

Running title: Traumatic brain injuries and dementias

Title: What do we know about the risks of developing dementia after traumatic brain injury?

Running title: Traumatic brain injuries and dementias

Authors: Vanessa RAYMONT^{1*}, Tony THAYANANDAN¹

1 Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford OX3 7JX, UK

*** Corresponding author: Vanessa Rayment, Department of Psychiatry, University of Oxford, Warneford Hospital, Oxford OX3 7JX, UK. E-mail: vanessa.rayment@psych.ox.ac.uk**

Abstract

Traumatic brain injury (TBI) is considered to be a risk factor for the later development of dementia, but although the evidence dates back to the early 20th century, the nature of any association and its mechanistic pathways remain unclear. There has been greater focus on this subject over recent years, in part because of increasing reports around sports-related TBIs, especially in the US. Differences in research methods and clinical sampling remain the primary reason for the variable findings, although there is clearly increased prevalence of neurodegenerative disorders in general. Duration of follow up, definition of both TBI and dementia, and differences in the extent to which other dementia risk factors are controlled, as well as concerns about medical record accuracy are all issues yet to be resolved in TBI research,

Running title: Traumatic brain injuries and dementias

as is an absence pathological evidence. In addition, TBI has been reported to initiate a cascade of pathological processes related to several neurodegenerative disorders, and as such, it is likely that the risks vary between individuals. Given the evidence that dementia risk may increase with injury severity and frequency, a detailed account of age and type of injury, as well as lifetime TBI exposure is essential to document in future studies, and further longitudinal research with biomarker assessments are needed.

Keywords: Traumatic brain injury, head injury, dementia, mild cognitive impairment, chronic traumatic encephalopathy

Running title: Traumatic brain injuries and dementias

Summary of evidence to date

Traumatic brain injury (TBI) is a major cause of death and disability. Long term outcomes are inconsistent, but cognitive and psychiatric difficulties are common and overall costs worldwide are estimated to be \$400billion ¹. Cognitive problems that occur post TBI can range from loss of memory, poor concentration and executive functioning, but can also progress onto significant decline and the development of dementia; which evidence suggest is mostly as a result of Alzheimer's disease ².

Numerous studies have explored the relationship between TBI and dementia, but given the huge variability in study design, results are inconsistent. There is no doubt a significant association between TBI and dementia, certainly with regard to single moderate to severe TBI, and a recent meta-analysis demonstrated a 1.6 times risk of dementia after head injury ². Additionally, a recent population-based study of 30,000 people showed a dose-response relationship between TBI and neurodegenerative disease. Overall, moderate to severe TBI had 1.8 times the risk of dementia compared with mild TBI ³. While single mild TBI has also been associated with an increased risk of dementia, the evidence is less robust, although elevated dementia rates have been reported in two large studies ⁴. A 2014 systematic review found only one study of sufficient quality to warrant inclusion and did not report an overall effect ⁵. A military study of almost 200,000 US veterans found that TBIs of increasing severity were associated with a similarly increasing risk of subsequent dementia, but this has not been replicated ⁶.

Overall it is estimated that 5-15% of all dementia cases are attributable to TBI⁵, but studies on the risk for dementia following TBI are also challenging to compare due to differences in study

Running title: Traumatic brain injuries and dementias

design, duration of follow up, definition of both TBI and dementia, and differences in the extent to which other dementia risk factors are controlled. One major concern is that many studies have collected limited details around participants' TBIs. As a result, the severity and the age of the injury are often not or poorly documented. In addition, there is also no universal classification of TBI, making generalization of the findings difficult. For example, some have defined TBI based on conventional clinical criteria (mild, moderate, and severe based on duration of loss of consciousness (LOC) and/or posttraumatic amnesia), some on mere presence of a history of TBI with LOC or presence of any TBI, while others have identified TBI according to a history of intracranial injury. Finally, although several epidemiological studies exist, all have relied on examining population medical records, which may vary in their accuracy and the details recorded.

To further complicate the understanding of the long-term effects of TBI, it was previously thought that TBI produced a fixed injury, but evidence now suggests it triggers progressive pathological cascades, which can lead to neurodegeneration and dementia ⁵. The mechanism remains uncertain though, as TBI could potentially activate a specific neurodegenerative process, accelerate already present neurodegenerative disorders or disrupt neuronal functioning. Dementias have an insidious onset and may evolve over decades ⁷, so findings from nearly all longitudinal studies examining whether older individuals progress into dementia are limited, as most studies cover relatively short durations.

Normal ageing and Mild Cognitive Impairment

Running title: Traumatic brain injuries and dementias

Approximately 15% of the population over the age of 65 have some degree of cognitive dysfunction and how the concept of brain reserve impacts on that is vital in understanding the relationship between TBI and neurodegenerative diseases associated with aging ⁸. As part of normal brain ageing, there is some atrophy of cerebral tissue in a regional and sex-dependent manner ⁹. After a TBI, decreases in brain volume and myelin density can occur at an accelerated rate and such loss has a correlation with injury severity and poor recovery ¹⁰. The longitudinal brain changes of chronic TBI are gradual mild-to-moderate ventricular enlargement and sulcal prominence ¹¹, although type of injury has an impact, so that ventriculomegaly is more prominent in a chronic diffuse injury and focal injury results in more cortical atrophy ¹². It is apparent that inflammation and atrophy contribute to white matter damage, and gliosis can increase after multiple injuries, such that brain imaging of elderly individuals with a history of diffuse axonal injury has shown progressive atrophy many years later ¹³. Studies in functional MRI have also shown that there is a change in network connectivity during normal aging that is exacerbated by TBI ¹⁴, which may manifest as cognitive deficits ^{15, 16} and have been associated with dementia ¹⁷. Network damage has also been found to be a strong predictor of outcome after TBI ¹⁸.

Mild cognitive impairment (MCI) is often a prodromal stage between normal aging and dementia, constituting a period of objective cognitive difficulties but only mildly affected functional abilities. Not all those diagnosed with MCI will progress to dementia however ¹⁹. One study compared subjects with MCI (N=3,187) to a cohort of participants with normal cognition (N=3,244) from a large, national database and found that a self-reported history of TBI with LOC was related to a 1.3 times increased likelihood of an MCI diagnosis ²⁰. This relationship remained even after accounting for sociodemographic, genetic and vascular factors, although the link between TBI and MCI was influenced by a history of depression.

Running title: Traumatic brain injuries and dementias

Those with a history of TBI were diagnosed with MCI approximately 2.5 years earlier than those without a TBI history, indicating that a history of TBI may be linked to an earlier onset of MCI potentially from reducing cognitive reserve ²⁰, with similar results found in another study ²¹. The difficulty with making such procedural connections, however, is the heterogeneous aetiology and trajectory of MCI.

Alzheimer's dementia

Alzheimer's disease is the commonest cause of dementia (Alzheimer's dementia; AD) and leads to the deposition of amyloid- β plaques and hyperphosphorylated tau neurofibrillary tangles in the temporal lobes initially, before extension to the frontal and parietal regions ²². The clinical presentation of AD involves initial deficiencies in short term memory followed by global cognitive deterioration, but one difficulty for research around the development of AD is that it still requires post mortem evidence in order to make a confirmed diagnosis ²³.

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. Some of the most robust evidence of a link between TBI and AD comes from studies of military populations. A study by Plassman and colleagues (2000) evaluated 548 World War II veterans who had suffered a TBI 40 years earlier and compared them to a cohort of veterans who had sustained a non-TBI medical condition (N=1,228) ²⁴. Those with a history of moderate and severe TBI were found to have a 2- and 4-fold higher likelihood of developing AD later in life, while those with a history of mild TBI did not. Barnes et al. (2014) compared older veterans with a diagnosis of AD and a history of TBI of any severity to those with no TBI history ²⁵. Veterans with a history of TBI were found to have a 1.6-fold increased risk for developing AD during a nine year follow-up.

Running title: Traumatic brain injuries and dementias

In one population study, Mehta et al. (1999) examined whether a self-reported TBI increased the incidence of AD in individuals aged 55 years or older ²⁶. They found that a history of TBI with LOC, duration of LOC, time since injury and multiple TBIs were unrelated to the development of AD. Dams-O'Connor et al. (2013) followed up over 4,000 individuals aged 65 years and older every two years for an average of seven years, assessing for the development of AD ²⁷. Subjects who self-reported a history of TBI with LOC were found to have a similar risk for developing AD as those without a TBI history, regardless of when in the life span the TBI occurred. The authors also found no relationship between a history of TBI and AD neuropathology, although TAR DNA-binding protein 43 (TDP-43) pathology was more commonly seen in the TBI group. TDP-43 is a feature in a number of neurodegenerative diseases, and recent data indicate that a TDP-43 proteinopathy might occur after repetitive mild TBI ²⁸.

Meta-analyses of the link between TBI and AD have produced mixed results. In 1991, Mortimer et al. performed a meta-analysis of case-control studies examining the relationship between AD and TBI, and found an association in men but not women ²⁹. One more recent meta-analysis concluded that a history of any head injury was not a significant risk factor for a diagnosis of AD ³⁰, contrary to another meta-analysis that found TBI with any LOC was a risk, with the relative risk of AD after TBI estimated to be increased by 1.5 ³¹, again, in men, but not women. Since TBI is a heterogeneous condition, any meta-analysis which includes TBI with and without LOC could potentially produce a false negative, as any potential association with moderate to severe TBI was likely lost within a more nonspecific TBI group. The Kentucky BRAiNS study used post mortem data for 238 patients with TBI and reported higher rates of AD neuropathology in men, but not in women with dementia ³². This mirrors a general

Running title: Traumatic brain injuries and dementias

trend towards greater post-TBI dementia risk in men in observational studies. Therefore, it would be a mistake to assume that everyone with a TBI is at an increased risk for developing AD. However, it does appear that some individuals who sustain a TBI are at increased risk of later developing AD, for reasons that may relate to injury severity as well as other factors which require further investigation.

In addition to increasing the risk of developing AD in some individuals, TBI may also affect the age of onset. LoBue et al. (2017) recently conducted a retrospective study of the National Alzheimer's Coordinating Center dataset and found that those with a history of TBI with LOC had an onset of symptoms of AD 2.5 years earlier than those without a TBI history ³³. These findings suggest that a history of TBI could lead to reduced cognitive reserve, which could later interact with neurodegenerative processes to lower the threshold for onset of symptoms, or might accelerate the onset of AD in some individuals by contributing directly to an underlying neurodegenerative process. Another study of post mortem-confirmed AD cases reported an earlier symptom onset by 3.6 years in patients with prior TBI ³⁴, but overall, studies with neuropathological data show varied results.

Since TBI may contribute to an acceleration of the neurodegenerative processes that underlie AD, it is also possible that TBI influences the course of decline in AD. In one study that followed individuals diagnosed with AD for up to 11 years, Gilbert et al. (2014) reported that a history of TBI with LOC within 10 years was linked to more rapid decline in dementia severity after AD onset, but more remote TBIs were not ³⁵. As such, it could be that while a remote history of TBI may be a risk factor for earlier onset of AD, a remote TBI does not affect the course of AD.

Running title: Traumatic brain injuries and dementias

Some research has suggested that the onset of AD may be accelerated by repetitive concussions or mild TBIs. One study of retired professional American football players with a history of three concussions found a five-fold greater prevalence of mild cognitive impairment and an earlier onset of AD than in the general population ³⁶. Similar findings have been reported in other studies with multiple neurotrauma being associated with an increased risk of AD or accelerated progression ³⁷⁻⁴⁰.

Frontotemporal dementia

Frontotemporal dementia (FTD) comprises three main related dementia types; behavioural variant FTD, primary progressive aphasia and progressive nonfluent aphasia, depending on which areas of the brain are affected ⁴¹. Individuals may present with changes in personality, disinhibition, impulsivity and apathy (behavioural variant), changes in speech (primary progressive aphasia) or loss of semantic knowledge (progressive nonfluent aphasia). FTD characteristically involves degeneration of the frontal lobes and the anterior temporal regions ⁴², and as TBI often affects the frontal lobes, any relationship has been investigated across several studies.

Studies have assessed incidence of FTD after single TBIs and report increased risks ranging from 1.5 to 4.5 times depending on injury severity ⁴³, with no evidence of a relationship between mild or repeated mild TBI and FTD. The authors also examined whether those with a history of TBI demonstrated more severe cognitive impairment. However, no neuropsychological differences were seen between subjects with and without a history of TBI diagnosed with primary progressive aphasia or progressive nonaffluent aphasia, and those with a TBI history diagnosed with behavioural variant FTD actually performed significantly better.

Running title: Traumatic brain injuries and dementias

Two other research groups found similar results. Rosso et al. (2003) examined several lifetime medical risk factors for being diagnosed with behavioural variant FTD ⁴⁴. Despite a limited sample size, a history of TBI was found to be associated with a significantly higher risk for a diagnosis of behavioural variant FTD, whereas other medical factors were not. Kalkonde et al. (2012) compared veterans with behavioural variant FTD to those with any other dementia type ⁴⁵. While TBI cases were again limited, patients with a history of TBI with LOC showed a significantly higher likelihood for being diagnosed with behavioural variant FTD compared to other types of dementia.

As with AD, it has been suggested that TBI may accelerate the onset of FTD symptoms. LoBue et al. (2016) examined age of symptom onset and diagnosis in behavioural variant FTD subjects and found those with a history of TBI with LOC had an onset of symptoms three years earlier than those without a TBI history ⁴⁶.

Dementia with Lewy bodies

Dementia with Lewy bodies (DLB) is associated with diffuse accumulation of Lewy bodies and alpha-synuclein proteins within the brain ⁴⁷. Its classic clinical presentation consists of impaired and fluctuating cognition, extrapyramidal symptoms and visual hallucinations. Despite DLB being the second most common dementia, very little is known about TBI as a risk factor. Boot et al. (2013) reported that a history of TBI was not associated with an increased risk for a diagnosis of DLB, but another study of individuals aged 50 years and older from three cohorts (Crane et al., 2016) 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

Running title: Traumatic brain injuries and dementias

at autopsy ^{18, 48}. Interestingly, this association was reversed when the authors only examined subjects with injuries occurring decades earlier, but as there were only four cases with more severe injuries and presence of any Lewy body pathology, this potential association remains unclear.

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 ⁴⁹. It was first described in a 1928 case report which described a boxer who developed symptoms similar to Parkinson's disease ⁵⁰. Since then it has been referred to as "punch drunk syndrome" or dementia pugilistica ⁵¹, with the term CTE only reintroduced in 2005. Interest was revived when similar observations and neuropathological findings were reported in others contact sports prone to repetitive mild TBI and military personnel ²⁸. Establishing the relationship between TBI, CTE and dementia is complicated by the fact that there has long been no formally accepted clinical criteria for the diagnosis of CTE, and the clinical presentations described in the literature have varied over time. Speech, movement and memory changes were historically reported in autopsy-identified cases, but alterations in personality, depression, irritability, impulsivity and cognitive problems have been described in cases in more recent years ⁵². Given relatively few cases have been identified, the lack of a consensus around diagnostic criteria and the absence of large population-based studies contributes to our poor understanding of the syndrome. Neuropathological studies suggest a heterogeneous clinical phenotype, with substantial overlaps to the cognitive and psychiatric problems produced directly by TBI ⁵³. Additionally, many of the symptoms believed to be related to CTE overlap with those seen in other psychiatric conditions, most notably depression

Running title: Traumatic brain injuries and dementias

and types of dementia, and while a history of repetitive TBI has been reported in many cases of CTE, this is also the case with FTD and other conditions. Thus, it is likely that some cases of clinically suspected CTE have been misclassified in the absence of neuropathological data.

A consensus meeting in 2013 was held to determine whether CTE could be reliably distinguished from other neuropathological processes ⁵⁴. Seven neuropathologists blindly evaluated brain tissue from 25 cases, including 10 presumed to have CTE (70% also showed presence of some AD-related pathology), 13 considered to have a tau-related dementia and two with age-related changes. Although it is unclear how the 25 cases were selected for review, there was good agreement in classification and high agreement (>90%) for recognizing CTE, leading the consensus panel to develop the initial neuropathological criteria for this entity. But in one study of sixty one athletes with a history of repetitive mild TBI ⁵³ 25% had clinical symptoms and CTE pathology, but nearly 25% had clinical symptoms without CTE pathology, and approximately 25% had CTE pathology without clinical symptoms. Additionally, almost 75% had neuropathological processes present that were related to other neurodegenerative disorders.

As a result, CTE has been highly debated, with some hypothesizing that repetitive mild TBI can activate a neurodegenerative process leading to CTE and others proposing that TBI merely accelerates the expression of other neurodegenerative conditions, with some overlap of pathological processes. Yet despite the link between TBI and CTE being associational rather than mechanistic at this point, the growing prevalence among military blast and sports injuries increases the urgency for understanding of the relationship and identifying potential pharmaceutical treatments. While advances in the use of PET imaging compounds (e.g. for

Running title: Traumatic brain injuries and dementias

brain tau) have increased the potential for in vivo diagnosis of CTE ⁵⁵ our understanding of its mechanism remains limited.

Potential mechanisms

Mechanistic processes that can explain the associations between TBI and the later development of neurodegenerative conditions have not been well established. This in part reflects the lack of evidence around the pathway of the long term pathological effects of TBI. We are starting to understand a great deal more about how underlying neurodegenerative disorders can start decades before progressing into dementia, so how the chronic effects of TBI act in relation to other risk factors and biomarkers of dementia will also need to be understood.

Neuroimaging studies have found that beyond the acute phase (before 30 months post-TBI), there is atrophy of frontal and temporal connections in moderate to severe TBI ^{42, 56}. Between 1 and 4 years after injury, greater diffuse white matter atrophy seems to occur ⁵⁷, and it has been hypothesised that white matter tracts damage may be the key change that promotes a cascade of pathological processes related to neurodegenerative dementias ⁵⁸. Both post mortem studies and animal models have found evidence of tau in moderate to severe TBI or repetitive mild TBI, with pathological models showing progression and neuronal cell death ^{59, 60}. The presence of neurofibrillary tangles (NFTs) is one of the most consistent pathologies reported in CTE, and was even documented in the earliest described case ⁶¹. Tau NFTs show an increased distribution in the cerebral cortex in CTE, involving the superficial neocortical layers and the depths of sulci. This sulcal distribution has been suggested to be pathognomonic of CTE ⁶².

Running title: Traumatic brain injuries and dementias

The presence of amyloid β ($A\beta$) pathology has emerged as a less consistent feature than tau pathologies, although pathological studies of CTE, in particular, tend to have limited control samples. In CTE plaques are usually diffuse and do not display the histochemical or morphological features of the neuritic plaques that are characteristic of AD. As regards the origin of these plaque pathologies, axonal injury is proposed to have a role, at least in the acute phase. Specifically, diffuse axonal injury (DAI) is an early and frequent event documented in all severities of TBI ⁶³ and DAI could provide a potential means for $A\beta$ genesis following trauma. Axonal pathology was previously thought to be an acute event, soon after injury, but studies have now found ongoing axonal degeneration persisting years following TBI ⁵⁸. But whether this process contributes to ongoing amyloid plaque deposition is unclear.

La Bohue and colleagues (2018) have suggested that TBI contributes to the development of pathological burden across several, overlapping neurodegenerative processes and may interact with normal ageing⁶⁴. When the overall brain changes surpass a threshold, impairments become clinically visible, which could explain why some individuals develop MCI at an earlier age before progressing to AD, while others may have a direct acceleration of onset of symptoms related to AD and behavioural variant FTD. However, the pathological burden may plateau shortly after onset of a dementia process, resulting in a similar course of decline between those with and those without a history of TBI. In contrast, individuals who proceed to DLB might show a similar course regardless of whether they have a remote history of TBI or not. This model best supports descriptions in the literature indicating that although a history of TBI can accelerate onset of AD and FTD, a remote history of TBI does not appear to confer greater levels of impairment or more rapid decline in most individuals,

Running title: Traumatic brain injuries and dementias

Other mechanisms have been implicated in the neuropathology of TBI and dementia. Endoplasmic reticulum stress is a prominent theory for the progression of chronic neurodegenerative tauopathies and occurs secondary to a disruption of calcium homeostasis, eventually causing a cessation of normal protein folding ^{65, 66}. Mitochondrial function or dysfunction may play an important role as it has been noted that reactive oxygen species can damage mitochondria leading to axonal degeneration following TBI ⁶⁷. Cells that survive the primary insult are subject to tau-mediated mitochondrial damage, which occurs over an extended period of time ⁶⁸. Tau can increase glutathione leading to increased permeability of mitochondrial membranes. In AD, damaged mitochondria can no longer generate ATP leaving neuronal cells susceptible to metabolic crisis, and in CTE, mitochondrial damage accelerates the cell stress response and has the potential for further neurodegeneration ^{69, 70}. Mitochondrial biomarkers might also offer improved diagnostic potential as evidence has confirmed that mutated mitochondrial DNA are a clear indicator of future neurodegenerative pathology ⁷¹.

The role of sustained neuroinflammation in neurodegeneration after TBI has been well established pathologically since the 1950s, and is strongly supported by preclinical and clinical studies. While an acute inflammatory response seems likely, it would seem reasonable that inflammation would resolve following the acute phase. However, evidence is accumulating that neuroinflammation persists in some single moderate to severe TBI for many years ⁷². Manifested by extensive microglial and astroglial activation, such chronic traumatic brain inflammation may be the most important cause of post-traumatic neurodegeneration in terms of prevalence. Reactive gliosis following TBI can lead to chronic inflammation and neurodegeneration ⁷³ and neuroinflammatory genes are increased following injury ⁷⁴. CTE and AD can confound recovery by perpetually activating microglia ⁷⁵ and persistent neuroinflammation and associated neurodegeneration may prove to be treatable long after the

Running title: Traumatic brain injuries and dementias

initial TBI. But whether inflammation following occurs as a response to coincident pathologies or is the primary pathology remains unknown.

Oxidative stress has been found to occur as early as three hours following TBI ⁷⁶ and leads to mitochondrial dysfunction and contributes to chronic neurodegeneration ⁷⁷. Over time oxidative stress triggers neuronal apoptosis and can contribute to hippocampal synaptic protein loss ^{76, 78, 79}. Oxidative stress has been associated CTE ⁸⁰ and DNA damage induced by oxidative stress is common in AD ⁸¹. Even a single TBI has been reported to increase the risk for early onset AD by 30% partly due to oxidative damage ⁸². Further research is needed to investigate potential antioxidant solutions following TBI.

Conclusions

Without doubt, traumatic brain injury (TBI) remains the main strongest environmental risk factor for dementia and current evidence suggests a possible dose dependent relationship, with more severe and frequent injuries increasing risk of any development of subsequent dementia. Thus, that TBI represents a major risk factor for the later development of neurodegenerative disease is well accepted. But drawing firm conclusions about the relationship with dementia has been limited by the insidious nature of neurodegenerative disorders and the research methods and limitations of available studies and findings. In addition, more comprehensive assessment of TBI history (TBI severity, age at injury, presence of multiple injuries) is needed. Without due consideration of these factors, researchers will not be able to determine which ones potentiate TBI's effects on the subsequent development of dementia.

Running title: Traumatic brain injuries and dementias

The pathological evidence around long term outcome post-TBI is varied, and includes amyloid- β , tau and TDP-43 pathologies, together with white matter degradation, neuronal loss and neuroinflammation. This seems similar to a certain extent following both single and repetitive injuries, but comparative studies are lacking. More studies of neuropathologically confirmed cases of different types of dementia may help resolve mixed findings in the literature. Since several lines of research point to TBI accelerating the onset of some dementias, so future studies need to examine whether TBI influences the course of cognitive decline. It is likely that longitudinal biomarker assessments (e.g., tau imaging) after TBI will be needed to reveal whether TBI initiates a progressive development of neurodegenerative pathology, if such changes eventually stabilize and if persistent neurodegenerative changes occur in milder injuries.

A lack of prospective, population studies means the prevalence of TBI-related dementia in the population remains unknown. It is even possible that some individuals may be ‘resistant’ to developing dementia following TBI. Following a single moderate to severe TBI, evidence to date supports an initial spike in pathology immediately after the event, which subsequently resolves. But it could be that in a proportion of individuals there is only a partial resolution of this acute phase response, leading to subsequent accelerated further changes and the threshold for clinical dementia symptoms being crossed at an earlier age. Similarly, each successive mild TBI may lead to acute pathology followed by partial resolution, which triggers accelerated accumulation of pathology and earlier onset symptomatology.

Overall, research on TBI and its relationship with the later development of various types of dementia is still in its early stages. In summary, there is evidence to support a link between a history of TBI and the later development of neurodegenerative conditions, but individual risk

Running title: Traumatic brain injuries and dementias

cannot be determined. TBI appears to be associated with earlier onset of some neurodegenerative disorders but may not influence the course of decline. Future studies need to include more detailed information about TBI history and injury characteristics as well as using more recent neuropsychological, neuroimaging, and biomarker techniques and assays. Fluid biomarkers such as neurofilament light can complement neuroimaging, representing sensitive potential methods to track neurodegenerative processes that develop after TBI. These biomarkers could characterise endophenotypes associated with distinct types of posttraumatic neurodegeneration. In addition, they might profitably be used in clinical trials of neuroprotective and disease-modifying treatments, improving trial design by providing precise and sensitive measures of neuronal loss. Further post mortem led research is also needed in well-characterised clinical populations and ideally more ‘real world’ data. Such approaches to research could inform the development of urgently needed disease-modifying and symptomatic interventions.

REFERENCES

1. Maas AIR, Menon DK, Adelson PD, Andelic N, Bell MJ, Belli A, et al. Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research. *Lancet Neurol*. 2017 Dec;16(12):987-1048.
2. Li Y, Li Y, Li X, Zhang S, Zhao J, Zhu X, et al. Head Injury as a Risk Factor for Dementia and Alzheimer's Disease: A Systematic Review and Meta-Analysis of 32 Observational Studies. *PLoS One*. 2017;12(1):e0169650.
3. Raj R, Kaprio J, Korja M, Mikkonen ED, Jousilahti P, Siironen J. Risk of hospitalization with neurodegenerative disease after moderate-to-severe traumatic brain injury in the working-age population: A retrospective cohort study using the Finnish national health registries. *PLoS Med*. 2017 Jul;14(7):e1002316.
4. Nordstrom A, Nordstrom P. Traumatic brain injury and the risk of dementia diagnosis: A nationwide cohort study. *PLoS Med*. 2018 Jan;15(1):e1002496.
5. Graham NS, Sharp DJ. Understanding neurodegeneration after traumatic brain injury: from mechanisms to clinical trials in dementia. *J Neurol Neurosurg Psychiatry*. 2019 Nov;90(11):1221-33.
6. Barnes DE, Byers AL, Gardner RC, Seal KH, Boscardin WJ, Yaffe K. Association of Mild Traumatic Brain Injury With and Without Loss of Consciousness With Dementia in US Military Veterans. *JAMA Neurol*. 2018 Sep 1;75(9):1055-61.
7. Braak H, Braak E. Frequency of stages of Alzheimer-related lesions in different age categories. *Neurobiol Aging*. 1997 Jul-Aug;18(4):351-7.
8. Griesbach GS, Masel BE, Helvie RE, Ashley MJ. The Impact of Traumatic Brain Injury on Later Life: Effects on Normal Aging and Neurodegenerative Diseases. *J Neurotrauma*. 2018 Jan 1;35(1):17-24.

Running title: Traumatic brain injuries and dementias

9. Arani A, Murphy MC, Glaser KJ, Manduca A, Lake DS, Kruse SA, et al. Measuring the effects of aging and sex on regional brain stiffness with MR elastography in healthy older adults. *Neuroimage*. 2015 May 1;111:59-64.
10. Maxwell WL, MacKinnon MA, Stewart JE, Graham DI. Stereology of cerebral cortex after traumatic brain injury matched to the Glasgow outcome score. *Brain*. 2010 Jan;133(Pt 1):139-60.
11. Turkheimer E, Cullum CM, Hubler DW, Paver SW, Yeo RA, Bigler ED. Quantifying cortical atrophy. *J Neurol Neurosurg Psychiatry*. 1984 Dec;47(12):1314-8.
12. Massman PJ, Bigler ED, Cullum CM, Naugle RI. The relationship between cortical atrophy and ventricular volume. *Int J Neurosci*. 1986 Aug;30(1-2):87-99.
13. Levin HS, Williams DH, Valastro M, Eisenberg HM, Crofford MJ, Handel SF. Corpus callosal atrophy following closed head injury: detection with magnetic resonance imaging. *J Neurosurg*. 1990 Jul;73(1):77-81.
14. Filippi M, van den Heuvel MP, Fornito A, He Y, Hulshoff Pol HE, Agosta F, et al. Assessment of system dysfunction in the brain through MRI-based connectomics. *Lancet Neurol*. 2013 Dec;12(12):1189-99.
15. Schiff ND. Measurements and models of cerebral function in the severely injured brain. *J Neurotrauma*. 2006 Oct;23(10):1436-49.
16. Maas AI, Menon DK. Traumatic brain injury: rethinking ideas and approaches. *Lancet Neurol*. 2012 Jan;11(1):12-3.
17. Arenaza-Urquijo EM, Bosch B, Sala-Llonch R, Sole-Padullés C, Junque C, Fernández-Espejo D, et al. Specific anatomic associations between white matter integrity and cognitive reserve in normal and cognitively impaired elders. *Am J Geriatr Psychiatry*. 2011 Jan;19(1):33-42.

Running title: Traumatic brain injuries and dementias

18. Crane PK, Gibbons LE, Dams-O'Connor K, Trittschuh E, Leverenz JB, Keene CD, et al. Association of Traumatic Brain Injury With Late-Life Neurodegenerative Conditions and Neuropathologic Findings. *JAMA Neurol.* 2016 Sep 1;73(9):1062-9..
19. Parfenov VA, Zakharov VV, Kabaeva AR, Vakhnina NV. Subjective cognitive decline as a predictor of future cognitive decline: a systematic review. *Dement Neuropsychol.* 2020 Jul-Sep;14(3):248-57.
20. LoBue C, Denney D, Hynan LS, Rossetti HC, Lacritz LH, Hart J, et al. Self-Reported Traumatic Brain Injury and Mild Cognitive Impairment: Increased Risk and Earlier Age of Diagnosis. *J Alzheimers Dis.* 2016;51(3):727-36.
21. Li W, Risacher SL, McAllister TW, Saykin AJ. Traumatic brain injury and age at onset of cognitive impairment in older adults. *J Neurol.* 2016 Jul;263(7):1280-5.
22. Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. *Acta Neuropathol.* 1991;82(4):239-59.
23. Alzheimer's A. 2015 Alzheimer's disease facts and figures. *Alzheimers Dement.* 2015 Mar;11(3):332-84.
24. Plassman BL, Havlik RJ, Steffens DC, Helms MJ, Newman TN, Drosdick D, et al. Documented head injury in early adulthood and risk of Alzheimer's disease and other dementias. *Neurology.* 2000 Oct 24;55(8):1158-66.
25. Barnes DE, Kaup A, Kirby KA, Byers AL, Diaz-Arrastia R, Yaffe K. Traumatic brain injury and risk of dementia in older veterans. *Neurology.* 2014 Jul 22;83(4):312-9.
26. Mehta KM, Ott A, Kalmijn S, Slooter AJ, van Duijn CM, Hofman A, et al. Head trauma and risk of dementia and Alzheimer's disease: The Rotterdam Study. *Neurology.* 1999 Dec 10;53(9):1959-62.

Running title: Traumatic brain injuries and dementias

27. Dams-O'Connor K, Gibbons LE, Bowen JD, McCurry SM, Larson EB, Crane PK. Risk for late-life re-injury, dementia and death among individuals with traumatic brain injury: a population-based study. *J Neurol Neurosurg Psychiatry*. 2013 Feb;84(2):177-82.
28. Smith DH, Johnson VE, Stewart W. Chronic neuropathologies of single and repetitive TBI: substrates of dementia? *Nat Rev Neurol*. 2013 Apr;9(4):211-21.
29. Mortimer JA, van Duijn CM, Chandra V, Fratiglioni L, Graves AB, Heyman A, et al. Head trauma as a risk factor for Alzheimer's disease: a collaborative re-analysis of case-control studies. EURODEM Risk Factors Research Group. *Int J Epidemiol*. 1991;20 Suppl 2:S28-35.
30. Xu W, Tan L, Wang HF, Jiang T, Tan MS, Tan L, et al. Meta-analysis of modifiable risk factors for Alzheimer's disease. *J Neurol Neurosurg Psychiatry*. 2015 Dec;86(12):1299-306.
31. Fleminger S, Oliver DL, Lovestone S, Rabe-Hesketh S, Giora A. Head injury as a risk factor for Alzheimer's disease: the evidence 10 years on; a partial replication. *J Neurol Neurosurg Psychiatry*. 2003 Jul;74(7):857-62.
32. Abner EL, Nelson PT, Schmitt FA, Browning SR, Fardo DW, Wan L, et al. Self-reported head injury and risk of late-life impairment and AD pathology in an AD center cohort. *Dement Geriatr Cogn Disord*. 2014;37(5-6):294-306.
33. LoBue C, Wadsworth H, Wilmoth K, Clem M, Hart J, Jr., Womack KB, et al. Traumatic brain injury history is associated with earlier age of onset of Alzheimer disease. *Clin Neuropsychol*. 2017 Jan;31(1):85-98.
34. Schaffert J, LoBue C, White CL, Chiang HS, Didehbani N, Lacritz L, et al. Traumatic brain injury history is associated with an earlier age of dementia onset in autopsy-confirmed Alzheimer's disease. *Neuropsychology*. 2018 May;32(4):410-6.
35. Gilbert M, Snyder C, Corcoran C, Norton MC, Lyketsos CG, Tschanz JT. The association of traumatic brain injury with rate of progression of cognitive and functional

Running title: Traumatic brain injuries and dementias

impairment in a population-based cohort of Alzheimer's disease: the Cache County Dementia Progression Study. *Int Psychogeriatr*. 2014 Oct;26(10):1593-601.

36. Guskiewicz KM, Marshall SW, Bailes J, McCrea M, Cantu RC, Randolph C, et al. Association between recurrent concussion and late-life cognitive impairment in retired professional football players. *Neurosurgery*. 2005 Oct;57(4):719-26; discussion -26.

37. Lee YK, Hou SW, Lee CC, Hsu CY, Huang YS, Su YC. Increased risk of dementia in patients with mild traumatic brain injury: a nationwide cohort study. *PLoS One*. 2013;8(5):e62422.

38. Schofield PW, Tang M, Marder K, Bell K, Dooneief G, Chun M, et al. Alzheimer's disease after remote head injury: an incidence study. *J Neurol Neurosurg Psychiatry*. 1997 Feb;62(2):119-24.

39. Wang HK, Lin SH, Sung PS, Wu MH, Hung KW, Wang LC, et al. Population based study on patients with traumatic brain injury suggests increased risk of dementia. *J Neurol Neurosurg Psychiatry*. 2012 Nov;83(11):1080-5.

40. Nemetz PN, Leibson C, Naessens JM, Beard M, Kokmen E, Annegers JF, et al. Traumatic brain injury and time to onset of Alzheimer's disease: a population-based study. *Am J Epidemiol*. 1999 Jan 1;149(1):32-40.

41. McKhann GM, Albert MS, Grossman M, Miller B, Dickson D, Trojanowski JQ, et al. Clinical and pathological diagnosis of frontotemporal dementia: report of the Work Group on Frontotemporal Dementia and Pick's Disease. *Arch Neurol*. 2001 Nov;58(11):1803-9.

42. Ng AS, Rademakers R, Miller BL. Frontotemporal dementia: a bridge between dementia and neuromuscular disease. *Ann N Y Acad Sci*. 2015 Mar;1338:71-93.

43. Deutsch MB, Mendez MF, Teng E. Interactions between traumatic brain injury and frontotemporal degeneration. *Dement Geriatr Cogn Disord*. 2015;39(3-4):143-53.

Running title: Traumatic brain injuries and dementias

44. Rosso SM, Landweer EJ, Houterman M, Donker Kaat L, van Duijn CM, van Swieten JC. Medical and environmental risk factors for sporadic frontotemporal dementia: a retrospective case-control study. *J Neurol Neurosurg Psychiatry*. 2003 Nov;74(11):1574-6.
45. Kalkonde YV, Jawaid A, Qureshi SU, Shirani P, Wheaton M, Pinto-Patarroyo GP, et al. Medical and environmental risk factors associated with frontotemporal dementia: a case-control study in a veteran population. *Alzheimers Dement*. 2012 May;8(3):204-10.
46. LoBue C, Wilmoth K, Cullum CM, Rossetti HC, Lacritz LH, Hynan LS, et al. Traumatic brain injury history is associated with earlier age of onset of frontotemporal dementia. *J Neurol Neurosurg Psychiatry*. 2016 Aug;87(8):817-20.
47. McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology*. 2005 Dec 27;65(12):1863-72.
48. Boot BP, Orr CF, Ahlskog JE, Ferman TJ, Roberts R, Pankratz VS, et al. Risk factors for dementia with Lewy bodies: a case-control study. *Neurology*. 2013 Aug 27;81(9):833-40.
49. McKee AC, Stein TD, Kiernan PT, Alvarez VE. The neuropathology of chronic traumatic encephalopathy. *Brain Pathol*. 2015 May;25(3):350-64..
50. Martland HS. Punch drunk. *J Amer Med Assoc*. 1928 Jul-Dec;91:1103-7.
51. Gardner A, Iverson GL, McCrory P. Chronic traumatic encephalopathy in sport: a systematic review. *Br J Sports Med*. 2014 Jan;48(2):84-90.
52. Baugh CM, Robbins CA, Stern RA, McKee AC. Current understanding of chronic traumatic encephalopathy. *Curr Treat Options Neurol*. 2014 Sep;16(9):306.
53. McKee AC, Stern RA, Nowinski CJ, Stein TD, Alvarez VE, Daneshvar DH, et al. The spectrum of disease in chronic traumatic encephalopathy. *Brain*. 2013 Jan;136(Pt 1):43-64.

Running title: Traumatic brain injuries and dementias

54. McKee AC, Cairns NJ, Dickson DW, Folkerth RD, Keene CD, Litvan I, et al. The first NINDS/NIBIB consensus meeting to define neuropathological criteria for the diagnosis of chronic traumatic encephalopathy. *Acta Neuropathol*. 2016 Jan;131(1):75-86.
55. Small GW, Kepe V, Siddarth P, Ercoli LM, Merrill DA, Donoghue N, et al. PET scanning of brain tau in retired national football league players: preliminary findings. *Am J Geriatr Psychiatry*. 2013 Feb;21(2):138-44.
56. Greenberg G, Mikulis DJ, Ng K, DeSouza D, Green RE. Use of diffusion tensor imaging to examine subacute white matter injury progression in moderate to severe traumatic brain injury. *Arch Phys Med Rehabil*. 2008 Dec;89(12 Suppl):S45-50.
57. Farbota KD, Sodhi A, Bendlin BB, McLaren DG, Xu G, Rowley HA, et al. Longitudinal volumetric changes following traumatic brain injury: a tensor-based morphometry study. *J Int Neuropsychol Soc*. 2012 Nov;18(6):1006-18.
58. Johnson VE, Stewart W, Smith DH. Axonal pathology in traumatic brain injury. *Exp Neurol*. 2013 Aug;246:35-43.
59. Johnson VE, Stewart W, Smith DH. Widespread tau and amyloid-beta pathology many years after a single traumatic brain injury in humans. *Brain Pathol*. 2012 Mar;22(2):142-9.
60. Kondo A, Shahpasand K, Mannix R, Qiu J, Moncaster J, Chen CH, et al. Antibody against early driver of neurodegeneration cis P-tau blocks brain injury and tauopathy. *Nature*. 2015 Jul 23;523(7561):431-6.
61. Brandenburg W, Hallervorden J. [Dementia pugilistica with anatomical findings]. *Virchows Arch Pathol Anat Physiol Klin Med*. 1954;325(6):680-709. Dementia pugilistica mit anatomischem Befund.
62. Baugh CM, Stamm JM, Riley DO, Gavett BE, Shenton ME, Lin A, et al. Chronic traumatic encephalopathy: neurodegeneration following repetitive concussive and subconcussive brain trauma. *Brain Imaging Behav*. 2012 Jun;6(2):244-54.

Running title: Traumatic brain injuries and dementias

63. Adams JH, Doyle D, Ford I, Gennarelli TA, Graham DI, McLellan DR. Diffuse axonal injury in head injury: definition, diagnosis and grading. *Histopathology*. 1989 Jul;15(1):49-59.
64. LoBue C, Cullum CM, Didehbani N, Yeatman K, Jones B, Kraut MA, et al. Neurodegenerative Dementias After Traumatic Brain Injury. *J Neuropsychiatry Clin Neurosci*. 2018 Winter;30(1):7-13.
65. Kohler C, Dinekov M, Gotz J. Granulovacuolar degeneration and unfolded protein response in mouse models of tauopathy and Abeta amyloidosis. *Neurobiol Dis*. 2014 Nov;71:169-79.
66. Montague K, Malik B, Gray AL, La Spada AR, Hanna MG, Szabadkai G, et al. Endoplasmic reticulum stress in spinal and bulbar muscular atrophy: a potential target for therapy. *Brain*. 2014 Jul;137(Pt 7):1894-906.
67. Bros H, Millward JM, Paul F, Niesner R, Infante-Duarte C. Oxidative damage to mitochondria at the nodes of Ranvier precedes axon degeneration in ex vivo transected axons. *Exp Neurol*. 2014 Nov;261:127-35.
68. Saman S, Lee NC, Inoyo I, Jin J, Li Z, Doyle T, et al. Proteins recruited to exosomes by tau overexpression implicate novel cellular mechanisms linking tau secretion with Alzheimer's disease. *J Alzheimers Dis*. 2014;40 Suppl 1:S47-70.
69. Naviaux RK. Metabolic features of the cell danger response. *Mitochondrion*. 2014 May;16:7-17.
70. Khatri N, Man HY. Synaptic activity and bioenergy homeostasis: implications in brain trauma and neurodegenerative diseases. *Front Neurol*. 2013 Dec 11;4:199.
71. Hroudova J, Singh N, Fisar Z. Mitochondrial dysfunctions in neurodegenerative diseases: relevance to Alzheimer's disease. *Biomed Res Int*. 2014;2014:175062.

Running title: Traumatic brain injuries and dementias

72. Gentleman SM, Leclercq PD, Moyes L, Graham DI, Smith C, Griffin WS, et al. Long-term intracerebral inflammatory response after traumatic brain injury. *Forensic Sci Int*. 2004 Dec 16;146(2-3):97-104.
73. Avila-Munoz E, Arias C. When astrocytes become harmful: functional and inflammatory responses that contribute to Alzheimer's disease. *Ageing Res Rev*. 2014 Nov;18:29-40.
74. Fenn AM, Skendelas JP, Moussa DN, Muccigrosso MM, Popovich PG, Lifshitz J, et al. Methylene blue attenuates traumatic brain injury-associated neuroinflammation and acute depressive-like behavior in mice. *J Neurotrauma*. 2015 Jan 15;32(2):127-38.
75. Loane DJ, Kumar A, Stoica BA, Cabatbat R, Faden AI. Progressive neurodegeneration after experimental brain trauma: association with chronic microglial activation. *J Neuropathol Exp Neurol*. 2014 Jan;73(1):14-29.
76. Ansari MA, Roberts KN, Scheff SW. A time course of contusion-induced oxidative stress and synaptic proteins in cortex in a rat model of TBI. *J Neurotrauma*. 2008 May;25(5):513-26.
77. Wang F, Franco R, Skotak M, Hu G, Chandra N. Mechanical stretch exacerbates the cell death in SH-SY5Y cells exposed to paraquat: mitochondrial dysfunction and oxidative stress. *Neurotoxicology*. 2014 Mar;41:54-63..
78. Itoh T, Imano M, Nishida S, Tsubaki M, Mizuguchi N, Hashimoto S, et al. Increased apoptotic neuronal cell death and cognitive impairment at early phase after traumatic brain injury in aged rats. *Brain Struct Funct*. 2013 Jan;218(1):209-20.
79. Ansari MA, Roberts KN, Scheff SW. Oxidative stress and modification of synaptic proteins in hippocampus after traumatic brain injury. *Free Radic Biol Med*. 2008 Aug 15;45(4):443-52. PubMed PMID: 18501200.

Running title: Traumatic brain injuries and dementias

80. Kochanek PM, Dixon CE, Shellington DK, Shin SS, Bayir H, Jackson EK, et al. Screening of biochemical and molecular mechanisms of secondary injury and repair in the brain after experimental blast-induced traumatic brain injury in rats. *J Neurotrauma*. 2013 Jun 1;30(11):920-37. PubMed PMID: 23496248.
81. Smith JA, Park S, Krause JS, Banik NL. Oxidative stress, DNA damage, and the telomeric complex as therapeutic targets in acute neurodegeneration. *Neurochem Int*. 2013 Apr;62(5):764-75.
82. Sivanandam TM, Thakur MK. Traumatic brain injury: a risk factor for Alzheimer's disease. *Neurosci Biobehav Rev*. 2012 May;36(5):1376-81.

NOTES

Conflicts of interest. The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

AUTHORS' CONTRIBUTION

Both Vanessa Rayment and Tony Thayanandan researched, drafted and completed the manuscript. All authors read and approved the final version of the manuscript.