outcomes for females (Gupte et al., 2019b). This review also found that when included studies were categorized

by TBI severity, the majority of studies of mild-moderate TBI found that females fared worse than males (60%) whereas studies of moderate-severe TBI indicated females fared *better* than males (46%) (versus 34% indicating worse outcomes for females). However, we also found that females with a severe TBI performed better than males on recognition recall. Furthermore, the present study suggests another moderating factor (i.e., BDNF/NGF genotype) may influence sex differences seen in APOE genotype. Amongst all other significant and trending interactions between TBI and genotypes explored in the present study, females were associated with worse cognitive scores when there was a sex difference.

With respect to the *timing* of TBI over the life span, there were several trends suggesting an association. For instance, females with a last reported TBI in late life scored lower than males with no reported TBI in working memory. In verbal delayed recall, females with a last reported TBI in early adulthood (e.g., ages 18-30) also scored lower than males. The limited research examining age of injury effects on late-life cognition indicate poorer cognitive functioning for those who experienced a TBI later in life (Chanti-Ketterl et al., 2023, Eramudugolla et al., 2014; Senathi-Raja et al., 2010). One explanation for this is that recovery post TBI involves re-myelination of axons, which is a process that occurs more slowly and less efficiently with older age (Franklin et al., 2002). Additionally, a recent twin study of over 8,600 older male veterans found that individuals with a history of multiple brain injuries, LOC, and older age (e.g., over age 25) at time of TBI performed worse on cognitive test scores compared to twins with only one TBI, no LOC, and TBI before the age of 25 (Chanti-Ketterl et al., 2023). This is inconsistent with a trend association found in the current study where individuals with a

first reported TBI in late life scored higher on a spatial task than individuals with no reported TBI, independent of sex.

Despite the well-known role of BDNF in brain health and late-life cognitive functioning, limited research has examined its role in recovery from TBI. Much of the research has focused on the BDNF Val66Met (rs6265) BDNF SNP which suggest Met carriers demonstrate better cognitive performance following TBI (Krueger et al., 2011; Merritt et al., 2020). This is consistent with the current study that found a trend along a similar direction for verbal learning. Research suggests this may be due to the role the BDNF Val66Met (rs6265) SNP plays in the BDNF signaling pathway. For instance, the Val to Met substitution occurs in the section of the BDNF gene that encodes for the precursor peptide (pro-BDNF) that is then cleaved to form the mature neurotrophin (mature-BDNF) (Finan et al., 2018). The BDNF Val66Met (rs6265) SNP influences the processing and release of pro-BDNF, which promotes apoptosis and suppresses axonal growth, as well as the secretion of mature-BDNF, which promotes neuronal survival, dendritic branching and synaptic plasticity (Borodinova & Salozhin, 2017; Finan et al., 2018). Furthermore, in individuals without the Met allele, pro-BDNF is upregulated following a TBI, whereas carriers of the Met allele have decreased pro-BDNF secretion (Barbey et al., 2014). Therefore, Met allele carriers may have a protective role against apoptosis of surviving cells following a TBI.

Pro-BDNF and mature-BDNF interact with different receptors and signaling cascades to enact these opposing effects in the brain. Specifically, pro-BDNF interacts with receptor p75NTR (rs2072446) whereas mature-BDNF interacts with receptor TrkB (rs2289656) (Chao, 2003; H. K. Teng et al., 2005). The relationship between TBI and

receptors p75NTR (rs2072446) and TrkB (rs2289656) and effects on cognitive outcomes after injury, as well as other neurotrophin SNPs are not well studied. In the current study, the SNP for receptor TrkB (rs2289656) significantly moderated the relationships between TBI severity and recognition recall in that individuals with a severe TBI and at least one minor allele for the SNP scored significantly worse than individuals with no reported TBI and presence of the minor allele, independent of sex. Several other interactions between presence of the minor allele for SNP receptor TrkB (rs2289656) and TBI characteristics were found in the current study at trend level significance. In particular, females with two or more TBIs and homozygous for the minor allele scored lower on a global cognition measure compared to males. Presence of the minor allele for this SNP was also associated with worse recognition recall, although also better on the CDT total, independent of sex. Although the latter result is contrary to expectation, this may reflect the heterogeneous nature of the CDT total scores, combining visuo-spatial abilities, executive functions, and other cognitive domains. An examination of sub scores by cognitive domain may have yielded different results. Research on induced TBI in animal models indicate TBI produces an acute increase in BDNF and TrkB (rs2289656) mRNA as a protective response to injury to promote neuronal survival (Wu et al., 2014). However, this acute reaction is transient, thus, the response to injury may not be predictive of the results of the current study, which examined long-term associations of TBI with cognition. With regards to the SNP for receptor p75NTR (rs2072446), the current study found individuals with a reported last TBI in late life and presence of the minor allele had lower DS Backwards scores at a trend level. Furthermore, individuals with two or more TBIs and at least one minor allele for the SNP for receptor p75NTR

(rs2072446) performed worse on a recognition recall task, also at a trend level. Lastly, in regards to a SNP in the BDNF gene promoter, C270T, individuals with at least one minor allele for the SNP for BDNF C270T (rs56164415) and two or more reported TBIs scored higher over time on a global cognition task compared to individuals without a history of TBI and no minor alleles, at a trend level significance. Research exploring BDNF C270T (rs56164415) polymorphisms suggest it may be important for late-life cognitive decline and risk for AD (Fukumoto et al., 2010). However, a meta-analysis with a diverse sample of people from various countries did not find this SNP to be significantly associated with AD (Kunugi et al., 2001). Furthermore, the current literature does not include other studies that have examined the interaction of TBI and BDNF C270T (rs56164415) on cognitive functioning in late life. Findings from the current study indicated the SNP for BDNF C270T (rs56164415) was not associated with cognitive decline in late life following TBI.

Although sex differences have been noted for various BDNF-related SNPs in risk for AD (Matyi et al., 2017) and cognitive decline (Wei et al., 2017), the present study did not yield any significant interactions between BDNF/NGFR-related SNPs and sex on late life cognitive decline following a TBI.

The current study has several strengths, including a large, population-based sample with a high participation rate (90% enrollment) and longitudinal follow up. This is especially relevant when examining long-term effects of TBIs as much of the current literature examining cognitive outcomes following a TBI have relatively short follow up times (e.g., less than five years) and generally focus on the acute stage of recovery. The present study was able to examine the various characteristics of TBI, such as

developmental and recency effects as well as severity, across the lifespan as predictors of late-life cognitive decline. It also examined individual differences including sex and various genes that are associated with late-life cognitive functioning as well as recovery from brain injury such as APOE and SNPs related to BDNF signaling. To our knowledge, no studies to date have included as large of a population-based sample with history of TBI across the lifespan over a lengthy follow-up period in late life.

There are also some limitations to the current study. Most notably, the CCSMA population characteristics include participants who are predominantly Caucasian, of Northern European heritage, of middle class social economic status, highly educated, and the majority of whom identify with a regional religious group, specifically The Church of Jesus Christ of Latter-Day Saints, thus limiting the generalizability to other culturally or racially diverse groups. The homogeneity of the sample is also relevant for APOE and SNPs related to BDNF signaling as previous research has suggested ethnic differences in the frequency of minor alleles for APOE (Abondio et al., 2019), BDNF SNPs or its receptors (Shen et al., 2018), and cognitive outcomes in late life (Kunugi et al., 2001, Matyi et al., 2017). Furthermore, lifetime history of TBI and TBI characteristics were obtained retrospectively which may have been impacted by recall bias with possible under or over reporting of TBI occurrence and inaccuracies in the characteristics of TBI including age of injury as well as LOC and PTA, which were used to determine TBI severity. Additionally, I was not able to include both severity and age of last TBI in fully adjusted models predicting cognitive decline and thus could not estimate their independent effects. However, exploratory work suggested the two characteristics of TBI

were not significantly related. Lastly, due to the exploratory nature of the present study, multiple analyses were conducted increasing the possibility of Type 1 error.

Future Directions

Given the significant number of individuals who experience a TBI in their lifetime [a predicted 69 million individuals globally (Dewan et al., 2018)], continued research in examining short- and long-term neurological and behavioral or cognitive effects and processes is paramount. The results of the current study build upon current research that investigated the neurobiological occurrences following a TBI and the long-term effects. Specifically, how neurobiological recovery processes are influenced by APOE ε4 and genes related to BDNF signaling. APOE genotype is well established in current literature as influencing the rate of cognitive decline in late life and increasing risk for AD (fan et al., 2019) especially in those with a history of TBI (Lawrence et al., 2015). However, the effects of TBI on BDNF and NGF related signaling cascades, outside of BDNF Val66Met (rs6265), are still largely unknown and calls for further research to understand their potential influence on late-life cognitive decline. Furthermore, current literature examining age effects of TBI on late-life cognition shows conflicting results with some indicating that older age at injury (i.e., more recent TBI) is associated with worse cognitive outcomes (Chanti-Ketterl et al., 2023; Li et al., 2017) whereas other studies indicate poorer cognitive functioning in long-term survivors (i.e., more remote TBI) (Senathi-Raja et al., 2010).

In regard to APOE, several mechanisms by which APOE ε4 may contribute to worse cognitive outcomes following TBI are being examined, but no viable treatment to offset its effects are established at this time. Despite APOE ε4's known role in the inflammatory response and neuronal repair mechanisms following TBI (Chen et al., 1997; Lynch et al., 2002) as well as AD in late life (Fan et al., 2019), its role in long-term recovery following TBI still remains in question. Future studies should continue to examine potential modifying relationships (such as BDNF/NGFR-related SNPs) that may explain the variance seen in studies examining the role of APOE in cognitive functioning following TBI.

Understanding neurobiological roles of BDNF/NGF and their receptors and how they contribute to injury recovery following TBI could be relevant for immediate care. For instance, several strategies for establishing neuroprotective effects that aim to salvage injured brain tissue and promote regeneration in the early stages of post injury are being explored including antagonists for NGF/BDNF receptor p75NTR (rs2289656). Receptor p75NTR expression is increased in the developing brain and downregulated in the adult brain, until it is re-expressed following injury (Underwood & Coulson, 2008) and associated with apoptosis. Animal research studies indicate pharmacological inhibition of the p75NTR signaling pathway limits post-injury cell death and offers one possible approach to limiting acute brain damage following injury (Sebastiani et al., 2015). Another target for treatment following brain injury is flavonoid 7,8-dihydroxyflavone (7,8-DHF) that acts as a TrkB (rs2289656) agonist and mimics BDNF function in the brain (Wurzelmann et al., 2017). 7,8-DHF is a naturally occurring compound found in fruits and vegetables which should encourage future studies to examine how lifestyle

factors, such as diet, interact with neurobiological pathways to moderate TBI cognitive outcomes and act as one form of treatment in the acute stages following injury.

In addition to nutritional habits, other lifestyle factors such as physical activity and sleep have also been associated with onset of age-related cognitive decline in late life (Dominguez et al., 2021) as well as preserving brain health and cognitive functioning following TBI (Bogdanov et al., 2017; Patel et al., 2023; Zhang et al., 2022). These lifestyle habits should be further explored in relation to how changes modify neurological pathways discussed above.

With one-third of older adults falling each year (Jehu et al., 2021), hospitalization rates for head injuries is highest amongst those over the age of 75 (Faul et al., 2010). In a systematic review and meta-analysis completed by Jehu and colleagues, associated risks for increased and repeated falls in older adults included mobility difficulties (e.g., gait), medication issues (e.g., polypharmacy), psychological issues (e.g., cognition), and sensory and neuromuscular impairments (e.g., poor vision). One avenue of research that could be beneficial in mitigating fall risk in older adults is examining modifiable risk factors, such as medication use and interactions, to prevent impairments in these domains. Clinically assessing for risk for falls in older adults and monitoring mobility, psychological, and muscular impairments can reduce falls and prevent head injuries.

Furthermore, as established in the current literature and supported with findings from the current study, females are more likely than males to have a TBI in late life. TBIs in older adult women are most commonly the result of falls thought to be the result of a less physically active lifestyle and loss of lower body strength (Blaya et al., 2022). In a study completed by Wagner and colleagues (2011) results indicated significant sex- and

age- specific altercations in hormonal levels in the acute stages following TBI. Therefore, in addition to lifestyle differences between males and females in late life, future studies should also examine hormonal and physiological changes and factors specific to the female lifespan such as the effect of endogenous circulating sex hormones, as well as changes in hormone levels, on TBI outcome at different points in the lifespan as well as late-life cognition in females.

A better understanding of long-term effects of TBI on late-life cognition would have a number of clinical implications with respect to differential diagnosis and neuropsychological intervention. Continued research in this field may identify modifiable factors to prevent brain injury and late life falls as well as potential interventions in the acute stages following injury to improve longevity of brain health and preserve cognitive abilities in late life and overall healthier aging.

In conclusion, the current study demonstrated that the course of cognitive decline in late life was associated with history of TBI and some characteristics of TBI, with some associations differing by sex.

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Appendix

Baseline Head Injury Questionnaire

D13. Have you had a head injury so severe that you lost consciousness, lost your memory for a period of time, or had to see a doctor?	YES . . . . . 1 NO (GO TO D17) . . . . . 2 RF (GO TO D17) . . . . . .7 DK (GO TO D17) 8
D14. How many times did this happen?	# OF TIMES . . . . . .__
D15. Now I want you to think about your (last) head injury. How old were you at that time?	AGE . . . . . .__
a. Could you please describe the injury to me.	RECORD:_____
b. Did you see a doctor or go to a hospital?	SAW DOCTOR (RECORD) . .. . 1 WENT TO HOSPITAL (RECORD). . . . . 2 NO DOCTOR OR HOSPITAL .. . . . . 3 RF . . . . . 7 DK 8
RECORD NAME AND ADDRESS OF DOCTOR OR HOSPITAL.	NAME:_____ ADDRESS:_____
c. Did you lose consciousness?	YES . . . . . 1 NO (GO TO e) . . . . . .2 RF (GO TO e) . . . . . 7 DK (GO TO e) 8
d. How long were you unconscious?	<5 MINS . . . . . 1 5-29 MINS . . . . 2 30-59 MINS . . . . 3 1-24 HRS . . . . . .4 >1 DAY . . . . 5 RF . . . . .7 DK 8
e. Sometimes, after a head injury, people experience amnesia or loss of memory. Did you have a period of amnesia after the injury?	YES . . . . 1 NO (GO TO g) . . . . . 2 RF (GO TO g) . . . . 7 DK (GO TO g) 8
f. How long did you have this memory loss?	0-24 HRS . . . . . 1 2-6 DAYS . . . . 2 >1 WEEK . . . . . 3 RF . . . . . 7 DK 8
g. At the time of this injury was there any penetration of the skull to the brain (e.g. such as from shrapnel, a bullet wound, or other object)?	YES . . . . . 1 NO . . . . . 2 RF . . . . 7 DK 8
INTERVIEWER CHECKPOINT: DID R. REPORT MORE THAN ONE HEAD INJURY IN D14?	YES (CONTINUE) . . . . . 1 NO (GO TO D17) . . . . .

D16. Now I want you to think about your previous head injury.

How old were you at that time?	AGE . . . . . .__
a. Could you please describe the injury to me.	RECORD:_____
b. Did you see a doctor or go to a hospital?	SAW DOCTOR (RECORD) . .. . 1 WENT TO HOSPITAL (RECORD). . . . . 2 NO DOCTOR OR HOSPITAL .. . . . . 3 RF . . . . . 7 DK 8
RECORD NAME AND ADDRESS OF DOCTOR OR HOSPITAL.	NAME:_____ ADDRESS:_____
c. Did you lose consciousness?	YES . . . . . 1 NO (GO TO e) . . . . . .2 RF (GO TO e) . . . . . 7 DK (GO TO e) 8
d. How long were you unconscious?	<5 MINS . . . . . 1 5-29 MINS . . . . 2 30-59 MINS . . . . 3 1-24 HRS . . . . . .4 >1 DAY . . . . 5 RF . . . . .7 DK 8
e. Sometimes, after a head injury, people experience amnesia or loss of memory. Did you have a period of amnesia after the injury?	YES . . . . 1 NO (GO TO g) . . . . . 2 RF (GO TO g) . . . . 7 DK (GO TO g) 8
f. How long did you have this memory loss?	0-24 HRS . . . . 1 2-6 DAYS . . . . 2 >1 WEEK . . . . . 3 RF . . . . . 7 DK 8
g. At the time of this injury was there any penetration of the skull to the brain (e.g. such as from shrapnel, a bullet wound, or other object)?	YES . . . . . 1 NO . . . . . 2 RF . . . . 7 DK 8
INTERVIEWER CHECKPOINT: DID R. REPORT MORE THAN 2 HEAD INJURIES IN D14?	YES (GO TO HEAD INJ. SUPP) . . . . . 1 NO (CONTINUE) 2