Consequences of single and repeated mild TBI on post-traumatic neurodegeneration



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Abstract

Traumatic brain injury (TBI) is a global public health issue, with mild TBI (mTBI) accounting for over 90% of cases. While repeated mTBI has been associated with cognitive deficits and a heightened risk of neurodegenerative conditions such as Alzheimer's disease (AD), the long-term impact of mTBI on mid-to-early late life cognitive and neural trajectories remains poorly understood.

This thesis investigates whether a history of single or repeated mTBI contributes to vulnerability to neurodegeneration or accelerates cognitive decline. Using harmonised datasets from two large cohorts, the PREVENT and EPAD studies, this research uniquely focuses on mid-life, an underrepresented period in TBI research. The Brain Injury Screening Questionnaire (BISQ) was employed to comprehensively assess lifetime TBI history, while advanced harmonisation techniques addressed variability across cohorts, enabling robust analyses of cognitive and neural changes over time.

Findings revealed limited evidence of attentional deficits, subtle increases in white matter hyperintensities (WMHs) in repeated mTBI cases, and no significant differences in brain volumes or diffusion tensor imaging (DTI) metrics. Longitudinal analyses showed no significant acceleration of cognitive or neural decline in individuals with a history of mTBI, suggesting that mid-life individuals may exhibit resilience to the long-term effects of TBI. These results provide reassurance that mTBI in mid-life does not necessarily lead to early cognitive or neural decline, although longer follow-up is needed to confirm these patterns.

By integrating harmonised data and a longitudinal approach, this thesis advances understanding of mTBI as a potential modifiable risk factor for neurodegeneration. It emphasizes the importance of mid-life research and provides a foundation for future studies aimed at early detection and intervention in at-risk populations.

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List of Abbreviations

Aβ: Amyloid-beta

ACRM: American Congress of Rehabilitation Medicine

AD: Alzheimer's Disease

AD: Axial Diffusivity

ALS: Amyotrophic Lateral Sclerosis

ADNI: Alzheimer's Disease Neuroimaging Initiative

ANCOVA: Analysis of Covariance

ANOVA: Analysis of Variance

AP/PA: Anterior to Posterior/Posterior to Anterior

APOE: Apolipoprotein E

ASL: Arterial Spin Labelling

BBB: Blood Brain Barrier

BET: Brain Extraction Tool

BIANCA: Brain Intensity AbNormality Classification Algorithm

BISQ: Brain Injury Screening Questionnaire

CBF: Cerebral Blood Flow

CSF: Cerebral Spinal Fluid

CSP: Cavum Septum Pellucidum

CT: Computed Tomography

CTE: Chronic Traumatic Encephalopathy

CVR: cerebrovascular reactivity

DAI: Diffuse Axonal Injury

DLB: Dementia with Lewy Bodies

DTI: Diffusion Tensor Imaging

DTIFIT: Tool for fitting the diffusion tensor model in FSL

dMRI: Diffusion MRI

DWMH: Deep White Matter Hyperintensities

EPAD: European Prevention of Alzheimer's Dementia

EPI: Echo Planar Imaging

FA: Fractional Anisotropy

FDA: Food and Drug Administration

FDG-PET: 18-Fluoro-deoxyglucose positron emission tomography

FIRST: FMRIB's Integrated Registration and Segmentation Tool

FLAIR: Fluid-attenuated inversion recovery

FLIRT: FMRIB's Linear Image Registration Tool

fMRI: Functional magnetic resonance imaging

FNIRT: FMRIB's Nonlinear Image Registration Tool

FoV: Field of View

FTD: Frontotemporal Dementia

FWE: family wise error

FWMH: Full-width-half-maximum

GCS: Glasgow Coma Scale

GFAP: Glial Fibrillary Acidic Protein

GM: Grey Matter

GMV: Grey Matter Volume

HC: Healthy Controls

ICV: Intracranial Volume

IDPs: Imaging Derived Phenotypes

IPV: Intimate Partner Violence

KMO: Kaiser–Meyer–Olkin

LME: Linear mixed-effects models

LOC: Loss of Consciousness

MD: Mean Diffusivity

MNI: Montreal Neurological Institute

MO: Mode of anisotropy

MRI: Magnetic Resonance Imaging

MS: Multiple Sclerosis

mTBI: Mild Traumatic Brain Injury

MTL: Medial Temporal Lobes

NA: Not Applicable

NODDI: Neurite Orientation Dispersion and Density Imaging

OSU TBI-ID: Ohio State University TBI Identification Method

PC: Principal Components

PCA: Principal Component Analysis

PD: Parkinson’s Disease

PEd: Phase Encoding Direction

PET: Positron Emission Tomography

PTA: Post-Traumatic Amnesia

PTSD: Post-Traumatic Stress Disorder

PVEs: Partial Volume Estimates

PWMH: Periventricular White Matter Hyperintensities

RBANS: Repeatable Battery for the Assessment of Neuropsychological Status

RD: Radial Diffusivity

rmTBI: repeated mild Traumatic Brain Injury

ROI: Region of interest

SIENAX: Structural Image Evaluation, using Normalization, of Atrophy Cross-sectional

smTBI: single mild Traumatic Brain Injury

TAI: Traumatic Axonal Injury

TBI: Traumatic Brain Injury

TBIQ: Traumatic Brain Injury Questionnaire

TBSS: Tract-Based Spatial Statistics

TBV: Total Brain Volume

TDP-43: TAR DNA-binding protein of 43 kDa

TE: Echo time

TR: Repetition time

UCH-L1: Ubiquitin C-terminal hydrolase-L1

VBM: Voxel Based Morphometry

WM: White Matter

WMH: White Matter Hyperintensities

WMV: White Matter Volume

Publications during thesis

Publications resulting from this thesis

Raymont V, **Thayanandan T**. What do we know about the risks of developing dementia after traumatic brain injury? Minerva Med. 2021 Apr;112(2):288-297.

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Other publications during the DPhil

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Conference presentations and other talks

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Chapter 1: Overview and Objectives

1.1 Overview

Recent media interest surrounding the long-term consequences of concussion in sports has led to an increase in research investigating the impact of traumatic brain injuries (TBIs) on neurodegeneration. TBIs are common, with an estimated 50-60 million cases per year worldwide (Maas et al., 2022). Long term outcomes are still under investigation, but cognitive and psychiatric difficulties are frequent, and overall costs worldwide are estimated to be $400 billion (Maas et al., 2017). In the United Kingdom approximately 1.4 million people or around 2% of the population attend emergency services each year with a head injury (Davis et al., 2015) and it is one of the leading causes of death in people under 40.

TBI severity can be classified as mild, moderate, or severe. Mild TBI (mTBI) is characterized as a negligible loss of consciousness with minimal neuropathology (Menon et al., 2010; Ruff et al., 2009) and it is estimated to account for 90% of all TBI cases worldwide (Maas et al., 2022). mTBI following a single incident is difficult to detect, most cognitive and behavioural deficits usually resolve within weeks of the head injury (Losoi et al., 2016; Lovell et al., 2003; McCrea et al., 2003). However, a more pernicious, long-lasting condition may arise with repeated mTBI (Guskiewicz et al., 2003). Repeated mTBI is associated with more severe and protracted cognitive, motor, and behavioural complications that may last for months and even years (De Beaumont et al., 2012). Even after the remission of symptoms, there is accumulating evidence of persistent brain injuries (Palacios et al., 2020; Rajesh et al., 2017; Vergara et al., 2018) that are associated with an increased risk of developing neurodegenerative conditions, including Alzheimer's disease (AD), chronic traumatic encephalopathy (CTE), and Parkinson's disease (PD) later in life (Graham & Sharp, 2019). Recent studies have shown that a single mTBI can cause similar pathophysiological changes in the brain to that of repeated mTBI,

including diffuse axonal injury, neurotransmitter activity alterations and modified levels of brain excitability (Choe, 2016).

The relative risk of AD after TBI has been estimated in a large meta-analysis to be increased by about 1.5 times (Li et al., 2017), and researchers suggest that TBI is associated with both higher incidence of AD and earlier onset. While evidence linking moderate or severe TBI to increased AD risk is robust, the impact of mTBI on AD risk is not well understood. A systematic review of potential risk for dementia after mTBI found insufficient evidence to draw a direct link (Godbolt et al., 2014), Johnson & Stewart found a history mTBI only increased risk of AD in adults over 65 years of age (Johnson & Stewart, 2015). Interestingly, a recent retrospective study found that 571 patients with a diagnosis of AD and only a history of mTBI with loss of consciousness (LOC) (rather than TBI without LOC) had an onset of symptoms 2.5 years earlier than those without TBI; this increased risk was found irrespective of APOE4 status (LoBue et al., 2017). This suggests that a history of mTBI could lead to a reduction in cognitive reserve which in turn could lower threshold of the onset of clinical symptoms. It could also accelerate the onset of AD by directly influencing the underlying neurodegenerative process, accelerating Aβ toxicity in individuals with age-related Aβ plaques (Mann et al., 1990).

This lack of consensus and conflicting evidence surrounding mTBI as a risk factor for AD has huge implications due to the incidence rates of mTBI in the population. It could be theorised a history of mTBI, combined with brain changes associated with normal ageing, might lead to exacerbated cognitive decline in older adults. However, this decline may start earlier in those already at risk of AD.

The considerable variability in TBI settings (e.g., military, sports), characteristics (e.g., fall, blunt trauma), and severity (mild to severe), as well as in the resulting neuropathology (e.g., neuronal, axonal, vascular damage), may explain the conflicting evidence. Both preinjury (the person who is damaged) and postinjury (the person's reaction to the injury and the social environment) factors have

an impact on TBI outcomes. Conventional methods of data analysis have failed to thoroughly interrogate and integrate data on damage processes, effects, and recovery, failing to address the complexity of TBI and its multidimensional character. Studies often lack sufficiently precise criteria and terminology for classifying TBI, small sample sizes and a focus on younger and older adults with no information regarding mid-life change.

The principal objective of this DPhil is to understand whether a history of mTBI creates vulnerability to neurodegeneration or accelerates existing change in mid to early late life in participants at risk of AD. To do this, I will examine both baseline cognitive scores and neuroimaging outcomes in mid to early late life and their change over time in a large, harmonised dataset of participants with a history of TBI.

The key research questions for this thesis are:

1) Is a history of single or repeated mTBI associated with altered cognitive profiles in mid to early late life?
2) Do baseline neuroimaging measures characterize the impact of mTBI?
3) Does mTBI alter cognitive and neural trajectories?

We hypothesize that those with a history of single or repeated mTBI will perform worse on cognitive domains when compared to those without a history of head injury. Additionally, we hypothesize that these individuals will show greater neurodegeneration over time. A deeper understanding of the impact of single and repeated mTBI could have clinical impact by renewing efforts to prevent head injuries and greater vigilance and cognitive evaluations of individuals below 65 years of age.

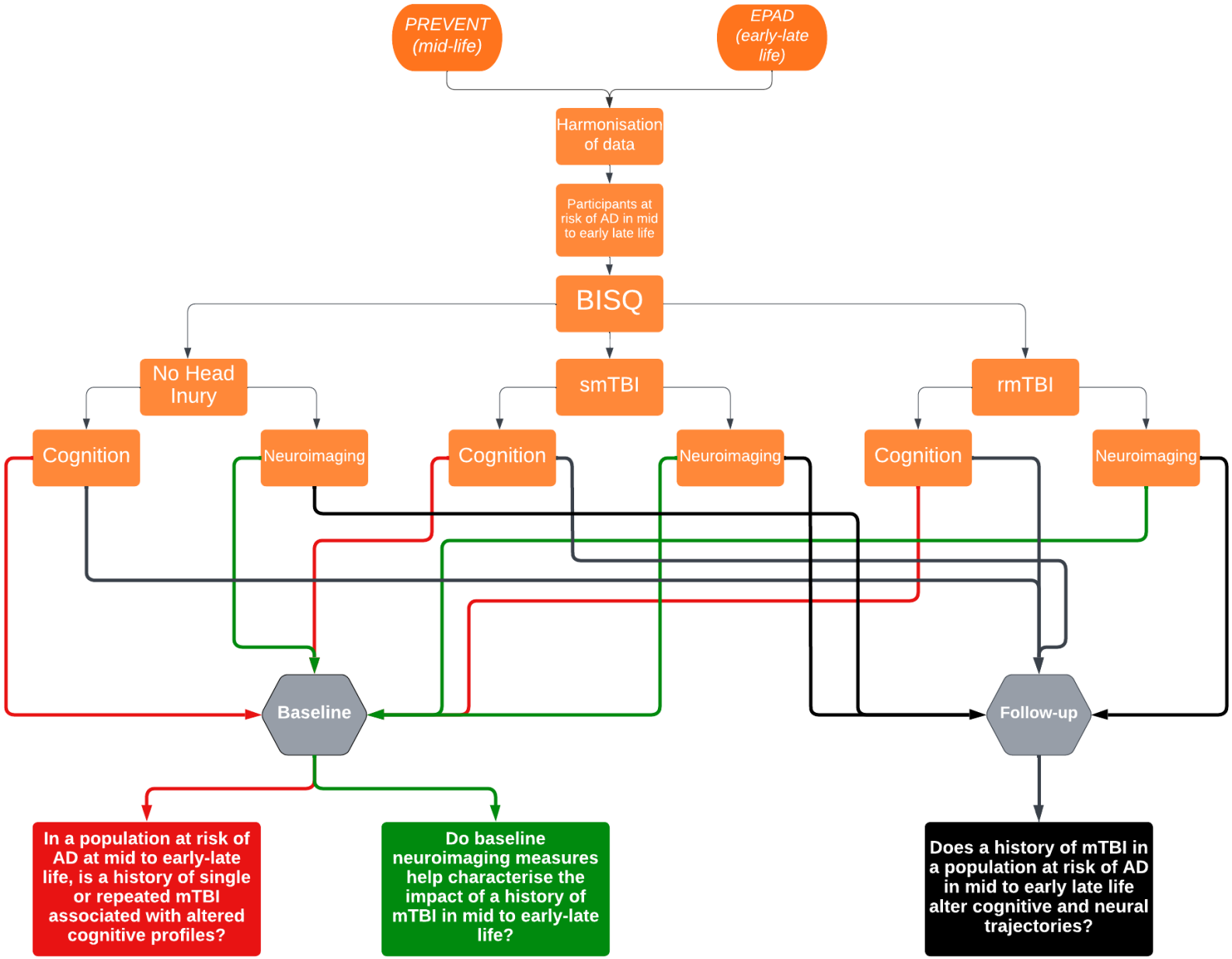


Figure 1.1. Overview of experimental questions to answer principal objective

1.2 Challenges in current TBI research

1.2.1 Classification

A lack of universal standards for classifying TBIs has led to the use of imprecise systems, such as the Glasgow Coma Scale (GCS), which relies on summative scores to categorize injuries as mild, moderate, or severe. For instance, two individuals with the same GCS score might present vastly different recovery outcomes, underscoring the limitations of this classification. This approach can introduce biases in the provision of care. There is a degree of variability regarding the definition of mTBI, which encompasses a minimum of 38 potential definitions. These definitions frequently rely on overlapping criteria (Carroll et al., 2004). Additionally, there exists a considerable variation in the nomenclature employed by clinicians from diverse medical disciplines to denote this ailment (e.g., "mTBI," "concussion," "minor head injury").

1.2.2 Diagnosis, prognosis, and monitoring

Currently, no validated instruments reliably predict the acute or chronic outcomes of TBI. This uncertainty makes it difficult to determine which patients will recover fully and which will face long-term complications. This gap in diagnostic tools means that two patients with seemingly similar injuries could face drastically different futures. One may recover fully, while the other could experience cognitive decline that remains undetected until much later. There is a commonly held belief that individuals with comparable injuries may exhibit a broad spectrum of recuperation patterns and functional consequences (Maas et al., 2017). At present, there exists no biomarker that has been approved by the Food and Drug Administration (FDA) which can reliably forecast outcomes following TBI. While some blood-based biomarkers like GFAP and UCH-L1 have shown promise for diagnosing TBI and aiding computed tomography CT triage, their predictive ability for long-term outcomes remains under investigation (Mondello et al., 2021; Zetterberg et al., 2013).

The predictive ability of serial CT scanning is limited unless it reveals an injury that is not survivable. CT imaging primarily identifies structural abnormalities but does not effectively predict functional or cognitive outcomes (Yue et al., 2019). Advanced imaging techniques, such as magnetic resonance imaging (MRI), may potentially serve a purpose. For instance, MRI can detect microstructural changes and diffuse axonal injury, which are often missed by CT scans (Sharp & Jenkins, 2015). However, there is little evidence that demonstrates its ability to precisely forecast long-term results (Bigler, 2013).

The task of tracking the progression of TBI as a medical condition over a period of time is a significant hurdle. Emerging research focuses on biomarkers to monitor progression and predict therapeutic response, yet further investigation is required to establish their clinical utility (Thelin et al., 2017; Yuh et al., 2014).

1.2.3 TBI research in ageing

Older individuals often face less complete recovery compared to younger patients, even when their injuries are similar. This may be due to factors such as reduced cognitive reserve and pre-existing health conditions. The aetiology of this phenomenon remains unclear; however, it could potentially be attributed to a decline in compensatory ability or diminished cognitive reserves, which are known to increase with age (Lye & Shores, 2000). Additionally, the elderly population is more prone to pre-existing medical conditions that can hinder the treatment process. Furthermore, age-related cognitive decline may affect the accuracy of tools utilised to assess the severity of TBI and predict its outcomes. Furthermore, it is noteworthy that the demographic of individuals in mid-life encompasses those who have encountered TBI during their earlier years, underscoring the significance of comprehending the intersection between prior TBI and the process of ageing, as well as the neurodegenerative mechanisms that may arise in later stages of life (Griesbach et al., 2018). Longitudinal research can facilitate the elucidation of associations between immediate and

long-term consequences, including but not limited to fatality, susceptibility to dementia, sleep disorders, or Parkinson's disease, and the fundamental mechanisms that underlie these associations.

1.3 Methods for investigating history of mild TBI in an at-risk population

In this thesis, I adopt three crucial approaches that are vital for unmasking the impact of mTBI on healthy ageing: self-reported history of TBI through the Brain Injury Screening Questionnaire (BISQ), harmonisation of neuroimaging and cognitive assessments and longitudinal evaluation.

The BISQ is a novel and validated TBI screening tool that is used to document lifetime history of self-reported TBI and the presence of current symptoms, if any, as well as to rule out alternative explanations for reported symptoms (e.g., other neurological or developmental conditions) (Dams-O'Connor et al., 2014). Using the BISQ tool, clinicians can track the severity and frequency of these incidents, providing a clearer picture of the long-term risks they may face. The BISQ can also be used to calculate severity of TBI history in participants. A full description of the BISQ can be found in chapter 2.

Harmonising neuroimaging and cognitive data is critical in TBI research for several reasons. First, it standardizes results across diverse studies, allowing researchers to compare findings more accurately. This uniformity is particularly valuable given the variability in neuroimaging techniques and cognitive assessments used in TBI research. Furthermore, the aggregation of harmonised data from two large datasets used in this DPhil significantly enhances the statistical power of analyses, a crucial factor in TBI research where individual studies often grapple with small sample sizes. This comprehensive approach is integral to the identification and validation of biomarkers related to TBI, facilitating the development of more precise diagnostic tools, and improving our understanding of the severity and impact of brain injuries.

Moreover, harmonisation plays a critical role in addressing the inherent heterogeneity of TBI, such as variations in injury severity, location, and individual patient factors. By analysing uniform data sets, researchers can delve deeper into how these diverse injury characteristics influence cognitive outcomes. Additionally, in the realm of clinical trials, harmonised data ensures that the outcomes measured are consistent and meaningful across different sites, bolstering the efficacy of trials in evaluating new treatments and interventions. This cross-disciplinary collaboration, fostered by data harmonisation, brings together experts from various fields, culminating in a more holistic and profound understanding of TBI and its implications (Esopenko & Levine, 2015; Lawrence et al., 2019). The harmonisation of diverse datasets, which will be discussed in detail in Chapter 3, forms the cornerstone of this investigation, enabling the analysis of both cognitive and neuroimaging markers across cohorts at risk for neurodegeneration. The methodology for harmonisation will be critical in addressing the variability introduced by multi-site data collection and will allow for reliable comparisons across cohorts affected by TBI.

Longitudinal data have been crucial in demonstrating cognitive and neural trajectories post TBI. Longitudinal assessment is crucial to monitor stability or decline over time, associate long-term outcomes with baseline metrics, and provide more sensitive, within-person measures to detect change. In my thesis, I have used data from existing studies to permit longitudinal investigations, not usually feasible in the timescale of a DPhil.

1.4 Data Cohorts

1.4.1 PREVENT

The PREVENT research programme (Ritchie et al., 2013) established a cohort of individuals to explore differences in the brain and cognitive functions in healthy people in mid-life (40 to 59 years), with the aim of eventual reduction of dementia incidence at a population level. The

PREVENT research programme sought to understand the origin point and sequence of pathological changes which lead to dementia. It also aimed to determine what clinical, environmental and genetic factors increase (or decrease) the risk of these changes initiating and developing. Participants are grouped into high-, mid- and low-risk based on their family history and APOE status. PREVENT is a multisite study conducted across five UK research centres. Participants are assessed on biological indicators including markers in blood, saliva, urine and spinal fluid as well as direct imaging of the brain's structure and function. Changes in all of these markers are monitored at two year follow-up. One of the main aims of the study is to identify the earliest signs of changes in the brain whilst people are still in good health.

1.4.2 EPAD

The European Prevention of Alzheimer's Dementia (EPAD) was a prospective, multicentre, pan-European cohort study that aimed to characterize the preclinical and prodromal stages of AD in early late life. It is a four year long multisite study, involving data collected from 15 research sites across Europe. EPAD recruited 2096 participants, aged over 50 without a diagnosis of dementia, who were seen annually to complete various assessments, which included cognition, neuroimaging, fluid biomarkers, genetics, lifestyle, clinical and psychiatric assessment, neuropsychiatric symptoms, function and basic demography (Ritchie et al., 2020). Together, PREVENT and EPAD provide complementary age coverage and harmonized protocols vital for the analyses in Chapter 5-7.

1.4.3 Age range chosen

The analytic window of 40-70 years was chosen because mid-life marks the point at which brain-age (an MRI-derived biomarker of biological ageing) begins to out-pace chronological age for sizeable minority of health adults, and because this divergence is strongly modulated by vascular risk, APOE4, and TBI history (Cole & Franke 2017; Elliott et al., 2019). In large normative datasets,

the mean brainAGE delta remains < 2 years until the late 30s, then accelerates ~0.25 years per chronological year between 40-65 years (Smith et al. 2020). Epidemiological studies also place the inflection point for TBI-associated dementia risk in the same interval (Barnes et al. 2018; Crane et al. 2016). Setting an upper limit of 70 years minimises survivor and prodromal-AD bias while retaining adequate case numbers; setting the lower limit at 40 years captures participants before neurodegeneration is likely to be clinically manifest yet after sufficient time has elapsed since the index trauma for chronic neuropathological sequelae to emerge. This mid-life focus therefore maximises sensitivity to the interaction between latent TBI effects and age-related neurobiological change, directly aligning with the thesis aim of identifying early vulnerability markers.

1.5 Characterising cognitive variability post mild TBI

In the acute phase of mTBI, memory, attention, processing speed, and cognitive flexibility are frequently impaired (Lunter et al., 2019; McCauley et al., 2014). In contrast, research into between-group differences in cognitive performance in the chronic stage of mTBI has yielded contradictory results. While some evidence suggests lower cognitive function in the aforementioned domains remains in the months to years following injury (Kinnunen et al., 2011; Konrad et al., 2011), other studies have found no long-term deficits in mTBI populations. According to a recent scoping analysis, nearly half of individuals with a single mTBI exhibit chronic cognitive impairment. However, these findings were demonstrated in older adults, in whom the impact of mTBI may have been obscured by other comorbidities that influence cognition. Few large-scale research studies have examined cognitive performance in individuals with a self-reported history of mTBI, which can include both reported and undetected traumas (i.e., population-based mTBI samples)(Belanger et al., 2005). Nevertheless, population-based mTBI samples are less researched than clinical samples and usually involved younger adults.

This creates a gap in knowledge surrounding the impact of a history of mTBI in mid to early late life, where the impact could be better elucidated due to the lack of comorbidities seen in older adults and recovery patterns demonstrated in younger adults. To address this gap, in chapter 5 I present data from two large cohorts (PREVENT & EPAD), with participants in mid to early late life who are at risk of developing AD, to establish if a history of self-reported single or repeated mTBI is associated with altered cognitive profiles.

Examination of these two cohorts could have clinical impact by establishing evidence for prevention and management of head injuries before mid-life and demonstrate greater vigilance and cognitive evaluations of individuals below 65 years of age.

1.6 Neuroimaging, Neurodegeneration and mTBI

Neuroimaging can be used to identify chronic pathological changes post TBI in addition to the acute injury. TBI disrupts white matter connections and results in cerebral atrophy (Maxwell et al., 2010). This finding tends to be worst in frontotemporal and limbic areas (Dodd et al., 2022), possibly due to trends in traumatic injury mechanisms (Hofman et al., 2002). T1 MRI can evaluate neurodegeneration after TBI in a sensitive but non-specific way by assessing cerebral atrophy and volume loss. Commonly, TBI-induced neurodegeneration leads to cerebral volumes comparable to that of older individuals with other neurodegenerative diseases; both demonstrating a yearly loss of 1.5% of cerebral volume occurring mostly in sulci and white matter tracts (Graham & Sharp, 2019; Maxwell et al., 2010). TBI with white matter injury demonstrates reduced FA and increased MD and RD (Farbota et al., 2012; Veeramuthu et al., 2015). These findings point to demyelination, loss of axonal integrity, and reduced axonal packing and coherence in frontotemporal and limbic structures such as the anterior limb of the internal capsule, corona radiata, optic radiations, and cingulum (Hellyer et al., 2013). Furthermore, changes in these DTI indices are associated with poor

neuropsychological performance, including executive function, memory, and functional outcomes (Dodd et al., 2022; Palacios et al., 2012; Stern et al., 2019).

Converging evidence indicates that neurodegenerative processes and traumatic axonal injury target partially overlapping networks. AD shows early vulnerability of the hippocampus, posterior cingulate/precuneus, and medial frontal cortex, whereas repetitive mTBI most consistently affects the hippocampus, thalamus, and long-range commissural fibres of the corpus callosum (Johnson et al 2013; Shenton et al. 2019). Both conditions are associated with accelerated cortical thinning in mesial temporal and frontoparietal regions, ventricular enlargement, and reduced white-matter integrity within default-mode and fronto-limbic tracts. By focusing our volumetric, DTI and WMH analyses on these canonical hotspots, this thesis explicitly tests whether the spatial pattern of brain change after mid-life mTBI mirrors that seen in prodromal neurodegeneration, thus providing a mechanistic bridge between the two literatures. Therefore, a number of imaging modalities are related to the various types of pathology they can identify. Use of a range of different modalities will be necessary to capture the heterogeneous pathology that characterizes TBI. However, interpretation of existing neuroimaging studies is hampered by heterogeneous protocols, small samples and variable follow-up intervals.

In Chapter 6, I addressed this by using a large harmonised multi modal neuroimaging cohort to identify multiple patterns of brain changes in individuals with a history of mTBI in their mid to early late life.

1.7 Cognitive and neural trajectories in mTBI

An improved understanding of the long-term sequelae after mTBI is important for ongoing clinical care. Chapters 5 and 6 capture only a snapshot of how a history of mTBI can affect cognitive and neuroimaging measures. To evaluate if a history of mTBI accelerates change in mid to early late life,

cognitive and neuroimaging change must be examined over time. In Chapter 7, I examined the longitudinal cognitive performance and neuroimaging measures of individuals with a history of mTBI. With this approach I aimed to establish if a history of mTBI causes an acceleration of cognitive impairment and neuroimaging changes in mid to early late life.

1.8 Summary of research questions

To investigate the impact of a history of mild TBI to create vulnerability to neurodegeneration or accelerate existing change in mid to early late life:

- In a population at risk of AD at mid to early-late life, is a history of single or repeated mTBI associated with altered cognitive profiles? (Chapter 5)

- Do baseline neuroimaging measures help characterise the impact of a history of mTBI in mid to early late life? (Chapter 6)

- Does a history of mTBI in a population at risk of AD in mid to early late life alter cognitive and neural trajectories? (Chapter 7)

Having established the significance of TBI as a potential contributor to neurodegeneration, Chapter 2 delves into the existing literature on neuroimaging biomarkers of TBI and cognitive decline. This next chapter identifies the strengths and limitations of current research, providing the rationale for the methodologies employed in this thesis.

Chapter 2: Neuroimaging, TBI and Neurodegeneration

2.1 Introduction

TBI is a growing global public health concern, with approximately 69 million cases each year (Dewan et al., 2019). While TBI's immediate impacts are well-studied, its long-term effects, particularly in mid-life, remain underexplored. The mid-life phase is a crucial period for cognitive resilience and vulnerability, where cumulative effects of lifestyle, genetics, and past injuries intersect, potentially accelerating age-related cognitive decline and increasing susceptibility to neurodegenerative conditions. With costs estimated at $400 billion worldwide (Maas et al., 2017) and its status as the leading cause of death among people under 40 in the United Kingdom (Davis et al., 2015), the impetus to understand and address TBI is underscored by its profound socioeconomic and health implications.

Recent advancements in neuroimaging techniques—such as MRI, DTI, and PET—have illuminated the intricate nexus between TBI and neurodegenerative processes, offering unprecedented insights into the sequelae of brain injuries. These modalities not only shed light on the immediate alterations in brain architecture and functionality following TBI but also delineate the pathophysiological pathways that precipitate chronic neurodegeneration. Importantly, the correlation between injury severity, genetic predispositions, and the augmented risk of developing neurodegenerative conditions like Alzheimer's disease and chronic traumatic encephalopathy is being unravelled (Goldstein et al., 2012; Johnson et al., 2013; Raj et al., 2017), enabling a more nuanced understanding of the long-term consequences of TBI.

TBI can cause neuronal dysfunction and cognitive decline through diffuse axonal injury (DAI), direct forces on brain tissue, interruption of the blood brain barrier and/or rupture of vasculature causing bleeding. These injuries result in acute direct damage, which is potentially followed by prolonged accumulation of proteins (e.g. tau, amyloid beta and TDP-43) with concomitant microglial activation, that continues for years post-TBI (Goldstein et al., 2012; Johnson et al., 2013). Most epidemiological literature focuses on moderate-severe TBI, but recent studies have shown that even a single mTBI can cause similar pathophysiological changes in the brain, including DAI, neurotransmitter activity alterations and modified levels of brain excitability (Choe, 2016).

A key issue of clinical research in TBI is heterogeneity. The inter-individual variability in TBI impacts at all levels, from physical, cognitive, and psychosocial profiles to injury characteristics and clinical classification. If there are differences at the demographic, psychosocial or cognitive levels prior to TBI, this will impact the trajectory even when the injury characteristics and severity are kept constant across individuals (Dahdah et al., 2016). TBI researchers, for the most part, have not been able to control for the marked heterogeneity in TBI mechanisms that likely affects outcomes and the consistency of findings across studies. As such, the identification of objective biomarkers for these injuries has become a research priority in recent years.

While much attention has been given to TBI in younger and older populations, the impact of TBI in mid-life is a crucial but underexplored area. In this chapter, we delve into the current landscape of TBI research, tracing the continuum from the classification of injury to the affected cognitive domains and the potential of neuroimaging in capturing the genesis of cognitive decline and neurodegeneration. The discussion will integrate neuroimaging findings that highlight promising biomarkers and disease detection methodologies prior to symptomatic onset (Choe, 2016). Through this integrative review, we aim to highlight the imperative role of advanced imaging in the diagnosis, prognosis, and rehabilitation of TBI, advocating for an interdisciplinary approach that

paves the way for improved therapeutic interventions and management strategies. Understanding the different classifications of TBI is essential for examining how these injuries can affect individuals as they transition into mid-life, where the cumulative effects may become more evident.

2.2 Classification of TBI

TBI comprises a range of conditions that impact millions of individuals annually. Here we delineate the classification of TBI severity, as established by the American Congress of Rehabilitation Medicine (ACRM), along with the associated cognitive impairments for each severity tier. We evaluate the predictive significance of various metrics such as the Glasgow Coma Scale (GCS), post-traumatic amnesia (PTA), and loss of consciousness (LOC) in determining outcomes and directing rehabilitation strategies.

2.2.1 Classification of TBI Severity

The ACRM classifies TBI severity into mild, moderate, and severe categories, mostly determined by the immediate consequences of the damage (Kay et al., 1993). The preliminary evaluation utilises the GCS, a neurological metric recognised for its interobserver reliability and predictive efficacy (Narayan et al., 2002; Teasdale & Jennett, 1974). However, it is observed that the GCS lacks sensitivity for newborns, young children, and individuals with pre-existing neurological impairments, especially in differentiating mTBI (Saatman et al., 2008).

2.2.2 Mild TBI

Mild TBI, defined by a GCS score of 13–15, accounts for the majority of TBI cases, with estimations between 80% and 95% of all injuries (Feigin et al., 2013). It includes, loss of consciousness for under 30 minutes and post-traumatic amnesia for less than 24 hours. Structural neuroimaging techniques, such as CT scans, often yield normal results; yet, modest neurochemical alterations that can lead to brain dysfunction may go undetected (Borg et al., 2004). Despite mTBI being seen as less severe,

its long-term effects, especially in mid-life, remain to be elucidated. This necessitates an examination of how moderate injuries incurred earlier in life may affect cognitive decline subsequently.

2.2.3 Moderate TBI

Moderate TBI is characterised by a GCS score ranging from 9 to 12, with loss of consciousness lasting over 30 minutes but under 24 hours, and post-traumatic amnesia exceeding 24 hours but less than 7 days. Cognitive deficits linked to moderate TBI are often more specific and may present with either normal or abnormal structural MRI results (Dikmen et al., 2009).

2.2.4 Severe TBI

Severe TBI is defined by a GCS score of 3-8, a LOC greater than 24 hours, and PTA lasting more than 7 days. The cognitive abnormalities are more generalised and persistent, with severity resulting in bigger and longer-lasting impairments than mild and moderate TBI (Levin et al., 1987; Rapoport et al., 2002).

Table 2.1. Classification of TBI severities

	Mild	Moderate	Severe
Glasgow Coma Scale	13-15	9-12	3-8
Loss of consciousness	<30 minutes	>30 minutes <24 hours	>24 hours
Post-traumatic amnesia	<24 hours	>24 hours <7days	≥7 days
Altered consciousness	≤24 hours	>24 hours	>24 hours
Structural imaging	Normal	Normal or abnormal	Normal or abnormal

2.3 Challenges in Classification

Classifying TBI into mild, moderate, and severe categories provides a foundation for understanding its clinical and cognitive outcomes. However, this traditional framework often oversimplifies the heterogeneity of TBI impacts, particularly in mid-life, where injury characteristics intersect with pre-existing conditions and cognitive reserve. Mild TBI, which accounts for the majority of cases (Feigin et al., 2013), is especially challenging to classify due to the absence of detectable structural changes in standard imaging, despite potential long-term neurochemical and cognitive effects (Borg et al., 2004).

Mid-life TBI introduces complexities that differ from early-life or later-life injuries. For example, while younger adults may recover more fully, mid-life individuals often face cumulative effects that diminish cognitive reserve and may accelerate age-related cognitive decline. Standard measures such as the Glasgow Coma Scale (GCS) and post-traumatic amnesia (PTA), while useful, may lack the sensitivity to capture these subtler, long-term changes.

2.3.1 Variability in Measurement Tools

The GCS has been a cornerstone in diagnosing TBI severity, but its limitations are significant, notably its low sensitivity for mTBI and certain groups such as newborns, young toddlers, and those with underlying neurological deficits (Saatman et al., 2008). While the scale is praised for its strong interobserver reliability and predictive capacities (Narayan et al., 2002), its effectiveness is limited in some circumstances, emphasising the necessity for additional or alternative evaluation instruments.

2.3.2 Post-Traumatic Amnesia (PTA) and Loss of Consciousness (LOC)

PTA and LOC are normal criteria for assessing the severity of TBI. PTA describes a state of confusion in which patients struggle to generate new short-term memories (Zuccarelli, 2000), whereas LOC length has historically been used as a prognostic indication (Cifu et al., 1997; Sherer et al., 2020). Despite their historical value, subsequent research has called into doubt the association between LOC and neuropsychological results, arguing that assessments performed later in the recovery process, such as PTA evaluations, may be more predictive of long-term outcomes (Cantu, 2001).

2.3.3 Definitional Discrepancies

The definition of mTBI, in particular, varies greatly, with some definitions needing no structural neuroimaging for diagnosis. This mismatch can lead to an underestimating of injury severity since, even in the absence of evident structural damage, neurochemical alterations sufficient to produce brain dysfunction are not visible by traditional neuroimaging methods (Borg et al., 2004).

2.3.4 Underreported Incidence of Mild TBI

The prevalence of mTBI has been historically undervalued. Conventional wisdom indicated that the distribution of TBI severity was 80%, 10%, and 10% for mild, moderate, and severe TBI, respectively. However, recent studies propose that mTBI may be more prevalent, constituting up to 95% of all TBI cases (Feigin et al., 2013). The underreporting may result from the lack of structural injury observed in standard neuroimaging following mTBI, despite the presence of neurochemical cascades that can induce dysfunction.

2.3.5 Cognitive Impairment Correlations

Cognitive impairments following TBI exhibit variability across the severity spectrum. Mild and moderate TBIs are linked to particular cognitive impairments, whereas severe TBIs typically lead to broader cognitive deficits across multiple domains. The severity of deficits correlates with injury

severity, where severe TBI results in more pronounced and enduring cognitive impairments compared to milder cases (Dikmen et al., 2009).

2.3.6 Consideration of Individual Factors

Assessing TBI requires careful consideration of individual patient factors beyond the injury, including age, extracranial injuries, and other physiological conditions. These factors can greatly influence recovery trajectories and outcomes, highlighting the necessity of a personalised approach to TBI classification and management (Weyer Jamora et al., 2013).

The complexities of TBI classification underscore the necessity for a dynamic and comprehensive assessment strategy that considers the diverse factors affecting recovery. The existing classification system serves as a foundational framework; however, ongoing research and refinement are essential for optimising treatment plans and enhancing outcome predictions for individuals with TBI.

Mid-life represents a critical period of vulnerability, where cumulative exposure to vascular risk factors, psychosocial stress, and lifestyle behaviours begin to impact structural and functional brain reserves. Empirical evidence suggests that cognitive reserve, shaped by education, occupation, and social engagement, begins to decline from the fifth decade of life, and that this decline is accelerated by comorbidities such as hypertension, diabetes, and prior brain injury (Stern 2009; Cabeza et al., 2018). Population studies indicate that individuals in mid-life with lower reserve and higher brain age estimates are more susceptible to early cognitive decline, even when performance remains within the normative range (Fischer et al., 2014; Tucker-Drob et al., 2019).

2.4 Screening Tools for TBI research

2.4.1 Ohio State University TBI Identification Method (OSU TBI-ID)

The OSU TBI-ID is a structured interview intended for administration in diverse settings and necessitates minimal training (Ohio State University). Although there are challenges in establishing concurrent validity with medical records, the tool effectively screens for a lifetime history of TBI, highlighting the necessity for medical attention or the need for it after head injuries (Corrigan & Bogner, 2007). This method has been recognised as effective for screening women who are survivors of intimate partner violence (IPV) (Goldin et al., 2016).

2.4.2 HELPS Screening Tool

The HELPS tool is a systematic, interview-driven screening approach designed for non-medical practitioners. The content includes enquiries related to the HELPS acronym, addressing head injuries, emergency room visits, loss of consciousness, daily life challenges, and serious illnesses. The utility of this screening has been evidenced in domestic violence settings, where 60% of individuals assessed in Iowa domestic violence shelters were found to have TBI (Costello & Greenwald, 2022).

2.4.3 TBI Questionnaire (TBIQ)

The TBIQ is a structured interview designed for diverse populations, including those who are incarcerated. The document encompasses enquiries pertaining to prevalent brain injury scenarios and a checklist of symptoms. The tool has shown reliability and validity in identifying TBI within a prison population and may offer advantages compared to checklists utilised during prison intake procedures (Diamond et al., 2007).

While screening tools such as the OSU TBI-ID and HELPS possess notable strengths, it is essential to recognise their limitations, especially regarding the detection of subtle or mTBIs. The dependence

on self-reported symptoms can result in under-reporting, particularly in populations where cultural norms influence symptom communication. The overlap of TBI symptoms with psychiatric conditions, including PTSD and depression, poses a considerable challenge, as existing tools may inadequately distinguish between these disorders. Future screening tools must prioritise improving sensitivity for the detection of mTBIs, while also accounting for the influence of co-morbidities and cultural contexts. The incorporation of biomarkers or neuroimaging techniques with these tools may provide a more thorough and precise evaluation of TBI.

2.4.4 Brain Injury Screening Questionnaire (BISQ)

The BISQ is a structured self-report screening tool developed with the intent to systematically identify individuals with a lifetime history of TBI. The BISQ is designed to differentiate between transient and chronic symptoms post-injury, and to rule out other health conditions that may account for the reported symptoms. Its comprehensive nature allows it to be used across various settings, revealing a prevalence of TBI events and chronic TBI higher than previous estimates suggested (Dams-O'Connor et al., 2014). The full questionnaire is reproduced in appendix 1.

2.4.4.1 Development and Structure

The BISQ is based on earlier screening tools like the HELPS card and has been augmented to provide detailed cueing for respondents. It queries lifetime TBI by asking about experiences of a blow to the head in 19 specific situations (Dams-O'Connor et al., 2014). The tool is divided into three main parts:

TBI History: This section of the BISQ asks respondents whether they have ever experienced a blow to the head that led to loss of consciousness or a feeling of being dazed and confused (Dams-O'Connor et al., 2014).

Symptoms: Part II is an inventory of 100 cognitive, physical, emotional, and behavioural symptoms to characterize post-injury symptoms. The BISQ includes a set of 25 symptoms associated with TBI, which, when endorsed, indicate a positive screen for TBI (Dams-O'Connor et al., 2014).

Other Health Conditions: This part documents other medical events or conditions that could contribute to or explain reported symptoms, thereby aiding in distinguishing TBI-related consequences from other health issues (Dams-O'Connor et al., 2014).

2.4.4.2 Validation and Use

The BISQ has been used in various studies to screen populations in different settings, ranging from public schools and community-based samples to high-risk populations like those in substance abuse treatment or juvenile justice systems (Dams-O'Connor et al., 2014). Its use has demonstrated that a significant proportion of these populations have experienced TBI events, many of which went previously unidentified.

In a study involving New York City public schoolchildren, 44% of the children reported a TBI event, with 10% of the total sample screening positive for chronic TBI. Those who screened positive exhibited cognitive impairments on neuropsychological testing, highlighting the BISQ's ability to uncover unreported cases of TBI with ongoing symptoms (Ashman et al., 2008; Cantor et al., 2004).

2.4.4.3 Practical Implications

Screening for TBI using the BISQ can be implemented efficiently and is relatively brief, taking about 10 to 15 minutes to complete. It has been proven to be a useful starting point for a comprehensive evaluation to establish a TBI diagnosis and facilitate access to appropriate interventions (Dams-O'Connor et al., 2014).

The prevalence of TBI uncovered by the BISQ in various settings underlines the importance of systematic screening to ensure individuals with TBI receive the support and accommodations they require. These efforts are critical for primary prevention efforts to reduce the risk of reinjury, especially in high-risk groups, and to provide interventions that can mitigate the personal and societal costs of TBI (Dams-O'Connor et al., 2014).

2.4.4.4 Limitations and Considerations

The BISQ, although a prevalent and clinically significant instrument, possesses limitations typical of structured TBI screening measures that depend on self-reported data, including possible recollection bias and the difficulty in distinguishing TBI-related symptoms from those induced by other diseases. Moreover, it is not intended to diagnose TBI or determine the causal relationship between symptoms and damage, highlighting the necessity for further clinical assessment to validate the screening outcomes (Dams-O'Connor et al., 2014).

The efficacy of the BISQ can be affected by its specificity and sensitivity across various demographics. In communities with elevated prevalence rates of other cognitive impairments or neurological illnesses, the questionnaire may exhibit less efficacy in differentiating symptoms caused by TBI from those arising from alternative diagnoses. This shortcoming may result in false positives, wherein persons are erroneously diagnosed as having a probable TBI, and false negatives, wherein TBIs remain undetected. Furthermore, cultural and linguistic disparities may influence the interpretation of enquiries and the reliability of answers, thereby constraining the questionnaire's effectiveness in multicultural contexts. Notwithstanding these issues, the BISQ is an essential preliminary measure in the diagnosis and management of TBIs, highlighting the necessity of creating supplementary diagnostic tools and techniques to alleviate these constraints.

2.4.4.5 Conclusion

The BISQ has shown good construct and criterion validity and is more sensitive to comprehensive TBI history than many existing measures. This sensitivity to TBI history is critical to appropriately identifying those at risk and ensuring proper management and care for individuals with TBI across diverse populations and settings.

2.5 Cognitive sequelae of TBI

A number of studies report that mTBI participants have reduced cognitive performance on tasks that assess attention (Maruta et al., 2010; Sterr et al., 2006), memory (Chen et al., 2007; Vanderploeg et al., 2005), executive function (Erez et al., 2009; O'Jile et al., 2006; Sterr et al., 2006), and information processing (O'Jile et al., 2006; Lachapelle et al., 2008; Johansson et al., 2009; Kinnunen et al., 2011). In contrast, research into between-group differences in cognitive performance in the chronic stage of mTBI has yielded contradictory results. Several studies have reported no significant impairment in cognitive performance among patients with mTBI in the long-term (Chen et al., 2004; Perlstein et al., 2004; Solbakk et al., 2005; Broglio et al., 2009; Tellier et al., 2009) or within three months following the injury (McAllister et al., 2001; Chen et al., 2004; Jantzen et al., 2004; Lange et al., 2009; Tellier et al., 2009; Slobounov et al., 2010). While some evidence suggests lower cognitive function in the aforementioned domains remains in the months to years following injury (Kinnunen et al., 2011; Konrad et al., 2011), other studies have found no long-term deficits in mTBI populations.

There appears to be a lack of consistency in the specific cognitive domain that is affected, even in studies that do identify a deficit (Tellier et al., 2009). The lack of uniformity and fluctuation observed in prior research on enduring cognitive function following mTBI can be attributed to the utilisation of diverse cognitive assessments and limited participant cohorts.

According to a recent scoping analysis, nearly half of individuals with a single mTBI exhibit chronic cognitive impairment. However, these findings were demonstrated in older adults, in whom the impact of mTBI may have been obscured by other comorbidities that influence cognition. Few large-scale research studies have examined cognitive performance in individuals with a self-reported history of mTBI, which can include both reported and undetected traumas (i.e., population-based mTBI samples)(Belanger et al., 2005). Nevertheless, population-based mTBI samples are less researched than clinical samples and usually involved younger adults.

This creates a gap in knowledge surrounding the impact of a history of mTBI in mid to early late life, where the impact could be better elucidated due to the lack of comorbidities seen in older adults and recovery patterns demonstrated in younger adults.

The following section explores the literature on the effect of mTBI on the cognitive domains examined in this study:

2.5.1. Memory

The outcomes of behavioural investigations that examine impairments in memory function persisting beyond the initial phase of injury have yielded inconsistent findings. A meta-analysis conducted in the early stages exclusively examined mTBI (excluding moderate or severe injuries) and limited the samples to those collected beyond the acute stage of recovery, which was greater than three months. The study conducted by the authors aimed to examine the potential emergent effects across various cognitive domains, such as memory acquisition and delayed memory performance. The results of the study indicated a lack of reliable evidence supporting the notion of memory costs (Binder et al., 1997). The majority of the included studies showed no memory deficits (Alterman et al., 1985, Bornstein et al., 1993), and those that did either tested participants under oxidative stress (Ewing, McCarthy, Gronwall, & Wrightson, 1980) or the study could have incorporated a wide range of injury severities instead of limiting the sample to individuals with

mTBI (Dikmen, Machamer, Winn, & Temkin, 1995). Therefore, although memory deficits were identified in association with head injury, it is probable that the outcomes were influenced by individuals with more severe injuries, rather than mild TBI. In accordance with this notion, individuals classified within the mildest severity group exhibited performance levels that were similar to those of the control group (Dikmen et al., 1995). The present study did not yield any indications of persistent memory impairments following mTBI. A subsequent re-examination of two meta-analytic datasets (Binder et al., 1997, Frencham et al., 2005) has shown that several of the aforementioned studies have indicated that memory impairments may be present in particular tasks, such as verbal paired memory. One of the most pertinent studies examined in that research revealed a deficiency in challenging paired-associate tasks in the prolonged phase of the injury. (average of one-year post-injury; Potter, Bassett, Jory, & Barrett, 2001). Interestingly, Rohling et al., (2011) re-analysed the studies included in Pertab et al. (2009) and found no substantial evidence of persistent impairments in any cognitive domain; none of the effect magnitudes displayed a significant deviation from the null hypothesis (Rohling et al., 2011).

A meta-analysis was conducted, comprising of 39 studies that explored the neuropsychological effects of mTBI. The studies were categorised based on whether their samples were collected during the acute stage (less than 3 months since mTBI) or the chronic stage (more than 3 months since mTBI) (Belanger, Curtiss, Demery, Lebowitz, & Vanderploeg, 2005). The researchers have reported significant impacts of mTBI during the chronic stage on immediate and delayed memory (ds = 0.35, 0.69), which suggests the existence of memory impairments that persist beyond the acute stage of injury. This finding is particularly relevant to the current study. The present meta-analysis, however, incorporated numerous samples wherein participants were chosen based on grievances resembling post-concussion syndrome, thereby constraining the extent to which the outcome can be applied to other populations.

Working memory deficits are frequently reported as a prevalent issue subsequent to mTBI. According to Dunning et al.'s (2016) meta-analysis, which included 21 studies and a total of 1164 participants, 577 of whom had experienced mTBI, deficits in both verbal and visuospatial working memory were observed (Cohen's d = 0.37 and 0.69, $p < 0.01$ and 0.01, respectively). The study revealed that the impairment in verbal working memory exhibited a deterioration over time post injury, particularly when compared to the control group. This suggests that instead of recuperating from the injury, there is an acceleration of chronic decline. Moreover, individuals who sustained the injury at an advanced age exhibited greater deficits, which may indicate a decline in cognitive reserve among older adults. Dobryakova et al. (2015) employed a unique battery of assessments to untangle the storage capacity and information manipulation mechanisms inherent in the intricate subdomains of working memory. The study revealed that individuals with TBI exhibited significantly poorer performance than the control group when faced with high demands for information manipulation. However, no significant differences were observed between the two groups when working memory storage capacity demands were high. The findings suggest that mTBI predominantly hinders the capacity to manipulate information in working memory, rather than affecting the storage capacity of working memory.

2.5.2 Attention

According to Jourdan et al. (2016), attentional problems are the second most commonly reported issue among survivors of TBI, following memory deficits. Specifically, 56.7% of patients reported difficulties with concentration, while 51.7% reported experiencing dual task difficulties four years after experiencing a moderate-to-severe TBI. The aforementioned grievances are substantiated by impartial neuropsychological evaluations conducted on individuals who have undergone TBI (Van Zomeren and Deelman, 1978; Ponsford and Kinsella, 1992). These assessments have revealed a significant correlation between the severity of TBI and impairments in attention and processing speed. Azouvi et al. (2004) reported that individuals who have undergone TBI exhibit slower

performance in attentional tasks compared to controls. Additionally, these individuals report greater mental effort during these tasks. However, no significant differences were observed in self-paced tasks where accuracy could be prioritised over speed. Mathias and Wheaton's (2007) meta-analysis, which comprised 44 studies, revealed that individuals who had suffered severe TBI exhibited significant impairments in processing speed and attention span. Specifically, Cohen's d effect sizes of 1.10 (95%CI [0.98, 1.22]) and 1.01 (95%CI [0.62, 1.40]) were observed for processing speed and attention span, respectively.

2.5.3 Visuospatial abilities

The consequences of mild traumatic brain injury on the hippocampus include compromised spatial learning. Additionally, research indicates that the extent and location of hippocampal lesions lead to varying degrees of impairment in spatial learning and memory (Broadbent NJ, Squire LR, Clark RE, 2004; Martin SJ, Clark RE.;2007).x

The acquisition of spatial knowledge is a crucial aspect of navigating unfamiliar surroundings in everyday life (O'Keefe J, Nadel L; 1978). Spatial learning refers to the cognitive process of creating mental maps based on environmental cues, coordinates, and associations that are acquired during the exploration of a new or altered familiar environment. Hence, individuals who experience a TBI leading to enduring spatial learning impairments will encounter persistent challenges in acquiring the ability to navigate within a new and intricate setting or an altered familiar setting. The authors Skelton et al. (2018) demonstrated that individuals who have experienced moderate to severe TBI exhibit challenges in spatial learning. Chuah et al. (2014) conducted a study to investigate the visual spatial learning and memory capacity of a functional group of university students with mild TBI. The findings revealed that the mild TBI group exhibited significantly poorer performance on the spatial learning task compared to the control group.

2.5.4 Language

Only a limited number of empirical studies have examined whether language deficits persist beyond one year after mTBI, particularly in verbal fluency, and most failed to assess response bias or somatoform symptomatology (Hannay, Howieson, Loring, Fischer, & Lezak, 2004; Mathias & Coats 1999; Raskin & Rearick, 1996; Whelan, Murdoch, & Bellamy, 2007). Heinly's study (2008) revealed that language impairment associated with mTBI was not evident, even after accounting for effort. Research has indicated that inadequate effort or response bias has a significantly greater impact on language-related abilities, such as verbal comprehension, confrontation naming, verbal fluency, and reading recognition, when compared to the effects of moderate or severe traumatic brain injury on these skills (Heinly, 2008).

Sevush and Brooks (1983) contend that certain types of speech impairments, such as paraphasias, perseverations, and anomia, which are typical of aphasic syndromes, are unexpected in functional illnesses. However, there is a dearth of empirical evidence that documents non-credible patterns of speech and language deficits. A search of PubMed yielded only a few published articles on this subject, which were limited to case reports involving feigned dementia presentations, foreign accent syndrome, atypical dysarthria, and severe expressive aphasia.

2.6 Mild TBI and Cognitive Impairments: Mid-Life vs. Later Life

2.6.1 Mid-Life Cognitive Resilience and Vulnerabilities

Cognitive resilience is essential for recovery from mTBI in mid-life. Cognitive resilience denotes the brain's capacity to preserve functionality in the face of damage or stress. Mid-life individuals who get mTBIs may initially recuperate, with many reverting to baseline functionality within a year. Nonetheless, recent studies suggest that even following apparent recovery, mTBI may diminish cognitive reserve—the brain's ability to mitigate cognitive deterioration. This diminished reserve

may predispose individuals to an earlier start of cognitive impairments, especially in memory and executive functioning, as they age (LoBue et al. 2017).

While most in their mid-life can recuperate from mTBI, enduring cognitive repercussions may emerge later in life, especially when coupled with other age-related variables. The influence of mid-life TBI on ageing trajectories is under investigation, with certain research indicating that persons with a TBI history may have accelerated cognitive decline as they age (Kaup et al. 2019).

For the purposes of this thesis, mid-life refers to ages 40-59 and early late life to ages 60-70, consistent with the stratifications used in PREVENT and EPAD studies. This distinction captures the period before and during which subtle cognitive and neural decline begins to manifest, while avoiding confounds from comorbidities more common in later old age. This age range also reflects the inflection point for divergence between chronological and biological brain age, as discussed in Chapter 1.

2.6.2 Later-Life Cognitive Decline and TBI

Conversely, mTBI in older persons exhibits more acute and prolonged cognitive repercussions. Older individuals are more susceptible to enduring cognitive deficits resulting from the synergistic effects of ageing and trauma. Memory, concentration, and processing speed are frequently impaired, and recovery is generally protracted and partial. Moreover, TBI acquired in later life correlates with a heightened risk of expedited cognitive deterioration and the emergence of neurodegenerative disorders, including Alzheimer's and Parkinson's disease (Smith et al. 2020).

The age-associated deterioration in cognitive abilities, along with the physiological impairment from TBI, can elevate older adults' risk of neurodegeneration. In such instances, even a mTBI might

act as a precursor to the earlier development of dementia and other cognitive impairments, complicating rehabilitation in later life.

2.6.3 Moderate to Severe TBI and Long-Term Cognitive Outcomes

Moderate to severe TBIs typically lead to more lasting and widespread cognitive impairments, in contrast to the frequently temporary cognitive effects linked with mTBI. Lannoo et al. (1998) identified significant deficits in attention, memory, and verbal fluency among moderate to severe TBI patients six months following the injury. The deficits observed are more persistent and generalised compared to those in mTBI, with numerous patients exhibiting considerable impairments across multiple cognitive domains.

Tate et al. (1991) investigated the long-term cognitive outcomes in severe TBI patients up to six years post-injury, revealing that most of these individuals experienced considerable difficulties in learning, memory, and executive functioning. The severity of the injury typically correlates with an increase in the intensity and duration of these impairments, frequently resulting in long-term disability and diminished quality of life.

2.7 Variability in Recovery Trajectories

The trajectory of cognitive recovery TBI exhibits considerable variability, shaped by factors such as injury severity, age, and pre-existing conditions. Cognitive recovery in older adults is generally slower, with impairments more likely to persist, especially when accompanied by additional health conditions like cardiovascular disease or psychiatric disorders. During mid-life, individuals may demonstrate increased cognitive resilience; however, mTBI can result in subtle long-term impairments that emerge later, especially when cognitive reserve is reduced.

Studies indicate that genetic factors, including the presence of the APOE4 allele, may increase susceptibility to cognitive decline following TBI, independent of the severity of the injury. This underscores the necessity for tailored strategies in the treatment and recovery of TBI, informed by individual risk factors.

2.8 Summary

The cognitive effects of TBI are complex and shaped by various factors, such as the timing of the injury, the age of the individual, and the severity of the injury. Mid-life TBI, despite potential for recovery, may have enduring consequences as individuals age, notably in diminishing cognitive reserve and heightening the risk of neurodegenerative disorders. TBI in later life often intensifies pre-existing cognitive weaknesses, hastening deterioration and elevating the likelihood of dementia and other cognitive disorders. Examining the relationship between traumatic brain injury and ageing is essential for creating focused interventions and enhancing long-term outcomes for individuals throughout their lives.

2.9 Which neurodegenerative disorders are associated with TBI?

2.9.1 Alzheimer's disease

Alzheimer's disease (AD) is the most common form of dementia characterised by the deposition of amyloid-β plaques and hyperphosphorylated tau neurofibrillary tangles in the temporal lobes initially before extension to the frontal and parietal regions (Braak 1991). The clinical presentation of AD involves initial deficiencies in short-term memory followed by global cognitive deterioration. DAI, the main neuropathology of TBI, is associated with build-up of amyloid precursor protein due to cytoskeletal disruption, which is cleaved to form amyloid-beta (Aβ), promoting formation of amyloid plaques characteristic of AD (Johnson VE et al., 2010). This process may be enhanced in individuals with at least one copy of the APOE e4 allele, which is itself associated with increased

release of amyloid precursor proteins and increased risk of AD by association with Ab plaques. While the risk of developing AD is increased twofold to threefold by the possession of one APOE4 allele and fivefold by the presence of two APOE4 alleles this risk increases to 10-fold in individuals with a history of TBI (Mayeux et al., 1995).

Many researchers have reported a history of TBI to be associated with an increased risk for developing AD, although not all have found an association. Plassman and colleagues evaluated 548 World War II veterans who had suffered a TBI 40 years earlier and those who did not suffer TBI (n=680). Those who had suffered a moderate or severe TBI had an increased risk of developing AD later in life when compared to those who suffered a mild or no TBI. However, Dams-O'Connor and colleagues followed up 4225 individuals aged 65 years and older every two years for an average of seven years. Subjects who self- reported a history of TBI with LOC (n=606) did not have a higher risk of AD when compared to individuals with no history of TBI. They also found no relationship between a history of TBI and AD neuropathology, except for TDP-43 pathology which was more commonly seen in the TBI group (Dams-O'Conner et al., 2012).

There is evidence to suggest TBI could increase the risk of developing AD in some individuals. However, TBI could also affect the age of onset. A recent retrospective study found that 7625 patients with a diagnosis of AD and a history of TBI with LOC had an onset of symptoms 2.5 years earlier than those with TBI, this increased risk was found irrespective of APOE4 status (LoBue et al., 2017). This suggests that a history of TBI could lead to a reduction in cognitive reserve which in turn could lower threshold of the onset of clinical symptoms. It could also accelerate the onset of AD by directly influencing the underlying neurodegenerative process.

2.9.2 Chronic traumatic encephalopathy

Chronic traumatic encephalopathy (CTE) is a neuropathological tauopathy characterized by hyperphosphorylated tau in the form of neurofibrillary tangles, astrocytic tangles and neurites

deep within the sulci of the brain, with Aβ deposition seen only in a subset of cases (Mckee AC et al., 2015). The gross neuropathology of CTE is characterized by global volume reduction and ventricular enlargement; callosal thinning; atrophy in the medial temporal lobes (MTLs), mammillary bodies, and brainstem; fenestrated cavum septum pellucidum; and scarring and neuronal loss of the cerebellar tonsils (Mckee AC et al., 2009). CTE is associated with dot-like or spindle-shaped tau-positive fibrillar astrocytic tangles in white matter, which differ from the threadlike tangles typically seen in AD, suggesting that damage associated with CTE may be at the axonal level.

CTE, formerly known as dementia pugilistica, was originally described in boxers but now more recently associated with other contact sports such as football and American football. CTE is associated with progressive changes in memory, executive functioning, emotion (particularly depression), and impulse control, as well as Parkinsonism (Victoroff J., 2013) with evidence for a distinction between syndromes dominated by mood and behaviour (earlier onset) versus cognitive impairment (later onset, determined retrospectively) (Stern RA et al., 2013). CTE can be detected as early as the late teen years, and in professional athletes symptoms of CTE are seen almost 10 years after retirement.

Even with distinct neuropathological features, there is no agreement of clinical diagnostic criteria for CTE. A meeting was held to determine whether CTE could be distinguished from other neuropathological process such as AD (McKee et al., 2017). Neuropathologists blindly examined brain tissue from 25 cases which included 10 with alleged CTE, however they also showed more than 70% of AD related pathology, 13 cases with tau related dementia and 2 age related cases. The neuropathologists were in high agreement for the classification and recognition of the CTE cases, leading to the development of the initial neuropathological criteria for CTE. However, a study conducted not long after the meeting found that in 61 athletes with a history of repetitive mTBI,

nearly 25% had clinical symptoms with no CTE pathology. Moreover, almost 75% had neuropathology related to other neurodegenerative disorders.

This lack of consensus leaves CTE highly debated, with some researchers hypothesizing that repetitive mTBI can lead to neurodegeneration that is CTE and other believing that TBI simply accelerates the expression of other neurodegeneration with some overlap of pathology. McKee and colleagues examined 85 individuals with a history of repetitive mTBIs post-mortem. CTE was diagnosed in 43 cases, 8 diagnosed with motor neuron disease, 7 with AD, 11 with DLB and 4 with FTD. The authors concluded that due to the links between CTE and other neurodegeneration, repeated repetitive head injury and hyperphosphorylated tau protein deposition promote the build-up of other abnormally aggregated proteins including TDP-43, Ab and alpha-synuclein.

Despite the lack of robust evidence, there does seem to be a link between TBI and CTE if associational rather than mechanistic. However, with advances in neuroimaging such as tau PET, an understanding of potential mechanisms underlying CTE could soon well be understood.

2.9.3 Parkinson's disease

Parkinson's Disease (PD) is characterized by damage to dopaminergic neurons in the substantia nigra and midbrain and the presence of Lewy bodies. A history of TBI has been shown to increase the risk of developing PD. Goldman and colleagues conducted a case control study in 93 twin pairs discordant in PD and discovered that a history of LOC following head injury was associated with an increased risk of PD. Additionally, the authors demonstrated in a subset of 18 pairs concordant for PD, the twin with the younger onset PD was more likely have sustained a head injury (Goldman SM et al., 2006). However, due to the small number, Maher and colleagues investigated age of onset in 203 sibling pairs with PD to see if a more robust association could be determined. The authors discovered siblings with a history of TBI have been shown to have an earlier onset of PD, compared with siblings with no history of TBI (Maher NE et al., 2002). Bower and colleagues investigated

association of PD following TBI in 196 individuals who developed PD. The authors discovered evidence that the risk of PD following TBI is associated with TBI severity and that mTBI without loss of consciousness does not increase risk (Bower JH et al., 2003). This indicated a dose dependent relationship. Like AD, researchers have demonstrated an association between APOE genotype and the onset of PD. Li and colleagues discovered APOE4 carriers showed a greater risk and earlier onset of PD in 658 PD affected families. They also showed, as in AD, APOE e3 decreases risk (Li YJ et al., 2004).

2.9.4 Dementia with Lewy Bodies

Dementia with Lewy bodies (DLB) is associated with diffuse accumulation of Lewy bodies and alpha-synuclein proteins within the brain. Studies reporting an association between history of TBI and DLB have been mixed. Boot and colleagues found no association with a history of TBI and increased risk of DLB diagnosis (n=147). However, Crane and colleagues studied 7130 individuals aged 50 years and older from three cohorts and found that a history of TBI with LOC for more than an hour was associated with the presence of Lewy bodies in frontal and temporal areas of the brain at autopsy (Crane et al., 2016).

2.9.5 Frontotemporal dementia

Frontotemporal dementia (FTD) comprises three main related dementia types; behavioural variant FTD, primary progressive aphasia and progressive non-fluent aphasia, depending on which areas of the brain are affected. FTD pathology includes accumulation of either tau or TAR DNA-binding protein of approximately 43 kd (TDP-43)-positive cellular inclusion bodies, with some subtypes showing ubiquitin positive inclusions and mutations to other proteins. Deutsch and colleagues assessed incidence of FTD after single TBIs and report increased risks ranging from 1.5 to 4.5 times depending on injury severity. The researchers also noted those with and without a history of TBI showed no neuropsychological differences in primary progressive aphasia or progressive non-

fluent aphasia. Kalkonde and colleagues examined veterans with behavioural variant FTD and veterans with other forms of dementia and found those with a history of TBI with LOC showed significantly higher likelihood for being diagnosed FTD than other dementias (Kalkonde YV et al., 2012). As with AD, it has been suggested that TBI may accelerate the onset of FTD symptoms. LoBue and colleagues examined 678 individuals with behavioural FTD and found those with a TBI history with LOC had an onset of symptoms three years earlier than those without a history of TBI (LoBue et al., 2016).

2.9.6 Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a rapid progressive neurodegenerative disease characterized by progressive damage to motor neurons in the spinal cord, brain stem, and cortex. Like CTE and FTD, TDP-43 proteinopathy is also prevalent in ALS. Abel (2007) examined almost 4000 former professional football players in the US and discovered a sixfold increase in rates of ALS relative to the population (Abel E., 2007). Chio and colleagues also investigated football players in Italy and demonstrated a dose-response relationship between duration of football activity and the risk of ALS, indicating that playing football is a risk factor for ALS (Chio A et al., 2005). Weisskopf and colleagues investigated over 5000 veterans of the Gulf war and demonstrated an increased risk of ALS. However, the increase in risk appeared to be dependent on branch of service with army or national guard, air force and coast guard demonstrating increased risk of ALS while service in the marine corps showed no difference (Weisskopf MG et al., 2005). Chen and colleagues conducted a meta-analysis of case controls studies of ALS. The researchers confirmed increased risk of ALS from previous findings in professional athletes, particularly when exposure occurred 10-15 years prior to diagnosis. A more recent meta-analysis confirmed that head injury, especially severe head injury, could increase ALS risk (Lui G., 2021).

2.9.7 Multiple Sclerosis

Multiple Sclerosis (MS) is a progressive inflammatory disease of the spinal cord and brain characterized by inflammation, demyelination, astrocytosis, neuronal and axonal degeneration, and the development of sclerotic plaques in the later stages of the disease. As in CTE, an accumulation of hyperphosphorylated tau has been found in the secondary progressive stage of the disease. It is hypothesized that head trauma, even mTBI or concussion, causes alterations in the blood brain barrier, allowing foreign elements to enter the nervous system, which can lead to the development or enlargement of lesions and make the system more vulnerable to the development of sclerotic plaques.

Kang & Lin (2012) investigated 72,765 patients with a history of TBI. The authors concluded that patients with TBI are at a higher risk for following MS over a 6 year follow up period (Kang & Lin, 2012). As with other neurodegenerative discussed above, APOE4 has been associated with MS. APOE4 has been associated with severe forms of MS and faster disease progression. However, no studies have examined the link between APOE, MS and TBI.

2.9.9 Summary

TBI is associated with an increased risk of neurodegenerative diseases, although research on the mechanisms conferring this risk is still in its early stages. While there is evidence that neurodegeneration may result directly from TBI-related neuropathology, as seen in the case of chronic traumatic encephalopathy (CTE), other pathways may indirectly mediate this risk. For example, in Alzheimer's disease (AD), this risk may be exacerbated in carriers of one or two APOE e4 alleles. The overlap in neuropathology (e.g., TDP-43 inclusions in frontotemporal dementia [FTD], amyotrophic lateral sclerosis [ALS], and CTE) suggests potential shared mechanisms, though distinct pathologies exist in other conditions such as AD and multiple sclerosis (MS).

TBI characteristics—including the dose, timing, and repetition of injuries—play a significant role in determining the risk for specific neurodegenerative conditions. For instance, more severe TBIs are generally required to detect an increased risk of AD and Parkinson's disease (PD), whereas repetitive mTBIs, not necessarily involving loss of consciousness, are more closely linked to conditions like CTE and ALS in athletes. Importantly, the timing of TBI—whether occurring in mid-life or later life—can differentially impact the trajectory of neurodegenerative diseases. Individuals who sustain TBIs in mid-life may experience a reduction in cognitive reserve, increasing their vulnerability to cognitive decline in later years. Conversely, TBIs sustained in later life often accelerate cognitive decline and the onset of neurodegenerative conditions due to pre-existing vulnerabilities associated with aging.

While TBI's impact on cognitive decline is well-documented, understanding its neural underpinnings necessitates the use of neuroimaging techniques. The next section explores these methods and their application in TBI research.

2.10 How can neuroimaging help show the earliest neurodegenerative changes post TBI?

A crucial goal of neurodegenerative research is to identify people in the preclinical phase of disease progression. However, detection of neuropathological hallmarks associated with neurodegeneration in vivo can be invasive (i.e., lumbar puncture) or expensive (PET imaging). Standardized neuropsychological testing provides useful information concerning cognitive changes following TBI, however it is inconsistently sensitive to more subtle shortfalls in information processing, executive function, and attention that can be seen in association with focal frontal or diffuse damage following TBI. Application of sensitive cognitive neuroscience methods to those at risk for neurodegenerative disease at a stage prior to disease onset would contribute to detection of risk and understanding of neural correlates of the interaction between TBI and

neurodegenerative disease, enabling intervention prior to the onset of disease-related impairment. Most research on TBI concerns effects in the acute, sub-acute, and chronic recovery phases. Neuroimaging research has identified neural correlates of deficits at the acute and chronic phases, including parenchymal volume loss, disrupted integrity of white matter as assessed with diffusion tensor imaging (DTI), and changes in brain metabolism or deposition of neuropathological consequences from neurodegeneration. Evidence suggests that most macrostructural brain changes (i.e., volume loss or functional changes) after severe TBI plateau within 12-24 months (Ng et al., 2019; Bigler et al., 2010). In contrast, changes following mTBI may stabilise within weeks to months though subtle alterations in network efficiency and white matter integrity may persist for years depending on injury severity, age, and comorbid risk factors (Palacios et al., 2012; Dean et al., 2015). Few studies have addressed longer-term degeneration or atrophy following this period. Below we review the evidence from neuroimaging studies. Although most TBI research, especially repeated TBI, has focused on athletes and military personnel the conclusions can be extended to TBI in general.

While both mTBI and neurodegenerative diseases can impact memory, attention, and executive functions, the temporal profile and neural substrates often differ. For example, AD typically involves early episodic memory loss linked to hippocampal atrophy, whereas chronic effects of mTBI more commonly affect processing speed, attention, and executive control, particularly when white matter injury is prominent (Shenton et al., 2012; McInnes et al., 2017). This thesis therefore prioritises sensitivity to chronic mTBI effects over strict early-AD biomarkers, selecting cognitive domains and imaging metrics that reflect the underlying biology of DAI while maintaining relevance to prodromal dementia pathways.

2.10.1 MRI

2.10.1.1 T1/Structural

TBI is associated with changes in cortical thickness and ventricular size (Bigler & Maxwell, 2012; Fagerholm et al. 2015), as well as abnormalities in white matter that are associated with cognitive changes in adults and in children and youth, possibly synergistically enhancing age-related volume loss and promoting the development of cognitive deficits and neurodegenerative disease. Severe forms of TBI can result in DAI, focal contusions, or haemorrhages observable on conventional clinical MRI or CT. Prevailing theories suggest that repetitive asymptomatic head trauma, concussion, and mTBIs result in damage to cortical and subcortical microstructures despite observable findings on conventional MRI being rare (Irimia et al., 2012).. Hippocampal volume differences in particular may result from steeper age-related atrophy in those with repetitive head trauma (Misquitta et al., 2018). A reduction in hippocampal volume following TBI has been associated with memory deficits and diminished cortical activity in later life (Monti et al., 2013).

Bernick and colleagues investigated the relationship between exposure to repeated head trauma and regional brain volume in boxers, measured by volumetric MRI. An increased number of bouts was correlated with decreased caudate, hippocampus, amygdala and thalamic volume. A reduction in these areas resulted in lower scores on speed of processing tasks (Bernick & Banks., 2013). Another study using the same cohort identified an association between increased impulsivity and lower processing speed with decreased overall brain volume in boxers, again mediated by number of bouts (Banks et al., 2014). This suggests a dose dependency relationship with TBI and reduction of volume in certain areas of brain. Singh and colleagues (2014) demonstrated a significant inverse relationship between exposure to concussion and hippocampal volume in American football players (Singh et al., 2014). Players with a history of concussion had smaller hippocampal volumes than those without. Also, researchers discovered the more years of experience in football, the slower their reaction time. Zhou and colleagues (2013) demonstrated global brain atrophy as well

as changes in regional GM and WM in several regions a year following TBI (Zhou et al., 2013). Patients with lower WM volumes in the cingulate gyrus, showed worse memory and attention and had higher clinical scores for anxiety. The studies above did not examine how comorbid conditions could affect the volumetric differences and cognitive performance post TBI. A study of cortical thickness and brain volumes in 24 current and former rugby players found no significant differences in cortical thickness. However, reduced whole-brain, hippocampus, and amygdala volumes were seen in the former players compared to controls (Wojtowicz et al., 2018). Former players also performed significantly worse on visual memory performance. Importantly, there was an association between greater alcohol use and smaller hippocampal and amygdala volumes. These results suggest that comorbid conditions could also play a role in the changes observed in these studies and should be taken into consideration when evaluating neuroimaging results in former sport athletes.

An interesting potential novel biomarker in TBI is the cavum septum pellucidum (CSP). CSP refers to separation of the septum pellucidum usually best observed on coronal view of conventional T1 MRI as hypointense (CSF filed) space between the two septal leaflets. CSP has been observed at a striking, but variable, rate within repetitive head trauma cohorts in recent years. Koerte and colleagues found CSP abnormalities in half of their sample which included 72 symptomatic former American football players. Koerte and colleagues discovered those with a greater length of CSP have poorer performance on a list learning task. CSP was also investigated in 164 active professional boxers and 43 controls. Although the between-group difference did not reach significance for the presence of CSP, the boxers had greater length of CSP compared to controls with 8 boxers exhibiting CSP on subsequent follow up scans (see figure 2) (Aviv et al., 2010). Limited evidence from a small subset of serially imaged boxers suggests CSP develops and increases in size during repetitive trauma exposure (Jordan BD et al., 1992).

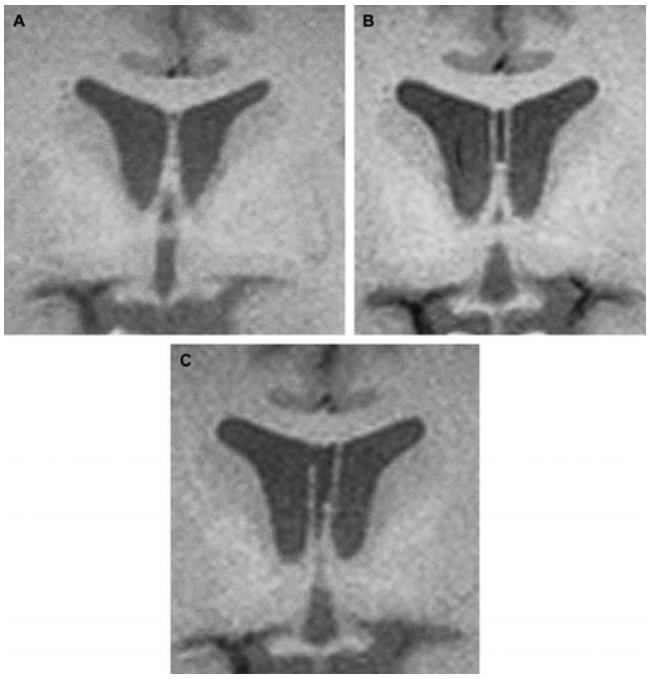


Figure 2.1. Serial coronal T1 W MRI at the level of the chiasm. (A) The initial study, dated January 29, 2000, revealed a normal study. (B) Two years later (April 29, 2002), CSP had developed. (C) One year later (May 15, 2003), the right leaflet of cavum had perforated. (Taken from Aviv et al., 2010)

The high frequency of CSP in repetitive head trauma cohorts, particularly those experiencing neurologic changes, has encouraged proposals that CSP may be a neuroimaging biomarker for CTE (Montenigiro et al., 2014).

2.10.1.2. T2/FLAIR

White matter hyperintensities (WMHs), observed on T2-weighted and FLAIR MRI scans, are markers of microvascular pathology, demyelination, or gliosis. Traditionally studied in ageing and cerebrovascular disease, WMHs are increasingly recognised as critical indicators of long-term brain changes following TBI. These lesions, categorized into periventricular WMHs (PWMHs) near the ventricles and deep WMHs (DWMHs) within the white matter, provide valuable insights into the relationship between TBI and neurodegeneration.

The development of WMHs after TBI is believed to involve multiple pathophysiological mechanisms, including DAI, microvascular disruption, and chronic inflammation. DAI, a hallmark of moderate and severe TBI, often overlaps with regions prone to WMHs, such as the corpus callosum, corona radiata, and internal capsule (Sharp & Jenkins, 2015). In addition, blood-brain barrier (BBB) disruption caused by TBI facilitates neuroinflammatory cascades, allowing neurotoxic substances to exacerbate vascular damage and white matter degeneration (Hay et al., 2015). These processes are particularly concerning in middle-aged adults, where the cumulative effects of TBI and age-related cerebrovascular changes may amplify WMH burden during a critical period of cognitive resilience and vulnerability.

WMHs have been implicated in cognitive decline following TBI, with higher WMH burden linked to deficits in attention, executive function, and memory (Debette & Markus, 2010). For example, individuals with repeated mTBI often show increased WMHs in periventricular regions, correlating with slower processing speed and impaired executive function (Tremblay et al., 2013). In middle-aged adults, WMHs may signify not only prior brain trauma but also an accelerated trajectory toward neurodegeneration. TBI-induced reductions in cognitive reserve may make middle-aged individuals more vulnerable to the cognitive impacts of WMHs, potentially increasing their risk for AD and other dementias (LoBue et al., 2017).

WMHs are also emerging as a bridge between TBI and the neurodegenerative processes associated with AD. Studies suggest that WMHs promote amyloid deposition and exacerbate vascular contributions to cognitive impairment. Brickman et al. (2012) demonstrated that periventricular WMHs were associated with accelerated progression to clinical AD, reinforcing the role of WMHs as both markers and mediators of neurodegeneration. In TBI populations, the interplay between WMHs and chronic inflammation or vascular dysregulation may further compromise brain integrity, increasing the likelihood of long-term cognitive decline (Hannay et al., 2017).

Despite their importance, the study of WMHs in TBI populations faces methodological challenges. Variability in imaging protocols, scanner parameters, and lesion quantification methods complicates cross-study comparisons (Wardlaw et al., 2015). Advances in automated segmentation techniques, such as the Brain Intensity Abnormality Classification Algorithm (BIANCA) pipeline, have improved the reliability of WMH measurements in multi-site studies (Iorio-Morin et al., 2018). BIANCA is an automated, supervised machine learning tool implemented in FSL to segment white matter hyperintensities on T2-FLAIR images (Griffanti et al, 2016). It uses manually-labelled training data to identify outliers in signal intensity, spatial location and tissue class, allowing robust quantification of periventricular and deep WMHs across sites. However, longitudinal research is needed to understand how WMHs evolve post-TBI, particularly in middle-aged adults who may experience a convergence of injury-related and age-related brain changes.

The inclusion of WMHs in TBI research has significant clinical implications. WMHs may serve as early biomarkers for identifying individuals at greater risk for cognitive and functional decline. In middle-aged adults, WMHs could indicate accelerated brain ageing, highlighting the need for early monitoring and intervention. Integrating WMH assessments with advanced imaging modalities such as DTI could provide a more nuanced understanding of white matter integrity and its relationship to cognitive outcomes (Tur et al., 2021). Furthermore, tailoring interventions to address vascular health and neuroinflammation may help mitigate the progression of WMHs and their associated cognitive impacts.

2.10.1.3 Diffusion Weighted Imaging

Diffusion MRI (dMRI) is an advanced MRI technique used to measure diffusion properties of water molecules in the brain (Basser & Jones, 2002). Diffusion measures give indirect information about how the tissue's microstructure influences the motion of water molecules (Koerte et al., 2016).

Measures are often conveyed for either global WM and GM, or for brain regions, or specific WM tracts (i.e., tractography) (Wiegand et al., 2021). DTI provides scalar measures, such as fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD). FA is a unitless scalar value ranging from 0 to 1 that quantifies the degree to which water diffusion within a voxel is spatially constrained. Isotropic diffusion is where water can diffuse freely such as in the CSF space, here the FA values are close to 0. Anisotropic diffusion refers to the opposite, where water diffuses along a single main axis, like those in tightly packed WM fibre tracts. FA and MD are usually found to be inversely associated. Reduction in FA is understood to reflect microscopic damage to myelin sheaths or axon membranes and/or axonal packing density (Pierpaoli et al., 2001). While, RD has been shown to measure myelin and AD measures axonal diffusion (Song et al., 2003).

Lipton and colleagues examined 37 active amateur football players completing a detailed history of heading the ball, reporting 32–5400 times over the previous year. Heading was associated with lower FA at three locations in temporo-occipital white matter. Lower FA was also associated with poorer memory performance. Lifetime concussion history was not significantly associated with either FA or cognitive performance (Lipton et al., 2013). Xiong and colleagues found a reduction in FA and an increase in MD within several WM tracts in patients a month after a single mTBI when compared to controls. This same study also showed these patients had higher MD in the uncinate fasciculus which is associated with poorer working memory. Also, those with higher FA performed better on the Mini Mental State Examination (MMSE) (Xiong et al., 2014).

DTI delivers a robust measure of clinically important traumatic axonal injury (TAI) at cross-section, despite the variability in characteristics of patients with TBI as well as study differences in data acquisition and analysis methods. However, the interpretation of diffusion measures remains challenging as they represent many different structures and types of cells within a given voxel.

Larger longitudinal studies with specificity of number and severity of head injury will be needed for the assessment of DTI as a prognostic biomarker in TBI.

2.10.1.4 Arterial Spin Labelling

Various neurobiological mechanisms may contribute to cerebral blood flow (CBF) changes after TBI (Toth et al., 2016). Arterial spin labelling (ASL) is a technique used for perfusion MRI that allows for quantification of CBF using magnetically labelled arterial blood water as an internal contrast agent (Hunter et al., 2012). ASL perfusion brain MRI has been used to assess CBF as a surrogate marker of brain function and metabolism in numerous clinical populations, such as neurodegeneration and stroke (Haller et al., 2016).

Yang and colleagues compared CBF of concussed and non-concussed contact sports players (n=24), 24-48hr after injury. Correlations were found between decreased CBF in acute concussed players and impairment on memory, impulse control and balance tasks (Yang W et al., 2019). However, the players were not followed up and so no conclusions could be drawn for the longitudinal effects. It is feasible the players returned to a stable state following the injury weeks or months later. Ge and colleagues examined patients with a history of mTBI (n=21 with a median time since onset of injury of 25 months) using ASL perfusion MRI. The researchers discovered a reduction in thalamic perfusion which correlated with lower performance on neurocognitive measures including processing and response speed, memory/learning, verbal fluency and executive function (Ge et al., 2009). It is important to note that other factors such as genetics and pre-existing conditions (hypertension, etc.) will likely play a role in CBF differences between individuals post injury. However, no study to date has examined these factors using ASL in TBI.

Two recent studies reported no global CBF difference between mTBI and control groups, one at the acute/ early subacute stage after sport related concussion (Churchill et al., 2019) and another at

the chronic stage after injury (Coverdale et al., 2020). However, Coverdale et al., 2020 demonstrated that cerebrovascular reactivity (CVR), not CBF, differed between concussed and control groups in regions where working memory fMRI showed difference between groups (ventral anterior cingulate cortex, superior frontal gyrus, the medial temporal gyrus and the lateral occipital cortex).

ASL MRI methods might be useful for detecting and tracking the longitudinal course of underlying neurophysiological recovery from concussion.

2.10.1.5 Summary

No characteristic atrophy pattern has emerged as specific to repetitive head trauma exposure. There are somewhat consistent findings of lower medial temporal and subcortical (thalamus, corpus callosum) volumes in repetitive head trauma cohorts compared to controls across the lifespan, though interpreting group level volume differences in younger, active athletes is complicated by neurodevelopmental dynamics. We cannot readily attribute volumetric differences to a specific neurodegenerative pathology (e.g., CTE or AD) but susceptibility of these regions to traumatic forces implicates head trauma regardless of the underlying pathophysiologic process. Collective evidence indicates that presence of CSP in clinically impaired adults with repetitive head trauma exposure should increase suspicion that the presence of any neurodegenerative disease, whether CTE or otherwise, is attributable at least in part to the patient's repetitive head trauma. Emerging research in DTI and ASL strongly implicate the importance of further studying neuroimaging modalities that characterize white matter changes and blood flow in head trauma cohorts. Despite these advances, current neuroimaging studies face several limitations, particularly in multi-site data variability and cohort differences. Addressing these challenges is crucial for accurate interpretation of results.

2.10.2 PET imaging

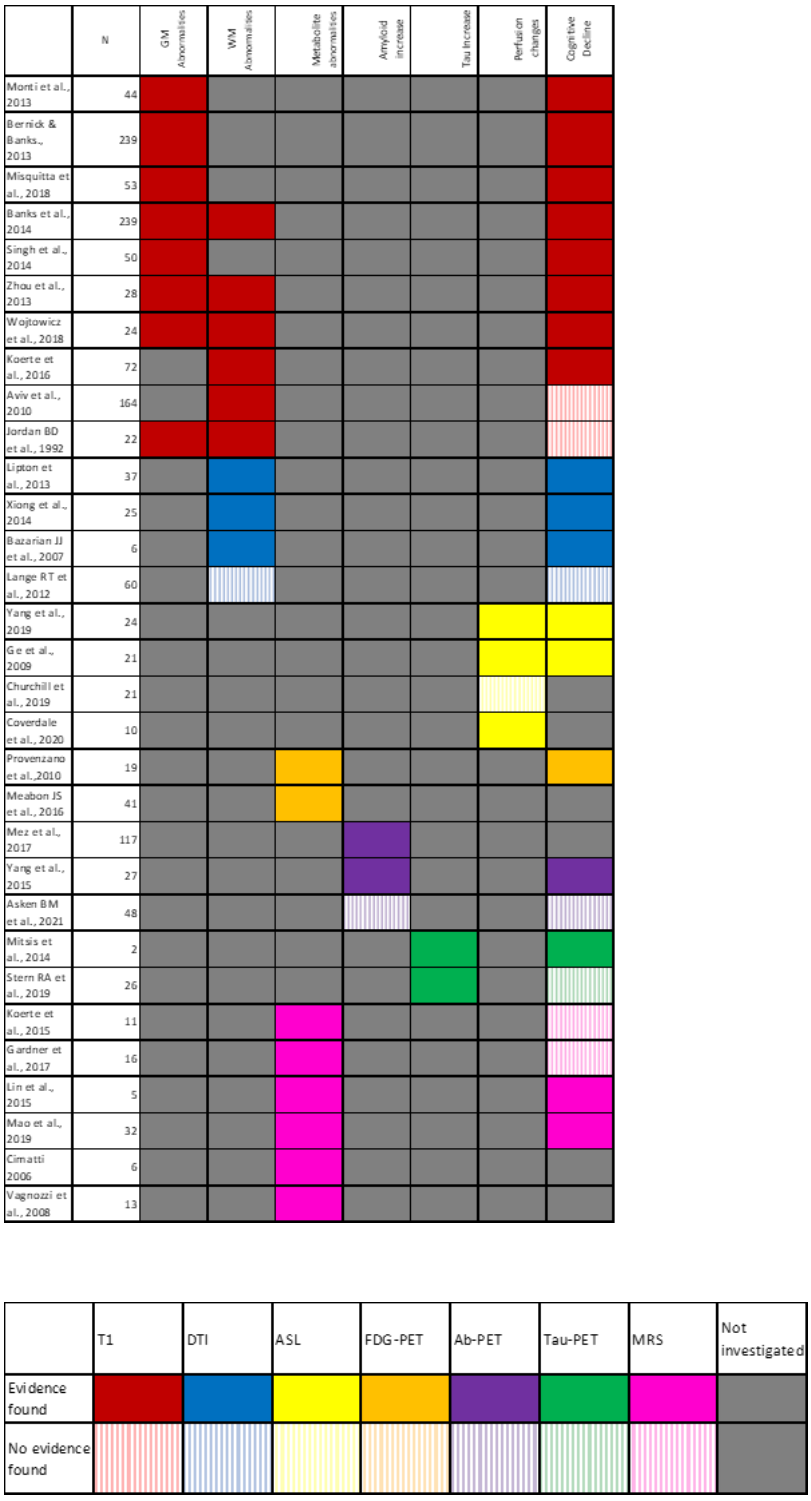
PET imaging offers valuable insights into the metabolic and pathological consequences of TBI, though its application remains exploratory due to inconsistencies and methodological challenges. While not a central focus of this thesis, PET imaging serves to contextualize broader neuroimaging efforts in the study of neurodegeneration and TBI, offering pathways for future research.

- **FDG-PET:** FDG-PET measures glucose metabolism as a proxy for synaptic activity. Studies in repetitive TBI cohorts, such as boxers and veterans, have identified regional hypometabolism, particularly in the cerebellum, posterior cingulate, and Broca's area, which correlates with cognitive impairments (Provenzano et al., 2010; Meabon et al., 2016). However, findings are inconsistent across populations, with variability in metabolic changes suggesting underlying heterogeneity in TBI pathology and its long-term effects.
- **Amyloid PET:** Amyloid PET has been primarily used to differentiate between AD and TBI-related pathologies. Early studies suggested an increased Aβ burden in TBI patients, especially APOE4 carriers (Yang et al., 2015). However, more recent research has questioned this association, finding no significant differences in cortical amyloid burden between TBI and control groups (Asken et al., 2021). Diffuse plaques, more common in TBI, may account for the weaker amyloid tracer binding compared to neuritic plaques in AD.
- **Tau PET:** Tau PET was initially considered a potential biomarker for CTE, given the role of phosphorylated tau in CTE pathology. However, tau PET tracers, such as Flortaucipir, exhibit low affinity for tau deposits in CTE compared to AD, limiting their diagnostic utility (Stern et al., 2019). While some studies have observed increased tracer uptake in TBI cohorts, these findings lack specificity and often overlap with other tauopathies.
- **Neuroinflammatory PET:** Tracers such as [11C]PK11195, which bind to the 18kDa translocator protein (TSPO) expressed in activated microglia, have highlighted the role of neuroinflammation in TBI. Increased tracer uptake has been observed in regions linked to cognitive impairments, such as the thalamus, suggesting chronic microglial activation post-

injury (Folkersma et al., 2011; Ramlackhansingh et al., 2011). However, the relationship between inflammation and TBI severity remains unclear.

PET imaging, while not central to this thesis, contributes to a broader understanding of TBI-related neurodegenerative processes. The modality highlights the metabolic, pathological, and inflammatory changes associated with TBI, offering potential biomarkers for long-term outcomes. However, the inconsistent findings and limited specificity of existing PET tracers underscore the need for targeted methodological advances. As this thesis focuses on other neuroimaging modalities, PET data are included to contextualize the potential for complementary diagnostic tools in future research.

Figure 2.2. Cross-sectional of neuroimaging research by modalities



	T1	DTI	ASL	FDG-PET	Ab-PET	Tau-PET	MRS	Not investigated
Evidence found								
No evidence found								

2.11 Long term impacts of TBI in mid-life

The investigation of TBI's long-term effects has been concentrated on the early and later periods of life, frequently neglecting the significant mid-life phase. Investigating TBI in mid-life is crucial for several reasons: this phase is critical for cognitive resilience and susceptibility, a time when the cumulative impacts of lifestyle and genetic variables on brain health become more evident. Moreover, mid-life signifies a period during which initial indicators of neurodegenerative disorders may manifest and may be intensified by previous TBIs. Therefore, comprehending the effects of TBI at this phase is essential for formulating tailored therapies that might alleviate long-term cognitive and psychological consequences, thereby improving the quality of life for survivors. A notable gap in the literature is the insufficient emphasis on mid-life as a distinct phase for investigating the ramifications of TBI. This error is significant, given the potential for TBI to affect the ageing process and heighten susceptibility to cognitive decline and neurodegenerative disorders.

Zijlmans et al. (2023) investigated 2005 individuals and found no direct link between a history of TBI and objective cognitive or structural brain abnormalities in mid-life. Nonetheless, the cross-sectional nature of that study constrains the capacity to deduce causality, and dependence on self-reported TBI history may add memory bias, so compromising the accuracy of TBI documentation. Graham et al. (2023) illustrated neurodegenerative patterns in TBI survivors compared to Alzheimer's disease patients, indicating distinct paths of neurodegeneration. This discovery underscores the necessity of differentiating between the neurodegenerative consequences of TBI and other types of dementia. Kaup et al. (2019) examined the relationship between TBI, psychiatric symptoms, and cognitive function, suggesting that psychiatric symptoms may serve as early indications of neurodegenerative processes generated by TBI, especially in late middle-aged males. Franke et al. (2021) proposed using auditory-evoked brain potentials as biomarkers for the chronic

TBI, offering a potential tool for early identification of neurodegenerative risk and underscoring the importance of biomarker research in TBI.

The collected findings from these studies clarify the future direction for study, highlighting the necessity for longitudinal and mechanistic investigations to elucidate the specific connection between mid-life TBI and neurodegeneration. Subsequent research should concentrate on the creation and validation of biomarkers for early detection and surveillance. The findings highlight the imperative for healthcare practitioners to maintain a cautious stance in monitoring TBI survivors for early indicators of cognitive loss during mid-life. Given the bidirectional relationship between mental health and cognitive decline, routine assessment and support for psychiatric symptoms following mTBI may improve functional outcomes and enhance resilience to age-related cognitive decline (van der Horn et al.,2017; Gould et al., 2020). While direct evidence for long-term neuroprotection is limited, integrated care models may reduce comorbidity burden and improve quality of life in TBI populations. The paramount significance of investigating the long-term effects of mid-life traumatic brain injury, especially its capacity to trigger or hasten neurodegenerative processes, is crucial. Nonetheless, research is constrained by inadequate TBI categorisation, small sample numbers, and insufficient complete cognitive and neuroimaging assessments. This field of study advances, promising to influence preventative and therapeutic techniques, therefore dramatically improving the prognosis for those at risk of neurodegenerative illnesses after a TBI.

2.12 Conclusions

TBI is a complex condition with profound implications for public health, cognitive function, and individual well-being. Its global prevalence underscores its significance as a widespread concern, while advances in neuroimaging techniques such as MRI and DTI provide critical insights into the intricate relationship between TBI and neurodegenerative processes. The diverse cognitive effects

of TBI, coupled with its heterogeneity, highlight the urgent need for accurate classification systems and reliable biomarkers to enhance diagnosis, prognosis, and treatment strategies.

Despite the growing body of research, the long-term effects of mid-life TBI remain insufficiently explored. Mid-life represents a pivotal period for understanding TBI's impact, as it combines the cumulative effects of earlier injuries with the onset of age-related cognitive vulnerabilities. The variability in TBI outcomes and the broad spectrum of cognitive, emotional, and behavioural consequences make it challenging to establish standardized classifications and biomarkers. This necessitates dedicated research initiatives focused on mid-life TBI to address these gaps and provide tailored therapeutic approaches.

This thesis aims to fill the information gap by focusing on the unique effects of TBI in mid-life to early late life, where the potential for interventions to mitigate long-term cognitive decline and postpone neurodegenerative disorders is greatest. By advancing our understanding of mid-life TBI, this work seeks to guide the development of therapies that improve quality of life and facilitate reintegration into social and professional environments.

A critical challenge in the field is the harmonisation of imaging and cognitive data across diverse cohorts, which has hindered progress in understanding TBI's long-term impacts. To address this, Chapter 3 outlines the innovative methodology employed in this thesis, including the use of harmonised datasets and advanced neuroimaging techniques. By addressing these methodological gaps, this research seeks to provide new insights into the long-term consequences of TBI, ultimately contributing to improved outcomes for individuals navigating the complexities of recovery and aging.

Chapter 3: Harmonisation of Cognitive and Neuroimaging data

3.1 Overview of PREVENT and EPAD Studies

The PREVENT and EPAD studies represent two landmark research programs designed to uncover early biomarkers and risk factors for Alzheimer's disease (AD) and other dementias. These studies have generated extensive longitudinal datasets incorporating cognitive evaluations, lifestyle factors, and neuroimaging measures, which are critical for advancing understanding of neurodegeneration and the impact of modifiable risk factors like TBI.

3.1.1 The PREVENT Study

The PREVENT project (n=702) is an innovative research program aimed at examining the early signs of Alzheimer's disease and other dementias. This longitudinal research focusses on individuals deemed at risk according to family history, however who have not manifested indications of cognitive impairment. PREVENT concentrates on middle-aged individuals, often aged 40 to 59, to uncover biomarkers and cognitive alterations that may manifest decades before the clinical signs of dementia. The research incorporates many data gathering approaches, such as genetic testing, cognitive evaluations, lifestyle surveys, and neuroimaging techniques over 2 years. PREVENT is a multisite study conducted across five UK research centres, each equipped with distinct MRI scanners and imaging protocols, necessitating harmonisation of neuroimaging data across these sites.

3.1.2 The EPAD Study

The European Prevention of Alzheimer's Dementia (EPAD) initiative extends this exploration to participants aged 60 and older a larger transcontinental cohort of 2096 individuals. EPAD focuses on those at risk of AD based on genetic and biomarker profiles, using innovative adaptive trial

designs to evaluate preventive interventions during the preclinical phase of the disease. Participants get annual follow-ups for 3 years comprising of cognitive evaluations, neuroimaging, and blood analyses to track alterations and reactions to therapies. This design not only improves comprehension of Alzheimer's pathogenesis but also allows researchers to customise therapies according to individual risk profiles, facilitating personalised medicine in Alzheimer's prevention. EPAD is also a multisite study, involving neuroimaging data collected from 15 research sites across Europe, each employing different MRI scanners and acquisition protocols. These variations introduce significant technical challenges for harmonisation, particularly for structural and diffusion-based imaging metrics.

3.1.3 Harmonisation Challenges and Focus Areas

Despite their shared objectives, integrating data from PREVENT and EPAD presents significant harmonisation challenges due to differences in:

- **Cognitive Assessment Protocols**: PREVENT uses the COGNITO battery, while EPAD employs the RBANS test. These differences necessitate harmonisation at the cognitive domain level (see sections 3.3.2.1 & 3.3.2.2).
- **Neuroimaging Pipelines**: The multisite nature of both studies introduces variability due to differences in MRI scanner types, acquisition parameters, and field-of-view adjustments. Robust harmonisation techniques, such as NeuroHarmonize, are employed to standardise metrics like total brain volume, white matter hyperintensities, and diffusion tensor imaging (DTI) measures (see section 3.5).

3.1.4 Aim

This chapter aims to detail the methodological process of harmonising cognitive and neuroimaging data from the PREVENT and EPAD studies, with the objective of constructing a large, integrated dataset to analyse how a history of TBI impacts individuals at risk for neurodegeneration. The

chapter will outline the specific steps taken to ensure compatibility and integration of diverse data types from these two landmark studies, emphasizing the standardization of cognitive assessment tools and neuroimaging protocols.

The emphasis will be on creating and executing a cohesive framework that integrates data from two cohorts with data from multiple sites, allowing for an extensive examination of the relationship between TBI and early indicators of neurodegeneration. This chapter will elucidate the obstacles and solutions faced throughout the harmonisation process, offering insights into the intricacies of data integration in multi-site, longitudinal research investigations. This investigation seeks to enhance our comprehension of mild TBI as a modifiable risk factor for neurodegeneration, perhaps guiding focused intervention initiatives for vulnerable groups.

3.2 TBI severity classification

Understanding the severity of TBI is critical for investigating their long-term cognitive and neurodegenerative impacts. This section outlines the categorisation process used to classify TBI severity, focusing on the application of the Brain Injury Screening Questionnaire (BISQ) and the creation of a standardised categorisation framework that can be generalised beyond the BISQ.

3.2.1 The Brain Injury Screening Questionnaire (BISQ)

As described in Chapter 2, BISQ is a validated tool designed to assess the history, severity, and consequences of TBIs. It gathers comprehensive information on:

- Incidence: Whether the participant has experienced one or more TBIs.
- Frequency: The number of head injuries sustained.
- Severity: Based on symptoms such as LOC, post-injury confusion, and the duration of symptoms.

- Consequences: Cognitive, emotional, and physical outcomes following the injury.

BISQ provides detailed scoring criteria to categorise TBIs as mild, moderate, or severe (item-by-item mapping shown in appendix 1). It also allows differentiation between single and repeated mild TBIs. In this study, the BISQ was used across the PREVENT and EPAD cohorts to capture detailed TBI histories while enabling a unified approach to data categorisation.

3.2.2 Classification of Severity Groups

Although the BISQ itself does not require harmonisation, a standardised TBI severity categorisation framework was developed to ensure compatibility with cohorts. This framework is generalisable and facilitates cross-cohort comparisons by relying on key variables such as the presence of LOC, symptom duration, and injury frequency. The procedure starts with determining if an individual has had a head injury, thereafter, evaluating the existence of LOC, a critical sign of damage severity. If there was no loss of consciousness and the BISQ severity score was below 4, the subject was categorised as having a minor head injury. This flowchart-based methodology facilitates distinct classification of mild, repeated mild, and more severe instances of TBI, contingent upon symptomatology and incidence frequency.

Table 3.1. Description of how TBI severity was classified in this thesis

No Head Injury	Simple Head Injury	Single Mild TBI	Repeated Mild TBI	Moderate/Severe TBI
Participants with no history of TBI, defined as no 'yes' answers on the BISQ	Participants with history of TBI and no LOC	Participants with a history of one mild TBI, characterised by: • BISQ severity score below 4. • No LOC or LOC lasting less than 30 minutes. • Only one instance of head injury	Participants with a history of multiple mild TBIs, meeting the following criteria: • BISQ severity score below 4 for each injury. • At least two mild TBIs reported, and LOC.	Participants with a history of moderate or severe TBI, characterised by: • BISQ severity score of 4 or higher. • LOC lasting more than 30 minutes or post-traumatic amnesia (PTA) exceeding 24 hours. • Significant post-injury symptoms and functional impairments.

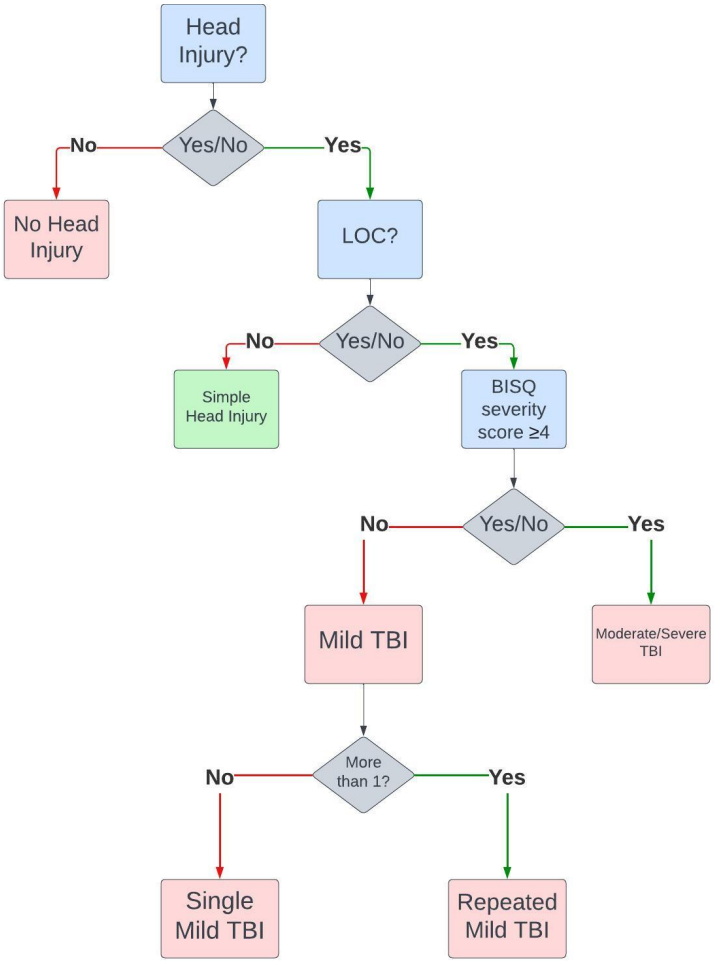


Figure 3.1. Classification of severity groups

3.2.3 Rationale for a Generalisable Framework

This categorisation ensures that TBI severity can be assessed consistently across cohorts. By relying on universal criteria such as LOC and symptom duration and utilising the BISQ, the framework provides a robust method for integrating data from various studies and enhances the generalisability of findings on TBI-related cognitive and neural changes.

3.2.4 Link to Cognitive and Neuroimaging Analyses

This categorisation forms the basis for subsequent analyses of cognitive and neuroimaging data. By standardising TBI severity classification, it is possible to examine the relationship between injury severity, cognitive outcomes, and neurodegenerative biomarkers consistently across the PREVENT and EPAD cohorts.

3.2.5 Limitations of the Classification Framework

The classification framework for TBI severity provides a robust and systematic approach to harmonising datasets across cohorts, enabling critical insights into the effects of injury severity. It represents a significant advancement in addressing the challenges of integrating data from diverse cohorts, particularly in the context of neurodegeneration research. However, as with any classification system, there are challenges and areas for enhancement that should be acknowledged to contextualize the findings and guide future research.

Reliance on Self-Reported Data

The classification process heavily depends on self-reported TBI history as documented through the Brain Injury Screening Questionnaire (BISQ). Although the BISQ is a validated tool, self-reported data are inherently prone to recall bias. Participants may underreport injuries, particularly if they perceive them as minor or if the events occurred many years ago. Conversely, overreporting may occur due to misinterpretation of questions or conflation of unrelated events with TBI incidents. This introduces variability and potential inaccuracies in the classification process, which may affect the reliability of group assignments. This limitation is further discussed in Chapter 5.4.5, where its potential impact on distinguishing the no-head-injury control group is highlighted.

Although BISQ data were available at the individual item level, several potentially informative variables, such as the mechanism of injury, age at injury, and time since injury were excluded from analysis. This was due to inconsistent reporting across participants, substantial missingness, and limitations in harmonising these fields across the PREVENT and EPAD datasets. For instance, many participants did not specify when the injury occurred, making it difficult to incorporate injury timing into severity classification or downstream models. As a result, the framework prioritised more reliably coded variables such as LOC, number of injuries, and BISQ severity score.

Heterogeneity in Injury Mechanisms

The BISQ does not account for the diversity of injury mechanisms, such as those resulting from falls, motor vehicle accidents, sports-related concussions, or assaults. Each mechanism could involve distinct biomechanical forces and lead to differing neuropathological outcomes. This variability within severity categories might obscure the relationships between TBI severity and subsequent neurodegeneration, particularly when comparing findings across cohorts with differing injury profiles. The variability in injury mechanisms and its implications for generalizability are further explored in Chapter 5.4.5.

Arbitrary Thresholds for Severity Classification

The thresholds used to differentiate between mild, moderate, and severe TBI are necessarily categorical and do not fully account for the continuum of injury severity. For instance, the distinction between single and repeated mild TBI (mTBI) is based on frequency, but it does not capture potential compounding effects of injury timing or inter-injury interval. Furthermore, the reliance on criteria such as loss of consciousness (LOC) duration or symptom severity may oversimplify the complex interactions between injury characteristics and long-term outcomes.

Limitations of the No Head Injury Group

The control group labelled as “No Head Injury” is assumed to have no history of TBI based on negative BISQ responses. However, this assumption may not fully hold. Participants could have experienced subclinical or unreported injuries that do not meet the BISQ’s criteria. Additionally, as discussed in Chapter 5.4.5, the no-head-injury group may not represent a true control population due to potential enrichment with risk factors for Alzheimer’s disease, such as APOE4 positivity or other unmeasured confounders. These factors complicate the interpretation of differences between control and mild TBI groups, particularly in cognitive or neuroimaging outcomes.

Generalizability Across Cohorts

The classification framework was specifically designed for use with the PREVENT and EPAD cohorts, which include middle-aged and older adults at risk for Alzheimer's disease (AD). While this approach ensures compatibility within these datasets, its applicability to more diverse cohorts—such as younger populations, individuals with military or sports-related TBIs, or those from different cultural or socioeconomic backgrounds—may be limited. Variations in participant demographics and injury characteristics could reduce the generalizability of findings.

Limited Integration of Biomarkers

Although the framework provides a structured approach to classifying TBI severity, it does not incorporate objective biomarkers, such as neuroimaging or blood-based measures, during the initial classification stage. These biomarkers could enhance diagnostic accuracy by identifying subtle or subclinical injuries that may not be captured by self-reported data alone. Additionally, as noted in Chapter 5.4.5, the exclusion of amyloid-positive participants from EPAD introduces a potential bias, which could affect the robustness of comparisons between the no-head-injury group and TBI groups.

Summary

Overall, the classification framework represents a significant advancement in harmonizing multi-cohort TBI research, providing a systematic approach to understanding the effects of injury severity. While limitations exist, they reflect the complexities inherent in TBI research. These insights offer a strong foundation for future enhancements, including the integration of biomarkers and longitudinal recovery data, to further refine classification and broaden its applicability. Addressing these challenges will be essential for advancing our understanding of TBI's impact on neurodegeneration.

3.3 Cognitive Data: Overview and Harmonisation Challenges

Cognitive data are central to understanding the impact of a history of mild TBI on long-term neurodegeneration and dementia risk. The PREVENT and EPAD studies employ distinct cognitive batteries to assess various cognitive domains, providing rich datasets. However, while some tasks are comparable across cohorts, others require harmonisation due to differences in testing methodologies and scoring systems.

3.3.1 Common Tests

Although certain cognitive tests are shared between the PREVENT and EPAD cohorts and are identical in administration and scoring, they were still included in the harmonisation process to maintain methodological consistency. These tests were categorised under the visuospatial domain, despite some inherent limitations and considerations.

- Four Mountains Task: Evaluates spatial memory, specifically sensitive to hippocampal dysfunction.
- Supermarket Trolley Task: Measures visuospatial skills, executive function, assessing planning and organisational abilities.

3.3.1.1 Rationale for Inclusion in Harmonisation

Including these tasks in the harmonisation process ensures a uniform methodology across all cognitive measures, allowing for consistent comparisons across cohorts. Categorising these tests under the visuospatial domain enables their integration with similar tasks from COGNITO and RBANS but also introduces limitations:

1. Domain Overlap: While these tasks primarily assess visuospatial abilities, they also engage other cognitive functions (e.g., executive planning in the Supermarket Trolley Task), potentially confounding the domain-specific analysis.

2. Task Specificity: The Four Mountains Task is highly specific to hippocampal function, which may not align with the broader constructs assessed by other visuospatial tasks.
3. Interpretation Challenges: Combining these tests with broader visuospatial metrics from COGNITO and RBANS may obscure nuanced findings specific to these unique assessments.

By addressing these limitations in subsequent analyses (see Section 3.4.3), this harmonisation approach provides a comprehensive framework for integrating all cognitive data, including these shared tasks, into a domain-based analysis.

3.3.2 Cognitive Batteries

The cognitive batteries used in the PREVENT and EPAD cohorts differ in their design and scope, necessitating harmonisation for cross-cohort comparisons. The following sections provide a brief overview of each battery, highlighting common and distinct tests.

3.3.2.1 PREVENT COGNITO battery

The COGNITO cognitive battery (Karen et al., 2014) is a thorough computerised neuropsychological evaluation intended to examine various cognitive functions. It includes attention, memory, language, and visuospatial skills, rendering it particularly appropriate for investigations into brain ageing, longitudinal analyses of cognitive development, and extensive population-based studies. The battery's design enables the meticulous documentation of reaction latencies, mistake kinds, and qualitative factors such as perseveration and hemi-spatial field neglect, which are essential for differentiating between normal and abnormal cognitive alterations. Furthermore, its versatility enables use across diverse age demographics and for individuals with differing cognitive capacities. Originally designed to identify early indicators of dementia and other cognitive deficits, COGNITO integrates both conventional and novel assessments, each followed by practice sessions to guarantee comprehension. The battery, requiring around 40 minutes for completion, may be operated via a tactile screen, therefore improving its use and accuracy. It generates a

comprehensive variety of data appropriate for clinical evaluation and research objectives, underscoring its dual use in many investigative contexts. The battery comprises four distinct domains: memory, attention, language, and visuospatial abilities.

Memory

1. Articulation and Immediate Recall

Objective: To test the ability to articulate names and subsequently recall them.

Process: Subjects articulate names shown on-screen, then attempt to recall these names after a delay.

Results Recorded: Numbers of names pronounced and recalled correctly, plus errors like intrusions and perseverations.

2. Delayed Recall of Names

Objective: To assess the ability to recall a list of names after a period.

Process: Subjects try to recall names they learned earlier without visual cues, then with initial letters, and finally from a multiple-choice list.

Results Recorded: Correctly recalled names, intrusions, perseverations, and name recognition accuracy.

3. Implicit Memory

Objective: To evaluate recognition memory for names constructed progressively on-screen.

Process: Subjects must identify names as they appear in stages; some names are familiar, others are not.

Results Recorded: Success or failure for each trial, the number of steps needed for recognition, and comparative metrics for new versus known names.

4. Narrative Recall

Objective: To measure the ability to recall and sequence story elements.

Process: After hearing a story, subjects must recount the story elements in order.

Results Recorded: The order and accuracy of recalled elements, intrusions, and whether the task was refused.

5. Description Recall

Objective: Similar to narrative recall but focuses on visual sequence recall.

Process: Subjects recall and describe visual elements from a sequence they were shown.

Results Recorded: Order and accuracy of the recalled visual elements, intrusions, and refusal of task.

6. Name Face Association

Objective: To test recall and association between previously learned names and faces.

Process: Subjects are shown faces and must decide if they recognise them and recall the associated names.

Results Recorded: Accuracy of face recognition, name recall, and correct associations.

Attention

1. Auditory Attention

Objective: To distinguish and count varying sounds.

Process: Subjects listen to sounds of differing lengths and count specific types based on instruction.

Results Recorded: Number of correct counts, total errors, overestimations, and underestimations.

2. Visual Attention

Objective: To quickly identify similar shapes from a group.

Process: Subjects must spot and select identical shapes on a touch screen.

Results Recorded: Number of correct identifications, incorrect trials, time errors, and non-responses.

3. Visual and Auditory Attention

Objective: Combines tasks of visual and auditory attention.

Process: Subjects perform a visual identification task while counting auditory stimuli.

Results Recorded: Accuracy in visual and auditory tasks, time errors, and non-responses.

Language

1. Reading and Syntax Comprehension

Objective: To evaluate reading comprehension and the ability to follow instructions.

Process: Subjects read and execute commands of increasing syntactic complexity.

Results Recorded: Number of correctly read sentences, comprehension accuracy, and response times.

2. Phoneme Comprehension

Objective: To identify objects matching spoken words among visual and phonetic distractors.

Process: After hearing a word, subjects must select the corresponding object from a set.

Results Recorded: Correct responses, time for each correct response, and types of errors (shape, semantic, phonetic).

3. Naming Functional, Semantic, and Conceptual Associations

Objective: To name objects and categorize them based on function and semantic relationships.

Process: Subjects name objects and then choose related items from a group.

Results Recorded: Total correct responses, generalizations, partial responses, and response times.

Visuospatial Skills

1. Visuo-Spatial Span

Objective: To assess spatial memory and the ability to recall location sequences.

Process: Subjects observe a pattern of locations and must replicate the sequence.

Results Recorded: Sequence accuracy and time taken for each trial.

2. Matching Geometric Figures

Objective: To match complex geometric figures based on form and orientation.

Process: Subjects select the matching figure from a series of distractors.

Results Recorded: Response times, selected figures, and error types such as field neglect.

3. Drawing House

Objective: To replicate a complex visual figure (a house).

Process: Subjects are provided with a drawing and must copy it accurately.

Results Recorded: Quality of reproduction, element placement, and perspective accuracy.

4. Drawing Abstract Figure

Objective: Similar to the drawing house task but involves an abstract figure.

Process: Subjects copy an abstract design shown on the screen.

Results Recorded: Similar metrics as the house drawing, assessing execution and placement.

3.3.2.2 EPAD RBANS Battery

The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) is a neuropsychological assessment tool specifically designed to evaluate cognitive decline or dysfunction across several domains. It is commonly used for both clinical and research purposes to detect and monitor various cognitive disorders, including dementia, Alzheimer's disease, and other neurodegenerative conditions (Randolph et al., 1998).

Immediate Memory Domain

1. **List Learning**: In this task, participants are read a list of words multiple times and are asked to recall as many words as possible after each presentation. This test primarily measures verbal learning and memory, which are key components in diagnosing and understanding the progression of neurodegenerative diseases like Alzheimer's. Immediate memory recall can indicate the integrity of temporal lobe functions, particularly the hippocampus, which is crucial for forming new memories.

2. **Story Memory**: Participants are read a brief story and then asked to recall as much of it as possible immediately after hearing it. This task assesses memory for narrative information, engaging both verbal memory and comprehension. It requires integrating episodic memory processing, which is often compromised early in dementia and other cognitive impairments, providing essential insights into a patient's ability to process and remember extended discourse.

Visuospatial/Constructional Domain

1. **Figure Copy**: In this task, individuals are shown a complex figure and asked to copy it exactly. This test assesses visuospatial construction skills and visual memory, important for diagnosing conditions where the parietal lobe might be compromised, such as in Alzheimer's disease or after certain types of strokes. It evaluates a person's ability to perceive spatial relationships and to reproduce them accurately.
2. **Line Orientation**: Participants are required to match the orientation of lines within a series of paired lines. This task tests visuospatial judgment and is indicative of right hemisphere brain function. It is crucial for assessing spatial orientation skills, which are necessary for everyday navigational tasks and can be affected in various neurocognitive disorders.

Language Domain

1. **Picture Naming**: This task presents a series of pictures to the participant, who must name each item. It assesses language production and is sensitive to left hemisphere dysfunctions, particularly in the language-dominant areas like Broca's area. This task can help identify expressive language impairments, which are common in stroke, TBI, and progressive neurological disorders like frontotemporal dementia.
2. **Semantic Fluency**: Participants are asked to generate as many words as possible from a given category in a limited time. This task measures language function, specifically semantic memory and executive function, as it requires accessing vocabulary and a

strategic search through semantic networks. It is particularly useful in assessing the integrity of temporal and frontal lobe functions.

Attention Domain

1. **Digit Span**: This test involves repeating digits forward and backward. It measures attention and working memory, relying on the frontal lobe's executive functions. This task is fundamental in clinical settings to evaluate attention capacity and immediate memory recall, which are often affected in psychiatric and neurological disorders.
2. **Coding**: Participants transcribe a digit-symbol code within a specified time, measuring processing speed, sustained attention, and visual motor coordination. It is a good indicator of psychomotor speed and can be particularly revealing of subcortical and frontal lobe damage.

Delayed Memory Domain

1. **List Recall**: This task requires participants to recall the previously learned list of words after a delay filled with other tasks. It measures the ability to retain verbally presented information, which can highlight impairments in strategic retrieval and memory consolidation processes.
2. **Story Recall**: Similar to the immediate recall, but after a delay, this task evaluates delayed memory for narrative information, crucial for understanding episodic memory impairments.
3. **Figure Recall**: After a delay, participants are asked to draw the figure initially copied, assessing visual memory retention. It taps into the visuo-constructive abilities and the delayed recall capabilities of the visual memory system.
4. **List Recognition**: A recognition task for the words presented in List Learning, this assesses recognition memory, helping to differentiate between retrieval and recognition memory deficits, which can be informative for differential diagnosis in clinical assessments.

3.3.3 Harmonisation Challenges

Harmonising cognitive data across COGNITO and RBANS presents specific challenges, particularly in:

- **Domain-Level Comparisons**: While some domains are well-represented in both batteries (e.g., memory), others (e.g., executive function) have limited overlap, complicating cross-cohort analyses.
- **Scoring Systems**: COGNITO often provides detailed reaction times and error metrics, whereas RBANS relies on total scores, requiring careful standardisation.
- **Test Constructs**: Some tests assess similar cognitive functions but differ in their format and administration (e.g., narrative recall in COGNITO vs. immediate story recall in RBANS).

The first step in the harmonisation process involves mapping individual tests to broader cognitive domains (e.g., memory, attention) and conducting principal component analysis (PCA) within each domain to extract shared components (see Section 3.4).

By addressing these challenges, the harmonisation framework enables robust cross-cohort comparisons, allowing for a unified analysis of TBI-related cognitive changes.

Full access to raw cognitive task-level data was available for both cohorts, including detailed scores and error metrics for each item. However, not all available variables were incorporated into the harmonisation process. Variables that lacked cross-cohort equivalency, demonstrated poor data quality, or were redundant for domain-level PCA (e.g., latency metrics when accuracy was primary) were excluded. The focus was to retain core, interpretable indicators across all four cognitive domains, ensuring maximal comparability and statistical power for harmonised analyses.

3.4. Harmonisation of cognitive data

3.4.1 Introduction

The harmonisation of cognitive test batteries across research platforms is critical for enhancing the robustness and comparability of neurocognitive research, particularly in studies spanning multiple cohorts. In this study, cognitive data from the COGNITO battery and the RBANS were harmonised across the PREVENT and EPAD cohorts to examine the impact of a history of TBI on cognitive functioning. Although both batteries comprehensively assess various cognitive domains, differences in constructs and scoring systems pose significant challenges when combining datasets or comparing results (Gur et al., 2012). Principal Component Analysis (PCA) was chosen as the primary harmonisation approach due to its ability to reduce dimensionality while preserving key variance, facilitating meaningful cross-cohort comparisons (Jolliffe, 2002). Other methods, such as factor analysis, were considered, but PCA's broad application in neuropsychological research and ease of interpretation made it the optimal choice (Pomponio et al., 2020; Fortin et al., 2018; McKenzie et al., 2018

3.4.2 Methodology

Step 1: Categorization of Cognitive Tasks into Domains

The first step in the harmonisation process was to categorize each cognitive test administered in the PREVENT and EPAD cohorts into broader cognitive domains: Memory, Attention, Language, and Visuospatial Processing. The cognitive tests were grouped according to their primary cognitive demands based on established neuropsychological literature (Lezak et al., 2012). For example, tasks that assessed recall and recognition abilities were grouped under Memory, while those measuring attention span and selective attention were placed in the Attention domain.

This categorization is a common approach in harmonising heterogeneous cognitive data, as it allows for a domain-level assessment that minimizes discrepancies arising from task-specific characteristics (Thomas et al., 2019). The categorization aimed to retain meaningful variance in cognitive performance while reducing the noise associated with individual task differences across cohorts (Pomponio et al., 2020).

Step 2: Principal Component Analysis (PCA) within Each Domain

Once tasks were grouped by domain, a PCA was conducted separately within each cognitive domain for each cohort. PCA is a statistical technique that reduces data dimensionality by identifying the most informative components—i.e., those that capture the maximum variance in the dataset (Jolliffe & Cadima, 2016). In the context of cognitive data, PCA helps explain the shared variance within a domain, creating a single or a few component scores that represent core abilities in that cognitive area. This approach is particularly useful in harmonisation as it minimizes the influence of cohort-specific test variations, extracting domain-level performance indicators that are less reliant on the specific tasks administered (McKenzie et al., 2018; Fortin et al., 2018).

Each PCA produced one or more principal components per domain, depending on the amount of variance captured by each component. Only the principal component(s) that explained a substantial proportion of variance within each domain were retained. For example, in the Memory domain, component scores captured shared variance from immediate recall, delayed recall, and recognition tasks in both cohorts, representing a generalized memory performance score.

Step 3: Standardization of Component Scores (Z-Scoring)

Following the extraction of component scores from each domain, the scores were standardized within each cohort. Standardization, or z-scoring, transforms scores to have a mean of zero and a standard deviation of one. This step ensures that component scores across domains and cohorts

are directly comparable, as it controls for differences in score distributions that could otherwise confound cross-cohort analyses (McKenzie et al., 2018).

Standardizing scores also enables the combination of harmonised scores across domains in subsequent analyses, making this a critical step for ensuring consistent scaling (Thomas et al., 2019). By using z-scores, cognitive performance could be interpreted relative to the mean performance within each cohort, providing a robust metric for cross-cohort comparisons of cognitive function.

Step 4: Cross-Cohort Domain-Specific Z-Scoring

After completing Steps 1 to 3 within each cohort separately, the next phase of harmonisation involved combining the domain-specific scores across both PREVENT and EPAD cohorts. For each cognitive domain, the z-scored component scores from PREVENT and EPAD were pooled. For instance, the attention scores derived from PCA in the PREVENT cohort were combined with the corresponding attention scores from EPAD.

Once pooled, an additional z-scoring step was applied to each combined domain, placing all participants on a common scale. This process generated harmonised, domain-specific scores (e.g., Memory, Attention, Language, Visuospatial) across both cohorts, enabling meaningful cross-cohort comparisons within each cognitive domain. The final z-scoring controlled for cohort-specific variance, ensuring that the scores reflect cognitive performance across the entire combined sample, rather than being biased by cohort differences (Pomponio et al., 2020; Fortin et al., 2018).

3.4.3 PCA and Standardisation: Rationale, Advantages, and Limitations

3.4.3.1. Rationale for PCA and Standardisation

Principal Component Analysis (PCA) was employed as a key step in harmonising cognitive data across the PREVENT and EPAD cohorts. The primary objective was to reduce the dimensionality of the data while preserving the core variance within each cognitive domain. This approach allowed for the integration of diverse cognitive batteries (COGNITO and RBANS) into a unified framework, ensuring comparability and minimising cohort-specific influences. Standardisation (z-scoring) was applied within and across cohorts to ensure consistent scaling and facilitate domain-level analyses. The decision to use PCA was driven by its ability to distil shared variance across cognitive tasks within a domain, creating composite scores that are less reliant on the specific tasks administered. This was critical for addressing variability in task design and scoring between the two cohorts.

3.4.3.2 Advantages of PCA and Standardisation

1. **Dimensionality Reduction**: PCA simplified the data structure by reducing multiple variables into a smaller number of principal components, making analyses more manageable without sacrificing meaningful variance.
2. **Noise Reduction**: By focusing on components that account for the most variance, PCA filtered out noise and irrelevant variability, improving the reliability of findings.
3. **Domain-Level Insights**: PCA facilitated the grouping of tasks into cognitive domains (e.g., memory, attention), enabling a more targeted exploration of domain-specific performance.
4. **Standardisation Across Cohorts**: Z-scoring normalised task scores within each cohort, ensuring consistency and comparability when pooling data across the PREVENT and EPAD studies.

5. **Facilitation of Data Integration**: PCA provided a framework for integrating datasets with different cognitive batteries, enabling meaningful cross-cohort comparisons and supporting robust statistical analyses.

3.4.3.3 Limitations and Considerations

1. **Potential Information Loss**: Lower variance components, which were excluded, may have contained subtle but important information relevant to specific research questions such as an executive function domain.
2. **Challenges in Interpretation**: Principal components are mathematical abstractions of the original variables, making it difficult to relate them to traditional cognitive constructs or specific functions.
3. **Assumption of Linearity**: PCA assumes linear relationships among variables, which may not fully capture the complexity of cognitive test data.
4. **Sensitivity to Scaling**: Variations in how test scores were standardised across batteries could influence PCA results, potentially introducing bias.
5. **Variance-Centric Approach**: By prioritising variance, PCA may underrepresent clinically significant but less variable aspects of cognitive performance.
6. **Sampling Adequacy**: The inability to extract finer-grained domains, such as executive function, due to suboptimal Kaiser-Meyer-Olkin (KMO) values, limits the ability to detect specific cognitive changes associated with TBI or neurodegeneration. Incorporating more diverse cognitive tests or increasing sample sizes to improve KMO adequacy could enhance the specificity of future harmonisation efforts.

While PCA has inherent limitations, such as potential residual cohort-specific variability and the challenges of capturing the full complexity of cognitive constructs across diverse batteries, it provides a robust and systematic method for harmonising cognitive data. By balancing theoretical grounding with statistical rigor, this methodology ensures meaningful cross-cohort comparisons

and represents a practical solution to the challenges of integrating heterogeneous datasets, making it well-suited for application in this research. A full summary boxplot of each domain separated by severity is provided in appendix 2.

3.4.4 Conclusion

The harmonisation of cognitive data across the PREVENT and EPAD cohorts was achieved through a systematic process involving the categorisation of cognitive tasks into domains, followed by the application of PCA and standardisation. This methodology addressed the inherent variability in cognitive batteries, enabling domain-level comparability while preserving meaningful variance within each cohort.

While PCA provided a robust and systematic approach to reduce dimensionality and minimise cohort-specific influences, challenges such as potential information loss, residual variability, and the complexity of cognitive constructs across diverse batteries were carefully considered. By balancing theoretical grounding with statistical rigor, the methodology ensures meaningful cross-cohort comparisons and represents a practical solution to the challenges of integrating heterogeneous datasets.

This harmonisation process not only facilitates robust analyses of the cognitive impacts of TBI but also lays the foundation for integrating multimodal data, such as neuroimaging, which will be discussed in the following sections. Despite its inherent limitations, the approach provides a scalable and reliable framework for future multi-cohort research.

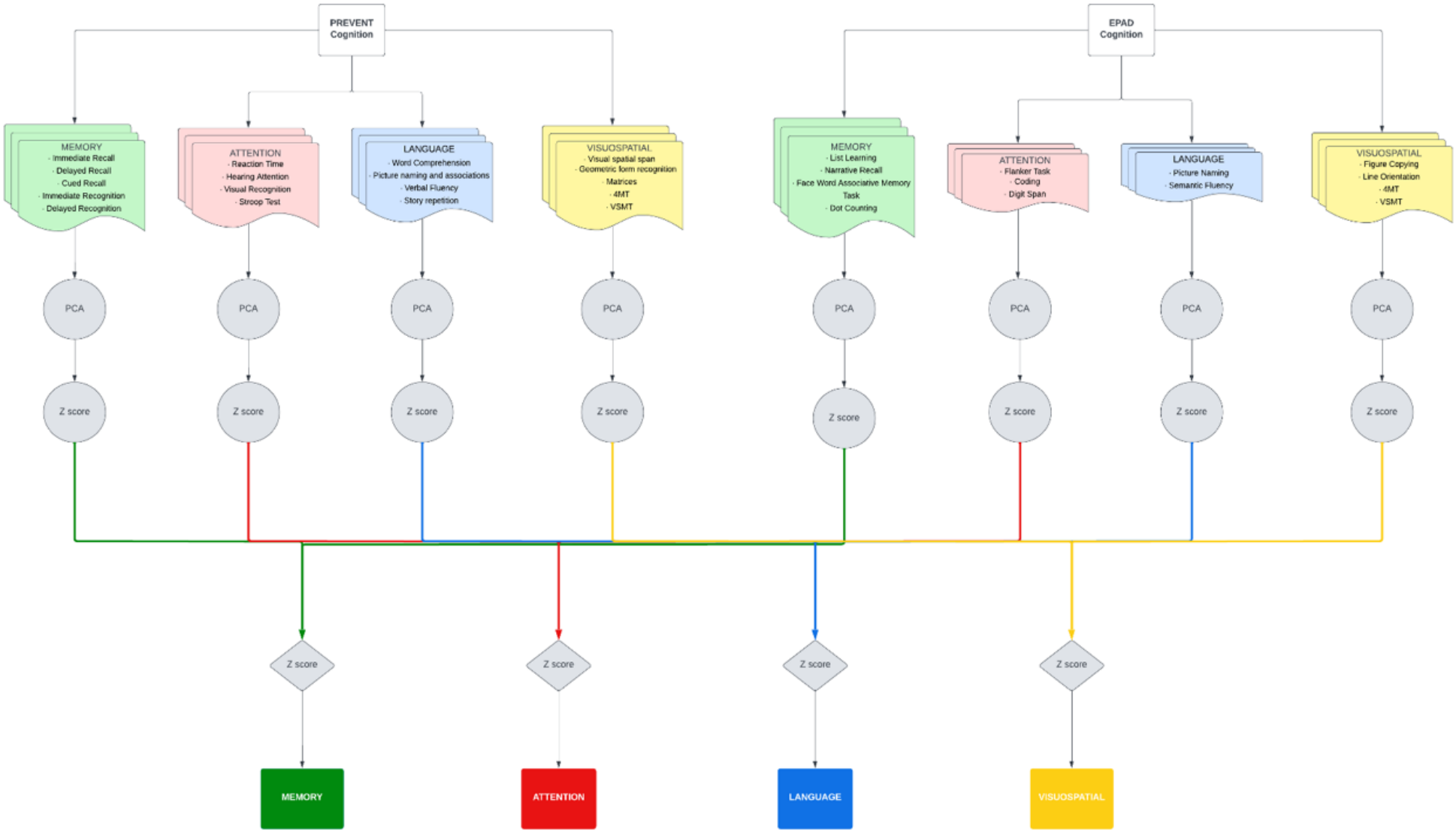


Figure 3.2 Flowchart of Cognitive harmonisation

3.5. Brain imaging analysis: overview, optimised preprocessing, and harmonisation challenges

The UK Biobank imaging pipeline, originally designed for large-scale population studies, was adapted in this project to meet the specific needs of both the PREVENT and EPAD cohorts. Modifications were implemented to reconcile variations between the two datasets, ensuring data comparability despite the use of disparate scanners and acquisition protocols. The objective of employing this pipeline was to guarantee equivalent processing of all imaging data across both cohorts, facilitating consistent and comparable results for volumetric and diffusion-based studies to assess GM and WM. Multiple harmonisation techniques were assessed, such as z-score normalisation and linear mixed-effects models (LME), but NeuroHarmonize was selected for its capacity to employ empirical Bayes to address intricate batch effects, thereby preventing scanner-related discrepancies from obscuring authentic biological signals.

3.5.1. UKB pipeline adaptations for anatomical scans (T1 and T2-FLAIR)

The UK Biobank imaging pipeline, initially developed for large-scale neuroimaging studies, was adapted in this project to address the specific requirements of the PREVENT and EPAD datasets (Alfaro-Almagro et al., 2018; Miller et al., 2016). T1-weighted and T2-weighted FLAIR MRI images were processed using a multi-step pipeline to obtain high-quality imaging-derived phenotypes (IDPs), with robust segmentation, alignment, and quality control procedures (Smith et al., 2004; Jenkinson et al., 2012). Key tools utilised in this process included BET for brain extraction (Smith, 2002), FAST for tissue segmentation (Zhang et al., 2001), and FNIRT for nonlinear registration to standard space (Andersson et al., 2007). The resulting IDPs provide detailed measures of neuroanatomical structures, supporting analyses of TBI-related and neurodegenerative changes.

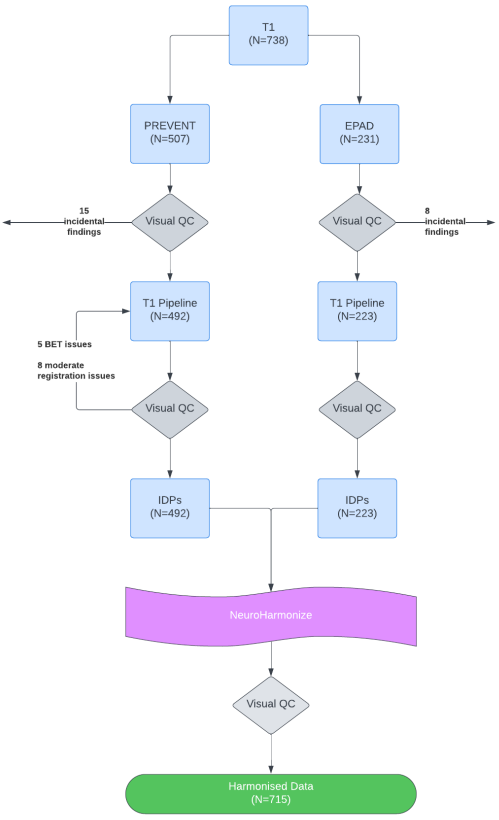


Figure 3.3. T1 data flowchart

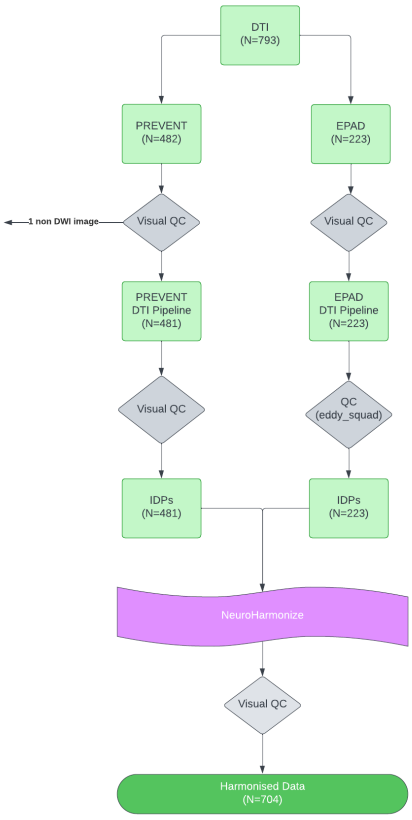


Figure 3.4. DTI data flowchart

3.5.1.1. T1-weighted Image Processing

The T1-weighted structural images provide high-resolution anatomical detail, essential for segmenting brain tissue types and calculating volumetric measurements. The processing of T1-weighted images followed a structured pipeline (see figure 7):

Field-of-View Reduction and Initial Preprocessing

- The initial stage of T1 processing involved was defacing the images before the field of view (FoV) was reduced to exclude background and non-brain tissue (e.g. neck), thereby optimizing processing efficiency and improving segmentation accuracy. This was achieved using FSL's robustfov tool, which automatically adjusts the FoV to focus on brain tissue (Jenkinson et al., 2012).

- A combination of recursive brain extraction techniques and the application of a standard MNI152 "nonlinear 6th generation" template (Evans et al., 1993) helped refine the initial brain boundaries, creating a preliminary brain-extracted T1 image.

Linear and Nonlinear Registration to Standard Space

- To facilitate accurate cross-subject comparisons, each T1 image was registered to MNI152 standard space (Fonov et al., 2009) using both affine and nonlinear transformations. First, FLIRT (Jenkinson and Smith, 2001) was applied for linear registration, followed by FNIRT (Andersson et al., 2007) for nonlinear warping.
- These transformations yielded a warp file (T1_to_MNI_warp), which standardized each image's spatial orientation, aligning individual brains to a common template while preserving anatomical details critical for voxel-based morphometry.
- A standard-space brain mask was then back-transformed into the native space of each T1 image and applied to create a refined, brain-extracted T1 (T1_brain). This brain mask ensured that subsequent tissue segmentation focused exclusively on brain tissue, minimizing partial volume effects from skull or other non-brain structures.

Tissue Segmentation and Bias Field Correction with FAST

- T1 images were then segmented into cerebrospinal fluid (CSF), grey matter (GM), and white matter (WM) using FSL's FAST (FMRIB's Automated Segmentation Tool; Zhang et al., 2001). FAST employs a hidden Markov random field model to improve segmentation accuracy by incorporating spatial context, thereby reducing noise and misclassification in tissue boundaries.
- This segmentation process also provided partial volume estimates (PVEs) for each tissue type, allowing for refined volume measurements in complex regions with mixed tissue composition.
- Bias field inhomogeneities, often present in MRI data due to scanner variations, were corrected using FAST's integrated bias field correction algorithm. This step generated an

unbiased version of the brain-extracted T1 image (T1_unbiased_brain), which enhanced the accuracy of subsequent volumetric analyses (Zhang et al., 2001).

Volume Estimation and Normalization with SIENAX

- Following segmentation, SIENAX (Structural Image Evaluation, using Normalisation, of Atrophy; Smith et al., 2002) was employed to estimate brain tissue volumes, including total brain, grey matter, and white matter volumes. SIENAX scales each individual's brain volume relative to their skull size to account for inter-individual differences in head size, allowing for standardized comparisons of brain volume across subjects.
- SIENAX used the brain-extracted and bias-corrected T1 image to delineate the outer brain boundary, which served as the basis for calculating normalized brain volumes against the MNI152 template.

Subcortical Structure Modelling with FIRST

- Finally, subcortical structures were segmented and modelled using FSL's FIRST (FMRIB's Integrated Registration and Segmentation Tool; Patenaude et al., 2011), which provides shape and volumetric estimates for 15 key subcortical structures, such as the hippocampus, thalamus, and caudate. FIRST employs a Bayesian model of shape and appearance to reliably identify these regions, supporting analyses of subcortical morphometry that may be relevant to dementia-related changes.
- The volumetric and shape outputs generated by FIRST were integral to investigating potential neurodegenerative changes, particularly in regions vulnerable to Alzheimer's disease pathology.
- Voxel-based morphometry (VBM) is not described in this chapter but is included in the overview (Figure 3.5) to illustrate the broader image processing framework. The VBM-specific methodology, results, and interpretation are detailed in Chapter 6, which focuses on baseline neuroimaging measures associated with a history of TBI.

3.5.1.2. T2 FLAIR Processing

T2-weighted FLAIR imaging was utilised to enhance visualization of pathological features, particularly white matter hyperintensities (WMHs), which are often indicative of white matter lesions. The processing of T2-weighted FLAIR images followed a structured pipeline:

Preprocessing and Registration

- The original T2 FLAIR images were defaced and underwent pre-scan normalisation at the time of acquisition on the scanner, as part of the standardised imaging protocol in both the PREVENT and EPAD studies. This helped reduce intensity variability across participants and sites (Bischoff-Grethe et al., 2007). These images were then linearly aligned to the T1-weighted image space using FLIRT, enabling integrated analysis with T1-based segmentation results (Jenkinson & Smith, 2001). This alignment provided T2 FLAIR brain-extracted and bias-corrected versions for both native and MNI-standard spaces (Smith et al., 2004).

White Matter Hyperintensity Estimation

- To quantify WMHs, the BIANCA tool was used to segment lesions within the white matter (Griffanti et al., 2016). This step generated three WMH-related IDPs: the total WMH volume, the peri-ventricular WMH volume (lesions within 10 mm of the ventricles), and the deep WMH volume (lesions located farther than 10 mm from the ventricles). The T2 FLAIR image, in combination with the T1 segmentation, allowed for precise localization and volumetric analysis of these lesion types (Wardlaw et al., 2015).

The outputs from these processing steps, particularly the IDPs for brain volume, grey matter volume, and white matter lesion load, form the basis of cross-sectional and longitudinal analyses within this study. These rigorous preprocessing and normalization procedures ensure that extracted metrics are both robust and reliable, facilitating meaningful interpretation in the context of traumatic brain injury and neurodegenerative change.

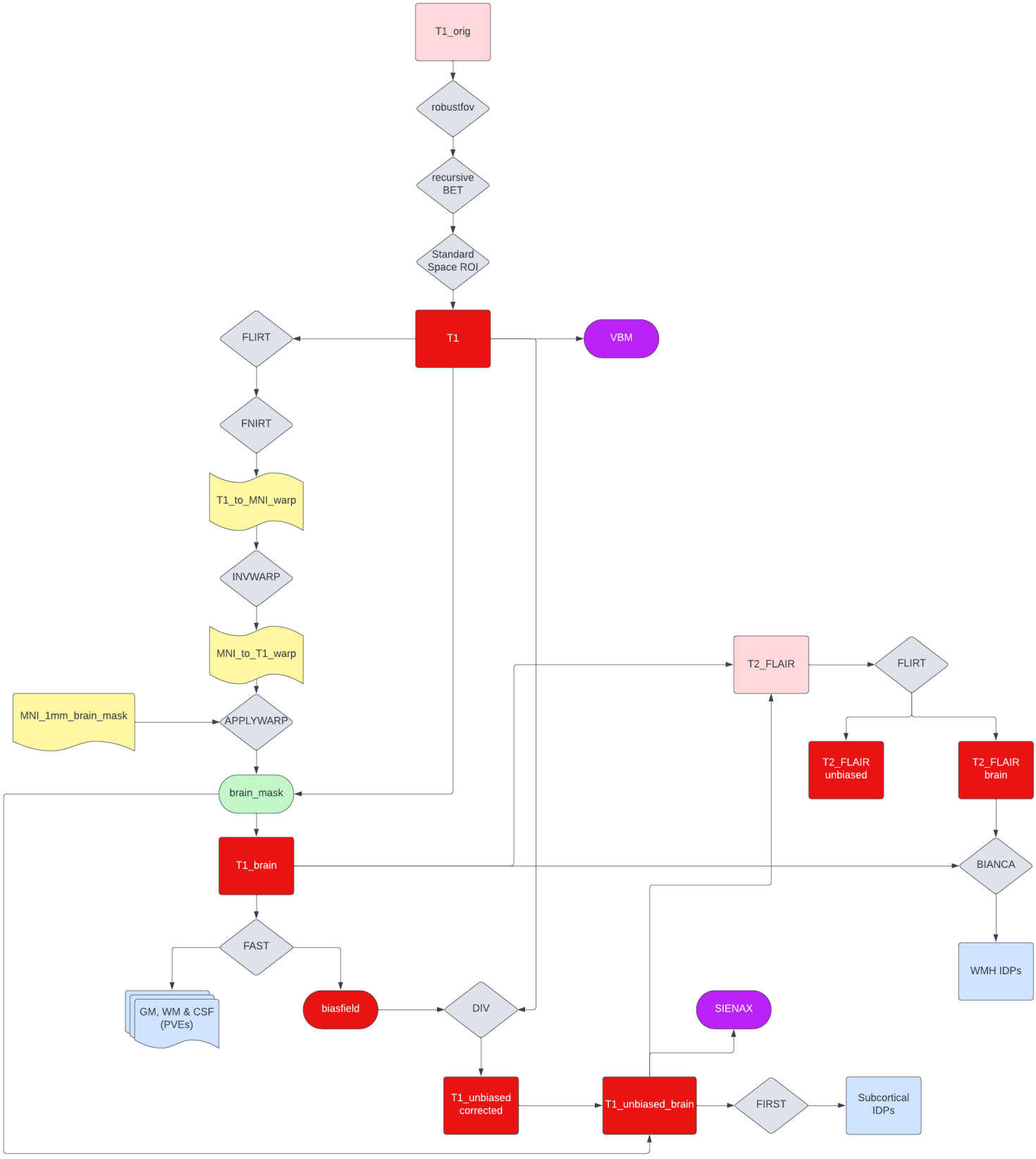


Figure 3.5. Flowchart of the T1 and T2 FLAIR pipeline

3.5.2. Diffusion-weighted imaging pipeline

This study employed a detailed DTI analysis pipeline for data from both the EPAD and PREVENT cohorts. Given differences in acquisition protocols between these cohorts, the DTI processing was adapted to maximize comparability while maintaining methodological rigor. DTI allows for the assessment of white matter integrity through the measurement of fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and mode of anisotropy (MO), which are sensitive markers of white matter microstructure and are relevant to understanding potential neurodegenerative changes associated with dementia risk (Basser and Pierpaoli, 1996; Beaulieu, 2002).

3.5.2.1. EPAD DTI Processing

Preprocessing and Distortion Correction:

- The EPAD protocol incorporated two B0 images with opposing phase-encoding directions (anterior-posterior and posterior-anterior) to facilitate susceptibility-induced distortion correction, a common issue in echo-planar imaging (EPI) sequences used in diffusion MRI (Jezzard and Balaban, 1995).
- These B0 images were first reoriented to MNI standard space and combined to create a 4D B0_PA_AP image, ensuring that any differences due to phase encoding were harmonised.
- FSL's TOPUP (Andersson et al., 2003) was then applied to generate a field map based on the differences between the phase-encoding directions. This field map was subsequently applied using applytopup to correct the susceptibility distortions in the DTI data. This process results in a single, distortion-corrected B0 image, crucial for accurate spatial alignment of the diffusion-weighted images.

Brain Extraction and Motion Correction:

- After distortion correction, non-brain tissue was removed from the diffusion images using FSL's BET (Brain Extraction Tool; Smith, 2002), which improves the accuracy of subsequent analyses by focusing processing efforts solely on brain structures.
- Motion and eddy current distortions, other common artifacts in diffusion imaging, were corrected using FSL's eddy (Andersson and Sotiropoulos, 2016), which applies affine transformations to align each volume to a reference and adjust for eddy current distortions. This step is particularly important in diffusion MRI as even slight movements can lead to misestimations of diffusion metrics (Jones and Cercignani, 2010).

Tensor Fitting:

- Following preprocessing, diffusion tensors were fitted to the corrected dMRI data using FSL's DTIFIT (Behrens et al., 2003), which models water diffusion within each voxel. This step yielded tensor-based maps, specifically fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and mode of anisotropy (MO). FA reflects the degree of directionality in water diffusion, while MD, RD, and MO provide insights into the magnitude and pattern of diffusion, all of which are indicative of microstructural integrity in white matter.

3.5.2.2. PREVENT DTI Processing

Quality Control and Brain Extraction:

- The PREVENT DTI data underwent a preliminary visual inspection to ensure sufficient image coverage and minimal eddy-current distortions. This step allowed for the identification and exclusion of low-quality data, a crucial consideration when working with multi-site data (Alfaro-Almagro et al., 2018).
- Non-brain tissue was removed using FSL's BET tool, similarly to the EPAD pipeline, to improve the robustness of subsequent processing.

Eddy-Current and Motion Correction:

- Eddy currents and participant movement were corrected using eddy (Andersson and Sotiropoulos, 2016). However, the PREVENT protocol did not include AP/PA B0 acquisitions or a separate field map for susceptibility distortion correction. As a result, *topup* could not be applied to this dataset. To mitigate the impact of distortions, additional quality control was implemented, focusing on excluding low-quality images. This highlights a key challenge in harmonising dataset processed under different protocols and the solution of leveraging the best tools available for the type of data collected.

Tensor Fitting:

- As in the EPAD pipeline, DTIFIT was applied to calculate FA, MD, MO, and RD maps. These maps serve as core metrics for assessing white matter structure and integrity, which are often affected in neurodegenerative conditions.

Post-Processing and Analysis (Conducted separately for each cohort)

Creation of a Mean FA Skeleton:

- FA Maps were aligned to a cohort-specific template and skeletonized independently for each cohort using TBSS (Tract-Based Spatial Statistics; Smith et al., 2006). Skeletonization, with an FA threshold set at 0.2, isolates the core white matter tracts, reducing the influence of partial volume effects but ensures consistency in the derived measures across participants.

Projection of Diffusion Metrics onto the Skeleton:

- Each participant's FA, MD, MO, and RD maps were projected onto the mean FA skeleton by identifying the peak FA values perpendicular to the skeletonized white matter tracts (Smith et al., 2006). This process enhances the comparability of diffusion metrics across subjects by standardizing measurements within a central white matter framework.

Extraction of Regional Diffusion Metrics:

- Region-specific values for FA, MD, MO, and RD were extracted from 15 predefined white matter regions of interest (ROI) using FSL's *fslmaths* tool. These ROIs were identified from the JHU (John Hopkins University) atlas, which is widely used in diffusion MRI studies including the UKBiobank. Selection of these regions was informed by prior research on TBI and dementia (Wakana et al., 2004; Ritchie et al., 2017). While FA, MD, MO, and RD values were initially extracted from 15 JHU-defined white matter regions, only FA and MD were retained for further analysis. MO and RD were excluded due to their lower interpretability and inconsistent associations with TBI outcomes in past studies (e.g., Kumar et al., 2009; Niogi & Mukherjee, 2010; Wang et al., 2011). FA and MD remain the most widely validated diffusion metrics in TBI research, correlating with axonal damage and extracellular water content, respectively (Shenton et al., 2012).
- Tract-Based Spatial Statistics (TBSS): To facilitate voxel-wise comparisons across the cohorts, FA images were aligned to a standard space and skeletonized using TBSS. Mean FA and MD values were extracted from skeletonized images for major white matter tracts, including the corpus callosum, corona radiata, and superior longitudinal fasciculus. Although TBSS was used to project individual data onto a skeletonized white matter tract, no voxel-wise statistical comparisons were conducted. This decision was taken to preserve comparability across PREVENT and EPAD and to mitigate multiple comparison issues associated with voxel-wise inference, which would have reduced power given the sample size (Smith et al., 2006; Bach et al., 2014).

This standardized approach ensured that despite initial differences in protocol between the PREVENT and EPAD cohorts, the preprocessing steps minimized biases introduced by the original imaging protocols. Additional preprocessing applied to the PREVENT data accounted for protocol-specific effects on image quality and characteristics, allowing for a more comparable foundation

for downstream analyses across cohorts. By unifying the preprocessing pipelines, we addressed differences at the image level while maintain the integrity of each cohort's data.

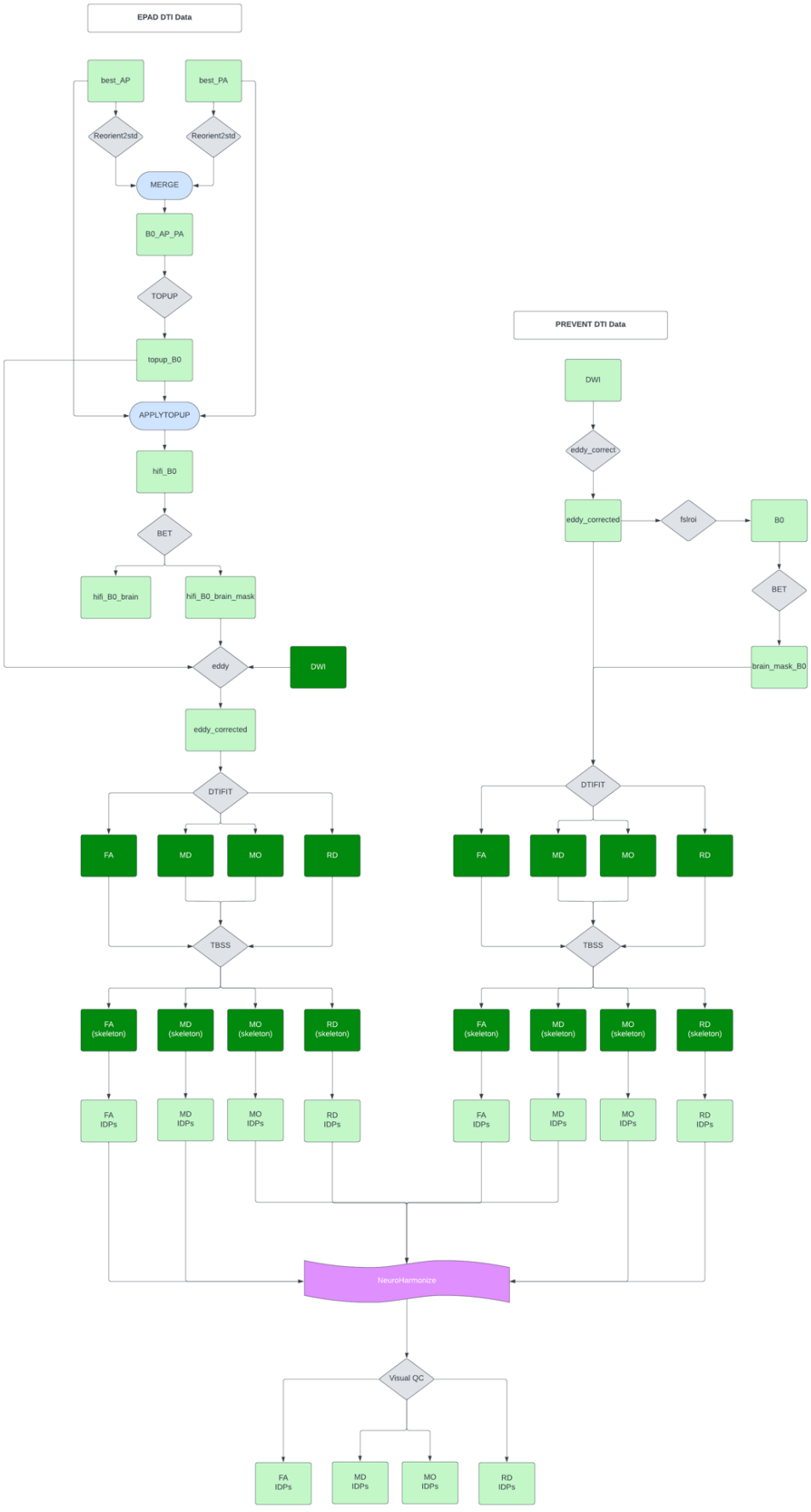


Figure 3.6. DTI pipeline for both EPAD and PREVENT

3.5.3. Importance and challenges of imaging harmonisation

Neuroimaging is critical for understanding the biological mechanisms underlying neurodegenerative diseases, including Alzheimer's disease (AD). Large datasets like those from the EPAD and PREVENT studies provide invaluable opportunities for research into early biomarkers and therapeutic targets. However, the use of neuroimaging data collected from multiple sites introduces challenges, as variations in scanner hardware, acquisition protocols, and site-specific practices can influence imaging-derived phenotypes (IDPs) and potentially confound results (Yamashita et al., 2021).

The inclusion of participants with a history of TBI in these datasets further complicates analyses, as TBI can introduce heterogeneity in imaging findings due to its varying effects on brain structure and function. To ensure valid comparisons, robust preprocessing pipelines and harmonisation techniques are essential to account for technical inconsistencies while preserving genuine biological signals (Smith et al., 2016).

3.5.4. Multi-Site Imaging Variability and Preprocessing

The PREVENT and EPAD studies exemplify the challenges of multi-site neuroimaging. The PREVENT dataset was collected using 3-T Siemens MRI scanners (Verio, PRISMA, Prisma Fit, Skyra) across four sites, with consistent acquisition parameters to reduce inter-site variability. Conversely, EPAD involved data acquisition from 21 sites using scanners from Siemens, Philips, and GE Healthcare, covering seven distinct models with varying hardware and software specifications. While EPAD adopted a harmonised core protocol, these hardware differences inevitably led to variability in IDPs.

To highlight the potential impact of such variability, Warrington et al. (2020) conducted a traveling-heads study, demonstrating that even when protocols are nominally harmonised, scanner-related variability can match or exceed the magnitude of biological differences. Their findings underscore the importance of robust preprocessing pipelines—such as correcting for motion, field inhomogeneity, and geometric distortions—prior to harmonisation to minimize technical artifacts. For example, differences in diffusion MRI (dMRI) metrics like fractional anisotropy (FA) and mean diffusivity (MD)

were significantly influenced by scanner hardware, emphasizing the need for stringent preprocessing steps to standardize data.

3.5.5. Acquisition Protocol Differences

PREVENT and EPAD shared a focus on structural and diffusion-weighted imaging, but notable differences in acquisition protocols and scanner models were present. The tables below provide an overview of the main parameters in PREVENT and EPAD:

Table 3.2. PREVENT MRI acquisition protocol

	PREVENT			
	T1-weighted	T2-weighted	FLAIR	DTI
Sequence	MPRAGE	-	-	1b=0, 1000 s/mm2 volume, and 64 gradient directions
TR (ms)	2300	1500	9000	11700
TE (ms)	2.98	80	94	90
Flip angle	9o	150o	150o	90o
Voxel size (mm^3)	1.0x1.0x.10	0.69x0.69x4.0	0.43x0.43x4.0	2.0x2.0x2.0
Slices	160	32	27	63
Duration (min:s)	5:03	0:50	4:50	13:16
Scanners	Siemens Verio, Siemens PRISMA, Siemens Prisma Fit, Siemens Skyra			

Table 3.3. EPAD MRI acquisition protocol

	EPAD								
	T1-weighted	**FLAIR**	**DTI**	**T1-weighted**	**FLAIR**	**DTI**	**T1-weighted**	**FLAIR**	**DTI**
Sequence	MPRAGE		N_B0 = 1, N_B1000 = 54, PEd = A > P,	MPRAGE		N_B0 = 1, N_B1000 = 48, PEd = P > A,	MPRAGE		
TR (ms)	2300	5000	7400	1672.6/1526.6	5000	6836	7184	5000	NA
TE (ms)	2.95	393	81	3.11	395	70	3.09	155	
Voxel size (mm^3)	1.2x1.05x1.05	1.0x1.0x1.0	2.0x2.0x2.0	1.1x1.1x1.2	1.0x1.0x1.0	2.0x2.0x2.0	1.2x1.2x1.05	1.0x1.0x1.0	
Duration	5:03	7:02	7:22	5:34	4:35	6:08	4:31	8:31	
Scanners	Siemens Verio (3T), Siemens PRISMA (3T), Siemens Prisma Fit (3T), Siemens Skyra (3T), Siemens Aera (1.5T), Siemens Magnetom Vida (3T)			Philips Ingenia (3T) & Philips Achieva (3T)			GE Signa (1.5T), GE Signa PET/MR (3T)		

For each sequence, derived data, common uses and average vendor's parameters are given. The shown acquisition parameters are acquisition voxel size (in mm), echo time (TE, in ms), repetition time (TR, in ms), phase encoding direction(PEd), number of B = 0 volumes (N_B0), number of B = 1000 volumes (N_B1000), FLAIR = fluid attenuated inversion recovery; A > P = anterior to posterior; NA = not applicable.

Building on findings from studies like Warrington et al. (2023), the preprocessing steps implemented ensure that the variability introduced by scanner hardware and acquisition differences is minimized before harmonisation. This approach strengthens the reliability of multi-site analyses by ensuring that observed differences in IDPs reflect true biological variations rather than methodological artifacts.

The harmonisation process is particularly critical for diffusion MRI (dMRI), where small inconsistencies can disproportionately affect metrics of white matter microstructure. In the PREVENT study, TOPUP-based distortion correction could not be applied because b=0 images with opposite phase encoding directions (e.g., AP and PA) were not acquired, which is a prerequisite for this method. While TOPUP is compatible with single-shell data, the absence of the reverse-phase encoding scans limited its applicability in PREVENT. In contrast, EPAD's multi-vendor setup introduced variability in dMRI acquisition, with differences in b-values, gradient directions, and phase encoding direction among scanners. These protocol differences necessitated tailored preprocessing to mitigate artifacts before harmonisation.

3.5.6. Conclusion

Harmonising multi-site imaging data is essential for leveraging the full potential of large datasets like EPAD and PREVENT. While harmonisation techniques can reduce variability, the importance of robust preprocessing cannot be overstated, as it ensures a standardized starting point for all analyses. By incorporating insights from Warrington et al. (2023) and transparently reporting acquisition protocols, this thesis addresses the inherent challenges of multi-site neuroimaging studies. This rigorous approach enhances the validity of findings, contributing to the broader understanding of TBI's role in neurodegeneration and mid-to-late-life cognitive decline.

3.6. Harmonisation of imaging data

3.6.1 Overview of candidate tools and techniques

3.6.1.1 Z-Score Normalization

This method entails normalising the data to get a mean of zero and a standard deviation of one. It is utilised to render data similar by eliminating scale discrepancies. Z-score normalisation is simple; nonetheless, it fails to address batch effects arising from varying acquisition techniques or scanner kinds. It is frequently employed in uncomplicated contexts where batch effects are negligible or when data from various batches do not require extensive integration.

3.6.1.2 Linear Mixed-Effects Model (LME)

LME models integrate site-specific random intercepts to account for inter-site variability in imaging data. This is especially pertinent in TBI research, because the effects of localised injury may change subtly among various groups. This may be crucial for managing variability in long term studies of TBI patients, aiding in the differentiation of true neurodegenerative alterations from site-induced variability.

3.6.1.3 LME with Age-Related Slopes

This methodology considers the interplay between age and site effects, which is essential in TBI research, as age can affect both the healing path and the likelihood of eventual neurodegeneration. This method may elucidate the variations in age-related cortical thickness changes across different locations in TBI patients, hence enhancing the comprehension of age as a determinant in TBI outcomes.

3.6.1.4 NeuroHarmonize

NeuroHarmonize is a data harmonisation methodology derived from the ComBat method, initially designed to rectify batch effects in genomic data, then modified to address scanner-related variability in multi-site neuroimaging investigations. It compensates for variations in scanner technology, acquisition techniques, and other site-specific elements while maintaining physiologically significant variability. The approach operates by modelling scanner effects as additive and linear, eliminating these effects while preserving the authentic underlying brain structure information. NeuroHarmonize can be utilised both cross-sectionally, ensuring comparability across various sites at a single time point, and longitudinally, accommodating repeated measures over time, thereby preserving within-subject variations and facilitating the precise monitoring of cerebral changes in extensive cohort studies. This approach is especially useful for its capacity to synchronise data across many sites and timepoints while maintaining biological signals pertinent to TBI and neurodegeneration (Fortin et al., 2018).

3.6.1.5 Challenges and Considerations

Implementing these harmonisation techniques in TBI research presents particular problems, notably the necessity to reconcile the correction of technical variability with the maintenance of therapeutically pertinent biological variability. Excessive correction may mask genuine variations attributable to TBI severity, whereas insufficient correction could result in erroneous interpretations of neurodegenerative patterns.

3.6.1.6 Conclusion

Harmonisation approaches, such as NeuroHarmonize, are essential in neuroimaging research, especially for studies examining the long-term impact of traumatic brain injury on neurodegeneration. These methodologies facilitate the comparability of data across several sites, hence enabling more reliable conclusions regarding the course of neurodegeneration post-TBI.

3.6.2 NeuroHarmonize

NeuroHarmonize was utilised to standardise neuroimaging data across many sites (Fortin et al., 2018). Fortin et al. (2018) demonstrated that NeuroHarmonize can be effectively utilised with MRI data, rendering it an essential instrument for studies such as EPAD and PREVENT, where accurate, longitudinal evaluation of cerebral alterations is vital for comprehending the advancement of neurodegenerative disorders and the aggravating influence of TBI.

3.6.2.1. Methodology

Implementation of NeuroHarmonize

NeuroHarmonize harmonisation is executed via statistical programming environments like Python. Essential factors during implementation encompass delineating the batch variables (e.g., scanner kinds, acquisition settings) and regulating covariates such as age, gender, and, in this case, TBI severity.

Detailed Mathematical Framework

NeuroHarmonize's mathematical model for adjusting neuroimaging data involves several key steps:

1) Data Modelling: Each neuroimaging data point (e.g., voxel intensity) from several batches (e.g., different scanners) is presumed to adhere to a normal distribution, with batch effects represented as alterations in the mean (location) and variance (scale) of these distributions.

2) Parameter Estimation:

Location (Mean) Adjustment: The mean shift associated with the batch impact is calculated for each batch. NeuroHarmonize employs an empirical Bayes approach to adjust individual batch means towards the overall grand mean. This reduction is especially beneficial in mitigating overfitting when batch sizes are minimal.

Scale (Variance) Adjustment: NeuroHarmonize estimates scale parameters for each batch, compensating for variability discrepancies among batches. This entails computing a pooled variance

estimate for each batch and adjusting individual variances towards this pooled estimate, utilising empirical Bayes techniques.

3) Data Adjustment: After estimating the batch-specific position and scale parameters, each data point is modified by eliminating the estimated batch effects. This process involves standardising the data within each batch using the estimated parameters and subsequently rescaling it to the overall grand normal deviation. This modification not only standardises the data across various batches but also minimises the potential for bias in later analyses due to non-biological variability.

General Formulation:

The observed imaging measure Y_{ij} for subject i and scanner j is modelled as:

$$Y_{ij} = X_{ij}\beta + g_j + \epsilon_{ij}$$

Where:

- X_{ij} represents the design matrix for covariates such as age, ,TBI severity, sex and other factors
- β is the vector of regression coefficients corresponding to these covariates
- g_j represents the scanner-related effect of scanner j
- ϵ_{ij} is the residual error term, capturing biological variability

In this model, NeuroHarmonize aims to remove yj, the scanner related effects, while preserving the residual error, which contains the meaningful biological information.

Application in Multi-Site Studies:

This approach has been extensively verified in large-scale, multi-site research, including the Alzheimer's Disease Neuroimaging Initiative (ADNI) and the UK Biobank. These investigations demonstrate that cross-sectional harmonisation efficiently reduces the impact of varying scanners, facilitating direct comparisons of neuroimaging results across multiple locations.

Fortin et al. (2018) revealed that cortical thickness measurements, after harmonisation via ComBat, could be consistently compared across 21 distinct scanners within the ADNI cohort. Alfaro-Almagro et al. (2018) similarly validated harmonisation methodologies in the UK Biobank dataset, which encompassed data from more than 10,000 subjects gathered from several imaging facilities.

3.6.2.2 Application to PREVENT and EPAD

Evaluating TBI Impact

The integration of NeuroHarmonize in EPAD and PREVENT allows researchers to refine their analysis of how TBI influences neurodegeneration progression. Harmonised data ensure that any observed differences in brain pathology are due to underlying disease processes or history of injury impacts rather than artifacts of imaging technology variations. Statistical analyses post-harmonisation can then robustly assess correlations between TBI history and neurodegenerative markers, providing insights into the biological impact of brain injuries. To compare scanner-related differences in total brain volume before and after harmonisation, a one-way ANOVA was conducted. This parametric test was chosen after confirming normality and homogeneity of variances using Shapiro-Wilk and Levene's tests, respectively. The p-values and effect sizes (η^2) reported in Table 3.4 reflect the outcome of these ANOVAs, indicating the extent of scanner-related variance in TBV prior to and following the application of NeuroHarmonize.

Table 3.4. Mean and SD of Total Brain volume before and after NeuroHarmonize by scanner

	Mean Total Brain Volume (TBV)	**TBV Standard Deviation**	**p-value**	**η^2**
Before NeuroHarmonize	1534361.93	82305.61830	**0.000**	0.115
After NeuroHarmonize	1534259.25	77309.18027	0.772	0.007

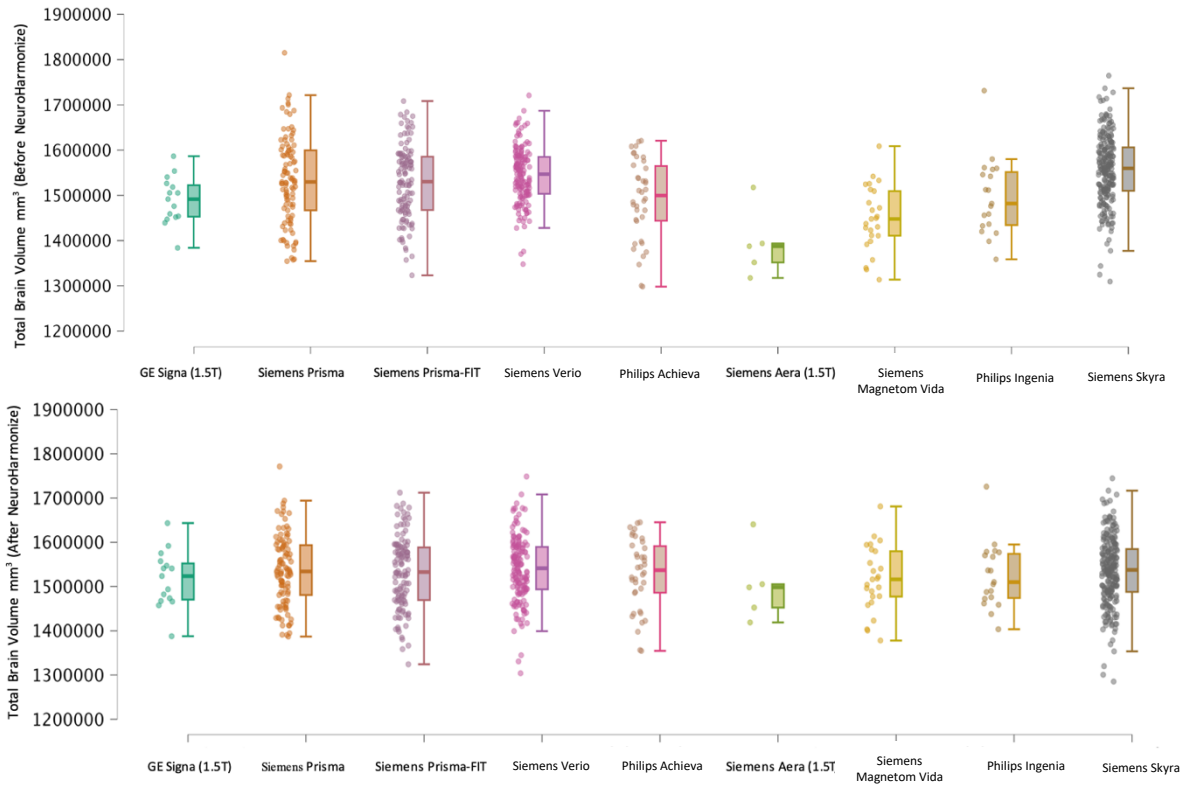


Figure 3.7. an example of NeuroHarmonize within PREVENT and EPAD. Boxplot of TBV by scanner type before and after NeuroHarmonize

Table 3.5. Mean and SD of Total Brain volume before and after NeuroHarmonize by severity group

Severity Group		**No head Injury (n=334)**	**Single mTBI (n=90)**	**Repeated mTBI (n=248)**	**Moderate/Severe TBI (n=40)**	**p-value**	**η^2**
Mean TBV (SD)	**Before NeuroHarmonize**	$1.544x10^{+6}$ (75444)	$1.520x10^{+6}$ (90446)	$1.536x10^{+6}$ (84233)	$1.449x10^{+6}$ (61672)	**<0.001**	0.07
	After NeuroHarmonize	$1.539x10^{+6}$ (72797)	$1.521x10^{+6}$ (84748)	$1.535x10^{+6}$ (79626)	$1.454x10^{+6}$ (77494)	**<0.001**	0.06

The table 3.5 presents the mean TBV and standard deviations for different severity groups (No Head Injury, Single mTBI, Repeated mTBI, and Moderate/Severe TBI) both before and after NeuroHarmonize. Group-level comparisons were assessed using one-way ANOVA to determine whether TBI severity groups differed in total brain volume before and after harmonisation. Assumptions of normality and homogeneity of variance were tested and satisfied. The calculated p-

values and effect sizes (η^2) highlights changes resulting from the harmonisation process. Before NeuroHarmonize, the effect size (η^2=0.07) indicated that 7.0% of the variance in TBV was explained by group differences, with a highly significant p-value (p<0.001) After harmonisation, the effect size decreased slightly to η^2=0.06, (p<0.001).

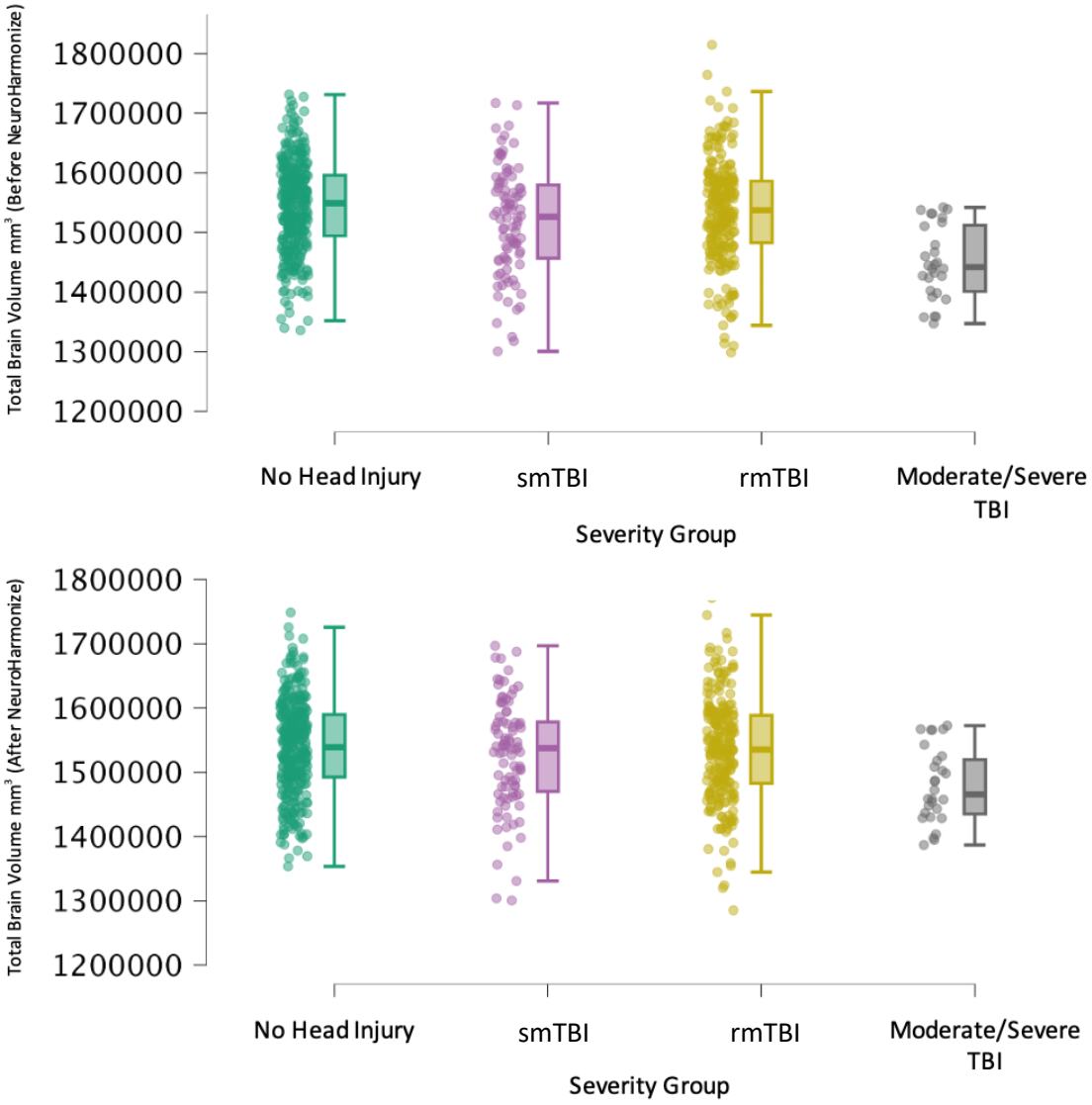


Figure 3.8. an example of NeuroHarmonize. Boxplot of TBV by severity group before and after NeuroHarmonize

These findings are critical for the robustness of the analysis when comparing groups. NeuroHarmonize is designed to minimize unwanted variability caused by scanner or site differences while preserving biologically meaningful variance. The slight reduction in effect size after harmonisation suggests that

some variability tied to group differences may have been attenuated, though the strong statistical significance indicates that the underlying group differences remain robust. This supports the validity of comparing severity groups after harmonisation, ensuring that observed differences are more likely attributable to biological variation rather than technical confounds. Going forward, this robustness strengthens confidence in any comparisons of imaging outcomes between severity groups, particularly when addressing subtle differences that might be influenced by scanner or site effects. Comprehensive pre and post harmonisation boxplots for all IDPs are collated in appendix 3.

3.6.2.3 Longitudinal Harmonisation Using NeuroHarmonize

In addition to cross-sectional harmonisation, longitudinal NeuroHarmonize was applied to handle neuroimaging data collected over multiple time points. Longitudinal harmonisation extends the cross-sectional model by incorporating within-subject variability over time, ensuring that repeated measures data are comparable across scanners and time points while preserving biologically meaningful changes.

3.6.2.3.1 Technical Details of Longitudinal Harmonisation

Longitudinal NeuroHarmonize introduces a subject-specific random effect to account for the repeated measures design. This extension of the ComBat model enables the separation of scanner-related effects from true biological changes over time.

General Formulation:

In longitudinal studies, the imaging measure Y_{ijk} for subject i, scanner j, and time point k is modelled as:

$$Y_{ijk} = X_{ijk}\beta + g_j + \zeta_i + \epsilon_{ijk}$$

where:

- X_{ijk} is the design matrix for covariates.
- β represents the regression coefficients.

- g_i represents the scanner-related effect.
- ζ_i is the subject-specific random effect, capturing temporal correlations in repeated measures.
- ϵ_{ijk} is the residual error term, representing the within-subject biological variation over time.

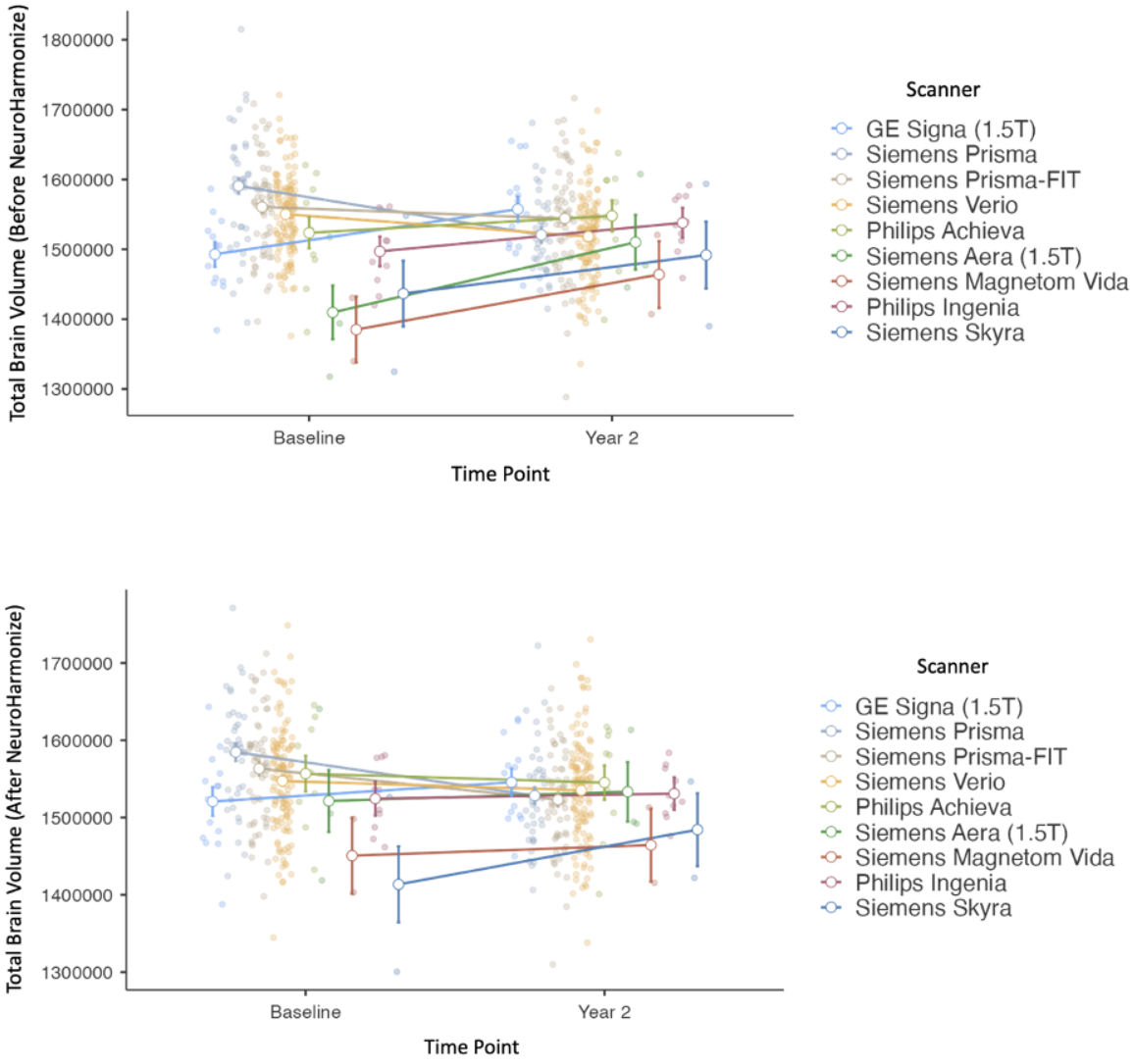


Figure 3.9. Scatterplot of longitudinal TBV by scanner before and after NeuroHarmonize

Table 3.6. Mean and SD of Total Brain volume before and after NeuroHarmonize by severity group over time

		Mean Total Brain Volume (TBV)	**TBV Standard Deviation**	**p-value**	**η^2**
Before NeuroHarmonize	Baseline	1534361.93	82305.61830	**0.015**	0.102
	Year 2	1537021.30	65584.94051		
After NeuroHarmonize	Baseline	1534259.25	77309.18027	0.368	0.044
	Year 2	1525218.19	65626.32737		

To evaluate longitudinal changes in TBV, repeated-measures ANOVA was employed, comparing baseline and year 2 measurements across timepoints and accounting for within-subject dependencies. Tests were conducted before and after harmonisation. Statistical assumptions were verified, and effect sizes (η^2) indicate the proportion of within-subject variance explained by time.

3.6.2.4 Longitudinal Data in Multi-Site Studies

Longitudinal harmonisation has been effectively implemented in extensive neuroimaging studies, including the Alzheimer's Disease Neuroimaging Initiative (ADNI). Jack et al. (2019) showed that longitudinal harmonisation enhances the precision of monitoring neurodegenerative alterations, including hippocampus atrophy, over various time intervals, despite data being collected on disparate scanners.

3.6.2.5 Application to this study

This study required longitudinal harmonisation to analyse the temporal course of neurodegenerative alterations in participants with a history of TBI. By adjusting for scanner-related variability across various time points, we confirmed that the alterations in brain structure were due to biological processes rather than technical artefacts.

3.6.3 Necessity of Harmonising FA and MD Values

Despite initial ANOVA findings revealing no significant scanner-related variability in fractional anisotropy (FA) and mean diffusivity (MD) values, harmonisation of these metrics using NeuroHarmonize was subsequently conducted to guarantee consistency and methodological rigour throughout the neuroimaging assessments in this thesis.

There are several reasons why harmonising FA and MD values was essential:

1. Consistency Across Imaging Metrics: Standardising FA and MD values in conjunction with structural volumetric data guaranteed that all neuroimaging measures were processed

through a uniform pipeline. This consistency reduces methodological differences, enabling better comparisons across modalities and improving the dependability of the results.

2. Comprehensive Reduction of Scanner Effects: Although ANOVA findings indicated negligible scanner impact, harmonisation acts as a precaution against any subtle, non-significant fluctuations that may affect the sensitivity of subsequent studies. This is especially crucial in exploratory research, where nuanced effects may go unnoticed yet could introduce undesirable noise or bias.
3. Alignment with Best Practices in Multi-Site Studies: NeuroHarmonize has emerged as a recognised technique for addressing site effects in multicentre investigations, where even minimal scanner variability can disrupt precise biological interpretation. This study fits with standard practices by harmonising FA and MD values, hence confirming the validity of cross-site comparisons.
4. Consistency in Longitudinal Analyses: Due to the longitudinal design of the study, standardising FA and MD values guarantees that subsequent analyses over time are not influenced by any scanner-related discrepancies that may occur when analysing different timepoints.

In conclusion, the application of NeuroHarmonize to FA and MD data enhances the robustness and reproducibility of this study's findings, confirming that any identified patterns arise from biological differences rather than unrecognised scanner-related noise. This harmonisation method enhances the trustworthiness of the findings, especially in assessing minor neurodegenerative alterations linked to TBI.

3.6.4 Challenges and Considerations

3.6.4.1 Site-Specific Variability and Residual Effects

A primary problem associated with NeuroHarmonize is the possibility of residual site-specific variability. NeuroHarmonize rectifies scanner-related discrepancies by employing an empirical Bayes methodology to model and mitigate site effects. Nonetheless, in certain instances, non-linear or higher-order discrepancies between scanners may remain inadequately addressed. These residual effects may induce minor biases, particularly in multi-site investigations when image acquisition parameters differ considerably. This poses a potential danger of nuanced yet significant site-related discrepancies persisting in the harmonised data, which may impact the validity of subsequent analysis. To address this, I supervised the collection and verification of detailed site-specific metadata for correctness, facilitating more precise modelling of site effects.

3.6.4.2 Balancing Between Over-Correction and Under-Correction

A significant issue lies in achieving the *correct balance* between excessive correction and insufficient correction during the implementation of harmonisation. Excessive correction may eliminate biologically significant variance, thereby reducing the capacity to identify modest neurodegenerative alterations linked to TBI. Conversely, insufficient correction may result in residual scanner-related variability, thereby introducing noise or bias into the analysis. Attaining the appropriate *balance* is essential, particularly in research where nuanced biological indicators, such as those associated with TBI, are of primary concern. To prevent over- or under-correction, I conducted an ANOVA to assess significance and effect size before and after the harmonisation procedure, comparing essential neuroimaging measures to evaluate the retention of biological variation. These evaluations guaranteed the preservation of significant neurobiological signals, especially those associated with TBI, while reducing site-specific variability.

3.6.4.3 Generalizability of Harmonisation to New Sites or Cohorts

While NeuroHarmonize has proven effective in harmonising the PREVENT and EPAD datasets in this study, its generalizability to other cohorts or sites remains an open question. The model was tailored to correct site-specific variability in these particular datasets, but applying NeuroHarmonize to new datasets with different scanner types, acquisition protocols, or participant characteristics may yield less reliable results. This raises concerns about the extent to which NeuroHarmonize can be applied to datasets beyond those it was initially developed for.

3.6.4.4 Dependence on Accurate Metadata

The efficacy of NeuroHarmonize in compensating for scanner-related discrepancies is significantly reliant upon the accessibility and precision of metadata, encompassing details regarding the scanner hardware, acquisition parameters, and site-specific attributes. If metadata are deficient, erroneous, or inaccessible, the harmonisation process may fail to adequately mitigate site-related variability, resulting in biassed or incomplete harmonisation. This is a crucial factor when dealing with legacy or historical datasets, where metadata may have been inconsistently documented. To guarantee optimal harmonisation, I meticulously cross-referenced various information sources for each site, scanner, and acquisition parameter. While metadata were carefully checked for the PREVENT and EPAD cohorts, future studies should emphasize rigorous metadata collection standards and implement quality control checks during data acquisition.

3.6.4.5 Conclusion

Implementing NeuroHarmonize harmonisation in multicentre neuroimaging studies like EPAD and PREVENT significantly enhances data quality and comparability. This approach improves our capacity to perform dependable multi-site and multi-project studies, essential for monitoring the advancement of neurodegenerative disorders and comprehending the enduring impacts of TBI. NeuroHarmonize enhances the reliability and comparability of neuroimaging data in multi-site studies, facilitating the

evaluation of whether individuals with a history of traumatic brain injury exhibit greater evidence of neurodegenerative change compared to those without. While this approach cannot establish direct causal relationships, it strengthens exploratory analyses within cohorts at risk for AD. In Chapter 4, I will validate my harmonisation results by replicating them and comparing my data with that from an other study, therefore effectively reproducing the study to verify the dependability of my harmonisation procedure.

3.6.5 Comparative Analysis of NeuroHarmonize and Z-Score Normalization in Neuroimaging Data Harmonisation

Conventional techniques such as z-score normalisation, which standardises data within a single batch to eliminate scale discrepancies, frequently do not account for more profound, systematic variations arising from diverse data acquisition sources, including varying MRI scanners and protocols. Unaddressed variations may introduce substantial biases, thereby compromising the outcomes of the study. This paper argues for the advantages of NeuroHarmonize harmonisation compared to z-score normalisation in relevant contexts. NeuroHarmonize improves data reliability and scientific validity through an empirical Bayes framework, supporting its use in multicentre neuroimaging studies, especially regarding data from the EPAD and PREVENT studies.

3.6.5.1 Theoretical Foundations

Z-Score Normalization

Z-score normalisation is a common statistical technique that standardises data by adjusting each data point's mean to zero and its standard deviation to one. This method is essential in neuroimaging for standardising voxel-wise intensity values across subjects from various groups. Utilising z-score normalisation enables researchers to compare neuroimaging data across various study populations, thereby aiding in the detection of patterns independent of data scaling variations (Lazar et al., 2008). Z-score normalisation effectively addresses scale differences; however, it fails to rectify more complex

batch effects frequently encountered in multicentre neuroimaging studies. NeuroHarmonize harmonisation transcends simple standardisation.

3.6.5.2 Methodological Comparison

Applicability to Neuroimaging

Z-score normalisation is effective for normalising data within a single batch; however, its simplicity may pose limitations in multicentre studies. The Z-score fails to consider batch effects, which frequently occur in neuroimaging datasets obtained from various scanners or locations. Batch effects can result in substantial biases if not adequately addressed.

NeuroHarmonize is designed to specifically address inter-site variations by modelling both additive and multiplicative batch effects. NeuroHarmonize is especially effective for neuroimaging data, as variations in scanner types and imaging protocols can significantly influence the assessment of brain activity or structure (Fortin et al., 2017).

3.6.5.3 Challenges and Limitations

NeuroHarmonize presents specific benefits; however, it also faces certain challenges. This method presupposes that batch effects are identifiable and can be modelled, which is not universally applicable. Z-score normalisation does not necessitate specific assumptions, rendering it more broadly applicable; however, it may lack precision regarding batch effects.

3.6.5.4 Conclusion

To summarise, while both NeuroHarmonize and z-score normalisation are useful methods for data harmonisation in neuroimaging investigations, NeuroHarmonize's capacity to address complicated inter-site heterogeneity makes it the better choice for multicentre neuroimaging studies. Future research should focus on improving NeuroHarmonize's versatility and ease of implementation, so that it can be used across a wide range of neuroimaging datasets without considerable customisation.

3.7 General Conclusion

In this chapter, we used PCA, advanced preprocessing techniques and NeuroHarmonize to successfully integrate and harmonise cognitive and neuroimaging data from the PREVENT and EPAD populations. The harmonisation method for cognitive data included applying PCA to minimise dimensionality and align cognitive measures across both cohorts, allowing tests from different batteries to be directly compared. Similarly, the neuroimaging data were standardised, and site-specific variances were reduced while retaining critical biological signals associated with TBI and neurodegeneration.

This full harmonisation of cognitive and neuroimaging data is critical for establishing trustworthy and comparable findings across cohorts. To demonstrate the reliability of this process, Chapter 4 will replicate the findings of a well-known study on the effects of moderate to severe TBI on cognitive performance and brain shrinkage. By applying our harmonisation framework to this replication study, we hope to show that harmonised datasets could offer consistent and comparable results, hence supporting the validity of our approach. The successful replication of these findings will give more evidence that our harmonisation technique accurately reflects the underlying neurodegeneration and cognitive abnormalities associated with TBI, confirming its suitability for future multi-site neuroimaging research.

Chapter 4: Replication Study of Neurodegeneration Patterns Post Moderate/Severe TBI

4.1 Introduction

As outlined in Chapter 1, TBI is a common neurological disorder associated with long-lasting effects, such as cognitive decline and neurodegeneration. This chapter endeavours to replicate the findings by Graham et al. (2023), who delineated specific patterns of neurodegeneration subsequent to moderate to severe TBI. This replication study seeks to validate the capacity of our harmonised dataset to reproduce the identified patterns by employing the harmonisation techniques described in Chapter 3, utilising data from the PREVENT and EPAD cohorts.

Moderate to severe TBI correlates with extensive damage to both grey matter (GM) and white matter (WM) (Johnson et al., 2018; Smith et al., 2015). White matter comprises myelinated axons that interconnect various brain regions, thereby enabling communication among them. Diffuse axonal injury (DAI) represents a prevalent and debilitating consequence of moderate to severe TBI resulting from damage to axons. DAI raises significant concerns due to its association with enduring cognitive deficits, despite the lack of apparent brain damage detectable through standard imaging methods (Johnson et al., 2013; Bigler & Maxwell, 2012). Disruption of connectivity among brain regions due to diffuse axonal injury (DAI) may lead to deficits in executive function, memory, attention, and various other cognitive domains.

Longitudinal studies indicate that TBI can result in considerable brain atrophy, especially in white matter regions (Graham et al., 2023). The corpus callosum, the largest white matter structure in the brain, is essential for interhemispheric communication and is notably susceptible to damage after TBI (Bigler, 2013; McAllister et al., 2001). Additional white matter tracts, including the corticospinal tracts

and the superior longitudinal fasciculus, are frequently impacted (Graham et al., 2023; Farbota et al., 2012). TBI is associated with grey matter atrophy, particularly in regions such as the hippocampus and prefrontal cortex, in addition to WM atrophy (Ariza et al., 2006; Sidaros et al., 2009). The degeneration of these regions is closely linked to cognitive decline, as they are essential for memory, learning, and executive function (Monti et al., 2013; Kraus et al., 2007).

The relationship between TBI and neurodegenerative diseases, especially AD, has emerged as a significant area of investigation. Research indicates that individuals with a history of moderate to severe TBI face a heightened risk of developing AD in later life (Fleminger et al., 2003; Nordstrom et al., 2014; Wilson et al., 2017). This may be partially attributed to the potential of TBI to induce the accumulation of amyloid-beta plaques and tau tangles, which are characteristic pathologies of Alzheimer's disease. TBI is believed to worsen neuroinflammation, potentially facilitating the advancement of neurodegenerative diseases.

Due to these complexities, neuroimaging has emerged as a crucial instrument for examining the long-term consequences of TBI. Advanced neuroimaging techniques, including DTI and subcortical volumetric MRI, have yielded significant insights into the structural alterations in the brain post TBI (Bigler, 2013; Niogi & Mukherjee, 2010; Palacios et al., 2020). Volumetric MRI has been employed to assess brain atrophy longitudinally, enabling researchers to monitor the advancement of neurodegeneration in both grey and white matter areas. Longitudinal studies, including the one by Graham et al. (2023), utilised volumetric MRI to discern specific atrophy patterns in TBI patients, underscoring the significance of WM atrophy as a critical indicator of neurodegeneration in this group.

This chapter seeks to replicate the findings of Graham et al. (2023) utilising harmonised data from the PREVENT and EPAD cohorts. This replication study concentrates on participants with moderate to severe TBI, as delineated by the inclusion criteria established in our prior harmonisation efforts. We

compare our results with those of Graham et al. to validate the robustness of our harmonisation process and to demonstrate that our harmonised dataset accurately captures the neurodegenerative processes associated with TBI. Nonetheless, like any harmonisation process, further validations across diverse cohorts and data types will be essential to comprehensively determine the generalisability and robustness of our methodology. This study is a significant component of a larger initiative aimed at validating the reliability of harmonised cognitive and neuroimaging datasets in traumatic brain injury research.

4.2 Replication Study Design

4.2.1 Original Study Overview

A seminal study on the long-term impact of TBI on brain structure was carried out by Graham et al. in 2023 (Graham et al., 2023). The study looked at changes in brain volume over a two-year period using longitudinal data from 55 patients with moderate to severe TBI. The authors employed volumetric MRI to assess atrophy in grey matter and white matter. The selected regions are recognised for their susceptibility to damage after TBI, and prior research indicates that they may significantly contribute to the cognitive deficits seen in TBI patients.

Graham et al. also examined grey matter degeneration in the hippocampus, prefrontal cortex, and temporal lobes. These regions are essential for memory, learning, and executive function, and their degeneration is strongly linked to cognitive decline. The scientists discovered that TBI patients had considerable shrinkage in both grey and white matter, with the hippocampus showing the most extensive atrophy. These findings were in line with prior studies, which had suggested that TBI leads to widespread brain atrophy, particularly in regions involved in cognitive function.

One of the most important discoveries of the Graham et al. investigation was the finding of a specific pattern of white matter atrophy in TBI patients. The scientists discovered that the corpus callosum,

the brain's largest white matter structure, showed considerable atrophy in TBI patients, with the degree of atrophy corresponding to the severity of the damage. TBI patients showed substantial degeneration in the corticospinal pathways, superior longitudinal fasciculus, and corpus callosum. These findings imply that white matter atrophy is a significant component of neurodegeneration following TBI, and that disruption to white matter pathways may explain the cognitive abnormalities found in TBI patients.

4.2.2 Justification for Replication

Replicating Graham et al.'s findings is critical for a number of reasons. First, replication is an essential part of the scientific method (Poldrack et al., 2017). By reproducing prior studies' findings, we can confirm their validity and ensure that they are not the result of chance or methodological flaws. Second, replication is especially critical in neuroimaging, where differences in data collecting and analysis methodologies might result in inconsistencies. Replicating the findings of Graham et al. (2023) is especially essential in the context of this thesis since it presents a crucial test of the harmonisation procedures used on the PREVENT and EPAD data sets. Neurodegeneration after moderate to severe TBI is a complex process, and by validating our findings in a new dataset, we want to prove the harmonisation process' generalisability. Furthermore, the replication assures that critical neurobiological indicators associated with TBI, such as white matter degradation, are consistently visible across diverse populations.

Furthermore, this replication study will help to further the area of TBI research by giving additional evidence of TBI's long-term impacts on brain structure. While multiple studies have revealed that TBI causes widespread brain atrophy, notably in white matter regions, the precise processes behind this neurodegeneration remain unclear. By reproducing Graham et al.'s findings, we can provide more support for the concept that white matter atrophy is a critical hallmark of neurodegeneration following TBI, and that damage to white matter tracts may play a central role in the cognitive

abnormalities found in TBI patients. As previously indicated, this replication provides good preliminary proof of the process's effectiveness; nonetheless, further research will be required to expand its generalisability.

4.2.3 Study Overview

This replication study employed harmonised data from the PREVENT and EPAD cohorts to investigate patterns of brain atrophy in individuals with moderate to severe TBI. We assessed atrophy in both grey and white matter regions, emphasising critical white matter networks like the corpus callosum, corticospinal tracts, and superior longitudinal fasciculus. Furthermore, we investigated atrophy in grey matter areas including the hippocampus, prefrontal cortex, and temporal lobes.

Our primary aim was to corroborate the findings of Graham et al. by illustrating that TBI patients display considerable atrophy in white matter tracts. Our objective was to reproduce the observation that traumatic brain injury patients demonstrate substantial shrinkage in grey matter regions, notably the hippocampus and the prefrontal cortex. Ultimately, we sought to reproduce the cognitive findings of Graham et al. by investigating the correlation between brain atrophy and cognitive deterioration in TBI patients.

4.3 Methodology

4.3.1 Data Acquisition and Cohorts

This replication study employed neuroimaging and cognitive data from the PREVENT and EPAD cohorts, as detailed in previous chapters. Both groups comprise patients susceptible to neurodegeneration, emphasising moderate to severe traumatic brain injury in this investigation. Data were gathered from various locations employing distinct MRI scanners, acquisition processes, and cognitive assessments, requiring harmonisation approaches to ensure dataset comparability.

4.3.2 Neuroimaging standardisation procedure

This replication study employed the harmonisation technique described in Chapter 3, utilising NeuroHarmonize to mitigate site-specific variability within the PREVENT and EPAD cohorts. NeuroHarmonize adjusts for discrepancies in scanner hardware, acquisition settings, and site-specific variability through an empirical Bayes methodology. Utilising this harmonisation technique, we aimed to ensure that data from several sites could be aggregated and evaluated collectively with minimal loss of biologically meaningful signal, as demonstrated in previous applications (Fortin et al., 2018). Harmonisation enabled the comparison of essential neuroimaging indicators associated with white matter integrity and grey matter atrophy between the PREVENT and EPAD cohorts. The selection of NeuroHarmonize was based on its capacity to accommodate site-specific heterogeneity while preserving the biological integrity of neuroimaging data. This was essential for preventing scanner discrepancies from skewing the results, especially in multi-site TBI studies, where inter-scanner variability could mask minor neurodegenerative alterations.

4.3.3 Cognitive Data Standardisation

Alongside neuroimaging harmonisation, we standardised cognitive data by PCA, as elaborated in Chapter 3. Principal Component Analysis (PCA) was utilised to diminish the dimensionality of cognitive test results (Jolliffe & Cadima, 2016), facilitating the comparison of cognitive performance across the several batteries performed in the PREVENT and EPAD trials. This harmonisation enabled the integration of cognitive data into a unified analytical framework, facilitating the evaluation of the correlation between cognitive decline and neurodegeneration in TBI patients.

4.3.4 Adjustment for Covariates

Several covariates were included in our analyses to account for demographic and physiological differences that could influence both cognitive performance and brain atrophy. Age, sex, years of

education and APOE4 status were included as covariates in the linear mixed-effects models used for statistical analysis.

4.3.5 Dataset Overview and Variables

The dataset was extracted from the PREVENT and EPAD cohorts, consisting of individuals who met the inclusion criteria for moderate/severe TBI as outlined in Chapter 3. Participants were required to have both baseline and follow-up neuroimaging data, as well as comprehensive cognitive assessments. The variables analysed in this study included:

- Cognitive Data: Baseline and Year 2 cognitive scores were included, covering domains such as attention, memory, and language.
- Neuroimaging Data: Volumetric data such as grey and white matter volumes were extracted from MRI scans.
- Demographics: Age, sex, years of education and APOE4 status were included as covariates to control for individual differences in risk and demographic factors.

4.3.6 Statistical Analysis

Volumetric Changes: Calculated by comparing harmonised neuroimaging metrics at baseline and at Year 2. Differences were computed by subtracting baseline values from Year 2 values to assess longitudinal changes in brain volume and structure.

Group Comparisons: Independent t-tests and ANCOVA were used to compare TBI and no-head-injury groups, adjusting for covariates such as age, sex, education, and APOE4 status.

DTI Metrics: Differences in FA and MD were assessed for key white matter tracts using ROI-based analysis.

Correction for Multiple Comparisons: To account for the multiple tests performed in this study, we applied the Bonferroni correction. This strategy controls for Type I errors, confirming that the substantial findings reported in our study were not the result of chance. The adjustment is especially significant in neuroimaging investigations, where numerous comparisons between brain regions might result in increased false positive rates.

4.4 Results

Table 4.1. Summary of study population characteristics by study and severity group

	Graham et al., 2023		PREVENT & EPAD	
	HC (n=23)	**TBI+ (n=48)**	**No head injury (n=408)**	**Moderate/Severe TBI (n=43)**
Age, years, median	68.5	40.0	56.0	61.0
Education, years, mean (SD)	17.3 (3.6)	17.3 (3.9)	17.0 (3.8)	15.0 (2.5)
Gender (% female)	60	60	63.6	64.2
Race (% Caucasian)	85.2	83.0	97.1	96.2

4.4.1 Demographic and Clinical Characteristics

The demographic characteristics of the groups revealed some key differences that may influence both cognitive outcomes and brain structure. The Moderate/Severe TBI group had the lowest mean years of education (15.0 ± 2.5 years), which was significantly lower than the No head injury group (17.0 ± 3.8). Lower educational attainment is often linked to reduced cognitive reserve, suggesting that this group may be more vulnerable to cognitive decline following TBI.

4.4.2 Volumetric Analysis

Table 4.2. Baseline and longitudinal brain volumes (ratio total intracranial volume [TICV]) by study and severity group

	Graham et al., 2023		PREVENT & EPAD	
	HC (n=23)	**TBI+ (n=48)**	**No head injury (n=408)**	**Moderate/Severe TBI (n=43)**
Baseline Volume, median (IQR)				
TBV	0.81 (0.05)	0.76 (0.06)	0.76 (0.07)	0.72 (0.06)
GM	0.48 (0.02)	0.45 (0.04)	0.45 (0.05)	0.42 (0.01)
WM	0.33 (0.02)	0.31 (0.03)	0.31 (0.02)	0.30 (0.05)
Change after 2 years				
TBV	0.1 (0.6)	-0.3 (0.5)	0.1 (0.9)	-0.6 (0.5)
GM	0.0 (0.5)	-0.2 (0.5)	0.3 (0.1)	-0.8 (0.8)
WM	0.1 (0.7)	-0.3 (0.7)	0.1 (0.3)	-0.2 (0.9)

Total Brain Volume (TBV)

At baseline, the moderate/severe TBI group (0.72 ± 0.06) exhibited lower total brain volumes compared to the no head injury group (0.76 ± 0.05) consistent with Graham et al findings. A group comparison using independent sample t-test confirmed this difference was statistically significant ($p = 0.002$, Cohen's $d = 0.73$). This suggests that individuals with a history of TBI may have a reduced brain reserve, which could predispose them to accelerated atrophy as they age. The reduction in TBV in the moderate/severe TBI group is consistent with previous findings linking TBI to early neurodegenerative processes.

Over the two-year follow-up period, the moderate/severe TBI group experienced the most significant decline in TBV (-0.6 ± 0.5), compared to a slight increase in the no head injury group (0.3 ± 0.6), in line with the work from Graham et al. The group x time interaction was also significant $p = 0.008$, $\eta^2 = 0.06$. This decline in TBV suggests a large and clinically meaningful impact of TBI on brain volume loss.

Grey Matter Volume

At baseline, the moderate/severe TBI group exhibited significantly lower grey matter volume (GMV) (0.42 ± 0.01) compared to the No head injury group (0.45 ± 0.05), $p < 0.001$, Cohen's $d = 0.75$. Which may reflect the early effects of TBI on brain structure. Over the two-year period, the moderate/severe TBI group showed a significant decline in GMV (-0.8 ± 0.8), compared to a slight increase in the no head injury group (0.3 ± 0.1), $p < 0.01$, $\eta^2 = 0.05$. Though fine-grained regional analysis was limited to predefined ROIs such as the hippocampus; voxel-wise or atlas wide parcellations were not conducted.

White Matter Volume

White matter volume (WMV) also showed a notable decline in the moderate/severe TBI group (-0.2 ± 0.9), while the no head injury group exhibited a modest increase (0.1 ± 0.3). This group difference was statistically significant ($p = 0.036$), with a small-to-moderate effect size (Cohen's $d = 0.48$). The decline in WMV in the TBI groups is consistent with widespread white matter degeneration following TBI, likely reflecting DAI, which disrupts long-range communication between brain regions. Previous research suggests that key tracts like the corpus callosum and superior longitudinal fasciculus are particularly vulnerable, which could explain the observed cognitive and motor deficits.

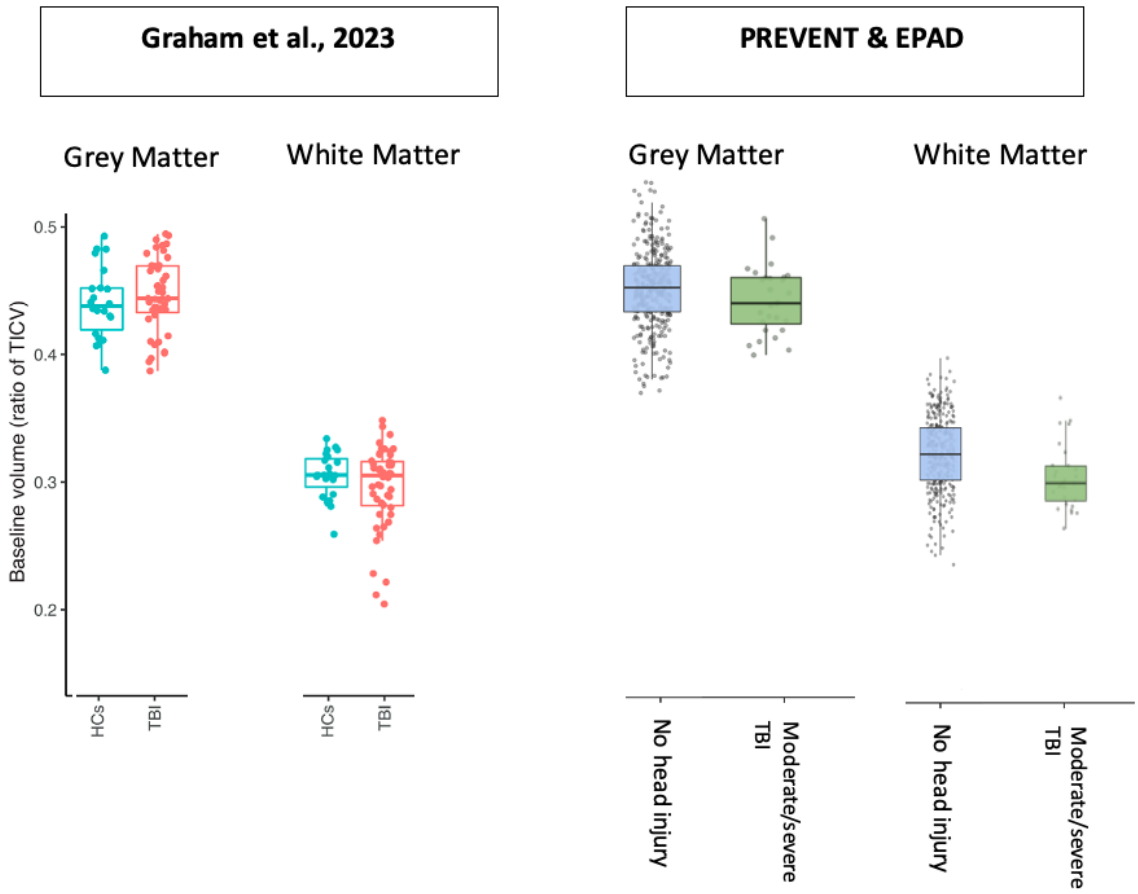


Figure 4.1. Grey and White matter boxplots separated by study and severity group

4.4.3 DTI analysis

The DTI analysis revealed microstructural changes consistent with diffuse axonal injury (DAI), replicating and extending findings from Graham et al. (2023). Independent samples t-tests were conducted with a Bonferroni correction applied to control for multiple comparisons (adjusted $\alpha = 0.0083$). Below are the findings from the independent samples t-tests:

Significant FA Reductions:

- Anterior corona radiata (bilaterally): $p < 0.001$.
- Splenium of the corpus callosum: $p = 0.007$.
- Optic radiations (bilaterally): $p < 0.001$.

Non-Significant Findings:

- Genu of the corpus callosum: FA reductions approached significance ($p = 0.074$).
- Superior longitudinal fasciculus: No significant differences observed

Cognitive Outcomes

Our analysis revealed significant declines in memory and attention over the two-year period among participants with moderate/severe TBI. Specifically, the mean reduction in memory scores was 15%, which is comparable to the 17% decline reported by Graham et al. (2023). Due to the unavailability of time-since-injury information, we are unable to investigate whether impairments change as a function of the post-injury interval.

4.5 Discussion

4.5.1 Interpretation of Volumetric Changes

Our findings indicate a significant decline in both grey and white matter volumes in the moderate/severe TBI group, aligning with previous studies that document brain atrophy following moderate to severe traumatic brain injury. This suggests that TBI may initiate an accelerated neurodegenerative process, particularly in regions such as the hippocampus and prefrontal cortex, which are critical for memory and executive function.

The decline in white matter volume further supports the notion of DAI as a central mechanism in TBI-related neurodegeneration. Although specific tracts were not measured, the overall reduction in white matter volume is consistent with previous literature suggesting that long-range white matter pathways—such as the corpus callosum and superior longitudinal fasciculus—are vulnerable to injury. These tracts are essential for interhemispheric communication and higher-order cognitive processing, explaining the cognitive deficits observed in the moderate/severe TBI group.

4.5.2 DTI findings

These findings replicate some of the key results from Graham et al. (2023), specifically in regions such as the anterior corona radiata, cingulum, and splenium of the corpus callosum. The significant FA reductions in the optic radiations and midbrain cerebellum further underscore the vulnerability of these tracts to DAI.

However, some discrepancies were noted:

- **Corpus Callosum**: While significant reductions were observed in the splenium, the genu differences only approached significance, differing from the referenced study's findings of global callosal vulnerability.
- **Cingulum**: The unexpected increase in FA in the right cingulum may reflect compensatory mechanisms, cohort variability, or methodological differences.

- **Superior Longitudinal Fasciculus**: The absence of significant differences suggests variability in tract-specific sensitivity to injury.

4.5.3 Integration with Structural Data

The structural analyses in this chapter demonstrated reduced grey matter volumes in TBI patients, particularly in regions like the hippocampus. The microstructural changes observed in the anterior corona radiata and splenium of the corpus callosum complement these findings, suggesting that diffuse axonal injury underpins both structural atrophy and functional impairment.

4.5.4 Implications for Neurodegeneration

The FA reductions observed in the anterior corona radiata, splenium, and optic radiations align with the hypothesis that DAI contributes to progressive neurodegeneration and cognitive decline in TBI patients. These regions are implicated in executive function, memory, and visual processing, highlighting the functional consequences of these injuries.

4.5.5 Cognitive and Functional Implications

While cognitive measures were not directly included in this analysis, the observed volumetric reductions in both grey and white matter are likely contributing factors to cognitive decline, particularly in memory, attention, and executive function. For instance, hippocampal atrophy has been closely linked to memory impairments in previous studies, suggesting that grey matter loss in the moderate/severe TBI group may explain deficits in memory performance observed in similar populations. Additionally, white matter degeneration, particularly in tracts responsible for motor control and executive function, likely contributes to impairments in processing speed and attentional regulation.

While replication was successfully implemented for the neuroimaging harmonisation using a published dataset (Graham et al., 2023), a comparable replication analysis was not conducted for the

cognitive harmonisation. This decision was based on the lack of a suitable external dataset that matched the specific combination of cognitive domains, harmonisation procedures, TBI stratification, and population characteristics found in this study. Most available datasets use different cognitive batteries, do not include TBI history, or would have required the development of an entirely new harmonisation framework. Such an approach would have constituted a new exploratory analysis rather than a formal replication. Instead, internal validation methods were employed, including assessments of score distributions, correlations between cognitive domains, and expected associations with age and education. These checks provided support for the robustness of the harmonised cognitive scores. Future research may benefit from incorporating a third cohort that shares cognitive and imaging features, enabling replication of both cognitive and neuroimaging findings in parallel.

4.5.6 Clinical Implications

Our findings underscore the importance of monitoring both grey and white matter integrity in individuals with a history of moderate to severe TBI. The significant declines in brain volume observed in the moderate/severe TBI group suggest that these individuals are at elevated risk for long-term neurodegeneration. Importantly, these changes in brain structure may precede overt cognitive and functional decline, indicating a potential window for early intervention.

Interventions aimed at preserving white matter integrity, such as cognitive rehabilitation programs and physical therapy, could play a crucial role in mitigating the progression of neurodegeneration. Additionally, while WMH were not directly measured in this study, they are well-known indicators of vascular injury and have been associated with cognitive decline in previous research. As such, WMH assessments should be integrated into clinical evaluations of TBI patients, particularly those with cardiovascular risk factors, to identify early markers of cognitive decline.

4.5.7 Link to Thesis Objectives

This replication study directly contributes to the overarching aims of this thesis by validating the harmonisation process and demonstrating its effectiveness in capturing neurodegenerative patterns post-TBI. Specifically, by replicating findings from Graham et al., (2023), this study integrates volumetric MRI and DTI metrics to assess the structural and microstructural consequences of moderate to severe TBI.

The inclusion of DTI findings strengthens the replication by demonstrating that our harmonised dataset captures significant changes in white matter integrity, including reductions in fractional anisotropy (FA) in key tracts such as the anterior corona radiata, cingulum, and splenium of the corpus callosum. These results align with Graham et al. (2023), providing evidence that diffuse axonal injury (DAI) is a prominent feature of moderate/severe TBI. Importantly, this replication underscores the effectiveness of harmonisation in reducing variability across imaging protocols and improving the reliability of neuroimaging results in multi-centre studies.

Moreover, this study provides valuable insights into the long-term effects of TBI on both brain structure and cognitive function. By replicating the findings of Graham et al. (2023), we confirm that TBI is associated with widespread white matter damage, atrophy, and cognitive decline. Notably, FA reductions in the anterior corona radiata and cingulum are consistent with regions most vulnerable to shear forces during trauma, and their involvement in memory and executive functions highlights the functional consequences of these injuries. These findings directly support the thesis objectives of investigating the neurodegenerative effects of TBI and identifying potential biomarkers for predicting cognitive outcomes.

4.6 Conclusion

This replication study has demonstrated the robustness of the harmonisation process developed in Chapter 3, successfully replicating key findings from Graham et al. (2023) and validating the methodological approach used in this thesis. Our results provide strong evidence that individuals with a history of moderate to severe TBI experience significant declines in both grey and white matter volumes over time. These volumetric changes are likely contributing to the cognitive and motor deficits reported by participants, particularly in areas such as memory, attention, and motor coordination.

We also confirmed significant reductions in FA in the anterior corona radiata and left cingulum, regions critically implicated in DAI and associated with cognitive deficits in TBI. Additionally, significant FA reductions in the optic radiations and splenium of the corpus callosum further highlight the widespread nature of white matter damage following TBI.

Our findings support the hypothesis that TBI accelerates neurodegenerative processes, particularly in vulnerable regions such as the anterior corona radiata and cingulum, which are integral to memory and executive function. These microstructural changes complement the observed volumetric reductions in grey matter, particularly in the hippocampus, reinforcing the relationship between structural and functional brain impairments in moderate/severe TBI.

The replication of both volumetric and DTI findings underscores the robustness of the harmonisation process developed in Chapter 3, providing strong evidence for its effectiveness in reducing inter-cohort variability and ensuring reliable results across imaging modalities. This replication demonstrates that harmonised neuroimaging data can provide meaningful insights into the structural and microstructural changes associated with TBI, advancing the field's understanding of neurodegeneration in this population.

4.7 Future Directions

Building on these findings, future research could focus on expanding the diversity of the cohorts studied, including participants from a wider range of demographic backgrounds and with different injury severities. Additionally, future studies should explore the use of advanced neuroimaging techniques, such as functional MRI (fMRI), to further elucidate the mechanisms underlying brain health and cognitive decline in TBI patients. These techniques could provide a more detailed understanding of how TBI disrupts white matter integrity and connectivity, and how these disruptions contribute to cognitive deficits.

Another promising direction for future research is the development of predictive models that integrate neuroimaging, cognitive, and genetic data to identify individuals at risk for rapid cognitive decline following TBI. By identifying early biomarkers of neurodegeneration, such as white matter atrophy and white matter hyperintensities, researchers and clinicians may be able to intervene earlier in the disease process, potentially slowing the progression of cognitive decline and improving outcomes for TBI patients.

Finally, future studies should explore the potential for targeted interventions aimed at preserving white matter integrity and improving vascular health in TBI patients. For example, pharmacological treatments that promote remyelination or reduce neuroinflammation could help to protect white matter tracts from further degeneration. Similarly, lifestyle interventions that target cardiovascular risk factors, such as hypertension and diabetes, could help to reduce the burden of white matter hyperintensities and improve cognitive outcomes in TBI patients.

By reinforcing the impact of moderate/severe TBI and validating our harmonisation methods, this chapter contributes significantly to the field of TBI research and supports the overall objectives of this thesis. Through continued research, we can improve our understanding of the long-term effects of TBI

and develop more effective strategies for preventing and treating neurodegeneration in this population.

Following the application and initial validation of the harmonisation framework, Chapter 5 explores whether individuals with a history of single or repeated mTBI exhibit differences in cognitive profiles. These analyses provide insight into how mTBI influences cognitive performance in populations at risk for Alzheimer's disease.

Chapter 5: In a Population at Risk of AD at Mid to Early-Late Life, is a history of single or repeated mTBI associated with altered Cognitive Profiles?

5.1 Introduction

mTBI is a prevalent condition, often resulting from accidents, sports injuries, or military service. While mTBI is commonly considered transient, with symptoms resolving within weeks or months, growing evidence suggests that mTBI may have lasting cognitive and neurological consequences, particularly in populations vulnerable to neurodegenerative diseases such as Alzheimer's disease (AD). As discussed in Chapter 2, the neurobiological impact of mTBI—including diffuse axonal injury (DAI) and chronic neuroinflammation—creates conditions conducive to the acceleration of pathological processes associated with AD. Notably, mTBI can trigger mechanisms such as amyloid-beta accumulation and neuroinflammation, both of which have been shown to overlap with those involved in AD pathogenesis (Rosenbaum & Lipton, 2012). These mechanisms, introduced in Chapter 2, form the biological framework for understanding the intersection between mTBI and cognitive decline.

Previous chapters have also emphasized the complex relationship between mTBI and cognitive aging. Chapter 3 laid out the methodology for harmonising cognitive data across the PREVENT and EPAD cohorts, both of which are enriched for individuals at elevated risk for AD due to factors like family history and APOE4 positivity. These cohorts provide a robust foundation for investigating cognitive trajectories in at-risk populations. This chapter builds on that methodological foundation by specifically examining the role of mTBI in modifying cognitive profiles within these cohorts.

The relationship between mTBI and cognitive decline is not fully understood, particularly in aging populations at risk for AD. Research has indicated that mTBI can exacerbate the deposition of amyloid-beta plaques and tau tangles, hallmarks of AD pathology, through mechanisms involving oxidative

stress and neuroinflammation (Johnson et al., 2013). These processes may accelerate cognitive decline in mid-to-late life, especially in individuals already on a trajectory toward neurodegeneration. Investigating whether mTBI interacts with AD risk factors to produce more pronounced cognitive impairments is crucial for understanding the broader impacts of mTBI on brain health in aging populations.

Aging individuals are especially vulnerable to the long-term effects of mTBI due to diminished brain plasticity (Monti et al., 2013). As the brain ages, its capacity for synaptic reorganisation, neurogenesis, and repair mechanisms declines, reducing its ability to compensate for injury related disruptions (Burke & Barnes, 2006; Grady, 2012). This diminished plasticity limits the brain's ability to form new neural connections or reroute around damaged areas, which can impede functional recovery. Moreover, ageing is associated with chronic inflammation and oxidative stress, which can exacerbate injury-related damage and prolong recovery (Cao et al., 2022). Recovery from mTBI is often assessed using cognitive performance, return to baseline function and symptom resolution timelines. In older adults , recovery tends to be slower and less complete, with persistent deficits in domains such as attention and executive function. As discussed in Chapter 3, individuals at risk for AD often display early, subclinical cognitive changes, which may be further compounded by the effects of mTBI. Deficits in attention, executive function, and memory, common after mTBI, overlap with cognitive domains typically affected in early AD (Silverberg et al., 2020). This overlap raises important questions about whether mTBI accelerates or amplifies cognitive decline in populations predisposed to neurodegeneration.

Despite growing awareness of the potential long-term impact of mTBI, few studies have examined the effects of single and repeated mTBI in populations at risk for AD. Most existing studies, as reviewed in earlier chapters, focus on acute recovery or on younger populations, such as athletes or military personnel, leaving a gap in knowledge regarding cognitive profiles in older adults who have

experienced mTBI. Given the complex interactions between aging, neurodegeneration, and brain injury, this chapter aims to address how mTBI affects cognitive function in mid-to-late life, particularly in populations already vulnerable to AD.

Building on the harmonisation of cognitive assessments presented in Chapter 3, this chapter specifically investigates whether a history of single or repeated mTBI is associated with altered cognitive profiles in a population at risk for AD in mid-to-early late life. The principal aim is that individuals with a history of mTBI will perform worse across key cognitive domains—including memory, attention, and executive function—compared to those without a history of head injury. By leveraging the PREVENT and EPAD cohorts, which have been carefully selected and harmonised for analysis, this chapter seeks to clarify whether mTBI exacerbates cognitive decline in populations already on a neurodegenerative trajectory.

This research contributes to the growing body of literature suggesting that mTBI may serve as a significant modifier in the development of cognitive impairments, particularly in populations vulnerable to neurodegenerative changes. The findings from this chapter may have important implications for early intervention and risk stratification in individuals at risk for AD, as they will help identify specific cognitive domains most affected by mTBI in these populations. Furthermore, these findings will be expanded upon in the next chapter, where baseline neuroimaging measures will be explored to examine whether structural brain changes underlie the cognitive profiles observed in this chapter.

This study is particularly novel because it examines the cognitive effects of mTBI in mid-to-late life among individuals at increased risk for Alzheimer's disease. The convergence of neurodegenerative risk factors, including a family history of AD and APOE4 positivity, with a history of mTBI offers a unique opportunity to explore whether these factors interact to accelerate cognitive decline. Midlife

represents a critical period where subtle neurodegenerative processes may begin, and the lasting impact of mTBI during this phase could shed light on the early cognitive markers of both mTBI-related impairments and AD risk (Johnson et al., 2013; Stern, 2012).

5.2 Methodology

The data for this analysis were drawn from two large cohorts: the PREVENT and EPAD studies, both of which have been described in detail in Chapter 3. These cohorts were selected for their neuropsychological assessments and well-documented histories of AD risk factors, including genetic predispositions (e.g., APOE4 status) and family history.

Data Sources

- PREVENT Cohort: The PREVENT cohort comprises individuals aged 40-59 at varying levels of risk for AD, with participants stratified into high, medium, and low-risk groups based on factors such as family history of dementia and APOE genotype. Detailed cognitive and neuroimaging assessments have been conducted at baseline and 2 year follow-up intervals, providing longitudinal data on brain health and cognitive trajectories. For this chapter, baseline cognitive assessments will be used to examine the association between mTBI history and cognitive function.

- EPAD Cohort: The EPAD study is a pan-European initiative that recruited over 2,000 participants aged 50 and above, all at increased risk for AD but without a formal diagnosis of dementia. Participants underwent annual cognitive assessments and biomarker evaluations, including genetic testing, fluid biomarkers, and multimodal neuroimaging. This cohort is particularly suited for examining preclinical AD processes and their interaction with risk factors such as mTBI.

5.2.1 Participants

1,558 participants from both the PREVENT cohort and EPAD cohort were grouped by severity based on BISQ scores (single mTBI, repeated mTBI, simple head injury, moderate/severe TBI, no head injury). Due to a focus on difference between single and repeated mTBI, only participants in the single mTBI (smTBI), repeated mTBI (rmTBI) and no head injury groups were included (see figure 3.1). This left 683 participants with no history of head injury, 210 with a history of single mTBI and 511 with a history of repeated mTBI.

5.2.2 Cognitive Data and Harmonisation

As outlined in Chapter 3, cognitive performance data were drawn from two large cohorts: PREVENT, utilizing the COGNITO battery, and EPAD, which employed the RBANS battery. While both cohorts also assessed participants with the four mountains and supermarket trolley tasks. These assessments captured a broad spectrum of cognitive functions relevant to aging and neurodegeneration.

To ensure compatibility between the different cognitive test batteries across these cohorts, a harmonisation process was undertaken using PCA. This approach allowed for the extraction of common latent cognitive constructs, facilitating direct comparisons across the studies. The harmonised data enabled the creation of four key cognitive domains, which form the basis of the analyses in this chapter.

The cognitive domains produced through this harmonisation are as follows:

1. Memory: Immediate and delayed recall tasks, including name-face association and narrative recall, capturing both visual and verbal memory performance.
2. Attention: Tasks measuring selective attention and sustained focus, including visual and auditory stimuli response assessments.
3. Language: Tasks evaluating reading comprehension, phoneme identification, and naming abilities, providing insights into linguistic processing.

4. Visuospatial Skills: Visual construction and spatial memory tasks, including replication of complex figures, assessing the participant's ability to interpret and organise visual information.

5.2.3 Classification of covariates

Sex was coded in binary (0 - men, 1 - women). Smoking was coded as a three-level variable; 0 = Never smoked, 1 = Previous Smoker and 2 = Current Smoker. All fully adjusted analyses included a previously validated vascular risk scoring system (Makkar et al., 2020), as vascular risk factors are known contributors to cognitive decline, vascular dementia and Alzheimer's disease (Kivipelto et al., 2001; Lennon et al., 2019) and may confound the effect of TBI. A score out of 5 was calculated, as the sum of five dummy variable co-morbidities; hypertension, stroke, coronary heart disease, diabetes and high cholesterol. Individual history of any previous psychiatric diagnosis was coded as a dummy variable (0 = no previous diagnoses, 1 = any previous diagnoses). APOE4 status was coded as binary (0 = non carrier or 1 = carrier).

5.2.4 Statistical analysis

As discussed previously, PCA was conducted to reduce the neuropsychological factors into the cognitive domains listed above. Direct scores were then transformed into Z scores for standardized data. Participants who obtained more than +/- 4 Z scores were retired for posterior analysis. A total of 12 participants across both cohorts were identified with z-scores exceeding ±4 on one or more cognitive domain scores. These cases were considered extreme outliers and excluded from the main inferential analyses to reduce the risk of skewing group means and violating assumptions of normality. While these individuals were flagged for potential posterior descriptive follow-up, no formal subgroup analysis was conducted due to limited sample size and heterogeneity across measures. However, their presence may reflect true heterogeneity in cognitive responses to mTBI, suggesting a need for larger samples in future research to investigate these potential subtypes more thoroughly. A bivariate

correlation was used to test the linear relationship between variables, and only significant associations were considered for analysis. Before PCA procedure, the Kaise-Meyer-Olkin (KMO) measure of sampling adequacy and the Bartlett's test of sphericity were performed. Varimax rotation for PCA analysis was used and items with factor loadings >0.3 were entered into a factor. For the number of principal components (PC) extracted the standard eigenvalues >1 criterion was considered. Statistical analyses were performed using IBM SPSS (version 29.0). With the components taken and transformed into z score, the scores were compared according to the severity group (no head injury, smTBI, rmTBI), a covariance analysis (ANCOVA) with years of education, age, APOE4 positivity and sex as covariates. In the cases where significant differences were found, a post hoc analysis was also carried out with Bonferroni correction.

5.3 Results

5.3.1 Demographics and sample characteristics

Table 5.1. Summary of study population characteristics by severity groups

	No Head Injury (N=683)	Single mTBI (N=210)	Repeated mTBI (N=511)	p value
Age mean (SD)	63.0(8.9)	57.5(9.5)	54.9(9.4)	<0.001
Years of Education mean (SD)	14.9(3.9)	15.9(3.7)	16.3(3.6)	<0.001
Sex (Male%/Female%)	37%/63%	36%/64%	47%/53%	0.002
Ethnicity (% Caucasian)	97.3%	97.4%	96.0%	0.054
Hypertension (Y%)	23.4%	24.4%	23.2%	<0.001
Stroke (Y%)	1.2%	1.1%	1.0%	<0.001
Coronary disease (Y%)	4.2%	3.5%	3.2%	<0.001
Diabetes (Y%)	2.5%	2.6%	2.5%	<0.001
High Cholesterol (Y%)	5.3%	5.1%	5.5%	<0.001
Any history of psychiatric illness (Y%)	33.2%	32.1%	34.4%	<0.001

5.3.2 Principal Component extracted

PREVENT

The KMO index and Bartlett's of sphericity for attention (0.637, $p<0.001$), language (0.854, $p<0.001$), memory (0.831, $p<0.001$) and visuospatial (0.723, $p<0.001$) indicated the data was suitable for factor analysis. Factor scores were then transformed into z scores for standardized data.

EPAD

The KMO index and Bartlett's of sphericity for attention (0.843, $p<0.001$), language (0.788, $p<0.001$), memory (0.888, $p<0.001$) and visuospatial (0.984, $p<0.001$) indicated the data was suitable for factor analysis. Factor scores were then transformed into z scores for standardized data.

5.3.3 Differences in cognitive scores based on severity groups

ANCOVA revealed a significant difference between the groups in attention scores ($F=5.72$, $p=0.003$). However, when applying the Bonferroni correction for multiple comparisons across the four cognitive domains (memory, attention, language, and visuospatial skills), the p-value threshold for significance becomes stricter ($p<0.0125$). After adjusting for multiple comparisons, the observed difference in attention scores ($p=0.033$) does not remain statistically significant, suggesting that the evidence for attentional impairment is weaker than initially indicated. The use of a Bonferroni correction was necessary to account for the multiple cognitive domains analysed, thus reducing the likelihood of Type I errors (false positives) (Bland & Altman, 1995). However, this correction also reduces sensitivity, potentially masking weaker trends that might still be clinically relevant (Perneger, 1998). The attenuation of the significance in attention scores suggests that while attentional deficits may exist, further studies with more targeted cognitive measures and larger sample sizes may be needed to verify this trend.

No significant differences were found for the memory, language, or visuospatial domains across the severity groups.

Table 5.2. ANCOVA for comparisons between groups according to components extracted. Z score and SD reported for each cognitive domain

	No Head Injury	Single mTBI	Repeated mTBI	p value	Post Hoc Comparisons
MEMORY	-0.03(0.9)	0.08	0.005	0.32	N/A
ATTENTION	0.09(0.9)	-0.14	-0.05	**0.03**	smTBI>No head injury
LANGUAGE	-0.02(0.9)	0.01	0.02	0.78	N/A
VISUOSPATIAL	-0.05(1.0)	0.12	0.03	0.16	N/A

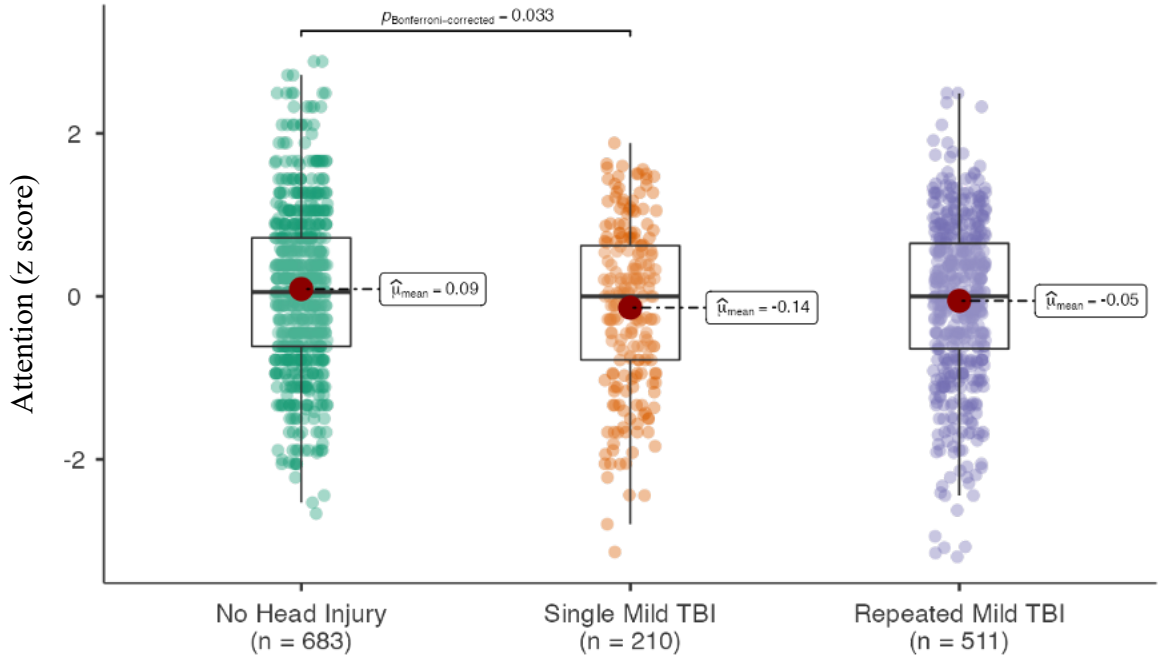


Figure 5.1. Barplots depicting mean performance for attention task among severity groups. Individual data points are superimposed on each barplot.

5.3.4 ANCOVA of sociodemographic variables in attention

Sex (p=0.875), years of education (p=0.224), cardiovascular (p=0.450) and psychiatric illness (p=0.665) do not have any significant effect on the attention component. In contrast, age had a significant effect on attention (F=10.10, p=0.002, η^2p=0.007). Correlation analyses revealed that in the no head injury group, age was negatively associated with attention performance (r = -0.19, p<0.001). In the single mTBI group, this negative association was more pronounced (r = -0.30, p=0.003), and in the repeated mTBI group, a similarly significant negative association was observed (r = -0.27, p<0.001). These

findings suggest that attention performance declines with age across all groups, but the decline is more marked in those with a history of mTBI. This is illustrated in figure 5.2.

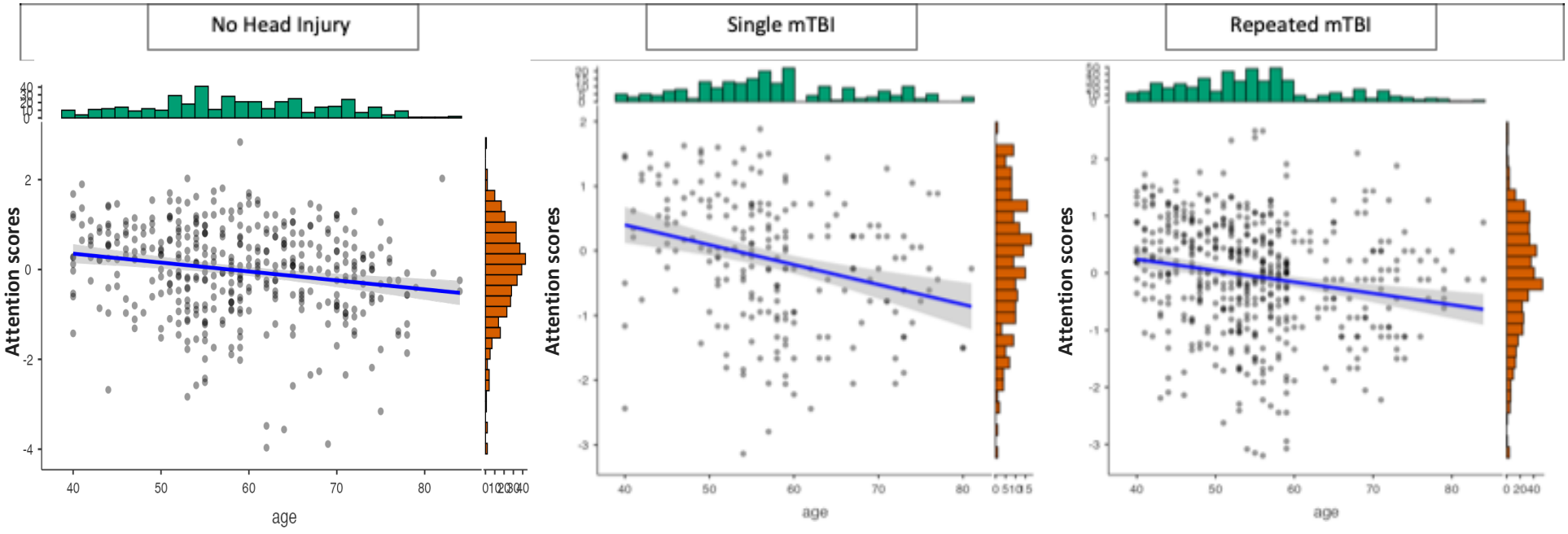


Figure 5.2. Scatterplot depicting attention scores across age among

5.4 Discussion

This study aimed to explore whether a history of single or repeated mTBI in mid-to-early late life is associated with altered cognitive profiles, particularly in attention, memory, language, and visuospatial domains. The findings provide weak evidence for attentional deficits in individuals with a history of mTBI, though no significant deficits were observed in other cognitive domains. Despite the lack of statistically significant results after correcting for multiple comparisons, these trends are clinically relevant and offer important insights into the long-term effects of mTBI in populations at risk for neurodegenerative diseases, particularly AD in mid to early late life.

5.4.1 Cognitive Implications of mTBI

The weak evidence for attentional deficits in this study aligns with previous research suggesting that attention may be one of the cognitive domains most affected by mTBI (Silverberg et al., 2020). However, the lack of statistically significant findings in other domains, such as memory and language, raises important questions about the role of cognitive reserve in mitigating the cognitive effects of mTBI.

As discussed in Chapter 1, cognitive reserve, which includes factors such as education, occupational complexity, and intellectual engagement, has been shown to buffer against the cognitive consequences of brain pathology, including both mTBI and neurodegenerative diseases (Stern, 2012). While this study controlled for years of education, which is a key aspect of cognitive reserve, other factors—such as lifelong intellectual engagement—were not fully captured. These unmeasured components of cognitive reserve may have allowed participants to compensate for the cognitive effects of mTBI, particularly in domains like memory and language, where individuals with high cognitive reserve may be better able to maintain cognitive function despite injury (Robertson, 2014). The timing of the mTBI relative to cognitive testing may also explain the lack of significant findings in some domains. Cognitive impairments following mTBI may resolve over time, particularly in less

complex domains such as memory, which often show recovery post-injury (Kinnunen et al., 2011). Participants in this study may have had sufficient time for functional recovery, making it more difficult to detect persistent cognitive deficits.

Despite the lack of significant findings, the results still contribute to our understanding of how mTBI may affect cognition in mid-to-early late life, particularly in populations at risk for AD. This study builds on the existing literature by demonstrating trends that suggest attention may remain a vulnerable domain even after many years post-injury, reinforcing the need for further research into long-term cognitive changes in individuals with a history of mTBI.

5.4.2 Lack of Deficits in Other Cognitive Domains

One notable finding in this study is the absence of significant deficits in cognitive domains such as memory, language, and visuospatial skills, all of which have been implicated in prior research on mTBI (Kinnunen et al., 2011). This raises several possibilities. First, it is possible that these domains are less affected in midlife individuals who have a history of single or repeated mTBI, especially compared to populations with more severe injuries. Alternatively, the lack of significant findings in these domains may point to recovery or compensation over time, particularly in individuals with high levels of education or intellectual engagement.

The lack of significant memory deficits was unexpected, given that memory impairment is a hallmark of both mTBI and early AD. One possible explanation for the absence of memory impairments is that compensatory mechanisms may have allowed participants to maintain memory performance despite a history of mTBI. Alternatively, the memory tasks used in this study may not have been sensitive enough to detect subtle deficits, particularly in individuals with high baseline cognitive functioning. This suggests that the relationship between mTBI and long-term memory performance in mid-to-early

late life may be more complex than initially thought and warrants further investigation using more sensitive cognitive measures.

5.4.3 Evaluation and Limitations of the BISQ

As discussed in Chapter 2, the BISQ has known limitations when it comes to assessing mTBI in large cohort studies. Although the BISQ is widely used and provides a practical means of classifying individuals with a history of head injury, it relies heavily on retrospective self-report, which can be prone to recall bias, particularly for individuals who experienced mTBI many years prior. This raises the possibility of misclassification, where participants with a history of mTBI may be placed in the no-head-injury group or vice versa, thereby diluting the observed group differences.

5.4.4 Evaluation and Limitations of the Cognitive Harmonisation Approach

In Chapter 3, the cognitive harmonisation process was introduced as an essential step in making the cognitive data from the PREVENT and EPAD cohorts comparable. PCA was used to extract common cognitive domains, such as memory, attention, language, and visuospatial skills, across the different neuropsychological test batteries used in these cohorts. Although this study encountered certain limitations, it offers important methodological contributions to the field. The use of PCA to harmonise cognitive data across the PREVENT and EPAD cohorts is a significant strength of this work. By employing PCA to create common cognitive domains across different neuropsychological batteries, the study was able to account for variability across cohorts and improve the comparability of results. Additionally, controlling for key covariates, such as APOE4 status and years of education, added further robustness to the analyses, ensuring that the results were not confounded by these factors. The statistical rigor applied in this study, including the Bonferroni correction for multiple comparisons (Bland & Altman, 1995), demonstrates a commitment to producing reliable findings, even if this conservative approach reduced the ability to detect subtle cognitive differences.

While PCA is an effective tool for reducing dimensionality and ensuring cross-cohort comparability, it also introduces certain limitations, which were acknowledged in previous chapters but warrant further discussion in the context of the current study.

An important consideration is that, during the harmonisation process, the idea of creating more specific cognitive domains, such as executive function, was explored. However, the cognitive batteries in both the PREVENT and EPAD cohorts did not yield adequate KMO values to perform reliable PCA for these more specific domains. The KMO measure of sampling adequacy is used to determine whether the data is suitable for PCA, and in this case, the cognitive measures related to executive function did not meet the required thresholds. As a result, the more detailed cognitive domains like executive function could not be extracted, limiting the ability to isolate deficits in areas particularly relevant to mTBI.

By reducing the cognitive data into broad domains, PCA sacrifices some specificity, potentially masking subtle deficits that could have been detected with more fine-grained assessments. This limitation is especially important when considering that executive functioning—which is often affected by mTBI—was not isolated as a distinct domain in this study. The inability to perform PCA on specific cognitive domains such as executive function may have contributed to the lack of significant findings in certain areas. Similarly, the harmonisation process may have diluted the sensitivity of the cognitive tests to detect subtle differences in areas such as processing speed and working memory, which are also important in understanding the cognitive consequences of mTBI. While the cognitive harmonisation approach enabled cross-cohort comparisons, it may have limited the ability to detect more domain-specific impairments, contributing to the overall lack of significant findings across most cognitive domains.

The harmonisation of cognitive data, while challenging, underscores the feasibility and utility of pooling data from multiple cohorts to study the long-term effects of mTBI. This approach makes the study's findings more generalizable to other populations at risk for AD, highlighting the innovation of the methodology used.

Another key limitation concerns the interpretability of attention scores in relation to normative cognitive performance. Although harmonisation allowed for z-scoring across the PREVENT and EPAD cohorts, the resulting scores were normed within the combined study population, not against external, age-adjusted norms from the general population. As a result, individuals in the no head injury group aged 70 or older frequently scored within one standard deviation of the harmonised mean, despite evidence from normative studies showing measurable declines in attention and processing speed from midlife onward (Salthouse, 2010; Harada et al., 2013). This suggests that either (1) the combined cohort represents a high-functioning, research-engaged population with above-average cognitive performance for age, or (2) the harmonisation process, particularly PCA-based domain reduction and z-scoring, compressed age-related variance and limited detection of subtle decline. While the modest negative correlation observed between age and attention in the no injury group ($r = -0.19$) supports some age sensitivity, the shallow slope and narrow distribution raise concerns about the suitability of the attention domain for detecting clinically meaningful change over time.

This limitation also links to the issue raised in Chapter 2, regarding whether the cognitive domains selected are optimally sensitive to long-term effects of mTBI or to the early onset of neurodegeneration. While attention deficits are common in mTBI, early Alzheimer's disease is typically characterised by episodic memory impairment. Thus, by focusing on broad domains present across cohorts, the harmonised scores may have achieved comparability at the expense of specificity. Future studies may benefit from integrating harmonised scores with externally normed references or

selecting tasks specifically designed to capture age-related and disease-specific change, especially in executive and episodic memory domains.

5.4.5 Limitations of the No Head Injury Group as a Control

Another limitation of this study is the composition of the no-head-injury group, which was drawn from cohorts enriched for AD risk factors, including APOE4 positivity and a family history of AD. Although APOE4 status was included as a covariate in the analyses, other unmeasured risk factors—such as preclinical cognitive decline—may have influenced the results. This population may already have been on a trajectory toward cognitive decline, which could have diluted the differences between the head injury and no-head-injury groups. Previous research suggests that APOE4 carriers may be more susceptible to cognitive decline following brain injury due to impaired neuroplasticity and repair mechanisms (Mahley & Huang, 2012). Future studies should explore the potential interaction between APOE4 and mTBI to better understand how genetic risk for AD influences cognitive recovery or deterioration in this population (Petrache et al., 2021).

This limitation is further compounded by the lack of amyloid and tau biomarker data for the PREVENT cohort. To ensure consistency and maintain a clean dataset, amyloid-positive individuals were excluded from the EPAD group. While this methodological choice minimized the risk of dataset contamination and improved comparability between cohorts, it also introduces a critical limitation: the no-head-injury group may not represent a true control population. By excluding individuals with elevated amyloid—a key biomarker for AD pathology—the study limited the potential to explore the interaction between mTBI and Alzheimer's disease pathology, particularly in those already showing early signs of AD-related biomarker changes. This exclusion may also have contributed to a no-head-injury group that, while free of prior mTBI, remains at elevated risk for cognitive decline due to its underlying enrichment for AD risk factors.

The no-head-injury group, therefore, may not represent a true control population, as it is comprised of individuals who are at elevated risk for cognitive impairment. This limitation complicates the interpretation of the findings, as the observed cognitive profiles may not fully reflect the independent impact of mTBI on cognition. Future studies should consider incorporating a more representative control group, one that does not include individuals with elevated risk for neurodegenerative disease, to better isolate the cognitive effects of mTBI.

5.4.6 Comparison with Existing Literature

The results of this study align with some aspects of the existing literature on mTBI, while also highlighting areas where further investigation is needed. Studies examining the long-term cognitive effects of mTBI have produced mixed findings. Some research suggests that mTBI may lead to persistent deficits in attention, memory, and executive function, particularly in older adults (Silverberg et al., 2020; Konrad et al., 2011). However, other studies report cognitive recovery within months or years of injury, especially in domains such as memory (Kinnunen et al., 2011).

The findings from this study—specifically, the weak evidence for attentional impairments—align with those studies that suggest attention may be particularly vulnerable to long-term disruption following mTBI. However, the absence of significant deficits in other domains such as memory and language are consistent with research indicating cognitive recovery over time, particularly in populations with higher levels of cognitive reserve (Stern, 2012). These mixed results underscore the need for further research to clarify the cognitive trajectories of individuals with mTBI in mid-to-early late life, particularly in populations at risk for AD.

5.4.7 Clinical Relevance of the Findings

While this study did not find statistically significant differences in cognitive performance between groups, the weak trend observed in attention scores, particularly in individuals with mTBI, suggests

that this domain may warrant closer examination in future research. However, given the cross-sectional nature of the data and the lack of robust group-level effects across domains, these findings alone do not justify immediate changes to clinical practice or large-scale cognitive screening in individuals with a history of mTBI.

The results underscore the complexity of disentangling the cognitive consequences of mTBI in mid-to-early late life populations at risk for AD. Previous studies have shown that even in the absence of overt cognitive deficits, individuals with a history of mTBI may exhibit subtle alterations in attention, processing speed, or executive function that could become clinically meaningful over time (McInnes et al., 2017; LoBue et al., 2019). Longitudinal investigations are needed to determine whether such changes persist or worsen and to clarify their clinical relevance. If future research consistently identifies progressive deficits in attention or executive domains among individuals with mTBI, it may then be appropriate to explore targeted interventions such as cognitive rehabilitation or risk-reduction strategies (Belanger et al., 2005; Rohling et al., 2011). At present, the findings of this study support cautious monitoring rather than definitive clinical recommendations, and any intervention strategies must be guided by stronger evidence from prospective, long-term studies.

5.5 Future Directions

The findings from this chapter suggest several important avenues for future research into cognitive profiles in individuals with a history of mTBI during midlife, particularly in populations at risk for AD. One critical area for future research is the need for longitudinal studies that follow individuals over time to assess whether cognitive deficits associated with mTBI, such as attentional impairments, persist, worsen, or stabilize as individuals age. Longitudinal designs would provide valuable insights into whether mTBI serves as an early marker for accelerated cognitive decline, particularly in domains like memory and executive function, which may remain unaffected in cross-sectional studies but could show deterioration over time. These findings also have potential clinical implications for the

monitoring and treatment of individuals with a history of mTBI in mid-to- early late life. Given the weak evidence for attentional deficits, clinicians might consider incorporating routine cognitive screenings for subtle changes in attention and executive function, particularly in populations at risk for AD (Silverberg et al., 2020). Moreover, early interventions such as cognitive rehabilitation could be explored as a means to mitigate the long-term cognitive effects of mTBI, especially in areas where compensatory mechanisms might not fully protect against decline (Cicerone et al., 2011).

Additionally, future research should consider more diverse populations, including individuals with different levels of cognitive reserve, to better understand how factors such as education, socioeconomic status, and lifestyle might buffer against or exacerbate the long-term effects of mTBI. The interaction between cognitive reserve and mTBI remains underexplored, and understanding how these factors influence recovery or decline could lead to more targeted interventions aimed at promoting cognitive resilience.

Furthermore, the use of more sensitive cognitive assessments may be necessary to detect subtle deficits that may be missed by traditional neuropsychological tests. Advanced cognitive testing methodologies, such as computerized cognitive batteries or tasks specifically designed to challenge attentional and executive function, could be employed in future studies to capture more nuanced aspects of cognitive performance post-mTBI.

Another important direction for future research is the inclusion of neurobiological markers, such as neuroimaging and fluid biomarkers, to identify underlying mechanisms that contribute to cognitive decline in individuals with a history of mTBI. Studies should investigate whether structural and functional changes in the brain, such as white matter integrity, cortical thinning, and the presence of neuroinflammatory markers, are linked to the cognitive profiles observed in this population.

Finally, future research may explore whether specific interventions, such as cognitive rehabilitation, physical activity, or strategies targeting neuroinflammatory processes, could play a role in supporting cognitive health in individuals with a history of mTBI. Although this study does not provide direct evidence for the efficacy of such interventions, identifying approaches that mitigate long-term cognitive vulnerability in this group could be valuable for future preventative strategies. This is particularly relevant in populations also at risk for Alzheimer's disease, where even small improvements in cognitive reserve may influence long-term outcomes.

While this chapter has focused on cognitive outcomes, as stated earlier, the inclusion of neuroimaging data in future studies will be critical for understanding the relationship between mTBI and structural brain changes. The next chapter of this thesis will address this gap by investigating whether individuals with a history of mTBI show differences in brain volume, grey matter concentration, and white matter integrity and hyperintensities compared to those without a history of head injury.

5.6 Conclusion

This study provides reassuring evidence that a history of single mTBI is not strongly associated with widespread cognitive impairments in mid-to-early late life, particularly in populations at risk for AD. While there was weak evidence suggesting a potential association between mTBI and attentional impairments, these findings did not remain statistically significant after correcting for multiple comparisons. This suggests that any attentional deficits related to mTBI may be subtle and not readily detectable with the cognitive measures used in this study. Nevertheless, the absence of strong associations across other cognitive domains indicates that mTBI may not necessarily heighten vulnerability to significant cognitive decline in this population.

These findings offer a positive perspective for individuals with a history of mTBI, particularly in midlife, as they suggest that the long-term cognitive effects of mTBI may be less severe than expected. However, it is important to consider that more sensitive cognitive assessments or longitudinal studies

may reveal more nuanced impairments over time. Factors such as the timing of injury, variability in injury severity, and sample size limitations may also have contributed to the lack of significant findings in certain cognitive domains.

This study demonstrates the feasibility of harmonising cognitive data across multiple cohorts, contributing valuable insights into the effects of mTBI on cognitive aging. Future research should prioritize longitudinal studies to track cognitive changes over time and employ more sensitive tools to assess domain-specific impairments, particularly in attention. Furthermore, incorporating a more representative control group free from AD risk factors would allow for better isolation of the cognitive effects of mTBI, offering a clearer picture of its potential impact.

While Chapter 5 highlights cognitive deficits associated with mTBI, understanding the neural correlates of these changes requires a closer examination of structural and functional brain alterations. Chapter 6 explores baseline neuroimaging measures, focusing on brain volume and white matter integrity.

Chapter 6: Do Baseline Neuroimaging Measures Help Characterize the Impact of a History of mTBI in Mid to Early-Late Life?

6.1 Introduction

TBI is known to have long-lasting effects on brain structure and function, particularly in individuals who experience mTBI . While the cognitive implications of mTBI have been explored in Chapter 5, where subtle attentional deficits were identified, the neuroimaging correlates of these cognitive changes remain poorly understood, particularly in individuals at mid to early-late life. Neuroimaging studies have increasingly recognised that mTBI is associated with structural changes in the brain, including grey matter atrophy, white matter hyperintensities (WMH), and alterations in the microstructural integrity of white matter (Gorgoraptis et al., 2019). However, existing research is often hampered by methodological challenges such as small sample sizes, heterogeneous participant groups, and variability in imaging protocols, making it difficult to draw consistent conclusions about the structural brain changes associated with mTBI.

As discussed in Chapters 1 and 3, advances in neuroimaging harmonisation techniques, such as the use of NeuroHarmonize (derived from ComBat), offer the opportunity to overcome many of these methodological limitations. By using a large, harmonised, multi-modal neuroimaging dataset, this chapter aims to investigate the structural brain changes associated with mTBI in a population at risk for Alzheimer's disease (AD). Specifically, this study will employ a range of neuroimaging modalities—including T1-weighted MRI, T2-FLAIR, and diffusion tensor imaging (DTI)—to explore whether individuals with a history of mTBI exhibit distinct patterns of brain changes compared to those without a history of head injury.

The key hypotheses of this chapter are as follows:

1. Individuals with a history of single or repeated mTBI will exhibit lower brain volumes and reduced grey matter concentrations compared to those without a history of head injury.
2. Individuals with a history of mTBI will show higher white matter hyperintensity (WMH) burden, particularly in deep white matter hyperintensities (DWMH) and periventricular white matter hyperintensities (PWMH).
3. Individuals with a history of mTBI will have decreased fractional anisotropy (FA) and increased mean diffusivity (MD) in white matter tracts vulnerable to TBI, such as the corpus callosum and frontal white matter.

By integrating the cognitive findings presented in Chapter 5 with structural neuroimaging data, this chapter seeks to elucidate the neuroanatomical correlates of mTBI and assess whether these brain changes are consistent with patterns of neurodegeneration typically seen in Alzheimer's disease.

6.2 Methodology

6.2.1 Participants and Neuroimaging Data

As described in Chapter 3, the neuroimaging data used in this chapter were obtained from the PREVENT and EPAD cohorts. These cohorts provide comprehensive neuroimaging and cognitive data from individuals at varying levels of risk for Alzheimer's disease, including those with a history of mTBI. A total of 90 participants with a history of single mTBI and 248 with repeated mild TBI were compared with 334 participants without a history of head injury. The neuroimaging modalities included in this study were T1-weighted MRI for grey matter volume assessment, T2-FLAIR for white matter hyperintensity analysis, and diffusion tensor imaging (DTI) for assessing the microstructural integrity of white matter.

This reduction in sample size was due to incomplete imaging datasets, scanner artefacts, or preprocessing failures (e.g., motion, distortion, poor alignment). Participants were excluded if they lacked one or more core imaging sequences (T1-weighted, T2-FLAIR, or DTI), or if image quality did not meet standard thresholds for registration and segmentation. These figures reflect baseline imaging only and represent the final set of participants used for each modality-specific analysis.

Table 6.1. Demographic data across severity groups

	No Head Injury (N=334)	**Single mTBI (N=90)**	**Repeated mTBI (N=248)**	**Significance of intergroup differences**
Age	63.0(8.9)	57.5(9.5)	54.9(9.4)	<0.001
Years of Education	14.9(3.9)	15.9(3.7)	16.3(3.6)	<0.001
Sex (Male%/Female%)	37%/63%	36%/64%	47%/53%	0.002
Ethnicity (% Caucasian)	97.6%	97.3%	96.2%	0.404
Hypertension (Y%)	10.4%	13.9%	12.0%	0.357
Stroke (Y%)	0.6%	0%	0.8%	0.446
Coronary disease (Y%)	24.9%	32.0%	28.0%	0.119
Diabetes (Y%)	3.5%	1.9%	2.8%	0.458
History of drug use (Y%)	28.0%	34.0%	32.2%	0.150
Any history of psychiatric illness (Y%)	38.3%	39.5%	39.7%	0.871

6.2.2 NeuroHarmonize and Preprocessing of Neuroimaging Data

To account for site-specific variability across different imaging centres, the NeuroHarmonize approach, based on ComBat, was applied to the neuroimaging data. As detailed in Chapter 3, this method adjusts for scanner differences while preserving biological variability, ensuring that structural and diffusion metrics are comparable across the PREVENT and EPAD cohorts.

T1-Weighted Structural Imaging Pipeline

T1-weighted structural MRI scans were processed using the UK Biobank-derived pipeline, as described in detail in Chapter 3 (Section 3.5.1.1). Briefly, this included defacing and field-of-view reduction, followed by brain extraction (BET), linear and non-linear registration to MNI152 space (FLIRT and FNIRT), and segmentation into grey matter, white matter, and CSF using FAST with bias field correction. Total brain, grey matter, and white matter volumes were estimated using SIENAX, which scales for head size based on outer skull size. Subcortical structures, including the hippocampus, thalamus, caudate, and amygdala, were segmented using FIRST. All segmentation outputs were visually inspected, and participants with misaligned or poor-quality data were excluded. The resulting volumetric measures were used in group comparisons across TBI severity categories, controlling for scanner site, age, sex, and years of education.

6.2.3 Voxel-Based Morphometry (VBM) Analysis

The Voxel-Based Morphometry (VBM) analysis was employed to assess differences in grey matter (GM) volumes between individuals with a history of mTBI and those without. VBM allows for the voxel-wise comparison of GM concentrations, identifying local brain atrophy or volume changes.

Preprocessing Pipeline for VBM

1. Grey-matter (GM) maps were obtained by rerunning the above T1 sequence through FAST, extracting only the GM posterior probabilities.
2. Creation of Study-Specific GM Template:

2.1 Initial warp: Native GM maps were non-linearly registered to MNI-152 (FNIRT, 10 mm warp resolution).

2.2 Symmetrisation: To minimise registration bias, half of the warped images were randomly selected and were left-right flipped, concatenated with the un-flipped set, and averaged. The resulting template therefore contains equal hemispheric contributions, mitigating population-level asymmetry.

2.3 Template smoothing: the symmetric template was smoothed with a 2mm FWHM Gaussian kernel to supress residual interpolation artefacts

2.4 QC: Visual inspection in fsleyes confirmed accurate alignment and no gross artefacts after each sub-step.

3. Modulation: Each participant's native GM map was re-warped to the symmetric template; voxel intensities were modulated by the Jacobian determinant of the warp to encode local volumetric expansion or contraction introduced during registration.
4. Harmonisation with NeuroHarmonize: The unsmoothed, modulated GM maps were harmonised across scanners using neuroHarmonize (ComBat, empirical Bayes). Each voxel was treated as an independent feature, with scanner as the batch factor and age, TBI severity, sex retained as biological covariates. neuroHarmonize estimated voxel-specific adjustments, producing harmonised NIfTIs that reduce scanner-related variance while preserving true biological signal.
5. QC: density plots of mean GM volume per scanner before/after ComBat confirmed removal of site effects without distorting age correlations.
6. Smoothing: Harmonised, modulated GM maps were smoothed with a 5 mm FWHM Gaussian kernel. Smoothing enhances the signal-to-noise ratio, ensures validity of random-field-based assumptions, and retains sufficient spatial specificity for detecting focal GM differences.

Statistical Analysis of GM Volume

1. Voxel-Wise General Linear Model (GLM): A one-way GLM was fitted at every voxel with three binary regressors coding the study groups (no head-injury, single mTBI and repeated mTBI) and with age, sex, years of education and intracranial volume entered as covariates of no interest. This design allows both an omnibus group comparison and pair-wise contrasts (single mTBI > no head injury, repeated mTBI > no head injury, repeated mTBI > single mTBI).
2. Non-Parametric Permutation Testing: Inference was performed with randomise (FSL 6.0.7), using 5 000 random permutations of the design matrix to build the empirical null distribution for each contrast. Permutation testing is distribution-free and therefore well suited to voxel-wise neuroimaging data.
3. Cluster-Based Thresholding: The TFCE option was applied to every permutation, combining cluster extent and height information without the need for an arbitrary cluster-forming threshold. For completeness, a classical cluster analysis with an initial $Z > 2.3$ threshold was run as a sensitivity check.
4. Family-Wise Error (FWE) Correction: Voxel-wise p-values were derived from the permutation distribution and corrected for the family-wise error across the whole GM mask. Voxels, or contiguous clusters in the $Z > 2.3$ analysis, were deemed significant at $p < 0.05$, FWE-corrected. Corrected statistical maps were over-laid on the study-specific GM template for visualisation; peak coordinates are reported in MNI space.

6.2.4 Comparison of GM Templates

In addition to using the study-specific GM template, the VBM analyses were repeated using the UK Biobank GM template. This additional step was performed to assess the robustness of the results across different reference templates. Comparing results from both the study-specific and external GM templates allowed for a validation of the findings and ensured that the group differences observed were not dependent on the template used for spatial normalization.

White Matter Hyperintensity (WMH) Analysis Using the UK Biobank Pipeline

WMH burden was assessed using the UK Biobank pipeline, as detailed in Chapter 3 (Section 3.5.1.2). The following steps were employed:

1. Image Alignment and Registration: T2-FLAIR images were first defaced and linearly registered to the corresponding T1-weighted image using FSL's FLIRT tool, then transformed into MNI standard space.
2. WMH Segmentation: White matter lesions were segmented using the BIANCA tool (Griffanti et al., 2016), which identifies and quantifies WMH. Two specific WMH metrics were extracted:
    - Periventricular WMH (PWMH): Lesions within 10mm of the ventricles.
    - Deep WMH (DWMH): Lesions located more than 10mm away from the ventricles (Griffanti et al., 2018).
3. Normalization to Intracranial Volume (ICV): All WMH volumes were normalised to intracranial volume (ICV) to account for inter-individual differences in head size. Quality control included visual inspection of segmentation masks, and participants with poor-quality output were excluded from analyses. The resulting PWMH and DWMH volumes were compared across TBI severity groups using ANCOVA, adjusting for age, sex, scanner site, and education.

6.2.5 Diffusion Tensor Imaging (DTI) Analysis

DTI data were processed using the cohort-specific pipelines detailed in Chapter 3 (Section 3.5.2). Briefly, diffusion-weighted images underwent standard preprocessing including motion and eddy-current correction using FSL's eddy, with additional susceptibility distortion correction (topup) applied to EPAD data only. Tensor fitting was performed using DTIFIT, producing maps of fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and mode of anisotropy (MO). After projection onto a common white matter skeleton using Tract-Based Spatial Statistics (TBSS), region-specific FA and MD values were extracted from 15 white matter regions of interest defined by the JHU atlas. MO and RD were not included in subsequent analyses due to lower interpretability and

weaker associations with clinical outcomes in prior TBI studies. Voxel-wise statistical inference was not performed; rather, mean FA and MD values were compared between groups using region-level summary statistics to maintain comparability across cohorts and minimise multiple comparison concerns.

6.2.6 Statistical Analysis and Covariates

For all analyses, age, sex, APOE4 status, and years of education were included as covariates to control for potential confounding factors.

6.3 Results

6.3.1 Total Brain Volume and Subcortical Structure Volumes

Table 1 shows the comparisons of total brain volume (TBV), grey matter volume (GMV), white matter volume (WMV), and subcortical structure volumes across the no head injury, single mTBI, and repeated mTBI groups. No significant differences were observed in total brain volume ($p = 0.440$), grey matter volume ($p = 0.780$), or white matter volume ($p = 0.970$) between the groups.

Table 6.2. Cortical and subcortical volumes by severity group (mean ± SD)

	No Head Injury (n=334)	Single mTBI (n=90)	Repeated mTBI (n=248)	p
Total Brain Volume (mm^3)	1520670.12 (58973)	1518838.84 (61628)	1520286.00 (61262)	0.440
Grey Matter Volume (mm^3)	767778.74 (43964)	774278.40 (45973)	778189.02 (38830)	0.780
White Matter Volume (mm^3)	742715.70 (40432)	747728.81 (41301)	749403.18 (38830)	0.970
SUBCORTICAL STRUCTURES				
Left Hippocampal Volume (mm^3)	4994 (716)	4968 (630)	4974 (689)	0.450
Right Hippocampal Volume (mm^3)	5135 (713)	5111 (626)	5068 (708)	0.150
Right Amygdala Volume (mm^3)	1711 (295)	1684 (292)	1692 (316)	0.391
Left Amygdala Volume (mm^3)	1716 (299)	1694 (311)	1678 (355)	0.310
Left Thalamus Volume (mm^3)	10145 (869)	10195 (880)	10300 (946)	0.532
Right Thalamus Volume (mm^3)	9856 (876)	9968 (797)	10056 (919)	0.304
Left Caudate Volume (mm^3)	4290 (513)	4352 (511)	4407 (529)	0.846
Right Caudate Volume (mm^3)	4544 (513)	4569 (511)	4615 (546)	0.817
Left Putamen Volume (mm^3)	6170 (767)	6297 (631)	6323 (795)	0.743
Right Putamen Volume (mm^3)	6130 (775)	6295 (612)	6344 (713)	0.617

Left Pallidum Volume (mm^3)	2374 (370)	2293 (264)	2319 (309)	0.428
Right Pallidum Volume (mm^3)	2409 (366)	2369 (273)	2398 (306)	0.342

Similarly, the volumes of the subcortical structures, including the hippocampus, amygdala, thalamus, caudate, putamen, and pallidum, did not significantly differ across groups. For example, left hippocampal volume (p = 0.450) and right hippocampal volume (p = 0.150) showed no significant differences between groups. The same pattern was observed for other structures, including the thalamus, amygdala, and caudate. This indicates that mTBI, whether single or repeated, does not appear to be associated with significant changes in these subcortical volumes in this population.

6.3.2 White Matter Hyperintensities (WMH)

Table 6.3. Total white matter hyperintensity (WMH) volume, deep WMH volume, and periventricular WMH volume (mm^3) across severity groups. Mean and SD reported.

	No Head Injury	Single mTBI	Repeated mTBI	P value	Post hoc
Total WMH	2598 (6121)	3281 (6836)	5721 (12693)	0.097	N/A
Deep WMH	1876 (5046)	1353 (3143)	1043 (2943)	0.321	N/A
Periventricular WMH	1555 (3928)	1928 (4099)	3845 (8004)	**0.049**	rmTBI>no head injury rmTBI>smTBI

While no significant differences were observed for total WMH volume (p = 0.097) or deep WMH volume (p = 0.321), periventricular WMH volume was significantly higher in the repeated mTBI group compared to both the no head injury and single mTBI groups (p = 0.049). However, this result does not survive correction for multiple comparisons, suggesting that the observed increase in periventricular WMH in repeated mTBI should be interpreted with caution.

6.3.3 Grey Matter Concentration

Table 6.4. Results from VBM analysis comparing grey matter concentration across severity groups

T-test	Study specific template p-value	UKB template p-value
No head injury > smTBI	0.78	0.58
smTBI > no head injury	0.23	0.80
No head injury > rmTBI	0.18	0.71
rmTBI > no head injury	0.20	0.53
smTBI > rmTBI	0.12	0.94
rmTBI > smTBI	0.46	0.64

No significant differences in grey matter concentration were detected across any of the comparisons, whether using the study-specific GM template or the UK Biobank GM template. For example, the comparison of grey matter concentration between the no head injury and repeated mTBI groups yielded non-significant p-values of 0.18 (study-specific template) and 0.71 (UKB template). This suggests that grey matter concentration is not significantly altered by mTBI in this cohort, regardless of injury severity.

6.3.4 Correlation Between Subcortical Volumes and Cognitive Scores

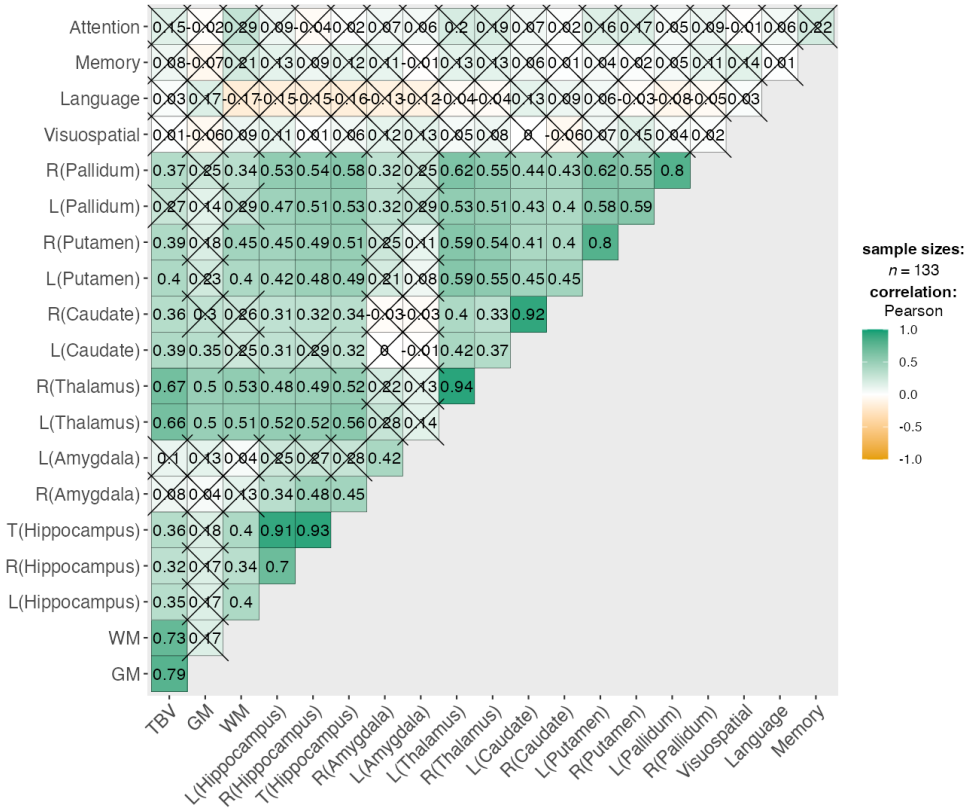


Figure 6.1. Correlation matrix for no head injury group

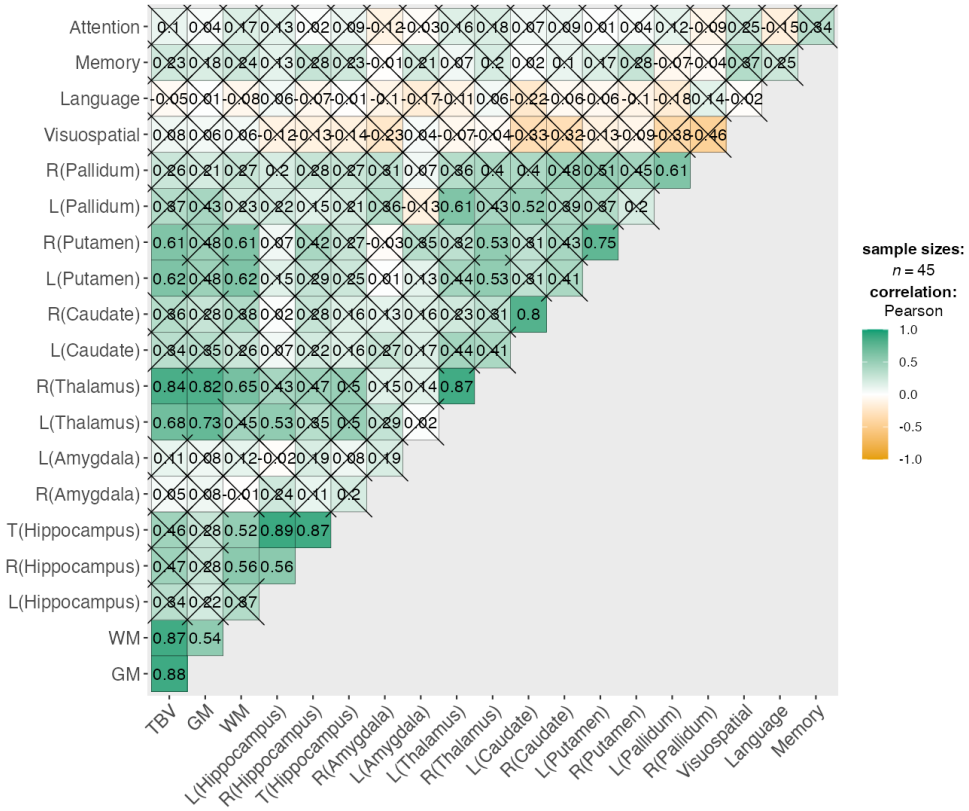


Figure 6.2. Correlation matrix for single mild TBI

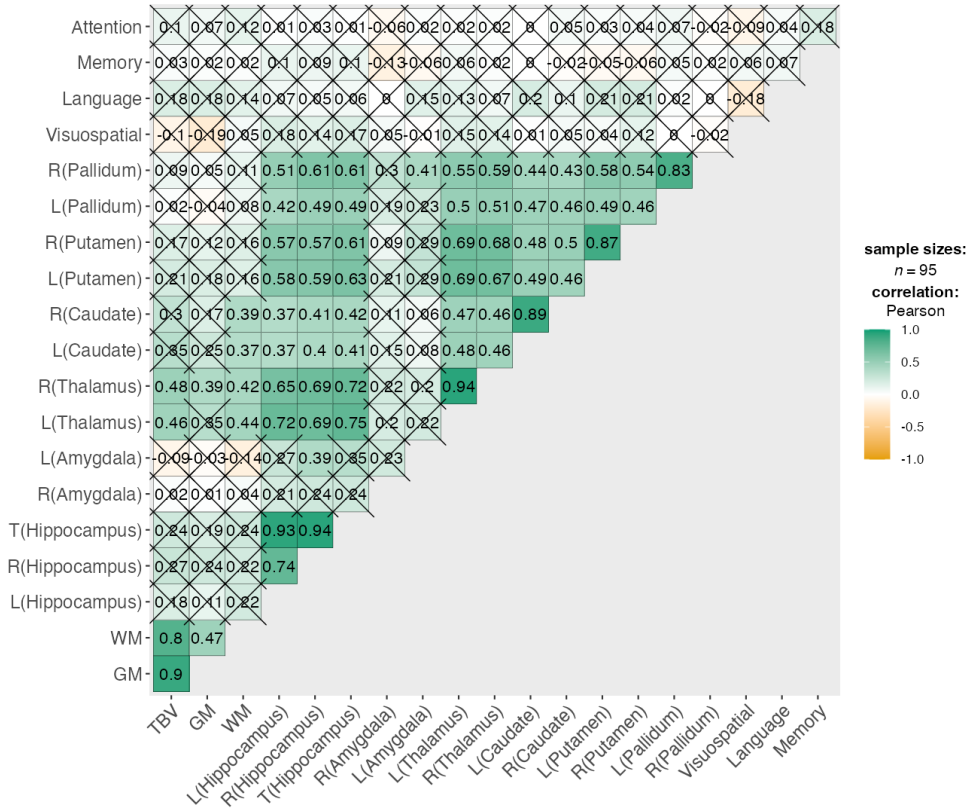


Figure 6.3. Correlation matrix for repeated mild TBI

Figures 6.1 to 6.3 illustrate the correlations between subcortical volumes and cognitive scores across cognitive domains such as visuospatial ability, language, memory, and attention. No significant correlations were found between any subcortical structure volume and cognitive performance in any of the groups, as indicated by the absence of significant Pearson correlations ($p > 0.05$). This finding further supports the absence of a clear relationship between subcortical brain volumes and cognitive outcomes in individuals with mTBI or no head injury.

6.3.5 Fractional Anisotropy (FA) and Mean Diffusivity (MD) in White Matter Tracts

Table 6.5. FA and MD values for multiple white matter tracts across severity groups

	FA Values Mean (SD)				**MD Values Mean (SD)**			
	No Head Injury	**smTBI**	**rmTBI**	**p**	**No Head Injury**	**smTBI**	**rmTBI**	**p**
Middle cerebellar peduncle	0.608 (0.029)	0.609 (0.027)	0.608 (0.030)	0.696	7.4×10^{-4} (0.000041)	7.4×10^{-4} (0.000040)	7.4 × 10-4 (0.000041)	0.823
Left Corona radiata	0.483 (0.031)	0.486 (0.027)	0.488 (0.0310)	0.941	7.7×10^{-4} (0.000040)	7.7×10^{-4} (0.000038)	7.6 × 10-4 (0.000039)	0.674
Right Corona radiata	0.492 (0.031)	0.493 (0.028)	0.494 (0.030)	0.931	7.6×10^{-4} (0.000040)	7.6×10^{-4} (0.000038)	8.0 × 10-4 (0.000038)	0.682
Left Anterior limb of internal capsule	0.614 (0.024)	0.613 (0.022)	0.616 (0.023)	0.579	7.1×10^{-4} (0.000036)	7.1×10^{-4} (0.000032)	7.1 × 10-4 (0.000037)	0.877
Right Anterior limb of internal capsule	0.615 (0.024)	0.616 (0.022)	0.618 (0.023)	0.671	7.1×10^{-4} (0.000033)	7.1×10^{-4} (0.000031)	7.1 × 10-4 (0.000035)	0.763
Left Posterior limb of internal capsule	0.523 (0.027)	0.524 (0.025)	0.521 (0.028)	0.905	6.78×10^{-4} (0.000024)	6.80×10^{-4} (0.000024)	6.80 × 10-4 (0.000024)	0.780

Right Posterior limb of internal capsule	0.52 (0.027)	0.523 (0.026)	0.522 (0.030)	0.994	6.82×10^{-4} (0.000025)	6.82 × 10^{-4} (0.000025)	6.8 × 10-4 (0.000024)	0.865
Left Cingulum	0.633 (0.024)	0.633 (0.022)	0.637 (0.023)	0.256	7.7×10^{-4} (0.000030)	7.7 × 10^{-4} (0.000027)	7.66 × 10-4 (0.000030)	0.432
Right Cingulum	0.666 (0.0223)	0.666 (0.022)	0.670 (0.022)	0.165	7.76×10^{-4} (0.000032)	7.76 × 10^{-4} (0.000030)	7.60 × 10-4 (0.000031)	0.443
Left Superior longitudinal fasciculus	0.711 (0.025)	0.713 (0.022)	0.712 (0.024)	0.452	7.11283 × 10^{-4} (0.0000246628)	7.1 × 10^{-4} (0.0000253434)	7.1 × 10-4 (0.0000260826)	0.651
Right Superior longitudinal fasciculus	0.707 (0.027)	0.708 (0.024)	0.708 (0.0242)	0.978	7.16435 × 10^{-4} (0.000027128)	7.18774× 10^{-4} (0.0000272266)	7.15185× 10^{-4} (0.0000267303)	0.661
Left Optic radiation	0.503 (0.020)	0.504 (0.019)	0.505 (0.0200)	0.989	7.77362 × 10^{-4} (0.0000266197)	7.75825× 10^{-4} (0.0000260784)	7.77228× 10^{-4} (0.0000281145)	0.998
Right Optic radiation	0.504 (0.020)	0.505 (0.019)	0.506 (0.020)	0.890	7.75119 × 10^{-4} (0.0000292682)	7.76001× 10^{-4} (0.000028152)	7.73587× 10^{-4} (0.0000298264)	0.799
Genu of corpus callosum	0.734 (0.030)	0.735 (0.029)	0.740 (0.030)	0.483	7.99888 × 10^{-4} 4(0.000048418)	7.99973× 10^{-4} (0.0000402035)	7.92271× 10^{-4} (0.0000458637)	0.344
Splenium of corpus callosum	0.814 (0.021)	0.813 (0.020)	0.814 (0.020)	0.610	7.03305 × 10^{-4} (0.0000321796)	7.08719× 10^{-4} (0.0000335043)	7.0303× 10^{-4} (0.0000337768)	0.200

Additionally, figures 6.4 to depict the correlations between FA and MD values, respectively, and cognitive scores across the cognitive domains of visuospatial ability, language, memory, and attention across severity groups. As with subcortical volumes, no significant correlations were observed between FA or MD values in any white matter tracts and cognitive performance. This suggests that changes in white matter integrity, as measured by FA and MD, are not closely related to cognitive outcomes in this cohort.

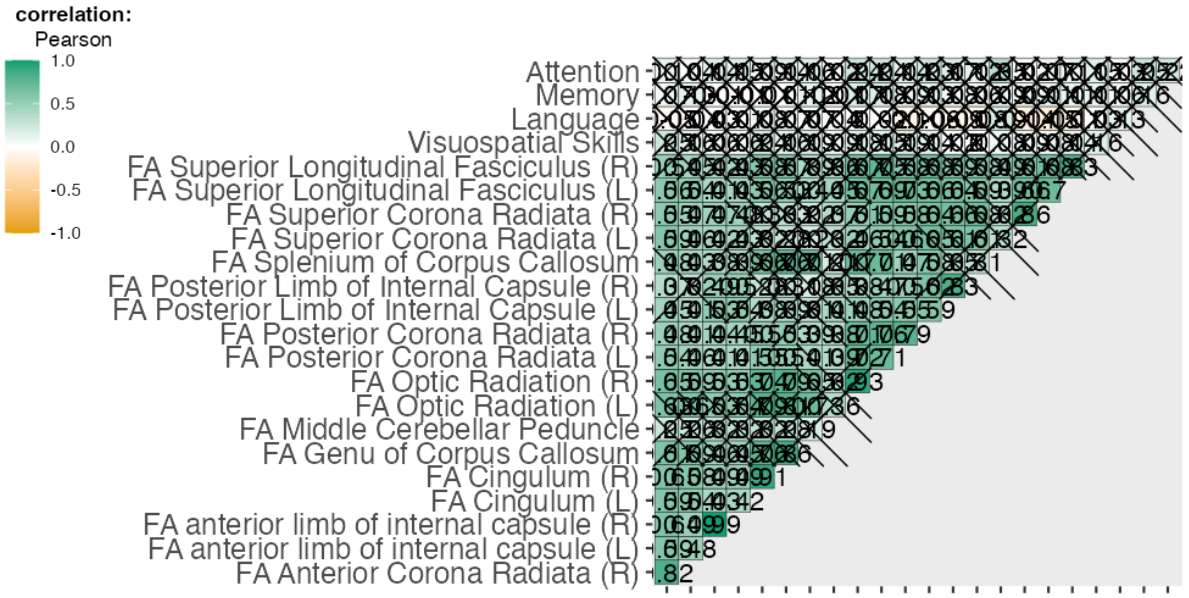


Figure 6.4. FA correlation matrix for no head injury group

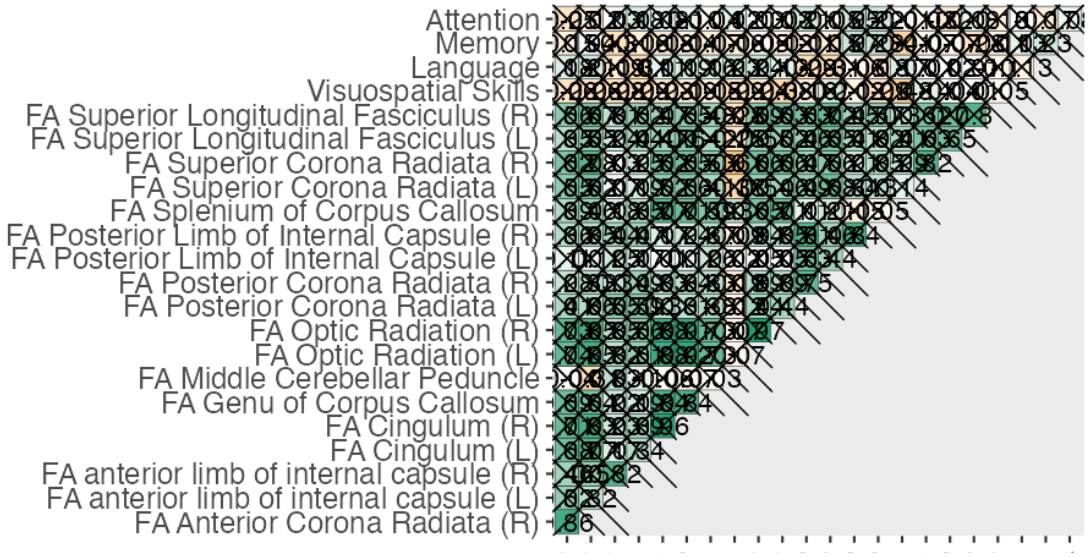


Figure 6.5. FA correlation matrix for smTBI group

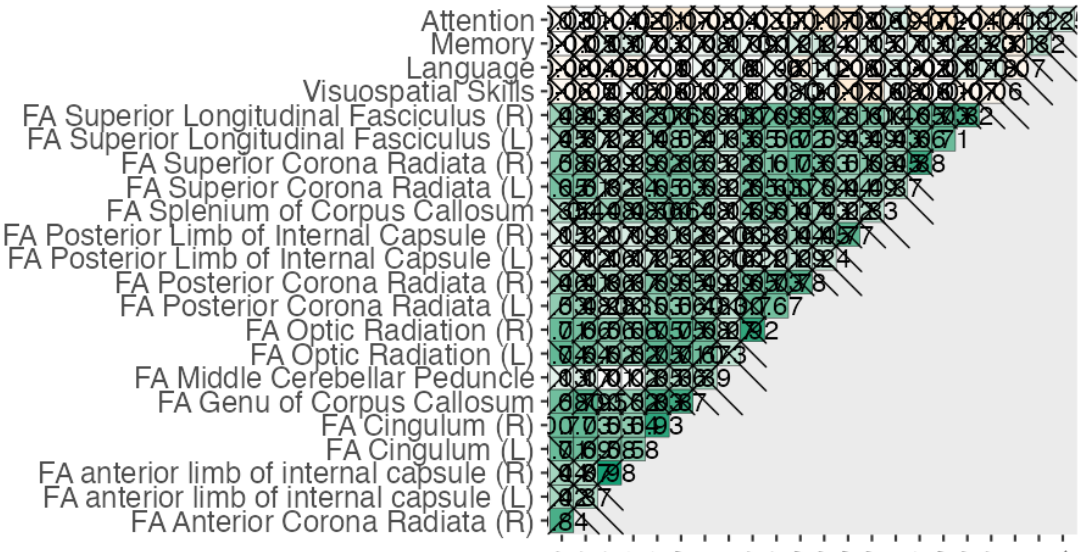


Figure 6.6. FA and cognition correlation matrix for rmTBI group

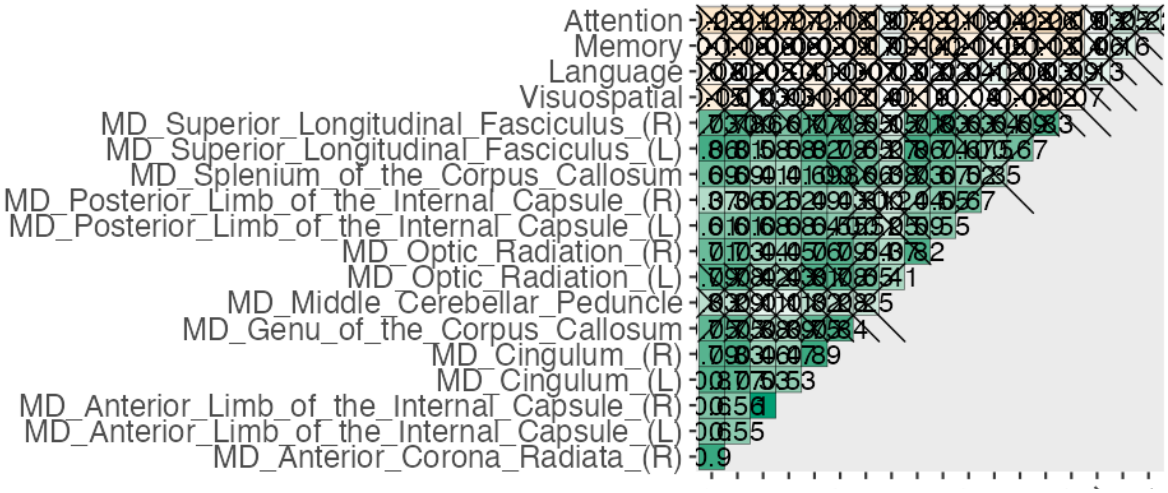


Figure 6.7. MD and cognition correlation matrix for no head injury group

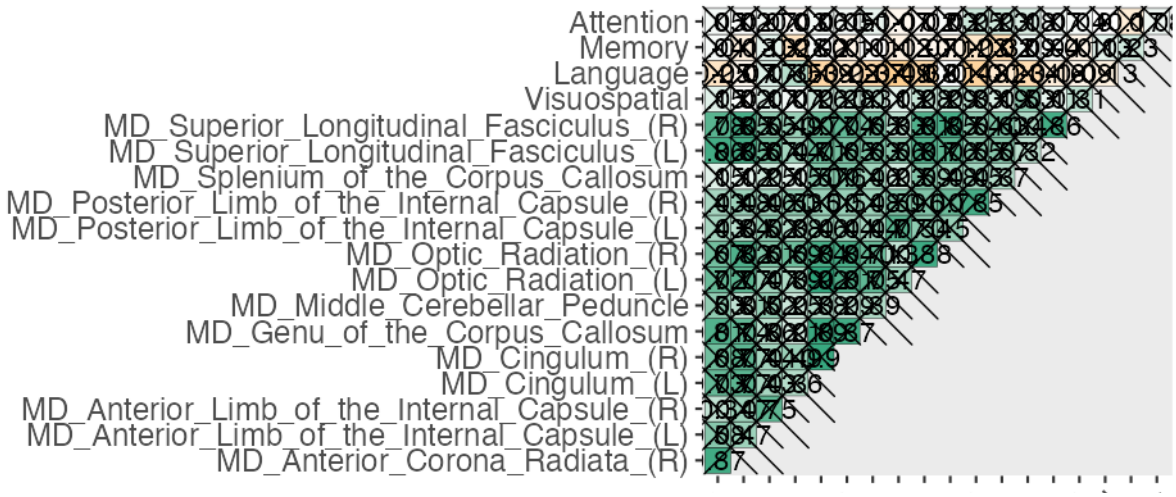


Figure 6.8. MD and cognition correlation matrix for smTBI group

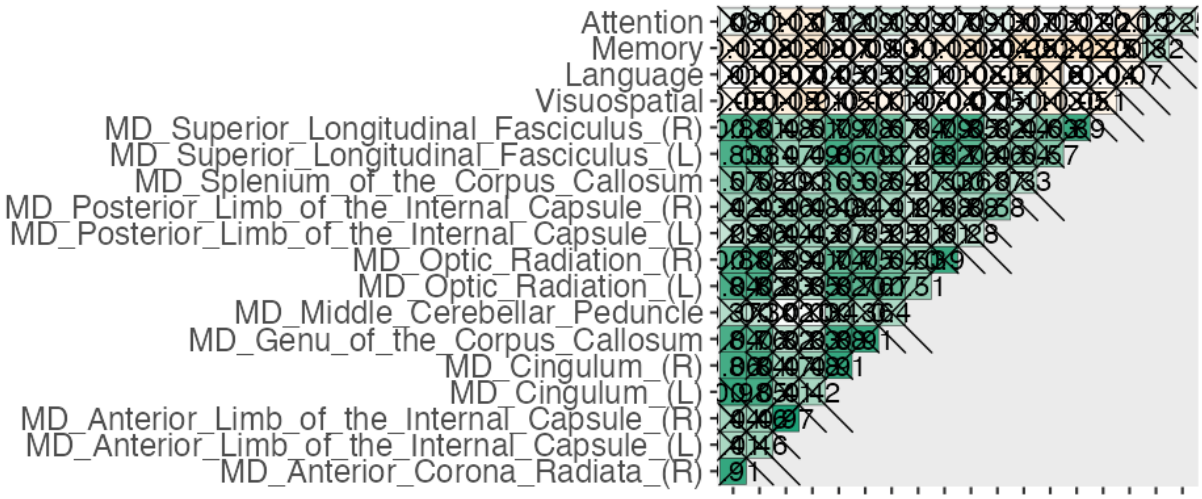


Figure 6.9. MD and cognition correlation matrix for rmTBI group

6.4 Discussion

This study aimed to investigate the impact of a history of single or repeated mTBI on brain structure and white matter integrity in mid to early-late life using a harmonised multimodal neuroimaging dataset. While the results did not support the primary hypotheses, several important observations were made that contribute to the broader understanding of mTBI's impact on brain structure in this population. Additionally, some methodological choices, including the decision not to use NODDI due to limitations in the imaging protocols of the PREVENT cohort, also shape the interpretation of the findings.

6.4.1 Absence of Group Differences in Total Brain Volume and Subcortical Volumes

Contrary to the initial hypothesis, no significant differences in total brain volume (TBV), grey matter volume (GMV), or white matter volume (WMV) were observed between the no head injury, single mTBI, and repeated mTBI groups. Similarly, there were no significant differences in the volumes of subcortical structures, including the hippocampus, amygdala, thalamus, caudate, and putamen. This absence of group-level differences may reflect the subtlety of neuroanatomical changes associated with mTBI, particularly within mid-life populations. Prior research suggests that the brain atrophy

observed in more severe TBI or in conditions such as chronic traumatic encephalopathy (CTE) is typically more pronounced than what is seen in mild or repeated mTBI (McKee et al., 2013).

To contextualise these findings, hippocampal volume in the no-injury group was compared to published normative data from large-scale cohorts such as UK Biobank and ADNI. In this sample, mean bilateral hippocampal volume in the no-injury group was approximately 3.45 cm^3. This is consistent with normative values reported for healthy individuals aged 55 to 70 years, which typically range from 3.4 to 3.6 cm^3 after adjusting for intracranial volume (Fjell et al., 2009; Nobis et al., 2019). These findings indicate that the control group was cognitively and neurologically typical for their age, supporting the notion that structural integrity was preserved across all groups.

One possible explanation for the null findings is the influence of cognitive reserve. Individuals with higher reserve—often associated with factors such as educational attainment, occupational complexity, and lifelong intellectual engagement—are thought to possess a greater capacity to compensate for neural injury. In this study, years of education was included as a covariate in all statistical models, which may have reduced residual group differences by accounting for this protective factor. As discussed in Chapter 5, cognitive reserve can modulate the clinical impact of neural pathology. Although reserve cannot be directly measured in this analysis, it may contribute to the observed preservation of subcortical volume across groups.

Taken together, these findings suggest that, within this relatively well-educated and high-functioning cohort, mTBI is not associated with detectable reductions in subcortical volume at mid-life. This does not preclude the possibility of late-onset decline, nor does it exclude the potential for subtle regional changes undetectable using the methods applied here. Longitudinal data and more sensitive multimodal imaging techniques may be required to identify individual-level vulnerabilities that emerge later in life.

6.4.2 White Matter Hyperintensities and Repeated mTBI

One of the more notable findings was the significant increase in periventricular white matter hyperintensities (PWMH) in the repeated mTBI group compared to both the no head injury and single mTBI groups. Although this result did not survive multiple comparisons correction, it suggests that repeated mTBI may accelerate the development of white matter pathology, particularly in periventricular regions. Increased WMH burden, especially periventricular WMHs, has been associated with aging, vascular pathology, and neurodegenerative conditions such as AD (Debette & Markus, 2010). This finding provides some support for the hypothesis that repeated head injuries contribute to cumulative damage over time, even if these changes are not yet detectable in total brain volume or subcortical structure measurements.

However, another limitation of this study is the use of self-reported mTBI history to classify participants. This could introduce recall bias, where participants may underreport or misclassify the severity of their injuries. This could affect the accuracy of group classifications, potentially obscuring real differences between groups. Future studies should aim to use medical records or clinical assessments to confirm the presence and severity of mTBI more reliably.

6.4.3 Grey Matter Concentration and mTBI

The VBM analysis did not reveal significant differences in grey matter concentration across the no head injury, single mTBI, and repeated mTBI groups, regardless of whether the study-specific GM template or the UK Biobank GM template was used. While some prior studies have reported reduced grey matter in the frontal cortex and hippocampus following mTBI (Bigler, 2013), our results suggest that grey matter alterations may be less pronounced in this midlife population or may require more sensitive imaging techniques to detect.

An important consideration in interpreting these findings is again the role of cognitive reserve. As previously discussed, cognitive reserve might act as a protective buffer, allowing individuals to maintain normal cognitive function despite underlying brain damage. This protective effect could mask potential grey matter loss in populations with higher cognitive reserve, such as those with higher education levels, which were controlled for in this analysis (Stern, 2009). While VBM is a robust method for detecting structural brain changes, it may not fully capture more subtle, diffuse changes that occur at the microstructural level in mTBI populations.

6.4.4 White Matter Integrity (FA and MD) and Cognitive Correlations

The diffusion tensor imaging (DTI) analysis revealed no significant differences in fractional anisotropy (FA) or mean diffusivity (MD) values across white matter tracts, and there were no significant correlations between FA/MD values and cognitive performance.

Additionally, no significant correlations were found between FA or MD values and performance on cognitive domains. This aligns with emerging literature that questions the sensitivity of conventional DTI metrics in detecting subtle microstructural changes associated with mTBI, particularly in cohorts with predominantly mild injuries (Mayer et al., 2010; Eierud et al., 2014).

In this study, white matter integrity was assessed by extracting average FA and MD values from large regions of interest (e.g., splenium, internal capsule), derived from a skeletonised TBSS pipeline. While this method allows for efficient and anatomically standardised comparisons across individuals, it may lack the spatial resolution necessary to detect small, focal changes characteristic of mTBI.

More spatially sensitive approaches, such as voxel-wise tract-based statistical analyses, fixel-based analysis (Raffelt et al., 2017), or region-specific tractometry (Chamberland et al., 2021), have demonstrated greater sensitivity in identifying subtle changes in fibre density, orientation dispersion,

or axonal integrity. These methods allow for more nuanced characterisation of injury patterns, particularly in regions with complex fibre geometry.

The absence of significant FA or MD differences in this analysis may therefore reflect the methodological limitations of using global summary statistics rather than a true lack of microstructural disruption. Similarly, the lack of correlation between diffusion metrics and cognitive outcomes suggests that either (1) mTBI-related white matter injury was too subtle or spatially localised to be captured with the methods used, or (2) white matter integrity, as captured by conventional tensor-based measures, is not the dominant substrate of cognitive change in this population.

6.4.5 Absence of NODDI Analysis and Its Impact

One of the key limitations of this study is the absence of NODDI (Neurite Orientation Dispersion and Density Imaging) analysis. NODDI offers a more advanced approach to assessing microstructural white matter changes, providing metrics related to neurite density and orientation dispersion, which may be more sensitive to the subtle effects of mTBI than FA and MD (Zhang et al., 2012). However, due to the limitations of the PREVENT cohort's imaging protocol, NODDI was not feasible for this study. The PREVENT cohort did not include the multi-shell diffusion acquisition necessary for NODDI, which limited our ability to assess more detailed microstructural changes.

The decision to harmonise the PREVENT and EPAD datasets, despite differences in imaging protocols, was necessary to ensure consistency across the two cohorts. However, this precluded the use of more advanced imaging techniques in the EPAD cohort alone. This represents a limitation, as previous research has shown that NODDI can reveal microstructural changes in white matter that are not captured by traditional DTI metrics (Palacios et al., 2020). Future studies should prioritize multi-shell diffusion protocols to enable the use of NODDI or similar techniques, which may provide greater sensitivity in detecting the microstructural consequences of mTBI.

6.4.6 Implications for Alzheimer's Disease Risk

The findings of this study also have important implications for understanding the potential links between mTBI and AD. As discussed in Chapter 1, mTBI has been associated with an increased risk of developing AD, particularly in individuals with a history of repeated head trauma. The observed increase in periventricular WMH in the repeated mTBI group, even if not significant after correction, may point to early white matter changes that could predispose individuals to AD pathology.

WMH have been consistently linked to an increased risk of cognitive decline and AD, particularly in mid to late life (Debette & Markus, 2010). Given that this cohort is enriched for individuals with a family history of Alzheimer's and the APOE4 allele, the potential for mTBI to exacerbate white matter pathology in these vulnerable individuals warrants further investigation.

However, the homogeneity of the sample (participants enriched for Alzheimer's disease risk), while valuable for studying this specific at-risk group, may limit the generalizability of the findings to broader populations. Future research should aim to study a more diverse sample to assess whether these findings hold true in populations with lower genetic risk for Alzheimer's.

6.5 Future Directions

While this chapter provides important insights into the structural brain changes associated with a history of mTBI, several areas remain unexplored that warrant further investigation. One of the key limitations of the present study is its cross-sectional design, which only allows for a snapshot of the brain at a single point in time. To fully understand the long-term impact of mTBI, it is crucial to investigate whether mTBI accelerates ongoing cognitive decline and neurodegeneration in populations at risk for Alzheimer's disease. The next chapter will address this critical gap by employing longitudinal analyses to track changes in brain structure and cognitive performance over time.

Moreover, advanced neuroimaging techniques, such as NODDI, could provide a more detailed understanding of microstructural changes in white matter that were not captured by traditional DTI measures in this chapter. By incorporating such techniques in future studies, researchers could identify earlier or more subtle markers of white matter damage associated with mTBI. Additionally, exploring neural biomarkers related to Alzheimer's disease, such as amyloid or tau pathology, may offer further insight into how mTBI contributes to neurodegenerative processes in midlife and later.

Lastly, future studies should aim to conduct longitudinal analyses of both cognitive and imaging data to determine whether mTBI not only creates vulnerability to neurodegeneration but also accelerates these changes over time. By addressing these questions, we can gain a clearer understanding of the long-term risks associated with mTBI and identify potential targets for early intervention.

6.6 Conclusion

In conclusion, this study did not find evidence to suggest that a history of mTBI creates vulnerability to neurodegeneration in mid to early late life. These results are encouraging, particularly for individuals who may be concerned about the long-term effects of mTBI on brain health. Despite widespread concerns about the link between mTBI and neurodegeneration, the absence of significant differences in total brain volume, subcortical volumes, grey matter concentration, and white matter integrity suggests that mTBI may not necessarily heighten vulnerability to Alzheimer's disease in this cohort.

It is important to note that these findings are based on cross-sectional data, which provides only a snapshot in time. While the lack of significant structural changes in the mTBI group is reassuring, more subtle or progressive changes may emerge over time. Longitudinal studies will be critical to determining whether mTBI contributes to an accelerated trajectory of cognitive decline or

neurodegeneration in later life. Additionally, incorporating more advanced neuroimaging techniques, such as NODDI, may reveal microstructural changes in white matter that were not captured by traditional DTI metrics in this study.

In this study, amyloid and tau biomarker data were not available for the PREVENT cohort, and to ensure consistency and avoid potential bias, amyloid-positive participants were excluded from the EPAD cohort. While this approach reduced the possibility of contamination of the dataset, it limits the ability to explore the specific interaction between mTBI and Alzheimer's disease pathology in those who are already amyloid-positive. Future research should seek to integrate biomarker data across cohorts to provide a clearer picture of how mTBI may interact with Alzheimer's disease-related biomarkers.

Ultimately, while the current findings offer a positive outlook for individuals with a history of mTBI, further research is essential to confirm these results and explore the longer-term implications of mTBI on brain health. This study provides a solid foundation for understanding the potential structural impacts of mTBI in midlife, but future work should aim to track cognitive and neuronal trajectories over time to fully understand the role of mTBI in aging and neurodegenerative disease risk.

Chapter 7: Does a history of mTBI in a population at risk of AD in mid to early-late life alter cognitive and neural trajectories?

7.1 Introduction

TBI, particularly mild TBI (mTBI), has emerged as a potential risk factor for accelerated cognitive decline and neurodegenerative changes, especially in populations predisposed to Alzheimer's disease (AD) (Fann et al., 2018). Mild TBI is common, often resulting from falls, sports injuries, or accidents, and while its immediate effects can be subtle, accumulating evidence suggests that even mild injuries may have long-term impacts on brain health. Prior chapters in this thesis explored cross-sectional relationships between mTBI history and neurodegeneration, finding limited evidence that self-reported mTBI alone predisposes individuals to significant cognitive impairments in mid-to-early-late life. However, the potential for mTBI to accelerate age-related changes in both cognitive and neural trajectories over time remains a crucial area of investigation. This chapter addresses this gap by exploring whether a history of single or repeated mTBI is associated with distinct cognitive and neural trajectories in an AD-risk population, leveraging longitudinal data to assess changes in memory, attention, language, and visuospatial abilities, alongside neuroimaging metrics.

The long-term effects of mTBI on cognition and brain structure have been an area of mixed findings. Some studies suggest that individuals with repeated mTBIs experience accelerated declines in cognitive domains such as memory, attention, and language, and may exhibit early signs of neurodegeneration, including structural changes in white matter integrity and cortical atrophy (e.g., Fann et al., 2014; Wang et al., 2015). Others, however, report limited or non-significant associations, particularly over short follow-up periods (Smith et al., 2019). Meta-analyses highlight this inconsistency, suggesting that outcomes may depend on factors such as injury severity, frequency, and individual differences in cognitive reserve (Rabinowitz & Levin, 2014). Therefore, longitudinal

studies are essential to disentangle these effects and identify potential early indicators of cognitive and neural decline in populations at elevated risk for AD.

One important framework for understanding these mixed results is cognitive reserve, a concept describing the brain's resilience to pathology, which is often influenced by factors like education, occupation, and intellectual engagement (Stern, 2012). Higher cognitive reserve is thought to buffer against cognitive impairments following brain injuries, including mTBI, possibly by enabling alternative neural pathways or compensatory mechanisms. In populations with lower reserve, however, repeated mTBI may contribute to more rapid cognitive and neural decline, especially in domains sensitive to aging and neurodegeneration, such as episodic memory and processing speed (Koenig et al., 2020). The concept of cognitive reserve provides a valuable lens for understanding the potential variability in mTBI outcomes, particularly in this study's population, where participants have varying levels of education and life experiences that may moderate the impact of mTBI.

Neuroinflammation has also been implicated as a mechanistic link between mTBI and neurodegeneration. Research has shown that TBI, even at mild levels, can trigger a sustained inflammatory response in the brain, potentially accelerating the deposition of amyloid-beta and tau proteins—hallmarks of AD pathology (Ramlackhansingh et al., 2011; Johnson et al., 2013). This prolonged inflammatory response may lead to disruptions in white matter integrity, synaptic loss, and cortical thinning, which are detectable via advanced neuroimaging techniques like diffusion tensor imaging (DTI) and volumetric MRI (Bramlett & Dietrich, 2015). By examining neuroimaging metrics longitudinally, this study aims to explore whether individuals with a history of mTBI show structural brain changes consistent with accelerated neurodegeneration, providing potential biomarkers for early identification of at-risk individuals.

This chapter utilizes data from the PREVENT and EPAD cohorts, two longitudinal studies that follow individuals in mid-to-late life who are at heightened risk for AD. These cohorts are particularly suitable for examining the cumulative impact of mTBI over time due to their extensive baseline cognitive and neuroimaging data and regular follow-up assessments. Our approach involves examining cognitive changes across multiple domains (memory, attention, language, and visuospatial abilities) over a 24-month period while also integrating neuroimaging data to assess changes in brain structure, including white matter integrity and grey matter volume. The integration of both cognitive and neuroimaging data aims to provide a more comprehensive understanding of how mTBI affects both cognitive function and brain health in an AD-risk population.

7.2 Research Aims and Hypotheses

The primary aim of this chapter is to investigate whether a history of single or repeated mTBI is associated with accelerated decline in cognitive performance and neural integrity in individuals at risk for AD. We hypothesize that:

1. **Cognitive Trajectories**: Participants with a history of mTBI, particularly those with repeated injuries, will exhibit a more pronounced decline in memory, attention, language, and visuospatial abilities over the 24-month follow-up period, compared to those with history no head injury history.
2. **Neuroimaging Trajectories**: Participants with mTBI histories will show greater structural changes, including reduced white matter integrity, and lower grey matter volumes over the study period.

These hypotheses are grounded in literature suggesting that mTBI may exacerbate age-related cognitive and neural decline, especially in those with lower cognitive reserve or more frequent injuries (Barnes et al., 2016; Iverson et al., 2017). By exploring both cognitive and neural trajectories

longitudinally, this study aims to contribute critical insights into the potential role of mTBI as a modifiable risk factor for accelerated aging in populations at risk for AD.

7.3 Clinical and Research Implications

Understanding the long-term impact of mTBI on cognitive and neural health in an at-risk population has significant clinical implications. If a history of mTBI is associated with accelerated cognitive and neural decline, this could inform early intervention strategies, such as regular cognitive assessments and targeted rehabilitation programs for individuals with mTBI history. Additionally, neuroimaging biomarkers of mTBI-related decline could aid in identifying those at highest risk, potentially guiding personalized interventions to delay or mitigate progression toward AD. Furthermore, this research contributes to a growing body of literature emphasizing the need for tailored clinical approaches that account for individual variability in cognitive reserve and injury history.

In conclusion, this chapter seeks to advance our understanding of how mTBI affects cognitive and neural trajectories in individuals at risk for AD. By leveraging longitudinal cognitive data and neuroimaging data, this study offers a comprehensive approach to assessing the potential long-term effects of mTBI on brain health, with a particular focus on identifying early indicators of neurodegeneration. Such findings could ultimately support the development of prevention and intervention strategies tailored to individuals with mTBI history, contributing to improved outcomes in populations vulnerable to AD.

7.4 Methodology

7.4.1 Participants

As previously discussed, participants were categorized into three groups based on their self-reported history of TBI: no head injury (N=380), single mTBI (N=71), and repeated mTBI (N=108). This categorization enabled a focused investigation of whether differing TBI histories impact cognitive and

neural trajectories over time. This study followed a longitudinal design, with cognitive and neuroimaging assessments conducted at baseline and at a 24-month follow-up. The two-year period was selected as an initial window for detecting potential changes in cognitive and neural trajectories associated with TBI.

7.4.2 Demographic and Clinical Characteristics

To address potential confounding variables, demographic and clinical characteristics, including age, sex, years of education, and health conditions (e.g., hypertension, coronary disease, history of psychiatric illness), were collected and compared across groups. Significant differences were found in age, years of education, and sex ($p < 0.001$ for age and education, $p = 0.002$ for sex), with the repeated mTBI group being slightly younger, more educated, and having a higher proportion of males. These variables were included as covariates in the subsequent analyses to mitigate their potential influence on cognitive and neuroimaging outcomes.

Table 7.1. Demographic and clinical characteristics by severity group

	No Head Injury (N=380)	**Single mTBI (N=71)**	**Repeated mTBI (N=108)**	**Significance of intergroup differences**
Age	63.1(8.8)	57.6(9.4)	55.1(9.3)	<0.001
Years of Education	15.0(3.9)	15.8(3.7)	16.2(3.5)	<0.001
Sex (Male%/Female%)	32%/68%	37%/63%	46%/54%	0.002
Ethnicity (% Caucasian)	97.6%	97.2%	96.0%	0.405
Hypertension (Y%)	10.4%	13.7%	12.2%	0.360
Stroke (Y%)	0.6%	0%	0.9%	0.440

Coronary disease (Y%)	24.7%	31.8%	28.1%	0.120
Diabetes (Y%)	3.6%	2.0%	2.7%	0.460
History of drug use (Y%)	28.0%	33.8%	32.0%	0.155
Any history of psychiatric illness (Y%)	38.1%	39.4%	39.7%	0.870

7.4.3 Cognitive Assessment

Cognitive function was evaluated across four domains: memory, attention, language, and visuospatial abilities. These domains were chosen based on prior research indicating their sensitivity to TBI-related cognitive dysfunction and their relevance as indicators of neurodegenerative processes in individuals at risk for AD. Each domain has been discussed in detail in previous chapters as part of the theoretical framework guiding this study. Scores for each cognitive domain were recorded at baseline and again at a 24-month follow-up, allowing us to observe potential changes over time.

7.4.4 Neuroimaging Data Collection and Processing

Neuroimaging data were collected and processed as detailed in Chapter 3. For this study, a longitudinal approach was applied to assess structural and diffusion MRI data. Longitudinal neuroimaging data were harmonised using Longitudinal NeuroHarmonize, ensuring compatibility across imaging sites and timepoints, and processed for metrics such as TBV, FA, MD, and WMHs.

7.4.5 Statistical Analysis

Two main analyses were conducted:

1. **Cognitive Analysis**: Repeated measures analysis of covariance (ANCOVA) was employed to assess changes in cognitive performance over time across TBI severity groups, with age, sex,

APOE4 and education included as covariates. This approach was chosen for its robustness in handling within-subject changes while accounting for between-group differences.

2. **Neuroimaging Analysis**: Longitudinal analyses on neuroimaging metrics were compared from baseline and follow-up measures to determine whether TBI severity is associated with accelerated neural decline.

For both cognitive and neuroimaging data, significance was set at $p < 0.05$. Post hoc tests were planned to further investigate any significant interactions. Effect sizes (η^2) and confidence intervals were reported to aid interpretation.

7.5 Results

7.5.1 Cognitive Performance Over Time

Table 7.2. Repeated Measures ANCOVA for cognitive performance across severity groups. Z score and SD reported for each time point of each domain

		No Head Injury	**Single mTBI**	**Repeated mTBI**	**p value**	**Post hoc comparisons**
Memory	Baseline	0.13 (0.04)	0.19 (0.08)	0.13 (0.06)	0.93	N/A
	Year 2	-0.071 (0.05)	0.13 (0.10)	0.04 (0.07)		
Attention	Baseline	-0.004 (0.05)	-0.37 (0.10)	-0.29 (0.07)	0.27	N/A
	Year 2	0.07 (0.05)	-0.18 (0.11)	-0.11 (0.08)		
Language	Baseline	0.08 (0.05)	0.10 (0.10)	0.17 (0.08)	0.25	N/A
	Year 2	-0.04 (0.05)	0.03 (0.12)	0.26 (0.10)		
Visuospatial	Baseline	0.13 (0.05)	0.08 (0.11)	0.23 (0.09)	0.25	N/A
	Year 2	-0.02 (0.05)	0.09 (0.12)	-0.02 (0.10)		

The repeated measures ANCOVA revealed no statistically significant group-by-time interactions across any cognitive domains, indicating that cognitive trajectories were similar across TBI groups over the two-year period.

- **Memory**: Baseline memory scores were comparable across groups, with means (SE) of 0.13 (0.04) for the no head injury group, 0.19 (0.08) for the single mTBI group, and 0.13 (0.06) for the repeated mTBI group. At 24 months, memory scores showed minor, non-significant changes in each group ($p = 0.93$, $\eta^2 = 0.001$).
- **Attention**: Attention scores improved slightly in the no head injury group from baseline (-0.004, SE = 0.05) to 24 months (M = 0.07, SE = 0.05), while declines were observed in the single and repeated mTBI groups. These changes were not statistically significant ($p = 0.27$, $\eta^2 = 0.004$).
- **Language**: Minor increases in language scores were seen across groups, with baseline and 24-month scores remaining stable overall. The interaction effect was non-significant ($p = 0.25$, $\eta^2 = 0.005$).
- **Visuospatial Abilities**: Baseline visuospatial scores were similar across groups, with minor fluctuations by the 24-month follow-up. There was no significant group-by-time interaction ($p = 0.25$, $\eta^2 = 0.004$).

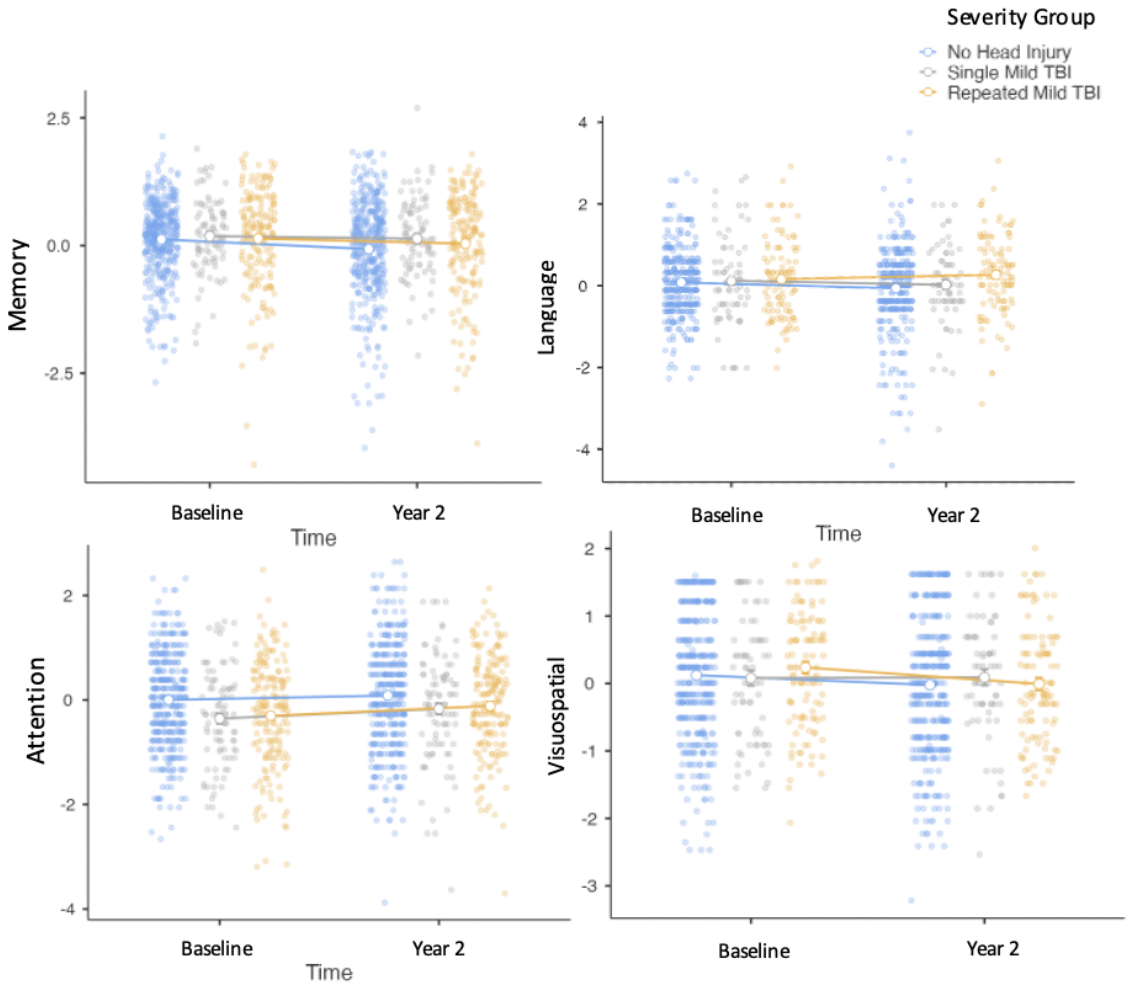


Figure 7.1. Scatterplots of cognitive domain performance over time

7.5.2 Neuroimaging Analysis

Table 7.3. Cortical and subcortical volumes across severity group over time

		No Head Injury (n=136)	Single mTBI (n=36)	Repeated mTBI (n=90)	p
Total Brain Volume (mm^3)	Baseline	1520670.12 (58973)	1518838.84 (61628)	1520286.00 (61262)	0.150
	Year 2	1520641.75 (61848)	1534254.92 (65369)	1534840.57 (72107)	
Grey Matter Volume (mm^3)	Baseline	767778.74 (43964)	774278.40 (45973)	778189.02 (38830)	0.626
	Year 2	775910.19 (38475)	774457.82 (38035)	773533.00 (44687)	

White Matter Volume (mm^3)	Baseline	742715.70 (40432)	747728.81 (41301)	749403.18 (38830)	0.468
	Year 2	752579.42 (37437)	759160.03 (39597)	762073.05 (38999)	
SUBCORTICAL STRUCTURES					
Left Hippocampal Volume (mm^3)	Baseline	4994 (716)	4968 (630)	4974 (689)	0.163
	Year 2	5903.0 (871)	5727.0 (1074)	5771.0 (872)	
Right Hippocampal Volume (mm^3)	Baseline	5135 (713)	5111 (626)	5068 (708)	0.450
	Year 2	5896.0 (981)	6045.0 (811)	5950.0 (971)	
Right Amygdala Volume (mm^3)	Baseline	1711 (295)	1684 (292)	1692 (316)	0.328
	Year 2	1951 (354)	2039 (334)	1986 (353)	
Left Amygdala Volume (mm^3)	Baseline	1716 (299)	1694 (311)	1678 (355)	0.412
	Year 2	1955 (390)	2015 (364)	1981 (425)	
Left Thalamus Volume (mm^3)	Baseline	10145 (869)	10195 (880)	10300 (946)	0.902
	Year 2	11862 (1328)	11966 (1346)	12062 (1463)	
Right Thalamus Volume (mm^3)	Baseline	9856 (876)	9968 (797)	10056 (919)	0.210
	Year 2	11511 (1283)	11741 (1275)	11696 (1457)	
Left Caudate Volume (mm^3)	Baseline	4290 (513)	4352 (511)	4407 (529)	0.767
	Year 2	5025 (690)	4920 (744)	5112 (729)	
Right Caudate Volume (mm^3)	Baseline	4544 (513)	4569 (511)	4615 (546)	0.275
	Year 2	5271 (757)	5227 (754)	5444 (782)	
Left Putamen Volume (mm^3)	Baseline	6170 (767)	6297 (631)	6323 (795)	0.713
	Year 2	7249 (977)	7204 (1006)	7285 (861)	
Right Putamen Volume (mm^3)	Baseline	6130 (775)	6295 (612)	6344 (713)	0.528
	Year 2	7249 (905)	7324 (794)	7338 (883)	
Left Pallidum Volume (mm^3)	Baseline	2374 (370)	2293 (264)	2319 (309)	0.900
	Year 2	2695 (435)	2692 (377)	2744 (445)	
Right Pallidum Volume (mm^3)	Baseline	2409 (366)	2369 (273)	2398 (306)	0.927
	Year 2	2764 (431)	2784 (335)	2801 (442)	

Total Brain Volume (TBV)

Repeated Measures ANOVA revealed significant within-subject effects for TBV across time points ($F = 50.89$, $p < 0.001$, $\eta 2 = 0.013$), indicating measurable changes over the two-year period. However, no significant interaction between time and severity group ($F = 1.91$, $p = 0.150$, $\eta 2 = 0.001$) was observed, suggesting that TBV changes were consistent across the no-head-injury, single-mTBI, and repeated-mTBI groups. Between-subjects effects revealed no significant differences in overall TBV by severity group ($F = 0.274$, $p = 0.76$). All analyses controlled for sex, age, years of education, and APOE4 status.

Grey Matter (GM) Volume

A highly significant within-subject effect was found for GM volume over time ($F = 42{,}273.42$, $p < 0.001$, $\eta 2 = 0.97$). The interaction of time and severity group was not significant ($F = 0.47$, $p = 0.626$), suggesting that GM volume changes over time were uniform across groups. Between-subject effects did not reveal significant differences across severity groups ($F = 0.343$, $p = 0.71$). Post-hoc tests with Bonferroni correction confirmed uniform reductions across groups. All results accounted for sex, age, years of education, and APOE4 status.

White Matter (WM) Volume

WM volume demonstrated significant within-subject changes over time ($F = 61.02$, $p < 0.001$, $\eta 2 = 0.064$). However, as with TBV and GM, the interaction between time and severity group was non-significant ($F = 0.761$, $p = 0.468$, $\eta 2 = 0.002$), and no significant between-group differences were observed ($p = 0.461$). Post-hoc corrections confirmed significant reductions over time but no between-group differences. Sex, age, years of education, and APOE4 status were included as covariates.

Subcortical Structures

Regional analyses of subcortical structures revealed significant within-subject effects for multiple regions:

- Left Hippocampus: $F = 515.34$, $p < 0.001$, $\eta 2 = 0.168$.
- Right Hippocampus: $F = 519.36$, $p < 0.001$, $\eta 2 = 0.154$.
- Left Amygdala: $F = 178.38$, $p < 0.001$, $\eta 2 = 0.094$.
- Right Amygdala: $F = 317.38$, $p < 0.001$, $\eta 2 = 0.131$.
- Left Thalamus: $F = 17{,}202.34$, $p < 0.001$, $\eta 2 = 0.968$.
- Right Thalamus: $F = 846.93$, $p < 0.001$, $\eta 2 = 0.250$.
- Left Caudate: $F = 658.07$, $p < 0.001$, $\eta 2 = 0.157$.
- Right Caudate: $F = 703.16$, $p < 0.001$, $\eta 2 = 0.166$.

Post-hoc comparisons, adjusted for multiple comparisons using the Bonferroni method, did not reveal significant group-level differences for subcortical volume changes between the no head injury group, repeated mTBI and single mTBI. While significant reductions in subcortical volumes were observed between baseline and Year 2 across all groups (main effect of time, $p < 0.001$), these changes did not differ significantly by mTBI severity group. Analyses were adjusted for covariates including sex, age, years of education, and APOE4 status.

7.5.3 White Matter Hyperintensities (WMH)

Table 7.4. Total white matter hyperintensity (WMH) volume, deep WMH volume, and periventricular WMH volume (mm^3) across the no head injury, single mTBI, and repeated mTBI groups over time. Means and SD reported.

		No Head Injury	Single mTBI	Repeated mTBI	P value	Post hoc
Total WMH	Baseline	2598 (6121)	3281 (6836)	5721 (12693)	0.088	N/A
	Year 2	1392 (2947)	2733 (8707)	2006 (7638)		
Deep WMH	Baseline	1876 (5046)	1353 (3143)	1043 (2943)	0.163	N/A
	Year 2	630 (1073)	1424 (4369)	814 (2311)		
Periventricular WMH	Baseline	1555 (3928)	1928 (4099)	3845 (8004)	0.063	N/A
	Year 2	762 (2163)	1309 (4503)	1192 (5523)		

White Matter Hyperintensities (WMH)

Mixed-design repeated-measures ANCOVA examined the effects of TBI severity group (no history, single mTBI, repeated mTBI) on total WMH, deep WMH, and periventricular WMH volumes across two time points (baseline and Year 2).

Total WMH

The between-subjects effect of severity group approached significance ($F(2, 216) = 2.46$, $p = 0.088$, $\eta 2 = 0.02$), with higher total WMH volumes in the repeated mTBI group at baseline. However, no significant main effect of time ($F(1, 216) = 0.305$, $p = 0.581$) or interaction between time and severity

group (F(2, 216) = 0.319, p = 0.727) was observed. Post-hoc comparisons did not reveal significant differences across groups at either time point.

Deep WMH

No significant between-group differences were detected (F(2, 216) = 1.83, p = 0.163), and the main effect of time was not significant (F(1, 216) = 0.084, p = 0.772). Interaction effects were also non-significant (F(2, 216) = 0.582, p = 0.560). Post-hoc comparisons showed no statistically significant differences between groups at either baseline or Year 2.

Periventricular WMH (PWMH)

The between-subjects effect approached significance (F(2, 216) = 2.80, p = 0.063, η2 = 0.025), with the repeated mTBI group showing higher PWMH volumes at both baseline and Year 2 compared to other groups. The main effect of time (F(1, 216) = 0.619, p = 0.432) and the interaction between time and severity group (F(2, 216) = 0.216, p = 0.806) were not significant. Post-hoc comparisons suggested trends for greater PWMH in the repeated mTBI group at Year 2, but these differences were not statistically significant.

Table 7.5. FA and MD values of ROIs over time across severity groups

		FA Values Mean (SD)				MD Values Mean (SD)			
		No Head Injury	**smTBI**	**rmTBI**	**p**	**No Head Injury**	**smTBI**	**rmTBI**	**p**
Middle cerebellar peduncle	Baseline	0.608 (0.029)	0.609 (0.027)	0.608 (0.030)	0.376	7.4×10^{-4} (0.000041)	7.4×10^{-4} (0.000040)	7.4 × 10-4 (0.000041)	0.727
	Year 2	0.677 (0.031)	0.669 (0.032)	0.677 (0.031)		6.50 (4.70)	6.45 (4.45)	6.39 (5.27)	
Left Corona radiata	Baseline	0.483 (0.031)	0.486 (0.027)	0.488 (0.031)	0.556	7.7×10^{-4} (0.000040)	7.7×10^{-4} (0.000038)	7.6 × 10-4 (0.000039)	0.175
	Year 2	0.499 (0.031)	0.498 (0.031)	0.504 (0.032)		7.6×10^{-4} (0.000044)	7.6×10^{-4} (0.000042)	7.5×10^{-4} (0.000042)	
Right Corona radiata	Baseline	0.492 (0.031)	0.493 (0.028)	0.494 (0.030)	0.326	7.6×10^{-4} (0.000040)	7.6×10^{-4} (0.000038)	8.0 × 10-4 (0.000038)	0.265
	Year 2	0.507 (0.031)	0.502 (0.032)	0.510 (0.033)		7.6×10^{-4} (0.000042)	7.5×10^{-4} (0.000035)	7.5×10^{-4} (0.000037)	
Left Anterior limb of internal capsule	Baseline	0.614 (0.024)	0.613 (0.022)	0.616 (0.023)	0.461	7.1×10^{-4} (0.000036)	7.1×10^{-4} (0.000032)	7.1 × 10-4 (0.000037)	0.107
	Year 2	0.634 (0.028)	0.632 (0.028)	0.638 (0.029)		7.07×10^{-4} (0.000049)	7.08×10^{-4} (0.000051)	7.01×10^{-4} (0.000052)	

Right Anterior limb of internal capsule	Baseline	0.615 (0.024)	0.616 (0.022)	0.618 (0.023)	0.521	7.1×10^{-4} (0.000033)	7.1×10^{-4} (0.000031)	7.1 × 10-4 (0.000035)	0.162
	Year 2	0.644 (0.029)	0.642 (0.026)	0.647 (0.029)		7.09×10^{-4} (0.000044)	7.09×10^{-4} (0.000045)	7.36×10^{-4} (0.000045)	
Left Posterior limb of internal capsule	Baseline	0.523 (0.027)	0.524 (0.025)	0.521 (0.028)	0.308	6.78×10^{-4} (0.000024)	6.80×10^{-4} (0.000024)	6.80 × 10-4 (0.000024)	0.135
	Year 2	0.714 (0.032)	0.717 (0.032)	0.719 (0.035)		6.82×10^{-4} (0.000046)	6.79×10^{-4} (0.000048)	6.74×10^{-4} (0.000051)	
Right Posterior limb of internal capsule	Baseline	0.52 (0.027)	0.523 (0.026)	0.522 (0.030)	0.380	6.82×10^{-4} (0.000025)	6.82×10^{-4} (0.000025)	6.8 × 10-4 (0.000024)	0.213
	Year 2	0.714 (0.033)	0.714 (0.034)	0.717 (0.035)		6.86×10^{-4} (0.000046)	6.86×10^{-4} (0.000050)	6.78×10^{-4} (0.000054)	
Left Cingulum	Baseline	0.633 (0.024)	0.633 (0.022)	0.637 (0.023)	0.538	7.7×10^{-4} (0.000030)	7.7×10^{-4} (0.000027)	7.66 × 10-4 (0.000030)	0.684
	Year 2	0.686 (0.037)	0.683 (0.036)	0.696 (0.036)		7.44×10^{-4} (0.000050)	7.48×10^{-4} (0.000050)	7.36×10^{-4} (0.000045)	
Right Cingulum	Baseline	0.666 (0.0223)	0.666 (0.022)	0.670 (0.022)	0.198	7.76×10^{-4} (0.000032)	7.76×10^{-4} (0.000030)	7.60 × 10-4 (0.000031)	0.461
	Year 2	0.647 (0.039)	0.639 (0.037)	0.656 (0.037)		7.27×10^{-4} (0.000048)	7.28×10^{-4} (0.000037)	7.19×10^{-4} (0.000046)	
	Baseline	0.711 (0.025)	0.713 (0.022)	0.712 (0.024)	0.674	7.11283×10^{-4} (0.0000246628)	7.1×10^{-4} (0.0000253434)	7.1 × 10-4 (0.0000260826)	0.098

Left Superior longitudinal fasciculus	Year 2	0.033 (0.029)	0.558 (0.026)	0.558 (0.029)		7.18 × 10^{-4} (0.0000372)	7.20 × 10^{-4} (0.0000340)	7.14 × 10^{-4} (0.0000372)	
Right Superior longitudinal fasciculus	Baseline	0.707 (0.027)	0.708 (0.024)	0.708 (0.024)	0.404	7.16435 × 10^{-4} (0.000027128)	7.18774× 10^{-4} (0.0000272266)	7.15185× 10^{-4} (0.0000267303)	0.210
	Year 2	0.557 (0.029)	0.557 (0.027)	0.562 (0.030)		7.23 × 10^{-4} (0.0000403)	7.23 × 10^{-4} (0.0000356)	7.17 × 10^{-4} (0.0000433)	
Left Optic radiation	Baseline	0.503 (0.020)	0.504 (0.019)	0.505 (0.020)	0.881	7.77362 × 10^{-4} (0.0000266197)	7.75825× 10^{-4} (0.0000260784)	7.77228× 10^{-4} (0.0000281145)	0.266
	Year 2	0.663 (0.037)	0.660 (0.037)	0.667 (0.035)		7.79 × 10^{-4} (0.0000541)	8.01 × 10^{-4} (0.0000564)	7.93 × 10^{-4} (0.0000515)	
Right Optic radiation	Baseline	0.504 (0.020)	0.505 (0.019)	0.506 (0.020)	0.824	7.75119 × 10^{-4} (0.0000292682)	7.76001× 10^{-4} (0.000028152)	7.73587× 10^{-4} (0.0000298264)	0.805
	Year 2	0.672 (0.040)	0.671 (0.046)	0.676 (0.038)		7.83 × 10^{-4} (0.0000659)	7.83 × 10^{-4} (0.0000649)	7.80 × 10^{-4} (0.0000595)	
Genu of corpus callosum	Baseline	0.734 (0.030)	0.735 (0.029)	0.740 (0.030)	0.133	7.99888 × 10^{-4} 4(0.000048418)	7.99973× 10^{-4} (0.0000402035)	7.92271× 10^{-4} (0.0000458637)	0.237
	Year 2	0.770 (0.039)	0.7691 (0.039)	0.777 (0.033)		7.54 × 10^{-4} (0.0000505)	7.57 × 10^{-4} (0.0000480)	7.44 × 10^{-4} (0.0000445)	
Splenium of corpus callosum	Baseline	0.814 (0.021)	0.813 (0.020)	0.814 (0.020)	0.394	7.03305 × 10^{-4} (0.0000321796)	7.08719× 10^{-4} (0.0000335043)	7.0303× 10^{-4} (0.0000337768)	0.520

	Year 2	0.823 (0.032)	0.820 (0.036)	0.829 (0.033)	6.94 × 10^{-4} (0.0000558)		7.03 × 10^{-4} (0.0000617)		6.86 × 10^{-4} (0.0000597)		

Repeated Measures ANOVA for FA and MD revealed significant within-subject effects across various subregions:

- FA - Left Anterior Corona Radiata: $F = 163.815$, $p < 0.001$, $\eta 2 = 0.028$.
- FA - Right Anterior Corona Radiata: $F = 192.05$, $p < 0.001$, $\eta 2 = 0.030$.
- FA - Left Anterior Limb of Internal Capsule: $F = 164.585$, $p < 0.001$, $\eta 2 = 0.081$.
- FA - Right Anterior Limb of Internal Capsule: $F = 253.165$, $p < 0.001$, $\eta 2 = 0.148$.
- MD - Left Cingulum: $F = 88.017$, $p < 0.001$, $\eta 2 = 0.075$.
- MD - Right Cingulum: $F = 164.859$, $p < 0.001$, $\eta 2 = 0.140$.

Interactions between time and severity group were non-significant for both FA and MD values, suggesting consistent trajectories across groups.

7.6 Discussion

7.6.1 Global Changes in Brain Volume

Significant within-subject effects for TBV, GM, and WM volumes underscore the presence of detectable structural changes over time across all participants. These findings align with the known trajectory of brain aging, characterized by progressive reductions in brain volume and alterations in white matter integrity (Fjell & Walhovd, 2010; Raz et al., 2005). The absence of significant between-group differences or interactions suggests that these changes are driven more by systemic factors such as age, rather than by a history of mTBI.

However, it is important to note that the observed increases in total brain volume (TBV) and hippocampal volume over time are likely to be artefactual, as they are inconsistent with normative aging data, which show expected annual declines of approximately 0.2 to 0.5% for TBV and 1 to 1.5% for hippocampal volume in mid-to-late life (Fjell et al., 2009; Scahill et al., 2003). These findings likely reflect scan-rescan variability, segmentation error, or harmonisation artefacts. As such, they must be interpreted cautiously and are unlikely to indicate genuine structural gains.

The minor trends in the repeated-mTBI group towards greater volume loss, while non-significant, may still warrant further investigation over a longer follow-up window. These findings are consistent with studies demonstrating delayed or progressive atrophy following repetitive head trauma (Montenigro et al., 2017; Singh et al., 2014).

The longitudinal data presented here suggest that while baseline measures may not capture injury effects, subtle changes may accumulate over time, particularly in populations with repeated mTBI. These findings also extend the observations in Chapter 6, where global measures of brain volume at baseline did not indicate significant differences, highlighting the importance of longitudinal designs to uncover subtle or emerging patterns.

7.6.2 Microstructural Changes in FA and MD

The reductions in FA and increases in MD observed in white matter regions, such as the anterior corona radiata and cingulum, highlight potential microstructural degradation associated with repeated mTBI. These findings align with previous studies suggesting that these regions are particularly vulnerable to diffuse axonal injury (Sharp & Jenkins, 2015; Xiong et al., 2014).

However, the direction of change was not always consistent with expectations. For example, a small increase in splenial FA was noted across groups, which contradicts age-related decline patterns reported in the literature (Barrick et al., 2010). This may again reflect variability in scanner conditions or processing inconsistencies, rather than biological change.

Although interaction effects were not significant, the repeated-mTBI group exhibited more pronounced changes in these metrics, suggesting that mTBI may exacerbate underlying neurodegenerative processes.

These results expand upon the findings in Chapter 6, where baseline FA and MD differences across TBI groups were not significant. While this may indicate emerging change over time, the trends remain non-significant and inconsistent in direction. The longitudinal analysis highlights how mTBI may accelerate age-related microstructural changes, emphasizing the need for studies with extended follow-up periods to determine whether these trends evolve into significant group differences. Advanced imaging methods, such as neurite orientation dispersion and density imaging (NODDI), could enhance sensitivity to microstructural changes (Zhang et al., 2012; Elliott et al., 2019). By quantifying neurite density and complexity, NODDI could provide greater insight into white matter integrity and complement traditional FA and MD analyses. Future studies employing such methodologies could help uncover more nuanced effects of mTBI on microstructural integrity.

7.6.3 White Matter Hyperintensities (WMH)

The WMH analysis revealed consistently higher levels of total WMH, deep WMH, and PWMH in the repeated-mTBI group, particularly for PWMH, which approached statistical significance. While the absence of significant findings limits definitive conclusions, these results suggest that repeated mTBI may predispose individuals to greater white matter vulnerability, especially in periventricular regions. Periventricular WMH is often linked to vascular and neuroinflammatory processes, both of which are exacerbated by repeated head injuries (Brickman et al., 2012; Hannay et al., 2017).

However, an unexpected reduction in WMH volume over time was observed across all groups, including repeated-mTBI. This contradicts normative patterns in healthy ageing, where WMH burden typically increases with age (Habes et al., 2016). It is likely that these findings reflect technical limitations, such as segmentation variability or scanner noise, rather than true reductions in lesion burden.

These findings add nuance to the baseline data discussed in Chapter 6, where WMH differences across groups were minimal at a single time point. Nonetheless, the trends observed here should be interpreted cautiously in light of the measurement inconsistencies. Future studies should incorporate advanced lesion characterization techniques to improve segmentation accuracy and assess the clinical relevance of these trends (Wardlaw et al., 2015; Tur et al., 2021).

7.6.4 Cognitive Performance Over Time

Cognitive trajectories across memory, attention, language, and visuospatial domains did not differ significantly between groups, indicating comparable patterns over the two-year follow-up period. However, subtle declines in attention scores for the single and repeated-mTBI groups highlight potential vulnerabilities in this domain. Attention deficits are a well-documented consequence of mTBI and may reflect disruptions in neural networks critical for executive function (Azouvi et al., 2004; Mathias & Wheaton, 2007).

That said, across all groups, including the no head injury group, cognitive performance was largely stable or improved, particularly in the attention domain. This pattern is likely influenced by practice effects, which are common in longitudinal cognitive testing and may obscure genuine decline (Calamia et al., 2012). These effects are especially pronounced in highly educated and motivated research participants, as seen in this cohort.

The cognitive results extend the baseline findings from Chapter 5, which showed no significant differences across cognitive domains at a single time point. The current longitudinal data underscore the importance of tracking cognitive performance over time to identify early, subtle changes that may not be evident in cross-sectional analyses. These results further emphasize the potential for cumulative injury effects, particularly in repeated-mTBI populations (Tellier et al., 2009; Kinnunen et al., 2011).

7.6.5 Critical Evaluation of Non-Significant Findings

The lack of significant group-by-time interactions across structural, microstructural, and cognitive domains reflects several potential limitations. Small effect sizes ($\eta^2 < 0.05$) suggest that the observed changes, while present, may be too subtle to detect within the current sample size.

A post hoc power calculation was conducted using the observed variability in left hippocampal volume in the no-injury group. With a standard deviation of approximately 871 mm^3 and a hypothesised effect size of 100 mm^3 over two years (corresponding to 1% annual hippocampal decline), the estimated Cohen's *d* was 0.115. Detecting such a small group-by-time interaction with 80% power at an alpha level of 0.05 would require approximately 990 participants per group, or nearly 2000 total participants, using a simple between-group comparison. In the context of a repeated measures framework, with additional covariates and inter-scan variability, the required sample size would likely be higher. The left hippocampus was selected for this calculation due to its established vulnerability to both ageing and mTBI (Bigler, 2013), and because normative benchmarks for annualised volume loss are well-documented (Fjell et al., 2009). Additionally, it showed the highest variability among the subcortical structures in the current dataset, making it a conservative and clinically relevant reference region. This analysis supports the conclusion that the current study was underpowered to detect subtle longitudinal effects of mTBI on brain structure or cognition.

Additionally, the reliance on self-reported TBI history introduces variability, potentially diluting the effects of true injury severity. Self-reported data are inherently prone to recall bias and inaccuracies, which may obscure more precise classification of injury severity and frequency (Dams-O'Connor et al., 2014).

Systemic factors, such as cognitive reserve and lifestyle differences, may also play a protective role, mitigating the impact of mTBI on neurodegeneration. While the inclusion of covariates like years of education helps account for some of these influences, such adjustments may inadvertently obscure group differences by capturing broader, non-injury-related effects. These limitations underscore the need for larger, more diverse cohorts and objective measures of TBI exposure to clarify the true impact of mTBI (Stern, 2012; Robertson, 2014).

7.6.6 Future Directions

Future research should address these limitations and build upon the findings of this study to advance our understanding of the long-term impact of mTBI on neurodegeneration and cognitive trajectories. Several directions are particularly important for advancing the field

First , inclusion of more sensitive and biologically specific imaging modalities may help uncover subtype neural changes that conventional metrics like FA and MD fail to detect. Techniques such as neurite orientation dispersion and density imaging (NODDI), diffusion kurtosis imaging (DKI) and fixel-based analysis can provide more granular insight into axonal integrity, neurite density, and microstructural complexity. Resting-state and task-based fMRI, in combination with structural imaging, could also reveal functional connectivity disruptions that are not detectable through anatomical measures alone. These methods have shown promise in recent mTBI studies and would complement the structural focus of the current work.

Second, longer follow-up periods are essential. The two-year follow-up may be insufficient to observe significant group differences or accelerated neurodegenerative processes. Extending the follow-up to five years or more would allow for the detection of more robust structural and cognitive change and could clarify whether early trends evolve into meaningful group differences. Such follow-up would also increase power to detect non-linear patterns of decline or delayed emergence of pathology.

Third, the integration of fluid and molecular biomarkers would provide a more direct measure of neurodegenerative processes. The addition of amyloid and tau PET imaging, CSF-based assays, or blood biomarkers such as neurofilament light (NfL), glial fibrillary acidic protein (GFAP), and UCH-L1 could help determine whether mTBI contributes to the biological cascade associated with Alzheimer's disease and other dementias. Biomarker data could also help validate imaging and cognitive signals, particularly in ambiguous or non-significant cases.

Fourth, future studies should prioritise stratified analyses to identify subgroups who may be more vulnerable to mTBI effects. Stratification by APOE4 status, baseline cognitive reserve, vascular risk, and psychiatric history could reveal meaningful interactions that are masked in group-level analyses. Individuals with lower cognitive reserve or comorbid risk factors may show earlier or more pronounced neurodegenerative change following mTBI. Identifying such subgroups would inform clinical monitoring and targeted intervention strategies.

Finally, larger and more diverse samples will be necessary to improve generalisability and statistical power. A post hoc analysis in this study demonstrated that detecting subtle longitudinal group differences would require sample sizes exceeding 1,000 participants per group. Recruitment efforts should aim to include individuals from a broad range of demographic and clinical backgrounds to capture the heterogeneity of mTBI outcomes and allow for robust modelling of individual differences.

Together, these directions underscore the need for multimodal, longitudinal, and population-informed approaches to fully characterise the long-term consequences of mTBI. The harmonised framework developed in this thesis provides a scalable foundation for such future research.

Chapter 8: General Discussion

8.1 Introduction

This thesis aimed to investigate the long-term cognitive and neural consequences of a history of mild traumatic brain injury (mTBI) in mid-to-early late life, focusing on populations at heightened risk for Alzheimer's disease (AD). Through a harmonised integration of data from two large cohorts, the PREVENT and EPAD studies, the research addressed whether a history of single or repeated mTBI creates vulnerability to neurodegeneration or accelerates cognitive decline. The overarching goals of the thesis were to assess baseline cognitive and neuroimaging profiles, examine longitudinal changes, and identify whether a history of mTBI acts as a risk factor for cognitive and neural decline during mid-life.

While the findings did not reveal significant group-level differences in cognitive or neural decline, they provide critical insights into the complexity of mTBI outcomes in mid-life and suggest that this period may reflect a phase of relative resilience rather vulnerability. The longitudinal design and methodological advancements, such as the implementation of the Brain Injury Screening Questionnaire (BISQ) and development of advanced data harmonisation techniques, position this research as a valuable contribution to the field. To the best of my knowledge, the use of these techniques enabled the assembly of one of the largest cohorts for mid-life mTBI research reported in the literature, providing enhanced statistical power to detect subtle effects. The findings must be interpreted in the context of a broader lifespan perspective. Previous research has demonstrated that both younger and older individuals with mTBI often show persistent structural and cognitive alterations. In younger cohorts, midline white matter structures such as the corpus callosum and cingulum frequently show reduced FA and elevated MD, sometimes persisting for months or years after injury (Koerte et al., 2012; Davenport et al., 2016). In older adults, mTBI has been associated with earlier onset of cognitive impairment and steeper neuroanatomical decline, particularly in individuals

at genetic risk for dementia (LoBue et al., 2017). Against this backdrop, the lack of measurable deficits in the current mid-life sample appears to deviate from these patterns and raises the possibility that compensatory mechanisms, higher cognitive reserve, or methodological factors may obscure early markers of decline.

This chapter summarises the findings, situates them within the broader literature, and critically evaluates their implications for clinical practice, methodological advancement, and future research directions.

8.2 Addressing the Research Questions

This thesis posed three key research questions, which were systematically addressed through the analyses presented in Chapters 5, 6, and 7. These questions are revisited here to highlight how the findings align with the study's objectives.

1. Is a history of single or repeated mTBI associated with altered cognitive profiles in mid-life? The results did not reveal significant group-level differences in cognitive performance across domains, except for limited evidence of attentional impairments in individuals with repeated mTBI. This finding challenges the assumption that mTBI invariably leads to widespread cognitive deficits. Previous studies have reported heterogeneity in cognitive outcomes following mTBI, influenced by factors such as injury severity, cognitive reserve, and comorbidities (Belanger et al., 2005; LoBue et al., 2017).

However, in contrast to younger samples, where attentional and executive dysfunction often persist following mTBI (McAllister et al., 2006), and older cohorts, where mTBI is associated with more pronounced memory and language decline (LoBue et al., 2017), the present findings suggest either a true absence of effect or methodological insensitivity.

The potential influence of practice effects, ceiling effects in cognitive tests, or the over-correction introduced by repeated z-score standardisation may have obscured subtle decline in this mid-life cohort. Furthermore, the timeframe of cognitive decline in preclinical neurodegeneration is typically measured in 5- to 10-year intervals, raising the possibility that early change may not yet have emerged over the two-year follow-up in this study (Sperling et al., 2011; Salthouse, 2010).

2. Do baseline neuroimaging measures characterize the impact of mTBI?

Baseline neuroimaging analyses revealed no significant differences in brain volumes, grey matter concentration or diffusion tensor imaging (DTI) metrics between groups. However, subtle increases in white matter hyperintensities (WMHs) were observed in individuals with repeated mTBI. WMHs have been implicated in neurovascular dysfunction and inflammation, processes that may predispose individuals to future cognitive decline (Brickman et al., 2012; Sharp & Jenkins, 2015). While these findings suggest the presence of subtle neural changes, their clinical relevance remains uncertain.

Importantly, these null findings diverge from extensive literature reporting persistent alterations in midline white matter microstructure following mTBI in younger populations. Reductions in FA and increases in MD in the corpus callosum and cingulum have been consistently reported months or even years after injury (Davenport et al., 2016; Koerte et al., 2012). The absence of such effects in this study may be due to greater cognitive reserve, a lack of power to detect small group differences, or use of summary DTI metrics that lack spatial specificity.

It is also possible that measurement noise or harmonisation artefacts contributed to the inconsistencies in DTI findings, especially given the biologically implausible increase in FA over time. Future studies employing voxel-wise analysis or advanced diffusion models (e.g., NODDI) may improve sensitivity (Hay et al., 2015).

3. Does mTBI accelerate cognitive and neural decline in mid-life?

Longitudinal analyses showed no evidence of accelerated cognitive or neural decline in individuals with a history of mTBI compared to those without. This result provides a reassuring narrative for mid-life individuals, suggesting that mTBI does not necessarily predispose them to rapid neurodegeneration.

However, this conclusion must be treated with caution. Normative longitudinal studies indicate that even in cognitively healthy adults, brain volume and memory performance typically decline over time (Fjell et al., 2009; Singh-Manoux et al., 2012). The fact that this cohort showed minimal decline in either domain over two years suggests that scanner variability, practice effects, or selection bias may have contributed to the apparent resilience. Moreover, hippocampal and WMH data showed unexpected patterns, including volumetric increases and WMH reductions, which likely reflect measurement artefacts rather than biological changes.

In addition, the study was underpowered to detect small effect sizes. Therefore, the null findings may reflect limited statistical power rather than the absence of group differences. Extended follow-up periods and more sensitive methods are required to determine whether mid-life mTBI contributes to longer-term neurodegenerative risk or interacts with ageing processes over time.

8.3 Clinical Implications

Chapter 2 highlighted the diverse neuropathological sequelae of TBI, including CTE, vascular injury and Lewy-body pathology. Although the present work focused on dementia-related neurodegeneration, the absence of pronounced grey-matter loss of WMH acceleration in our mTBI cohort implies that similar null findings may extend to other TBI-linked pathologies that follow vascular or α-synuclein pathways. Conversely, the subtle attentional trend we observed could still be germane to conditions such as CTE, where fronto-subcortical circuitry is preferentially affected. Therefore, while our data

argue against a broad, multi-modal neurodegenerative cascade, they cannot rule out selective vulnerability patterns characteristic of other TBI-associated disorders.

These findings offer important insights for clinicians, researchers and public-health practitioners. The absence of significant cognitive or neural decline provides reassurance to mid-life individuals with a history of mTBI, challenging deterministic narratives about the inevitability of neurodegeneration following such injuries. This is particularly relevant for individuals who experience anxiety about mTBI long-term outcomes, such as athletes and military personnel.

However, the subtle increases in WMHs observed in individuals with repeated mTBI warrant attention. WMHs are emerging as biomarkers of early neurovascular changes, which have been linked to impairments in executive function and processing speed (Brickman et al., 2012). While these changes were not associated with significant cognitive decline in this study, they are consistent with findings in older adults and in those at elevated risk of dementia, where WMHs represent one of the earliest radiological markers of small vessel disease and are predictive of future cognitive decline (Habes et al., 2016). Therefore, they could represent an early signal of vulnerability that becomes more clinically relevant with aging.

Routine cognitive assessments and advanced imaging could play a pivotal role in monitoring these individuals, particularly those with additional risk factors such as APOE4 positivity, vascular comorbidities, or low cognitive reserve. However, the clinical decision to monitor should be tailored based on symptomatology, history of cumulative exposure, and individual risk profile, rather than mTBI history alone.

From a public health perspective, this thesis underscores the importance of striking a balance between prevention and reassurance. Efforts to reduce the incidence of mTBI remain critical, particularly in high-risk groups, but the results suggest that many individuals can maintain stable cognitive and neural

function over time. Public health messaging should therefore aim to reduce undue alarm while promoting evidence-based strategies for prevention, monitoring, and early intervention.

Crucially, in the absence of measurable deficits in asymptomatic individuals, broad application of cognitive rehabilitation programs may not be justified. Instead, the emphasis should shift toward modifiable lifestyle factors, including physical activity, sleep, blood pressure control, and mental health management, which have been shown to mitigate dementia risk and improve post-TBI outcomes (Livingston et al., 2020). Targeted intervention may be more appropriate for individuals who present with clear symptoms or comorbid vulnerabilities, particularly in clinical or high-exposure subgroups.

8.4 Methodological Contributions

This thesis makes several methodological contributions that enhance the field of mTBI research. The use of harmonised data from the PREVENT and EPAD cohorts addressed a critical challenge in multi-site research: variability in data acquisition and analysis protocols. By employing NeuroHarmonize, this study standardized neuroimaging metrics, enabling robust cross-cohort comparisons and enhancing the reliability of the findings. This approach establishes a methodological framework for future studies seeking to integrate diverse datasets.

The inclusion of the BISQ was an asset to the research design, providing a validated tool to systematically document lifetime TBI history and distinguish TBI-related symptoms from other health conditions. Its detailed cueing and comprehensive symptom inventory allowed for a more accurate characterization of participants' injury histories, ensuring that subtle but relevant differences in exposure to mTBI were captured. By capturing comprehensive information on injury severity, frequency, and outcomes, the BISQ allowed for nuanced subgroup analyses that revealed subtle differences between single and repeated mTBI cases. While the reliance on self-reported data introduces potential recall bias, the structured nature of the BISQ tries to mitigate this limitation,

making it a valuable tool for large-scale epidemiological studies. Future work may benefit from supplementing BISQ responses with external verification, such as medical records, wearables, or sensor data, to further strengthen classification accuracy.

Finally, the focus on mid-life populations addresses a critical gap in the literature. As previously discussed, most TBI research has concentrated on young athletes or older adults at the clinical stages of dementia, leaving mid-life as an underexplored period. This thesis highlights mid-life as a window of relative resilience, providing a foundation for understanding how aging processes may interact with prior injuries over time.

8.5 Limitations and General Directions

While this thesis makes important contributions, it is not without limitations. The reliance on self-reported TBI history introduces potential inaccuracies, particularly for injuries occurring decades earlier. Future studies would benefit from triangulating self-report data with objective sources such as medical records, biomechanical monitoring, or proxy informant interviews, especially when investigating injury severity, mechanism, or timing.

The relatively short follow-up period limits the ability to detect late-onset effects of mTBI. Cognitive and structural decline in at-risk individuals often unfolds gradually over five to ten years, and a two-year window may be insufficient to capture meaningful group-by-time divergence. This is particularly relevant in the context of neurodegenerative processes, where preclinical changes may only become detectable after extended follow-up or in the presence of interacting risk factors such as APOE4 carriage, metabolic disease, or vascular burden.

Incorporating advanced neuroimaging techniques represents another area for development. Although this study applied a standardised DTI pipeline, other methods, such as neurite orientation dispersion and density imaging (NODDI), diffusion kurtosis imaging, or fixel-based analysis, may offer improved

sensitivity to microstructural changes. These techniques provide richer models of tissue complexity and have been shown to detect subtle white matter alterations that conventional FA and MD metrics may overlook. Additionally, functional MRI and connectomic approaches could complement structural data by identifying changes in network efficiency, functional integration, or compensation.

Another limitation was the absence of biomarker data in the PREVENT cohort. Biomarkers such as Aβ, tau, NfL, and inflammatory markers would have allowed for a more comprehensive understanding of the biological pathways linking mTBI and neurodegeneration. As recent studies have demonstrated, combining imaging with biofluid or PET markers enhances the ability to differentiate between normal ageing and pathological change, particularly in preclinical AD populations (Zetterberg and Blennow, 2021).

8.6 Future Work

This thesis has provided critical insights into the long-term impact of single and repeated mTBI on neurodegeneration and cognitive decline. However, as with any scientific endeavour, it has also highlighted areas that warrant further investigation. This section outlines key directions for future research, reflecting on the challenges encountered, the opportunities to advance this field, and the characteristics of an ideal cohort for mTBI research.

8.6.1 Ideal Cohort Design

To build upon the findings presented in this thesis, future studies should aim to establish a prospective, well-powered cohort with the following features:

Larger and More Diverse Samples

A larger sample size is critical for detecting small-to-moderate effects sizes and for conducting subgroup analyses that stratify by risk factors such as APOE4, injury severity, and comorbidities. Future

cohorts should include balanced representation across single mTBI, repeated mTBI, and no head injury groups, encompassing a range of socioeconomic backgrounds and cultural contexts.

Integration of Advanced Neuroimaging Techniques

Future cohorts should leverage state-of-the-art neuroimaging modalities, such as NODDI, tau PET imaging, and ultra-high-resolution diffusion imaging. NODDI, in particular, provides a more detailed characterization of microstructural changes in white matter, such as neurite density and orientation dispersion, which may be affected by mTBI (Zhang et al., 2012). This approach can complement traditional DTI and enhance sensitivity to subtle microstructural alterations. Tau PET, which enables direct in vivo assessment of tau deposition, may be particularly informative in those with repeated mTBI exposure, given its established role in traumatic encephalopathy and AD pathology (McKee et al., 2015).

Biomarker Profiling

Future studies should integrate serial collection of blood and cerebrospinal fluid (CSF) biomarkers including, glial fibrillary acidic protein, total tau, phosphorylated tau, and inflammatory cytokines. These biomarkers could help identify early pathophysiological signals that may precede structural or cognitive changes. In combination with imaging data, they may improve early detection of neurodegenerative processes and allow for mechanistic investigations into the relationship between mTBI and dementia risk (Zetterberg & Blennow, 2021).

Longitudinal Follow-Up

Extending follow-up periods will allow researchers to better understand how mTBI interacts with aging and other risk factors for neurodegeneration (Dewan et al., 2018). This study found no significant decline over two years; however, normative ageing and AD-related changes typically become evident over five to ten years. Future cohorts should therefore follow participants across multiple timepoints,

ideally for at least a decade, to examine non-linear and delayed effects of mTBI on brain and cognitive health.

8.6.2 Addressing Major Challenges

The research presented in this thesis faced several methodological and logistical challenges. Future studies should aim to address the following:

Standardisation of Neuroimaging Protocols

Despite harmonization efforts using tools like NeuroHarmonize, variability in imaging parameters remains a challenge in multi-site studies. Adoption of fully standardised acquisition protocols and the use of travelling heads or calibration phantoms can help ensure comparability across scanners (Esopenko & Levine, 2015).

Reliance on Self-Reported TBI History

Self-report tools such as the BISQ provide a pragmatic and cost-effective way of assessing mTBI history, but they are vulnerable to recall bias and may lack temporal precision. Future studies should combine self-report with electronic health records. More detailed characterisation of injury mechanism, location and recovery trajectory will also be critical in understanding heterogeneous outcomes(Dams-O'Connor et al., 2014).

Participant Attrition in Longitudinal Studies

The PREVENT and EPAD cohorts demonstrated attrition over time, which reduced the availability of longitudinal data. Strategies to improve retention, such as remote data collection through virtual assessments or at-home biomarker kits, should be explored (Ritchie et al., 2020). Investing in participant engagement strategies and logistical flexibility will be key to retaining diverse cohorts over extended follow-up periods.

8.6.3 Enhancing Research Efficiency

To streamline future research efforts, several strategies are proposed:

Development of Standardized Diagnostic Tools

The field would benefit from the creation of integrated diagnostic toolkits that combine imaging, fluid biomarkers, and cognitive performance data to stratify individuals by likely disease trajectory. Incorporating digital health technologies, including smartphone-based cognitive tasks and wearable devices to track sleep or activity, may provide scalable, real-time data for detecting early risk markers (Thelin et al., 2017).

Investment in Longitudinal Multi-Site Datasets

Large-scale datasets that harmonise across studies and institutions will be essential for identifying reproducible mTBI effects. Research consortia should focus on developing common data elements, interoperable platforms, and collaborative agreements to facilitate pooled analyses and cross-cohort validation (Yue et al., 2019).

Fostering Inter-Institutional Collaboration

Collaboration across institutions can improve access to diverse datasets and facilitate standardized protocols, increasing the statistical power and generalizability of analyses (Lawrence et al., 2019).

8.6.4 Exploring Mechanisms and Interventions

Understanding the mechanisms underlying the effects of mTBI and identifying effective interventions are critical future directions:

Mechanistic Studies

There remains a need for research into the molecular and cellular processes linking mTBI with neurodegeneration. Animal models and human post-mortem tissue studies will continue to be

essential in investigating tauopathy, amyloid dynamics, chronic inflammation, and blood–brain barrier dysfunction following mTBI (McKee et al., 2015).

Preventive and Therapeutic Approaches

While cognitive rehabilitation may not be warranted for all individuals with mTBI history, selected subgroups may benefit from targeted interventions. Future trials could examine the effectiveness of cognitive training, aerobic exercise, anti-inflammatory agents, or tau-modifying therapies in those with persistent symptoms or imaging biomarkers of risk (LoBue et al., 2017). Importantly, prevention efforts remain critical, particularly in sports and occupational settings where repeated mTBI exposure is common.

8.6.5 Broader Implications for Policy and Practice

The findings from this thesis and future studies have implications beyond academia, informing public health and policy initiatives:

Policy Advocacy

If mTBI contributes to subtle, early-onset structural change, this would justify continued advocacy for head injury prevention policies, particularly in sport, military, and labour-intensive professions. Standardised protocols for injury documentation and reporting should be considered in these settings (Guskiewicz et al., 2003).

Educational Campaigns

Clear communication about the long-term risks of mTBI is needed. Public messaging should reflect the nuanced nature of the findings, emphasising both the potential for resilience and the importance of early detection in at-risk individuals.

8.6.6 Conclusion

This thesis has identified several important directions for future research in the field of mTBI and neurodegeneration. While the findings did not reveal widespread structural or cognitive differences, they highlighted key methodological challenges, areas of subtle vulnerability, and the need for deeper mechanistic understanding.

Rather than concluding that the future of mTBI research lies solely in addressing the challenges highlighted in this thesis, it is more appropriate to state that this work contributes a rigorous and scalable methodological framework upon which others can build. Through harmonised multi-cohort design, application of validated tools like the BISQ, and careful longitudinal follow-up, this thesis demonstrates how mid-life mTBI can be studied with increased precision and reproducibility.

Future studies should prioritise extended follow-up periods, larger and more diverse samples, and multimodal assessments that include advanced imaging and fluid biomarkers. The integration of wearable technology, decentralised data collection methods, and coordinated multi-site initiatives will be essential for improving research efficiency and generalisability. Importantly, the field must also move beyond cross-sectional group comparisons to examine individual trajectories, biological moderators, and the complex interactions between injury, ageing, and resilience.

As research advances, findings will not only refine risk models and screening strategies but may also inform targeted interventions for those most vulnerable to long-term mTBI effects. In doing so, future studies can contribute to early detection, prevention, and personalised care in populations at risk for neurodegenerative disease.

8.7 Conclusion

This thesis represents a significant contribution to understanding the long-term impacts of a history of mild traumatic brain injury (mTBI) in mid-life populations. By addressing critical gaps in the

literature, it provides valuable insights into the cognitive and neural outcomes of individuals with a history of single or repeated mTBI. Through the harmonisation of data from two large cohorts, PREVENT and EPAD, this research offered a comprehensive examination of baseline profiles and longitudinal changes.

The findings challenge deterministic narratives that mTBI inevitably leads to significant cognitive or neural decline. The absence of group-level differences across cognitive and neural measures in this harmonised cohort provides reassurance that mid-life individuals with a history of mTBI may exhibit resilience to long-term effects.

However, subtle increases in white matter hyperintensities (WMHs) in those with repeated mTBI suggest possible early indicators of neurovascular change, and these findings warrant further longitudinal investigation.

Crucially, the null findings must be interpreted with caution. The follow-up period was relatively short, the sample sizes limited the ability to detect small group-by-time interactions, and practice effects may have obscured subtle decline. Post hoc power calculations confirmed that detecting realistic longitudinal changes would require substantially larger samples. Therefore, the current findings should not be taken as definitive evidence of the absence of long-term mTBI effects, but rather as a starting point for more targeted and extended investigation.

Future studies should integrate advanced neuroimaging, biomarker profiling, and extended longitudinal designs to further elucidate the relationships between mTBI, brain ageing, and neurodegenerative risk. A more granular exploration of individual-level factors, such as genetic vulnerability, injury characteristics, and lifestyle profiles, will also be critical in identifying those most likely to benefit from early monitoring or intervention.

This work underscores mid-life as a critical phase for studying brain resilience and vulnerability. While many individuals in this age range appear to maintain stable function after mTBI, subtle neural changes may already be underway in subgroups with repeated injuries or interacting risk factors. By building on the methodological and conceptual foundations laid in this thesis, future research can advance the precision of mTBI science, contribute to the early identification of at-risk individuals, and support more personalised strategies for prevention and care.

Appendix 1 – BISQ with SPSS codings

Brain Injury Screening Questionnaire

- The purpose of this questionnaire is to determine if you have experienced an injury to the brain at any time. Such injuries can have consequences that are hard to predict- from barely noticeable, to life shattering. And sometimes we are not aware that a brain injury is creating problems for ourselves. **Part One** of this questionnaire will help you recall events where such an injury may have occurred. If you have not experienced any of these events, the questionnaire is complete. If you *have* experienced any of these events, you will be asked to complete Part Two and Three. **Part Two** documents the kinds of problems in daily life that people with brain injuries sometimes experience. You should remember as you complete Part Two that most people have *some* of the difficulties listed. **Part Three** asks a few additional important questions.
- The information in this questionnaire is important, as it can help identify a brain injury that may be unknown to you ad identify the particular problems this injury may have caused. This information may be useful, because often the problems caused by brain injury can be helped- but only if the cause of the problems is known.

Today's Date

Day Month Year

☐☐/☐☐/☐☐☐☐

Participant ID Number

PREV_ID

What is your age?

☐☐ years old BISQ_AGE

What is your gender?

0 ☐ Male
1 ☐ Female BISQ_GENDER

What country do you live in?

BISQ_COUNTRY

What is your postal/zip code?

BISQ_POSTALCODE

Approximately, what is the current annual income in your household?

0 ☐ £0 to £6,000
1 ☐ £6,001 to £12,000
2 ☐ £12,001 to £24,000
3 ☐ £24,001 to £36,000 BISQ_INCOME
4 ☐ £36,001 to £60,000
5 ☐ More than £60,000
-8 ☐ Don't Know
-9 ☐ Refuse to reply

Check one box to best describe the highest level you completed in school.

☐ No education
☐ Primary/ Elementary School
☐ High school/ Secondary School
☐ College/ University
☐ Trade/ Technical/ Non-University
☐ Post-Graduate
☐ Refuse to reply

What is your ethnic background?

0 ☐ Caucasian
1 ☐ Hispanic
2 ☐ Black BISQ_ETHNICITY
3 ☐ Asian other
4 ☐ Indian Subcontinent
5 ☐ Other: BISQ_OTHERETHNIC

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Part One: Injuries and Hospitalizations

Participant ID _____

Listed in **Column A** are situations in which people may experience a blow to the head. For each event listed, **record the number of times** you experienced a blow in that type of situation.

For each blow to the head recorded in Column A, please answer the questions in Column B. How many times did you lose consciousness? (Record zero if you never lost consciousness). What was the longest period of loss of consciousness? How many times were you dazed and confused after a blow to the head? What was the longest period you experienced this?

**********COLUMN A**********		********** COLUMN B **********			
		Ever Lose Consciousness?		**Ever Dazed and Confused?**	
A blow to the head in this situation?	**How many times?**	**How many times?**	**Longest Period?**	**How many times?**	**Longest Period?**
1. In a car/van/truck/bus crash?	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_1**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_1A**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_1B**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_1C**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_1D**
2. In a motorcycle or an all-terrain vehicle crash?	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_2**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_2A**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_2B**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_2C**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_2D**

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COLUMN A		**COLUMN B**			
		Ever Lose Consciousness?		**Ever Dazed and Confused?**	
A blow to the head in this situation?	**How many times?**	**How many times?**	**Longest Period?**	**How many times?**	**Longest Period?**
3. As a pedestrian hit by a vehicle?	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_3**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_3A**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_3B**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_3C**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_3D**
4. Being hit by a falling object?	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_4**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_4A**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_4B**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_4C**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_4D**

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**********COLUMN A**********		**********COLUMN B**********			
		Ever Lose Consciousness?		**Ever Dazed and Confused?**	
A blow to the head in this situation?	**How many times?**	**How many times?**	**Longest Period?**	**How many times?**	**Longest Period?**
5. Being hit by equipment?	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_5**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_5A**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_5B**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_5C**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_5D**
6. Falling down stairs?	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_6**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_6A**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_6B**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_6C**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_6D**

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COLUMN A		**COLUMN B**			
		Ever Lose Consciousness?		**Ever Dazed and Confused?**	
A blow to the head in this situation?	**How many times?**	**How many times?**	**Longest Period?**	**How many times?**	**Longest Period?**
7. Falling from a high place?	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_7**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_7A**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_7B**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_7C**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_7D**
8. Falling during a fainting spell?	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_8**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_8A**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_8B**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_8C**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_8D**

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**********COLUMN A**********		**********COLUMN B**********			
		Ever Lose Consciousness?		**Ever Dazed and Confused?**	
A blow to the head in this situation?	**How many times?**	**How many times?**	**Longest Period?**	**How many times?**	**Longest Period?**
9. Falling during a drug or alcohol blackout?	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_9**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_9A**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_9B**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_9C**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_9D**
10. Falling in a way not otherwise mentioned?	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_10**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_10A**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_10B**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_10C**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_10D**

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**********COLUMN A**********		**********COLUMN B**********			
		Ever Lose Consciousness?		**Ever Dazed and Confused?**	
A blow to the head in this situation?	**How many times?**	**How many times?**	**Longest Period?**	**How many times?**	**Longest Period?**
11. While biking?	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_11**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_11A**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_11B**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_11C**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_11D**
12. While rollerblading or skateboarding?	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_12**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_12A**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_12B**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_12C**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_12D**

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Part One: Injuries and Hospitalizations

Participant ID _____

Listed in **Column A** are situations in which people may experience a blow to the head. For each event listed, **record the number of times** you experienced a blow in that type of situation.

For each blow to the head recorded in Column A, please answer the questions in Column B. How many times did you lose consciousness? (Record zero if you never lost consciousness). What was the longest period of loss of consciousness? How many times were you dazed and confused after a blow to the head? What was the longest period you experienced this?

**********COLUMN A**********		**********COLUMN B**********			
		Ever Lose Consciousness?		**Ever Dazed and Confused?**	
A blow to the head in this situation?	**How many times?**	**How many times?**	**Longest Period?**	**How many times?**	**Longest Period?**
13. While horseback riding?	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_13**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_13A**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_13B**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_13C**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_13D**
14. While skiing or snowboarding?	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_14**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_14A**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_14B**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_14C**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_14D**

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Part One: Injuries and Hospitalizations

Participant ID _____

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For each blow to the head recorded in Column A, please answer the questions in Column B. How many times did you lose consciousness? (Record zero if you never lost consciousness). What was the longest period of loss of consciousness? How many times were you dazed and confused after a blow to the head? What was the longest period you experienced this?

**********COLUMN A**********		**********COLUMN B**********			
		Ever Lose Consciousness?		**Ever Dazed and Confused?**	
A blow to the head in this situation?	**How many times?**	**How many times?**	**Longest Period?**	**How many times?**	**Longest Period?**
15. In sports (football, baseball, basketball, etc.)?	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_15**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_15A**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_15B**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_15C**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_15D**
16. While on the playground?	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_16**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_16A**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_16B**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_16C**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_16D**

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Part One: Injuries and Hospitalizations

Participant ID _____

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For each blow to the head recorded in Column A, please answer the questions in Column B. How many times did you lose consciousness? (Record zero if you never lost consciousness). What was the longest period of loss of consciousness? How many times were you dazed and confused after a blow to the head? What was the longest period you experienced this?

COLUMN A		**COLUMN B**			
		Ever Lose Consciousness?		**Ever Dazed and Confused?**	
A blow to the head in this situation?	**How many times?**	**How many times?**	**Longest Period?**	**How many times?**	**Longest Period?**
17. While diving into water?	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_17**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_17A**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_17B**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_17C**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_17D**
18. Being assaulted or mugged?	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_18**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_18A**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_18B**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_18C**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_18D**

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Part One: Injuries and Hospitalizations

Participant ID _____

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For each blow to the head recorded in Column A, please answer the questions in Column B. How many times did you lose consciousness? (Record zero if you never lost consciousness). What was the longest period of loss of consciousness? How many times were you dazed and confused after a blow to the head? What was the longest period you experienced this?

**********COLUMN A**********		**********COLUMN B**********			
		Ever Lose Consciousness?		**Ever Dazed and Confused?**	
A blow to the head in this situation?	**How many times?**	**How many times?**	**Longest Period?**	**How many times?**	**Longest Period?**
19. Being physically abused?	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_19**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_19A**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_19B**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_19C**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_19D**
20. While in combat (i.e. a blast injury)?	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_20**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_20A**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_20B**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_20C**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_20D**

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Part One: Injuries and Hospitalizations

Participant ID _____

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For each blow to the head recorded in Column A, please answer the questions in Column B. How many times did you lose consciousness? (Record zero if you never lost consciousness). What was the longest period of loss of consciousness? How many times were you dazed and confused after a blow to the head? What was the longest period you experienced this?

COLUMN A		**COLUMN B**			
		Ever Lose Consciousness?		**Ever Dazed and Confused?**	
A blow to the head in this situation?	**How many times?**	**How many times?**	**Longest Period?**	**How many times?**	**Longest Period?**
21. Other? Please Specify: BISQPART1_21S	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more BISQPART1_21	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more BISQPART1_21A	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month BISQPART1_21B	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more BISQPART1_21C	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month BISQPART1_21D

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Part One: Injuries and Hospitalizations

Participant ID _____

Please indicate the number of times you have been seen in a hospital emergency room or have been hospitalized for any of the reasons listed in **Column C**.

For each type of medical emergency checked in Column C, please answer the questions below under Column D. How many times did you lose consciousness during this type of medical emergency? How many times were you dazed and confused? For any of the situations where you cannot remember if you lost consciousness or were dazed and confused, check "Don't Know".

COLUMN C		**COLUMN D**				
		Ever Lose Consciousness?		**Ever Dazed and Confused?**		
Ever been hospitalized or seen in the emergency room for the reasons listed?	**How many times?**	**How many times?**	**Longest Period?**	**How many times?**	**Longest Period?**	
22. Concussion?	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_22**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_22A**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_22B**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_22C**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_22D**
23. Fracture of the head, neck or face?	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_23**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_23A**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_23B**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_23C**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_23D**

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Part One: Injuries and Hospitalizations

Participant ID _____

Please indicate the number of times you have been seen in a hospital emergency room or have been hospitalized for any of the reasons listed in **Column C**.

For each type of medical emergency checked in Column C, please answer the questions below under Column D. How many times did you lose consciousness during this type of medical emergency? How many times were you dazed and confused? For any of the situations where you cannot remember if you lost consciousness or were dazed and confused, check "Don't Know".

COLUMN C		**COLUMN D**			
		Ever Lose Consciousness?		**Ever Dazed and Confused?**	
Ever been hospitalized or seen in the emergency room for the reasons listed?	**How many times?**	**How many times?**	**Longest Period?**	**How many times?**	**Longest Period?**
24. Seizures?	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_24**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_24A**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_24B**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_24C**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_24D**
25. High fever?	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_25**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_25A**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_25B**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_25C**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_25D**

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COLUMN C		**COLUMN D**				
		Ever Lose Consciousness?		**Ever Dazed and Confused?**		
Ever been hospitalized or seen in the emergency room for the reasons listed?	**How many times?**	**How many times?**	**Longest Period?**	**How many times?**	**Longest Period?**	
26. Near drowning or poisoning?	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_26**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_26A**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_26B**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_26C**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_26D**
27. Electrical power injury or hit by lightning?	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_27**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_27A**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_27B**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_27C**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_27D**

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Part One: Injuries and Hospitalizations

Participant ID _____

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COLUMN C		**COLUMN D**			
		Ever Lose Consciousness?		**Ever Dazed and Confused?**	
Ever been hospitalized or seen in the emergency room for the reasons listed?	**How many times?**	**How many times?**	**Longest Period?**	**How many times?**	**Longest Period?**
28. Gunshot injury?	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_28**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_28A**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_28B**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_28C**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_28D**
29. Stroke or brain hemorrhage?	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_29**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_29A**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_29B**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_29C**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_29D**

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Part One: Injuries and Hospitalizations

Participant ID _____

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For each type of medical emergency checked in Column C, please answer the questions below under Column D. How many times did you lose consciousness during this type of medical emergency? How many times were you dazed and confused? For any of the situations where you cannot remember if you lost consciousness or were dazed and confused, check "Don't Know".

COLUMN C		**COLUMN D**			
		Ever Lose Consciousness?		**Ever Dazed and Confused?**	
Ever been hospitalized or seen in the emergency room for the reasons listed?	**How many times?**	**How many times?**	**Longest Period?**	**How many times?**	**Longest Period?**
30. Brain Infection or Tumor?	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_30**	☐0 Never ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 or more **BISQPART1_30A**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_30B**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_30C**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_30D**
31. Other? Please Specify: **BISQPART1_31S**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_31**	☐0 Never ☐1 ☐2 ☐3 ☐4 ☐5 ☐6 ☐7 ☐8 ☐9 ☐10 or more **BISQPART1_31A**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_31B**	☐0 Never ☐1 1 ☐2 2 ☐3 3 ☐4 4 ☐5 5 ☐6 6 ☐7 7 ☐8 8 ☐9 9 ☐10 10 or more **BISQPART1_31C**	☐-9 Don't know ☐1 Less than 1 minute ☐2 1 to 10 minutes ☐3 More than 10 minutes up to 20 minutes ☐4 More than 20 minutes up to 30 minutes ☐5 More than 30 minutes up to 45 minutes ☐6 More than 45 minutes up to 1 hour ☐7 More than 1 hour up to 1 day ☐8 More than 1 day up to 1 week ☐9 More than 1 week up to 1 month ☐10More than 1 month **BISQPART1_31D**

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Part Two: Problems and difficulties in daily living?

Participant ID _____

Please check one of the boxes below to indicate how often, *within the past month*, you have experienced each of the difficulties listed. Some of the problems may not be applicable to you. For example, "making spelling errors" would not be applicable if one never learned to write or cannot write. In such cases, please mark "Not applicable". Remember that most people have *some* of the problems listed.

In the past month, how often has this been a problem in your daily life?	Daily or almost daily	Several times	One or two times	Never	Don't Know	Not Applicable	**In the past month, how often has this been a problem in your daily life?**	Daily or almost daily	Several times	One or two times	Never	Don't Know	Not Applicable
1. Having trouble staying awake? **BISQSX001**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9	8. Feeling dizzy? **BISQSX008**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9
2. Having trouble falling asleep or staying asleep? **BISQSX002**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9	9. Losing your balance? **BISQSX009**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9
3. Having trouble waking up after sleep or a nap? **BISQSX003**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9	10. Experiencing ringing in the ears or having trouble hearing? **BISQSX0010**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9
4. Having nightmares? **BISQSX004**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9	11. Having double vision or blurred vision? **BISQSX0011**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9
5. Blacking out, having blackout spells or seizures? **BISQSX005**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9	12. Eating too much? **BISQSX0012**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9
6. Being clumsy, dropping or tripping over things? **BISQSX006**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9	13. Having little or no appetite? **BISQSX0013**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9
7. Feeling cold? **BISQSX007**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9	14. Food not tasting right? **BISQSX0014**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9

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Participant ID _____

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In the past month, how often has this been a problem in your daily life?	Daily or almost daily	Several times	One or two times	Never	Don't Know	Not Applicable	**In the past month, how often has this been a problem in your daily life?**	Daily or almost daily	Several times	One or two times	Never	Don't Know	Not Applicable
15. Having difficulty smelling things? **BISQSX015**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9	22. Becoming confused in familiar places? **BISQSX022**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9
16. Having headaches? **BISQSX016**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9	23. Difficulty concentrating, having a poor span of attention? **BISQSX023**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9
17. Feeling tired? **BISQSX017**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9	24. Being easily distracted? **BISQSX024**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9
18. Moving slowly? **BISQSX018**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9	25. Losing your train of thought? **BISQSX025**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9
19. Increased or decreased sexual interest or behaviour? **BISQSX019**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9	26. Forgetting what you just said? **BISQSX026**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9
20. Friends or relatives seeming unfamiliar? **BISQSX020**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9	27. Forgetting what happened yesterday or other recent events? **BISQSX027**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9
21. Thinking slowly? **BISQSX021**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9	28. Forgetting the names of common objects? **BISQSX028**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9

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Participant ID _____

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In the past month, how often has this been a problem in your daily life?	Daily or almost daily	Several times	One or two times	Never	Don't Know	Not Applicable	**In the past month, how often has this been a problem in your daily life?**	Daily or almost daily	Several times	One or two times	Never	Don't Know	Not Applicable
29. Forgetting names of people, including family members? **BISQSX029**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9	36. Losing track of time? **BISQSX036**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9
30. Forgetting well-known phone numbers or addresses? **BISQSX030**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9	37. Getting lost? **BISQSX037**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9
31. Forgetting to eat? **BISQSX031**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9	38. Being disorganized? **BISQSX038**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9
32. Forgetting to take medication? **BISQSX032**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9	39. Misplacing things, forgetting where things are? **BISQSX039**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9
33. Forgetting if you have done things? **BISQSX033**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9	40. Forgetting to turn off appliances? **BISQSX040**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9
34. Forgetting to do chores, homework or work at home? **BISQSX034**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9	41. Difficulty making decisions? **BISQSX041**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9
35. Forgetting, missing or being late for appointments? **BISQSX035**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9	42. Difficulty solving problems? **BISQSX042**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9

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In the past month, how often has this been a problem in your daily life?	Daily or almost daily	Several times	One or two times	Never	Don't Know	Not Applicable	**In the past month, how often has this been a problem in your daily life?**	Daily or almost daily	Several times	One or two times	Never	Don't Know	Not Applicable
43. Difficulty planning future events? **BISQSX043**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9	50. Forgetting what you just read? **BISQSX050**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9
44. Difficulty setting priorities? **BISQSX044**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9	51. Having difficulty understanding what you read or what is read to you? **BISQSX051**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9
45. Difficulty following instructions, written or oral? **BISQSX045**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9	52. Writing slowly? **BISQSX052**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9
46. Difficulty learning from experience? **BISQSX046**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9	53. Writing illegibly, poor handwriting? **BISQSX053**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9
47. Difficulty learning new skills and new information? **BISQSX047**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9	54. Making spelling mistakes? **BISQSX054**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9
48. Learning slowly? **BISQSX048**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9	55. Difficulties with reading, writing and math? **BISQSX055**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9
49. Reading very slowly, having difficulty reading? **BISQSX049**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9	56. Handling your personal affairs and finances? **BISQSX056**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9

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In the past month, how often has this been a problem in your daily life?	Daily or almost daily	Several times	One or two times	Never	Don't Know	Not Applicable	**In the past month, how often has this been a problem in your daily life?**	Daily or almost daily	Several times	One or two times	Never	Don't Know	Not Applicable
57. Unexplained change in performance at work or school? **BISQSX057**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9	64. Speaking in ways that others can't make sense of? **BISQSX064**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9
58. Difficulty performing chores? **BISQSX058**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9	65. Talking too fast or too slow? **BISQSX065**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9
59. Difficulty in understanding jokes and humor? **BISQSX059**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9	66. Repeating what others say? **BISQSX066**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9
60. Difficulty making conversation? **BISQSX060**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9	67. Experiencing others as talking too fast? **BISQSX067**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9
61. Talking too much? **BISQSX061**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9	68. Feeling moody? **BISQSX068**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9
62. Not listening when being spoken to? **BISQSX062**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9	69. Experiencing rapid changes in mood? **BISQSX069**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9
63. Trouble understanding conversation or difficulty pronouncing words? **BISQSX063**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9	70. Feeling impatient or irritable? **BISQSX070**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9

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In the past month, how often has this been a problem in your daily life?	Daily or almost daily	Several times	One or two times	Never	Don't Know	Not Applicable	**In the past month, how often has this been a problem in your daily life?**	Daily or almost daily	Several times	One or two times	Never	Don't Know	Not Applicable
71. Feeling frustrated? **BISQSX071**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9	78. Sitting around doing nothing, feeling bored? **BISQSX078**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9
72. Breaking or throwing things? **BISQSX072**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9	79. Having repeated thoughts? **BISQSX079**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9
73. Being heedless to danger, as in driving recklessly? **BISQSX073**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9	80. Having difficulty getting started on things? **BISQSX080**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9
74. Feeling angry? **BISQSX074**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9	81. Laughing for no reason? **BISQSX081**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9
75. Screaming or yelling, having temper outbursts? **BISQSX075**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9	82. Making comments that are inappropriate? **BISQSX082**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9
76. Cursing at or threatening others or self? **BISQSX076**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9	83. Behaving in appropriately? **BISQSX083**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9
77. Hitting or pushing others? **BISQSX077**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9	84. Feeling jumpy, restless or unable to stay still? **BISQSX084**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9

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In the past month, how often has this been a problem in your daily life?	Daily or almost daily	Several times	One or two times	Never	Don't Know	Not Applicable	**In the past month, how often has this been a problem in your daily life?**	Daily or almost daily	Several times	One or two times	Never	Don't Know	Not Applicable
85. Crying easily or for no reason? **BISQSX085**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9	93. Doing things without thinking, being impulsive? **BISQSX0093**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9
86. Feeling lonely? **BISQSX086**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9	94. Difficulty coping with unexpected changes? **BISQSX0094**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9
87. Feeling sad or blue? **BISQSX087**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9	95. Avoiding family members or friends? **BISQSX0095**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9
88. Not feeling confident? **BISQSX088**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9	96. Arguing? **BISQSX0096**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9
89. Feeling misunderstood? **BISQSX089**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9	97. Being rude to others, interrupting others? **BISQSX0097**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9
90. Feeling hopeless, worthless? **BISQSX090**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9	98. Dealing with people? **BISQSX0098**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9
91. Feeling life is not worth living, expressing thoughts about wanting to die? **BISQSX091**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9	99. Feeling uncomfortable around others? **BISQSX0099**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9
92. Feeling scared or frightened? **BISQSX092**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9	100. Experiencing difficulties being in crowds? **BISQSX00100**	☐ 3	☐ 2	☐ 1	☐ 0	☐ -8	☐ -9

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Summary variables:

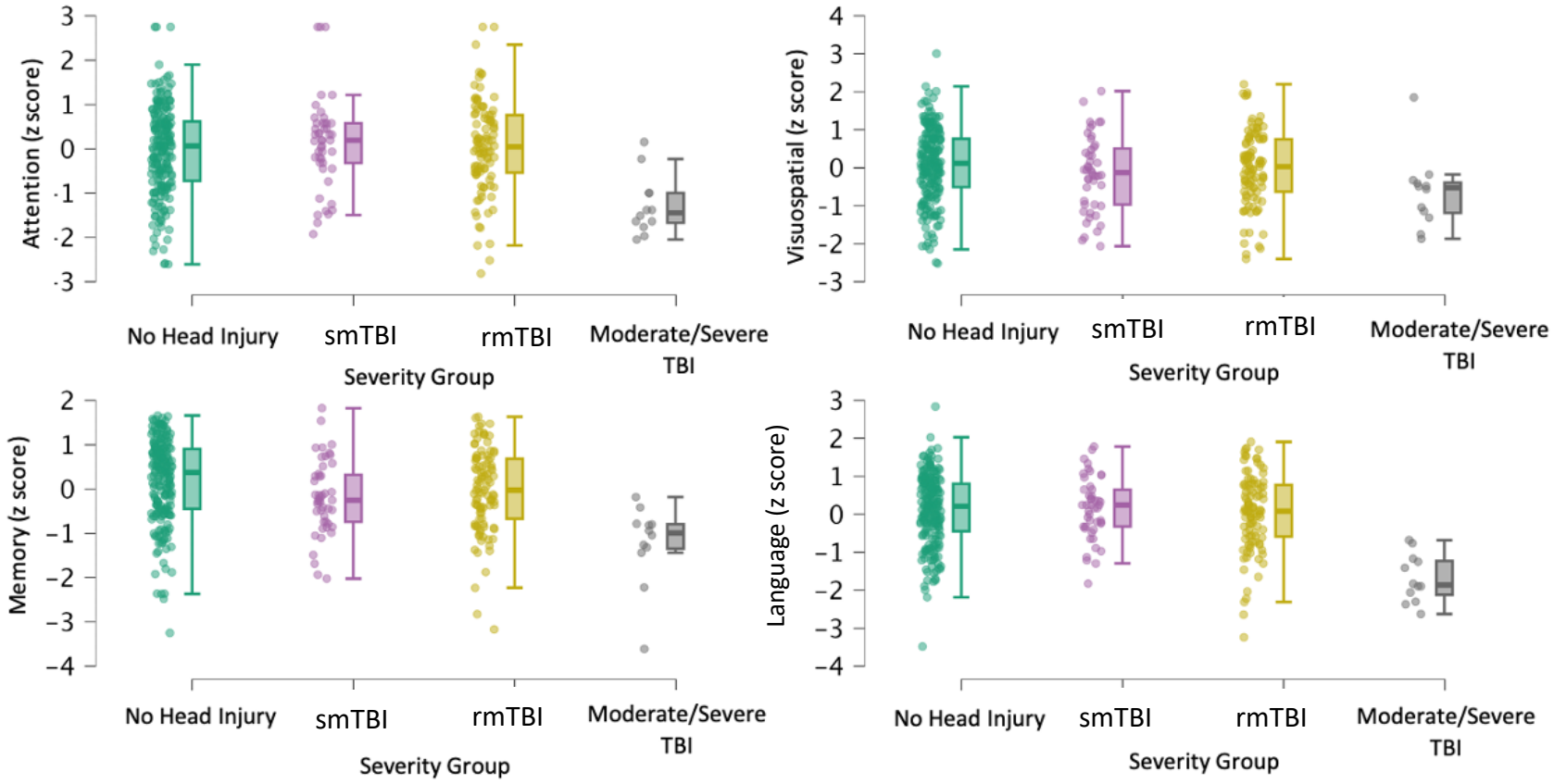
- **Number of times that participant has been dazed and confused after a blow head:** **NUMDAC**
- **Number of times that participant has lost consciousness after a blow head:** **NUMLOC**
- **The longest period where participant has been dazed and confused after a blow head** (**-9**: Don't know, **0**: None blow to the head, **1**: Less than 1 minute, **2**: 1 to 10 minutes, **3**: More than 10 minutes up to 20 minutes, **4**: More than 20 minutes up to 30 minutes, **5**: More than 30 minutes up to 45 minutes, **6**: More than 45 minutes up to 1 hour, **7**: More than 1 hour up to 1 day, **8**: More than 1 day up to 1 week, **9**: More than 1 week up to 1 month, **10**: More than 1 month) : **HIGHDAC**
- **The longest period where participant has lost consciousness after a blow head** (**-9**: Don't know, **0**: None blow to the head, **1**: Less than 1 minute, **2**: 1 to 10 minutes, **3**: More than 10 minutes up to 20 minutes, **4**: More than 20 minutes up to 30 minutes, **5**: More than 30 minutes up to 45 minutes, **6**: More than 45 minutes up to 1 hour, **7**: More than 1 hour up to 1 day, **8**: More than 1 day up to 1 week, **9**: More than 1 week up to 1 month, **10**: More than 1 month) : **HIGHLOC**
- **Number of times that participant experienced a blow to the head:** **TOTBLOWS**
- **The highest severity of all blows to the head** (.: Missing DAC, missing LOC/ Unknown DAC,No or unknown LOC; **1**:No DAC, No or unknown LOC; **2**:DAC, No or unknown LOC; **3**=LOC up to 20 mins; **4**=LOC >20 mins-1 day; **5**=LOC >1 day- 1 week; **6**=LOC >1 week -1 month; **7**=LOC > 1 month): **SEVERITY**

- **Memory and Attention:** **WTDMENATT**
- **Depression Anxiety and Mood Sxs:** **WTDDEPANXMOOD**
- **Aggression and Impulsivity:** **WTDAGGLMP**
- **Physical Sxs:** **WTDPHYS**

The Exact formulas cannot be given currently.
But they are averages of various combinations of the 100 symptoms, weighted by frequency of occurrence.

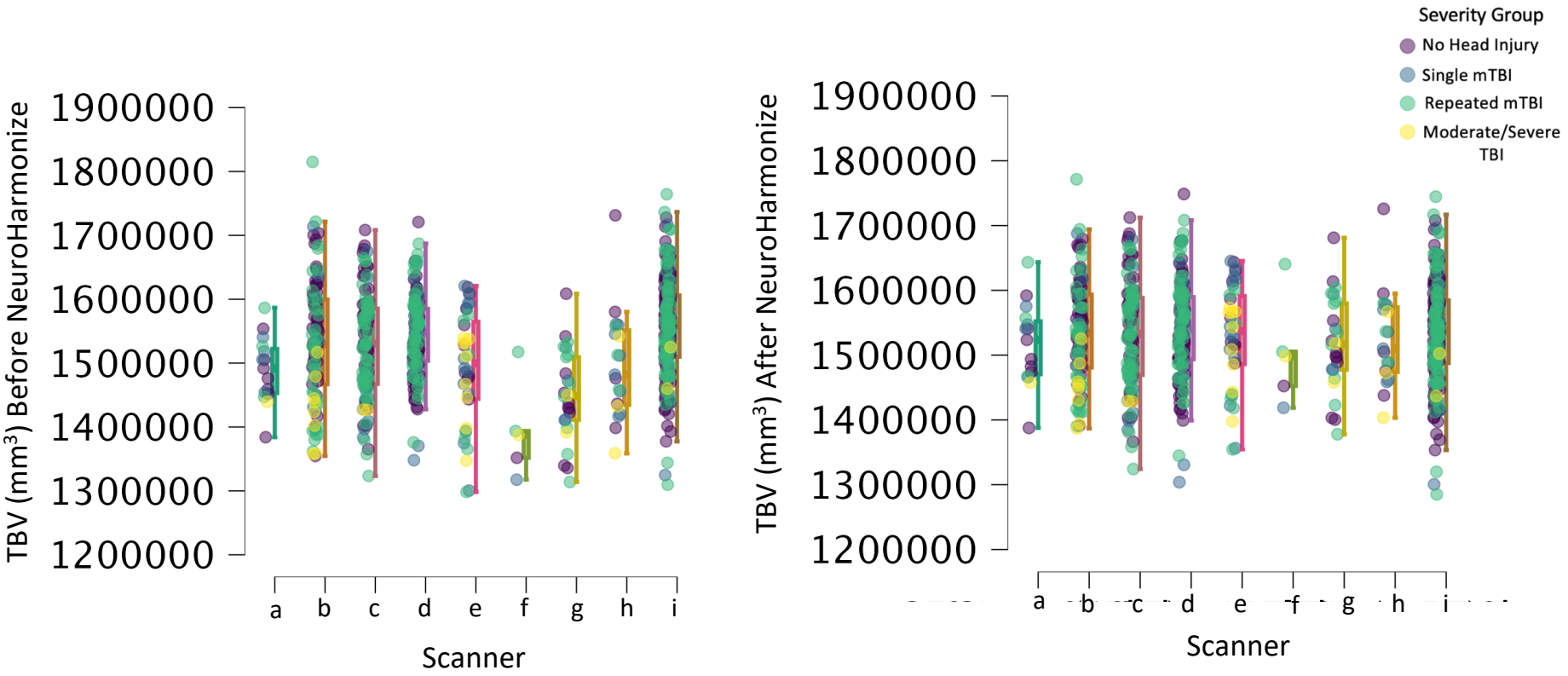
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Appendix 2 - Boxplots of cognitive domains after harmonisation by severity groups

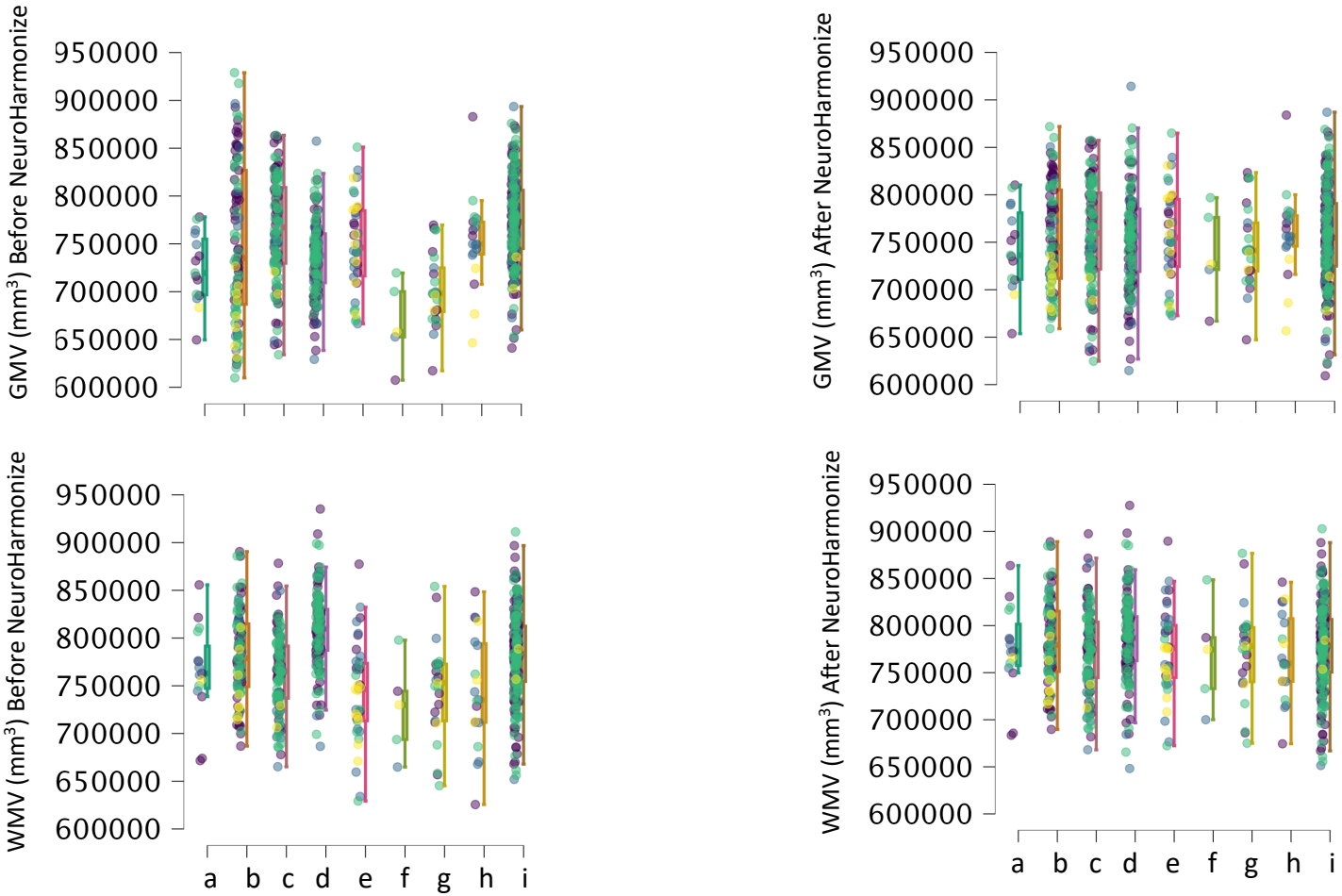


Appendix Figure 2.1 Boxplots of cognitive domain z scores by severity group

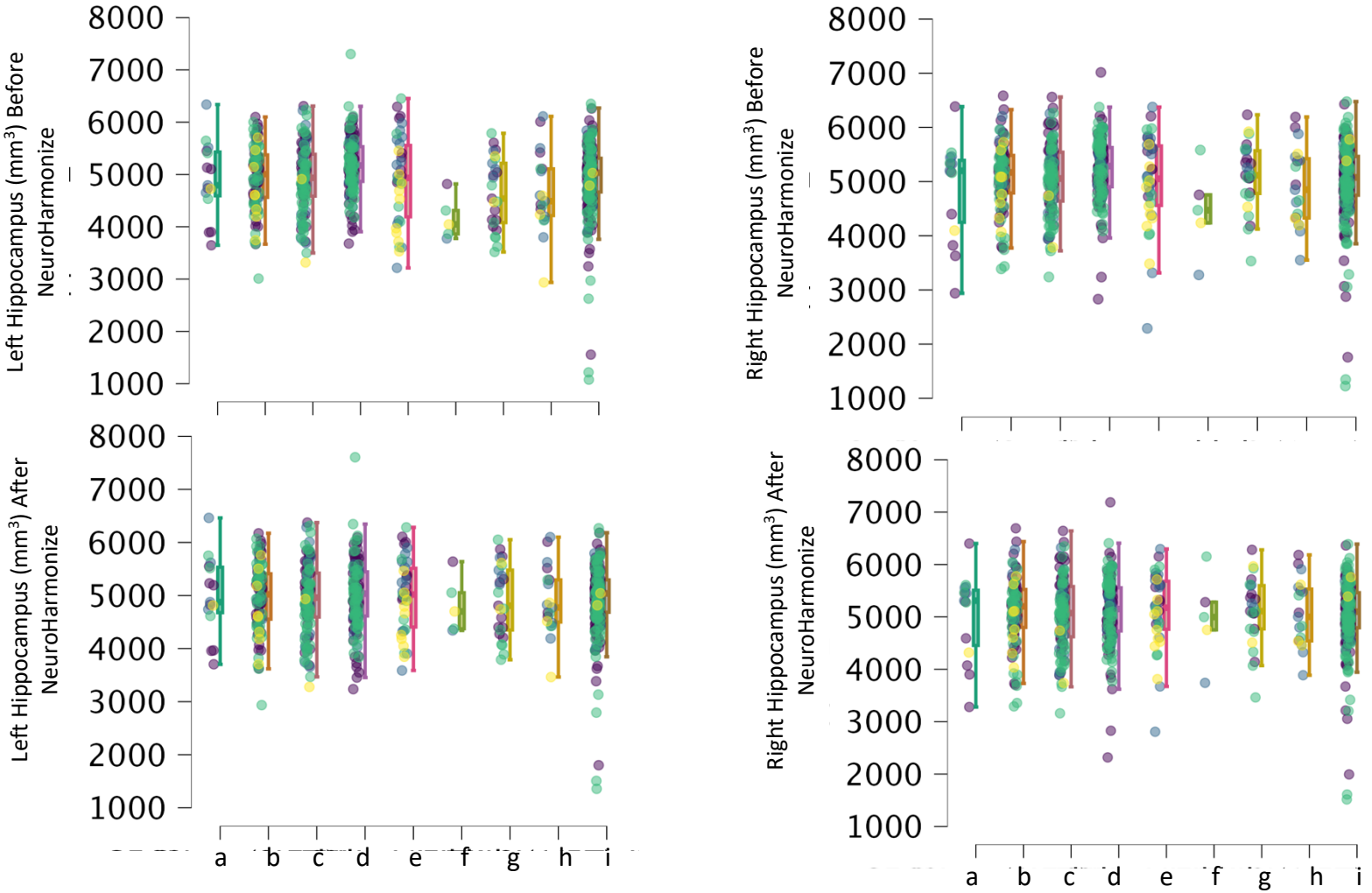
Appendix 3 - Boxplots of brain metrics before and after harmonisation by scanner and severity groups



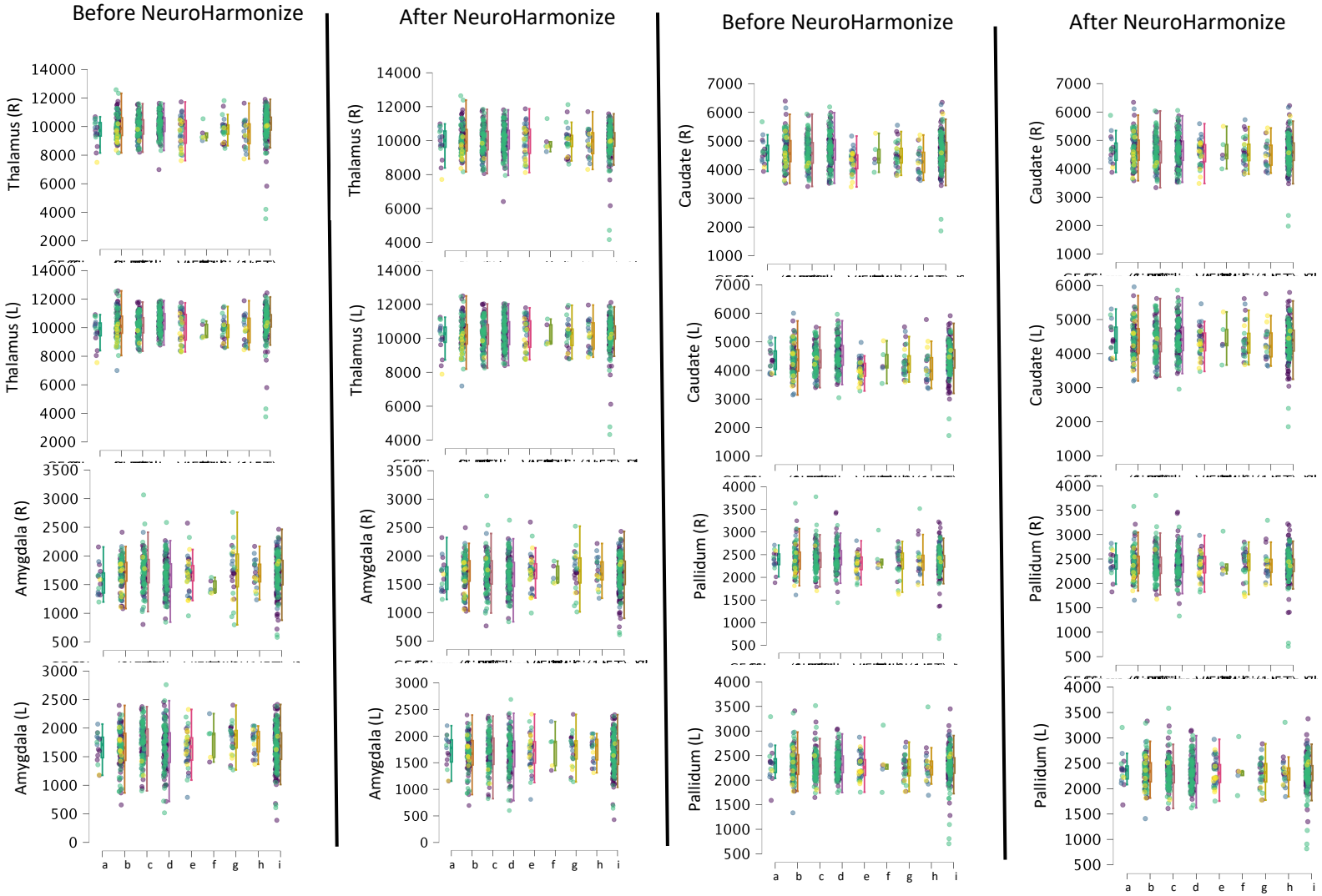
Appendix Figure 3.1 Boxplots of total brain volume (TBV) before and after NeuroHarmonize separated by scanner and severity groups. (a) GE Signa (1.5T) (b) Siemens Prisma (c) Siemens Prisma-FIT (d) Siemens Verio (e) Philips Achieva (f) Siemens Aera (1.5T) (g) Siemens Magnetom Vida (h) Philips Ingenia (i) Siemens Skyra



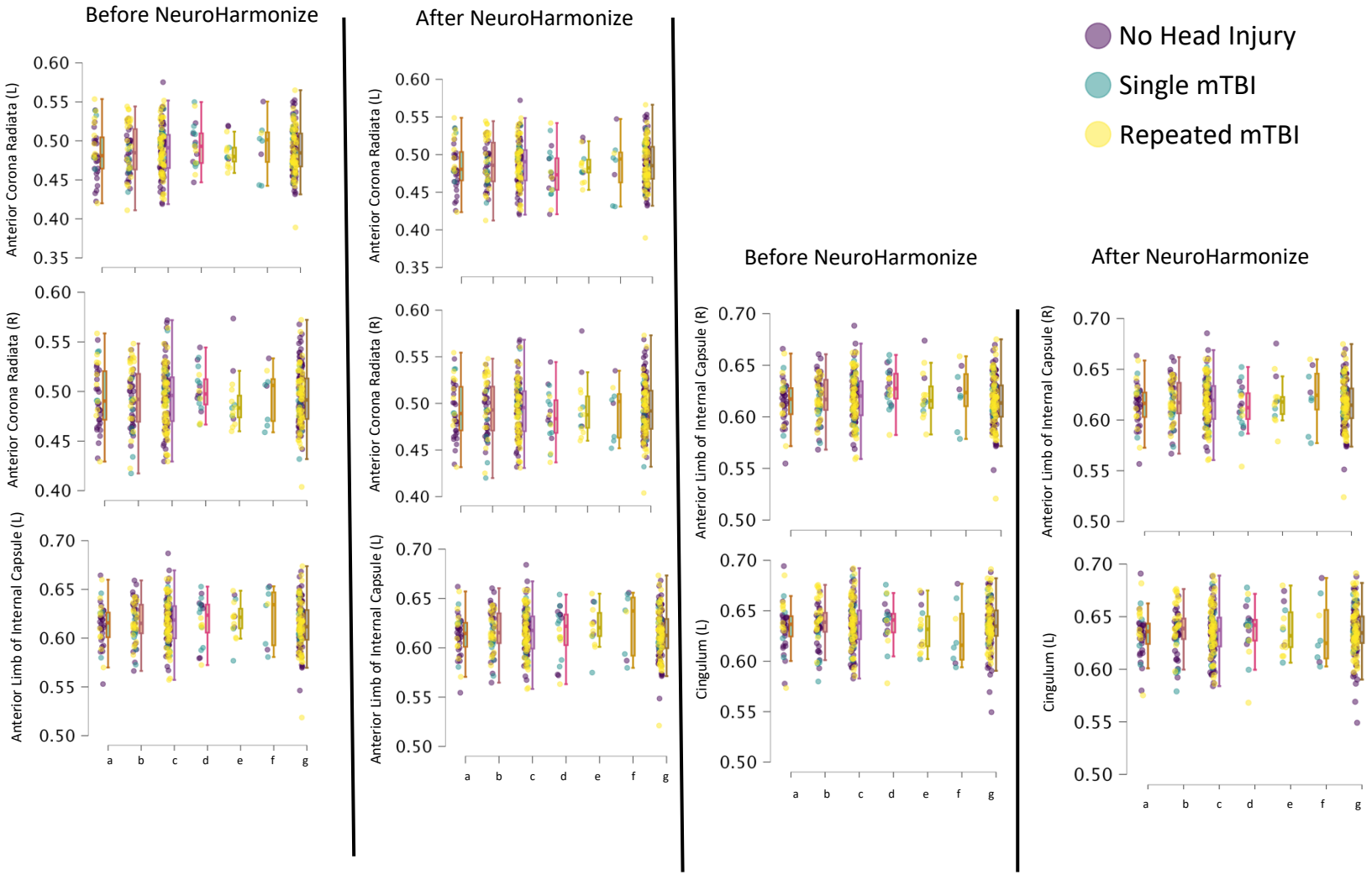
Appendix Figure 3.2 Boxplots of Grey (GM) and White Matter (WM) Volume before and after NeuroHarmonize separated by scanner and severity groups. (a) GE Signa (1.5T) (b) Siemens Prisma (c) Siemens Prisma-FIT (d) Siemens Verio (e) Philips Achieva (f) Siemens Aera (1.5T) (g) Siemens Magnetom Vida (h) Philips Ingenia (i) Siemens Skyra



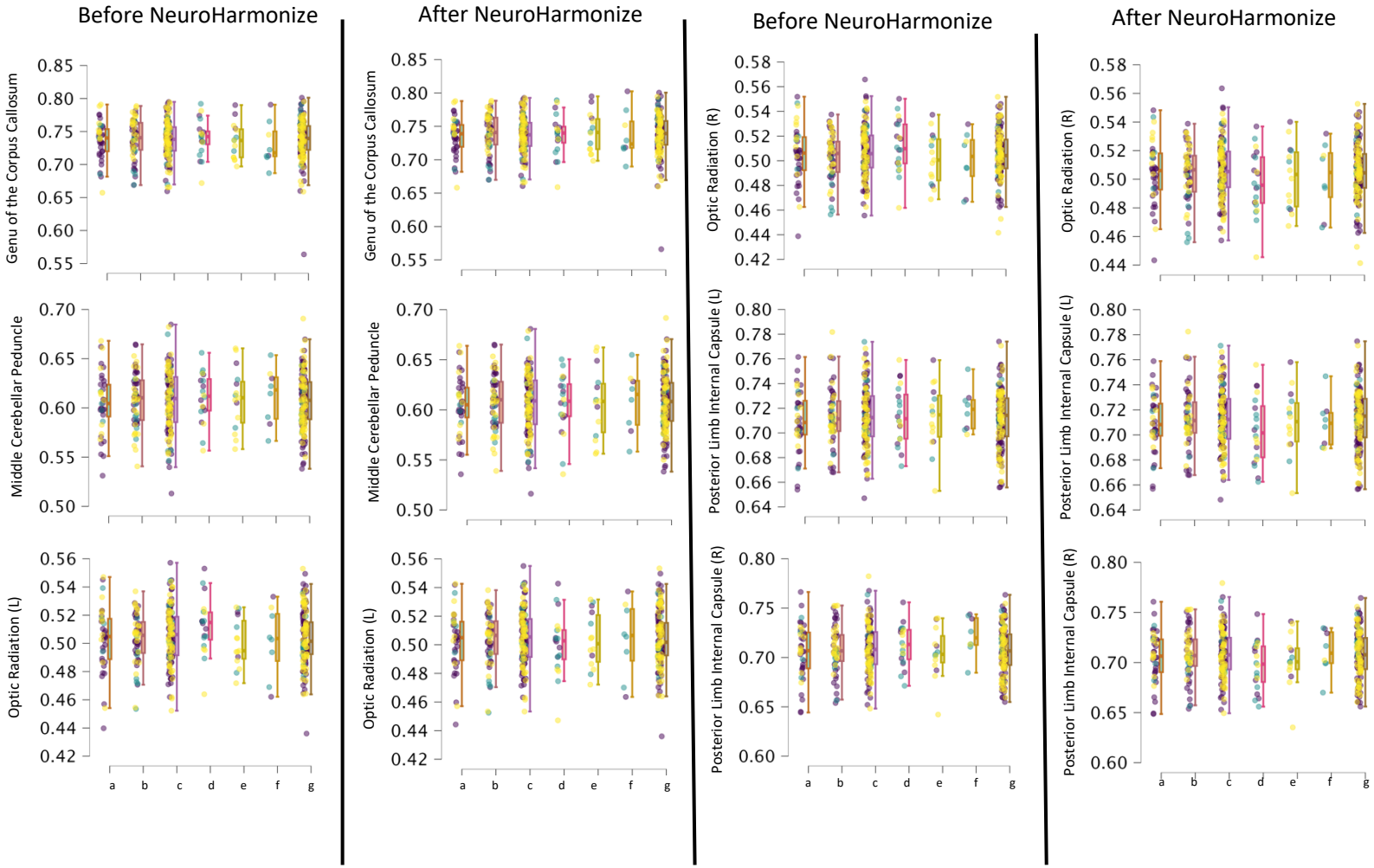
Appendix Figure 3.2 continued. Boxplots of Hippocampal Volume (left and right) before and after NeuroHarmonize separated by scanner and severity groups. (a) GE Signa (1.5T) (b) Siemens Prisma (c) Siemens Prisma-FIT (d) Siemens Verio (e) Philips Achieva (f) Siemens Aera (1.5T) (g) Siemens Magnetom Vida (h) Philips Ingenia (i) Siemens Skyra



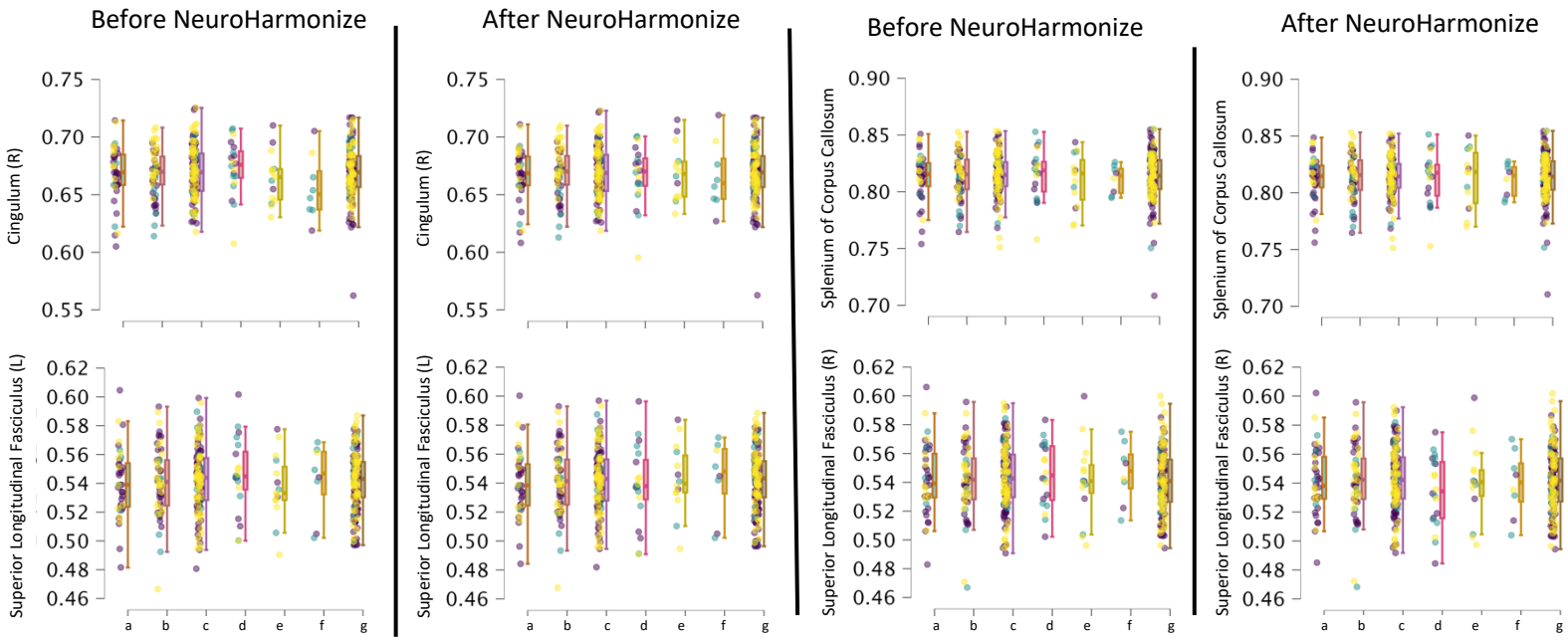
Appendix Figure 3.2 continued. Boxplots of subcortical structure volumes (mm^3) before and after NeuroHarmonize separated by scanner and severity groups. (a) GE Signa (1.5T) (b) Siemens Prisma (c) Siemens Prisma-FIT (d) Siemens Verio (e) Philips Achieva (f) Siemens Aera (1.5T) (g) Siemens Magnetom Vida (h) Philips Ingenia (i) Siemens Skyra



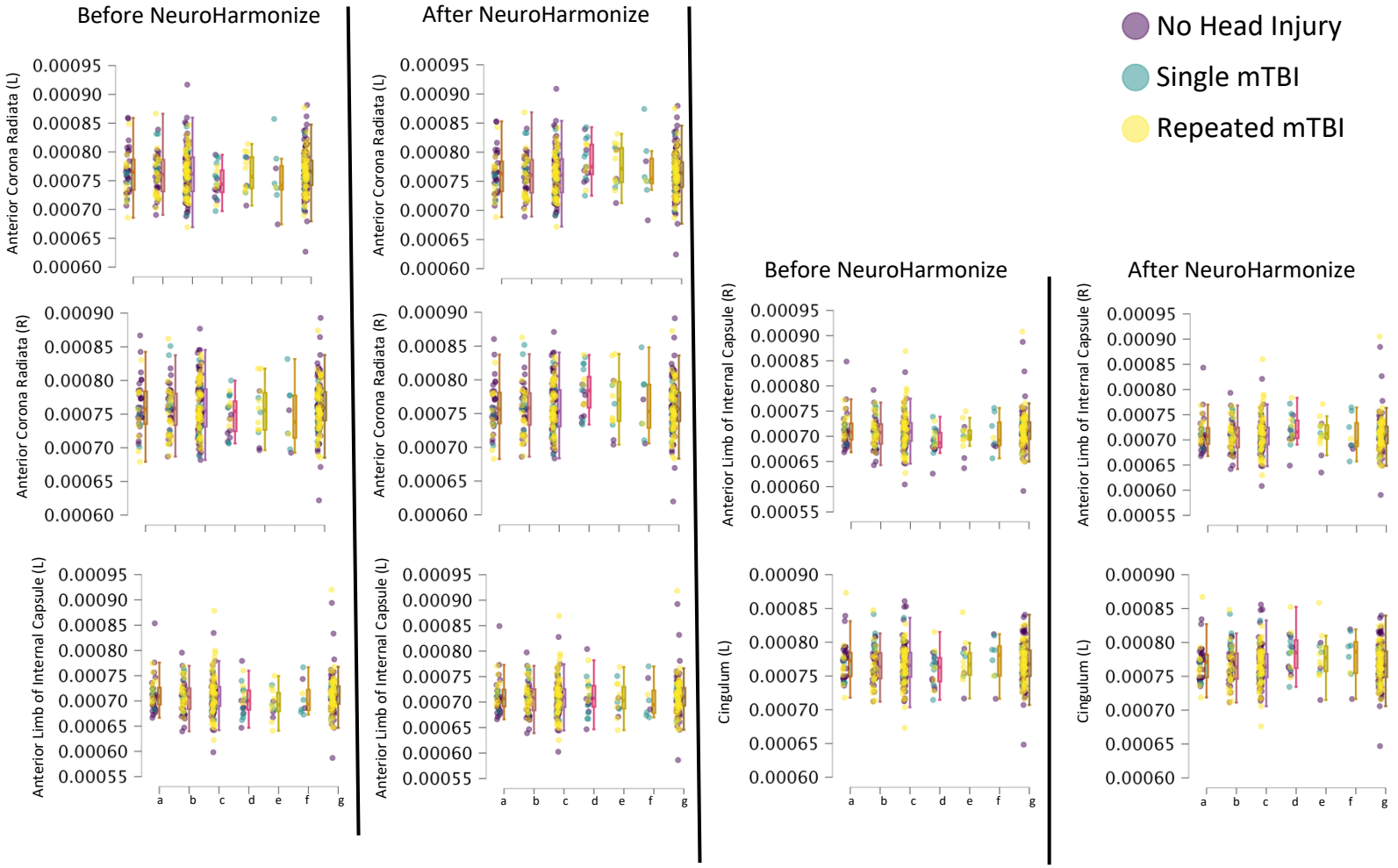
Appendix Figure 3.3 Boxplots of subcortical FA values before and after NeuroHarmonize separated by scanner and severity groups. (a) Siemens Prisma (b) Siemens Prisma-FIT (c) Siemens Verio (d) Philips Achieva (e) Siemens Magnetom Vida (f) Philips Ingenia (g) Siemens Skyra



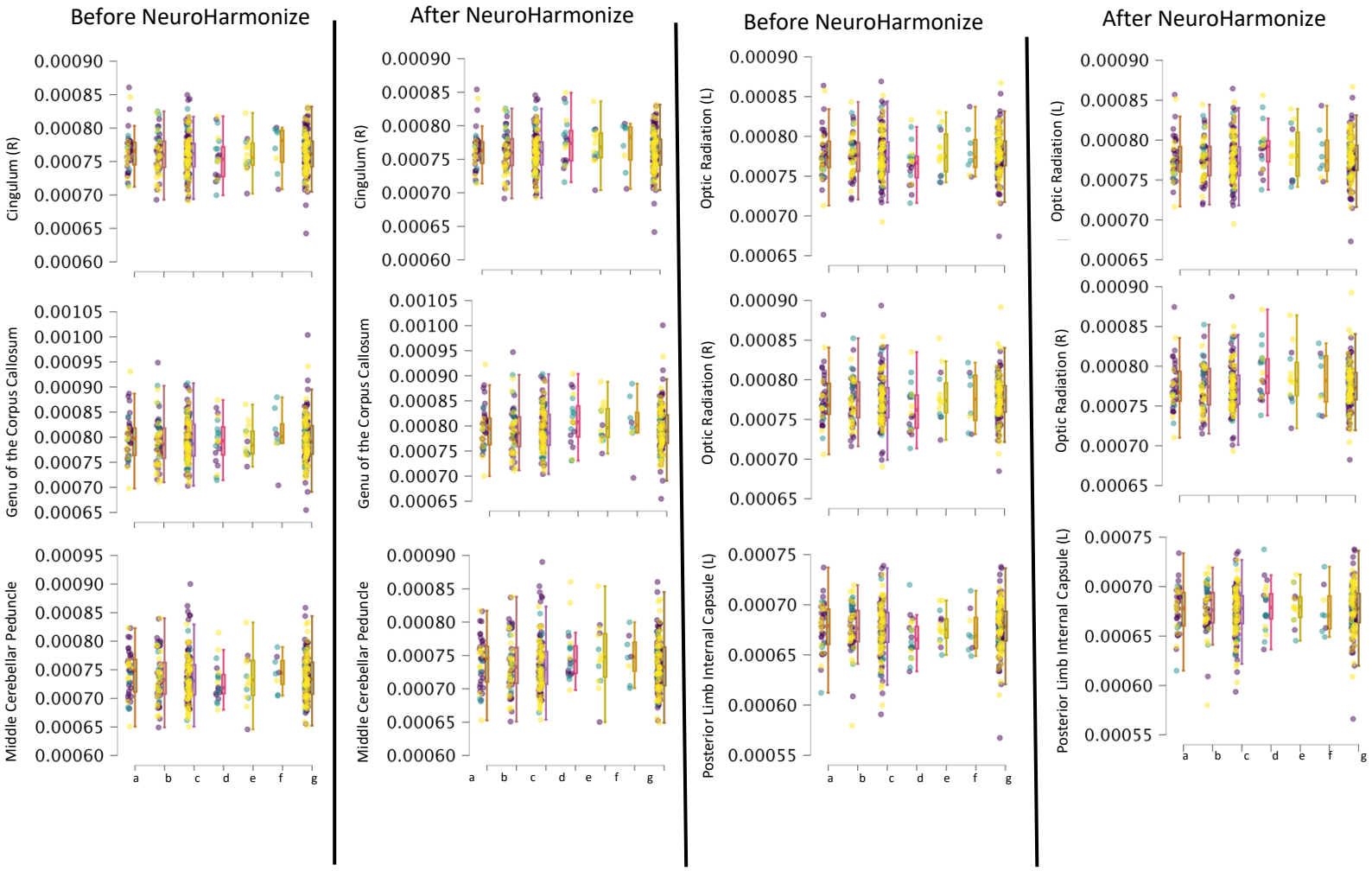
Appendix Figure 3.3 continued Boxplots of subcortical FA values before and after NeuroHarmonize separated by scanner and severity groups. (a) Siemens Prisma (b) Siemens Prisma-FIT (c) Siemens Verio (d) Philips Achieva (e) Siemens Magnetom Vida (f) Philips Ingenia (g) Siemens Skyra



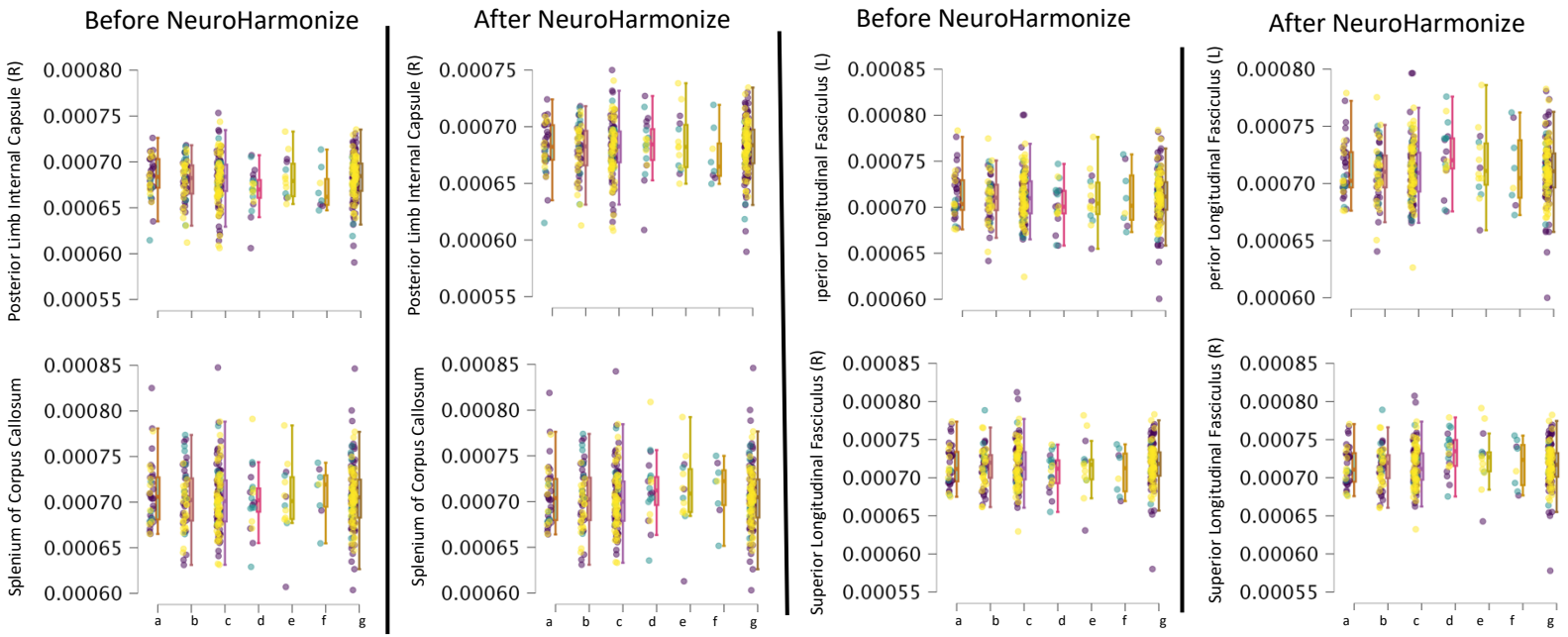
Appendix Figure 3.3 continued Boxplots of subcortical FA values before and after NeuroHarmonize separated by scanner and severity groups. (a) Siemens Prisma (b) Siemens Prisma-FIT (c) Siemens Verio (d) Philips Achieva (e) Siemens Magnetom Vida (f) Philips Ingenia (g) Siemens Skyra



Appendix Figure 3.4 Boxplots of subcortical MD values before and after NeuroHarmonize separated by scanner and severity groups. (a) Siemens Prisma (b) Siemens Prisma-FIT (c) Siemens Verio (d) Philips Achieva (e) Siemens Magnetom Vida (f) Philips Ingenia (g) Siemens Skyra



Appendix Figure 3.4 Boxplots of subcortical MD values before and after NeuroHarmonize separated by scanner and severity groups. (a) Siemens Prisma (b) Siemens Prisma-FIT (c) Siemens Verio (d) Philips Achieva (e) Siemens Magnetom Vida (f) Philips Ingenia (g) Siemens Skyra



Appendix Figure 3.4 continued Boxplots of subcortical MD values before and after NeuroHarmonize separated by scanner and severity groups. (a) Siemens Prisma (b) Siemens Prisma-FIT (c) Siemens Verio (d) Philips Achieva (e) Siemens Magnetom Vida (f) Philips Ingenia (g) Siemens Skyra

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